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Altered supraspinal motor networks in survivors of poliomyelitis: A cortico-muscular coherence study

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HIGHLIGHTS

- Abnormal coherence patterns provide neurophysiologic evidence of supraspinal change in those affected by poliomyelitis.
- Cortico-Muscular Coherence changes in Polio patients reflect functional re-organisation of the central-peripheral network.
- Cortico-Muscular Coherence is a potential biomarker of altered Motor network function in Polio, SMA and other related conditions.

ABSTRACT

Objective: Poliomyelitis results in changes to the anterior horn cell. The full extent of cortical network changes in the motor physiology of polio survivors has not been established. Our aim was to investigate how focal degeneration of the lower motor neurons (LMN) in infancy/childhood affects motor network connectivity in adult survivors of polio.
Methods: Surface electroencephalography (EEG) and electromyography (EMG) were recorded during an isometric pincer grip task in 25 patients and 11 healthy controls. Spectral signal analysis of cortico-muscular (EEG-EMG) coherence (CMC) was used to identify the cortical regions that are functionally synchronous and connected to the periphery during the pincer grip task.
Results: A pattern of CMC was noted in polio survivors that was not present in healthy individuals. Significant CMC in low gamma frequency bands (30–47 Hz) was observed in frontal and parietal regions.
Conclusion: These findings imply a differential engagement of cortical networks in polio survivors that extends beyond the motor cortex and suggest a disease-related functional reorganisation of the cortical motor network.

Abbreviations: ADM, abductor digiti minimi; APB, abductor pollicis brevis; APL, abductor pollicis longus; CMC, corticomuscular coherence; DFT, discrete Fourier transform; EDC, extensor digitorum communis; EEG, electroencephalography; EMG, electromyography; EPB, extensor pollicis brevis; FDI, first dorsal interosseous; FDR, false discovery rate; FDS, flexor digitorum superficialis; FPB, flexor pollicis brevis; FDMB, flexor digiti minimi brevis; LMN, lower motor neuron; MRC, medical research council; MVC, maximum voluntary contraction; PPS, post polio syndrome; SMA, spinal muscular atrophy.

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Significance: This research has implications for other similar LMN conditions, including spinal muscular atrophy (SMA). CMC has potential in future clinical trials as a biomarker of altered function in motor networks in post-polio syndrome, SMA, and other related conditions.

1. Introduction

15–20 million people across the world experience the late sequelae of poliomyelitis (Mehndiratta et al., 2014). There is evolving evidence that central pathways for movement may be affected in polio survivors, either directly as a result of the original illness, or as a compensatory process following the loss of motor neurons (Allen et al., 1994; Lupu et al., 2008; Bodian, 1949, 1952). Moreover, post-mortem studies have demonstrated supraspinal involvement, as evidenced by gliosis of white matter tracts (Bruno et al., 1994), punctate lesions of grey matter within motor midbrain areas (particularly the reticular formation) (Bruno et al., 1994; Bodian, 1949, 1952) and lesions of the motor cortex (Bodian, 1949, 1952).

Despite the presence of pathologic evidence, there have been few detailed neurophysiological studies to investigate the nature and extent of alteration in network dynamics in the supraspinal components of the motor system.

Cortico-muscular coherence (Boonstra, 2013; Conway et al., 1995) is an emerging neurophysiological approach that can be applied to examine the integrated physiology of cortical, corticospinal and neuromuscular systems in neurological conditions (Proudfoot et al., 2018).

Cortico-muscular coherence provides a measure of coupling between cortical oscillations and motor unit firing patterns along the corticospinal tract (Mima and Hallett, 1999; Boonstra, 2013). The presence of coherence can be explained by an adequate number of motor neurons receiving temporally synchronised transmissions of synaptic input from cortical projections, coupled with afferent feedback from muscle to spinal and cortical networks (Conway et al., 1995). CMC frequency bands and their physiological correlates have been described in literature in healthy subjects (see Table 1), as such we aim to build on these findings and explore CMC changes in lower motor neuron conditions.

We have used cortico-muscular coherence to investigate the presence of alterations in the motor networks in survivors of poliomyelitis. We show that patients who suffered polio in childhood exhibit distinct changes in cortical connectivity that extend beyond the primary motor cortex.

2. Methods

2.1. Ethics

The study was approved by the *Tallaght University Hospital/St. James's Hospital Joint Research Ethics Committee – Dublin* [REC Reference: 2019-05 List 17 (01)] and performed in accordance with the Declaration of Helsinki. All patients provided informed written consent to the procedures before undergoing assessment.

