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Connectivity measures suggest a sub-cortical generator of myoclonus in Angelman syndrome

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HIGHLIGHTS

- Studies on myoclonus in Angelman syndrome lead to contrasting results.
- We analysed EEG-EMG coherence and connectivity in a series of Angelman patients.
- Our findings suggest a subcortical generator of myoclonus in Angelman Syndrome.

ABSTRACT

Objective: The clinical and neurophysiological characteristics of myoclonus in Angelman syndrome (AS) have been evaluated in single case or small cohorts, with contrasting results. We evaluated the features of myoclonus in a wide cohort of AS patients.
Methods: We performed polygraphic EEG-EMG recording in 24 patients with genetically confirmed AS and myoclonus. Neurophysiological investigations included jerk-locked back-averaging (JLBA), cortico-muscular coherence (CMC) and generalised partial directed coherence (GPDC). CMC and GPDC analyses were compared to those obtained from 10 healthy controls (HC).
Results: Twenty-four patients (aged 3–35 years, median 20) were evaluated. Sequences of quasi-continuous rhythmic jerks mostly occurred at alpha frequency or just below (mean 8.4 ± 1.4 Hz), without EEG correlate. JLBA did not show any clear transient preceding the jerks. CMC showed bilateral over-threshold CMC in alpha band that was prominent on the contralateral hemisphere in the patient group as compared to HC group. GPDC showed a significantly higher alpha outflow from both hemispheres toward activated muscles in the patient group, and a significantly higher beta outflow from contralateral hemisphere in the HC group.
Conclusions: These neurophysiological findings suggest a subcortical generator of myoclonus in AS.
Significance: Myoclonus in AS has not a cortical origin as previously hypothesised.

1. Introduction

Angelman syndrome (AS) is a genetic condition caused by defective expression of the maternal allele of ubiquitin protein ligase E3A (UBE3A) gene on chromosome 15q11-q13, resulting from gene deletion, paternal uniparental disomy, imprinting defect, or mutations in the maternal copy of UBE3A (Bird, 2014). Common features of AS include intellectual disability, absent

Abbreviations: AR, autoregressive; AS, Angelman Syndrome; C, central; CMC, cortico-muscular coherence; Co, contralateral; Cz, central vertex; F, frontal; Fz, frontal vertex; GPDC, generalised partial directed coherence; HC, healthy controls; Ip, ipsilateral; JLBA, jerk-locked back-averaging; P, parietal; Pz, parietal vertex; ROI, region of interest; Ve, vertex.

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speech, facial dysmorphisms, sleep disturbances, seizures and movement disorders (Williams et al., 2006), with clinical variability among different genetic subgroups (i.e. deletion genotype showing the most severe phenotype) (Guerrini et al., 2003).

Movement disorders are reported in up to 100% of subjects with AS, described as "tremulous movements of limbs, unsteadiness, clumsiness, or quick jerky motions" (Williams et al., 2006). The clinical and neurophysiological features of myoclonus in AS have been evaluated in single case reports or small cohort studies, with contrasting results. Some studies suggested a cortical origin of myoclonus assessed in all examined patients or in a patient subset by means of jerk-locked back-averaging (JLBA) (Guerrini et al., 1996; Goto et al., 2015). In particular, Guerrini et al. (1996) described a fast-bursting myoclonus at about 12–15 Hz in 11 patients with AS, often associated with a fronto-central rhythmic activity at EEG. Such EEG finding correlated with myoclonus was not confirmed by other authors (Stecker and Myers, 2003; Pollack et al., 2018).

