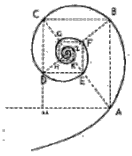

UNIVERSITÀ DEGLI STUDI DI MILANO

DOTTORATO IN MEDICINA MOLECOLARE E TRASLAZIONALE

CICLO XXX

Anno Accademico 2016/2017

TESI DI DOTTORATO DI RICERCA

MED/25

Emotional and cognitive abnormalities in patients affected by functional motor symptoms: towards a biological marker

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Abstract

INTRODUCTION: Functional motor symptoms (FMS) encompass weakness and movement disorders (e.g. tremor, ballism, gait disturbances, dystonia or tic) that are genuine but are not due to an organic cause. According to the recent edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), they are part of the wide spectrum of Conversion Disorders (Functional Neurological Symptom Disorders), which also include non-epileptic seizures and functional sensory disturbances. Although their high prevalence, aetiological mechanisms underlying FMS are still unknown.

AIMS: Aim of this thesis was to determine a possible biological marker for FMS. To this aim, I first examined the role of emotional and cognitive abnormalities in patients affected by FMS. In particular, I aimed to explore: 1. the prevalence of alexithymia; 2. the degree of interoceptive awareness; 3. the deception ability (as a measure of mild multifacet cognitive impairment); 4. the neuromodulatory effect of a single anodic Transcranial Direct-Current Stimulation (tDCS) on interoceptive sensitivity and on spatial attention in a sample of patients affected by FMS and in a sample of healthy subjects served as a control group. Second, I aimed to explore the level of various brain metabolites (N-Acetyl-aspartate - a neuronal marker, creatine - an energy buffer and shuttle, myo-inositol - a glial cell marker, choline - involved in cell membrane synthesis and degradation and the sum of glutamate - the major excitatory neurotransmitter - and glutamine) in the anterior cingulate cortex (ACC)/medial prefrontal cortex (mPFC) and in the occipital cortex (OCC) (control region), using magnetic resonance spectroscopy as neuroimaging technique, in a group of patients with FMS and in a group of healthy controls.

MATERIALS & METHODS: For each part of the study, I enrolled a number of patients with FMS and a number of age and gender-matched healthy controls. Methods included: rating scales for the assessment of psychological variables (alexithymia, depression, anxiety, personality disorders, self-objectification, quality of life), the heart beat detection task for the assessment of interoceptive awareness, the guilty knowledge task (GKT) to detect the deception ability and the Posner paradigm to detect the spatial attention. A single anodic tDCS session over the right posterior parietal cortex was used to assess the neuromodulatory effect. To explore the level of various brain metabolites I used magnetic resonance spectroscopy.

RESULTS: My results showed that patients with FMS have: 1. significantly higher level of alexithymia than healthy controls; 2. significantly lower degree of interoceptive awareness than healthy controls; 3. significantly longer reaction times at the GKT than healthy controls. I also showed that there was a significant difference between the levels of interoceptive awareness after real and sham tDCS stimulation in the whole group of participants. When considering the two groups separately, this difference still remained significance only in patients with FMS. Finally, a significant increase in glutamate+glutamine/creatine was found in the ACC/mPFC but not the OCC in patients with FMS.

CONCLUSION: My results contribute to the understanding of the aetiopathogenesis of functional motor symptoms, opening a novel window for future research and possibly novel treatments.

Sommario

INTRODUZIONE: I sintomi motori funzionali (FMS) comprendono debolezza e disturbi del movimento (es. tremore, ballismo, disturbi della marcia, distonia o tic) che sono autentici ma non dovuti a cause organiche. Secondo la recente edizione del Manuale Diagnostico e Statistico dei Disturbi Mentali (DSM-5), fanno parte dell'ampia gamma dei Disturbi di Conversione (Disturbi da Sintomi Neurologici Funzionali), che includono anche le crisi psicogene non epilettiche e i disturbi sensoriali funzionali. Nonostante la loro elevata prevalenza, i meccanismi eziologici sottostanti i FMS sono ancora sconosciuti.