Table 1
Frequency bands and their physiological correlates described in literature in healthy controls.

Band	Frequency	Physiological Correlates
Alpha Band	8–12 Hz	Physiological tremor (McAuley and Marsden, 2000)
Beta Band	15–30 Hz	Sustained muscle contraction (Conway et al., 1995)
Gamma Band	30–60 Hz	Dynamic force output (Omlor et al., 2007)

2.2. Patient cohort

Patients were prospectively recruited in this cross-sectional study between June 2017-November 2019 through the national clinic for polio survivors at Beaumont Hospital. All patients had a verified diagnosis of poliomyelitis in childhood, and all had supportive clinical and electromyographic findings. Healthy controls, age-matched to patients, were recruited from database of healthy controls interested in taking part in research.

Subjects with a history of major head trauma or other neurological conditions that could affect cognition, alcohol dependence syndrome, current use of neuroleptic medications or high-dose psychoactive medication were excluded. Those with diabetes mellitus, a history of cerebrovascular disease, and those with neuropathy from other causes were also excluded.

2.3. Clinical assessment

On the day of EEG recording all patients underwent an extensive clinical assessment. Disease duration from symptom onset and site of disease onset were recorded. Muscle strength was assessed using the Medical Research Council (*MRC*) score in 9 bilateral (i.e. 18) upper limb muscles, including deltoid, triceps, biceps, wrist flexors and extensors, fingers flexors and extensors, and abductors of the index fingers and thumbs. The degree of clinical lower motor neuron (LMN) involvement in the upper limbs was graded by a LMN score (de Carvalho et al., 2003) from these MRC scores, which ranged from 90 (absent LMN signs) to 0 (severe LMN signs).

Handedness was assessed in all participants with the Edinburgh Handedness Inventory (Oldfield et al., 1971).

2.4. Experimental paradigm

Assessment was conducted in the same manner for the patients and control groups. All participants were asked to minimise their eye movements and to relax during the experiment. Subjects sat in a comfortable chair that supported them in a stable posture, in front of a 23″ computer monitor (distance from eyes: ~1 m), with upper arm elevated at approximately 40° from shoulder and elbow at 90° resting on a pillow over a desk.

Participants attempted maximum voluntary contraction (MVC) of the pincer grip between the thumb and the index finger of their right hand (Fig. 1) guided by visual cues. Each MVC exertion was requested for 5 s, with 30 s delays between trials. MVC was taken as the average peak force of the three trials which were within 10% of each other. Note MVC trials were used for the purpose of calibration of force and visual interface and not for physiological signal recordings.

Participants attempted 30 voluntary isometric pincer grips between the thumb and the index finger of their right upper limb, according to visual cues. The onset and offset of the exertion were signalled to the subject by visual cues. Each exertion was requested at 10%MVC for 5 s, with 10 s delays between trials for rest. Partic-

ipant were instructed to use their *preferred pace* for increasing and decreasing the grip force and to avoid making abrupt changes in force. The force level exerted by the participant was deemed to be acceptable if the error was less than 10% of the range. The aim was to capture the cortico-muscular coherence, only during the exertion of these low-levels of steady-state force at 10% MVC. A visuomotor force-control isometric task was used, rather than *position-control* grip task at lower force levels, with a view to maintaining a low level of baseline CMC. We verified this by comparing the beta-band CMC between C3-FPB in a pilot position control task (significant classic CMC present, p = 0.0102) and our main visuomotor task (non-significant CMC, p = 0.9429), were a significant difference (p = 0.0068, corrected for multiple comparisons) was observed. This was asserted by preliminary analysis of CMC in our control group, and according to previous findings on CMC (Liu et al., 2019). It was anticipated that this would permit discrimination across patient groups. The time window during steady-state force was used for analysis.

2.4.1. Force

Grip force was recorded using 2 flat resistive force sensors (FlexiForce A201 Sensor, Tekscan, Inc., Boston, MA, USA) with their circular sensing area (d = 9.7 mm) attached to the 2 bases of a wooden hexagon (Fig. 1). The resistance was converted to analogue voltage using a small circuit board (Tekscan, Inc., Boston, MA, USA) and was recorded and digitised using a Data Acquisition Card (PCIe-6321, National Instruments, Austin, TX, USA) at 2000 Hz in real time, and subsequently visualised and presented to the participant.

