Mu rhythm: State of the art with special focus on cerebral palsy

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Josselin Démas (1,2), Mathieu Bourguignon (3,4,5), Maximilien Périvier (6,7), Xavier De Tiège (3,5), Mickael Dinomais (1,8) and Patrick Van Bogaert (1,9).

(1) Laboratoire Angevin de Recherche en Ingénierie des Systèmes (LARIS), Université d'Angers, France.

(2) Institut Régional de Formation aux Métiers de Rééducation et de Réadaptation (IFM3R), Nantes, France.

(3) Laboratoire de Cartographie Fonctionnelle du Cerveau (LCFC), UNI – ULB Neuroscience Institute, Université Libre de Bruxelles (ULB), Brussels, Belgium.

(4) Laboratoire Cognition Language et Développement, UNI – ULB Neuroscience Institute, Université libre de Bruxelles (ULB), Brussels, Belgium.

(5) Department of functional Neuroimaging, Service of Nuclear Medicine, CUB Hôpital Erasme, Université libre de Bruxelles (ULB), Brussels, Belgium.

(6) Service de Neuropédiatrie et handicaps de l'enfant, Hôpital pédiatrique Gatien de Clocheville, CHRU de Tours, France.

(7) Université de Tours, France.

(8) Département de Médecine Physique et de Réadaptation, CHU d'Angers –Les Capucins, France.

(9) Unité de Neuropédiatrie et de Neurochirurgie de l'enfant, CHU d'Angers, France.

Abstract

Various specific early rehabilitation strategies are proposed to decrease functional disabilities in patients with cerebral palsy (CP). These strategies are thought to favour the mechanisms of brain plasticity that take place after brain injury. However, the level of evidence is low. Markers of brain plasticity would favour validation of these rehabilitation programs. In this paper, we consider the study of mu rhythm for this goal by describing the characteristics of mu rhythm in adults and children with typical development, then review the current literature on mu rhythm in CP. Mu rhythm is composed of brain oscillations recorded by electroencephalography (EEG) or magnetoencephalography (MEG) over the sensorimotor areas. The oscillations are characterized by their frequency, topography and modulation. Frequency ranges within the alpha band (~10 Hz, mu alpha) or beta band (~20 Hz, mu beta). Source location analyses suggest that mu alpha reflects somatosensory functions, whereas mu beta reflects motor functions. Event-related desynchronisation (ERD) followed by event-related (re-)synchronisation (ERS) of mu rhythm occur in association with a movement or somatosensory input. Even if the functional role of the different mu rhythm components remains incompletely understood, their maturational trajectory is well described. Increasing age from infancy to adolescence is associated with increasing ERD as well as increasing ERS. A few studies characterised mu rhythm in adolescents with spastic CP and showed atypical patterns of modulation in most of them. The most frequent findings in patients with unilateral CP are decreased ERD and decreased ERS over the central electrodes, but atypical topography may also be found. The patterns of modulations are more variable in bilateral CP. Data in infants and young children with CP are lacking and studies did not address the questions of intra-individual reliability of mu rhythm modulations in patients with CP nor their modification after motor learning. Better characterization of mu rhythm in CP, especially

in infants and young children, is warranted before considering this rhythm as a potential neurophysiological marker of brain plasticity.

Key words. cerebral palsy, magnetoencephalography, electroencephalography, mu rhythm, rehabilitation, plasticity

Introduction

Cerebral palsy (CP) is the most common cause of neurological physical disability in childhood, with an estimated prevalence of 17 million people in the world [1]. It is a heterogeneous group of disorders of movement and posture that are due to non-progressive brain injury that occurred during early development (foetal life or the first 2 years of life). Heterogeneity of the clinical picture is related to the complex interactions between the early brain damage (which varies from case to case in terms of location, nature, extent and timing), the individual child's specific genetic background, and subsequent epigenetic and environmental factors.

Various interventions are proposed for rehabilitation of people with CP to stimulate the reorganisation of the sensorimotor networks after the early brain injury. Even if some interventions are considered effective (e.g., including child-initiated movement, task-specific training and environmental modification), the level of evidence for the effectiveness is low for most of them [2,3]. To validate a specific modality of rehabilitation, the usual observational and behavioural approach will benefit from a complementary comprehensive approach to the mechanisms of brain plasticity that take place after rehabilitation. This combined approach is especially relevant in young children in whom the evaluation of a specific therapy may be puzzling because of the on-going neurodevelopmental processes [4].

In children with CP, brain plasticity may be imaged by using functional or structural brain imaging methods. Functional neuroimaging methods are used to study brain networks via analysis of neurophysiological signals captured by electroencephalography (EEG) or magnetoencephalography (MEG) that directly reflect the neural activity or more indirectly via the neurovascular coupling that leads to the blood oxygen level-dependent (BOLD) signals seen on functional MRI. Plasticity may also be assessed by changes in structural MRI images of the cortical mantle or the fibre tracts in white matter by using diffusion tensor imaging and tractography [4].

EEG is the oldest technique and has many advantages, so this technique is very appropriate to study plasticity in infants and children with CP. It has a temporal resolution in the order of milliseconds, allowing for the study of events with high frequency such as brain oscillations, is inexpensive, and can be replicated multiple times in the subject without any sedation. This is a crucial point because plasticity is a longitudinal process that needs multiple measures to be evidenced. EEG has been widely documented to result in poor spatial resolution, poorer than that with MEG and MRI. During the last decade, EEG has regained interest because of the development of high-density EEG (hdEEG), which records signals by using 64 to 256 scalp electrodes (Fig. 1). This set-up allows for estimating brain sources underlying scalp distributions of EEG signals with even sub-lobar precision [5]. In other words, hdEEG allows for finding a plausible solution to the inverse electric problem. For that purpose, it is crucial to model accurately the propagation of volume conduction electrical currents through the cerebral tissues, skull and scalp based on a precise head model built from MRI structural images. EEG and MEG need to be considered complementary techniques because they are not exactly sensitive to the same neocortical sources. MEG features heightened sensitivity to tangential sources, whereas EEG is sensitive to both radial and tangential sources. MEG also provides higher signal-to-noise ratio than EEG for most focal neocortical sources [6]. Therefore,

the spatiotemporal dynamics of neurophysiological signals may be different when studied by MEG or EEG [7].

