Electromyographic patterns of paratonia in normal subjects and in patients with mild cognitive impairment or Alzheimer's disease

Lucio Marinelli[a,b,*], Carlo Trompetto[a,c], Luca Puce[a], Fiammetta Monacelli[d,e], Laura Mori[a,c], Carlo Serrati[f], Francesco Fattapposta[g], Maria Felice Ghilardi[h], Antonio Currà[i]

[a] Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genoa, Genova, Italy

[b] IRCCS Ospedale Policlinico San Martino, Department of Neuroscience, Division of Clinical Neurophysiology, Genova, Italy

[c] IRCCS Ospedale Policlinico San Martino, Department of Neuroscience, Division of Neurorehabilitation, Genova, Italy

[d] Department of Internal Medicine, University of Genoa, Genova, Italy

[e] IRCCS Ospedale Policlinico San Martino, Department of Internal Medicine, Division of Geriatrics, Genova, Italy

[f] Department of Neurology, Imperia Hospital, Imperia, Italy

[g] Department of Human Neurosciences, Sapienza University of Rome, Roma, Italy

[h] Department of Physiology, Pharmacology & Neuroscience, CUNY School of Medicine, New York, NY, USA

[i] Department of Medical-Surgical Sciences and Biotechnologies, A. Fiorini Hospital, Terracina, LT, Sapienza University of Rome, Polo Pontino, Latina, Italy

Correspondence to Lucio Marinelli, MD, PhD
Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health
University of Genoa, Largo Daneo 3, 16132 Genova, Italy
Phone: +39 010 555 5648; E-mail: lucio.marinelli@unige.it

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ABSTRACT

Background: information on prevalence, pathophysiology and clinical assessment of paratonia are scarce. In a previous study, we suggested that surface electromyography (EMG) can be used to assess paratonia.

Objective: to assess clinical and EMG features of paratonia in both patients with cognitive impairment and healthy subjects.

Methods: we examined 18 patients with Alzheimer Disease (AD), 21 patients with Mild Cognitive Impairment (MCI), 30 healthy seniors (seniors), and 30 healthy juniors (juniors). Paratonia was assessed using the "Paratonia Scale". EMG bursts were recorded from biceps and triceps during manually applied passive movements of elbow joint. Continuous (sinusoidal) and discontinuous (linear) movements were applied at 2 different velocities (fast and slow).

Results: in comparison to juniors, seniors had higher clinical scores. In comparison to seniors, AD had higher oppositional scores, while MCI had higher facilitatory scores. EMG activity during passive movements correlated with paratonia clinical scores, was velocity-dependent and increased with movement repetition, most effectively for sinusoidal movements. Similar EMG activity was detected in not paratonic muscles.

Conclusions: paratonia increases with normal ageing and cognitive decline progression. While facilitatory paratonia is due to involuntary contraction of the shortening muscle, oppositional paratonia is due, at least partially, to involuntary contraction of the lengthening muscle. Most characteristic feature of this muscle contraction is the progressive increase with movement repetition, that helps distinguish oppositional paratonia from spasticity and rigidity. A similar EMG activity is detected in not paratonic muscles, showing that, during tone

assessment, the descending motor system is incompletely inactivated also in normotonic muscles.

Keywords muscle tone; rigidity; cognitive impairment; dementia; frontal lobe; mild cognitive impairment; Alzheimer's disease

Glossary BPM = beats per minute; FacEMG = facilitatory electromyographic activity; FacPS = facilitatory paratonia scale; IQR = inter-quartile range; MIVC = maximum isometric voluntary contraction; OppEMG = oppositional electromyographic activity; OppPS = oppositional paratonia scale

INTRODUCTION

Paratonia is a form of altered muscle tone. First observed by Dupré in 1910, it was described as ‘‘*an inability to relax muscles in the setting of cognitive impairment*’’ [1]. It manifests in two opposite ways: oppositional paratonia (also called “*gegenhalten*”) when the subject resists passive movements [2] and facilitatory paratonia (also called “*mitgehen*”) when the subject acts in the same direction of passive movements [3,4]. Paratonia is considered a cortically generated frontal disinhibition sign [4,5]. Although oppositional and facilitatory paratonia often coexist in the same patient [4,6], in the early stages of cognitive impairment facilitatory paratonia predominates, whereas in the late stages oppositional paratonia prevails [7]. In general, prevalence estimations of paratonia in cognitively impaired people are highly variable and mostly drawn by studies focusing on oppositional paratonia alone [8–11].

As other well-known frontal cortical disinhibition signs (e.g. snout, glabellar, grasp, palmomental, etc.), paratonia is typically present in childhood, inhibited during normal development, and may reappear in normal elderly [12,13]. Prevalence estimations of oppositional paratonia are highly variable in healthy elderly people [11,13–15], while facilitatory paratonia has never been investigated.

Distinguishing oppositional paratonia from other forms of muscle hypertonia, namely spasticity and rigidity, may be challenging [16]. An expert consensus [7] and the paratonia assessment instrument (PAI) [10] provide some clues to guide the diagnosis based on the observations made in clinical practice. Unlike rigidity, oppositional paratonia is velocity-dependent; unlike spasticity, it is evenly distributed in flexor and extensor muscles, and shows no clasp-knife phenomenon [7,17].

Unfortunately, clinical experience shows that these clues do not suffice, at least in some patients. Although rigidity is considered as a constant resistance to passive movement

irrespective that the limb is moved slowly or rapidly [18], studies show that rigidity can be sometimes velocity-dependent [19,20]. Additionally, whereas spasticity is thought predominant in upper limb flexors and lower limb extensors, several exceptions to this classical rule are found [21]. It is not uncommon to observe, for example, patients with spasticity either prevailing in the upper limb in extensor muscles or being evenly distributed in flexor and extensor muscles. Finally, though pathognomonic of spasticity, clasp-knife phenomenon is best observed in the quadriceps [21,22], while may be absent in the other muscles [23,24].

Clinical features and patho-physiological mechanisms of rigidity and spasticity have been the object of many studies conducted with electromyography (EMG) [21,25], but very little attention has been paid to paratonia. A few years ago, using this technique in a small number of people with cognitive impairment, we reported as a consistent feature of paratonia, that both "*gegenhalten*" and "*mitgehen*" progressively increased with the repetition of the passive movement applied to the limb [26]. If confirmed in a larger population, this observation should be crucial for distinguishing paratonia from spasticity and rigidity. Indeed, spasticity decreases with passive movement repetition [27–29]. As far as rigidity is involved, to our knowledge a progressive increase with passive movement repetition was never reported.

The main objectives of this study are three. First, to assess the prevalence of oppositional and facilitatory paratonia in patients with cognitive impairment and in healthy subjects. Second, to investigate in these two groups of subjects the characteristics of EMG bursts underlying paratonia, i.e., whether they change according to the number, type, and velocity of passive movement repetition. Third, to ascertain whether passive movements evoke EMG activity also in not paratonic muscles and to see whether this activity, if present, shares some features with that recorded in paratonic ones.