Cortico-muscular coherence (CMC) for distal muscles has potential value in diagnosing the anatomical origin of myoclonus and is usually preferred to JLBA in the study of high-frequency rhythmic myoclonus (Brown et al., 1999; Grosse et al., 2003). In patients with cortical myoclonus, CMC frequency analysis showed the presence of an exaggerated CMC peak in the beta band between sensorimotor cortical activity and EMG activity. Brown et al. (1999) first demonstrated a cortical origin of myoclonic jerks through CMC frequency analysis in eight patients with suspected cortical myoclonus of different ethology in whom JLBA failed to show a cortical correlate. To our knowledge, only three AS patients with myoclonus have been evaluated by mean of CMC but this study failed to reveal, on an individual basis, significant difference with healthy controls (HC) (Brown et al., 1999). EEG-EMG information flow can also be studied by generalized partial directed coherence (GPDC) analysis to better assess the cortical outflow and inflow toward and from the activated muscles (Panzica et al., 2014). GPDC analysis has never been used to study myoclonus in AS.

The aim of this study was to evaluate clinical and neurophysiological features of myoclonus in a wide series of AS patients by mean of video-polygraphy, JLBA and CMC, including GPDC, analyses.

2. Subjects and methods

2.1. Included subjects

We evaluated all patients with genetically confirmed AS followed at our 3 Italian Neurologic Centers (Reggio Calabria, Milano, Troina) as well as subjects participating to annual national meetings of the Italian Organization for AS (OrSA) from 2014 to 2017. All caregivers gave their informed consents to the study. Subjects uncooperative to polygraphic assessment were excluded from the study. CMC analyses from AS patients were compared to those obtained from controls (healthy voluntaries attending the Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan).

2.2. Neurophysiological investigation

All subjects underwent video-polygraphic EEG recordings (19 electrodes placed according to 10/20 International System) with surface EMG signals simultaneously recorded from pairs of electrodes placed bilaterally 2–3 cm apart over the belly of the wrist flexor and extensor muscles.

The recordings were obtained at rest and during voluntary mild left and right hand isometric contractions. The EEG and EMG signals were acquired using a computerized Micromed Brain Quick System at a sampling frequency of 256 Hz (band pass filters 1.6–120 Hz). The EEG signals were recorded using a montage with a common reference electrode that allowed off-line mathematical data analysis. A pre-processing spline surface Laplacian estimate was applied to the EEG channels to ensure reference-free and spatially sharpened data (Perrin et al., 1989).

2.2.1. JLBA

JLBA was performed in patients with at least 80 jerks associated with artefact free EEG epochs. Due to this inclusion criterion, JLBA was applied in 13 patients (Table 1). The polygraphic traces were visually examined using an expanded time scale and an appropriate amplitude display to evaluate the EEG and EMG waveforms and exclude superimposed artefacts. The jerk onset was established at the beginning of individual rectified jerks unmixed with not-negligible tonic EMG contraction, showing a relatively similar waveform. The time-window for averaging included the 100 ms before and the 100–200 ms after the point at which the rectified EMG potential diverged from baseline. In patients with jerks occurring during spike and wave (SW) discharges, we separately performed JLBA throughout the discharges including at least 40 EMG bursts.

2.2.2. CMC and GPDC

CMC and GPDC were performed in 10 patients aged 10–37 years (Table 1) using a block wise bivariate autoregressive (AR) model and was estimated in patients showing sufficiently long artefact-free EEG epochs associated with long or repeated sequences of quasi-rhythmic jerks. The AR model order was determined using the multichannel version of the Akaike criterion as a guideline and the goodness of the identification was verified by means of 'portmanteau' chi-square and Anderson's tests (Da Silva and Mars, 1987; Box and Jenkins, 1970). Coherence was defined as:

$$Coh_{xy}(f) = \frac{|S_{xy(f)}|^2}{S_{xx}(f)S_{yy}(f)}$$

where $S_{xx}(f)$ and $S_{yy}(f)$ are the power spectral densities of the EEG and EMG channels, and $S_{xy}(f)$ is the cross-spectral density. The critical value for the null hypothesis of zero-coherence at a significance level of 0.01 was computed according to Halliday et al. (1995), taking into account that the degree of freedom of an AR model is given by N/p (Jenkins and Watts, 1968), where N is the number of samples, p the model order.

