BRAIN COMMUNICATIONS

Sustained involuntary muscle activity in cerebral palsy and stroke: same symptom, diverse mechanisms

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Individuals with lesions of central motor pathways frequently suffer from sustained involuntary muscle activity. This symptom shares clinical characteristics with dystonia but is observable in individuals classified as spastic. The term spastic dystonia has been introduced, although the underlying mechanisms of involuntary activity are not clarified and vary between individuals depending on the disorder. This study aimed to investigate the nature and pathophysiology of sustained involuntary muscle activity in adults with cerebral palsy and stroke. Seventeen adults with cerebral palsy (Gross Motor Function Classification System I–V), 8 adults with chronic stroke and 14 control individuals participated in the study. All individuals with cerebral palsy or stroke showed increased resistance to passive movement with Modified Ashworth Scale >1. Two-minute surface EMG recordings were obtained from the biceps muscle during attempted rest in three positions of the elbow joint; a maximally flexed position, a 90-degree position and a maximally extended position. Cross-correlation analysis of sustained involuntary muscle activity from individuals with cerebral palsy and stroke, and recordings of voluntary isometric contractions from control individuals were performed to examine common synaptic drive. In total, 13 out of 17 individuals with cerebral palsy and all 8 individuals with stroke contained sustained involuntary muscle activity. In individuals with cerebral palsy, the level of muscle activity was not affected by the joint position. In individuals with stroke, the level of muscle activity significantly ($P < 0.05$) increased from the flexed position to the 90 degree and extended position. Cumulant density function indicated significant short-term synchronization of motor unit activities in all recordings. All groups exhibited significant coherence in the alpha (6–15 Hz), beta (16–35 Hz) and early gamma band (36–60 Hz). The cerebral palsy group had lower alpha band coherence estimates, but higher gamma band coherence estimates compared with the stroke group. Individuals with increased resistance to passive movement due to cerebral palsy or stroke frequently suffer sustained involuntary muscle activity, which cannot exclusively be described by spasticity. The sustained involuntary muscle activity in both groups originated from a common synaptic input to the motor neuron pool, but the generating mechanisms could differ between groups. In cerebral palsy it seemed to originate more from central mechanisms, whereas peripheral mechanisms likely play a larger role in stroke. The sustained involuntary muscle activity should not be treated simply like the spinal stretch reflex mediated symptom of spasticity and should not either be treated identically in both groups.

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Graphical Abstract
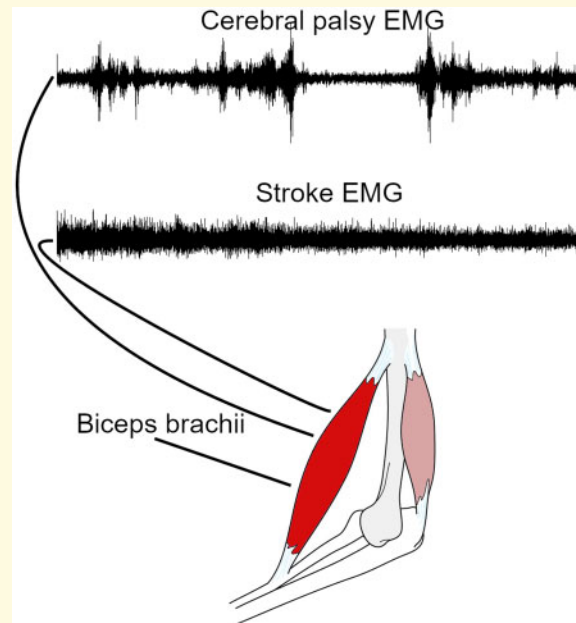
Introduction

A lesion to the central motor pathways is often followed by a development of muscle overactivity that causes body deformities and decreases joint mobility (Gracies, 2005; Sheean and McGuire, 2009; Lorentzen *et al.*, 2018).

The term muscle overactivity is not precise as it includes several different conditions that although presumed pathologically distinct are not always easily distinguishable. This can be the cause of confusion and misunderstanding among clinicians and researchers. The confusion is frequently encountered in the discussion of symptoms and classifications of cerebral palsy (CP) but can also be related to other conditions of central motor lesions such as stroke.