Among the neurophysiological signals that may be studied by EEG and MEG, the mu rhythm, first described by Henri Gastaut in 1952, is of particular interest in CP because it reflects the neural activity of the primary sensorimotor (SM1) cortex. Several review papers focused on the characteristics and functional roles of the mu rhythm in healthy adults [8-14] and in typically developing infants [15]. However, a review article of children did not include important studies published after 2014. Moreover, no review paper has been published on mu rhythm in CP. In this narrative review, we will first summarize the current knowledge on this rhythm in the normal population including children, then on studies using EEG or MEG to characterize the mu rhythm in individuals with CP.

Mu rhythm in typically developing individuals

Cortical oscillations or rhythms recorded by EEG and MEG are related to the synchronous activity of thousands of anatomically aligned dendrites of neurons [12]. Over SM1 areas, one particular brain rhythm called the "mu rhythm" can typically be recorded with MEG or EEG at rest (Fig. 2). This rhythm is characterized by a comb-like shape, which implies that it is composed of 2 main frequency components with a nearly harmonic relationship [9], the alpha (~10 Hz) and the beta (~20 Hz) frequency bands. These 2 frequency components of the mu rhythm are hereafter called "mu alpha" and "mu beta" according to their spectral characteristics. Faster oscillations are also described (see below). Mu rhythm components are analysed according to their precise topography, intrinsic frequency, and modality-specific reactivity [9]. The latter property relies on the study of event-related modulations of their spectral power by using time-frequency representations: transient increases of power are usually termed event-related enhancement or synchronization (ERS), and transient decreases are often termed event-related suppression or desynchronization (ERD) [14]. Modulation of mu

rhythm components occurs during motor execution tasks (e.g., a reach and grasp task), which are the most robust modulators of the mu rhythm. In such tasks, ERD typically starts about 2 sec before movement onset over the contralateral SM1 cortex and becomes bilateral and symmetrical immediately before movement execution. This ERD is followed by a post-movement rebound (i.e., ERS) that exceeds the baseline level [14]. Figure 3 illustrates the typical sequence of ERD followed by ERS induced by a hand finger extension task in a healthy adult. The 2 frequency components of the mu rhythm are modulated by other types of stimuli or tasks: somatosensory stimulations, imagined movement, observed movement, shifting spatial attention and anticipation of attended stimuli [16]. The time course of ERD and ERS are also modified by various movement parameters (strength, duration, frequency, complexity) [10,12]. Because mu rhythm is modulated by both action and observation of motor action, researchers have promoted using mu rhythm modulations as a valid tool to study the human mirror neuron system [17].

The fact that mu alpha and mu beta may occur separately or simultaneously suggests that these 2 components might arise from different neural generators. This suggestion is further supported by source reconstruction studies showing that mu beta is generated at the precentral motor cortex, whereas mu alpha is located at the postcentral somatosensory cortex [9]. Therefore, reported differences in mu alpha and mu beta modulation patterns are not surprising. The mu alpha ERD is spatially diffuse during the initial stages of movement execution. By contrast, mu beta ERD starts earlier, is more spatially focused, and is followed by a quicker and more marked ERS [12].

The functional roles of mu alpha and mu beta are still debated. At rest, they could reflect the maintenance of the current sensorimotor state (“status quo”) or an idling functional state allowing the system to start more rapidly. They could also have a functional role in coordinating the central and peripheral neural activities [9,13]. Mu rhythm (i.e., mu alpha and mu

beta) ERD is traditionally interpreted as reflecting activation of the sensorimotor network, whereas ERS or post-movement rebound would reflect top-down inhibitory control processes [11]. This view is probably too simplistic, and multiple factors associated with sensory and cognitive aspects of motor control likely contribute to mu rhythm ERD [10]. The same consideration applies to mu beta rebound. It probably reflects not only active inhibition of the motor network but could also reflect a "reset" of the motor system to prepare for a subsequent movement [8,10].

Crucially, several studies suggest that modulations of mu alpha and mu beta could be used as electrophysiological markers of the plasticity potential that may occur within the cortical sensorimotor system. First, the intra-individual test–retest reliability of mu modulations seems very high, as suggested by a study performed in healthy adults about power measures of movement-related mu beta, which supports that their measures reflect meaningful individual differences [18]. This is a prerequisite to consider these modulations as potential markers of response to therapy in patients with brain disorders. Second, studies have shown that these modulations are modified after motor learning but also predict performance for such a learning. An MEG study indeed showed event-related modulation of mu beta correlated with motor performance after the learning of a complex bimanual task [19]. An EEG study showed that the power of mu alpha at baseline as well as the importance of the mu rhythm ERD induced by a repetitive sensory stimulation session predicted subsequent perceptual learning [20]. An MEG experiment performed in young adults showed learning of a motor sequence associated with enhanced rebound for both mu alpha and mu beta, a finding that could reflect post-training plastic changes [21]. Third, a study of adults after stroke showed that the connectivity of mu beta with frontal-premotor regions was a robust marker of motor status at baseline and was increased in parallel with motor gains across rehabilitation [22].

Apart from mu alpha and mu beta modulations, cortical activities in the gamma band frequency range (>30 Hz), either in the low (30–60 Hz) or high (70–90 Hz) gamma frequency range, following movement or somatosensory stimulations have been described in the SM1 cortex [8]. Movements are indeed associated with transient-induced (i.e., oscillations not phase-locked but time-locked to task onset) gamma band responses that generally start slightly before movement onset and sustained for about 200 msec after movement onset [12]. Because these induced gamma band responses have been investigated by using EEG or MEG in the context of CP and results could bring interesting insights into the functional plasticity mechanisms in place following CP, we describe these results in the present review. These induced responses are hereafter called “transient gamma responses”.

Paediatric studies showed that a central rhythm is still present with eyes open from the first months of life and that it shows strong event-related modulations to motor execution and observation of movement but not to visual stimulation [15]. The frequency of mu alpha increases rapidly during the first year, from 2.75 Hz at 11 weeks to 8.25 Hz at 47 weeks [23]. After the first year of life, the frequency increases very slowly through adolescence. Transient high gamma responses during motor tasks are recorded over the contralateral M1 cortex from age 6 years [24].