Subjects with about one minute of polygraphic recording including non-continuous epochs free from artefacts and characterized by unilateral EMG bursts recorded from wrist flexor or extensor were selected for CMC analysis. Signals were normalized by subtracting the mean value and dividing the result by the standard deviation, and then divided into non-overlapping 1-second epochs. The epochs were considered multiple realizations of the same process and the autoregressive coefficients were estimated by means of the Levinson-Robinson-Wiggins algorithm (Pereda et al., 2005).

To evaluate CMC patterns, we selected the Frontal (F) Central (C), parietal (P) electrodes of both hemispheres and vertex frontal (Fz), central (Cz), and parietal (Pz) electrodes. Temporal electrodes were excluded to avoid muscular artefacts often affecting the signal in temporal regions also in epochs that were relatively artefact free on the other electrodes and because it was not expected that temporal electrodes were involved in CMC. Since patients presented jerks that could be recorded for a sufficient time unilaterally, we grouped the F, C, P electrodes as contralateral (Co) or ipsilateral (Ip) to the jerky movement, irrespectively to the side. GPDC analysis was also performed on the signal epochs selected

Table 1
Main clinical and neurophysiological findings in our AS subjects.

	Sex, age (years)	Rhythmic jerk (Hz)	Jerk location and course	JLBA	CMC	GPDC	AED
1	F, 2	9.6	B, isolated & sequences	negative	np	np	VPA
2	M, 5	–	B, isolated	np	np	np	CLN, LEV
3	M, 6	–	B, isolated	np	np	np	VPA, ETS
4	M, 6	7.0	B, isolated	np	np	np	VPA, ETS
5	F, 10	13.5	B, asynchronous > L	negative	yes	yes	VPA
6	M, 11	9.4	B, asynchronous	negative	yes	yes	VPA
7	M, 13	9.2	L, brief sequences	np	np	np	VPA, ETS
8	F, 14	8.7	B, brief sequences	np	np	np	CLB
9	M, 16	–	R, isolated	np	np	np	VPA, ETS
10	M, 17	11.2	B, asynchronous	np	np	np	-
11	F, 19	9.2	B, asynchronous > L	negative (*)	yes	yes	VPA
12	F, 20	10.2	B, asynchronous > R	np	np	np	CLB, VPA, ETS
13	F, 20	-	R, isolated	np	np	np	VPA
14	M, 23	9.0	B, asynchronous > R	negative	yes	yes	LTG, ETS
15	F, 26	7.8	B, asynchronous > L	negative	yes	yes	LEV
16	M, 26	9.8	B, brief sequences	np	np	np	VPA, ETS
17	M, 29	8.6	B, asynchronous	negative	yes	yes	CLN, VPA
18	F, 29	7.8	B, brief sequences	negative	np	np	CLB, VPA
19	M, 29	9.2	B, asynchronous	negative	yes	yes	VPA
20	F, 30	8.4	B, asynchronous	negative	yes	yes	CLB, VPA
21	F, 31	9.2	B, asynchronous > L	negative	np	np	VPA, LEV
22	M, 35	9.0	B, asynchronous	negative	yes	yes	CLB, VPA, LEV
23	M, 35	11.6	B, asynchronous > L	negative	yes	yes	VPA, ETS, PB
24	M, 37	7.6	B, brief sequences	np	np	np	CLN, VPA, LEV

Legend. B: bilateral; L: left; R: Right; JLBA: jerk-locked back averaging; CMC: cortico-muscular coherence; GPDC: generalised partial directed coherence; np: not performed; ETS: ethosuximide; CLB: clobazam; CLN: clonazepam; LEV: levetiracetam; LTG: lamotrigine; VPA: valproic acid.
(*) positive JLBA performed on jerks associated with spike and wave discharges.

for CMC analysis; Co, Ip electrodes were considered as regions of interest (ROIs) (Panzica et al., 2014). CMC and GPDC findings in patients with AS were compared to those of a HC group. All data analyses were made using custom-written routines in the Matlab environment (Version 8.1, R2013a; Mathworks Inc., Natick, MA, USA).