In the clinic, definitions by the Surveillance of Cerebral Palsy in Europe (SCPE) are commonly used to distinguish types of CP. The SCPE characterizes spastic CP by the symptoms abnormal pattern of posture and/or movement, persistently increased muscle tone and pathological reflexes (Cans, 2008). In research settings, however, the term muscle tone is often not considered scientifically precise enough, and we therefore prefer to use the term increased resistance to passive movement, which we believe refers to the same phenomenon. The definition of spasticity, as an 'enhancement of the velocity-dependent stretch responses' (Lance, 1980; Gracies, 2005), which is frequently used in research publications, is therefore contained within this classification but does not cover the full range of symptoms in spastic CP. We believe that the persistent increase in muscle tone described in the SCPE classification of spastic CP is partly due to dystonia, which in relation to the spastic movement disorder could be referred to as spastic dystonia (Denny-Brown, 1966; Sheean and McGuire, 2009; Lorentzen *et al.*, 2018; Trompetto *et al.*, 2019). The condition of spastic dystonia has received little attention in the scientific literature but is described as an inability to relax the muscle, persisting despite a lack of voluntary neural activation (Gracies, 2005; Sheean and McGuire, 2009; Lorentzen *et al.*, 2018; Trompetto *et al.*, 2019). It has therefore been suggested as an important contributor to body deformities, abnormal joint mobility and increased resistance during externally applied movement of affected joints (Sheean and McGuire, 2009; Lorentzen *et al.*, 2018). It is our understanding, that the conditions of muscle overactivity causing abnormal pattern of posture and/or movement in spastic movement disorder include
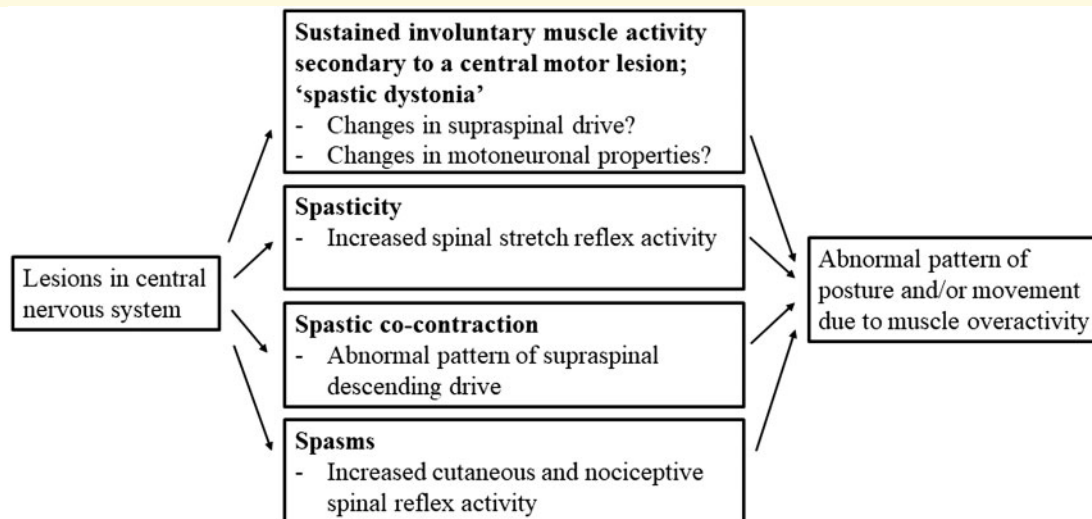
Figure 1 Muscle overactivity in spastic movement disorder. Muscle overactivity in spastic movement disorder causing abnormal patterns of posture and/or movement secondary to a central motor lesion. Adapted from Lorentzen *et al.* (2018) with permission from Elsevier.

spastic dystonia, spasticity, spastic co-contraction and spasms (Gracies, 2005; Fig. 1).

Historically, muscle overactivity following a central motor lesion has been viewed as an afferent phenomenon only, demonstrated by dorsal root section abolishing involuntary muscle activity in some animal studies (Sherrington, 1898) and individuals with spastic paralysis (Foerster, 1911). However, later studies (Pollock and Davis, 1930; Denny-Brown, 1966) found that tonic involuntary muscle contractions, indicative of spastic dystonia, persisted despite section of the dorsal roots in brain-lesioned cats and monkeys. This led to the hypothesis that the pathophysiology of spastic dystonia is, at least in part, independent of spinal stretch reflex activity. Despite these early observations on tonic muscle contractions (Pollock and Davis, 1930; Denny-Brown, 1966), the exact nature and cause of spastic dystonia remain to be explored further. Some authors propose that the severity of spastic dystonia is sensitive to the amount and duration of maintained muscle stretch (Gracies, 2005; Trompetto *et al.*, 2019) even though the phenomenon also exists in the absence of stretch or effort.

Several mechanisms have been hypothesized to be involved in spastic dystonia; changes in descending cortical- or subcortical drive [e.g. involving brainstem descending pathways (Miller *et al.*, 2014; Sukal-Moulton *et al.*, 2014a, b)], plastic changes in spinal interneuron networks and upregulation of persistent inward currents in motoneurons (Fig. 1; for reviews, see Gracies, 2005 or Lorentzen *et al.*, 2018). The treatment options for muscle overactivity are diverse, and the clinical population of individuals with muscle overactivity following central motor lesion represents several different types of lesions.

We hypothesize that the mechanisms responsible for involuntary muscle activity may vary according to the type of central motor lesion. This would promote the need for increased focus on treatment individualization. The study will, therefore, focus on two different groups with lesions to the descending motor pathways, CP and chronic stroke, differing mainly by the timing of the lesions. The brain damage during early development in CP might lead to different adaptations compared with brain damage during late adulthood in stroke. The aim of this study is, therefore, to investigate and identify the nature and pathophysiology of sustained involuntary muscle activity in individuals with CP or stroke and to relate this to the phenomenon of spastic dystonia.

Materials and methods

Participants

Two groups of individuals with movement disorder and increased resistance to passive movement [defined in this study as Modified Ashworth Scale (MAS) >1] due to central motor lesions and one group of healthy control individuals participated in the project. One group consisted of 17 adults with CP [corresponding to SCPE definition of spastic CP (Cans, 2008)] aged (mean ± SD) 43 ± 10 years (10 male, 7 female) with a Gross Motor Function Classification System (GMFCS) score from I to V. A second group consisted of eight adults with chronic stroke (>6 months since injury) and spastic hemiparesis aged 62 ± 5 years (four male, four female), all receiving treatment by botulinum toxin (onabotulinumtoxin) for muscle overactivity in the upper extremities. In this group, the injury had occurred 1–10 years ago. All experiments in the stroke group were carried out immediately before botulinum toxin injections to ensure the least

possible effect of the previous injections. The botulinum toxin injections were administered approximately every 12 weeks. No participants had undergone brachial biceps surgery (e.g. tenotomy).

The group of healthy adult control individuals aged 37 ± 13 years (five male, nine female) was recruited to obtain measurements of voluntary muscle activity to compare with the involuntary muscle overactivity in the CP and stroke group. Informed consent was obtained from all individuals participating in the study. The study was performed in accordance with the Declaration of Helsinki

and approved by the ethics committee for the capital region of Denmark (Approval no. H-16028528). Participants are further described in Table 1.

