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Scuola di Scienze Mediche e Farmaceutiche

Dipartimento di Neuroscienze, Riabilitazione, Oftalmologia, Genetica e Scienze Materno-Infantili

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"ASSESSMENT OF EYE BLINK REFLEX IN PATIENTS WITH FIBROMYALGIA SYNDROME"

Candidati:

Dott. PT Jacopo Fornaroli

Dott. PT Luca Palmieri

Relatore:

Dott. PT, OMT Luca Francini

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1. Intro

Blink Reflex (BR) is defined in literature like a defensive response, necessary to the eyes protection and conserve their function; it was studied from lot of years in clinical research, especially in neurology to evaluate the brainstem circuit function and/or dysfunction, and sometimes like evaluative/monitoring tool for different pathology. There are different ways to evoke BR, but today the most common and used way is by giving electric stimulation on to median nerve at the wrist, commonly named Hand Blink Reflex (HBR). Sambo et al. have used HBR in an innovative way, to find and evaluate the Defensive Peripersonal Space (DPPS) that today is considered as protection threshold, where, inside, the stimuli is perceived like dangerous capable to evoke enhanced reflex. DPPS is variable between people, and influenced by anxiety level, depression and proximity of the hand to the face. Clinically Fibromyalgia (FMS) is characterized by diffuse pain, hyperalgesia, allodynia, whit lots of associated problems like emotive disorders, mood disorders, anxiety, stress, depression, sleep disturbance etc. Considered that in FMS the Central Sensitization (CS) and an anxiety play a primary role, and that DPPS is wide spread in anxious patients, we have hypothesized that in FMS patients, different from healthy control group, DPPS is wide spread, and the HBR is enhanced not only inside the DPPS but, even, outside. Other aims of this study will be to see if prepulse condition, in our case cold pressure test, and placebo could modulate HBR component.

This study is divided into two main parts; in the first part will be described the different components, thus BR, HBR, FMS and DPPS, while in the second part will be described the three experimental purposes.

1.1 Blink Reflex

The Blink Reflex (BR) is defined in literature like a defensive response that happens in the orbicularis oculi muscle, leading to the eyelid closure, necessary to the eyes protection and to conserve their function (Esteban 1999). It was widely studied in literature, but the first that named this reflex was Kugelberg in 1952, finding the two main components. BR is formed by two parts, R1 and R2 (Fig. 1), both evoked in the pons of brainstem and registrable with EMG from the orbicularis oculi muscles. R1, ipsilateral to the side of stimulation, is the first

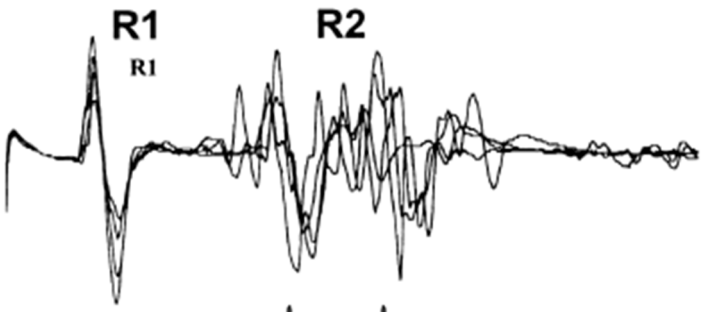

Fig. 1. Track of BR on EMG.

and early response that we can see on the EMG track (Figure 1), but not visible clinically (G. Cruccu et al. 2000). It has ~10 ms latency, rather stable latency (Esteban 1999), from the stimulation and the afferent impulse is carried by medium myelinated (A-β) fibers (Shaani BT. 1970) to the facial moto neurons, through a short oligo synaptic circuit that include from one to three interneurons in the mid pons (Kimura et al. 1994; A. Berardelli et al. 1999).

R2, the late response and more prolonged (Figure 1), is bilateral (sometimes called R2i the ipsilateral and R2c the contralateral), and has ~30 ms of latency, relatively variable and larger magnitude then R1 (Esteban 1999). The afferent impulse has carried by low-threshold (A-δ) fibers (Shaani BT. 1970). It's carried by the descending spinal tract through the dorsolateral region of the pons and medulla oblongata, and stop in the lower spinal trigeminal nucleus; from here start a polysynaptic medullary pathways that ascend, ipsilateral and contralateral to the stimulus side, and stop in the facial nuclei,

were take connections (A. Berardelli et al. 1999; Ongerboer de visser et al. 1978; kimura et al. 1972; kimura 1989). Clinically it is responsible for the closure of eyelids (A. Berardelli et al. 1999; G. Cruccu et al. 2000). Figure 2 show the brainstem circuits.

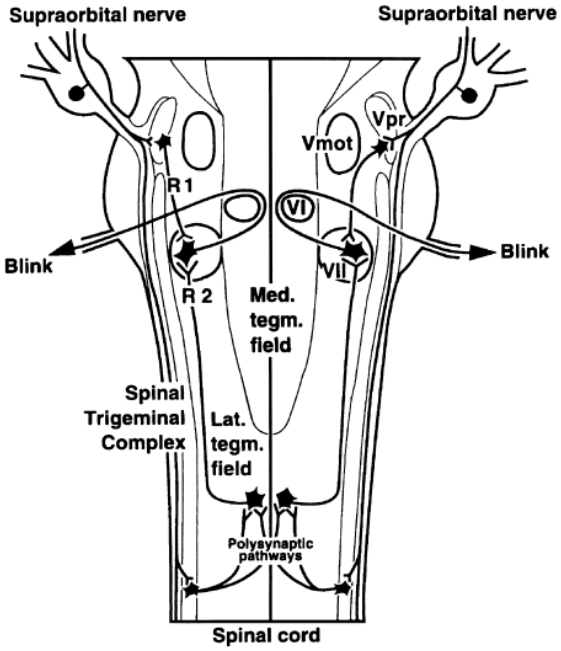

Fig. 2. Vpr→ trigeminal principal sensory nucleus; Vmot→ trigeminal motor nucleus; VI→ abducens nucleus; VII→ facial nucleus (modified from Aremideh et al., 1997).

In literature is also described R3 component of the BR.

