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Different patterns of movement-related cortical oscillations in patients with myoclonus and in patients with spinocerebellar ataxia

E. Visani [a], C. Mariotti [b], L. Nanetti [b], A. Mongelli [b], A. Castaldo [b], F. Panzica [a], S. Franceschetti [a,*], L. Canafoglia [a]

[a] Department of Neurophysiopathology, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy
[b] Department of Medical Genetics and Neurogenetics, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy

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HIGHLIGHTS

- EEG oscillations related to Go/No-go tasks are distinctive in patients with myoclonus or ataxia.
- Patients with myoclonus show abnormal desynchronization/synchronization due to defective inhibition.
- Patients with ataxia show a defect in the lateralization of the desynchronization.

ABSTRACT

Objective: To assess whether different patterns of EEG rhythms during a Go/No-go motor task characterize patients with cortical myoclonus (EPM1) or with spinocerebellar ataxia (SCA).
Methods: We analyzed event-related desynchronization (ERD) and synchronization (ERS) in the alpha and beta-bands during visually cued Go/No-go task in 22 patients (11 with EPM1, 11 with SCA) and 11 controls.
Results: In the Go condition, the only significant difference was a reduced contralateral beta-ERS in the EPM1 patients compared with controls; in the No-go condition, the EPM1 patients showed prolonged alpha-ERD in comparison with both controls and SCA patients, and reduced or delayed alpha- and beta-ERS in comparison with controls. In both conditions, the SCA patients, unlike EPM1 patients and controls, showed minimal or absent lateralization of alpha- and beta-ERD.
Conclusions: EPM1 patients showed abnormal ERD/ERS dynamics, whereas SCA patients mainly showed defective ERD lateralization.
Significance: A different behavior of ERS/ERD distinguished the two patient groups: the pattern observed in EPM1 suggests a prominent defect of inhibition occurring in motor cortex contralateral to activated segment, whereas the pattern observed in SCA suggested a defective lateralization attributable to the damage of cerebello-cortical network, which is instead marginal in patients with cortical myoclonus.

1. Introduction

Cerebral activation in relation to movements can be assessed using Go/No-go protocols that make it possible to explore movement-related, inhibition-related, and decision-related changes. The analysis of event-related desynchronization/synchronization (ERD/ERS) at specific frequencies (usually in the alpha and beta bands) has been used to measure physiological electroencephalogram (EEG) changes related to Go/No-go performances in healthy subjects (Leocani et al., 2001; Filipović et al., 2001), and during Go tasks in patients with Parkinson's disease (Defebvre et al., 1994; Heida et al., 2014; Heinrichs-Graham et al., 2014), multiple system atrophy (Levy et al., 2010), focal dystonia (Toro et al., 2000), myoclonic dystonia (Marelli et al., 2008), Tourette's syndrome (Franzkowiak et al., 2010) and paroxysmal kinesigenic dyskinesia (Hsu et al., 2013). Furthermore, in one of our own previous studies (Visani et al., 2006), we used a self-paced Go task to evaluate the ERD/ERS EEG patterns in patients with Unverricht-Lundborg progressive myoclonic epilepsy presenting with prominent and disabling cortical myoclonus, and found a

* Corresponding author at: Department of Neurophysiopathology, Fondazione IRCCS Istituto Neurologico Carlo Besta, Via Celoria 11, I-20133 Milano, Italy.
E-mail address: silvana.franceschetti@istituto-besta.it (S. Franceschetti).

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strong reduction in the beta-ERS power that correlated with myoclonus severity.

Unverricht-Lundborg disease (EPM1A, OMIM #254800) is due to inherited mutations in the cystatin B (*CSTB*) gene (Pennacchio et al., 1996) and the most frequently encountered form of progressive myoclonus epilepsy, which is characterized by action myoclonus, epileptic seizures, possible neurological deterioration, and some degree of ataxia (Kälviäinen et al., 2008; Canafoglia et al., 2017). The disease causes motor impairment due to myoclonus but it is difficult to establish the extent to which cerebellar dysfunction adds to the myoclonic jerks in determining the motor disability (Genton, 2010). The few neuropathological assessments made of EPM1 patients have indicated cerebellar atrophy with the loss of Purkinje cells (Haltia et al., 1969), which has been partially attributed to the toxic effect of the phenytoin that used to be used to treat them (Eldridge et al., 1983). Structural neuroimaging studies have provided conflicting information: some observations of individual patients indicate cerebellar atrophy (Mascalchi et al., 2002; Korja et al., 2007; Chew et al., 2008; Santoshkumar et al., 2008), but voxel-based morphometry has not revealed any significant cerebellar changes (Koskenkorva et al., 2009; Koskenkorva et al., 2012; Suoranta et al., 2013). In a previous study using a morphometric technique based on SUIT masks (Nigri et al., 2017), we found that EPM1 patients showed minimal cerebellar atrophy, while patients with ataxia due to autosomal dominant spinocerebellar atrophy (SCA) had obvious cerebellar degeneration. In agreement, functional MRI performed during motor tasks revealed normal activation both in motor cortex and in cerebellum in EPM1 but a severe cerebellar defect in SCA patients. Functional contribution of the cerebellum to the motor disability of EPM1 patients therefore requires further clarification.