Neurological examination

All individuals with CP or stroke were neurologically examined by an experienced neurological physiotherapist with >10 years of experience with neurological examinations (J.L.). During the examination of the elbow flexors, individuals were comfortably seated. The passive range of

Table 1 Subject information

# (Type)	Age (years)	Gender	Height (cm)	Weight (kg)	Affected side/limb (-plegia)	GMFCS (CP)	MAS Elbow flexor	Reflex	ROM Elbow joint	Anti-spastic medication
1 (CP)	44	Male	174	60	Hemi	II	3	1	Full	
2 (CP)	29	Male	172	69	Hemi	II	2	0	90° flex Full ext	
3 (CP)	44	Male	155	65	Tetra	III	3	1	90° flex 145° ext	
4 (CP)	24	Female	160	55	Hemi	II	2	1	Full	
5 (CP)	29	Male	184	65	Hemi	II	3	2	Full flex 120° ext	
6 (CP)	52	Female	150	50	Tetra	III	2	0	Full	
7 (CP)	36	Female	160	65	Hemi	II	2	2	Full	
8 (CP)	40	Male	165	47	Hemi	II	2	2	Full flex 150° ext	
9 (CP)	39	Male	172	65	Tetra	V	3	1	Full	Baclofen, Dantrium, Tizanidin
10 (CP)	49	Female	170	48	Tetra	V	3	0	Full	Dantrium, Baclofen
11 (CP)	50	Male	158	68	Tetra	IV	3	2	Full flex 120° ext	-
12 (CP)	45	Male	173	76	Tetra	IV	2	2	Full flex 150° ext	Baclofen
13 (CP)	40	Male	168	76	Tetra	III	2	1	Full	Dantrium, Baclofen
14 (CP)	61	Female	145	40	Tetra	V	2	1	Full	Baclofen, Dantrium
15 (CP)	65	Male	150	65	Tetra	III	2	1	Full	Baclofen
16 (CP)	38	Female	164	83	Tetra	IV	2	0	Full flex 150° ext	Baclofen
17 (CP)	43	Female	165	45	Tetra	III	3	1	Full	Baclofen, Dantrium
18 (Stroke)	58	Female	170	83	Hemi		3	2	Full	
19 (Stroke)	70	Female	170	61	Hemi		1+	2	Full	
20 (Stroke)	60	Male	175	105	Hemi		2	1	90° flex Full ext	
21 (Stroke)	62	Female	173	80	Hemi		2	2	Full	
22 (Stroke)	64	Male	169	80	Hemi		3	2	Full flex 120° ext	
23 (Stroke)	59	Female	168	75	Hemi		3	0	Full flex 155° ext	Baclofen
24 (Stroke)	55	Male	182	80	Hemi		3	2	Full flex 100° ext	Baclofen
25 (Stroke)	71	Male	181	71	Hemi		3	0	90° flex Full ext	
AVG	37	m=5, f=9	173	73	N/A	N/A	N/A	1	N/A	N/A

0 = no reflex; 1 = normal reflex; 2 = hyperactive reflex; ext = extension; flex = flexion; GMFCS = Gross Motor Function Classification System; MAS = Modified Ashworth Scale, Reflex is rated between 0 and 2; MS = muscle strength. Magnetic resonance imaging information in Supplementary Table 1.

motion was evaluated by slowly moving the elbow joint through the movement range, noting the positions of maximal flexion and extension using a goniometer. These positions were reached without causing discomfort to the participants due to contractures and other physical constraints. Subsequently, a MAS of the elbow flexors was determined and the presence and possible exaggeration of the biceps reflex evaluated using a reflex hammer.

Electromyographic recording

In all hemiplegic individuals, EMG was recorded from the hemiplegic side. In tetraplegic individuals, EMG was recorded from the side with the highest elbow flexor MAS score. EMG was recorded from the biceps muscle using two sets of surface electrodes (3.0 × 2.2 cm, Ambu Bluesensor N, Denmark), one set placed proximally and medially on the short head of the biceps brachii and one set placed distally and laterally on the long head of the biceps brachii. These positions were chosen to minimize the risk of cross-talk between the electrodes by maximizing the distance between them. A reference electrode was placed over the lateral epicondyle of the humerus. In a single instance, increased resistance to passive movement was atypically observed in the elbow extensors only (subject 25). Though this is an unusual pattern, the individual was clearly found to have increased resistance to passive movement associated with an overactive muscle and corresponding to a spastic catch. The individual was therefore included. Here, the medial set was placed on the long head of the triceps, while the lateral set was placed on the lateral head of the triceps. The distance between electrodes inside pairs was 2 cm and the distance between pairs varied according to muscle size and length. To minimize EMG noise factors, the skin was softly sanded with a very fine grain sandpaper (3M red dot). EMG recordings were made using a portable device fitted to a forearm orthosis. The device contains two EMG channels and samples at 1024 Hz. Data are then transferred to a computer via Bluetooth. The technical properties of the device are explained more thoroughly in Yamaguchi et al. (2018).

Characterizing sustained involuntary muscle activity

All EMG recordings of attempted rest lasted 2 min. They were visually examined and recordings that contained continuous muscle activity for at least 30 s were identified. In identifying muscle activity from electrical background noise, a steady presence of EMG spikes with high amplitude and variability in the firing pattern was sought. This EMG pattern is likely to be consistent with involuntary muscle contractions and unlikely to be consistent with electrical background noise. All identified EMG recordings of muscle activity were then rectified and a root mean square (RMS) of the full recording

calculated. The two effects of muscle stretch were investigated as follows. First, the effect of elbow extension on the sustained involuntary muscle activity (RMS of the three different recordings from each individual) was normalized to the recording in the maximally flexed position. This was done to enable evaluation of stretch sensitivity across groups despite differences in raw EMG amplitudes. As both increases and decreases in muscle activity were found with increased elbow extension, we performed logarithm transformation of the EMG data to ensure equal mathematical weighing of increasing and decreasing factors in the group averaging. Secondly, the effects of maintaining the muscle in a position of stretch, on the involuntary muscle activity, were investigated by dividing the 2-min recordings into four separate 30-s time periods ('bins') and testing if the mean RMS EMG would differ between the bins.