2.4.2. Visual interface

The visual stimuli and the visual feedback of the grip force was programmed in MATLAB® (Mathworks, Inc., Natick, MA, USA) using Psychophysics Toolbox (Brainard, 1997) at a screen refresh rate of 60 Hz. The typical delay between the visualisation loop and the recording loop was 1–3 ms.

2.5. Data acquisition

EEG data were recorded in a special purpose laboratory, electromagnetically shielded as a Faraday cage, using 128-channel scalp electrode cap, filtered over the range 0–400 Hz and digitized at 2048 Hz using the BioSemi® ActiveTwo system (BioSemi B.V, Amsterdam, Netherlands). Each participant was fitted with an appropriately sized EEG cap.

Surface EMG was recorded (Fig. 1) from 8 muscles in the right upper arm: FDI (first dorsal interosseous); EDC (Extensor Digitorum Communis); FDS (Flexor Digitorum Superficialis); APL (Abductor Pollicis Longus) and EPB (Extensor Pollicis Brevis); FPB (Flexor Pollicis Brevis); APB (Abductor Pollicis Brevis); ADM (Abductor Digiti Minimi); FDMB (Flexor Digiti Minimi Brevis). These 8 muscles were chosen for recording surface EMG and were not the same as the 9 muscle pairs chosen for strength-based clinical assessment. Bipolar channels were used according to the provided recommendation by SENIAM (Hermens et al., 2000; Merletti and Hermens, 2000). Surface EMG recordings were conducted using flat active sintered Ag-AgCl electrodes (BioSemi B.V., Amsterdam, The Netherlands), which provided a circular recording area (d = 3 mm) in a 17 × 10 mm support surface area. An interelectrode distance of 1 cm (up to a maximum of 2 cm) was used for bipolar recording. The placement of EMG electrodes with respect to the muscle locations followed previously reported recommendations (Lee et al., 2005; Barbero et al., 2012; Pease et al., 2007). The sampling frequency and the filter settings for the EMG channels were the same as the EEG channels.

2.6. Data analysis

EEG/EMG data analysis was performed by an engineer who was blind to clinical assessments. Five EEG channels (Cz, Pz, C4, Fz, C3) and 3 EMG channels (APB, FDI, FPB) were chosen prior to the analysis of cortico-muscular coherence (CMC). This selection was based on the biomechanical involvement of the muscles in the pincer grip task (Danna-Dos Santos et al., 2010), and the suitability of the EEG and EMG channels for assessing CMC (Witham et al., 2011). A time window/epoch duration of 4 s (starting 1 s after the visual cue) was chosen for analysis; data epochs where the target force was not correctly achieved were excluded. The raw EEG data was (re-)referenced using (large) surface Laplacian spatial filter (Bradshaw and Wikswo, 2001; McFarland et al., 1997) which is a spatial filter for removing spurious signal components in EEG channels, and EMG data (signal amplitude) were normalized with respect to the Force value during 100 % MVC. EEG/EMG data were filtered between 1 and 100 Hz using a dual-pass 4th order Butterworth bandpass filter. This was followed by a 50 Hz Discrete Fourier Transform (DFT) filter in the FieldTrip toolbox to remove power line noise (Supplementary Fig. S2). An automatic artefact detection and rejection was performed using FieldTrip toolbox (Oostenveld et al., 2011) to remove eye-blinks, muscle, and electrode jump artefacts from EEG signals. The auto-spectrum of each EEG/EMG signal, and cross-spectrum between all combinations of EEG-EMG signals (frequency resolution 1 Hz, bandwidth 2–100 Hz) was calculated using FieldTrip toolbox (Hanning taper and frequency smoothing at 1 Hz). The auto- and cross-spectra at each frequency (2–100 Hz) was converted into 8 band values-delta (2–4 Hz), theta (5–7 Hz), lower alpha (8–10 Hz), higher alpha (11–13 Hz), lower beta (14–20 Hz), higher beta (21–30 Hz), lower gamma (31–47 Hz), and higher gamma (53–97 Hz),

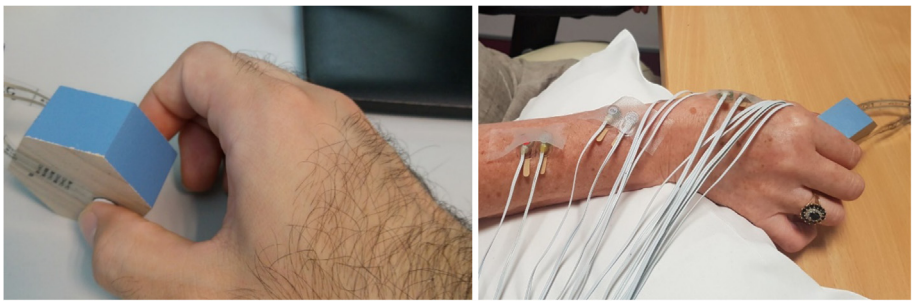

Fig. 1. Pincer grip isometric task used to assess cortico-muscular coherence (CMC) (left) and the recording of surface EMG during the experiment (right).

