The effect of cannabinoids on the stretch reflex in multiple sclerosis spasticity

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Abstract

The aim of this observational study was to assess the efficacy of tetrahydrocannabinol-cannabidiol oromucosal spray (THC:CBD) on spasticity using the stretch reflex in subjects with multiple sclerosis (MS). Numeric rating scale (NRS) for spasticity, modified Ashworth scale (MAS) and the stretch reflex were assessed before and during treatment in 57 MS patients with spasticity eligible for THC:CBD treatment. A significant reduction of stretch reflex amplitude, as well as significant reductions of NRS and MAS scores was observed. There was a low concordance between the three measures (stretch reflex, NRS and MAS), likely related to the different aspects of muscle hypertonia assessed. Stretch reflex responders were taking a significantly higher number of puffs, while no differences were found in the responders by the other scales, suggesting that higher dosage would add benefit if tolerated. The present study confirms the efficacy of cannabinoids in reducing spasticity in patients with MS, suggesting a higher sensitivity and specificity of the stretch reflex compared to other measures. As an objective and quantitative measure of spasticity, the stretch reflex is particularly useful to assess the effects of cannabinoids on spinal excitability and may have a role in future pharmacological studies.

Keywords: multiple sclerosis; cannabinoids; THC:CBD; nabiximols; Sativex; stretch reflex; spasticity; electromyography; tetrahydrocannabinol; cannabidiol; numeric rating scale; modified Ashworth scale

Introduction

Spasticity may affect up to 80% of patients with multiple sclerosis (MS), determining disability in at least one third of cases, as shown by an epidemiological survey based on questionnaires (Rizzo *et al*, 2004). Spasticity is often associated with a variety of symptoms including fatigue, pain and the presence of muscle spasms. In subjects with MS the use of drugs such as baclofen, dantrolene and tizanidine is difficult because of the side effects (drowsiness, weakness, dizziness) increasing the burden of the pre-existing symptoms related to the disease. The THC:CBD oromucosal spray (USAN name Nabiximols, Trademark Sativex) is an association of delta-9-tetrahydrocannabinol and cannabidiol administered by oral puffs and adsorbed via a transmucosal route, active on CB_1 and CB_2 cannabinoid receptors. Large studies demonstrated its efficacy in relieving symptoms related to spasticity in MS patients showing no significant benefit from other antispastic drugs (Collin *et al*, 2007; Flachenecker *et al*, 2014; Paolicelli *et al*, 2015; Wade *et al*, 2010; Zajicek *et al*, 2003).

Spasticity is traditionally defined as a motor disorder characterized by an exaggeration of the stretch reflex (Lance, 1980), resulting in a velocity-dependent increase in muscle tone during passive limb movements. From a clinical point of view, the examiner perceives a resistance that can be semi-quantitatively measured using scales such as the modified Ashworth scale (MAS), one of the most widely used. Although the neurophysiological recording of the stretch reflex would be the ideal parameter to quantitatively assess spasticity, its use is limited in a clinical setting. Most of the studies involving the stretch reflex measurement in fact use robotic devices which are expensive, bulky and often designed for a single joint. In many studies, spasticity was assessed using clinical scales often based on patient's own experience. In particular, the numeric rating scale (NRS) (Anwar and Barnes, 2009; Farrar *et al*, 2008), the MSSS-88 (Hobart *et al*, 2006) and the spasms frequency scale (Collin *et al*, 2007; Farrar *et al*, 2008) are basically subjective measures directly provided by the subjects.

The assessment of spasticity directly performed by a clinician usually includes MAS, which, although related to the NRS (Anwar and Barnes, 2009), is very imprecise and operator-dependent (Collin *et al*, 2007; Thaera *et al*, 2009) and not always correlate with the stretch reflex amplitude, especially with regard to the intermediate scores (Damiano *et al*, 2002). Indeed, in most of the studies assessing the effect of cannabinoids on spasticity, MAS failed to disclose a significant variation, probably because of its intrinsic limitations and lack of sensitivity (Collin *et al*, 2007; Killestein *et al*, 2002; Thaera *et al*, 2009; Zajicek *et al*, 2003). Conversely, NRS appeared much

more effective in detecting subjective changes in spasticity, becoming the gold standard in large pharmacological trials on the effect of cannabinoids and specifically THC:CBD (Collin *et al*, 2007; Zajicek *et al*, 2003). Nonetheless, NRS remains a subjective estimation of a phenomenon with a precise neurophysiological characterization, based on the subject's understanding and often including other clinical expressions of upper motor neuron damage. In this view, many studies advise the need of spasticity assessment tools which are sensitive and validated (Anwar and Barnes, 2009; Collin *et al*, 2007; Thaera *et al*, 2009; Zajicek *et al*, 2003).