The aim of this study was to compare EEG changes associated with the planning and production of movement in patients with cortical myoclonus due to EPM1 and patients with pure ataxia due to SCA type I or II. Cerebellar dysfunction has undoubtedly a dominant role in SCA patients, who are affected by the degeneration of the cerebellum and its afferent and efferent connections (Schöls et al., 2004; Taroni and DiDonato, 2004). It was expected that this protocol would be capable of evaluating not only the changes associated with active movement, but also those associated with the inhibition of action. Our hypothesis was that the two patient groups would show distinctive ERD/ERS patterns during a Go/No-go test that reflect the different involvement of the motor cortex and cerebellum.

2. Methods

2.1. Subjects

The study involved three groups of right-handed subjects: 11 healthy volunteer controls (four males; age 31.3 ± 8.9 years), 11 EPM1 patients (five males; age 37.2 ± 12.2 years), and 11 SCA patients (six males; age 39.5 ± 10.2 years). We did not find significant age differences comparing the three group subjects.

The EPM1 patients presented the typical features of the disease, and all had the typical *CSTB* gene expansion (Virtaneva et al., 1997). They had experienced seizures and myoclonus from adolescence (mean age 12.6 years, range 10–16), after which the seizures had been well controlled using anti-epileptic drugs but the action myoclonus remained resistant and worsened over time and, at the time of the present study, was scored 1–3 on simplified rating scale (Magaudda et al., 2004). They had a mean disease history of 24 ± 10.8 years (range 9–40 years), and were being treated with 1–5 anti-epileptic drugs. All of the patients experienced segmental jerks during posture maintenance and active movements; two (#3 and #7) showed unsteadiness when standing and walking.

The patients with SCA had mutations in the *ATXN1* (seven patients) or *ATXN2* genes (four patients), a mean disease history of 8.4 years (range 2–35), and a mean International Ataxia Rating Scale (SARA) (Schmitz-Hübsch et al., 2006) score of 11.2 (range: 4–18) indicating mild to moderate severity (Supplementary Table 1).

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.clinph.2019.01.021.

The study was approved by the Ethics Committee of Fondazione IRCCS Istituto Neurologico Carlo Besta and carried out in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All of the subjects gave their informed consent before being included in the study.

2.2. Data acquisition

The EEGs were recorded with 128 channels (ANT neuro, Enschede, The Netherlands) at a sampling frequency of 512 Hz with a resolution of 22 bits placed according to 10–5 International System. Electrode impedances were kept below 5 kΩ. Electromyogram (EMG) activity was simultaneously recorded from pairs of Ag/AgCl surface electrodes placed bilaterally 2–3 cm apart over the right and left index flexor muscles.

2.3. Go/No-go task

The visually cued Go/No-go paradigm was partially modified from Liddle et al., 2001, and the stimuli (a green circle for the Go trials and a red circle for the No-go trials) were presented on a monitor located in front of the study subjects, who were required to perform brisk extensions of the right hand when a Go cue was presented and to remain still in the case of a No-go cue. The task consisted of 100 Go and 100 No-go trials. The presentation of each trial began with a series of asterisks being shown on the screen to heighten alertness: an image of five asterisks was shown for 250 ms followed by a blank screen for 750 ms; then four asterisks for 250 ms followed by a blank screen for 750 ms; and so on until a single asterisk was shown for 250 ms, followed by a blank screen for 750 ms, and then either a Go or a No-go cue for 250 ms. After the Go or No-go stimulus, a blank screen was shown for 2.75, 3.75 or 4.75 s. The duration of each trial therefore lasted from eight to ten s (Fig. 1A). The time interval between the last asterisk disappearance and the Go/No-go cue (750 ms) was considered sufficient to avoid any influence of the visual response (normally lasting less than 300 ms) and the following cognitive processes, such as counting.

2.4. Data analysis

The data were analyzed using ASA software (ANT neuro) and custom-written MatLab software (R2013b, Mathworks Inc., Natick MA, USA) using scripts based on EEGLAB 4.51 (http://www.sccn.ucsd.edu/eeglab). Movement starting and ending were determined by manually tagging the onset and the offset of the EMG burst, identified as the time point in which the EMG signal exceeded 30% and returned under the 30% of the maximal voluntary contraction, respectively. The reaction time was calculated as the difference between the cue presentation and the EMG onset. The reaction time, EMG duration, and errors with respect to the cue were calculated for each subject. In the case of the EEG data, the DC offset was removed, and independent component analysis was then used to remove ocular and muscular artifacts. The surface Laplacian estimate was used in order to obtain reference-free and spatially sharpened EEG data (Perrin et al., 1989).