2.3. Statistical analysis

The data measured in AS and HC were compared using repeated measures ANOVA (RMANOVA); when RMANOVA showed a significant main effect, a post hoc analysis was made using ANOVA and *t*-test test for paired samples with Bonferroni correction for multiple comparisons. For CMC statistical evaluation, considering the limited number of the EEG electrodes and the variable location of the maximal CMC value, we considered the electrodes exploring sensorimotor regions of the hemisphere contralateral to activated muscles (Co-ROI), the ipsilateral hemisphere (Ip-ROI) and vertex regions (Ve-ROI), as ROIs.

3. Results

We performed 40 polygraphic EEG-EMG recordings in 40 AS patients. Myoclonic jerks were recorded in 32 patients. Muscular artefacts did not allow performing neurophysiological investigations in eight subjects. Hence, polygraphic recordings from 24 AS patients (10 F, age 3–35 years, median 20) were finally evaluated.

Myoclonic jerks occurred as synchronous EMG bursts on antagonist muscles at rest, during posture maintenance or during movements. When jerks occurred bilaterally, the EMG bursts were consistently asynchronous on the two body sides (Fig. 1). Jerks were isolated or in short sequences in 13 subjects, quasi-continuous in the remaining 11. Individual EMG bursts had variable duration, often exceeding 50 ms, and consistently occurred without EEG correlate (Table 1). Sequences of quasi-rhythmic jerks mostly occurred at alpha frequency or just below (mean 8.4 ± 1.4 Hz). When slow-SW discharges occurred, rhythmic myoclonic jerks regularly maintained their alpha-like frequency (Fig. 2).

JLBA, performed in 13 patients on jerks unrelated with SW discharges, did not show any clear EEG transient preceding the jerks. In 6 patients we separately evaluated JLBA on at least 40 jerks occurring during the SW paroxysm; in only one of these patients (# 11) we were able to detect a spike wave-like transient with a smoothed spike component preceding by about 17 ms the averaged jerks (Fig. 2 B, C and D).

3.1. CMC

CMC evaluation could be performed in 10 patients (4 F, age 9–35, median 26 years) (Table 1) with sufficiently long epochs unaffected by artefacts. In these patients, jerks occurred with a consistent location and moderate variations in frequency and duration of the EMG bursts, and they were enhanced by posture maintenance and active movements. Jerks were scored as frequent in two and quasi-continuous in eight. CMC measures were compared with those obtained in 10 HC (6 F, age 12–28 years, median 22 years) during moderate isometric hand extension.

The maximal CMC values were in alpha band in AS and in beta band in HC and involved C or F or P electrodes. All AS subjects showed over threshold CMC in alpha band on the Co-ROI with respect to contralateral muscles, while all HC showed over threshold CMC in beta band on Co-ROI with respect to activated muscle (Fig. 3). The between-group differences of CMC were statistically significant, with higher values in alpha band in AS on Co-ROI ($F = 4.5$, $p = 0.040$) and higher values in beta band in HC on Co-ROI ($F = 6.5$, $p = 0.020$). As expected, in HC, beta CMC showed significantly higher values on Co-ROI, with respect to both Ip-ROI ($F = 3.2$, $p = 0.009$) and Ve-ROI ($F = 2.7$, $p = 0.026$), while no significant between-group differences were found comparing the remaining ROIs.

Comparing the absolute values of CMC, irrespectively with their occurrence in alpha band (in AS) or in beta band (in HC), significantly higher values occurred in AS compared with HC on Ip-ROI ($t = 2.4$, $p = 0.036$) but not in Co-ROIs.