Neurophysiological methods suitable to measure the stretch reflex have been underused in clinical research. Our group has recently validated a method to elicit and measure the stretch reflex in a clinical setting with the use of surface electromyography and without robotic devices (Marinelli *et al*, 2013). The method is effective on major joints (wrist, elbow, knee and ankle) and allows a reproducible and quantitative evaluation of the stretch reflex in subjects with spasticity.

The present study measures the effect of THC:CBD in spastic MS subjects using the stretch reflex and compares it to other spasticity scales.

Materials and methods

Subjects

We recruited 57 consecutive MS subjects with spasticity, eligible for THC:CBD treatment within the Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health of the University of Genova, Italy. An unrestricted grant from Almirall S.A. was obtained to fund the study after submission of the project protocol and evaluation of an experts board external to the funder. The subjects we consecutively recruited had already been prescribed THC:CBD and were ready to start the treatment, so we had no time to organize a randomized controlled study. We therefore decided to parallel the standard clinical assessment with the stretch reflex evaluation limiting to an exploratory observational study.

Subjects were 26 males (46%) and 31 females (54%), mean age 52 years (range 27-79), mean expanded disability status scale (EDSS) 6.9 (range 5-8), mean disease duration 194 months (range 48-456). MS type was primary progressive in 11 (19%), secondary progressive in 43 (76%) and relapsing-remitting in 3 (5%). The inclusion criteria were: 1) presence of spasticity with MAS lower than 4 in at least one of the following muscle groups: flexor muscles of the wrist, flexor muscles of the forearm, extensor muscles of the leg, foot plantiflexors, 2) absence of significant peripheral nervous system pathology detectable on clinical basis, 3) absence of concomitant parkinsonism, 4) no exposure to oral or smoked cannabinoids in the 30 days before starting THC:CBD, 5) no

botulinum toxin injections and no dosage variation of other drugs potentially affecting spasticity and pain in the 30 days before starting THC:CBD, 6) Nabiximols approved label requirements.

No limitations related to age and degree of disability were applied for subjects selection. The subjects with questionable spasticity were rated 0 at the MAS and included only if a stretch reflex was well recognizable at angular velocities less than 180° (Thilmann *et al*, 1991).

The following sociodemographic data have been collected: gender, age, years with MS, muscles affected by spasticity. The present study has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; a written informed consent was obtained from all participants. The study was approved by the local Ethics Committee.

Experimental procedure

Preliminar setting and clinical evaluation

The subjects were evaluated in a quiet room with a temperature between 21 and 23°C. The muscle group with the highest level of spasticity but preserved range of motion (MAS<4) was selected among flexor muscles of the wrist, flexor muscles of the forearm, extensor muscles of the leg or foot plantiflexors. All subjects underwent a complete neurological examination and the range of motion of the selected joint was determined along with MAS. To assess the stretch reflex, the subjects rested in a seated position with the arms leaning on a pillow for flexor muscles of the wrist or flexor muscles of the forearm, while for the extensor muscles of the leg the subjects were lying supine on a comfortable examination table with head and shoulders slightly elevated, both legs over the end of the coach. To assess foot plantiflexors the subjects were lying prone with the feet protruding from the examination table in order to allow a full ankle range of movement.

The subjective perception of spasticity was assessed using NRS for spasticity, along with VAS for pain. All measures were collected by medical doctors specialized in neurology or rehabilitative medicine; in each subject the same physician performed the stretch reflex procedure before and during the treatment with THC:CBD.

Stretch reflex technical setup

With the subjects in the same position described above, the examiner perceived the tones produced by a software emulated metronome through headphones and was seated near the subject in order to

move the chosen limb comfortably. The EMG activity produced by the stretched muscle was recorded by surface preamplified electrodes with fixed 20mm inter-electrode distance (TSD150B, Biopac Systems Inc, USA) placed over the muscle belly following Seniam guidelines ("SENIAM recommendations for placement and fixation of the sensor," n.d.) and acquired by a Biopac MP150 unit (Biopac Systems Inc, USA). Joint angle during the movements was recorded by a twin-axis electronic goniometer placed across the joint (TSD130B, Biopac Systems Inc, USA) connected to the same MP150 unit.