Cross-correlation analysis

To examine the common synaptic drive to the two EMG channels of the biceps, a cross-correlation analysis was undertaken using the methods outlined in Halliday et al. (1995). The standard practice of full-wave rectification was adopted, and each recording was divided into non-overlapping segments with a duration of 1 s (1024 samples). A fast Fourier transformation was performed on each segment for frequencies up to 300 Hz and then averaged to construct estimations of the auto spectra, denoted $f_{xx}(j)$ and $f_{yy}(j)$, for each EMG channel and the cross-spectra, denoted $f_{xy}(j)$, 'j' referring to the given frequency being analysed. The cross-correlation analysis delivers results in form of the coherence, phase and cumulant density measures. 'Coherence' describes the correlation between frequency components of two processes (Rosenberg et al., 1989) and is defined for a given frequency as the absolute square of the cross-spectrum, normalized to the auto spectra of the two channels (Grosse et al., 2002). Because of this normalization procedure, the coherence values are bound to produce results between 0 and 1, with 1 meaning perfect linear association of the signals and 0 meaning no association. The objective of coherence values in this study is to estimate whether a common synaptic input to the motor neuron pool represents a significant driving force of the muscle activity, and which frequency components characterize this common synaptic drive. Where coherence describes the association in the frequency domain of the signals, the 'cumulant density function' describes the linear association in the time domain and is defined as the inverse Fourier transform of the cross-spectrum (Halliday et al., 1995). The cumulant density is an unbound measure describing the statistical dependence between the two signals with 0 meaning complete independence of the processes. A peak in the cumulant density function describes that the two signals are synchronized in time and are, therefore, used to validate the presence of a common

synaptic input to the motor neuron pool. The EMG–EMG coherence values and cumulant density functions were compared between the voluntary muscle activity of the control group and the involuntary muscle activity in both the CP and the stroke groups. To make the comparison, all results from individual recordings of muscle activity in each group were 'pooled'. Pooled coherence and cumulant density function are single representative group estimates from combining independent coherence estimates and the interpretation, therefore, is similar, except that it relays information about the group. Recordings that were contaminated by both sets of electrodes picking up the same signals (cross-talk) were identified by elevated coherence in all bands and zero phase delay (Grosse et al., 2004, 2002). Five recordings from individuals with CP, 2 recordings from individuals with stroke and 14 recordings from control individuals were excluded due to cross-talk.

Experimental design

In all individuals, paired 120-s EMG recordings from the investigated upper limb were obtained during attempted rest in three different positions; a maximally flexed position of the elbow, a 90-degree joint angle and a maximally extended position. The experimenter fixated the arm in the positions by supporting the subject's arm. In the flexed and extended positions, the experimenters made sure that the position did not cause any discomfort to the individual due to contractures and physical constraints of joint position. Between each resting recording the arm was held in a maximally flexed position for a minimum of 20 s before being placed in a new position. EMG recordings were started as soon as the individual's arm was placed in a new position. Furthermore, all control individuals were asked to perform 120 s of low-force static contractions against resistance from the experimenter corresponding to approximately 10% of maximum voluntary contraction in each position at the end of the experiment. These recordings were performed to obtain a measure of the EMG–EMG coherence from an isometric voluntary contraction of the biceps muscle that was comparable with the EMG–EMG coherence measures obtained from individuals with CP or stroke exhibiting sustained muscle activity during rest.

Statistical analysis

In analysing normalized and logarithm transformed EMG levels in different positions of the elbow joint and the difference between the 30-s bin groups mean a one-way repeated measures ANOVA was used. All data were tested for normality and equal variance before ANOVA analysis using the Shapiro–Wilk test and Brown–Forsythe test, respectively. If data failed tests for normality or equal variance, data were rank transformed before statistical analysis. It is noted in the figure legend, if the

statistical analysis was performed by ANOVA on ranks. Multiple pairwise comparisons were performed using the Holm–Sidak test. Both pooled coherence and group comparisons of coherence were compared by including a chi-squared test, which denotes the difference required for statistical significance in the frequency distribution. Significance was in all cases determined at a P-value of 0.05 and all values are given as means ± SD. Analyses were performed using Sigmaplot 13 (SYSTAT software) and MATLAB R2017a (The Mathworks Inc.).

Data availability

The data that support the findings of this study are available from the corresponding author, upon request.

Results

Electromyographic recordings

In total, 36 recordings from 13 out of 17 individuals with CP and 17 recordings from all 8 individuals with stroke contained sustained involuntary muscle activity (see Materials and methods section for identification criteria). The four individuals with CP who did not show signs of involuntary muscle activity were individuals #2, 3, 7 and 12 (Table 1). None of the 42 recordings from 14 control individuals contained sustained involuntary muscle activity at rest. The characteristics of the observed sustained involuntary muscle activity differed considerably, both between CP and stroke, between individuals in the same group and between individual recordings in different positions of the elbow joint from the same individual (Fig. 2A). Whereas some individuals (e.g. subject 4) exhibited involuntary muscle activity with sudden increases and decreases, other individuals (e.g. subject 24) exhibited more constant and stable involuntary muscle activity.

Figure 2B presents the effect of elbow joint position on the biceps muscle EMG levels. The RMS EMG of one position of the elbow joint is normalized to the same individual's flexed position RMS amplitude and then logarithm transformed. In the CP group, a repeated measures ANOVA showed no significant ($P > 0.05$) differences between RMS EMG levels in the investigated positions, indicating no effect of elbow joint position. However, in the stroke group, EMG levels increased with extension of the elbow joint from the flexed position to the 90-degree position ($P = 0.05$) and the extended position ($P = 0.01$). No difference was found comparing the 90-degree and the extended position ($P = 0.36$).