METHODS

Patients and healthy subjects

Patients with Alzheimer's disease (AD) or mild cognitive impairment (MCI) were recruited from the out-patient clinic for cognitive disorders at the Geriatric Memory Clinic, Geriatric Clinic, University Hospital "IRCCS Ospedale Policlinico San Martino" of Genova, Italy. The diagnosis of dementia of Alzheimer type was made according to the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) Alzheimer Disease and Related Disorders Association (ADRDA) criteria [30]. Clinical diagnosis of MCI was made according to Petersen revised criteria [31].

Elderly healthy subjects (seniors) were recruited among caregivers and unit staff; young healthy subjects (juniors) were recruited among residents and PhD students. All seniors were screened to confirm the lack of cognitive impairment. All participants or their legal guardians gave informed consent to all study procedures, which were performed according to the Declaration of Helsinki. This observational study was notified to the local ethics committee.

Clinical assessment of paratonia

Participants (both patients and healthy subjects) were evaluated on their non-dominant upper limb. To evaluate paratonia clinically, they were seated with the arms in their lap, and they were asked to remain relaxed during the whole procedure. The examiner, blinded to the diagnosis, while holding the wrist of the participant, passively mobilized her/his elbow joint throughout its range, as usually done to assess muscle tone [26,32]. The Paratonia Scale was used to rate both facilitatory paratonia (Facilitatory Paratonia Scale, FacPS) and oppositional paratonia (Oppositional Paratonia Scale, OppPS). Scoring is as follows: 0 = no paratonia (facilitatory or oppositional); 1 = trace paratonia (minimal assistance or resistance offered to

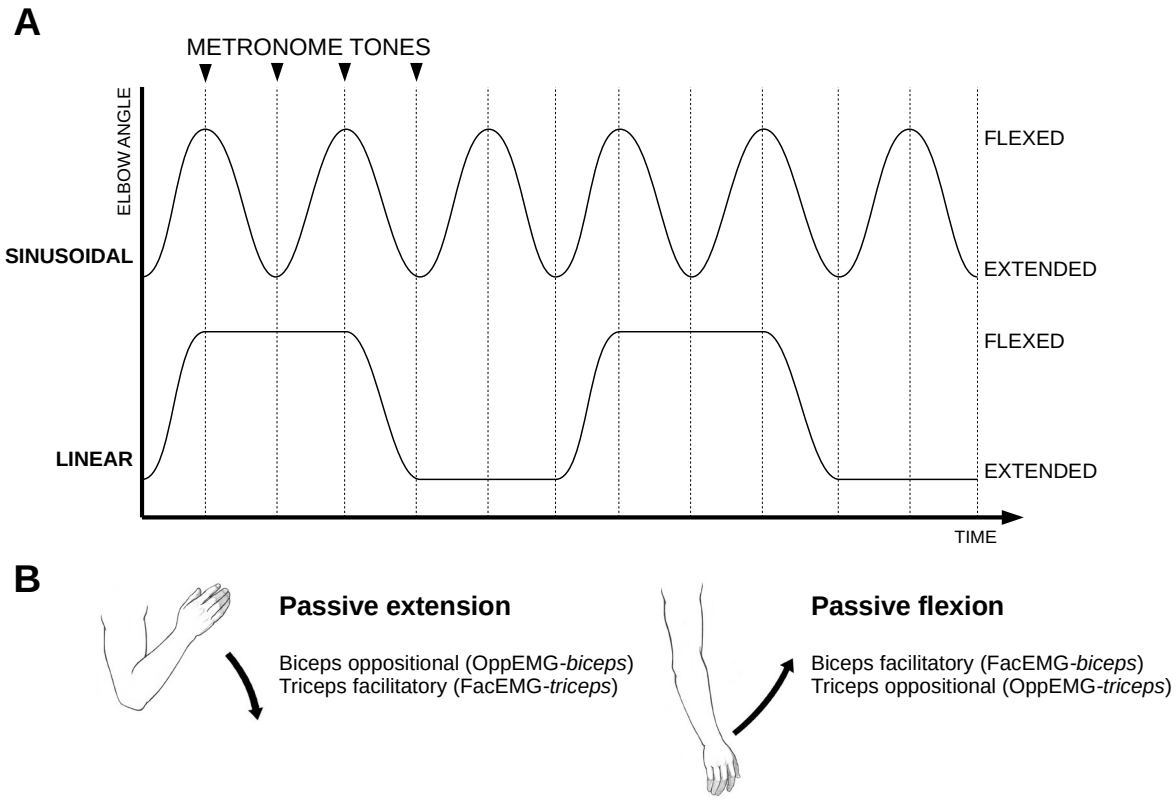
passive movement at elbow); 2 = moderate paratonia (moderate degree of assistance or resistance offered to passive movement at elbow); 3 = severe paratonia (marked degree of assistance or resistance offered to passive movement at elbow); 4 = extreme paratonia (full assistance offered to movement, or resistance offered is difficult to overcome) [4].

EMG assessment of paratonia

Surface preamplified electrodes with fixed inter-electrode distance (TSD150B, Biopac Systems Inc, USA) were placed over the muscle belly of biceps and triceps brachii of the left side according to SENIAM guidelines [33]. Elbow joint angle was monitored by an electronic goniometer placed across the joint (TSD130B, Biopac Systems Inc, USA). All signals were acquired by a Biopac MP100 unit (Biopac Systems Inc, USA) for offline analysis.

Participants and the examiner repeated an experimental paradigm described previously [26,32]. Briefly, the examiner applied repeated consecutive passive flexion-extension elbow movements (sinusoidal continuous movements) paced by consecutive metronome tones, so that maximal elbow flexion and subsequent maximal elbow extension positions corresponded to two consecutive metronome beats. Changing the number of beats per minute (BPM) resulted in different passive movement velocities. To obtain non-sinusoidal, discontinuous movements (also called linear movements), the examiner waited for a few metronome beats (randomly 1 to 4) while at maximal flexion or extension position, before performing the forthcoming movement, at the same velocity determined by BPM (Fig. 1).

Figure 1 - Sinusoidal and linear movements



(**A**) Consecutive or discontinuous passive flexion and extension elbow movements synchronized with metronome tones determine sinusoidal and linear conditions respectively. (**B**) Passive elbow extension is accompanied by involuntary EMG activity of biceps brachii that opposes to the passive movement (OppEMG-*biceps*) and EMG activity of triceps that facilitates it (FacEMG-*triceps*). Similarly, elbow flexion may be accompanied by involuntary EMG activity of the biceps brachii that facilitates the passive movement (FacEMG-*biceps*) and EMG activity of the triceps that opposes it (OppEMG-*triceps*).

To verify the subject's ability to remain relaxed, the EMG activity was recorded for 30 s preceding the onset of passive movements. Afterwards, the following 4 blocks of 15 consecutive flexion-extension movements were randomly collected: 1) 15 sinusoidal flexion-extension movements at 60 BPM; 2) 15 sinusoidal flexion-extension movements at 100 BPM; 3) 15 linear flexion-extension movements at 60 BPM; 4) 15 linear flexion-extension movements at 100 BPM.