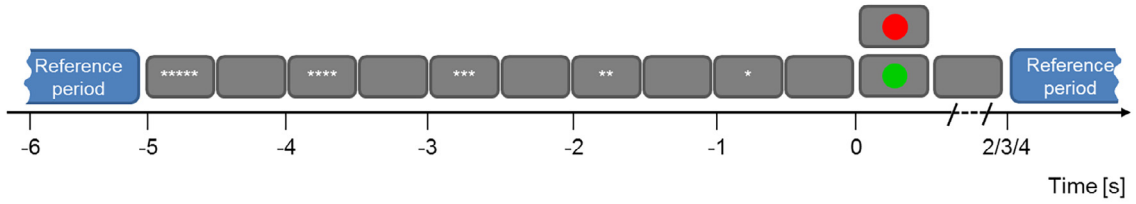

Fig. 1. A: Go/No-go protocol. The warning period lasted five seconds, and was followed by a Go/No-go cue. The reference period was defined as the one-second epoch before the presentation of the first warning stimulus.

The EEG data were epoched between −7 and 3 s with respect to the start of both cues, and between −6 and 3 s with respect to the end of movement. These two windows of analysis were used to verify the effect of movement duration on the post-movement beta synchronization. Single epochs with residual artifacts were excluded from the analysis.

For each subject, each epoch was digitally band-pass filtered in the band from 4 to 30 Hz by means of a zero-phase 512-point finite impulse-response filter. The filtered EEG signals were then squared, averaged over all epochs, and down-sampled with one data point every 100 ms. The relative ERD/ERS values were expressed as the percentage change in power with respect to the mean power recorded in the −6 to −5 second pre-cue reference period (Pfurtscheller and Lopes da Silva, 1999). The reference period was selected as it was far from both asterisks and cue. The most reactive alpha- and beta-band frequencies were respectively determined in the 8–13 and 13–30 Hz range as the frequency showing the maximal desynchronization value (for the alpha band) or the maximal peak-to-peak ERD-ERS value (for beta band). To do this the ERD/ERS calculation was repeated for all frequencies in alpha and beta bands with ±1 Hz steps. For both alpha and beta bands, ERD/ERS onset latency was defined as the first value leading to the minimum/maximum value, and the end of the ERD/ERS patterns was defined as the first value returning to baseline; duration was calculated as the time interval between these two measures. The desynchronization area under the curve (ERD-AuC) was also calculated. The peak α- and β-ERD values were calculated as the minimum values in the [−2 s, 0 s] epoch, whereas the peak α- and β-ERS values were defined as the maximum values in the [0 s, 2 s] epoch. We considered as a region of interest (ROIs) the FC3, C1, C3, C5, CP3 electrodes, where we consistently measured the higher value of both alpha-ERD and peak-to-peak beta ERD-ERS.

2.5. Statistical analysis

The statistical analyses were made on the mean values obtained in the ROI.

The clinical, behavioral and ERD/ERS parameters (duration, maximum value, latency to maximum and AuC) were compared between groups using one-way analysis of variance (ANOVA). Tukey's HSD test was used as the *post hoc* test: if the data did not meet the homogeneity of variance assumption, the Games-Howell test was used.

To assess group differences in response preparation and inhibition in the sensorimotor cortex, we evaluated the average desynchronization/synchronization values in the alpha and beta band in four-time windows: T1 (−1 to 0 s), T2 (0–1 s), T3 (1–2 s), and T4 (2–3 s). Repeated measure analysis of variance (RMANOVA) was used separately for the Go and No-go condition in order to evaluate the effects of group (controls, EPM1 and SCA), laterality (left, right) and time (T1, T2, T3 and T4 for the Go condition, and T1, T2 and T3 for the No-go condition). The Greenhouse Geiser degree of freedom correction factor was used when appropriate.

A paired *t* test was used to test the difference within each group between the Go and No-go conditions, and between the left and right hemispheres.

All of the statistical analyses were carried out using Statistical Package for the Social Sciences software, version 17 (SPSS Inc., Chicago, IL, U.S.A.).

3. Results

3.1. Behavioral results

All subjects performed the task adequately with few (if any) errors (controls: 0–3 errors, EPM1 patients: 0–8 errors, and SCA patients: 0–8 errors). One-way ANOVA showed between-group differences in movement duration (controls 1.03 ± 0.39 s; EPM1 1.61 ± 0.5 s; SCA 1.61 ± 0.28 s) and reaction times (controls 0.28 ± 0.01 s; EPM1 0.35 ± 0.10 s; SCA 0.41 ± 0.08 s) ($F(2, 29) = 3.983$, $p = 0.030$ and $F(2, 29) = 4.828$, $p = 0.016$). *Post hoc* tests revealed that both were longer in the SCA patients than in the controls ($p = 0.045$ and $p < 0.001$) without any within-group correlation.

3.2. ERD/ERS in the alpha band

3.2.1. Control group

Motor preparation was associated with a typical decrease in alpha power (alpha-ERD) in both the Go and the No-go condition: this was greater on the contralateral hemisphere, troughed during task execution, and was followed by synchronization (alpha-ERS) (Tables 1 and 2); in the No-go condition, the duration and amplitude of the desynchronization were reduced, whereas alpha-ERS increased in amplitude (Table 1).