Figure 2C presents the development of involuntary muscle activity following the positioning of the joint in the maximally extended joint position calculated as 30-s mean RMS EMG amplitude bins and then normalized to the first 30 s bin. In the CP group, the mean RMS EMG amplitudes were found to be significantly lower, when
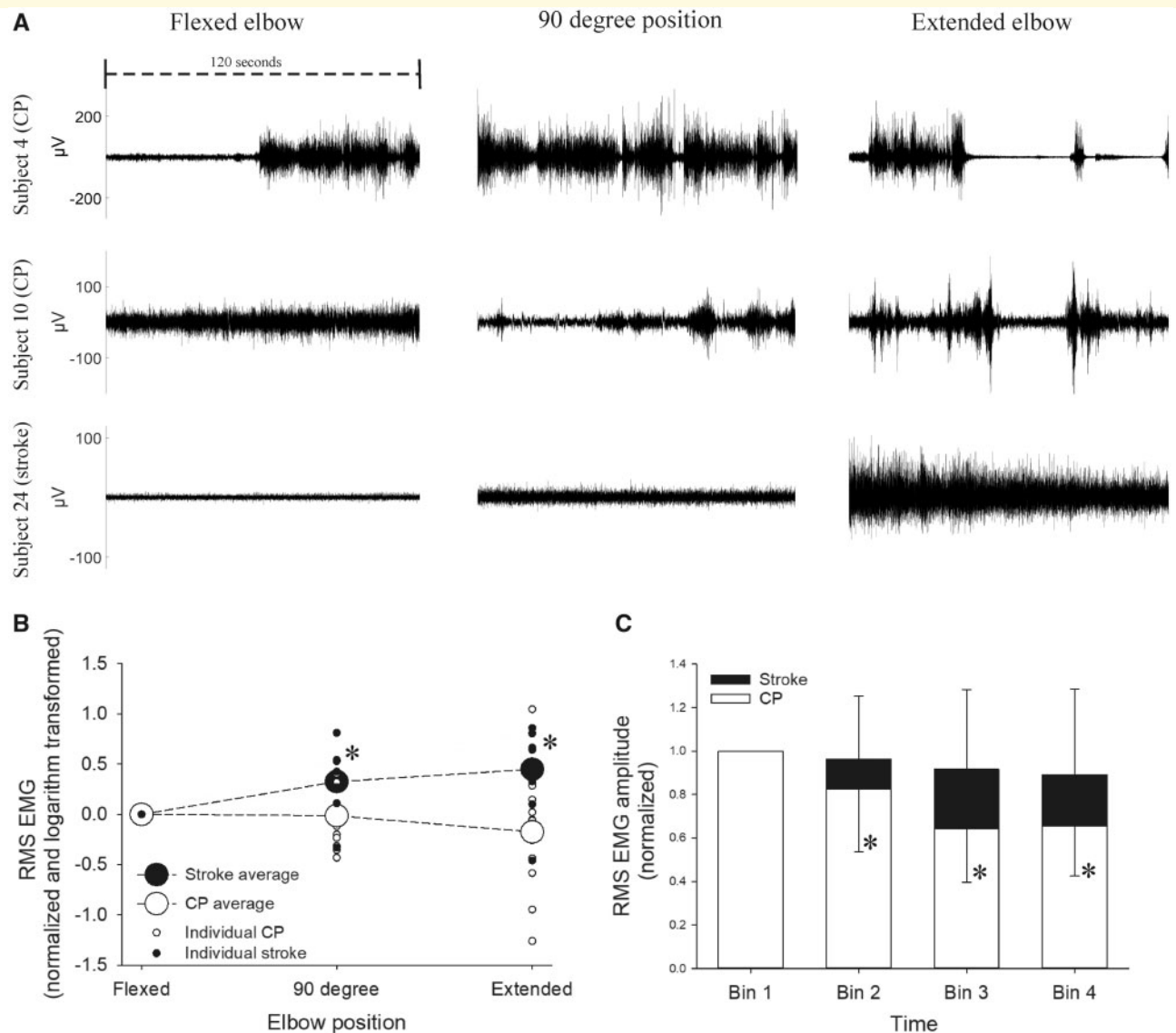
Figure 2 EMG activity in different positions. (**A**) Raw EMG activity in the flexed, 90 degree and extended position of the elbow in subject 4, 10 and 24, respectively. In subject 4 and 10, the recordings were identified with sustained involuntary muscle activity. In subject 24, the recordings performed in the 90 degree and extended position were identified with sustained involuntary muscle activity, the recording in the flexed position was not. (**B**) RMS EMG from different elbow positions normalized to the individuals' flexed position RMS amplitude and logarithm transformed including group means (large circles connected by dotted lines). Asterisk (*) signifies a significant difference compared with the flexed position. (**C**) The CP and stroke group mean RMS EMG amplitudes divided into four 30-s periods (bins) and then normalized to Bin 1. Bin 1: 0–30 s. Bin 2: 30–60 s. Bin 3: 60–90 s. Bin 4: 90–120 s. Asterisk (*) signifies a significant difference compared with Bin 1. The statistical testing in Fig. 2c was performed by an ANOVA on ranks test. The means of Fig. 2c are made from all individual recordings containing muscle activity, and therefore contain multiple recordings from some participants. In the stroke group, $n = 16$ recordings. In the CP group, $n = 31$ recordings.

compared to bin 1, in both bin 2 (1 ± 0 versus 0.83 ± 0.29, $P = 0.03$), bin 3 (1 ± 0 versus 0.64 ± 0.25, $P < 0.001$) and in bin 4 (1 ± 0 versus 0.66 ± 0.24, $P < 0.001$). Furthermore, bin 3 was found to be significantly lower compared with bin 2 ($P = 0.03$). In the stroke group, no differences were found between the bins. In the flexed- and 90-degree joint positions, no differences were found between the bins in either group.

Cross-correlation analysis

In Fig. 3, the pooled coherence results from CP, stroke and control individuals (A–C) are presented. In all groups, significant coherence was found in the alpha (6–15 Hz), beta (16–35 Hz) and early gamma band (36–60 Hz).