Velocity values of 60 and 100 BPM were chosen based on our previous studies aimed to assess muscle tone in the upper limbs [26,32]. These values were different enough to explore the effect of movement velocity, they were fast enough to permit the examiner to follow the metronome beats accurately, and they were slow enough to prevent fatigue in the examiner and discomfort in the subject.

EMG analysis

After visual inspection of raw data in order to reject artefacts, EMG data were filtered (band pass 20-250Hz) and rectified. For each one of the 15 flexion-extension movements of a block, EMG activity of the flexion phase (from the point of maximum extension to that of maximum flexion) and EMG activity of the extension phase (from the point of maximum flexion to that of maximum extension) were measured using the "mean EMG" function of the AcqKnowledge software (version 4.2, Biopac Systems Inc, USA), thus obtaining an average amplitude independently of movement duration. During the flexion phase, the activity from the biceps was considered facilitatory (FacEMG-*biceps*), while that from the triceps oppositional (OppEMG-*triceps*). The reverse was true during the extension phase: biceps activation was considered oppositional (OppEMG-*biceps*) and triceps activation was considered facilitatory (FacEMG-*triceps*). Considering all 4 blocks, in each subject 60

FacEMG-*biceps*, 60 FacEMG-*triceps*, 60 OppEMG-*biceps* and 60 OppEMG-*triceps* were measured.

In each subject, three 5 s periods of maximal isometric contractions were recorded from biceps and triceps, separated by 30 s resting intervals. Each one of these periods was divided into 500 ms time bins, and for each bin the "mean EMG" was measured. The highest value among the measured bins was considered as the maximal isometric voluntary contraction (MIVC).

Statistical analysis

To compare clinical scores (FacPS, OppPS) and EMG activity (FacEMG, OppEMG) of the 4 groups (AD, MCI, seniors and juniors), we used Kruskal-Wallis test for multiple comparisons and Mann-Whitney test for individual comparisons. Correlation analyses between clinical scores (FacPS, OppPS) and corresponding EMG measures (FacEMG, OppEMG) were performed using Spearman rank test (Rho ρ values corrected for ties are reported). FacEMG and OppEMG were calculated as the average value of all the 120 facilitatory and oppositional "mean EMG values" respectively, without distinguishing between biceps and triceps, as during clinical evaluation.

For further analysis, we distinguished biceps from triceps (FacEMG-*biceps*, FacEMG-*triceps*, OppEMG-*biceps* and OppEMG-*triceps*). In order to compare mean EMG between patients plausibly, EMG measures were normalized to MIVC of the corresponding muscle (biceps or triceps), thus obtaining a percentage value ranging from 0 (no EMG activity) to 100 (maximal EMG activity). Normalized values of FacEMG-*biceps* and FacEMG-*triceps* were compared between people with FacPS>0 and those with FacPS=0 using Mann-Whitney test. Similarly, normalized values of OppEMG-*biceps* and OppEMG-*triceps* were compared between people

with OppPS>0 and those with OppPS=0. Mann-Whitney test was also used to compare EMG amplitude between paratonic muscles of participants with (AD and MCI) and without (seniors and juniors) cognitive impairment. Furthermore, normalized values of FacEMG-*biceps*, FacEMG-*triceps*, OppEMG-*biceps* and OppEMG-*triceps* underwent mixed model-ANOVA with movement type (sinusoidal/linear) and movement speed (slow/fast) as between-subjects factors, and movement repetition (1-15) as within-subjects factor. Finally, a factorial ANOVA was performed to compare FacEMG-*biceps* vs. FacEMG-*triceps*, and to compare OppEMG-*biceps* vs. OppEMG-*triceps*. Both repeated measures- and factorial ANOVA were performed separately in participants exhibiting paratonia and participants who did not, and in paratonic cognitively impaired patients (AD and MCI) and paratonic healthy subjects (seniors and juniors).

RESULTS

We examined 99 participants: 18 with AD (15 women, median age 81 years, IQR 78-85); 21 with MCI (12 women, median age 80 years, IQR 78-83); 30 seniors (20 women, median age 79 years, IQR 75-82); 30 juniors (15 women, median age 28 years, IQR 27-31 years) (Table 1).

Clinical findings

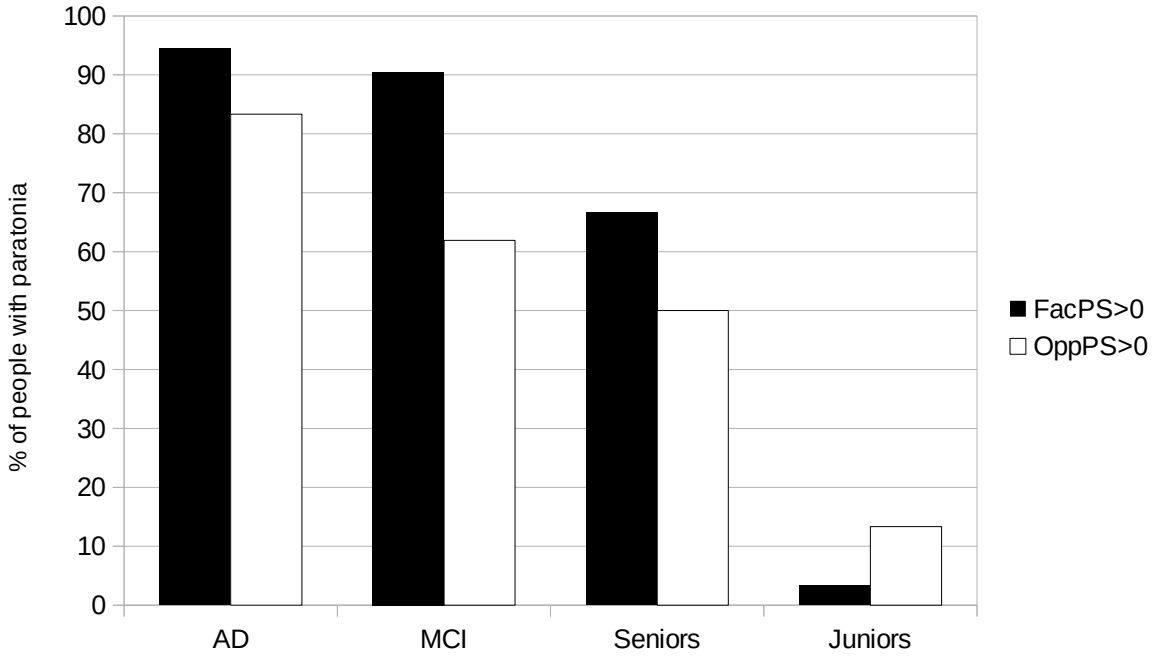
All participants were right-handed, so all were evaluated on their left non-dominant side. OppPS scored >0 (i.e., indicating oppositional paratonia) in 15 AD subjects (83%), 13 MCI subjects (62%), 15 seniors (50%) and 4 juniors (13%). FacPS scored >0 (i.e., indicating facilitatory paratonia) in 17 AD subjects (94%), 19 MCI subjects (90%), 20 seniors (67%) and 1 junior (3%) (Fig. 2 & Table 1).