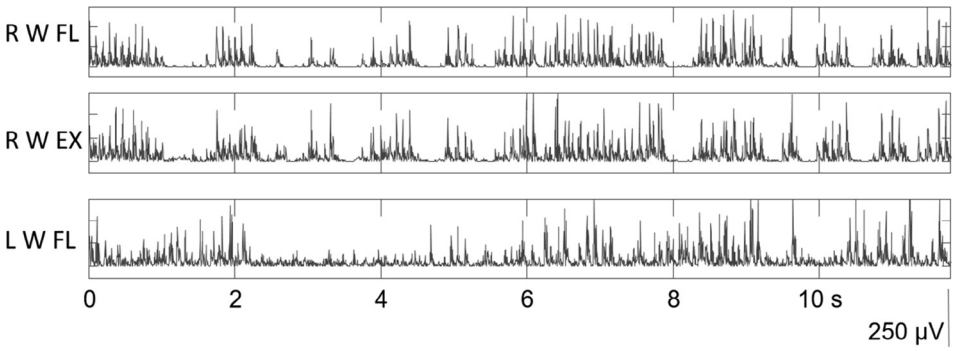

Fig. 1. Rectified EMG epochs recorded from flexor and extensor wrist muscles of the right hand and from the left wrist flexor in the presence of bilateral jerks (patient # 17) showing the synchronous bursts on antagonist muscles and the mostly asynchronous bursts occurring on contralateral wrist flexor.