It is considered like a sporadic and irregular finding, especially in young and when the intensity of stimulation grows progressively from low to high (Esteban 1999, Ellrich et al. 1996). Like R2 component, R3 is bilateral, and its latency is approximately 80 ms (Ellrich et al. 1996), but is not easily to find and distinguible from R2, especially in pathology (Esteban 1999).

In literature there are a lots factors that could modify BR in healthy, specially R2 because polysynaptic, resulting the only modifiable component, like intensity of stimuli, voluntary closing of the eyes, attention to the stimuli, tension, fear arithmetic calculation, execution of specific tasks (Esteban 1999) and tobacco (Leon-S et al. 1997).

In clinical it was seen variations on different component of BR in relation of site of lesion, like shows in Figure 3 (Esteban 1999).

Anatomical Lesion	*Lesional Type*	*Affected side stimulation*			*Unaffected side stimulation*		
		R1	*R2*		*R1*	*R2*	
			Ipsilateral	*Contralateral*		*Ipsilateral*	*Contralateral*
Trigeminal nerve	A	delay/ absent	delay/ absent	delay/ absent	normal	normal	normal
Pons	B	delay/ absent	normal	normal	normal	normal	normal
Spinal trigeminal tract/nucleus	C	normal	delay/ absent	delay/ absent	normal	normal	normal
As C plus laterobulbar reticular formation	D	normal	delay/ absent	delay/ absent	normal	normal	delay/ absent
Facial nerve	E	delay/ absent	delay/ absent	normal	normal	normal	delay/ absent

Figure 3. Anatomical lesion and different BR components (Esteban 1999)

The parameters of BR that take a primary role in the studies are:

- **Latency (ms)** → from the stimuli to the onset of both component to the BR;
- **Amplitude (in mV)** → is the maximal peak-to peak value, from the baseline to the top, in the EMG track;
- **Duration (ms)** → from the onset of the R1 to the end of R2.

Like shown before, the latency of R1 is more or less ~10 ms, and 30 ms for R2 component (Shaani BT. 1970). Amplitude and duration is largely variable between individual, and apparently influenced by recording method and intensity of stimulation (Esteban 1999), but the R1 duration, for Shaani, is 8-12 ms, R2 duration 30-40 ms (Shaani BT. 1970).

From the first studies, BR was evoked by different ways, like light on the cornea, eyelash touching or glabellar tapping, but today the most efficiency and easily way to provoke BR is the electrical stimulation. The stimulation on the supraorbital nerve, distal branch of the trigeminal nerve, is then most efficiency way to evoke the BR and its components. Like shows the Esteban's review on the BR, other ways to evoke it are acoustic stimuli, visual light, somatosensory stimuli and pain stimuli, especially given by electrical

stimulation, easily on the face and even on the lower and upper limb, respectively on the median nerve and sural nerve (Esteban 1999).
Sambo et al. was the first that have used the BR evoked by median nerve stimulation, named Hand Blink Reflex (HBR), to study the different component of BR and its variations in relation to the defensive peripersonal space (Sambo et al 2012 a,b, Sambo et al. 2013, Sambo et al. 2016).

Brainstem reflexes, especially BR, are largely studied and used in clinical neurology, due to the strategic position of the neural structure of BR, easily accessible of musculature belonging trigeminal and facial nerve and the highest brainstem representation (Esteban 1999). Is even used to improve clinical diagnostic like cervical cord injury, movement disorder, focal lesion in brain, brainstem, cranial neuropathies, facial neuropathy, hemi facial spasm, trigeminal neuropathy, craniofacial pain, intra-axial focal and multifocal lesion, spasticity, Huntington's disease, Parkinson's disease and syndromes, Dystonia, Cerebellar disease, essential tremor and Myoclonus (G. Cruccu et al. 2000). In conclusion, trigeminal-facial BR is one of the most brainstem reflex used in clinical neurology like diagnostic/prognostic method and to establish the evolution of disorders (Esteban 1999).

1.2 Hand Blink Reflex

HBR is a blink reflex (BR) evoked by median nerve stimulation at the wrist. It is a defensive response and is enhanced and evoked rapidly when the impulse is warned potentially threat (Margaret MB et al 2008) by the patient. It is formed by two parts, R1 and R2, both evoked in the pons of brainstem and registrable with EMG from the orbicularis oculi muscles. Its latency, like R2 component of trigeminal-facial BR, is ~45 ms and share the same subcortical circuit in the brainstem, even if the HBR involve the mesencephalic reticular formation (Leon et al. 2011).

It was largely used by Sambo et al., and thanks to this method, the Defensive Peripersonal space was measured for the first time (Sambo et al 2012 a, b). Whit the first study (Sambo et al 2012 a), they have seen that the BR was increased when the hand was near the face, even with the eyes closed, suggesting that the proprioception of the arm play a primary role. The second study (Sambo et al. 2012b) confirmed the previous results and improve a fine cognitive tuning of the DPPS, considering that with a screen between the face and the hand where the electrical stimuli was applied, the extension of DPPS was reduced, and the HBR was decreased.

Studies had shown a very important component of HBR that could be studied to evidence brainstem dysfunction and the excitability of BR, the Prepulse Inhibition (PPI) and the habituation phenomena. Prepulse is a first stimuli, low intensity, that can't elicit any response by itself, but is able to modulate the R2 component of HBR; the prepulse stimuli can be in different sensory modality, the same or differently from the stimuli used to evokes reflex (Berardelli et al. 1999). The Prepulse stimuli can be facilitator or inhibitory, in relation to the time between the prepulse and the stimuli (Valls-Solè et al. 1999). So, the role of PPI is to protect the brain from sensory overload, and create a uncorrected modulation of information, considered that a reduced PPI function is correlated with less filtering of information, and a lots of information flows from the periphery to the brain (Berardelli et al. 1999). The PPI seems to be the best neurophysiological mechanism of sensory gating in brainstem (Valls-solè et al. 1999, kumari et al. 2003), and directly linked with the abnormal perception and modulation of pain. Thus reduced mechanism of PPI, with central sensitization, could be the reasons that could try to explain hyperalgesia and allodynia, especially in patients with Fibromyalgia Syndrome. This last affirmation is improved with the evidence of brainstem dysfunction in FMS (Kofler et al. 2013).