Table 1 - Subjects and clinical paratonia scores

	n	Age	FacPS	OppPS	FacPS=0 & OppPS>0	FacPS>0 & OppPS=0	FacPS=0 & OppPS=0	FacPS>0 & OppPS>0
AD patients	18	81 (78-85)	2 (1-3)	2 (1-2)	0 (0.0%)	2 (11.1%)	1 (5.6%)	15 (83.3%)
MCI patients	21	80 (78-83)	2 (2-3)	1 (0-1)	0 (0.0%)	6 (28.6%)	2 (9.5%)	13 (61.9%)
Seniors	30	77 (73-80)	1 (0-2)	1 (0-1)	3 (10.0%)	8 (26.7%)	7 (23.3%)	12 (40.0%)
Juniors	30	28 (27-31)	0 (0-0)	0 (0-0)	3 (10.0%)	0 (0.0%)	26 (86.7%)	1 (3.3%)

Age and scores of facilitatory (FacPS) and oppositional (OppPS) paratonia are expressed as mean (I-III inter-quartile range). The number of subjects with (>0) or without (=0) facilitatory paratonia or oppositional paratonia are reported as absolute number (%).

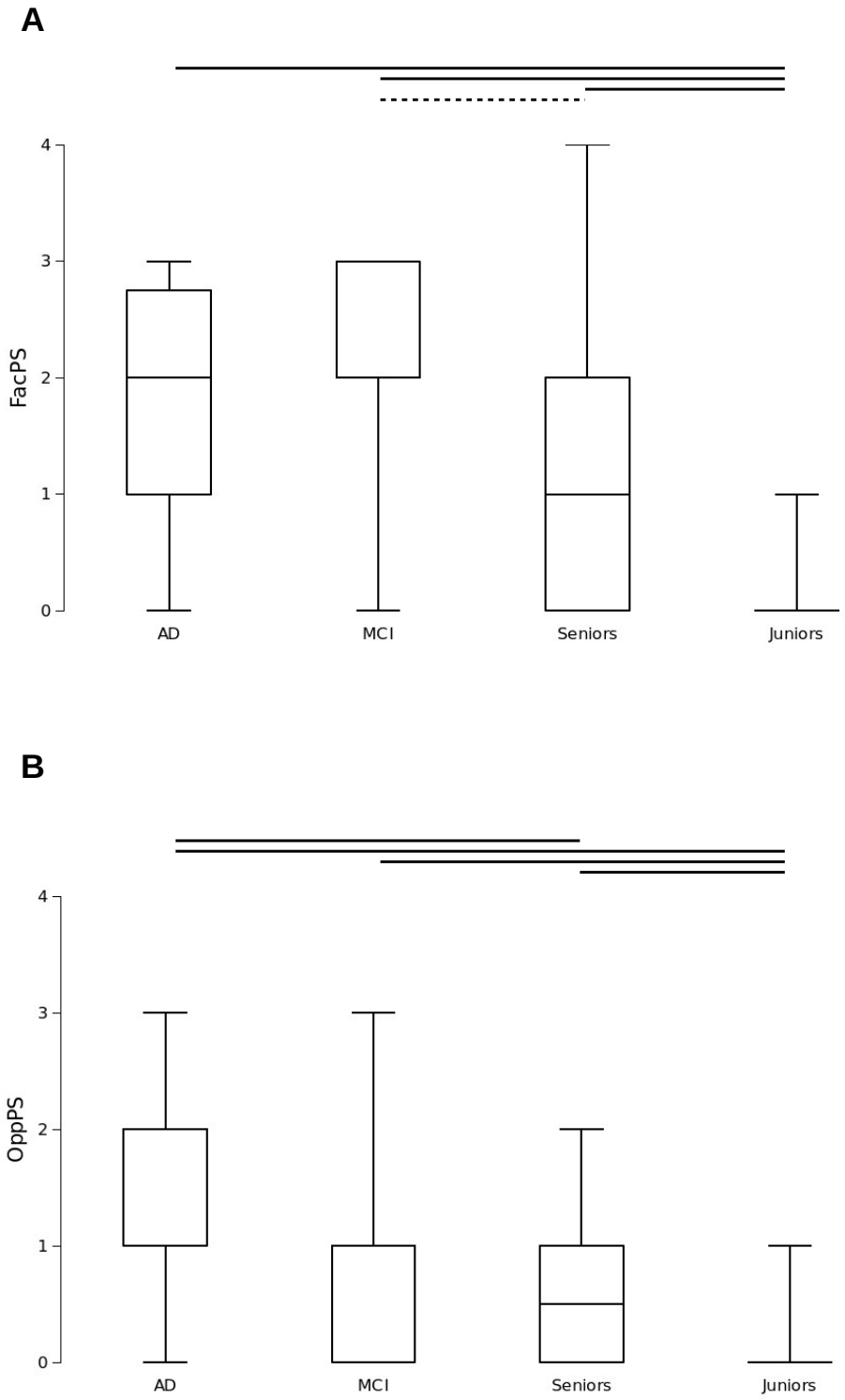
Figure 2 - Prevalence of paratonia



The prevalence of paratonia among the 4 groups is reported distinguishing those with facilitatory paratonia (FacPS>0) and those with oppositional paratonia (OppPS>0). The prevalence of paratonia increases with ageing, as well as with cognitive deterioration.

Clinical scores differed among groups (OppPS $p<0.0001$, FacPS $p<0.0001$). In comparison to juniors, seniors had higher OppPS scores ($p=0.009$) and FacPS scores ($p<0.0001$). In comparison to seniors, AD had higher OppPS scores ($p=0.006$), while MCI had higher FacPS scores ($p=0.011$) (Fig. 3).

Figure 3 - Comparison of paratonia scores (FacPS and OppPS) among groups



Box plot of paratonia scale scores for facilitatory (FacPS) and oppositional (OppPS) paratonia among groups. Solid bars indicate $p<0.01$ difference between groups, dashed bar $p<0.05$. As for prevalence (Fig. 2), facilitatory and oppositional paratonia scores increase with ageing and cognitive deterioration.

Facilitatory EMG activity (FacEMG-biceps and FacEMG-triceps) in participants with facilitatory paratonia (FacPS>0) and oppositional EMG activity (OppEMG-biceps and OppEMG-triceps) in participants with oppositional paratonia (OppPS>0)

Facilitatory EMG activity correlates with clinical scores of facilitatory paratonia, while oppositional EMG activity correlates with clinical scores of oppositional paratonia

Prior to passive movements, no EMG activity was recorded in any of the subjects.

In all the 57 subjects scoring FacPS>0 and in all the 47 subjects scoring OppPS>0, clear EMG activity respectively facilitating the passive movement (FacEMG-*biceps* and/or FacEMG-*triceps*), or opposing to the passive movement (OppEMG-*biceps* and/or OppEMG-*triceps*) was found. This EMG activity varied in amplitude across the 60 passive movements applied to each participant, occasionally being absent in some of these movements (Fig. 4A).

In the 57 participants scoring FacPS>0, FacPS and FacEMG positively correlated ($\rho=0.31$, $p=0.019$). Similarly, a positive correlation between OppPS and OppEMG emerged in the 47 participants scoring OppPS>0 ($\rho=0.33$, $p=0.026$).