excluding the 48–52 Hz range to avoid mains power noise. The formation of band-specific values was carried out by taking Spatial Median (a variation of the median operator for complex-valued spectra, chosen and preferred over the algebraic averaging to provide robustness against outlier values) (Niinimaa and Oja, 2014; Nasseroleslami et al., 2019) of the spectra at corresponding frequencies. The spectral coherence (cortico-muscular coherence in this study) was obtained by normalizing the cross-spectrum by the respective auto-spectra (Supplementary Fig. S2) (Nasseroleslami et al., 2019).

The selection of the parameters and methods for signal processing (e.g. band-specific analysis and the use of non-parametric methods) was based on our previous EEG studies (Nasseroleslami et al., 2017; Dukic et al., 2019) that provided robust estimations not sensitive to outliers or observations in individual subjects (Dukic et al., 2017).

2.7. Statistics

Participant-level statistics were calculated using one-sample non-parametric rank statistics for spectral coherence (Nasseroleslami et al., 2019). This method gave individual p-values for spectral cortico-muscular coherence in each frequency band for both patients and control groups (Fig. 2). Stouffer's method (Stouffer et al., 1949; Westfall, 2014) was used to combine individual p values to derive group average p value. This procedure is equivalent to the pooled coherence analysis (Halliday et al., 1995).

Correction for multiple comparisons was performed using the adaptive false discovery rate at q = 0.05 (Benjamini et al., 2006), which was applied by correcting the p-values in the coherence spectra. Negative logarithm of p-values, i.e. $-\log_{10}(p)$, was used to visualize cortico-muscular coherence. The band-specific values of coherence, expressed in $-\log_{10}(p)$, was used to represent the values for all of the frequencies in that frequency band.

3. Results

3.1. Patients' clinical profile

A total of 25 patients affected by Poliomyelitis were successfully recruited from a cohort Polio clinic based in Beaumont hospital, Dublin (see Tables 2 and 3). One patient was subsequently excluded from analysis as recording of the motor task was carried out using his left hand, due to inadequate strength in right hand. The analysed patient group included 17 female and 7 male patients (mean age of 67.04 ± 6.8 (Standard deviation), 22 right hand dominant). From this group, 8 patients suffered poliomyelitis in first 24 months of life with 16 contracting polio after 24 months of age. Muscle weakness, graded by the LMN score, was 85.2 ± 6.6 points. A total of 11 healthy controls were successfully recruited (mean age of 61.09 ± 14.8 standard deviation).

3.2. Abnormal cortico-muscular coherence in the PPS patient group

Cortico-muscular coherence (CMC), during steady low force isometric pincer grip (Fig. 3), was calculated between intrinsic hand muscles (using bipolar EMG) and surface EEG electrodes over scalp. In this context, we identified patterns of CMC in the PPS group that differed from those of the controls (see Table 1). Specifically, the CMC in the patient group did not show the typical beta-band CMC over contralateral motor area (as intended by the task selection), and the CMC across the 5 tested EEG electrodes, 3 muscles, and the frequency bands were scattered and inconsistent (Supplementary Fig. S1). These null findings were in accordance with expectations from our pilot study in controls, as well as the anticipation of typical beta-band cortico-muscular coherence primarily over primary motor cortex, C3 electrode (seen in low force sustained muscle contraction (Salenius et al., 1997, Mima and Hallett, 1999, Conway et al., 1995).