Numerous studies recently detailed the developmental trajectory of mu rhythm modulations. One study analysed groups of 12-month-old and 4-year-old children and adults by using hdEEG and reactivity of mu rhythm to a voluntary reaching/grasp movement. The mu rhythm defined functionally by movement-related ERD was locked to an alpha component that peaked at 7 to 8 Hz at 12 months, 8.5 to 10 Hz at 4 years and 10 to 12 Hz in adults. Topographic analysis showed distributed frontoparietal patterns, which were consistent across age groups. This finding suggests that the infant/child central rhythm should be considered a developmental analogue of the adult mu rhythm with the same functional dependence on

behaviour [16]. Mu rhythm modulations by a manual motor task were studied by using MEG in young children (4–6 years) and adolescents (11–13 years) as compared to adults [25]. The mean power of mu beta ERD increased with age and was consistently larger over the contralateral M1. This increasing power with age was hypothesized to be of multifactorial origin, including decreased distance from the cortex to the MEG sensors with increasing head size with age and maturational changes. In addition, Mu beta ERS showed increasing power with age. This finding was interpreted by the authors as reflecting reduced cortical inhibition, which could facilitate plasticity and motor learning in children [25]. These findings were confirmed in a large cross-sectional MEG study in children and adolescents (9–15 years old), which also showed that the power of movement-induced transient gamma responses decreased with age [26]. An MEG study of mu beta modulations during a knee motor task in 11- to 19-year-old individuals yielded similar conclusions; that is, the power of mu beta ERD during early isometric force production increases with age, which was associated with decreased reaction time with increasing age [27].

Mu rhythm and CP

We searched the databases MEDLINE via PubMed and Web of Science in June 2018 for studies on mu rhythm and its modulations in individuals with CP. The following MeSH and keyword combinations were used: (1) cerebral palsy and (2) keywords relative to cortical sensorimotor oscillations: alpha rhythm, beta rhythm, gamma rhythm, cortical activation, sensorimotor rhythm, mu rhythm, cortical oscillations, event related desynchronization, event-related synchronization, Rolandic alpha, cortical activity, sensorimotor oscillation, sensory oscillation, motor oscillation, and neural oscillation. We then selected 16 relevant studies that are summarized in the Table [28-44].

All these CP studies focused on spastic CP. Some focused on children with unilateral spastic CP (UCP) and others studied a mixed population of UCP and bilateral spastic CP (BCP).

Nearly all studies included CP patients > 5 years old. We found only 1 paper reporting a younger patient. This is a single case of UCP with extensive stroke studied by EEG at age 4 years, showing that both mu alpha and mu beta were displaced in the non-affected occipital region of the lesioned hemisphere [35].

In UCP, the authors found mu alpha and mu beta in nearly all patients. Modality-specific reactivity was studied with tasks or stimuli that concerned the upper limb and was found abnormal in most patients over the lesioned hemisphere, with decreased power for both ERD and ERS. The topography of the effects could be assessed reliably only in MEG studies, because methods of source reconstruction were not used in any of the EEG studies. Those MEG studies detected mu rhythm modulations mainly over the SM1 cortex, but effects in other frontal and parietal areas (i.e., premotor cortex, supplementary motor area, parietal lobules) were also identified.

Because individual patterns of mu rhythm modulations are quite variable among patients with UCP, group analyses are of interest to identify differences between patients and healthy controls at the group level. From this perspective, 2 studies deserve special comments. The first studied the reactivity of mu rhythm to median nerve stimulation by using MEG in 12 children with UCP aged 11 to 17 years and 12 age-matched controls [37]. At the group level, this study showed that in the lesioned hemisphere of patients with UCP, 1) both ERD and ERS of mu alpha and mu beta to contralateral stimulations were smaller than in the intact hemisphere, 2) the expected stronger modulation by contralateral stimulation compared to ipsilateral stimulation was not found, and 3) the frequencies for both suppression and rebound of mu beta were lower. These data suggest that the somatosensory processing in the lesioned hemisphere is abnormal and contributes to the unilateral motor deficit of these children. The second study examined mu rhythm modulations to a reach-to-grasp task in 13 UCP patients aged 6 to 14 years and age-matched controls by using hdEEG with 64 electrodes [38]. As

compared with controls, UCP children showed increased contralateral mu alpha ERD during the planning of paretic arm movement and decreased contralateral mu alpha ERD during the execution of paretic arm movement. These changes were positively correlated with functional scores for the motor deficit. The frequency and topography of these 2 modulations of mu alpha [mu alpha ERD during movement planning (Mu1) and mu alpha ERD during movement execution (Mu2)] were not identical. Mu1 had a frequency at 7.5 to 10 Hz and was localized in the fronto-central region. Mu2 had a frequency at 10 to 12.5 Hz and had a more central localization. From these findings, the authors hypothesized that they represent modulations of the activity of 2 different neuronal populations, in agreement with studies performed in healthy individuals [45]. Increased ERD during movement preparation was interpreted by the authors as reflecting over-action of the premotor region within the lesioned hemisphere to compensate for a planning deficit. Of note, the authors did not perform any reconstruction of the source of these 2 mu ERD phenomena to support this hypothesis, which is a major limitation of this study.

Concerning the study of BCP, the contribution from Kurz et al. is major and deserves special comments. These authors performed several experiments using MEG in adolescents, most with spastic diplegic, and age-matched healthy controls. In a first experiment, the authors studied the modulations of mu beta but also the transient gamma responses induced by a knee extension task. They showed increased mu beta ERD during planning and reduced transient gamma responses at the onset of movement in the children with CP versus the healthy controls [39]. With the hypothesis that abnormal movement in CP is at least in part related to abnormal somatosensory processing, The authors then studied the effect of a unilateral tactile stimulation at the bottom of the foot on mu rhythm modulations [40]. They found contralateral post-central mu alpha ERD in children with CP but also ERS in healthy individuals in the 4- to 14-Hz band during the 25- to 275-msec time window. Of note, the normalized power of

ERS was negatively correlated with patients' motor performance [40]. This finding suggests that BCP patients have aberrant synchrony in the somatosensory cortex that predicts motor performance. This dissociation of synchrony between CP patients and healthy individuals was not found after tactile stimulation of the hand, both groups showing ERS of similar amplitude [41].

To sum up, studies of mu rhythm modulations performed to date in CP by using MEG or hdEEG investigated mainly children > 5 years old and showed that decreased ERD, decreased ERS and atypical topographies of mu rhythm components as well as transient gamma responses are frequent findings. Still, studies did not address the questions of their predictive value for response to rehabilitation or their modification after rehabilitation.