Facilitatory and oppositional EMG activity increases with passive movement repetition

In participants scoring FacPS>0, FacEMG-*biceps* ($F[14,3178]=15.2$, $p<0.0001$) and FacEMG-*triceps* ($F[14,3178]=5.3$, $p<0.0001$) increased with movement repetition (from 1st to 15th repetition) (Fig. 5A).

Similarly, in participants with OppPS>0, OppEMG-*biceps* ($F[14,2618]=28.8$, $p<0.0001$) and OppEMG-*triceps* ($F[14,2618]=10.9$, $p<0.0001$) increased with movement repetition (Fig. 6A).

Facilitatory and oppositional EMG activity increases more effectively during sinusoidal than linear movements

In participants with FacPS>0, a significant interaction "repetition X type" was present for FacEMG-*triceps* ($F[14,3164]=1.8$, $p<0.035$), indicating that sinusoidal movements increased facilitatory EMG activity across repetitions more steeply than linear movements (Fig. 5A).

In subjects with OppPS>0, OppEMG-*biceps* was greater during sinusoidal movements than during linear movements ($F[1,186]=4.9$, $p=0.028$); moreover, a significant interaction "repetition X type" was present for OppEMG-*biceps* ($F[14,2604]=8.4$, $p<0.0001$), indicating that sinusoidal movements increased oppositional EMG activity more steeply than linear movements (Fig. 6A).

Facilitory and oppositional EMG activity are velocity-dependent

In participants scoring FacPS>0, FacEMG-*biceps* was greater for fast than slow movements ($F[1,226]=5.4$, $p=0.021$).

In participants scoring OppPS>0, OppEMG-*triceps* was greater for fast than slow movements ($F[1,178]=6.4$, $p=0.01$) (Fig. 5A-6A).

Facilitatory and oppositional EMG activity in cognitively impaired patients are larger in amplitude than those found in healthy subjects, but in both groups the EMG activity shares similar features

Facilitatory (FacEMG-biceps and/or FacEMG-triceps) and oppositional (OppEMG-biceps and/or OppEMG-triceps) EMG activity had higher amplitude in paratonic cognitively impaired patients (17 AD and 19 MCI patients) than in paratonic healthy subjects (23 seniors and 4 juniors) ($F[1,1006]=6.3$, $p=0.012$).

In both paratonic cognitively impaired patients ($F[14,8050]=28.0$, $p<0.0001$) and paratonic healthy subjects ($F[14,6034]=21.6$, $p<0.0001$), EMG amplitude increased during the 15 passive movements.

In both paratonic cognitively impaired patients ($F[1,574]=5.0$, $p=0.026$) and paratonic healthy subjects ($F[1,430]=5.9$, $p=0.016$), EMG amplitude increased with movement velocity.

Facilitatory EMG activity (FacEMG-biceps and FacEMG-triceps) in participants without facilitatory paratonia (FacPS=0) and oppositional EMG activity (OppEMG-biceps and OppEMG-triceps) in participants without oppositional paratonia (OppPS=0)

EMG reveals a clinically undetected facilitatory and oppositional muscle activation during passive movements

Prior to passive movements, no EMG activity was recorded in any of the participants.

In 40 out of the 42 subjects scoring FacPS=0 and in 51 of the 52 subjects scoring OppPS=0, a clear EMG activity respectively facilitating the passive movement (FacEMG-*biceps* and/or FacEMG-*triceps*) or opposing to the passive movement (OppEMG-*biceps* and/or OppEMG-*triceps*) appeared in at least one muscle. This EMG activity, highly variable in amplitude from movement to movement - and sometimes completely absent - was lower in amplitude than that recorded in subjects with paratonia ($p<0.0001$) (Fig. 4-5-6).

Clinically undetected facilitatory and oppositional EMG activity increases with passive movement repetition

In participants scoring FacPS=0, FacEMG-*biceps* ($F[14,2338]=8.2$, $p<0.0001$) and FacEMG-*triceps* ($F[14,2338]=2.8$, $p<0.008$) increased with movement repetition (Fig. 5B).

The same took place in subjects with OppPS=0 (OppEMG-*biceps* $F[14,2898]=7.9$, $p<0.0001$; OppEMG-*triceps* $F[14,2898]=4.7$, $p<0.0001$) (Fig. 6B).

Clinically undetected facilitatory and oppositional EMG activity increases more effectively during sinusoidal than linear movements

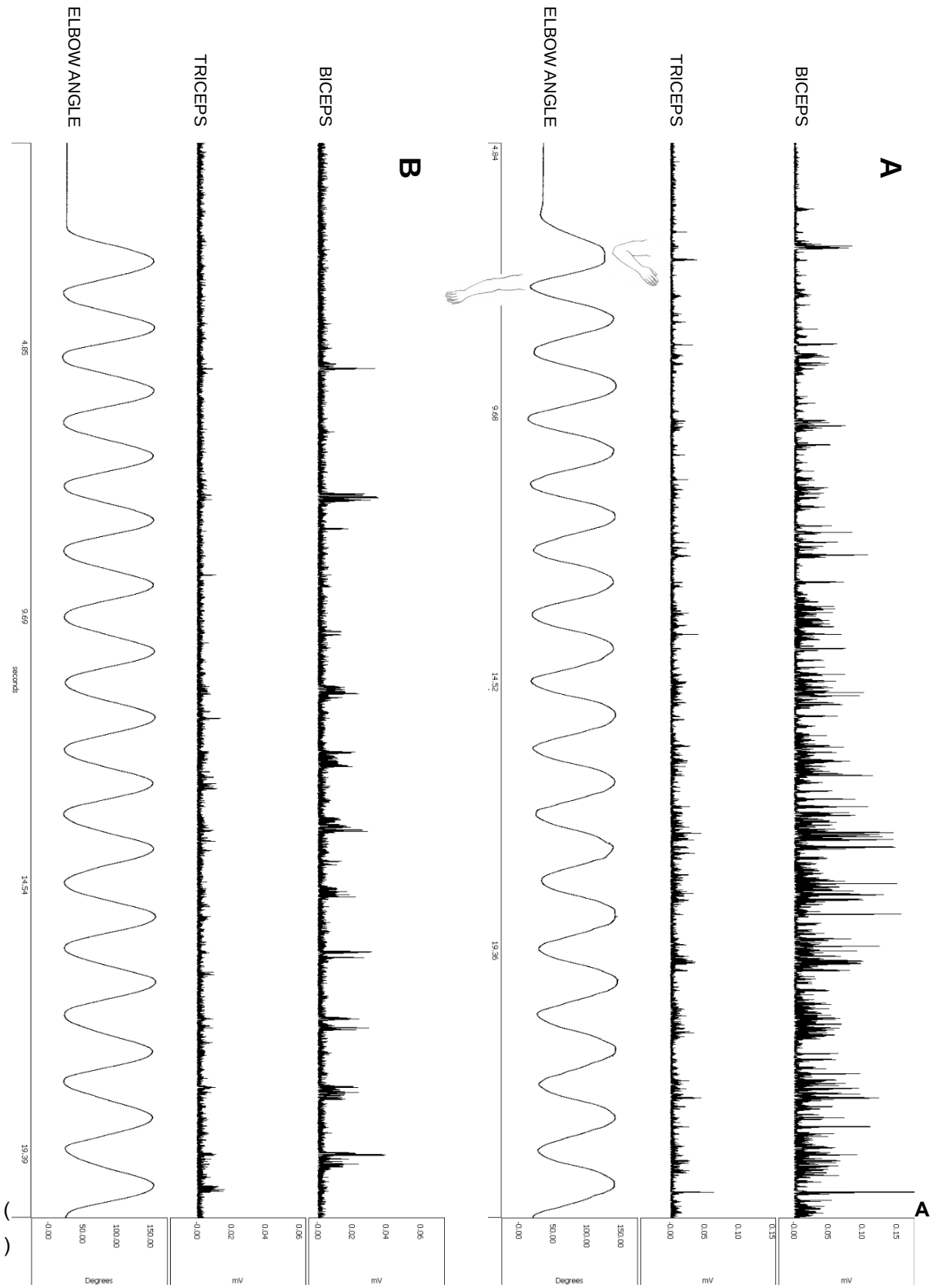
In participants scoring FacPS=0, a significant interaction "repetition X type" was present for FacEMG-*biceps* ($F[14,2324]=1.7$, $p=0.048$), indicating that facilitatory EMG activity increased more steeply during sinusoidal movements (Fig. 5B).