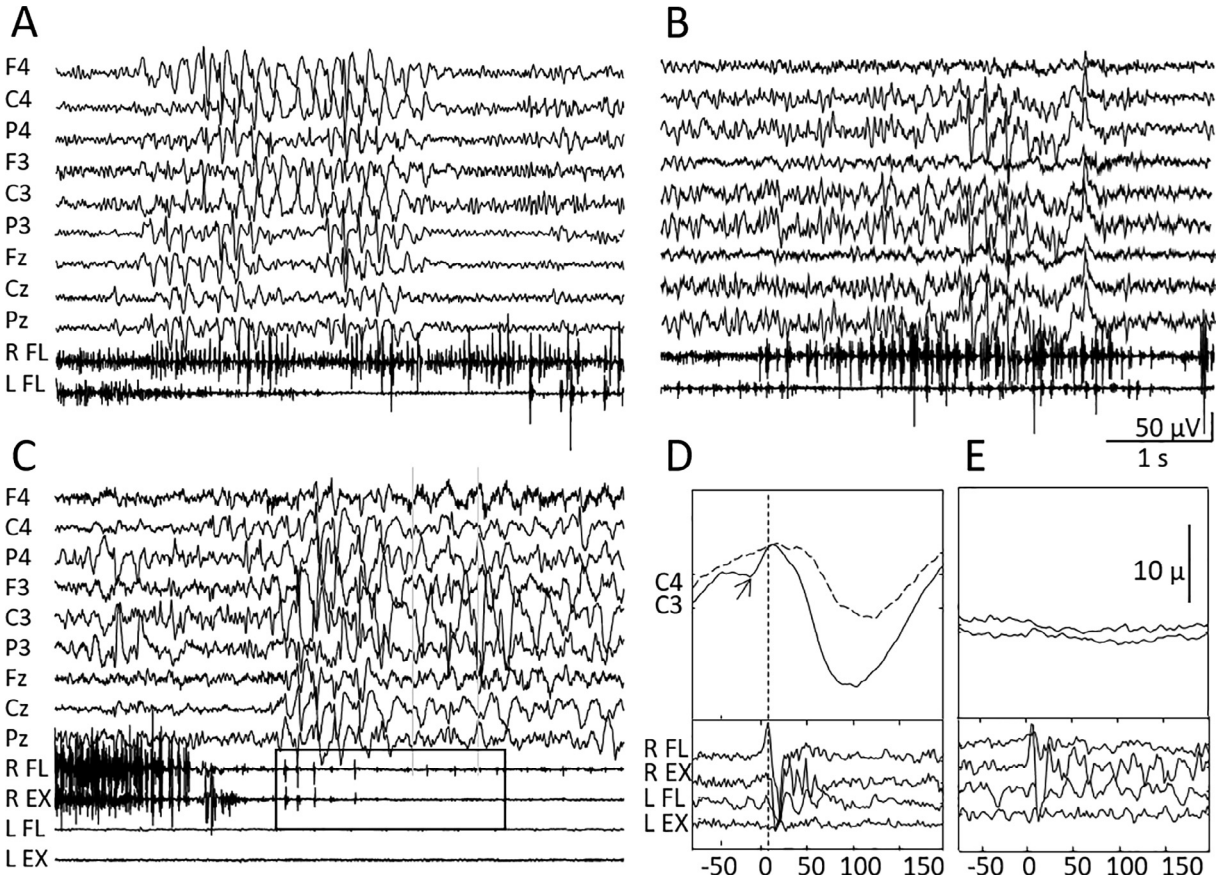

Fig. 2. EEG-EMG epochs including SW discharges, prominent on anterior regions in patient # 19 (A) and on posterior regions in patient # 23 (B). The EMG burst can be observed either during the discharge or outside their occurrence without changes in their repetition frequency. In the patient #11 (C), the EMG bursts conversely change their frequency during a diffuse SW discharges (box). In that case, the JLBA (80 epochs), performed on low frequency jerks during the SW discharge, shows a spike-wave-like EEG correlate, with the positive peak on C3 preceding by about 14 ms the averaged jerks (D), while, JLBA performed on jerks unassociated with SW paroxysms, did not associate with any clear EEG transient (E).

3.2. GPDC

GPDC was performed on the same polygraphic epochs evaluated for CMC. Only occasional over threshold outflow was found in delta, theta and gamma band.

In alpha band AS patients, compared with HC showed a significantly higher outflow from cortex toward activated muscles on both ipsilateral and contralateral hemisphere (Fig. 4A). However, the outflow from Co-ROI was not significantly different in comparison with that from Ip-ROI on both groups.

In beta band, HC but not AS, showed a significantly higher cortical outflow from contralateral hemisphere compared with compared with outflow from ipsilateral hemisphere (Co-ROI vs Ip-ROI: $t = 6.8$, $p < 0.001$) (Fig. 4, B).

Some AS patients but not HC showed a moderate alpha inflow from muscle to both Ip-ROI and Co-ROI while a moderate beta inflow was present in few HC and in AS (Fig. 4 C and D), however the low number of subjects showing over threshold inflow did not allow statistical evaluation.

4. Discussion

Neurophysiological assessments in this large series of AS patients suggest a subcortical generator of myoclonus. Myoclonic

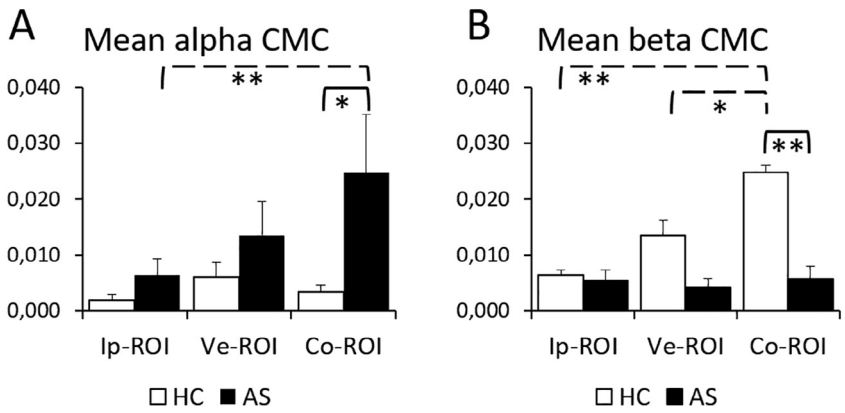

Fig. 3. CMC in alpha and beta band in AS and HC. Note the higher values of alpha CMC on Co ROI with respect to that measured on Ip ROI in AS (A, dotted line) and with respect to that measured in HC (A, continuous line) the moderate alpha CMC is present without differences on all ROIs in HC. CMC in beta band shows an opposing pattern, with significantly higher values on Co ROI in HC with respect to AS (continuous line) and with respect to other ROIs in HC (dotted line) (B).