Conclusions

Studies performed in adults have shown that measuring mu rhythm has high test–retest intra-individual reliability in the beta band and that changes after motor learning are proportional to the behavioural changes in healthy individuals and patients after stroke. The developmental trajectory of the mu rhythm and transient gamma responses has been well characterized from infancy to adulthood, but studies on intra-individual reliability are missing in this lifespan. The few studies using MEG or hdEEG in children with spastic CP have shown these SM1 cortex activities recorded in most patients but with frequent variations in frequency, topography and task-induced modulations as compared with typically developing children. The functional relevance of these alternative (mal-adaptive?) patterns regarding the mechanisms of plasticity that take place after brain injury and after rehabilitation are still unknown. Moreover, data in young children with CP are missing. Additional studies are warranted to cover these gaps to better understand the CP-related functional reorganization mechanism and subsequently guide new motor rehabilitation strategies in early intervention approaches.

Legends of figures

Figure 1. Net of 256 electrodes placed over the scalp of a 4-year-old boy.

Figure 2. Electroencephalography sample acquired in a 12-year-old healthy child when awake. A mu rhythm at a frequency of 10 Hz with a comb-like shape (mu alpha) is visually identified over the central regions (arrow). Note that the mu rhythm, as expected, is not modulated with eyes opening. YO=eyes open; YF=eyes closed.

Figure 3. Dynamics of the mu beta rhythm in a young healthy adult who participated in a magnetoencephalography (MEG) study that compared different methods aimed at localising the SM1 cortex [46]. The participant was instructed to make single brisk extensions of hand fingers in response to auditory stimuli (about 200 auditory stimulations, 1 kHz pure tones, 100-ms duration, 60 dB above hearing threshold, 2.5- to 3.5-sec random inter-stimulus interval) delivered via earplugs. MEG epochs were extracted from -1.5 to 3 sec relative to movement onset. A Morlet wavelet-based time-frequency decomposition was applied to all epochs with a standard time-frequency compromise. The figure is derived from a MEG sensor placed over the left SM1 cortex and at about 20 Hz, showing an event-related desynchronisation (dark blue in A, decreased power in B) between 0.1 and 0.5 sec, followed by an event-related (re-)synchronisation (red in A, increased power in B) peaking at about 0.7 sec.

References

1. Graham HK, Rosenbaum P, Paneth N, et al. Cerebral palsy. *Nature reviews Disease primers* 2016; **2**: 15082.

2. Morgan C, Darrah J, Gordon AM, et al. Effectiveness of motor interventions in infants with cerebral palsy: a systematic review. *Dev Med Child Neurol* 2016; **58**(9): 900-9.

3. Novak I, McIntyre S, Morgan C, et al. A systematic review of interventions for children with cerebral palsy: state of the evidence. *Dev Med Child Neurol* 2013; **55**(10): 885-910.

4. Reid LB, Rose SE, Boyd RN. Rehabilitation and neuroplasticity in children with unilateral cerebral palsy. *Nature reviews Neurology* 2015; **11**(7): 390-400.

5. Seeck M, Koessler L, Bast T, et al. The standardized EEG electrode array of the IFCN. *Clin Neurophysiol* 2017; **128**(10): 2070-7.

6. Goldenholz DM, Ahlfors SP, Hamalainen MS, et al. Mapping the signal-to-noise-ratios of cortical sources in magnetoencephalography and electroencephalography. *Hum Brain Mapp* 2009; **30**(4): 1077-86.

7. Hari R, Baillet S, Barnes G, et al. IFCN-endorsed practical guidelines for clinical magnetoencephalography (MEG). *Clin Neurophysiol* 2018; **129**(8): 1720-47.

8. Cheyne DO. MEG studies of sensorimotor rhythms: a review. *Experimental neurology* 2013; **245**: 27-39.

9. Hari R, Salmelin R. Human cortical oscillations: a neuromagnetic view through the skull. *Trends Neurosci* 1997; **20**(1): 44-9.

10. Kilavik BE, Zaepffel M, Brovelli A, MacKay WA, Riehle A. The ups and downs of beta oscillations in sensorimotor cortex. *Experimental neurology* 2013; **245**: 15-26.

11. Klimesch W, Sauseng P, Hanslmayr S. EEG alpha oscillations: the inhibition-timing hypothesis. *Brain research reviews* 2007; **53**(1): 63-88.

12. van Wijk BC, Beek PJ, Daffertshofer A. Neural synchrony within the motor system: what have we learned so far? *Front Hum Neurosci* 2012; **6**: 252.

13. Engel AK, Fries P. Beta-band oscillations--signalling the status quo? *Current opinion in neurobiology* 2010; **20**(2): 156-65.

14. Pfurtscheller G, Lopes da Silva FH. Event-related EEG/MEG synchronization and desynchronization: basic principles. *Clin Neurophysiol* 1999; **110**(11): 1842-57.

15. Cuevas K, Cannon EN, Yoo K, Fox NA. The Infant EEG Mu Rhythm: Methodological Considerations and Best Practices. *Developmental review : DR* 2014; **34**(1): 26-43.

16. Thorpe SG, Cannon EN, Fox NA. Spectral and source structural development of mu and alpha rhythms from infancy through adulthood. *Clin Neurophysiol* 2016; **127**(1): 254-69.

17. Fox NA, Bakermans-Kranenburg MJ, Yoo KH, et al. Assessing human mirror activity with EEG mu rhythm: A meta-analysis. *Psychological bulletin* 2016; **142**(3): 291-313.

18. Espenhahn S, de Berker AO, van Wijk BCM, Rossiter HE, Ward NS. Movement-related beta oscillations show high intra-individual reliability. *Neuroimage* 2017; **147**: 175-85.

19. Boonstra TW, Daffertshofer A, Breakspear M, Beek PJ. Multivariate time-frequency analysis of electromagnetic brain activity during bimanual motor learning. *Neuroimage* 2007; **36**(2): 370-7.

20. Freyer F, Becker R, Dinse HR, Ritter P. State-dependent perceptual learning. *J Neurosci* 2013; **33**(7): 2900-7.

21. Mary A, Bourguignon M, Wens V, et al. Aging reduces experience-induced sensorimotor plasticity. A magnetoencephalographic study. *Neuroimage* 2015; **104**: 59-68.

22. Wu J, Quinlan EB, Dodakian L, et al. Connectivity measures are robust biomarkers of cortical function and plasticity after stroke. *Brain* 2015; **138**(Pt 8): 2359-69.

23. Berchicci M, Zhang T, Romero L, et al. Development of mu rhythm in infants and preschool children. *Dev Neurosci* 2011; **33**(2): 130-43.