Stretch reflex procedure

The method was described in details in a previous validating work (Marinelli *et al*, 2013). During the procedure, the subjects were instructed to remain relaxed and to avoid resisting or facilitating the movements performed by the examiner. Initially the optimal audio tone frequency was decided and set on the metronome: for instance, when choosing a frequency of 60 beats per minute (BPM) the interval between consecutive tones is 1s. Since the examiner is required to move the limb throughout the full range of motion in the time corresponding to the interval between two consecutive metronome tones, the movement velocity increases linearly with BPM. The choice of the BPM was done taking into account that low values could not be able to elicit a stretch reflex (especially in subjects with a low degree of spasticity), while high values could produce discomfort to the subject and excessive fatigue in the examiner. Once the optimal BPM have been set, the examiner started performing consecutive flexion and extension movements following the rhythm reaching the extreme limb positions in synchrony with consecutive metronome tones. Performing about 5 of these continuous (or "sinusal") movements allowed the examiner to learn the appropriate velocity and therefore perform the movements also interposing a few tones interval between the movements, thus obtaining discontinuous (or "linear") movements. The procedure was repeated in order to obtain 40 flexion and 40 extension movements. The stretch reflex was measured during movements determining elongation of the spastic muscle. The procedure lasted about 15 minutes and was performed on a single muscle group.

<u>THC:CBD effect evaluation</u>

The stretch reflex procedure and the clinical evaluation have been performed twice: at the baseline condition (T0) before starting the treatment and 4 weeks later, the medication label required trial period, when the optimal THC:CBD dose has been reached (T1). During this trial period, the

number of puffs was titrated according to the medication label scheme, adding 1 or 2 puffs each day up to the highest tolerated number (no more than 12 puffs in a day: 5 in the morning and 7 in the afternoon or evening). Between T0 and T1 the subjects were asked to maintain concomitant medications unchanged. During T1 evaluation, the number of sprays/day and the possible adverse events were also recorded. In order to obtain a reproducible electrode positioning between T0 and T1, a picture of the electrode and its relation with nearby anatomical landmarks was taken in each subject. In order to reduce all possible sources of variability, the whole setup was the same at T0 and T1, including the subject's position, the examiner and obviously the metronome BPM to obtain reproducible velocity (Marinelli *et al*, 2013).

Data analysis

The main endpoint of the study is the reduction of spasticity assessed with the stretch reflex after 4 weeks treatment with THC:CBD at the maximal tolerated individual dose. To this aim, the electromyographic recordings were filtered, rectified and the mean amplitude ("mean" function of the analysis software) of the bursts during lengthening duration was calculated and defined "meanEMG" (Marinelli *et al*, 2013) using the dedicated AcqKnowledge analysis software (Biopac Systems Inc, USA). The baseline meanEMG values are very variable among subjects because of many factors such as thickness of subcutaneous tissue, muscle trophism, level of spasticity, etc. A normalization procedure using a parameter such as maximal M wave amplitude following nerve stimulation and maximal voluntary contraction would be indicated, however both appeared unfeasible. In fact, the majority of MS subjects showed spasticity in proximal limb muscles (such as biceps brachii and quadriceps femori) where nerve stimulation is difficult to perform and would have caused great discomfort. On the other side, maximal voluntary contraction could not be performed because of variable muscle weakness associated with spasticity. In order to measure meanEMG variation between T0 and T1, we therefore compared the average meanEMG using a paired T-test.

We also distinguished between subjects responders and non-responders to the treatment, as assessed by the neurophysiological procedure. To this aim, in each subject an unpaired t test was performed between the 40 meanEMG values at T0 and T1: if meanEMG values at T1 were significantly lower ($p<0.05$) compared to T0, the subject was considered a responder.

As secondary endpoints, NRS for spasticity, MAS and VAS for pain were compared between T0 and T1 using Wilcoxon test for semi-quantitative data. The number of responders for NRS and

MAS were also calculated as the number of subjects with a NRS reduction of at least 20% (Farrar *et al*, 2008) and MAS reduction of at least one point at T1. For analyses purpose, MAS values have been transformed in order to obtain values ranging from 0 to 6 (1+ becomes 2, 2 becomes 3, etc.) (Anwar and Barnes, 2009). Transformed MAS values are reported in the result section of the present manuscript and in the figures. The number of THC:CBD puffs between responders and non-responders have been compared using unpaired t test.

The sponsor of this study had no role in the study design, data collection, data analysis, data interpretation and writing of the report, providing support only for English language revision.

Results

Five of the 57 recruited subjects could not perform the stretch recording at T0 because of discomfort related to the position required to perform the evaluation. Out of the remaining 52 subjects, 15 (26%) stopped THC:CBD before the re-evaluation four weeks later (T1) because of side effects mostly referred as dizziness, sleepiness and nausea. One subject was unable to remain relaxed and could not be re-evaluated. Therefore, stretch recordings have been collected both at T0 and T1 in 36 subjects (mean age 54, range 31-79, 15 males) (Table 1); the remaining subjects have been excluded from the analysis also for non-neurophysiologic measures. Five subjects have been tested on flexor carpi radialis, 6 subjects on biceps brachii, 1 on triceps brachii and 24 on quadriceps, with metronome pacing ranging between 40 and 120 BPM.