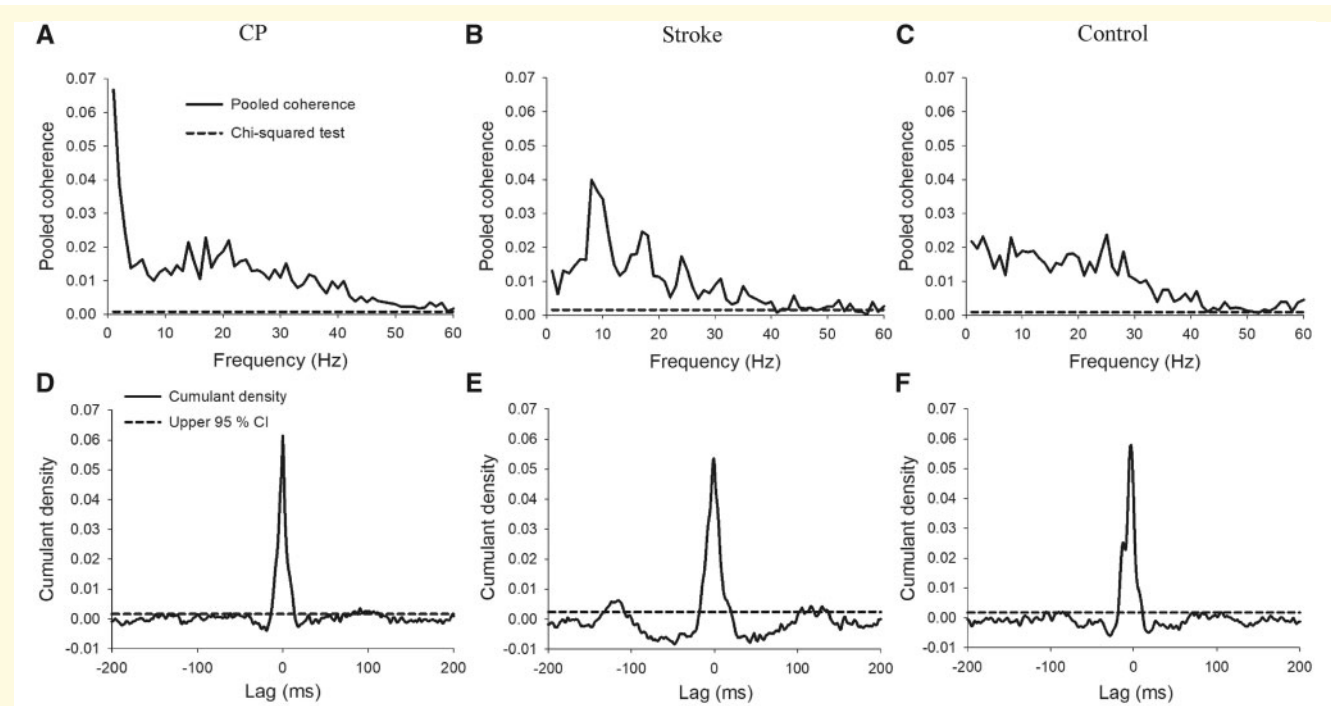The pooled coherence estimates are compared group-wise in Fig. 4A–C. When compared to the control group

Figure 3 Pooled coherence. A–C depicts the pooled coherence in the CP (**A**), stroke (**B**) and control group (**C**). The dotted lines note the chi-squared test level. **D–F** depicts pooled cumulant density functions from the CP group (**D**) stroke group (**E**) and control group (**F**).
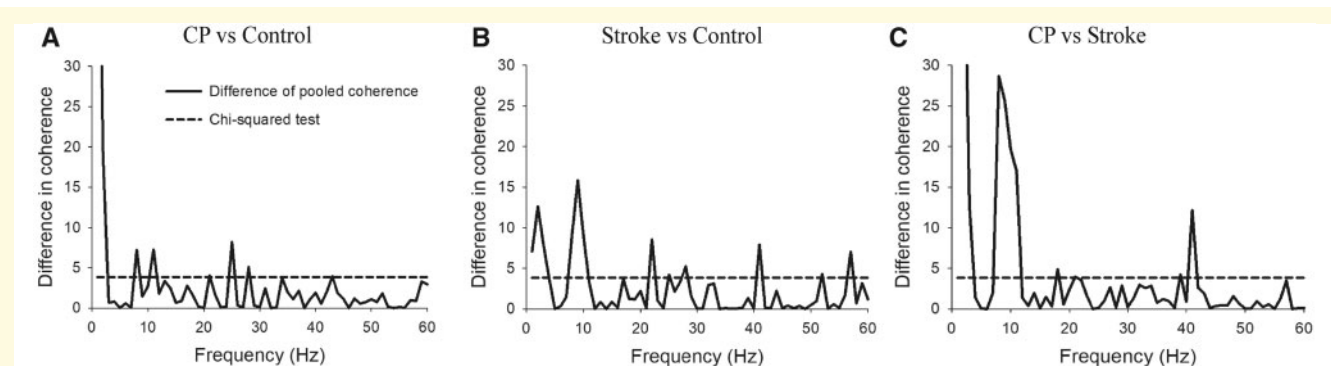

Figure 4 Difference in pooled coherence. A–C depicts differences in pooled coherence between the CP and control group (**A**), the stroke and control group (**B**) and the CP and stroke group (**C**). The dotted lines note the chi-squared test level.

(4B) and to the CP group (4 C), an increased coherence in the alpha band of the stroke group is visible mainly in the 8–11 Hz band. In the CP group, coherence is larger than in stroke in the early gamma band around 40 Hz (Fig. 4C). The pooled cumulant density functions (Fig. 3D–F) all show a significant central peak of synchronization. The average duration of the central peaks of synchronization was 19.5 (±7.2) ms for the CP group, 22.7 (±7.5) ms for the stroke group and 20.8 (±8.7) for the control group. No significant differences were found in either the percentage of individual recordings showing a significant central peak (100% for the CP and control

group, 93.4% for the stroke group), the duration of the peak or the amplitude of the peak (Table 2).