24. Huo X, Wang Y, Kotecha R, et al. High gamma oscillations of sensorimotor cortex during unilateral movement in the developing brain: a MEG study. *Brain Topogr* 2011; **23**(4): 375-84.

25. Gaetz W, Macdonald M, Cheyne D, Snead OC. Neuromagnetic imaging of movement-related cortical oscillations in children and adults: age predicts post-movement beta rebound. *Neuroimage* 2010; **51**(2): 792-807.

26. Trevarrow MP, Kurz MJ, McDermott TJ, et al. The developmental trajectory of sensorimotor cortical oscillations. *Neuroimage* 2018; **184**: 455-61.

27. Kurz MJ, Proskovec AL, Gehringer JE, et al. Developmental Trajectory of Beta Cortical Oscillatory Activity During a Knee Motor Task. *Brain Topogr* 2016; **29**(6): 824-33.

28. Lee JJ, Lee DR, Shin YK, Lee NG, Han BS, You SJ. Comparative neuroimaging in children with cerebral palsy using fMRI and a novel EEG-based brain mapping during a motor task--a preliminary investigation. *NeuroRehabilitation* 2013; **32**(2): 279-85.

29. Lee NG, Kang SK, Lee DR, et al. Feasibility and test-retest reliability of an electroencephalography-based brain mapping system in children with cerebral palsy: a preliminary investigation. *Archives of physical medicine and rehabilitation* 2012; **93**(5): 882-8.

30. Weinstein M, Green D, Rudisch J, et al. Understanding the relationship between brain and upper limb function in children with unilateral motor impairments: A multimodal approach. *Eur J Paediatr Neurol* 2018; **22**(1): 143-54.

31. Alves-Pinto A, Ehrlich S, Cheng G, Turova V, Blumenstein T, Lampe R. Effects of short-term piano training on measures of finger tapping, somatosensory perception and motor-related brain activity in patients with cerebral palsy. *Neuropsychiatric disease and treatment* 2017; **13**: 2705-18.

32. Kulak W, Sobaniec W, Bockowski L. EEG spectral analysis and coherence in children with hemiparetic cerebral palsy. *Medical science monitor : international medical journal of experimental and clinical research* 2005; **11**(9): CR449-55.

33. Shin YK, Lee DR, Hwang HJ, You SJ, Im CH. A novel EEG-based brain mapping to determine cortical activation patterns in normal children and children with cerebral palsy during motor imagery tasks. *NeuroRehabilitation* 2012; **31**(4): 349-55.

34. Rigoldi C, Molteni E, Rozbaczylo C, et al. Movement analysis and EEG recordings in children with hemiplegic cerebral palsy. *Experimental brain research* 2012; **223**(4): 517-24.

35. Basu A, Graziadio S, Smith M, Clowry GJ, Cioni G, Eyre JA. Developmental plasticity connects visual cortex to motoneurons after stroke. *Ann Neurol* 2010; **67**(1): 132-6.

36. Guo X, Xiang J, Mun-Bryce S, et al. Aberrant high-gamma oscillations in the somatosensory cortex of children with cerebral palsy: a meg study. *Brain Dev* 2012; **34**(7): 576-83.

37. Pihko E, Nevalainen P, Vaalto S, et al. Reactivity of sensorimotor oscillations is altered in children with hemiplegic cerebral palsy: A magnetoencephalographic study. *Hum Brain Mapp* 2014; **35**(8): 4105-17.

38. Inuggi A, Bassolino M, Tacchino C, et al. Ipsilesional functional recruitment within lower mu band in children with unilateral cerebral palsy, an event-related desynchronization study. *Experimental brain research* 2018; **236**(2): 517-27.

39. Kurz MJ, Becker KM, Heinrichs-Graham E, Wilson TW. Neurophysiological abnormalities in the sensorimotor cortices during the motor planning and movement execution stages of children with cerebral palsy. *Dev Med Child Neurol* 2014; **56**(11): 1072-7.

40. Kurz MJ, Heinrichs-Graham E, Arpin DJ, Becker KM, Wilson TW. Aberrant synchrony in the somatosensory cortices predicts motor performance errors in children with cerebral palsy. *J Neurophysiol* 2014; **111**(3): 573-9.

41. Kurz MJ, Becker KM, Heinrichs-Graham E, Wilson TW. Children with cerebral palsy have uncharacteristic somatosensory cortical oscillations after stimulation of the hand mechanoreceptors. *Neuroscience* 2015; **305**: 67-75.