OBIETTIVI: Scopo di questa tesi era quello di definire un possibile marker biologico per i FMS. Per raggiungere questo obiettivo ho dapprima esaminato il ruolo di anomalie emozionali e cognitive in pazienti affetti da FMS. In particolare, ho indagato: 1. la prevalenza di alessitimia; 2. il grado di consapevolezza enterocettiva; 3. la capacità di mentire (come misura di lieve decadimento cognitivo multiforme); 4. l'effetto neuromodulatorio di una singola stimolazione transcranica anodica a corrente diretta (tDCS) sulla consapevolezza enterocettiva e sull'attenzione spaziale in un campione di pazienti affetti da FMS e in un campione di soggetti sani (gruppo di controllo). In secondo luogo, ho perseguito l'obiettivo di esplorare il livello di diversi metaboliti cerebrali (N-acetil-aspartato - un marker neuronale, creatina - un tampone e trasportatore di energia, mio-inositolo - un marker di cellule gliali, colina - coinvolta nella sintesi e degradazione delle membrane cellulari e la somma di glutammato - il principale neurotrasmettitore a azione eccitatoria - e glutammina) nella corteccia anteriore cingolata (ACC)/corteccia mediale prefrontale (mPFC) e nella corteccia occipitale (OCC) (regione di controllo) utilizzando la spettroscopia a risonanza magnetica come tecnica di neuroimaging in un gruppo di pazienti con FMS e in un gruppo di controlli sani.

MATERIALI E METODI: Per ogni parte dello studio ho reclutato un numero di pazienti con FMS e un numero di controlli sani appaiati per età e per sesso. I metodi includevano: scale di valutazione per l'assessment delle variabili psicologiche (alessitimia, depressione, ansia, disturbi di personalità, self-objectification, qualità della vita), heart beat detection task per la valutazione della consapevolezza enterocettiva, guilty knowledge task (GKT) per rilevare la capacità di mentire e il paradigma di Posner per rilevare l'attenzione spaziale. Una singola sessione anodica di tDCS sulla corteccia parietale posteriore destra è stata utilizzata per valutare l'effetto neuromodulatorio. Per misurare il livello dei diversi metaboliti cerebrali ho utilizzato la spettroscopia a risonanza magnetica.

RISULTATI: I miei risultati hanno mostrato che i pazienti con FMS presentavano: 1. un livello di alessitimia significativamente superiore a quello dei controlli sani; 2. un grado di consapevolezza enterocettiva significativamente inferiore rispetto ai controlli sani; 3. Tempi di reazione più lunghi al GKT rispetto ai controlli sani. Ho anche evidenziato che vi era una significativa differenza tra i livelli di consapevolezza enterocettiva dopo la stimolazione reale e dopo la stimolazione sham con tDCS, nell'intero gruppo di partecipanti. Considerando separatamente i due gruppi, questa differenza rimaneva significativa solo nei pazienti con FMS. Infine, ho mostrato un aumento significativo dei livelli di glutammato+glutammina/creatina nell'ACC/mPFC ma non nelll'OCC nei pazienti con FMS.

<u>CONCLUSIONE</u>: I miei risultati contribuiscono alla comprensione dell'eziopatogenesi dei sintomi motori funzionali, aprendo una nuova finestra per la ricerca futura e eventualmente per nuovi trattamenti.

Index

Chapter 1:
General introduction to the pathophysiology of functional motor symptoms

1.1 Definition of functional motor symptoms

Functional motor symptoms (FMS) encompass weakness and movement disorders (e.g. tremor, ballism, gait disturbances, dystonia or tic) that are genuine but are not due to an organic cause. Symptoms are not under voluntary control and they should not be misinterpreted as feigning or malingering (Hallett et al., 2006). The diagnosis of FMS should not be a diagnosis of exclusion, but should be based on positive clinical signs of internal inconsistency (Stone et al., 2012). One of these signs has been called "Hoover's sign" and represents the pathognomonic sign for the diagnosis of functional unilateral leg weakness (power of hip extension will be weak when tested directly, but the apparently weak muscles will activate normally when the patient activates the opposite hip flexor) (Hoover, 1908).