3.2.2. EPM1 and SCA patients

As previously described (Visani et al., 2006, 2010), the EPM1 patients had a slightly lower reactive alpha frequency than the controls (9.1 ± 1.5 *vs* 10.6 ± 1.3 Hz, $p = 0.043$), whereas that of the SCA patients (9.7 ± 1.2 Hz) was more similar.

3.2.2.1. Go condition. RMANOVA revealed a main effect of laterality ($F(1.29) = 9.009$, $p = 0.005$) and time ($F(1.6, 46.3) = 34.2$, $p < 0.001$), and significant laterality × time × group interaction ($F(3.6, 53.0) = 3.8$, $p = 0.011$). Alpha-ERD was significantly greater on the hemisphere contralateral to the activated hand than on the ipsilateral hemisphere in the controls at T2 ($t(10) = -2.59$, $p = 0.027$), and in the EPM1 patients at T1 and T2 ($t(10) = -3.58$, $p = 0.005$ and $t(10) = -2.99$, $p = 0.014$), whereas the SCA patients did not show any significant lateralization at any time. There was no between-

Table 1
Contralateral ERD and ERS features in Go and no-Go conditions in all groups (significant differences are in bold; ns: not significant).

	Condition	Controls	EPM1	SCA	EPM1 vs Controls	SCA vs Controls	EPM1 vs SCA
Alpha ERD duration (s)	Go	4.4 ± 1.0	4.8 ± 0.7	4.0 ± 1.3	ns	ns	ns
	No-Go	2.3 ± 0.9	4.3 ± 1.1	3.0 ± 0.9	**p < 0.001**	ns	**p = 0.038**
	No-Go vs Go	**p < 0.001**	ns	ns			
Alpha ERD maximum (%)	Go	−69.0 ± 14.5	−66.3 ± 21.6	−59.6 ± 21.3	ns	ns	ns
	No-Go	−57.8 ± 19.8	−51.5 ± 23.8	−45.2 ± 22.7	ns	ns	ns
	No-Go vs Go	**p = 0.019**	**p = 0.008**	**p < 0.001**			
Alpha ERS duration (s)	Go	1.3 ± 0.5	1.2 ± 0.5	1.3 ± 0.5	ns	ns	ns
	No-Go	1.7 ± 0.6	1.5 ± 0.6	1.8 ± 0.8	ns	ns	ns
	No-Go vs Go	ns	ns	ns			
Alpha ERS maximum (%)	Go	53.4 ± 52.6	19.1 ± 6.1	27.0 ± 22.1	ns	ns	ns
	No-Go	83.7 ± 48.7	26.8 ± 22.0	43.8 ± 35.5	**p = 0.011**	ns	ns
	No-Go vs Go	**p = 0.029**	ns	ns			
Beta ERD duration (s)	Go	3.3 ± 0.8	3.2 ± 1.3	2.9 ± 1.1	ns	ns	ns
	No-Go	3.1 ± 1.6	2.6 ± 1.1	2.5 ± 1.8	ns	ns	ns
	No-Go vs Go	ns	ns	ns			
Beta ERD maximum (%)	Go	−41.5 ± 18.5	−37.2 ± 15.9	−33.6 ± 13.1	ns	ns	ns
	No-Go	−36.0 ± 21.8	−30.8 ± 13.9	−24.7 ± 12.6	ns	ns	ns
	No-Go vs GO	ns	ns	**p = 0.035**			
Beta ERS duration (s)	Go	1.3 ± 0.7	1.5 ± 0.4	1.5 ± 0.7	ns	ns	ns
	No-Go	1.2 ± 1.2	1.5 ± 0.8	1.4 ± 0.8	ns	ns	ns
	No-Go vs Go	ns	ns	ns			
Beta ERS time to maximum (s)	Go	2.0 ± 0.7	2.3 ± 0.7	2.2 ± 0.9	ns	ns	ns
	No-Go	1.1 ± 0.6	1.9 ± 0.5	1.7 ± 0.7	**p = 0.017**	ns	ns
	No-Go vs Go	**p = 0.001**	ns	ns			
Beta ERS maximum (%)	Go	69.8 ± 56.9	24.7 ± 12.1	33.2 ± 32.4	**p = 0.031**	ns	ns
	No-Go	47.4 ± 33.4	18.0 ± 18.3	26.4 ± 14.7	**p = 0.021**	ns	ns
	No-Go vs Go	**p = 0.001**	ns	ns			

Table 2
Comparison of alpha-and beta ERD-AuC occurring on hemisphere contralateral and ipsilateral with respect to activated hand (significant differences are in bold; ns: not significant).