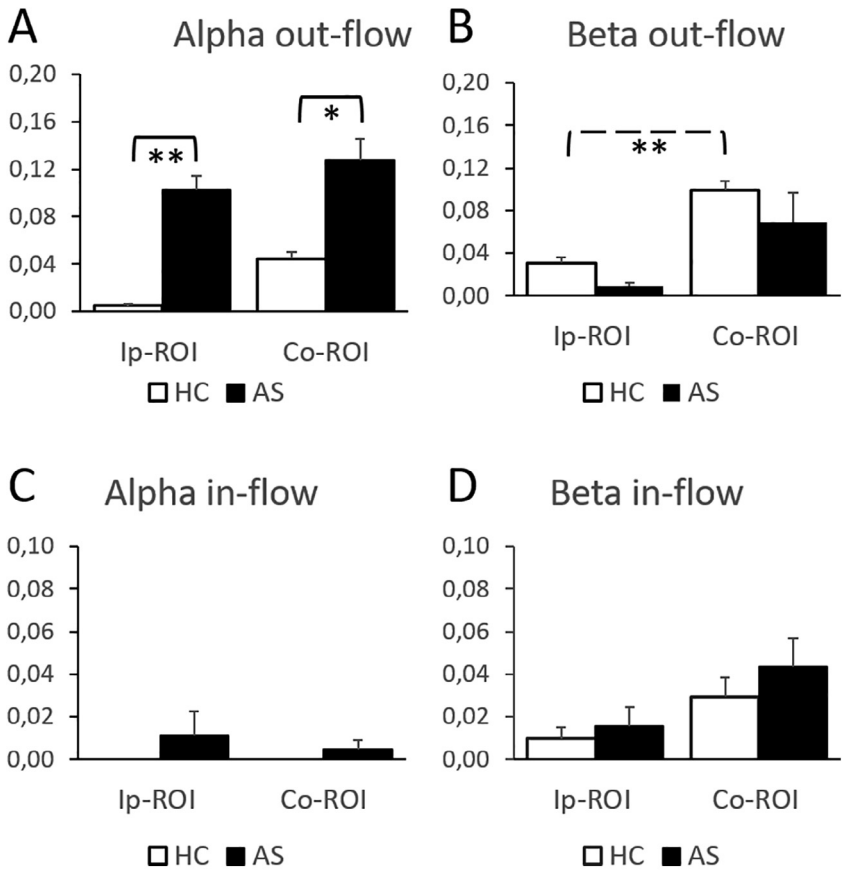

Fig. 4. Out and in flow measured on Co-ROI and Ip-ROI in AS and HC. Alpha outflow was significantly higher in AS than in HC on both Co-ROI and Ip-ROI, without significant difference comparing the two hemispheres (A). Beta out-flow was significantly higher on Co-ROI than in Ip-ROI only in HC (dotted line). None of the differences found in in-flow reached significant differences.

jerks were recorded in 80% of our AS subjects. This percentage is slightly lower than that reported in a previous study (Guerrini et al., 1996), in which myoclonus was recorded in all. This difference could be explained by the larger number of subjects evaluated in our series.