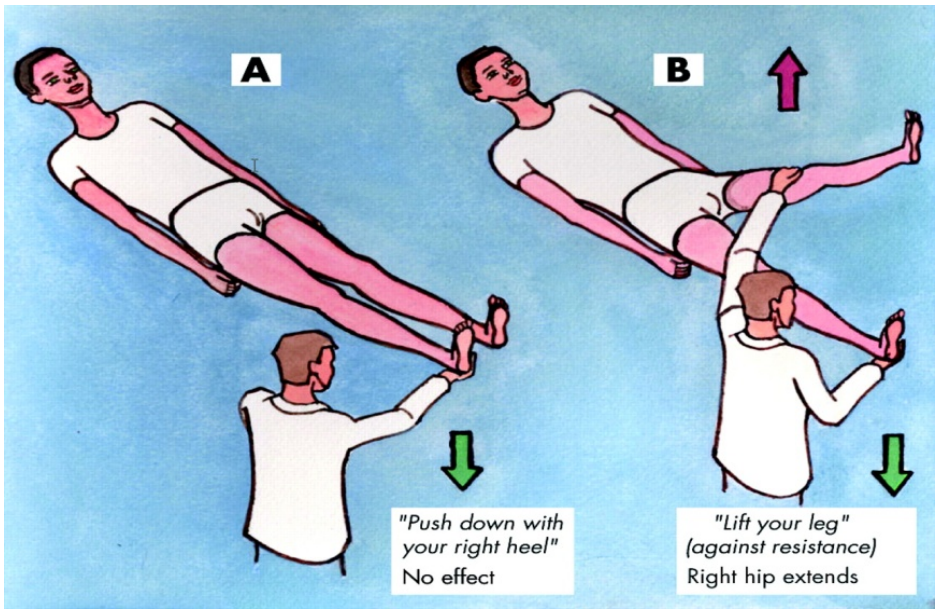


Figure 1.1 Hoover's sign

Another key clinical characteristic that distinguishes individuals with FMS from those with organic motor symptoms is that FMS require attention to manifest: when attention is distracted there is a significant reduction, even disappearance of the movement disturbance (Schwingenschuh et al., 2011).

According to the recent edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), FMS are part of the wide spectrum of Conversion Disorders (Functional Neurological Symptom Disorders), which also include non-epileptic seizures and functional sensory disturbances (DSM-5, 2013).

a	The patient has ≥1 symptoms of altered voluntary motor or sensory function.
b	Clinical findings provide evidence of incompatibility between the symptom and recognised neurological or medical conditions.
c	The symptom or deficit is not better explained by another medical or mental disorder.
d	The symptom or deficit causes clinically significant distress or impairment in social, occupational, or other important areas of functioning or warrants medical evaluation.
	Specify type of symptom or deficit as: • With weakness or paralysis • With abnormal movement (e.g. tremor, dystonic movement, myoclonus, gait disorder) • With swallowing symptoms • With speech symptoms (e.g. dysphonia, slurred speech) • With attacks or seizures • With amnesia or memory loss • With special sensory symptom (e.g. visual, olfactory, or hearing disturbance) • With mixed symptoms.
	Specify if: • Acute episode: symptoms present for less than six months • Persistent: symptoms present for six months or more.
	Specify if: • With Psychological stressor • Without Psychological stressor.

Table 1.1 DSM-5 Diagnostic Criteria for Conversion Disorders (Functional Neurological Symptom Disorders)

As outlined in a recent study by the Scottish group of Jon Stone, FMS represent the second commonest diagnose made in general neurological outpatient clinic,

after headache (Stone et al., 2010). Recent studies have shown that individuals affected by FMS present levels of perceived quality of life, disability, distress and health care usage that equals, and even surpasses, patients with organic neurological conditions such as Parkinson's disease or multiple sclerosis (Anderson et al., 2007; Stone et al., 2013).