In participants with OppPS=0, a significant interaction "repetition X type" was present for OppEMG-biceps ($F[14,2884]=5.3$, $p<0.0001$), indicating that oppositional EMG activity increased more steeply during sinusoidal movements (Fig. 6B).

Clinically undetected oppositional EMG activity is velocity-dependent

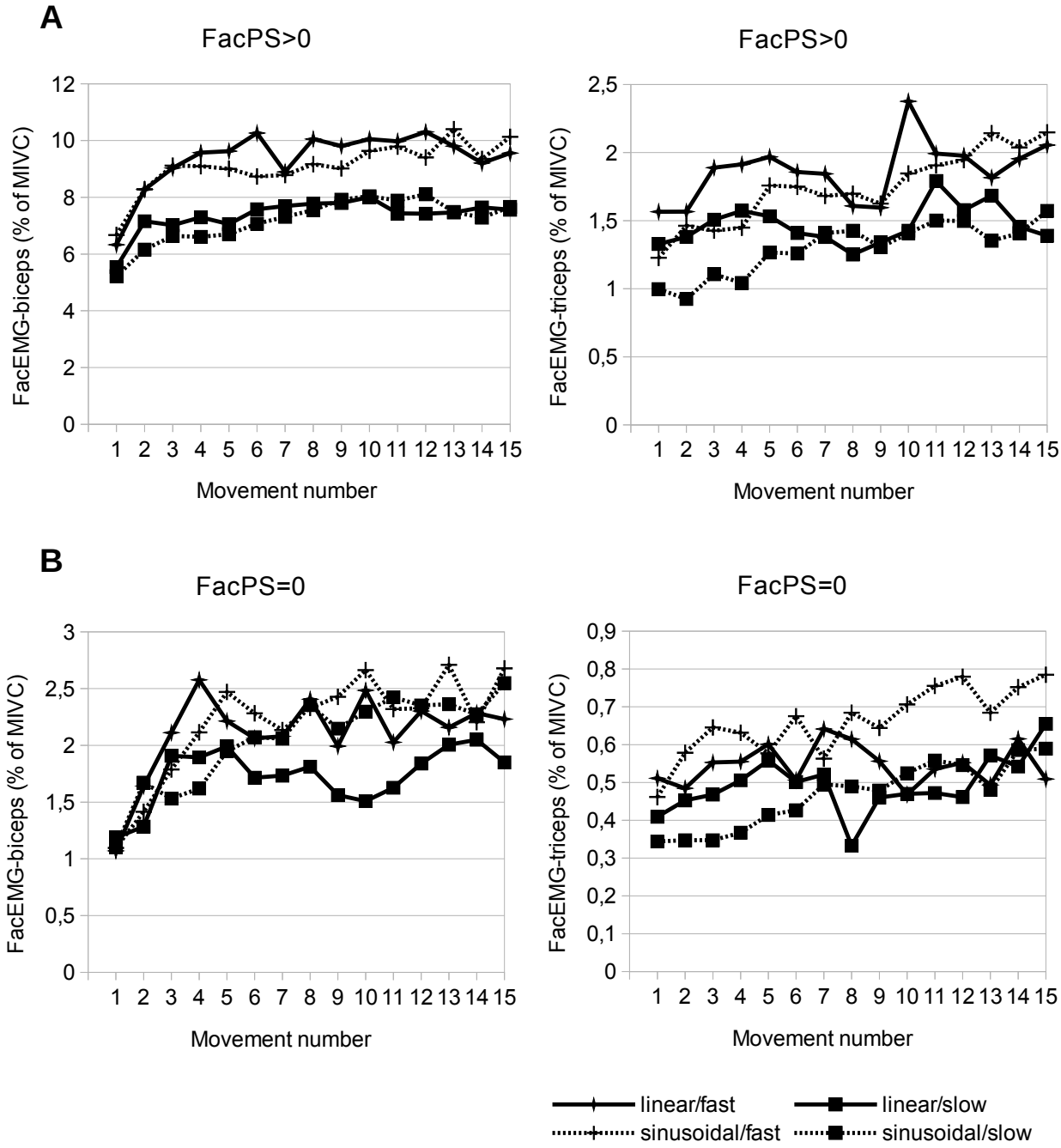
In subjects scoring OppPS=0, OppEMG-*triceps* was greater for fast than slow movements ($F[1,206]=4.0$, $p=0.048$) (Fig. 6B).