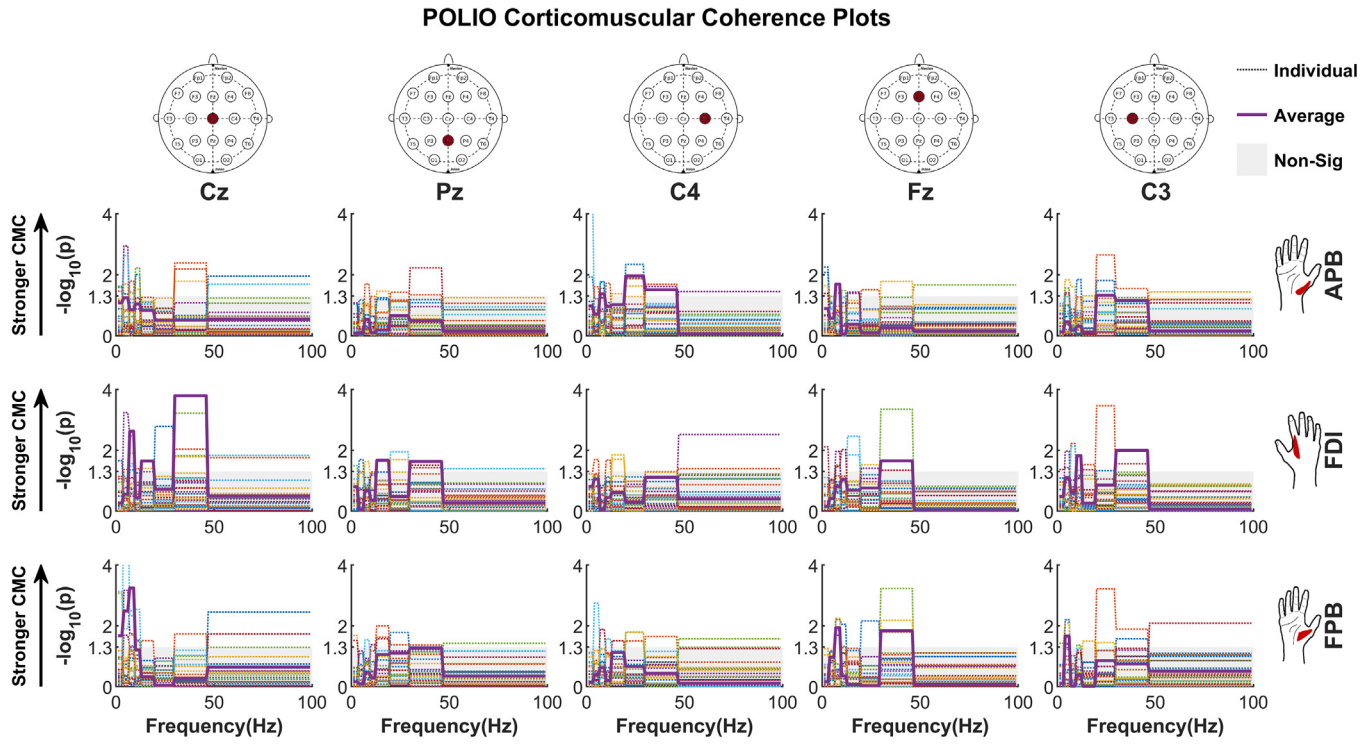

Fig. 2. The cortico-muscular coherence (CMC) spectra in the polio patient group, showing the significant values at individual and group-level. *Abductor Pollicis Brevis (APB); First dorsal interosseous (FDI); Flexor Pollicis Brevis (FPB).

Table 2
Clinical and demographic data of analysed patients.

	Patient Group	Controls
Gender (F/M)	17/7	4/7
Average age at recording (F/M)	68.5 ± 3.6/63.5 ± 10.8	64.7 ± 4.2/59 ± 18.5
Onset < 24 months	8/16	–
LMN score* (max 90)	85.2 ± 6.6	90

* LMN (Lower Motor Neuron Score).

Table 3
Clinical and demographic data of patient sub-groups.

	Infant-onset (<24 months)	Childhood-onset (>24 months)
Number of Patients	8	16
Average age of onset (in yrs)	0.97 ± 0.5	4.12 ± 2.4
LMN score*	86.6 ± 4.1	84.5 ± 7.6

* LMN (Lower Motor Neuron Score).

In the PPS group the CMC was statistically significant ($p < 0.05$, $q = 0.05$) at the group level (Fig. 3), and appeared at frequencies different from the commonly observed and expected beta (14–30 Hz) frequency bands. Instead, the significant CMC appeared consistently in the low gamma (31–47 Hz) frequency band across several EEG-EMG channels (see Fig. 2). Importantly, this abnormal low gamma-band coherence was observed not only over primary motor (C3 and Cz, and C4) areas, but also over parietal and frontal areas (Fz and Pz). The abnormal CMC appeared in other (e.g. alpha) frequency bands but was less consistently across EEG-EMG channels. These CMC patterns differed from the control cohort in frequency (beta vs. low-gamma) and location (contralateral motor C3 vs Frontal Fz and Parietal Pz) (Conway et al., 1995, Mehrkanoon et al., 2014), (Figs. 2 and 3).