1.2 Pathophysiology of functional motor symptoms

Although FMS are very common and severely disabling, their underlying pathophysiological mechanisms are still poorly understood. From a historical perspective, psychological factors, such as trauma, conflict or distress, have been considered for decades causal factors of these disorders. In 1895 Freud proposed a model according to which functional neurological symptoms might reflect a psychological trauma (mainly related to the sexual sphere) that is unconsciously repressed and "converted" into physical symptoms (often with a symbolic meaning) (Freud & Breuer, 1895). This interpretation is linked to the different alternative terms used to define these disturbances, such as conversion disorders, psychogenic disorders, psychosomatic disorders and hysteria. Recently, several studies have shown that psychological and emotional factors have been found at a higher prevalence in patients affected by FMS than the healthy population, but they have not been found to be sensitive or specific markers of FMS (Roelofs & Spinhoven, 2007). This innovative perspective has also been reflected in the DSM-5 diagnostic criteria for conversion disorders (functional neurological symptom disorders) where the presence of a psychological factor has been downgraded from an essential to a supportive criterion (DSM-5, 2013). Thus, an alternative, but equally problematic terminology concentrates on what patients do not have (non-organic disorders, medically unexplained symptoms). As a consequence, the related debate regarding the "psychogenic" or "non-organic" aetiology of FMS portrays a compartmentalised, dualistic brain and mind relation that has not been supported by decades of scientific research. A fundamental missing link that might help transcend this dualistic vision is the understanding of the pathophysiological processes by which cognitive factors (e.g. attention or memory) and emotional

factors (e.g. trauma, conflict or distress) could cause functional motor symptoms, in the context of a biopsychosocial approach. In this view, a one-dimensional approach to FMS, e.g. a purely psychological interpretation of symptoms, or one underlying only neurobiological mechanisms not considering emotional factors, is doomed to failure. In particular cases, concentrating on specific factors is proper and adequate, but it is fundamental not to lose the global picture in order to meet the aim of improving the health of patients with FMS.

Recent neurobiological models of the pathophysiology of FMS have focused more on "how" symptoms might be produced than on "why". Following this research line, Edwards et al have tried to define three putative mechanistic processes underlying FMS: abnormal attentional focus (Gupta & Lang, 2009), abnormal beliefs and expectations (Parees et al., 2012), and abnormalities in sense of agency (Kranick et al., 2013).

1.2.1 Abnormal attentional focus

As anticipated before, clinical examination in patients with FMS reveals the role of self-directed attention in developing these symptoms: when their attention is distracted, patients affected by FMS are significantly less symptomatic (Gupta & Lang, 2009). On the same line, it is not difficult to provoke new symptoms and worsen the ones present during clinical examination, via enhancing self-directed attention. This phenomenon has been examined experimentally, with evidence that duration of direct visual attention towards the body during movement (e.g. looking directly at the affected limb) is significantly higher in patients affected by FMS than in patients affected by organic neurological disorders (van Poppelan et al., 2011). Since the co-occurrence of symptoms is one of the main features of FMS, then an abnormal switch of attention towards the body should be a key pathophysiological characteristics of functional symptoms of all types.

1.2.2 Abnormal beliefs and expectations

Symptoms are clearly influenced by beliefs about how the brain and body work and how they may go wrong, producing symptoms that are incongruent with basic

anatomic and physiologic (and even physical) principles (e.g. tubular visual fields and pattern of functional amnesia). Therefore, a process by which beliefs and expectations about symptoms can affect function should be included in the pathophysiologic theory of FMS.

1.2.3 Abnormal sense of agency

The sense of agency is an important aspect of human self-consciousness. It is related to the subjective sense that a specific movement is self-generated and do not just "happen". The abnormal FMS seem to be produced deliberately and consciously because (1) attention is required for the movement to manifest and (2) the symptom is not congruent with basic neuroanatomical constraints. Therefore, functional motor symptoms would be predicted to be related with a high sense of agency. Nevertheless, patients with FMS report that their perception is that the movement is not under their control. Parees et al studied individuals affected by functional tremor scanned during their habitual functional tremor and when they have been asked to deliberately mimic their tremor. Results showed that patients had reduced temporoparietal junction activity only during their functional tremor (Parees et al., 2011). This temporoparietal junction hypoactivity was interpreted as reflecting the lack of an appropriate sensory prediction signal that one would usually associate with voluntary movement, namely a reduced sense of agency (Voon et al., 2010; Edwards et al., 2011).