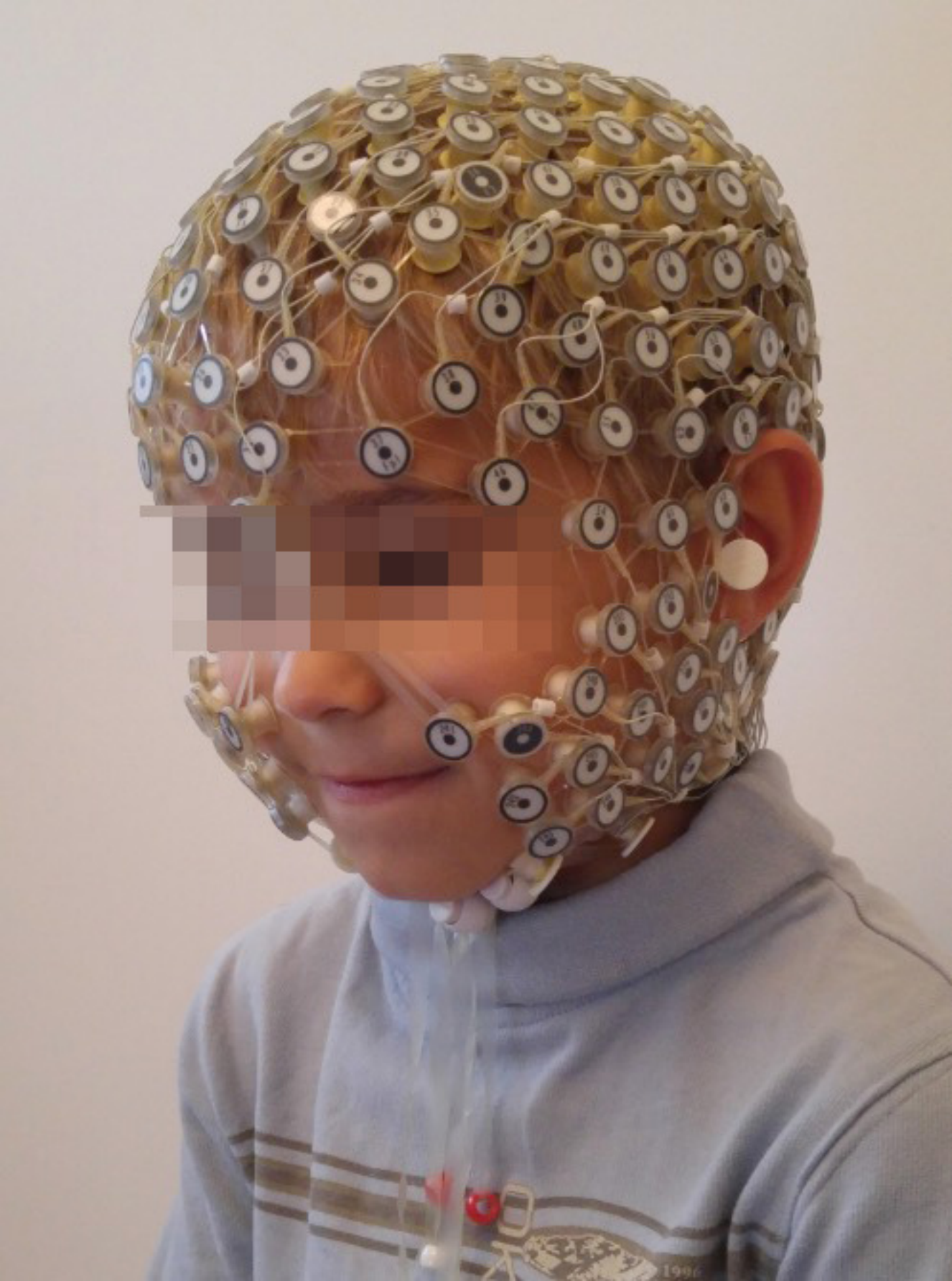
42. Kurz MJ, Proskovec AL, Gehringer JE, Heinrichs-Graham E, Wilson TW. Children with cerebral palsy have altered oscillatory activity in the motor and visual cortices during a knee motor task. *NeuroImage Clinical* 2017; **15**: 298-305.

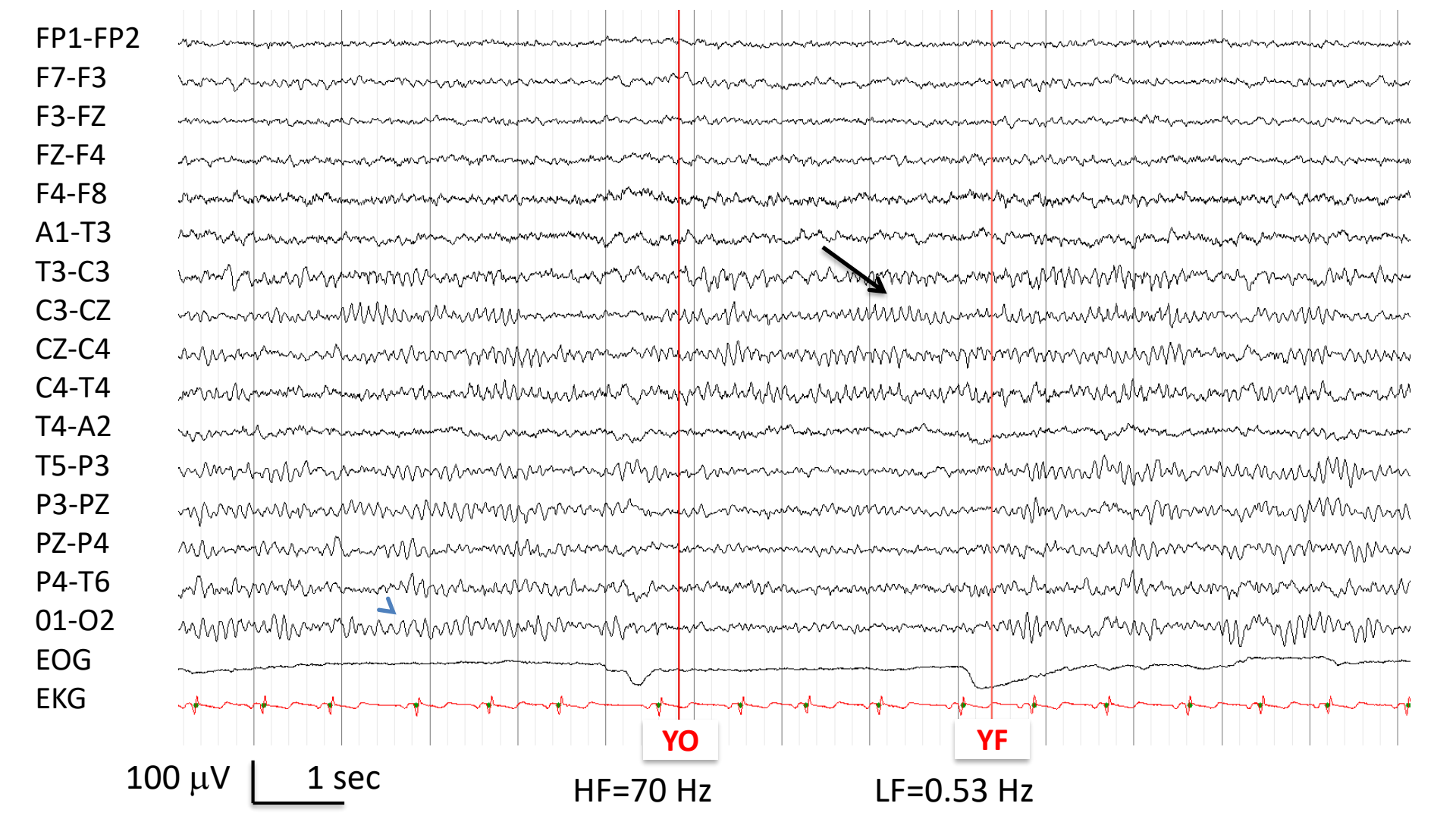
43. Papadelis C, Ahtam B, Nazarova M, et al. Cortical somatosensory reorganization in children with spastic cerebral palsy: a multimodal neuroimaging study. *Front Hum Neurosci* 2014; **8**: 725.

44. Kukke SN, de Campos AC, Damiano D, Alter KE, Patronas N, Hallett M. Cortical activation and inter-hemispheric sensorimotor coherence in individuals with arm dystonia due to childhood stroke. *Clin Neurophysiol* 2015; **126**(8): 1589-98.