	Condition	Side	Controls	EPM1	SCA
Alpha ERD (AuC)	Go	Contra	775.0 ± 440.7	715.7 ± 380.3	656.8 ± 331.7
	Go	Ipsilateral	508.6 ± 407.2	547.4 ± 365.4	569.3 ± 238.5
	Contra vs Ipsilateral		**p = 0.010**	**p = 0.031**	ns
	No-Go	Contra	386.3 ± 299.7	425.6 ± 211.6	352.4 ± 223.3
	No-Go	Ipsilateral	236.9 ± 303.7	322.7 ± 179.7	254.4 ± 164.1
	Contra vs Ipsilateral		**p < 0.001**	**p = 0.023**	ns
Beta ERD (AuC)	Go	Contra	289.0 ± 210.9	319.4 ± 257.2	269.1 ± 175.2
	Go	Ipsilateral	268.8 ± 207.4	238.8 ± 233.0	271.4 ± 162
	Contra vs Ipsilateral		ns	ns	ns
	No-Go	Contra	293.9 ± 281.8	225.8 ± 158.5	177.8 ± 150.8
	No-Go	Ipsilateral	105.3 ± 96.6	153.9 ± 166.9	138.1 ± 126.6
	Contra vs Ipsilateral		**p = 0.043**	**p = 0.042**	ns

group difference in alpha-ERD or alpha-ERS duration or maximum value on the contralateral hemisphere (Table 1). The ERD-AuC was significantly lower on the ipsilateral hemisphere in the controls ($t(10) = -3.17$, $p = 0.010$) and EPM1 patients ($t(10) = -2.52$, $p = 0.031$), but not in the SCA patients (Table 2, Fig. 2).

3.2.2.2. No-go condition. RMANOVA revealed a main effect of laterality ($F(1.28) = 12.6$, $p = 0.001$) and time ($F(1.6, 44.5) = 18.6$; $p < 0.001$). Alpha-ERD was significantly greater on the contralateral hemisphere in the controls at T3 ($t(10) = -2.41$, $p = 0.037$) and in the EPM1 patients at T2 ($t(10) = -2.28$, $p = 0.046$), whereas the SCA patients did not show any significant lateralization at any time. EPM1 patients showed significantly longer-lasting alpha-ERD on the contralateral hemisphere than the controls ($F(2,29) = 10,86$, $p < 0,001$; post-hoc test: EPM1 *vs* controls $p < 0.001$ and *vs* SCA patients $p = 0.038$), and their alpha-ERS was significantly lower than that of the controls ($F(2,29) = 3.38$, $p = 0.048$; post-hoc test: EPM1 *vs* controls $p = 0.011$, Table 1). The ERD-AuC was significantly greater on the contralateral hemisphere in the controls ($t(10) = -6.38$, $p < 0.001$) and EPM1 patients ($t(10) = -2.69$, $p = 0.023$), but not in the SCA patients (Table 2, Fig. 2).

3.2.2.3. No-go vs Go condition. Both patient groups and the controls showed significantly reduced alpha-ERD in the No-go condition, but the difference in duration was significant only in the controls. Alpha-ERS amplitude increased in all subjects but, once again, the difference was significant only in the controls (Table 1).

3.3. ERD/ERS in the beta band

3.3.1. Control group

Motor preparation was associated with typical beta-ERD that was prevalent on the hemisphere contralateral to movement in both the Go and No-go condition, which was followed by a sharp increase in beta power on the same hemisphere at the end of movement (beta-ERS); in the No-go condition, the duration and