The theory proposed by Edwards et al put its basis on a biologic theory of brain function called "active inference", which is linked to a statistical theory advanced by Bayes. According to this theory, the brain might be seen as a hierarchical structure with a flow of information in two directions, from sense organs upwards ("bottom-up") and from the cortex down ("top-down"). In the context of the hierarchy, bottom-up data meet top-down predictions about the content of the data, also called "priors". Bottom-up data and priors are compared in a statistical model considering different weightings given to the bottom-up data and to the priors. Therefore, in specific conditions, the resulting perception or movement might be strongly influenced by the bottom-up data than the priors or vice versa. The

precision or weighting of both bottom-up data and top-down priors is clearly linked to attention.

In the context of this theory, Edwards proposed a model for FMS where an event provokes the formation of an abnormally strong (precise) prior. The event might be a physiological one (e.g. fasciculations or hypnic jerks), a pathophysiological one (e.g. pain) or a psychological one (e.g. anxiety or panic). Authors speculate that the abnormal attention towards the body and specifically towards the symptom increases the precision of the abnormal prior, overwhelming any bottom-up data that are out of keeping with it (Edwards et al., 2012).

1.2.4 Neurobiological model

These three mechanistic processes have been combined in neurobiological models where abnormal beliefs linked to movement are triggered by self-focused attention, and the resulting motor symptom is generated without a normal sense of agency (Voon et al., 2011; Edwards et al., 2012).

The first step in the development of functional symptoms has been suggested to be the presence of an abnormal prediction or expectation related to the symptom. Recent studies have revealed that the instigation of this abnormal prediction might be the consequence not only of psychological or emotional factors, but also of physical triggering factors such as injuries or organic diseases, that are frequently reported at the onset of FMS (Stone et al., 2009). The second step required for symptom generation is the activation of the self-directed attention. The third step refers to the fact that the symptom is not accompanied by the normal neural "baggage" that accompanies voluntary movement and therefore it is misinterpreted by the patient as a physical symptom and out of his/her control (abnormal sense of agency).

1.2.5 The role of cognition

Another crucial point in the definition of the pathophysiology of FMS, linked to the neurobiological model proposed, refers to cognitive aspects.

At the beginning of 19th century, Janet was the first to hypothesize hysteria to present a neurocognitive component – in particular, as a disturbance of memory processing arising during a traumatic experience. Later aetiopathological models focused on deficits in both memory and attention, and suggested that these deficits would be more significant during the presence of symptoms and during testing conditions that provoked anxiety or distress (Ludwig et al., 1972; Whitlock et al., 1967). Recent studies have been interpreted as supporting these hypotheses, according to which patients with active FMS have a mild cognitive impairment and are even further compromised when subjected to additional stress during testing. A few studies have been conducted assessing neurocognitive function in patients with FMS and results have been quite controversial. In all these studies a traditional neurocognitive battery has been used (Reuber et al., 2008; Brown et al., 2014; Duncan & Oto, 2008; Kozlowska et al., 2015).

1.2.6 The role of emotional factors

As outlined before, for decades the role of emotional factors in the aetiopathology of FMS has been considered only in terms of psychological triggering events (e.g. traumatic experience, distress or conflict). The proposed model leads space to a different role for emotions, which might be studied at a more mechanistic level than focusing only on traumatic life events. At this purpose, fMRI studies, although mainly case reports and case series, have provided first evidences that emotional brain circuits (mainly involving amygdala and cingulate cortex region) might be differentially activated in individuals affected by FMS and interact with their motor symptom (Kanaan et al., 2007). The group by Voon pointed out that individuals affected by FMS have hypoactivity in areas usually associated with action selection (e.g. supplementary motor area), greater amygdala activity in response to arousing stimuli and impaired habituation along with greater functional connectivity between the amygdala and supplementary motor areas (Voon et al., 2010a; Voon et al., 2011). The hypoactivity of the supplementary motor area represents the basis for an impairment in the ability to inhibit or stop an action. These results fit with the