45. Neuper C, Pfurtscheller G. Event-related dynamics of cortical rhythms: frequency-specific features and functional correlates. *Int J Psychophysiol* 2001; **43**(1): 41-58.

46. Bourguignon M, Jousmaki V, Marty B, et al. Comprehensive functional mapping scheme for non-invasive primary sensorimotor cortex mapping. *Brain Topogr* 2013; **26**(3): 511-23.

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FZ-F4
F4-F8
A1-T3
T3-C3
C3-CZ
CZ-C4
C4-T4
T4-A2
T5-P3
P3-PZ
PZ-P4
P4-T6
01-O2
EOG
EKG
YO
YF
100 µV
1 sec
HF=70 Hz
LF=0.53 Hz

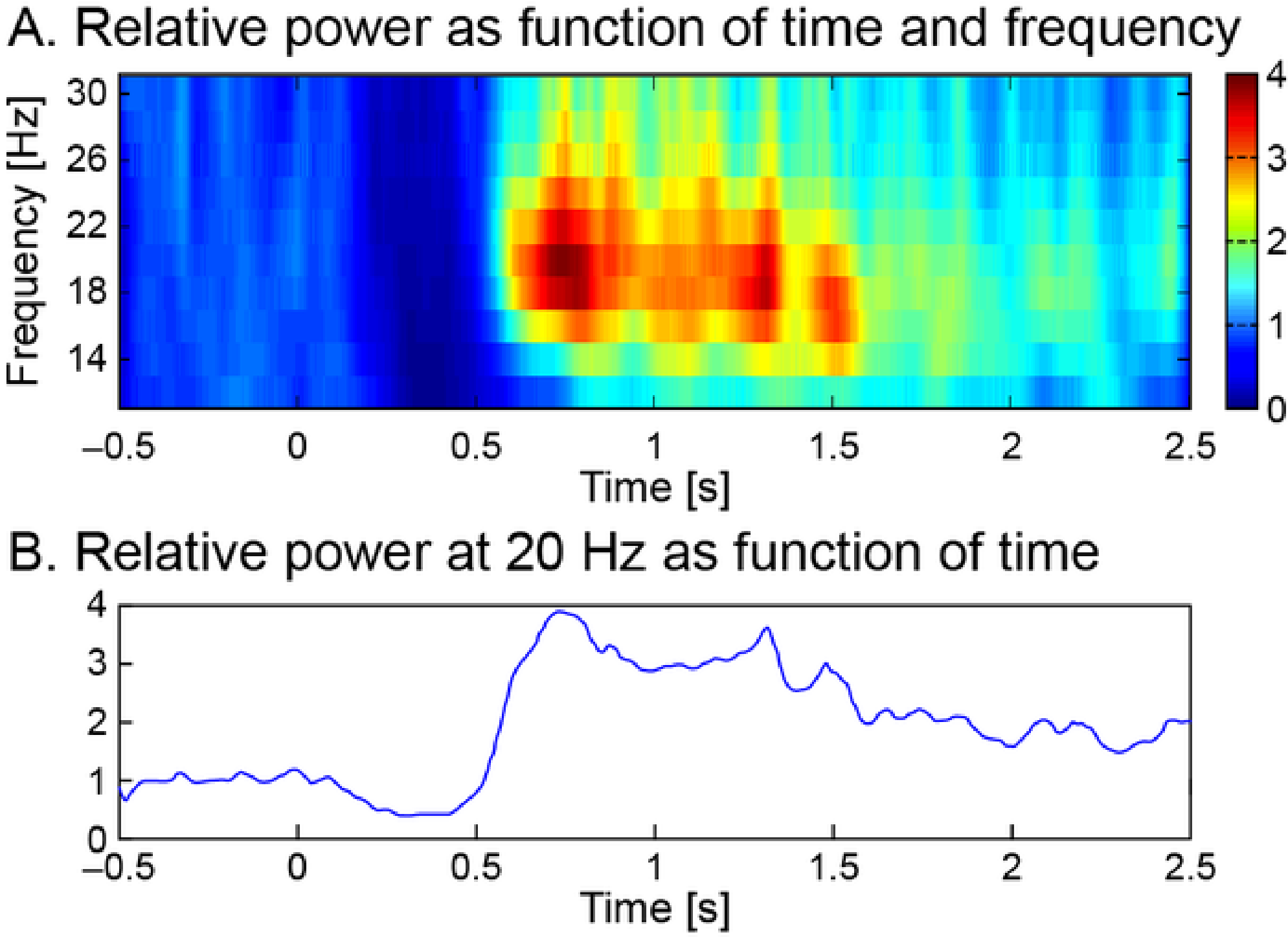
A. Relative power as function of time and frequency
Frequency [Hz]
30
26
22
18
14
4
3
2
1
0
–0.5
0
0.5
1
1.5
2
2.5
Time [s]
B. Relative power at 20 Hz as function of time
4
3
2
1
0
–0.5
0
0.5
1
1.5
2
2.5
Time [s]

Table. Summary of 16 articles with original data on mu rhythm in patients with cerebral palsy.