The other condition is habituation; it could be understood like transitory changes, no long term, induced to the reflex response by the same stimuli that provoke it (Esteban 1999). Is usually studied by rhythmic stimulation on order to 4-5 series of 8 stimuli at rate of 0.2, 0.5 and 1 Hz, and to avoid habituation shocks should be delivered at intervals of 7 s or more, while the subject is in alert state (Berardelli et al. 1999). Normally the habituation phenomena is used to measure the excitability of BR and thus study pathophysiological disease (Esteban 1999).

1.3 The Defensive Peripersonal Space (DPPS)

Like putted on evidence in the previously chapter, Sambo et al. have used HBR to identify and define DPPS.

The interaction with objects is the result of the visual information outside the body with tactile information arising on the body, and the representation of this intermediary space has also known as “Defensive Peripersonal Space” (DPPS).

This definition originates from electrophysiological studies on macaque monkeys that pointed out the existence of a population of particular neurons. The main characteristic of these neurons is that more of responding both to visual and tactile stimulation, their visually evoked response are modulated by the distance between the object and the tactile receptive field.

In humans DPPS represents a safety margin and he has a particular importance in survival: whenever a potentially dangerous stimulus enters it, the individual engages in more efficient actions aimed at self-protection (Cooke and Graziano, 2003).

In addition to the nature of the stimulus, this magnitude is also influenced by the distance between the body and the stimulus, in fact stimuli closer to our body will be perceived, as more minatory and defensive responses will be enhanced. (Cooke and Graziano, 2003; Combe and Fujii, 2011).

More, this magnitude can be influenced also by anxiety and fear.

Anxious and fearful subjects in fact, may transpose the spatial location of the threatening stimulus, judging it closer than it verily is.

For this reason, these subjects may have different defensive behaviors compared with normal individuals before minatory stimulus located at same distance from the body.

It has been recently identified in humans that when the hand is close to the face and therefore inside the DPPS, the BR, elicited by the stimulation of the median nerve (HBR), could be enhanced. (Sambo et al., 2012a, b).

In this condition in fact, the electrical stimulation of the hand could be perceived as a potentially dangerous event for the eye and this may elicit an increased response.

As we said DPPS represents a “safety margin” with the function to protect ourselves from potentially dangerous stimuli, but we have to say that this is variable from subject to subject because everyone differ in what he considers more or less dangerous.

1.4 Fibromyalgia and their criteria for the classification

In our study, we have included fibromyalgic patients. The diagnosis of fibromyalgia syndrome (FMS) is still today controversy, even because FMS presents a lots of disorders like other rheumatic, or not, disorders that could confuse the diagnosis; commonly is defined like chronic widespread pain, typically with allodynia and hyperalgesia, in absence of tissue inflammation or damage, and the diagnosis become to exclusion. Often the patients have a lot of associated symptoms, like sleep disturbance, mood disturbance, no cardiac chest pain, heartburn, palpitations, headache, irritable bowel, fatigue and cognitive dysfunction, where depression and anxiety are the most commonly seen (clauw,2009). The first important study that tried to understand and explain FMS was made in 1990 (Wolfe et al. 1990) and combination of:

- widespread pain (at least 3 months, axial pain, right and left side, upper and lower segment);
- tenderness at palpation of 11 or more of the 18 specific tender point;

Resulted to be the new criteria for the diagnosis. The sites of 18 tender point (9 bilaterally) are:

- *Occiput:* at the sub occipital muscles insertion;
- *Low cervical:* at the anterior aspect of the intertransverse spaces C5-C7;
- *Trapezius:* at the midpoint of upper border;
- *Supraspinatus:* at origins, above the scapula spine near the medial border;
- *Second rib:* at the second costochondral junction;
- *Lateral epicondyle:* 2 cm distal to epicondyles;
- *Gluteal:* in upper outer quadrants of buttocks in anterior fold of muscle;
- *Greater trochanter:* posterior to the trochanteric prominence;
- *Knee:* at the medial fat pad proximal to the joint line.

Other important characteristic, FM pain is typically diffuse or multifocal, often decreased or enhanced, and frequently migratory in nature (Clauw 2009).

However, these first diagnostic criteria received many objections, specially the tender point palpation criteria, because performed incorrectly, when tested, or even refused to do during the visit. Other findings versus tender point palpation was putted on evidence from two study, where random pressure showed high sensitive response of pain in FMS like palpation of trigger point (Harris et al. 2006, Geisser et al. 2007), and allodynia is not limited onto tender point sites (Desmeules et al. 2003). Therefore, to improve the first diagnostic criteria, the American college of rheumatology develop two important tools to simply define the severity of symptoms: the widespread pain index (WPI), that measure the painful body region (correlated with tender point), and symptom severity (SS) scale. At the results, new criteria improve the old: WPI≥7 and SS≥5, or WPI 3-6 and SS≥9. These new criteria improved the old, but not replaced (Wolfe et al. 2010).

From an overview, FMS could be more diffuse in female gender than male, and the patients shows two important conditions, that could be directly linked with central sensitization, deficit of pain inhibition mechanism (DNIC) and depression:

- **Hyperalgesia** → enhanced pain responses to normally painful stimuli
- **Allodynia** → pain responses to normally non painful stimuli

that could lead to abnormal sensory processing, and generalized pain, not confined to the site where the stimuli is applied on the body (Clauw 2009), and this could suggest a dysfunction of central pain mechanism.

The etiology is still today uncertain, but some environmental factors was been found that could lead to chronic widespread pain or fibromyalgia in 5-10% of the individuals affected like shows in figure 4 (Clauw 2009):

- Peripheral pain syndromes
- Infections (e.g., parvovirus, Epstein-Barr virus, Lyme disease, Q fever)
- Physical trauma (e.g., automobile accidents)
- Psychological stress/distress
- Hormonal alterations (e.g., hypothyroidism)
- Drugs
- Vaccines
- Certain catastrophic events (war, but not natural disasters)

Figure 4. “Stressor” capable of triggering FMS and related condition (Clauw 2009)