Figure 4 - Representative EMG recordings



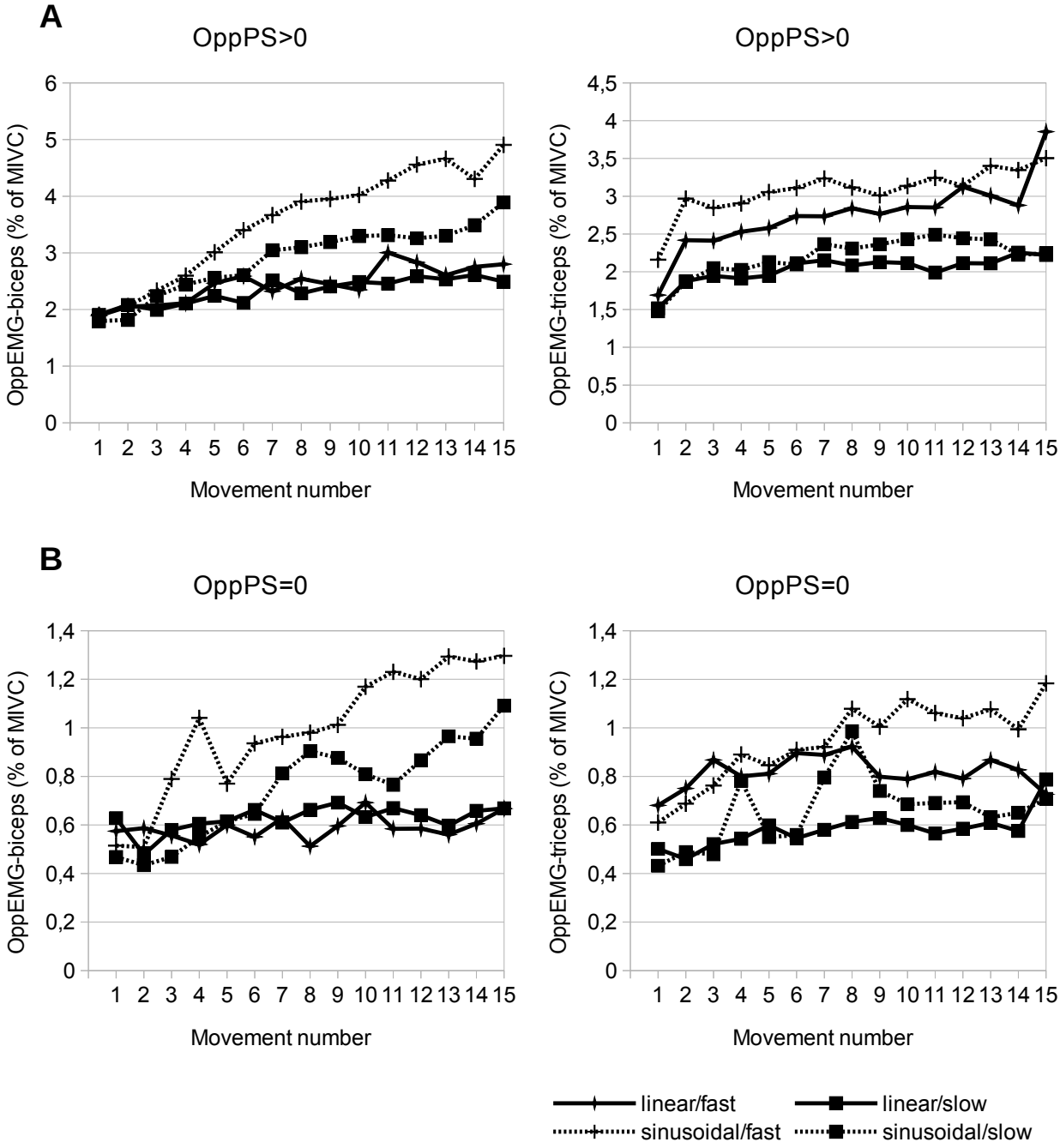
Sinusoidal recording at 100 BPM in a subject with mild paratonia (FacPS=1, OppPS=1). Before the start of passive movements, the subject is completely relaxed. On the contrary, during the 15 passive flexion-extension movements, a progressively increasing EMG activity (both facilitatory and oppositional) becomes evident. (**B**) Sinusoidal recording at 100 BPM in a subject without paratonia (FacPS=0, OppPS=0). EMG activity appears during passive movements as in the subject with paratonia. However, burst amplitude is much lower (notice the scale on the right side).

Figure 5 - Facilitatory EMG activity during the 15 movements



For each of the 4 tested conditions (sinusoidal slow movements at 60BPM, sinusoidal fast movements at 100BPM, linear slow movements at 60BPM, linear fast movements at 100BPM), the mean amplitude of facilitatory EMG activity in biceps (left part) and in triceps (right part) is plotted. In (**A)**, each point represents the mean amplitude among the 57 participants with facilitatory paratonia (FacPS>0). In (**B)**, each point represents the mean amplitude among the 42 participants without facilitatory paratonia (FacPS=0).

Figure 6 - Oppositional EMG activity during the 15 movements



For each of the 4 tested conditions (sinusoidal slow movements at 60BPM, sinusoidal fast movements at 100BPM, linear slow movements at 60BPM, linear fast movements at 100BPM), the mean amplitude of oppositional EMG activity in biceps (left part) and in triceps (right part) is plotted. In (**A)**, each point represents the mean amplitude among the 47 people with oppositional paratonia (OppPS>0). In (**B)**, each point represents the mean amplitude among the 52 people without oppositional paratonia (OppPS=0).

DISCUSSION

Clinical results (FacPS and OppPS scores)

Whereas in young healthy subjects (juniors) both prevalence of facilitatory (3%) and of oppositional paratonia (13%) were low, in seniors not only the prevalence of facilitatory paratonia (67%) and that of oppositional paratonia (50%) were high, but also, they were significantly higher than the values reported in previous studies. As stated in the Introduction, in the previous studies conducted in healthy participants, prevalence of oppositional paratonia varied widely from 0 to 21% [11,13–15,34]. A progressive increase in paratonia may occur with age, as shown by the present study and others published beforehand, for instance the study of a large cohort of 2029 subjects [13]. In addition, the variability of prevalence in healthy elderly greatly depends on the different methods used to assess paratonia. For example, the study that found no paratonia [15] is the only one to have used the PAI, a tool developed to assess paratonia in patients with cognitive impairment. According to this tool, to diagnose paratonia, not only the examiner must appreciate the increased resistance to passive mobilization, but also this resistance must correlate with the velocity of passive movement and be felt both in flexion and in extension [10]. Quite distinctly, our study is the only one to have used the "paratonia scale" [4], which discloses paratonia as soon as the examiner perceives any resistance to passive movement that is beyond the normal muscle tone. This may explain the higher rate of positive in the normal population found here.

In participants with cognitive impairment, we found that prevalence and severity of paratonia (both facilitatory and oppositional) were greater than in seniors, in line with the literature [17]. In comparison to seniors, facilitatory paratonia was more pronounced in MCI and oppositional paratonia in AD, confirming that facilitatory paratonia prevails in the initial

stages of cognitive impairment while oppositional paratonia is detected more frequently in overt dementia [10].

Denny-Brown first related oppositional paratonia to frontal lobe dysfunction [5]. Since then, paratonia has been considered a cortically generated frontal disinhibition sign. Facilitatory paratonia has also been linked to frontal lobe dysfunction in more recent times [4]. Paratonia in seniors and patients with cognitive impairment is usually attributed to reduced inhibitory efficiency of frontal areas due to physiological ageing or pathological degeneration [17], respectively.

Our results suggest that oppositional and facilitatory paratonia frequently coexist, as observed in 41 out of 99 participants. Facilitatory paratonia alone was found in 16 participants, whereas oppositional paratonia alone only in 6; in 36 participants neither form was detected (Table 1). These findings are clinically important, because they show that: 1) paratonia is very frequent both in patients with cognitive impairment and seniors; 2) facilitatory is more frequent than oppositional paratonia; 3) since oppositional paratonia is usually associated with facilitatory paratonia, this might help discriminate oppositional paratonia from other forms of hypertonia.