The pathological gamma-band CMC was a consistent finding, and was observed at both frontal and parietal electrodes and in both FDI and FPB muscles (Fig. 2 and Supplementary Fig. S1).

3.3. Polio sub-groups

The analysis of CMC in separate patient subgroups, revealed evidence of differences between those affected by polio virus in infancy (define as <24 months) and those who developed the paralysis in later childhood (>24 months) in frontal and parietal areas (Fig. 4).

4. Discussion

This study provides robust neurophysiologic evidence of extensive supraspinal changes in those affected by poliomyelitis in childhood. The physiological correlates of frequency bands have been described in literature, demonstrating that beta band coherence appears during weak tonic contraction especially when directed towards a motor task (Kristeva-Feige et al., 2002). Gamma band coherence becomes more apparent on strong muscle contraction (Kilner et al., 1999), while Alpha band coherence has been described in resting physiological tremor (McAuley and Marsden, 2000). The presence of all of these frequency bands in unexpected cortical areas within the patient group implies the presence of a disrupted central-peripheral network.

These abnormal patterns, with increases in the gamma band, were consistent at group level in 24 patients despite major differences and heterogeneity in clinical disability (affected limb), and age of first polio diagnosis. These changes most likely reflect functional re-organisation of the central-peripheral network, possibly as a compensatory response to continuous remodelling of the motor units (Oliveri et al., 1999).

Our observations are consistent with recent TMS studies which show enlarged motor maps in the cortical areas of Motor Evoked Potentials (MEPs) in adult patients who contracted polio prior to reaching 18 months of age (Oliveri et al., 1999). Our findings are also congruent with existing knowledge of cortical neurophysiology (Jaiser et al., 2016). The role of sensory feedback loops in regulating the motor cortex output has been well described (Fuhr et al., 1992; Cohen et al., 1991), and it is plausible that changes in the normal proprioceptive feedback due to muscle spindle dysfunction (as a consequent of both alpha and gamma motor neuron degeneration) contribute to the observed CMC changes (Oliveri et al., 1999). The observed CMC pattern may also be influenced by functional changes in projections from cortical layers to spinal cord, and transcortical and the corticofugal pathways, although multi-modal or source analysis studies will be required to further elucidate the underlying neuroanatomical and neurophysiological origins of the abnormal CMC.

The observed trend toward differences in CMC patterns between infancy and childhood onset patients are likely to reflect differences in compensatory patterns that occur as the neuroaxis matures. During development, the human cortex is closely linked to the spinal motor centre, reflecting the uniquely dominant role of the corticomotoneuronal system in human control of movement (Eyre et al., 2000; Galea and Darian-Smith, 1995; Williams et al., 2017). Early assaults to the anterior horn cell are more likely to radically alter motor circuitry, as formation and elimination of synapses occurs during infancy and childhood (Huttenlocher and Dabholkar, 1997). This "heterochronus synaptogenesis" (Graziadio et al., 2010) could differentially influence the development of a compensatory processes following anterior horn cell injury in infancy and later in life respectively.

This observation of alterations in corticomotor circuitry following poliomyelitis has implications for other conditions, notably spinal muscular atrophy (SMA), for which quantitative biomarkers of drug efficacy are urgently required. In conditions such as SMA, for example, a consistent abnormal CMC measure in (adult) SMA, could be used as a potential biomarker to track network function. Such biomarkers can identify network-level changes associated with lower motor neurons following administration of a disease modifying agent, thus providing a quantitative biomarker of efficacy in clinical trials. Indeed, recent imaging studies have suggested the presence of altered cortical connectivity in SMA patients (Querin et al., 2019), implying that the CMC changes observed may not be specific to polio patients, but rather a more generic compensatory physiologic reorganization of cortical circuitry following damage to the lower motor neuron.

This study is not without limitations, which include a small sample size which precluded detailed analysis of subgroups. This is a function of the relative rarity of polio survivors in European countries. Accordingly, while the overall group sample size provides robust statistical results, interpretation of the subsequent subcategorizations are preliminary. Source analysis of brain sources, increased sample sizes, and multivariate spectral analysis will be instrumental in further elucidating the patterned changes of motor circuitry in future studies.