Like the diagnosis, pathophysiology of FMS is controversy too; it seems that a primary role is played by increase of excitability in central nociceptive circuits (Lee YC et al. 2011) and decrease antinociceptive responds (Julien et al. 2005). In other words the Central Sensitization, intended like hyper excitability of spinal or higher brain center neurons without peripheral nerve dysfunction that process in wrong way the peripheral stimuli creating an abnormal expansion of receptive zone in periphery, overlooks the inhibitory pain modulation process, developing and keeping chronic spontaneous pain (Desmeules et al. 2003). Specifically, people with FMS show dysfunction in brainstem circuits, specially decrease of Prepulse Inhibition (PPI), sensory gating (M. Kofler et al. 2014) and Diffuse Noxious Inhibitory Controls (DNIC) (Dorit P. et al. 2009). PPI and sensory gating, either under control of Peduncle Pontine Nucleus (PPN), play a fundamental role in filtering afferent input information from the periphery to the brain; dysfunction at these level may lead to abnormal sensory perception in FMS, resulting from the lot of information arrived at the brain. Brain cannot process all these informations, and maybe this could be the neurophysiological mechanism of allodynia and hyperalgesia in FMS (M. Kofler et al. 2014). DNIC, instead, is a part of pain modulatory mechanism of the brain, representing its bottom-up part, and its decrease, could be responsible of abnormal pain processing that could lead to chronic pain (Dorit P. et al. 2009) and its widespread location. DNIC deficit in FMS was reported (Lautenbacher et al. 1997, Desmeules et al. 2003). Maybe these evidences from the literature could explain the mechanism that submit at altered responses to stimuli in FMS. To enforce this, another

study put on evidence that the affective distress in FMS patients are connected with enhanced defensive activation and this could be another evidence that improve the process of maintenance allodynia and hyperalgesia (Emily J. et al. 2009).

Like in other rheumatic disease, patients with FMS can show depression, and other psychological factors like hypervigilance, catastrophizing, external locus of pain control (Clauw 2009), that could enhance pain at rest and stress (Peter D. et al. 2013). Is furthermore underlined how anxiety and depression influence FMS, associating it with increased pain and experimentally-induced pain (Thieme et al. 2004) and persistent symptoms (Finset et al. 2004). The decrease of DNIC in FMS was studied even with experimentally-induced pain, especially with cold-pressor test, showing decrease in FMS respect to healthy group (Julien et al. 2005), more pronounced when FMS was correlated with depressive symptoms (Barcellos de souza et al 2009).

1.5 FIBROMYALGIA and DPPS

Fibromyalgia syndrome (FMS) is one of the main causes of chronic widespread pain. Is a disabling disease associated with distress.

Abnormal perception of pain is one of the main feature of FMS (Ceko et al., 2012). The most common symptoms in these patients are hyperalgesia, allodynia, sleep disturbance, cognitive dysfunction, fatigue, restless leg syndrome and headache. Hyperalgesia and allodynia may result from peripheral or central sensitization, to which several factors may contribute (Carville et al., 2009). Allodynia is a typical component of Fibromyalgia symptoms and is pain generating from innocuous mechanical stimuli. Furthermore, another important pathophysiological symptom is hyperalgesia that is an increased sensitivity to pain (Clauw, 2009). We wanted to compare then healthy subjects with subject with Fibromyalgia syndrome (FMS). An abnormal perception of pain is one of the main feature of FMS (Ceko et al., 2012). This second category of people belongs to chronic widespread pain population. Furthermore, these patients usually present also some characteristic symptoms like fear, anxiety.

The study we refer reports for the first time an increased blink reflex (BR) excitability and reduced prepulse inhibition in patients with FMS as compared to healthy subjects.

Results from the present study suggest that FMS is associated with an enhanced defensive activation to no painful threat-related stimuli. This can be explained as a deficit in central circuit that may ultimately be a marker for establishment or maintenance of FMS.

We hypothesized that DPPS may be increased in patients with FMS and we therefore compared the HBR detected in fibromyalgic patients to HBR observed in healthy control subjects in order to obtain an estimate of brainstem reflex excitability.

The rilevation has been in 3 different moments with the hand placed in 3 different distances from the face to define the different activity of DPPS at each level.

We would expect then an increased activation of HBR at a farther distance from the face in patients with FMS.

1.6 Placebo effect

The placebo effect is a psychobiological answer that happens in the patient's brain after the administration of inert substance, therapeutic treatment or sham, a lot of time associated to verbal suggestion, or other modalities, that could lead to suppose, at the patients, a clinical benefit (Price et al. 2008). This could happens with every therapeutic treatment, because the clinical outcome is linked with the specific effect of the treatment and, even, the contextual factors where the treatment is delivered.

From the psychological point of view, a lots of mechanisms contributes to placebo effect, including expectation, memory, motivation, conditioning, learning and somatic focus (awareness of owns symptoms) (De la Fuente-fernandez et al. 2009).

A fundamental mechanism of placebo effect is the expectation of future outcome, thus what the patient think that's going to happens, followed the placebo administration, where the patient prepare its brain/body to anticipate an event, in order to better adapting to it. To Improve this mechanism, suggestion and verbal stimuli could be associated to modulate the following cognitive answer, leading to better outcome possible, provoking positive or negative answer in patients (Finnis et al. 2010).

With the expectation, conditioning play a primary role in placebo effect, where a conditioned stimuli (neutral like could be placebo) become effective, able to reduce the patient's symptoms, if is associated with non-conditioned stimuli (active principle of the treatment). Expectation and conditioning are improved with other learning processes that could enhance the placebo effect, like past experiences, and social factors, that could lead to observation and imitation, where a person become influenced from the other people's behaviors and society's stereotype (Finnis et al. 2010). Therefore, placebo effect is a learning phenomenon, based on various mechanism, from the unconscious conditioning to the cognitive conditioning, built and enforced by the individual's expectation, and much influenced by contextual factors (Testa et al. 2016).

1.7 Aims of the study

The aims of this study are:

a) Could be the DPPS wider in FMS respect in healthy volunteers, and could be R2 component of HBR enhanced at different distance between two groups?

b) Can conditioned pain be considered a prepulse condition capable to modulate R2 component of BR?

c) Can placebo modulate R2 component of BR?

To answer at these questions we have planned three studies, below specifically described.

2. MATERIAL AND METHODS

Fibromyalgic and control group volunteers inclusion criteria

First, we identified Fibromyalgic patients at DIMI rheumatology center in Genoa. We based on Wolfe diagnostic criterias as we precedently said.

We administered to 50 of them the Central Sensitization Inventory questionnaire (CSI). Central sensitization (CS) is a hyperarousal of central nervous system neurons, and this result in a hypersensitivity to painful and non-painful stimuli. The Central sensitivity syndrome encloses nonspecific disorders as Fibromyalgia. The CSI was introduced then as a screening test to identify CSS patients.