Discussion

The primary findings of this study are that (i) sustained involuntary muscle activity exists in individuals with movement disorder due to lesions of the descending motor pathways and increased resistance to passive movement (MAS > 1) due to CP or stroke; (ii) the muscle activity of both individuals with CP and stroke showed

Table 2 Central peaks in the cumulant density function

	CP	Stroke	Control
Peaks (%)	100	93.4	100
Duration (ms)	19.5 ($\pm$7.2)	22.7 ($\pm$7.5)	20.8 ($\pm$8.7)
Amplitude	0.0795 ($\pm$0.0413)	0.0730 ($\pm$0.0497)	0.0747 ($\pm$0.0399)

large central peaks of synchronization in the cumulant density function; and that (iii) the muscle activity seemed to differ between the CP and stroke group with respect to the effect of passive joint extension and the EMG–EMG coherence estimates in specific frequency bands.

Shared characteristics in CP and stroke muscle activity

An overall shared characteristic was, that sustained involuntary muscle activity was often found to coexist with increased resistance to passive movement in adults affected by central motor lesions. This was observed in the majority of adults with CP (13/17) and in all individuals with stroke (8/8). EMG recordings of sustained involuntary muscle activity from the CP and stroke group as well as voluntary muscle activity from the control group all showed large central peaks of synchronization in the cumulant density function. The presence of significant synchronization suggests that the spinal motor neurons are not active due to an intrinsic mechanism. Conversely, it indicates that the sustained, involuntary muscle activity in both the CP and stroke group is caused to some extent by synaptic drive to the motor neurons from a common source. It follows from this that increased activity of persistent inward currents in spinal motor neurons is likely an insufficient explanation for the sustained involuntary muscle activity observed here (Fig. 1). This is consistent with previous findings for the sustained spontaneous firing of biceps brachii motor unit pairs in stroke survivors (Mottram *et al.*, 2010). However, this study cannot exclude that persistent inward currents might contribute to involuntary muscle activity in patients with various central motor lesions. Therefore, a central synaptic drive, possibly being facilitated by persistent inward currents, as has been previously proposed (Gorassini *et al.*, 2004; ElBasiouny *et al.*, 2010; D'Amico *et al.*, 2013), seems a likely cause of the sustained involuntary muscle contractions. The duration of the central peaks of synchronization was ~20 ms on average with no clear difference between groups (Table 2). This duration is too long to conclude with certainty that the synchronization is caused solely by a common synaptic input to the spinal motor neurons from last order neurons (Kirkwood *et al.*, 1982; Datta and Stephens, 1990; Vaughan and Kirkwood, 1997). As common input from last order neurones has been shown to synchronize motor neurons with a maximal duration of <10 ms (Sears and Stagg, 1976) it is likely that other synchronization mechanisms contribute to the observed peaks.

Differences in the characteristics of CP and stroke muscle activity

The position-dependent increases in sustained involuntary muscle activity recorded from the stroke group suggest that afferent feedback affected the level of sustained involuntary muscle activity. Individuals with CP would often have large increases or decreases in response to a change in position but did not significantly increase or decrease as a group. The individuals with CP would, however, often exhibit sudden increases or decreases in EMG activity during a recording without applied changes to the afferent feedback (Fig. 2). It is, therefore, likely that the position-dependent differences in individuals with CP were products of inherent variability rather than of altered afferent feedback. The analysis of mean EMG from the maximally extended joint position divided into 30-s bins (Fig. 2C) shows that on a group basis the sustained involuntary muscle activity of the CP group decreased significantly during maintained stretch of the muscle. Although the sustained involuntary muscle activity of the stroke group might visually appear to also decrease during maintained stretch, there were no statistically significant differences. The decrease in muscle activity during maintained stretch could imply a primarily inhibitory effect of the stretch in CP. Trompetto *et al.* (2019) observe both an increase in mean EMG levels from passive joint extension and a following decrease during 120-s maintained stretch in a stroke group. A noteworthy difference in Trompetto *et al.* (2019), however, is a higher velocity of passive joint extension, which likely leads to larger contribution from the spastic phasic stretch reflex, and subsequent larger decrease over time in the maintained position. Many afferent reflex circuits have been implicated in both spasticity (Nielsen *et al.*, 2007) and muscle overactivity following central motor lesions in general (Gracies, 2005). It is still unclear whether pathological reflex circuits drive spastic dystonia, or merely coexist as a part of spasticity. Further studies are needed to determine to what extent afferent reflex circuits are active during sustained involuntary muscle activity.

The stroke group was found to have increased alpha-band coherence compared with CP, with the main difference found in the 8–11 Hz frequency band (Fig. 4C). These coherence and afferent feedback EMG results are consistent with the finding that stimulations of afferent circuits have been associated with increased 10 Hz coherence and reduced beta-band coherence in healthy controls (Hansen and Nielsen, 2004). Coherence around the 10 Hz bandwidth is also found in physiological and essential tremor and is hypothesized to involve the cerebello-thalamo-cortical network (Elble and Randall, 1976; Hallett, 1998; Schnitzler *et al.*, 2006; Elble, 2013;

Albanese and Del Sorbo, 2016). As tremor can also be affected by the function of sensory afferents (Sanes, 1985), this could indicate afferent differences in stroke and CP, perhaps through different projections to the cerebello-thalamo-cortical network.

Coherence in the beta and gamma bands are often assumed to relate to activity originating in the primary motor cortex (Grosse et al., 2002), and could therefore imply reduced neural drive from the primary motor cortex in stroke compared with CP (Fig. 4). Reduced corticospinal input in stroke is consistent with observations of decreased corticospinal excitability (Dimyan and Cohen, 2010; Cortes et al., 2012). It is an interesting result, that the corticospinal input in sustained involuntary muscle activity in CP should be different from stroke. An explanation of this difference could be the maturation of the central nervous system at the time of injury in CP and stroke. CP might differ from stroke through extensive cortical and spinal adaptive reorganization following lesion during early development. One line of evidence supporting this hypothesis is that ipsilateral corticospinal projections from the non-affected hemisphere to the muscles of the affected side have been found in both children and adults with unilateral CP (Carr, 1996; Marneweck et al., 2018). The same has not been observed in individuals suffering from stroke (Brouwer and Ashby, 1990; Palmer et al., 1992). These cortical adaptations have been suggested beneficial for regaining some voluntary function in the paretic side during development (Carr, 1996; Bleyenheuft et al., 2015; Friel et al., 2016) but could also lead to disorganized motor control causing sustained involuntary muscle activity such as that observed here.