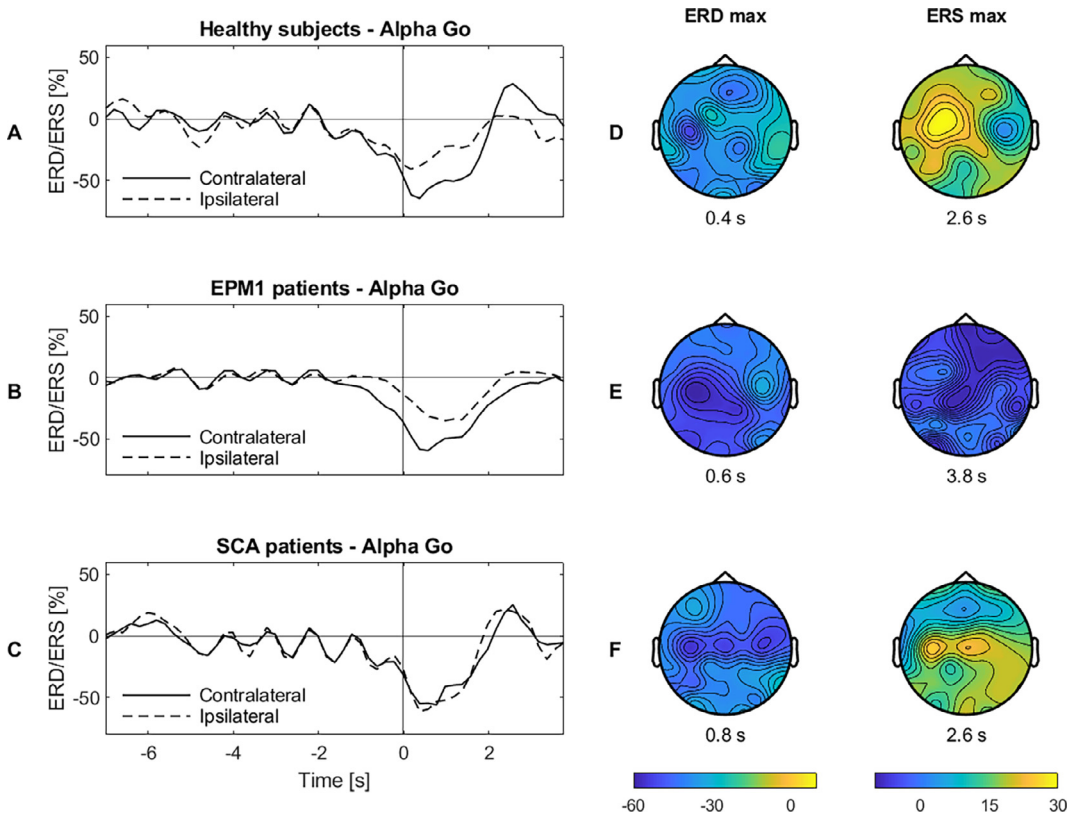

Fig. 2. (Left) Overall averages of the α-ERD time series on the contralateral (continuous line) and ipsilateral central electrode (dashed line) in the healthy subjects (A), EPM1 patients (B) and SCA patients (C). (Right) α-ERD color maps at the time of maximum desynchronization and synchronization in each group (D: healthy subjects, E: EPM1 patients, F: SCA patients). Maps are presented with the same color ranges.

amplitude of the desynchronization and the amplitude of beta-ERS were reduced.

3.3.2. EPM1 and SCA patients

Beta reactive frequency was similar in the three groups (controls 18.9 ± 1.8 Hz; EPM1 19.4 ± 2.3 Hz; SCA 19.0 ± 2.5 Hz).

3.3.2.1. Go condition. RMANOVA revealed a main effect of laterality ($F(1.29) = 7.269$, $p = 0.012$) and time ($F(2.269, 65.792) = 16.396$, $p < 0.001$), and significant laterality × group ($F(2, 29) = 4.234$, $p = 0.024$) and laterality × time × group interaction ($F(4.275, 61.989) = 3.717$, $p = 0.008$). Desynchronization was greater on the contralateral hemisphere in the controls at T3 and T4 ($t(10) = -2.28$, $p = 0.046$ and $t(10) = -2.96$, $p = 0.014$) and in the EPM1 patients at T4 ($t(10) = -3.89$, $p = 0.003$), whereas the SCA patients did not show any significant lateralization at any time. *Post hoc* tests did not reveal any between-group difference in beta-ERD. The beta-ERS peak on the contralateral hemisphere was significantly reduced in EPM1 patients only in comparison with the controls ($F(2,29) = 4.18$, $p = 0.025$; post-hoc test: EPM1 *vs* controls $p = 0.031$, Fig. 3). There was no difference in the ERD-AuC of the ipsilateral and the contralateral hemisphere in any of the groups (Table 2).

3.3.2.2. No-go condition. RMANOVA revealed a main effect of time ($F(2, 58) = 6.651$, $p = 0.003$) and a significant laterality × time interactions ($F(1.477, 40.922) = 4.074$, $p = 0.037$). Desynchronization was greater on the contralateral hemisphere only in the controls at T1 ($t(10) = -2.41$, $p = 0.037$). *Post hoc* tests revealed that the time to peak beta-ERS was significantly longer in the EPM1 patients than in the controls ($F(2,29) = 4.89$, $p = 0.015$; post-hoc test: EPM1 *vs* controls $p = 0.017$), and peak beta-ERS was significantly reduced ($F(2,29) = 4.42$, $p = 0.021$; post-hoc test: EPM1 *vs* controls $p = 0.021$) (Table 1, Fig. 3). The ERD-AuC was significantly larger on the contralateral hemisphere in the controls ($t(10) = -2.31$, $p = 0.043$) and EPM1 patients ($t(10) = -2.33$, $p = 0.042$), but not in the SCA patients (Table 2, Fig. 3).

3.3.2.3. No-go vs Go condition. Beta-ERD was significantly lower the No-go than in the Go condition only in the SCA patients, whereas beta-ERS was significantly reduced only in the controls (Table 1).

3.4. Measures made at movement onset and offset

In the Go condition, movement duration was longer in both patient groups than in the controls and significantly correlated with the time to reach peak beta-ERS ($r_s(32) = 0.418$, $p = 0.017$ and $r_s(32) = 0.357$, $p = 0.045$). To exclude the effect of movement duration, we re-analyzed the data using as a trigger the movement end. The average maximal amplitude of beta-ERS was greater in all of the groups with respect to that calculated with movement onset. Group comparisons did not reveal any deviations from the previously found statistically significant differences, showing reduced amplitude in the patients in comparison with the controls ($F(2, 31) = 4.452$, $p = 0.021$; post-hoc test: controls *vs* EPM1 $p = 0.040$ and *vs* SCA $p = 0.034$, Supplementary Fig. 1).

4. Discussion

The aim of this study was to compare movement-associated changes in EEG rhythms in EPM1 and SCA patients in order to identify any functional differences due to uneven circuitry and investigate the cortical neuronal behavior related to movement planning, execution and inhibition.