Later we selected subjects with the highest score at CSI booklet, and we kept them for the experiment.

Considered that we take like starting point the study made by Sambo, in order to be much clinically and statistically relevant, 15-20 FMS subjects (n° male and n° women) aged between n° - n° and 15-20 healthy group (n° male and n° women) aged between n°-n°, was recruited voluntarily. The two group (C → control and S → study) could be much homogeneous possible in gender and age, in order to do not represent a starting bias. The relevation has been realized in all participants at the right hand.

An example of CSI booklet is reported in the appendix.

a) Could be the DPPS wider in FMS respect in healthy volunteers, and could be R2 component of HBR enhanced at different distance between two groups?

In humans DPPS represents a safety margin and he has a particular importance in survival: whenever a potentially dangerous stimulus enters it, the individual engages in more efficient actions aimed at self-protection; we have previously seen how anxiety and the treating perception of the stimuli can spread DPPS, and enhance R2 component of HBR. These differences had been observe only in the healthy subjects. We have hypothesized that in FMS, where CS and altered stimuli perception, sometimes perceived like treating, play a primary role differently from healthy control group, DPPS is wide spread, and the HBR is enhanced not only inside the DPPS but, even, outside.

- **Participants Placement**

Subjects were on a comfortable and adjustable seat, and their legs were at 90° flexion at hip and knee. Their elbow was supported on a table which height allowed them to keep their right arm at 90° flexion at shoulder. The elbow angle will be obviously modified during the experiment.

We placed 3 bipolar electrodes, one on the median nerve at the right wrist and the others at the supraorbital nerve in proximity of orbicularis oculi muscle bilaterally.

We attached the stimulator with a Velcro strap to the wrist and the face.

- **Stimulation and Recordings of HBR**

We first adjusted the intensity of the stimuli for each subject until the elicitation of a noticeable BR (intensity of n°). The stimulus duration was (n°) ms and every stimuli is 30 second away from the other.

We recorded the EMG activity from the orbicularis muscles bilaterally.

The stimulator were linked to the Biopac that was linked to the pc for the detection.

We have studied modulated component of BR, R2, measuring latency, amplitude and duration.

- **Procedures**

Once obtained the right intensity to elicit the HBR we started to record in the “far” condition that should be outside of the DPPS. In this condition, participants had their right forearm at 120° respect to the arm and with the wrist at 60 cm from the ipsilateral eye, and a foam pillow on the table supported it.

Later we recorded the HBR in the “near” condition, that provided that forearm was at 90° respect to the arm and 20 cm from the ipsilateral eye.

Finally, the third condition, “ultra-near”, with their forearm at 75° respect to the arm and 4 cm from the ipsilateral eye.

In the ultra near condition, participants were not able to see their thumb twitching because this was upper their field of view.

Subjects were submitted to 15 stimulations to the wrist in 3 different conditions in 3 different blocks.

In both experiment will be used NRS, from 1 to 10, to evaluate pain perception of the subject. NRS will be asked to each subject before start the experiment and at the end of each electrical stimulation.

- **Expected Results**

Considered the evidences from the literature underlined in the introduction, we could suppose some findings.

- Considered that DPPS has been found and measured in healthy peoples;
- considered that this space is enhanced in anxious subjects;
- considered that in chronic pain is enhanced the painful perception, especially when the chronic pain is related with anxiety and depression;
- considered that in FMS painful perception is enhanced by central sensitization, and anxiety and depression are widely diffused;

we could expect an increase of R2 component of HBR in the study group (S) respect control (C), especially when the hand is in “near” and “ultra-near” conditions, because we could expect that the DPPS in S group is wider that in C group, and so the stimuli could be perceived dangerously in FMS patients respect healthy ones.

b) Can conditioned pain be considered a prepulse condition capable to modulate R2 component of BR?

We have seen previously how prepulse stimuli could modify the R2 response, decrease it or increase it, especially when the prepulse is experimentally-induced with cold pressor test or electrical stimulation that activate DNIC mechanism, leading to

“momentary desensitization” decreasing painful perception leading to R2 component decrease.

- **Participants placement**

Subjects were on a comfortable and adjustable seat, and their legs were at 90° flexion at hip and knee. Their elbow was supported on a table which height allowed them to keep their right arm at 90° flexion at shoulder. Bath container with cold-water will placed near subject.

- **Procedure**

Both participant, before delivering electric stimulation lead to evoke HBR, put one arm until the shoulder, the same where the successive stimulation will deliver, in a water with ice (12° C) for two minute.

In both experiment will be used NRS, from 1 to 10, to evaluate pain perception of the subject. NRS will be asked to each subject before placing arm into cold water and when he leaves it from the water.

- **Stimulation and recording of HBR**

Procedure, Stimulation and recording of HBR will be the same of the previous experiment.

- **Expected results**

In C group we could expect a decrease of R2 component, while in S group we could expect unchanged R2 component or even enhanced, considered that in FMS DNIC mechanism is decrease and central sensitization lead to enhance of perception with hyperalgesia and allodynia, and the prepulse stimuli, that normally is perceive like non painful, in FMS could be perceived like painful and enhance the perception of second stimuli that evoke HBR.

c) Can placebo modulate R2 component of BR?

- **Participant placement**

Both participant will placed supine on a bed.

- **Procedures**

At both participant, before delivering electric stimulation lead to evoke HBR, will be delivered a sham sub occipital PA, improved to a verbal placebo, where the therapist will say to the patient how the treatment could decrease the pain perception of electrical stimuli.
In both experiment will be used NRS, from 1 to 10, to evaluate pain perception of the subject. NRS will be asked to each subject before sham treatment and after the electrical stimulation.

- **Stimulation and recording of HBR**

Procedure, Stimulation and recording of HBR will be the same of the first experiment.

- **Expected results**

Considered that placebo is on cognitive level, we could expect that both S and C group responds with decrease of R2 component, and respond to placebo effect. This may differ from the previous experiment where the aim was to evaluate if S group presented DNIC mechanism. If the experiment will confirm the expected results, we might say that DNIC and placebo effect have two different mechanism, where placebo effect rely principally on cognitive stimuli.

Data analysis and statistics

The primaries outcomes will be:

- RMS, latency, amplitude and duration of R2 component of HBR;
- NRS of pain perception.