Information regarding the exact individual sites of the central motor lesion is of great interest, as lesions to the basal ganglia are a frequently cited likely cause of involuntary movements in both CP (Aravamuthan and Waugh, 2016) and stroke (Ghika-Schmid et al., 1997). As the participants with stroke had magnetic resonance imaging scans performed in relation to the injury, this information was available. Indeed, all eight individuals with stroke were found to have some degree of damage to the basal ganglia (Supplementary Table 1). As we did not have access to an magnetic resonance imaging scanner, it was unfortunately not possible to obtain this information from the individuals with CP. Basal ganglia lesions, however, are unlikely to provide the full explanation of sustained involuntary muscle activity following central motor lesions (Neychev et al., 2011). Results from interventions using deep brain stimulation to reduce dystonia in CP (Koy et al., 2013) and in stroke (Elias et al., 2018) have seen large effects in some individuals but no effect in others. This is consistent with the idea that the basal ganglia might contribute to sustained involuntary muscle activity, but that the complete origin of the condition involves more network-based complex causes such as maladaptive neural plasticity or defects in sensorimotor integration (Neychev et al., 2011; Quartarone and Hallett, 2013; Liuzzi et al., 2016).

As individuals with stroke were generally older than the individuals with CP, we are not able to exclude that the observed differences between the two groups could be partly due to age differences.

How does the sustained involuntary muscle activity compare to spastic dystonia?

In this study, we have attempted to depict with EMG, how the involuntary muscle activity presents itself in two different groups of individuals with central motor lesions. This has been done to illustrate the complex nature of the clinical examination of these populations. We present here, evidence that many individuals with movement disorder due to lesions of the descending motor pathways, experience involuntary muscle activity during rest, which should not be labelled spasticity. Whether the introduced condition of spastic dystonia can fully explain the sustained involuntary muscle activity in this study is however not clear. The sustained involuntary muscle activity resembling that of a dystonia exists to some degree in both populations, but the seemingly different patterns of involuntary muscle activity in the two groups point to other conditions of muscle overactivity also being present. Although no blatant choreoathetosis was found during the neurological examination, the variable pattern of involuntary muscle activity in the CP group could be interpreted as a sign hereof. Both dystonia and choreoathetosis have been accepted to constitute separate subclassifications of dyskinetic CP (Cans, 2008), but rather than interpreting this as an indicator of misclassification of this study's individuals with CP, our findings should exemplify the complexity and overlap of the classifications and symptoms of individuals with central motor lesions. The SCPE classifications are an attempt to characterize the difference between spastic and dyskinetic CP as whether the increase in involuntary muscle activity is persistent or varying (Cans, 2008), but many definitions of dystonia following central motor lesions would refer to it as long-lasting muscle contractions causing sustained abnormal posturing (Sanger et al., 2010; Siniscalchi et al., 2012; Albanese et al., 2013). We believe it is important to recognize, that the symptom of spasticity (Lance, 1980; Gracies, 2005) only is a part of the clinical picture in the individuals with central motor lesions, who are often characterized by the word spastic. Sustained involuntary muscle activity, perhaps referred to as spastic dystonia, should be considered as a separate symptom with a separate pathophysiology in this population. The distinction is important, as the study provides evidence suggesting that the sustained involuntary muscle activity is driven by a common synaptic drive to the motor neuron pool. This indicates that the treatment for

the spinal stretch reflex mediated symptom of spasticity might not be the same as the treatment for the centrally driven sustained involuntary muscle activity.

Clinical implications

This study found evidence suggesting that the underlying mechanisms causing sustained involuntary muscle activity differed between the CP and stroke groups. Whereas the sustained involuntary muscle activity was increased by afferent input in individuals with stroke, it appeared to have larger contributions from the motor cortex in individuals with CP. It, therefore, seems likely that the optimal treatment option in the CP group would not be identical to that of the stroke group. The involuntary muscle activity of the individuals with CP could originate from complex disorganized motor control following cortical adaptations to the lesion. This emphasizes the need for motor learning rehabilitation following a central motor lesion, not only to regain function for activities of daily living, but also to reduce involuntary muscle activity. It has previously been reported that even purely parietal lesions in stroke frequently lead to dystonia, perhaps due to the reduced integration of sensorimotor inputs to the motor cortex (Ghika *et al.*, 1998). Sensorimotor integration of afferent inputs has also been suggested as a mechanism for causing various types of focal dystonia (Neychev *et al.*, 2011; Avanzino and Fiorio, 2014; Patel *et al.*, 2014; Avanzino *et al.*, 2015; Liuzzi *et al.*, 2016). Regaining the sensorimotor integration in individuals suffering from involuntary muscle activity following a stroke is therefore an important therapeutic intervention.

Although this study has shed some light on the underlying mechanisms causing sustained involuntary muscle activity in individuals with CP or stroke, there is an urgent need for future studies to further explore these mechanisms in order to improve current treatment.

Conclusion

This study found that sustained involuntary muscle activity, like that described in spastic dystonia, was frequently present alongside increased resistance to passive movement in individuals with movement disorder due to lesions of the descending motor pathways. The sustained involuntary muscle activity of both CP and stroke was found to contain a common synaptic drive to the motor neuron pool, but coherence estimates indicate, that the origin of this common synaptic drive differed between the groups. Stroke seemed to have increased muscle activity from afferent neural feedback and an increased alpha-band coherence. CP was not found to have increased muscle activity from afferent neural feedback, but instead had increased gamma-band coherence, indicating contributions from cortical motor regions. We find these results to indicate that the sustained involuntary muscle activity

may require different treatment in the two groups. In some individuals, treatment should focus on plastic adaptations to central motor control, whereas other individuals might instead be affected by deficits in the integration of sensory feedback.

Supplementary material

Supplementary material is available at *Brain Communications* online.

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Competing interests

The authors report no competing interests.

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