Notwithstanding, our study demonstrates that CMC is a powerful tool that can evaluate the function of the motor circuits as an entire connected network. The unmasking of activity in networks upstream to the anterior horn suggests plasticity of motor circuitry especially when these disruptions occur at a younger age. Further investigation will be required to provide a more complete understanding of how modulation of cortical circuitry occurs in pure lower motor neuron disorders. However, this study provides a robust proof of concept demonstrating that interrogation of CMC

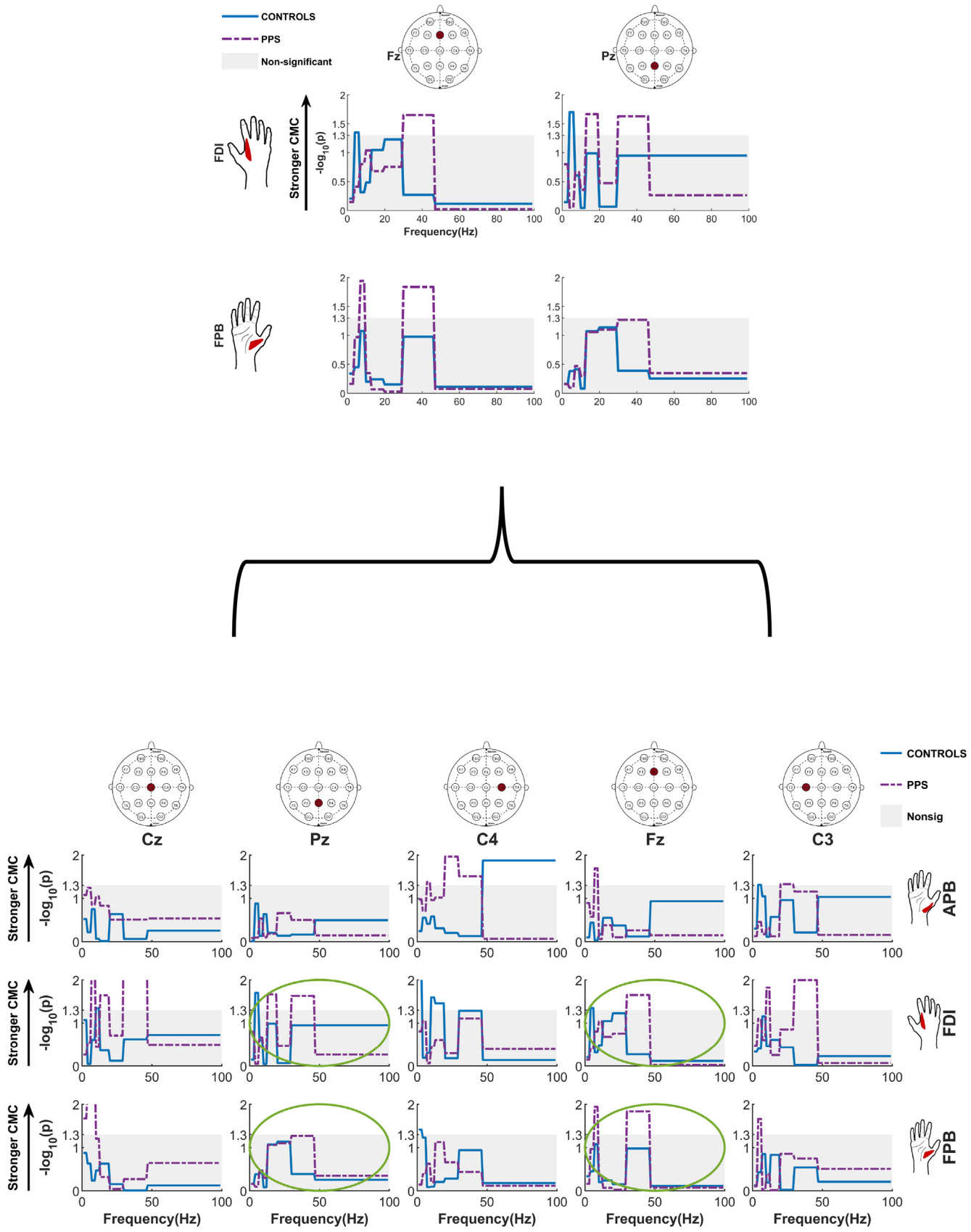

Fig. 3. Patients with Post-Polio Syndrome (PPS) show abnormal group-level Cortico-Muscular (EEG-EMG) Coherence (CMC) in non-primary motor area. The cortico-muscular coherence spectra, expressed in $-\log_{10}(p)$, show the synchrony between the EEG electrodes (over the frontal area, Fz, and parietal area, Pz) and EMG (First Dorsal Interosseous and Flexor Pollicis Brevis muscles) in different frequency bands. The lower values show less synchrony, whereas the higher value show higher EEG-EMG synchrony. The shaded area corresponds to the non-significant values at $\alpha = 0.05$ threshold for p-values (corrected for multiple comparison using false discovery rate (FDR) at $q = 0.05$). Notice the dominant abnormal coherence in PPS coherence in low gamma-band (30–47 Hz) which is present in both muscles and in both Pz and Fz electrodes. *Abductor Pollicis Brevis (APB); First dorsal interosseous (FDI); Flexor Pollicis Brevis (FPB).