A reproducible stretch reflex could be elicited in all subjects (Figure 1). Despite the high variability of baseline meanEMG values among subjects, related to the lack of normalization (see methods), the meanEMG reduction at T1 in the 36 subjects using a paired T-test was indeed statistically significant ($p=0.026$). Comparing the single stretch in each subject, a significant reduction of meanEMG was detected in 20 out of 36 subjects (56%), here defined “neurophysiological responders” (Figure 2). No significant difference was found in 8 (22%) and a significant increase in another 8 (22%) subjects.

Baseline spasticity in the selected muscle ranged between 0 and 4 (mean 2.4±1.2 SD, MAS transformed values) and decreased significantly ($p=0.0012$) at T1 (1.8±1.4). Two subjects (#3 and #19) had questionable spasticity at T0 scoring 0 at the MAS but showing a clearly recognizable stretch reflex; these two subjects have been excluded from MAS analysis. The number of responders considering MAS (“clinical responders”) were 15 out of 34 subjects (44%) (Figure 2) (3 points reduction in 2 subjects, 2 points in 4, 1 point in 9); in 18 subjects MAS was unaltered, while in one subject MAS increased by 1 point.

All 36 subjects scored at least 3 on NRS for spasticity at T0. On average, NRS for spasticity was 6.8±1.7 at T0 and 5.7±2.1 at T1, consistent with a statistically significant decrease (p=0.0007). NRS for spasticity underwent a reduction of at least 20% in 14 (39%) subjects ("subjective responders") (Figure 2), while in another 9 the reduction was lower than 20%. In 11 subjects the NRS was unchanged and in 2 increased of at least one point.

In the first 9 recruited subjects VAS for pain have not been collected. In the remaining 27 subjects VAS for pain was reduced of at least one point in 12 (44%) while remained unchanged in the other 15 (7 had no pain at baseline: VAS=0). No subjects reported pain increase at T1. In 10 of the 12 subjects (83%) pain was reduced of at least 20%. In the 27 analyzed subjects, mean values at T0 was 3.9±3.1 and 2.9±2.6 at T1. VAS for pain reduction was statistically significant (p=0.0048).

The number of neurophysiological responders (n=20; 56%) was higher than subjective (NRS) (n=14; 39%) and clinical (MAS) responders (n=15; 44%). This observation, along with the presence of a stretch reflex also in two subjects who had no spasticity detectable with MAS at baseline, suggests a higher sensitivity of the neurophysiological measure compared to the clinical assessment. We found only a partial agreement in the definition of responders using the three methods: comparing two methods at a time the sum of responders (white background) and non-responders (black background) in both methods ranged between 53% and 61% of the subjects (Figure 2).

To further assess the effect of THC:CBD on spasticity, we compared the number of puffs between responders and non-responders using subjective, clinical and neurophysiological measures. Considering subjective NRS measure, responders were taking 7.0±2.9 puffs, while non-responders 5.7±2.2. Considering instead clinical MAS evaluation, responders were taking 6.3±3.1 puffs, non-responders 6.2±2.1. Using the neurophysiological stretch reflex assessment, responders were taking 6.9±2.4 puffs, non-responders 5.4±2.5. Despite the similar number of THC:CBD puffs in the three groups, the number of puffs was significantly higher in subjects responders versus non-responders only using the stretch reflex recording (p=0.047), while comparing the number of puffs between NRS responders and non-responders (p=0.07) and also between MAS responders and non-responders (p=0.45) no significant difference could be found, although a trend to significance is present for NRS responders.

Discussion

This is the first study using stretch reflex to assess the effect of cannabinoids on spasticity. A significant reduction of spasticity during treatment was demonstrated assessing stretch reflex amplitude (meanEMG) in 36 subjects with MS when the examiner performed passive elongations