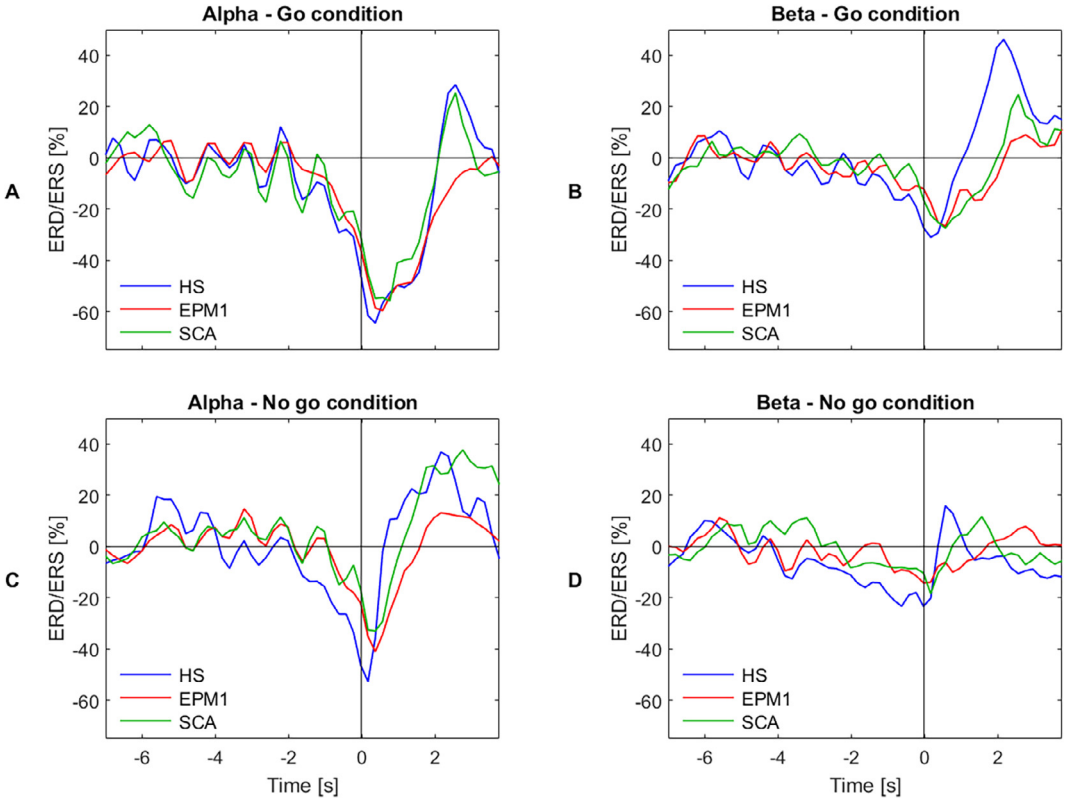

Fig. 3. Overall averages of the α- and β-ERD/ERS time series on the contralateral central electrode in healthy subjects (blue lines), EPM1 patients (red lines) and SCA patients (green lines). Upper panels) α- and β-ERD/ERS in the Go condition (A, B); lower panels) α- and β-ERD/ERS in the No-go condition (C, D).

Our previous studies of movement-related ERD/ERS in EPM1 patients using a self-paced movement task have consistently revealed changes in comparison with healthy subjects that are mainly characterized by greatly reduced post-movement beta-ERS (Visani et al., 2006, 2010), and we have interpreted this finding as the result of a decreased ability of the neuronal network to inhibit cortical excitability at the end of the movement. The Go/No-go algorithm used in this study requires sustained attention but also needs a special ability to inhibiting action under a subset of stimuli (Huster et al., 2013). As the electrophysiological responses evoked by No-go trials have been interpreted as indicators of inhibitory processes, we considered this protocol a better means of assessing defects in movement inhibition in the presence of cortical myoclonus or ataxia. No-go with respect to Go condition event-related responses to a Go/No-go task have previously indicated defective cerebellar inhibition on the frontal cortex in ataxic SCA patients, which has been interpreted as being due to defective primary cerebellar function (Harada et al., 2002).

The behavioral findings of this study indicate that both EPM1 and SCA patients were capable of performing the task well. In the Go condition, there were no significant differences between the controls and patients in any of the ERD parameters on the hemisphere contralateral to the activated hand, except for the previously observed significant reduction in peak post-movement beta-ERS in the EPM1 patients (Visani et al., 2006).

However, in the No-go condition, the EPM1 patients showed prolonged alpha-ERD on the hemisphere contralateral to the activated hand in comparison with both controls and SCA patients. Alpha desynchronization is generally considered a correlate of an activated cortical area (Neuper and Pfurtscheller, 1992; Pfurtscheller, 2001) and is associated with increased motor cortex excitability (Chen et al., 1998), which therefore seems to be more persistent in EPM1 patients, thus suggesting protracted cortical activation or delayed deactivation exceeding the time of movement planning (Cassim et al., 2001).