These outcomes will be analyzed with T di Student.

Another outcome will be take in consideration, the CSI booklet. For this outcome a descriptive statistic will be performed, and analyzed by ANOVA. The level of significance was set at $P < 0.05$ for all statistical analyses.

CONCLUSIONS

Like shows before, FMS is still today controversy, specially the diagnosis. This is in part because FMS presents lots of disorders like other rheumatic, or not, disorders that could confuse the diagnosis. Other important peculiarity of FMS is that there are not laboratory tests, blood examinations or gold standard like in other rheumatic disorders and often the doctors tells to the patients that could have FMS only for exclusion. Furthermore, we have underlined how FMS and HBR are closely connected, especially how the stimuli perception and the central sensitization components (allodynia and hyperalgesia) can modify the R2 component of BR, closely connected with the severity of the symptoms perceived by the patients.

If the aims of these studies will be confirmed, a new approach to FMS could be defined, especially to the take care and treatment of this pathology that is still today controversial, and very difficult in the diagnosis. Surely if the aim of the first study will confirm the differences between DPPS and the enhance of HBR in FMS, HBR could take part in diagnosis of FMS, improving the existent diagnostic criteria that is still today controversial. Unfortunately, we have not ended the study, but the literature and the rational that is on the base of study purpose, could demonstrate that HBR could be a diagnostic and evaluative test to improve the existing criteria for FMS. Maybe HBR could be used even to take over control the evolution of the FMS, especially when associated

with pharmacological treatment. Even, if the aims of second and third studies will confirm the DNIC deficit and a positive placebo effect on to the pain perception, counting that these two aspects are closely connected among them, we should take in consideration, whit the pharmacological treatment, to associate placebo treatment, verbal and manual, seen and considered that the FMS is a multifactorial pathology, and the only pharmacological treatment isn't enough.

Probably this study does not resolve controversies on to FMS, but could surely give some weapon to improve take care of FMS patient.

Appendix

CONSENSO INFORMATO PER PARTECIPAZIONE ALLO STUDIO E TRATTAMENTO DEI DATI SENSIBILI

TITOLO DELLO STUDIO: Adattamento cross-culturale in Italiano ed analisi della struttura interna e della validità di costrutto del Central Sensitization Inventory in soggetti con dolore cronico e soggetti sani.
INVESTIGATORI PRINCIPALI: Dr. Alessandro Chiarotto, Dr. Carlotta Viti, Dr. Marco Testa.

Dichiaro di aver ricevuto informazioni verbali adeguate da uno degli investigatori circa le finalità di questa ricerca scientifica e circa le motivazioni per una mia partecipazione. Dichiaro inoltre di aver avuto risposte esaustive ad ogni domanda che posso aver posto in relazione al presente studio.

Sono consapevole del fatto che il trattamento a cui mi sottoporrà il fisioterapista sarà indipendente dalla ricerca e non sarà modificato in nessuno modo dall' esito delle mie risposte. Sono informato/a del fatto che non potrò essere identificato/a in nessun report dello studio e che le mie risposte verranno raccolte in via confidenziale in accordo con la legislazione italiana sulla privacy. Sono altresì consapevole che gli sperimentatori dello studio potranno visionare le mie risposte al fine dell'elaborazione dei dati. Sono inoltre stato informato/a del fatto che posso rifiutarmi di rispondere a qualsiasi domanda contenuta in questo booklet.

Accetto di partecipare liberamente allo studio menzionato, avendo compreso i rischi ed i benefici che vi sono implicati.

Acconsento al trattamento dei dati personali e sensibili raccolti nell'ambito del presente studio, nei termini e modi indicati da uno degli investigatori principali, consapevole che verrà garantito l'anonimato nel trattamento di questi dati.

Acconsento che gli sperimentatori raccolgano ed elaborino i dati derivanti dalle indagini cui verrà sottoposto e ne curino la pubblicazione.

Cognome e Nome del paziente Data Firma di consenso del paziente

……..…

Cognome e Nome dello sperimentatore Data Firma dello sperimentatore

……

PARTE PER SPERIMENTATORE

Gruppo di Appartenenza per lo Studio:

□ Fibromialgia □ Artrosi delle Mani □ Artrite Reumatoide
□ Disturbi Temporo-Mandibolari

Data Insorgenza Patologia	Data Diagnosi Patologia	Terapia Farmacologica
……	……	……

PARTE PER PAZIENTE

Data _____

Nome e Cognome_____
Età _____ anni
Sesso: □ M □ F
Sposato: □ Sì □ No
Fumatore: □ Sì □ No

Ultimi livello scolastico completato:
□ Scuole Elementari □ Scuole Medie Inferiori □ Scuole Medie Superiori □ Laurea Universitaria □ Dottorato di Ricerca

Attività lavorativa:
□ Lavorando al momento □ Disoccupato/a, in cerca di lavoro □ In pensione

□ In malattia o maternitá □ In aspettativa □ Casalingo/a
□ Temporaneamente licenziato/a o sospeso/a
□ Disabile a causa del dolore, permanentemente o temporaneamente
□ Disabile a causa di ragioni diverse dal dolore
□ Altro, specificare:_____

Peso:_____ Altezza:_____ BMI (Kg/m2):_____

Da quanto tempo il dolore é un problema per Lei?

 Da meno di 1 mese 1-3 mesi 3-6 mesi

 6 mesi-1 anno 1-5 anni piú di 5 anni

Quanto spesso il Suo dolore é stato un problema per Lei negli ultimi 6 mesi?

 Tutti i giorni o quasi tutti i giorni negli ultimi 6 mesi
 Almeno la metá dei giorni negli ultimi 6 mesi
 Meno della metá dei giorni negli ultimi 6 mesi

Durata del dolore _____ mesi

Sedi del dolore:

 Lombare Toracico Cervicale

 Spalle Testa Gambe
 Braccia Altro, specificare: _____

Terapie in corso:

 Ansiolitici/antidepressivi Antidolorifici Miorilassanti
 FANS/cortisonici Altri farmaci, specificare:_____

Comorbidità

 Patol. Cardiache Patol. Respiratorie Patol. endocrine
 Patol. Gastro-intestinali Patol. Renali Ansia/Depressione
 Altre patol. app. locomotore

CENTRAL SENSITIZATION INVENTORY: PART A

QUESTIONARIO SULLA SENSIBILIZZAZIONE CENTRALE: PARTE A

Cerchiare la risposta più appropriata posta alla destra di ciascuna affermazione.