of the spastic muscle. Each subject was considered a responder when the comparison of 40 stretches revealed a significant reduction during the treatment. Such neurophysiological assessment was compared with the other two methods generally used: NRS for spasticity and MAS. In the 36 subjects included in the analysis, the stretch reflex disclosed the highest number of responders compared to the other standard procedures; in more than half of the subjects the stretch reflex significantly decreased during THC:CBD treatment. Given the low concordance in responder definition between the three methods, an obvious question rises about what they are measuring and which method is actually measuring spasticity. Interestingly, only the stretch reflex assessment was able to distinguish between responders and non-responders, defining two groups where the number of puffs was significantly different, despite the reduced sample size. The use of an objective instrumental neurophysiological measure is particularly interesting when assessing spasticity since the previous works were limited by subjective and clinical scales providing surrogate endpoints lacking objective and quantitative informations (Collin *et al*, 2007; Farrar *et al*, 2008; Flachenecker *et al*, 2014; Killestein *et al*, 2002; Paolicelli *et al*, 2015; Wade *et al*, 2004, 2010; Zajicek *et al*, 2003). The present study demonstrates that assessment of spasticity with the described stretch reflex procedure is feasible, not particularly time-consuming and well tolerated by the subjects. Most importantly, the described stretch reflex measure is sensitive and provides quantitative data which closely reflect both the mechanisms underlying spasticity and the assessment modality used during clinical practice (Marinelli *et al*, 2013).

In our group, 8 subjects showed a significant increase of the stretch reflex at T1. Many reasons could be discussed to explain this finding, however the most important is that stretch reflex, like other objective measures such as MAS, takes a snapshot of the situation in a specific moment, without the possibility to make an average estimation over a larger timespan. If during the evaluation the subjects for example feels more discomfort, pain or cold, spasticity might temporarily increase and sensitive tools such as the stretch reflex probably detect such increase. Of course subjective measures such as NRS overcome this intrinsic limitations of objective measures.

The poor concordance between subjective, clinical and neurophysiological responders could be related not specifically to spasticity but to different phenomena related to upper motor neuron syndrome measured by the three methods. A relevant MAS variability between examiners has often been discussed; moreover it is unable to distinguish between stiffness resulting from reflex muscle contraction (properly considered the equivalent of spasticity) and non-reflex components of muscle hypertonia related to the modification of the intrinsic visco-elastic properties of muscular tissue (such as fibrosis and sarcomeres shortening). The stretch reflex conversely measures the electric

activity produced by the contracting muscle in response to a passive stretch and is considered the most specific measure of spasticity (Trompetto *et al*, 2014). As a secondary endpoint, the present study confirms a significant reduction of the NRS for spasticity during THC:CBD treatment. The NRS for spasticity is a subjective estimation based solely on the individual interpretation of spasticity and is currently considered the gold standard to measure the effects of cannabinoids on spasticity (Anwar and Barnes, 2009; Collin *et al*, 2007; Farrar *et al*, 2008; Hobart *et al*, 2006; Wade *et al*, 2004). NRS acquisition is easy and quick, taking into account what spasticity means for the patient and the impact on daily life over a 24 hours time span (Anwar and Barnes, 2009). A good test-retest reliability has been demonstrated (Anwar and Barnes, 2009; Farrar *et al*, 2008), however, keeping in mind that spasticity is an exaggeration of the stretch reflex (Lance, 1980), the use of NRS raises certain perplexity. Given an acceptable subject's understanding of spasticity as an "increased stiffness in the limbs", the subject is probably unable to assess the amount of stiffness in his own paretic and reasonably hypoesthetic limbs. Talking with the subjects, our perception is that at least some subjects misunderstand the concept of "stiffness" with those of "decreased strength". Indeed, NRS for spasticity is strongly related to the motricity index: subjects who perceive higher spasticity actually have more objective difficulties in performing movements (Anwar and Barnes, 2009). The important relation of NRS for spasticity with the subjective measure of other symptoms related to spasticity such as the Spasms Frequency Scale and the Patient Global Impression of Change may support NRS reliability and validity (Farrar *et al*, 2008), but also underlines its limited specificity. Authors discuss that other symptoms such as pain and fatigue might influence the perception, as well as obvious pitfalls in subjects with cognitive impairment and communication difficulties (Anwar and Barnes, 2009). The low agreement between subjective and objective indicators of spasticity must be interpreted keeping in mind that one method is not necessarily less reliable or valid then the other, specially in the short term follow-up period studied; rather they measure complementary outcomes that join together for a thorough understanding of the phenomenon (Hobart *et al*, 2006).

A significant reduction of MAS scores during THC:CBD treatment is a secondary endpoint of the study. Previous studies did not show a significant reduction of clinically assessed spasticity (using traditional or modified Ashworth scale) both with THC:CBD and with other compounds containing cannabinoids (Collin *et al*, 2007; Killestein *et al*, 2002; Zajicek *et al*, 2003). It is likely that the absence of a placebo arm and the unblinded status of the examiners could have affected this finding. Many studies, however, underline the unreliability of MAS as a measure of spasticity (Collin *et al*, 2007; Thaera *et al*, 2009).