At the same time, both alpha- and beta-ERS were less and/or delayed in the EPM1 patients in comparison with controls. As physiologically occurs in healthy subjects, the behavior of alpha- and beta-ERS in both patient groups was different in the two conditions, with increased alpha and decreased beta synchronization in the No-go condition. Alpha-ERS has been more rarely evaluated than beta-ERS in healthy subjects and even less so in patients with neurological disorders. One previous study (Klostermann et al., 2007) indicated functional diversity in the networks generating alpha- and beta-ERS, which are simultaneously active in motor processing: alpha-ERS is probably generated in local and restricted neuronal networks of the sensory-motor cortex, whereas beta-ERS reflects the simultaneous activation of a cortico-basal ganglia network. Alpha-ERS may be considered a strong marker of inhibitory mechanisms (Suffczynski et al., 2001; Bočková et al., 2013), and is more evident when a task has to be suppressed. Enhanced alpha-ERS during the No-go task was preserved in both patient groups, in which the amplitude of the No-go alpha-ERS was more than twice than that observed during the Go task. However, in the No-go condition, alpha-ERS was significantly reduced in the EPM1 patients in comparison with the controls, thus further indicating a defective inhibitory response. The decrease in alpha-ERS observed in the EPM1 patients may indicate the persistence of cortical excitation for a period of time that exceeds that of movement planning and is in agreement with their prolonged alpha-ERD.

The main finding distinguishing the SCA patients from both the controls and the patients with EPM1 was the absence of the significant prominence of both alpha- (Go and No-go condition) and beta-ERD (No-go condition) on the hemisphere contralateral to the activated segment. It is known that alpha- and beta-ERD can occur on the hemisphere ipsilateral to the activated segment in

healthy subjects, particularly in the case of complex motor tasks (Ohara et al., 2000) and is commonly increased in patients with poor motor performances (such as those with extrapyramidal disorders) (Defebvre et al., 1994; Babiloni et al., 2000; Labyta et al., 2003).

In a previous study of EPM1 patients using self-paced finger movements (Visani et al., 2006), we found increased alpha-ERD on the central region of the contralateral hemisphere that was not confirmed in subsequent studies based on repetitive hand movements (Visani et al., 2010; Visani et al., 2015).

Conversely, SCA patients significantly lost the asymmetrical representation of rhythm desynchronization in both the alpha and beta band, thus suggesting a mainly non-local, distant dysfunction disrupting movement-related cortical activation. The greater activation of the ipsilateral hemisphere may reflect a bilateral loss of cerebellar steady inhibitory modulation, which is enhanced and becomes visible at the time of movement planning and execution. A functional imaging study of motor sequencing (Harrington et al., 2000) has found greater bilateral cerebellar activation in the case of complex motor tasks performed using right hand sequences. Our data suggest that the cerebellum bilaterally modulates both brain hemispheres at the time of a motor task, even in the case of a unilateral movement.

4.1. Study limitations

The main limitation of this study arises from the large intra-group variance in the evaluated changes in alpha and beta rhythms in all of the subject groups, including the healthy controls. A second limitation is the difficulty of evaluating the precise topographical dynamics of measures with a large variance, which is why we restricted this study to the consistent measures made using central electrodes. We are now planning to face this issue using more precise measures that can be made using magneto-encephalographic recordings in larger numbers of the same populations.

In our study, patients were on average slightly older than controls, however, the age difference was not significant, thus it is unlikely that this has influenced our results. In fact, the age effect on alpha and beta ERS/ERD reported in literature relates to very distant age groups (Labyt et al., 2004, Rossiter et al, 2014, Heinrichs-Graham and Wilson, 2016).

4.2. Conclusions

Our observations suggest that EPM1 and SCA patients have multiple defects in alpha and beta ERD and ERS that may indicate impaired cerebellar modulation of the motor cortex in both groups. However, the most important differences between them seem to be the prominent lack of local cortical inhibition in EPM1 patients, and a bilateral hemispheric dysfunction probably attributable to a lack of cerebellar control in SCA patients. Defective local inhibition in EPM1 patients is indicated by the depressed beta-ERS on the hemisphere contralateral to the activated hand in both Go and No-go conditions, and the defective dynamics of the contralateral sensorimotor cortex suggested by the lack of alpha ERD enhancement in the No-go condition.

The different behavior of EPM1 and SCA patients suggests that the cerebellum makes a limited functional contribution to the genesis of the motor disorder characterizing EPM1 patients with moderate myoclonus.

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Authors' contributions

E. Visani performed the experiments with A. Mongelli and L. Nanetti, processed the experimental data, made the analyses, drafted the manuscript, and designed the figures. L. Canafoglia and E. Visani conceived and designed the study. L. Canafoglia, C. Mariotti, L. Nanetti, A. Mongelli and A. Castaldo planned the experiments and enrolled the patients. F. Panzica verified the methods and contributed towards the final version of the manuscript. C. Mariotti, S. Franceschetti and L. Canafoglia supervised the study findings and wrote the final version of the manuscript. All of the authors discussed the results and contributed to the final manuscript.

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

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