1	Al risveglio mi sento stanco e non rigenerato	Mai	Raramente	Ogni tanto	Spesso	Sempre
2	Mi sento i muscoli rigidi e indolenziti	Mai	Raramente	Ogni tanto	Spesso	Sempre
3	Soffro di attacchi d'ansia	Mai	Raramente	Ogni tanto	Spesso	Sempre
4	Digrigno o serro i denti	Mai	Raramente	Ogni tanto	Spesso	Sempre
5	Soffro di diarrea e/o stitichezza	Mai	Raramente	Ogni tanto	Spesso	Sempre
6	Ho bisogno di aiuto per svolgere le mie attività quotidiane	Mai	Raramente	Ogni tanto	Spesso	Sempre
7	Sono sensibile alla luce intensa	Mai	Raramente	Ogni tanto	Spesso	Sempre
8	L'attività fisica mi stanca molto facilmente	Mai	Raramente	Ogni tanto	Spesso	Sempre
9	Ho dolori in tutto il corpo	Mai	Raramente	Ogni tanto	Spesso	Sempre
10	Soffro di mal di testa	Mai	Raramente	Ogni tanto	Spesso	Sempre
11	Sento fastidio alla vescica e/o bruciore, quando urino	Mai	Raramente	Ogni tanto	Spesso	Sempre
12	Non dormo bene	Mai	Raramente	Ogni tanto	Spesso	Sempre
13	Ho difficoltà a concentrarmi	Mai	Raramente	Ogni tanto	Spesso	Sempre
14	Ho problemi cutanei, quali secchezza, prurito o eruzioni cutanee	Mai	Raramente	Ogni tanto	Spesso	Sempre

15	Lo stress peggiora i miei sintomi fisici	Mai	Raramente	Ogni tanto	Spesso	Sempre
16	Mi sento triste o depressa/o	Mai	Raramente	Ogni tanto	Spesso	Sempre
17	Ho poca energia	Mai	Raramente	Ogni tanto	Spesso	Sempre
18	Ho tensione muscolare al collo e alle spalle	Mai	Raramente	Ogni tanto	Spesso	Sempre
19	Ho dolore alla mandibola/mascella	Mai	Raramente	Ogni tanto	Spesso	Sempre
20	Certi odori, quali i profumi, mi provocano vertigini e nausea	Mai	Raramente	Ogni tanto	Spesso	Sempre
21	Ho spesso bisogno di urinare	Mai	Raramente	Ogni tanto	Spesso	Sempre
22	Quando la notte cerco di addormentarmi, provo fastidio alle gambe e sento il bisogno di muoverle in modo irrequieto	Mai	Raramente	Ogni tanto	Spesso	Sempre
23	Ho difficoltà a ricordare le cose	Mai	Raramente	Ogni tanto	Spesso	Sempre
24	Ho subito un trauma da bambina/o	Mai	Raramente	Ogni tanto	Spesso	Sempre
25	Ho dolore nella regione pelvica	Mai	Raramente	Ogni tanto	Spesso	Sempre

CENTRAL SENSITIZATION INVENTORY: PART B

QUESTIONARIO SULLA SENSIBILIZZAZIONE CENTRALE: PARTE B

Barrare la casella corrispondente posta alla destra di ciascuna diagnosi e indicarne l'anno.

		NO	SÌ	Anno della diagnosi
1	Sindrome delle gambe senza riposo (RLS)			
2	Sindrome da stanchezza cronica			
3	Fibromialgia			
4	Disordini temporo-mandibolari (TMJ)			
5	Emicrania o cefalea/mal di testa tensivo			
6	Sindrome del colon irritabile			
7	Sensibilità chimica multipla			
8	Lesioni cervicali (incluso il colpo di frusta)			
9	Attacchi di ansia o di panico			
10	Depressione			

<u>Negli ultimi 7 giorni</u>, come giudicherebbe il Suo dolore in media?

0	1	2	3	4	5	6	7	8	9	10

NRS

Nessun Dolore

Il peggior dolore immaginabile

SF-36 (Short Form-36 Health Survey)

Sottoscala Funzionalità Fisica

Le seguenti domande riguardano alcune attività che potrebbe svolgere nel corso di una qualsiasi giornata. Ci dica, scegliendo una risposta per ogni riga, se attualmente la **Sua salute** La limita nello svolgimento di queste attività.

	Sì, **mi limita** **parecchio**	**Si,** **mi limita** **parzialmente**	**No,** **non mi limita** **per nulla**
1. **Attività fisicamente impegnative**, come correre, sollevare oggetti pesanti, praticare sport faticosi	**1**	**2**	**3**
2. **Attività di moderato impegno fisico**, come spostare un tavolo, usare l'aspirapolvere, giocare a bocce o fare un giretto in bicicletta	**1**	**2**	**3**
3. Sollevare o portare le borse della spesa	**1**	**2**	**3**
4. Salire **qualche** piano di scale	**1**	**2**	**3**
5. Salire **un** piano di scale	**1**	**2**	**3**
6. Piegarsi, inginocchiarsi o chinarsi	**1**	**2**	**3**
7. Camminare **per un chilometro**	**1**	**2**	**3**
8. Camminare **per qualche centinaia di metri**	**1**	**2**	**3**
9. Camminare **per circa cento metri**	**1**	**2**	**3**
10. Fare il bagno o vestirsi da soli	**1**	**2**	**3**

Hospital Anxiety and Depression Scale - H. A. D. S.

Indichi con una crocetta il quadrato corrispondente alla risposta che le sembra più appropriata a descrivere la Sua reale situazione. Indicare una sola risposta per ogni domanda. Le domande relative all'ansia sono segnate con "A", e quelle relative alla depressione sono segnate con "D".