Cannabinoids beneficial effect on pain has been known for millennia and previous studies in patients with MS demonstrated a significant effect of nabiximol on pain (Zajicek *et al*, 2003), even if a relevant placebo effect was also detected (Wade *et al*, 2004). In our case series VAS for pain was significantly reduced during treatment, even if this finding has a limited relevance considering that VAS for pain was available only in 27 of the analyzed patients and 7 had no pain at baseline. The relation between pain and spasticity is however very interesting and in our opinion deserves further investigation, in fact spasticity itself may be the cause of pain; on the other hand, pain increases the levels of spasticity (Trompetto *et al*, 2014).

The neurophysiological responders were taking more THC:CBD puffs compared to the non-responders. It is likely that responders benefit from higher THC-CBD levels in the central nervous system, with higher beneficial effect on spasticity than non-responders, who were taking fewer puffs. This could be the indirect demonstration that THC:CBD is effective in reducing spasticity in MS and we may also hypothesize that the threshold between responders and non-responders is related to the amount of side effects induced by the drug and therefore the number of puffs each subject is able to take. For example, a non-responder might become a responder if able to take and tolerate a higher number of puffs. An interesting consequence is that if side effects were lower, probably more subjects could be able to take more puffs and maybe become responders. The concept of "responders" could be therefore associated to the capability of bearing THC:CBD side-effects in the context of a pharmacogenetically-related response to the drug (Onaivi, 2010).

The majority of patients (23/36) were taking drugs potentially modulating pain and spasticity, in most cases baclofen, which were maintained stable during the study. Most of the associated drugs such as baclofen and diazepam can indeed modulate GABA transmission and thus potentially interact with the study drug. To our knowledge only animal studies are currently available (Méndez-Díaz *et al*, 2013). Considering the high variability of the stretch reflex among patients, we believe that the effects of an interaction should be negligible in this study. However, we believe that this issue deserves specific studies in humans.

Apart from stretch reflexes, other neurophysiological parameters have been used to assess cannabinoids effect on spasticity. Spinal cord excitability using H/M ratio showed no modification following THC:CBD treatment in a group of 20 subjects with MS (Centonze *et al*, 2009). H/M ratio however measures only part of the mechanisms underlying spasticity, estimating spinal cord neural circuits excitability by electrical stimulating a peripheral nerve. Differently from the stretch reflex, this technique does not take into account the whole neural systems involving peripheral and central connections that constitutes the network where spasticity develops (Lance, 1980). Another study on

the effects of cannabinoids on MS spasticity involving neurophysiological measures is actually focused on painful stimulus perception and tremor attenuation following smoked cannabis, but not spasticity itself (Meinck *et al*, 1989). A more recent double-blind placebo-controlled study on 44 patients with MS was unable to disclose modifications of the H/M ratio as well as measures of cortical excitability by mean of transcranial magnetic stimulation (Leocani *et al*, 2015).

The main limitation of this study is related to the lack of a placebo arm. Given the observational and exploratory nature of this study, the results are innovative and introduce an underused sensitive and specific measure of spasticity, thus supporting the feasibility of future double-blind placebo-controlled studies. The decision to evaluate the stretch reflex on one muscle group only is justified by the need to limit the duration of the assessments and subjects' discomfort. Moreover, we think unlikely that the drug may affect spasticity differently depending on muscle groups, even if further studies may properly address this issue.

The stretch reflex recording deserves more attention since it fulfills the urgent need for sensitive and validated spasticity assessment tools. Larger and longer studies would be advisable to track the stretch reflex responders and non-responders clinical evolution through time.

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Conflicts of interest

There are no conflicts of interest.

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Table and figures legends

Table 1

Demographic and clinical features of the 36 subjects included in the analysis. In the treatment column only drugs potentially affecting spasticity and pain have been reported. BB, biceps brachii; BPM, beats per minute; EDSS, expanded disability status scale; FCR, flexor carpi radialis; L, left; MAS, modified Ashworth scale; MS, multiple sclerosis; NRS, numeric rating scale; PP, primary progressive; QF, quadriceps femoris; R, right; RR, relapsing-remitting; SP, secondary progressive; TB, triceps brachii.

Figure 1

Stretches number 1, 10, 20, 30, 40 performed in subject #23 with a metronome pacing of 90 BPM before (T0) and during (T1) THC:CBD treatment on left quadriceps muscle. Each rectified electromyographic recording is extracted from the continuous online recording coupled with the corresponding joint displacement recorded by the electronic goniometer. The mean amplitude of the electromyographic recording (meanEMG) is significantly reduced in T1 compared to T0.