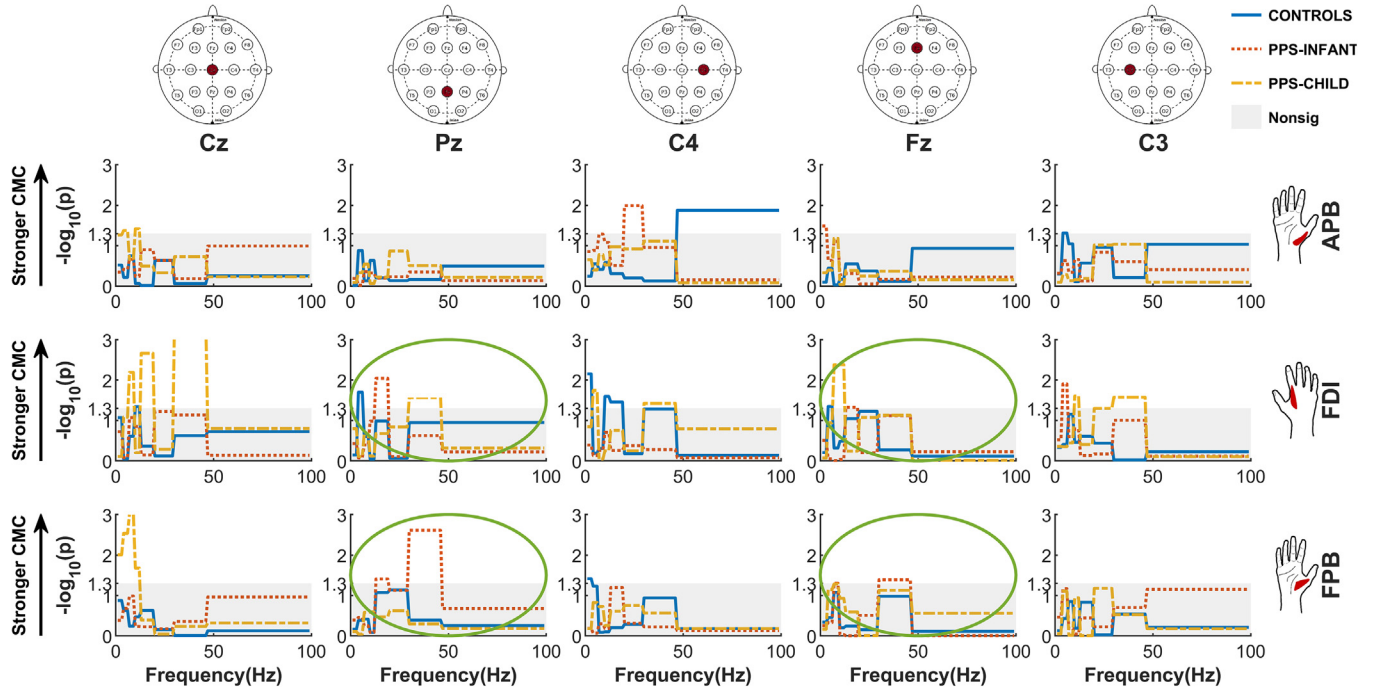

Fig. 4. Patient subgroups with onsets in infancy (<24 months) vs. childhood (>24 months) show different abnormal Cortico-Muscular (EEG-EMG) Coherence (CMC) patterns. The subgroups show subgroup-specific abnormal patterns. Notice the similarity to the group-level findings as well as differential trends in the 2 subgroups. The shaded area corresponds to the non-significant values at $\alpha = 0.05$ threshold for p-values (corrected for multiple comparison using false discovery rate (FDR) at q = 0.05). *Abductor Pollicis Brevis (APB); First dorsal interosseous (FDI); Flexor Pollicis Brevis (FPB).

patterns could be developed as a reliable marker of therapeutic efficacy in conditions such as PPS and SMA, where current quantitative clinical outcome measurements are limited by severe motor disability.

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All other authors have no financial disclosures.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2020.10.011.

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