EMG findings

<u>EMG can be used to measure paratonia</u>

All 47 participants exhibiting oppositional paratonia (OppPS>0) showed EMG activity in the lengthening muscle. This oppositional activity (OppEMG-*biceps* and OppEMG-*triceps*) directly correlated with paratonia severity (OppPS scores). Similarly, all 57 participants exhibiting facilitatory paratonia (FacPS>0), showed EMG activity in the shortening muscle (FacEMG-*biceps* and FacEMG-*triceps*), and this activity directly correlated with paratonia severity (FacPS scores). Correlation between clinical scores and EMG activity states that

muscle contraction is a major contributor of paratonia, confirming that EMG activity can be used to measure both facilitatory and oppositional paratonia [26].

Rather obviously, EMG activity recorded in a shortening muscle is the cause of facilitatory paratonia, since no reasonable mechanism other than involuntary contraction can be hypothesized. In contrast, during passive stretching, conditions other than muscle contraction may contribute to the resistance perceived by the examiner, i.e. increased muscle stiffness. As for spasticity and rigidity that both alter muscle biomechanics [35,36], also paratonia makes it necessary to distinguish neural-generated from mechanical-induced increased resistance, because oppositional paratonia has been found to change muscle biomechanics too [37,38]. Therefore, concurrent evaluation of clinical scores and EMG activity allows to confirm and indirectly to quantify the role of muscle contraction in the genesis of the oppositional paratonia.

EMG recordings show that paratonia does not impair the ability to relax muscles

In all participants, no EMG activity was recorded before the limb was passively mobilized by the examiner, and involuntary EMG activity always emerged during passive movements. This indicates that paratonia does not prevent the subject from relaxing completely in the absence of applied kinaesthetic stimuli. Conversely, many patients with spastic hypertonia are unable to relax even when they are sitting at rest and no passive limb movement (either lengthening or shortening their muscles) is applied to their limbs. That spontaneous, involuntary tonic contraction, is most frequent in the upper limb flexors, and is known as spastic dystonia [39].

Paratonia increases with passive movement repetition, movement type and with movement velocity

The EMG activity recorded during passive movements increased progressively with movement repetition, in both lengthening and shortening muscles. This means that severity of paratonia increases with repetitive passive movements, regardless of the facilitatory or oppositional type. Sinusoidal movements elicited severity progression more than linear movements, suggesting that the longer the kinaesthetic stimulus applied, the greater the induced paratonia. Although commonly taught and widely accepted [16], the increase of oppositional paratonia during muscle tone assessment is rather difficult to appreciate clinically, leading the physicians to overlook this important feature when differentiating oppositional paratonia from rigidity and spasticity [7,10]. But as far as we know, rigidity has never been reported to increase during passive movement repetition (i.e., lead-pipe hypertonia), whereas spasticity typically decreases on repeated muscle lengthening [27,29].

Our findings confirm that paratonia is velocity-dependent; however, this feature does not persist across all testing conditions, since only FacEMG-biceps and OppEMG-triceps (i.e. muscles activated by elbow flexion) increase with velocity. Further studies comparing movements at slower and faster speed (eg. 40 versus 120 BPM) will likely highlight this issue better.

Paratonia exhibits similar EMG features in healthy participants and in patients with cognitive impairment

In both paratonic healthy subjects and in paratonic cognitively impaired patients, EMG activity increases with the number of movement repetitions, and it is velocity-dependent. Therefore, paratonia has similar neurophysiological features regardless of whether it

manifests in healthy subjects or in cognitively impaired patients, although in the latter it shows a higher amplitude. Some may interpret these features as indicating that there is no pathological nor benign paratonia, but simply paratonia. Others may argue that the higher amplitude in patients unequivocally states a difference between healthy subjects and cognitively impaired patients. This twofold interpretation raises several questions. For example, is there a threshold that distinguishes a "healthy response" from a "pathological response"? At which stage does paratonia become disabling? When do healthy people with a paratonic EMG pattern develop paratonia? When does paratonia predict dementia? Unfortunately, data from the present study cannot give definite answers to these relevant questions, but they lay the foundations for further targeted studies.

In not paratonic muscles, EMG reveals a clinically undetected muscle activation during passive movements

In the vast majority of not paratonic muscles, EMG activity emerged in both the lengthening and shortening muscle. This EMG activity was definitely lower in amplitude than that evoked in paratonic muscles, but shared the same features, i.e., it was velocity-dependent, it increased progressively with movement repetition, and the amplitude progression was elicited more effectively by sinusoidal than linear movements.

Muscle relaxation is not the mere absence of contraction, but it is an active process that requires the activation of frontal cortical neurons [40,41]. For this reason, paratonia is rightly considered a cortically generated frontal disinhibition sign [4,5]. The present findings, showing EMG activity during tone assessment of not paratonic muscles, suggest that the efficiency of frontal cortical circuits to prevent involuntary muscle activation during passive movement is far from being perfect even in "normotonic" subjects. Therefore,

neurophysiologists are invited to feel confident to recognize the EMG activity evoked during tone assessment of normotic muscles as the subclinical counterpart of paratonia.

It must be said that we are not the first to have reported EMG activity during normal tone assessment. This EMG activity was interpreted as voluntary activity or inability to relax muscles. In 1986, recording EMG activity from the quadriceps during bilateral muscle tone assessment in 36 healthy subjects (72 muscles examined), van der Meché and van Gijn showed that 58 shortening muscles and 24 lengthening muscles respectively produced facilitatory and oppositional EMG activity. The authors interpreted this EMG activity as resulting from voluntary contraction, in their words: *"During passive movement of a limb, voluntary activity is present in most control subjects and is responsible for most of the resistance"* [42]. Also Sheean agrees that many healthy people are unable to relax during the assessment of muscle tone, this inability playing a role in the genesis of normal muscle tone: in his words *"It is very likely that our idea of normal muscle tone, which we have developed clinically, includes many people who are actually not completely relaxed"* [22].

Study limitations

Consistent with most previous works, in this study paratonia was assessed and recorded only in elbow flexors and extensors. Further studies assessing paratonia in other segments (such as wrist, knee and ankle) could confirm whether our results can be valid also outside the elbow.

Only the effects of age and cognitive impairment were investigated. However, it is possible that other clinic or demographic characteristics may impact on paratonia. For instance, some personal observations suggest that paratonia is reduced in subjects with more stringent motor control, deriving from genetic predisposition or sports training. We are planning further studies to explore this issue.

CONCLUSIONS

Paratonia becomes more prevalent and severe with normal ageing, as well as with progression of cognitive decline. Facilitatory paratonia is due to involuntary contraction of the shortening muscle, whereas oppositional paratonia is due, at least in part, to involuntary contraction of the lengthening muscle. Most characteristic feature of this muscle contraction is the progressive increase with passive movement repetition, that helps distinguish oppositional paratonia from spasticity and rigidity.

During tone assessment, EMG activity is detected also in not paratonic muscles. This electrical activity is lower than that recorded in paratonic muscles, but otherwise similar. As a result, the prevalence of paratonia cannot but depend upon the examiner's ability to appreciate muscle contractions, that genuinely emerge in almost all evaluated subjects. Clinical experience and sensitivity in detecting muscle contraction during passive movements could explain the extreme variability of literature reports on the prevalence of paratonia.

Rest assured the clinician that, while testing the muscle tone in healthy normotonic subjects attempting to remain relaxed, the descending motor system may be incompletely inactivated.

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