Reference	CP population studied	Stimulation used to modulate sensorimotor oscillations	Recording and localization (n of sensors)	Main findings
Alves-Pinto et al., 2017	N = 16 (9 adolescents and 7 adults) 9F, 7M Mean age of adolescents = 15 years Mean age of adults = 44 years Types of CP = 1 BCP(D); 7 BCP; 3UCP; 1 DyCP; 3ACP; 1 other Control group = Yes	Reach and press a button	EEG (13) SR = No	Mu alpha ERD described in most participants in the time window [0.5, 1.5] sec. No significant effect of a piano training session on ERD alpha.
Basu et al., 2010	N = 1 1M Age = 4 years Types of CP = 1 UCP Control group = Yes	Isometric contraction of first dorsal interosseous of the hand	EEG (13) SR = No	Contralateral Mu alpha ERD and mu beta ERD displaced in the non-affected occipital region of the lesioned hemisphere. Both ipsilateral and contralateral mu ERD induced by a movement of the paretic arm.
Guo et al., 2012	N = 6 2F, 4M Mean age (SD) = 8.8 (1.7) years Types of CP = 3 BCP(D); 1 BCP(Q); 2UCP(H) Control group = Yes	Electrical stimulation of index finger	MEG (275) SR = Yes	Higher incidence of ipsilateral transient high gamma response of the primary somatosensory (S1) cortex in patients compared to controls, thereby suggesting relative maintenance of the ipsilateral tracts in children with CP
Inuggi et al., 2017	N = 11 7F, 4M Mean age (SD) = 11.3 (1.2) years Types of CP = 11 UCP Control group = Yes	Reach and grasp a bottle	HD-EEG (64) SR = No	During paretic arm movement execution, a reduced ERD in the upper alpha band (10–12.5 Hz) over central electrodes, preceded by an increased fronto-central ERD in the lower alpha band (7.5–10 Hz) during movement preparation in children with CP.
Kukke et al., 2015	N = 11 3F, 8M Mean age (SD) = 18 (5) years Types of CP = 11 UCP Control group = Yes	Active extension of wrist	EEG (19) SR = No	Ipsilesional hemisphere power decrease over central electrode was significantly lower in children with CP during the paretic arm movement. These specific modulations correlated with motor deficits.
Kurz et al., 2014	N = 13 4F, 9M Mean age (SD) = 14.25 (0.75) years Types of CP = 9 BCP(D); 4 UCP(H) Control group = Yes	Knee extension	MEG (306) SR = Yes	Children with CP showed significantly stronger beta ERD in the postcentral gyri and superior parietal lobule. The children with TD exhibited significantly stronger gamma ERS in the medial post-central gyri and superior parietal lobule.
Kurz et al., 2014	N = 11 2F, 9M Mean age (SD) = 14.5 (0.7) years Types of CP = 8 BCP(D); 3 UCP(H) Control group = Yes	Tactile stimulation with airbladder of the first metatarsal of the foot	MEG (306) SR = Yes	Children with CP exhibited 4-14 Hz desynchonization in the contralateral postcentral gyrus and children with TD had strong synchonization in the same frequency band in the same area.
Kurz et al., 2015	N = 8 1F, 7M Mean age (SD) = 14.5 (0.7) years Types of CP = 4 BCP(D); 2 BCP(Q); 2 UCP(H) Control group = Yes	Tactile stimulation with airbladder of index finger	MEG (306) SR = Yes	In alpha band, ERS was not significantly different between the children with CP and TD children. In beta band, the modulations were significantly different between the 2 groups. TD children showed mu beta ERD and children with CP showed mu beta ERS.
Kurz et al., 2017	N = 13 5F, 8M Mean age (SD) = 15.5 (3) years Types of CP = 13 BCP(D) Control group = Yes	Isometric knee extension force with visual target	MEG (306) SR = Yes	During the motor planning period, the children with CP had significantly stronger alpha ERD and beta ERD in primary motor cortices, premotor area, inferior parietal lobule, and inferior frontal gyrus. Moreover in the same period, the strength of the alpha ERD in the primary motor cortices correlated negatively to the amount of error in matching the target. During the motor execution period, beta ERD for the children with CP were significantly stronger in the left premotor cortices and in the SMA.

Lee et al., 2012	N = 7 2F, 5M Mean age (SD) = 10.4 (1) years Types of CP = 3 BCP(D); 1 BCP(Q); 2 UCP(H); 1 ACP Control group = Yes	Reach and grasp motor task	EEG (32) SR = No	In children with CP, the mu alpha modulation was over the central electrodes and 3 other sites (F2, P1, P2, P5, PO2, PO3). However, in children with TD, the alpha modulation was mainly localized over the central electrodes.
Lee et al., 2013	N = 4 3F, 1M Mean age (SD) = 10.25 (2.86) years Types of CP = 2 BCP(D); 1 BCP(Q); 1 UCP(H) Control group = Yes	Reach and grasp motor task	EEG (30) SR = No	In children with CP, the mu alpha modulation was found over the central electrodes and 3 other sites (F1, F2, FC2, CP3, CP4, P1).
Papadelis et al., 2018	N = 10 4F, 6M Mean age (SD) = 12.2 (3.9) years Types of CP = 10 UCP Control group = Yes	Skin stimulation with plastic membrane of D1, D2 and D5 of the hand	MEG (76) SR = Yes	From ~10 to ~120 ms after the stimulus, no beta or gamma ERS differences were observed between the less affected and the more affected hemisphere in S1 area, but ERS were weaker than TD children.
Pihko et al., 2014	N = 12 7F, 5M Range age = 11 to 17 years Types of CP = 12 UCP(H) Control group = Yes	Electrical stimulation of median nerves	MEG (306) SR = Yes	All children with CP showed a mu alpha modulation over contralateral SM1, and an ipsilateral modulation except in one child. Mu beta was also detected in all children. However, modulations of mu beta on both hemispheres could not be evidenced in 3 children with CP after stimulations of the paretic arm. 2 of these 3 children had ipsilateral motor representation of the paretic arm. It should be noted that one normal control did not show any modulation of mu beta either.
Rigoldi et al., 2012	N = 21 ? Mean age (SD) = 10.33 (1.62) years Types of CP = 21 UCP(H) Control group = Yes	Pointing task	EEG (19) SR = No	Mu alpha ERS were obtained in all the children. Half of the children had a bilateral modulation pattern and the other half had a unilateral activation.
Shin et al., 2012	N = 4 3F, 1M Mean age (SD) = 10.3 (3.3) years Types of CP = 2 BCP(D); 1 BCP(Q); 1 UCP(H) Control group = Yes	Reach and grasp motor task, kinesthetic-motor imagery, observation of movement, visual motor imagery	EEG (30) SR = No	Alpha modulation was found for the 4 tasks and for the 2 groups. Different modulation areas were observed among children with CP and with the TD children.
Weinstein et al., 2018	N = 15 4F, 11M Mean age (SD) = 9.4 (2.5) years Types of CP = 15 UCP Control group = No	Squeezing task	EEG (32) SR = No	During paretic arm movement, in 6/7 children had stronger “mu-restoration” over the contralateral hemisphere and in one child this modulation was over the ipsilateral hemisphere.

ACP, ataxic cerebral palsy; BCP, bilateral cerebral palsy; D, diplegia; DyCP= dyskinetic cerebral palsy; ERD, event-related desynchronization; ERS, event-related (re-)synchronisation; F= female; H, hemiplegia; M, male; MACS, Manual Ability Classification System; MHC, Modified House Classification scale; Q, quadriplegia; SR, Source Reconstruction; SMA, Supplementary Motor Area; TD, typical development; UCP, unilateral cerebral palsy,