Various types of "jerky movements" have been reported in AS, including myoclonus associated with diffuse spike-wave discharges, cortical myoclonus associated with fronto-central rhythmic activity, myoclonic status epilepticus, tremor without EEG changes or prior cortical potentials, myoclonus without EEG changes (Guerrini et al., 1996; Goto et al., 2015; Galvan-Manso et al., 2005; Elia, 2009). In the present series, myoclonic jerks mostly occurred at around alpha frequency (mean 8.4 ± 1.4 Hz), without any EEG correlate. In recent AS series, the prevalence of non-epileptic myoclonus/tremor has shown to increase with age (Prasad et al., 2018) while the prevalence of seizures tends to decrease (Sueri et al., 2017). Most of our patients were adolescent or young adults presenting myoclonic jerks as a steady condition.

Moreover, polygraphic recordings revealed synchronous activation of antagonist muscles, "independent" occurrence on the two-body side and quasi-rhythmic time course of the bursts. These findings are similar to those occurring in patients with cortical myoclonus in various forms of progressive myoclonus epilepsies (PMEs). However, in this series, the frequency of jerks (at around alpha band) was lower as compared to the typical beta frequencies of cortical myoclonus observed in PMEs (Panzica et al., 2003; Panzica et al., 2014; Franceschetti et al., 2016) or in Dravet syndrome (Canafoglia et al., 2017). Moreover, while in PME the myoclonus is activated by action, in the present series the jerks showed an overlapping frequency during rest, moderate posture maintenance and action.

By analysing myoclonus with JLBA, we did not find the presence of consistent EEG transients proceeding the jerks, with the exclusion of a single patient (#11) in whom jerks occurred at low frequency during slow SW discharges.

Both AS and HC groups had low CMC values in beta band on both hemispheres. In AS group, the main findings were the relatively high values of alpha CMC and an increased cortical outflow at frequencies that were similar to that of the jerks. Alpha CMC was prominent on the hemisphere contralateral to the activated muscles. On Co-ROIs the values of alpha CMC in the AS group were similar to those of physiological beta CMC in the HC group. These findings are not in keeping with a cortical myoclonus, which is characterized by very high CMC values on the hemisphere contralateral to the activated muscles.

In the present study, CMC beta band in the HC group was low but over threshold, and it was clearly prominent on the hemisphere contralateral to activated muscles, as expected (Mima and Hallett, 1999). Moreover, CMC in alpha band was present in some HCs, as already observed in a subset of HCs during normal isometric contraction (Panzica et al., 2003; Budini et al., 2014). Of note, in our study, alpha CMC was never isolated and had lower values with respect beta-CMC in HC

The beta outflow from cortex to contralateral activated muscles, as recorded by GPDC, was absent in the AS group and present in the HC group, as previously observed (Panzica et al., 2014). The AS group showed a prominent alpha outflow from EEG toward activated muscles, and a non-significant lateralization, thus confirming the data obtained by CMC recordings. All these findings suggest that myoclonus-related, near-alpha oscillations involve both hemispheres, in keeping with a subcortical myoclonus generator in AS.

This study has some limits. The main difficulty was to obtain artefact-free epochs suitable for the post-analysis in AS subjects, which could limit the feasibility of various analysis algorithms. This limited the number of patients included for JLBA, CMC and GPDC studies. The age range of our patients was wide but we observed similar polygraphic findings in children, adolescent or adults. Of note, long-lasting sequence of jerks were observed in patients older than 10 years, allowing CMC and GPDV analysis in this age group. Lastly, all patients but one (# 10) were receiving antiepileptic drugs. We do not believe however that medications might have significantly changed the CMC pattern. Indeed, in subjects with cortical myoclonus, high CMC values persisted despite antiepileptic drugs (Panzica et al., 2014).

5. Conclusions

The absence of EEG transients preceding the jerks, the values of alpha CMC, similar to those measured in beta band in the healthy subjects, and the evidence of a bi-hemispheric cortical outflow toward the involved muscles did not support a cortical generator of the repetitive jerks occurring in AS, but rather suggest a subcortical origin.

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Declaration of Competing Interest

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

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None.

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