Figure 2

Percentage of subjects considered responders and non-responders according to NRS for spasticity (subjective responders), MAS (clinical responders) and stretch reflex (neurophysiological responders). The intersections between the three assessment methods show the number of subjects that were responders (white background) and non-responders (black background) in both methods reflecting an agreement, or where responder classification was different reflecting lack of agreement (grey background).

Table 1

Patient #	Sex	Age	Muscle	Side	BPM	Baseline MAS (6 points)	Baseline spasticity NRS	EDSS	Months with MS	MS type	Treatment
1	F	60	QF	L	120	3	8	6.5	242	SP	gabapentin, amitryptilin
2	M	48	FCR	R	100	2	7	6	160	PP	none
3	M	64	BB	R	120	0	2	8	240	SP	baclofen
4	F	68	BB	L	100	2	6	7.5	252	SP	venlafaxine, trazodone
5	F	45	QF	R	40	4	8	6.5	228	PP	none
6	F	49	QF	R	40	3	6.5	6.5	158	SP	baclofen
7	F	45	QF	L	120	3	7	7	180	SP	none
8	F	66	FCR	L	120	2	7	7	144	SP	baclofen
9	M	60	QF	R	120	1	5	6.5	276	SP	none
10	F	48	QF	R	60	4	7	6.5	120	SP	baclofen
11	M	57	QF	L	120	2	7	6	268	PP	none
12	F	52	QF	L	120	1	6	6.5	94	SP	baclofen, escitalopram
13	F	42	QF	R	60	3	6	7.5	96	SP	tizanidine
14	F	64	FCR	R	120	2	8	7.5	186	SP	baclofen, amitryptilin, bromazepam
15	F	49	QF	L	120	3	9	6.5	52	SP	4-aminopyridine, baclofen, duloxetin, pregabalin
16	M	40	QF	L	120	3	6	7	210	SP	prednisone
17	M	42	QF	L	60	2	8	6.5	260	SP	baclofen, modafinil
18	F	67	FCR	L	120	1	2	8	180	SP	pregabalin
19	F	60	QF	L	120	0	4	7	106	SP	gabapentin
20	M	60	QF	R	90	4	8	7	168	SP	none
21	F	50	QF	L	120	1	6	6	288	SP	none
22	M	56	QF	R	40	4	7	6.5	306	SP	none
23	M	43	QF	L	90	3	6	6.5	48	SP	none
24	M	53	BB	L	120	2	9	6.5	48	PP	naltrexone
25	F	50	QF	R	120	3	8	6	94	SP	none
26	M	47	TB	R	60	3	7	7.5	212	SP	baclofen, clonazepam
27	M	74	QF	L	60	2	5	6.5	48	SP	baclofen
28	F	53	QF	R	40	4	7	6.5	456	SP	baclofen
29	F	53	QF	L	120	4	9	7	214	SP	baclofen
30	F	67	QF	L	60	3	7	7.5	254	SP	fentanyl, sertraline
31	F	79	BB	L	60	4	8	7.5	132	PP	diazepam
32	F	31	QF	R	120	1	7	6.5	72	RR	none
33	M	44	FCR	R	120	3	7	7	220	SP	none
34	M	53	QF	R	120	1	6	6.5	180	SP	none
35	F	50	BB	L	120	2	10	7	154	SP	baclofen
36	M	47	BB	R	100	2	8	7.5	180	PP	4-aminopyridine