A) Mi sento teso o tirato

(3) La maggior parte del tempo

(2) Molto tempo

(1) Ogni tanto, occasionalmente

(0) Per niente

D) Mi piacciono ancora le cose che mi piacevano un tempo

(0) Decisamente come prima

(1) Di meno

(2) Soltanto un po'

(3) Quasi per niente

A) Ho una specie di timore come se dovesse accadere qualcosa di brutto

(3) Molto intenso e piuttosto preoccupante

(2) Sì, ma non troppo preoccupante

(1) Un po' ma non mi preoccupa

(0) Per niente

D) Riesco a ridere e a vedere il lato buffo delle cose

(0) Tutte le volte che ne ho l'occasione

(1) Ora di meno

(2) Decisamente di meno

(3) Per niente

A) Mi passano per la mente pensieri preoccupanti

(3) Una buona parte dei tempo

(2) Molto spesso

(1) Di volta in volta, ma non troppo spesso

(0) Soltanto occasionalmente

D) Sono gioioso

(3) Per niente
(2) Raramente

(1) Qualche volta

(0) La maggior parte del tempo

A) Posso sedermi tranquillamente e sentirmi rilassato

(0) Quasi tutto il tempo

(1) Molto spesso

(2) qualche volta

(3) Per niente

D) Mi sento come rallentato

(3) Decisamente

(2) Solitamente

(1) Raramente

(0) Per niente

A) Ho una sensazione di timore come "farfalle" nello stomaco

(0) Per niente

(1) Occasionalmente

(2) Piuttosto spesso

(3) Molto spesso

D) Ho perso interesse per il mio aspetto

(3) Decisamente

(2) Non mi prendo cura di me stesso come dovrei

(1) Non riesco ad avere sufficiente cura di me stesso

(0) Mi prendo cura di me stesso come al solito

A) Mi sento agitato come se dovessi essere in movimento

(3) Moltissimo

(2) Abbastanza

(1) Non molto

(0) Per niente

D) Guardo al futuro con gioia

(0) Come ho sempre fatto

(1) Un po' meno del solito

(2) Decisamente meno del solito

(3) Quasi per niente

A) Aspetto con gioia gli eventi futuri:

(0) nello stesso modo di sempre

(1) un po' meno del solito

(2) decisamente meno del solito

(3) molto difficilmente

D) Mi piace un buon libro o la radio o un programma in TV

(0) Spesso

(1) Qualche volta

(2) Raramente

(3) Molto raramente

Questionario MIDAS

Istruzioni: risponda alle domande dalla n° 1 alla n° 5 relativamente a TUTTI i mal di testa di cui hai sofferto negli ultimi 3 mesi. Scriva la sua risposta nello spazio a fianco di ogni domanda. Scriva zero se non ha svolto nel corso degli ultimi 3 mesi le attività indicate nella domanda.

1) Quanti giorni di assenza dal lavoro o da scuola ha fatto negli ultimi tre mesi a causa del mal di testa? Numero giorni

_____

2) Per quanti giorni, nel corso degli ultimi tre mesi, il suo rendimento sul lavoro o a scuola si è ridotto della metà o più a causa del mal di testa? (Non conteggi i giorni di assenza che ha già indicato nella risposta alla prima domanda) Numero giorni

_____

3) Per quanti giorni, nel corso degli ultimi tre mesi, non ha svolto i lavori di casa a causa del mal di testa? Numero giorni

_____

4) Per quanti giorni, negli ultimi tre mesi, il suo rendimento nei lavori di casa si è ridotto della metà o più a causa del mal di testa? (Non conteggi i giorni di assenza che ha già indicato nella risposta alla prima domanda) Numero giorni

_____

5) Per quanti, giorni, nel corso degli ultimi tre mesi, non ha partecipato ad attività familiari, sociali o di svago a causa del mal di testa? Numero giorni

_____

A. Per quanti giorni, nel corso degli ultimi tre mesi, ha sofferto di mal di testa? (Se un mal di testa è durato più di un giorno, sommi tutti i giorni) Numero giorni

_____

B. Su una scala da 0 a 10, quale è stata mediamente l'intensità del dolore durante questi mal di testa? (Dove 0 è uguale ad assenza di dolore e 10 dolore fortissimo, non potrebbe essere peggio)

Numero da 0 a 10

_____

Pain Self-Efficacy Questionnaire – PSEQ

Valuti con un punteggio quanto si sente sicuro nello svolgere le seguenti attività oggi, **nonostante il dolore**. Per indicare la sua risposta faccia un cerchio attorno a **uno** dei numeri sulla scala sotto ogni affermazione, dove 0 = per nulla sicuro e 6 = completamente sicuro.

Esempio:

0 1 2 3 4 5 6

Per nulla sicuro **Completamente sicuro**

Ricordi che questo questionario **non** le chiede se fa o non fa queste attività, ma **quanto si sente sicuro di poterle fare al momento**, **nonostante il dolore**.

---

1. **Posso vivere bene, nonostante il dolore.**

0 1 2 3 4 5 6

Per nulla sicuro **Completamente sicuro**

2. **Posso fare la maggior parte dei lavori domestici (mettere in ordine, lavare i piatti, ecc), nonostante il dolore.**

0 1 2 3 4 5 6

Per nulla sicuro **Completamente sicuro**

3. **Posso stare in compagnia di amici o famigliari come ho sempre fatto, nonostante il dolore.**

0 1 2 3 4 5 6

Per nulla sicuro **Completamente sicuro**

4. **Posso gestire il dolore nella maggior parte delle situazioni.**

0 1 2 3 4 5 6

Per nulla sicuro **Completamente sicuro**

5. **Posso svolgere delle attività lavorative, nonostante il dolore (per "attività lavorative" si intendono anche lavori di casa e lavori non pagati).**

0 1 2 3 4 5 6

Per nulla sicuro **Completamente sicuro**

6. **Posso ancora fare molte delle cose che mi piacciono, come hobbies o svaghi, nonostante il dolore.**

0 1 2 3 4 5 6

Per nulla sicuro **Completamente sicuro**

7. **Posso gestire il dolore senza ricorrere ai farmaci.**

0 1 2 3 4 5 6

Per nulla sicuro **Completamente sicuro**

8. **Posso ancora realizzare la maggior parte dei miei obiettivi, nonostante il dolore.**

0 1 2 3 4 5 6

Per nulla sicuro **Completamente sicuro**

9. **Posso avere uno stile di vita normale, nonostante il dolore.**

0 1 2 3 4 5 6

Per nulla sicuro **Completamente sicuro**

10. **Posso gradualmente diventare più attivo, nonostante il dolore.**

0 1 2 3 4 5 6

Per nulla sicuro **Completamente sicuro**

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