Figure 1

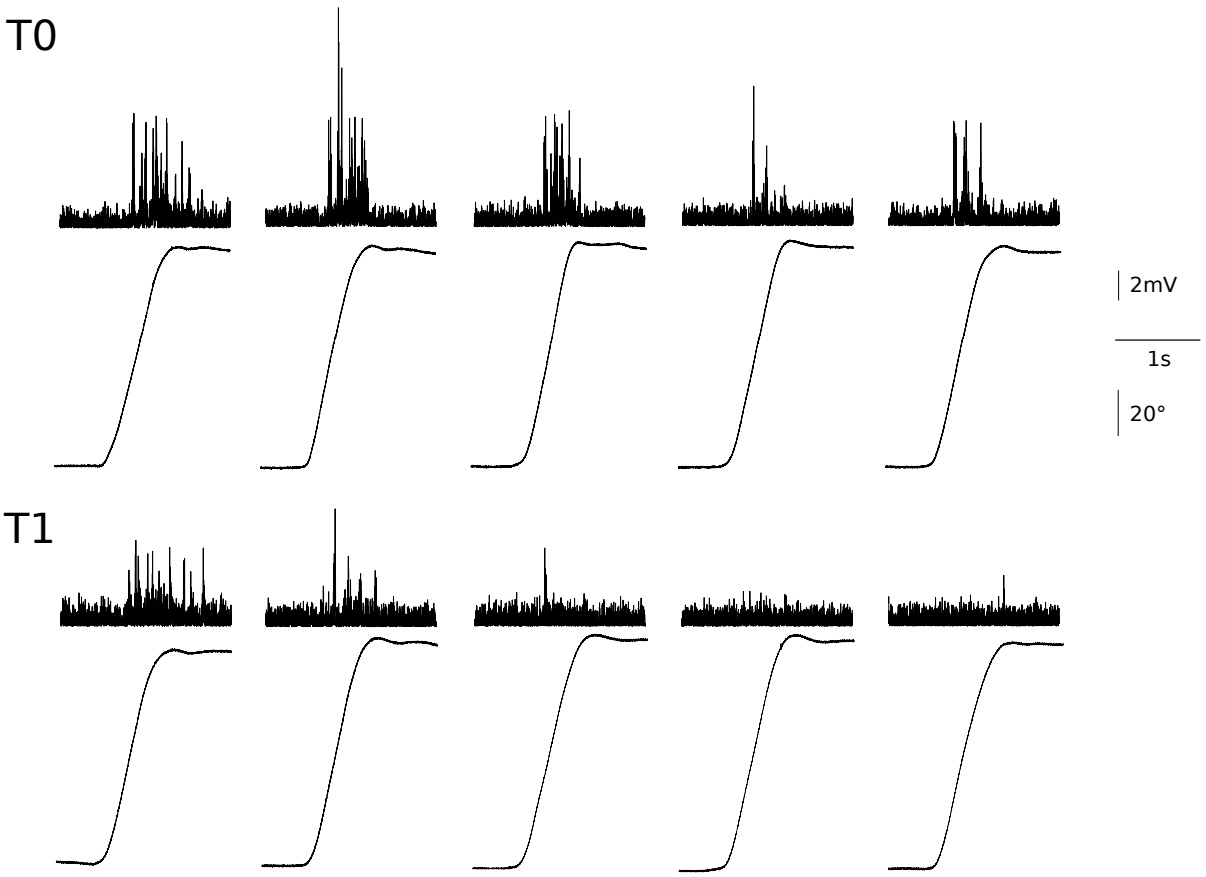
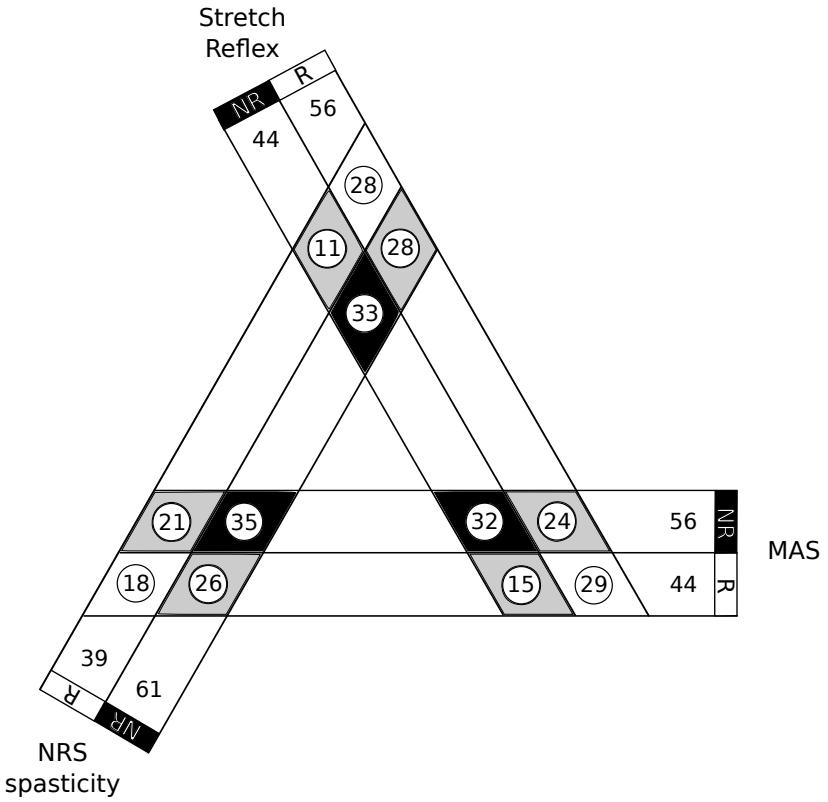


Figure 2


Stretch
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61
R
NR
NRS
spasticity