concept developed by Hallett and Voon of a “previously mapped conversion motor representation”, namely a pattern of movement established by a triggering factor (Voon et al., 2010a; Voon et al., 2010b; Voon et al., 2011; Voon et al., 2013). In fact, the previously mapped conversion motor representation is activated by the abnormal connectivity between the amygdala and the supplementary motor area; in addition, it cannot be inhibited because of a disconnection between the supplementary motor area and areas that normally inhibit unwanted action such as the prefrontal cortex. The result is the onset of a movement that arises without normal predictions of its sensory consequences and therefore is experienced by the patient as involuntary (Voon et al., 2011). These data provided a first potential neural mechanism that may explain why psychological or physical stressors can provoke FMS and gives space for further studies in order to assess the role of emotions in these patients from a different perspective.

1.2.7 Towards the definition of a biological marker

Given the proposed role for emotional and cognitive abnormalities in the pathophysiology of FMS and the preliminary evidence for the involvement of brain regions such as amygdala and cingulate cortex, the neurobiology of FMS needs to be study at a more mechanistic level, towards the definition of a biological marker, in the context of a biopsychosocial model.

Chapter 2:
Aims and Hypotheses

The background above provides a picture about the main pathophysiological themes in functional motor symptoms and emphasizes the hypothesis that emotional and cognitive abnormalities might have a crucial role, arguably representing the substrate that combined with other, yet unknown, factors might predispose to the development and maintenance of functional motor symptoms.

Aim of this thesis was to determine a possible biological marker for FMS. To this aim, I first examined the role of emotional and cognitive abnormalities in patients affected by FMS, in order to understand how different specific mechanisms might contribute to the aetiopathogenesis of FMS, in the context of the biopsychosocial model. To this aim, I conducted several preliminary and parallel experiments, to fully characterize the emotional and cognitive abnormalities in patients affected by FMS. Thus, I have explored:

1. The prevalence of alexithymia (failure to identify and describe emotions in oneself and a difficulty in distinguishing and appreciating the emotions of others), with the use of a self-rated scale (20-item Toronto Alexithymia Rating Scale) in patients with FMS. My hypothesis was that patients affected by FMS would have significantly higher rates of alexithymia than healthy controls.

2. The degree of interoceptive sensitivity (objective accuracy in detecting internal bodily sensations such as heartbeat or breathing), with the use of a specific device (heart beat detection task). I hypothesized that patients with FMS would have significantly lower levels of interoceptive sensitivity than healthy controls.

3. The deception (as a measure of mild multifacet cognitive impairment), with

the use of a computerised paradigm (guilty knowledge task). I hypothesized that patients affected by FMS would have significantly impaired deception ability (in terms of lie production and lie reaction times) than healthy subjects.

4. The neuromodulatory effect of a single anodic Transcranial Direct-Current Stimulation (tDCS) on interoceptive sensitivity (assessed by the heart beat detection task) and on spatial attention (assessed by the Posner paradigm). I hypothesized a neuromodulatory effect of the tDCS on interoceptive sensitivity and spatial attention (a significant improvement in the performance of heart beat detection task and Posner paradigm).

Second, to specifically define a possible biological marker of FMS, I decided to explore the level of various brain metabolites (N-Acetyl-aspartate - a neuronal marker, creatine - an energy buffer and shuttle, myo-inositol - a glial cell marker, choline - involved in cell membrane synthesis and degradation and the sum of glutamate - the major excitatory neurotransmitter – and glutamine) in the anterior cingulate cortex/medial prefrontal cortex and in the occipital cortex (control region), using magnetic resonance spectroscopy as neuroimaging technique. I expected to find patients affected by FMS to have higher level of glutamate+glutamine/creatine in the anterior cingulate cortex/medial prefrontal cortex than healthy subjects.

Chapter 3:

The role of alexithymia in the development of functional motor symptoms

3.1 Introduction

We have already seen in Chapter 1 how in the last few years there has been a reduction in the emphasis on identifiable traumatic events (such as sexual abuse) as causal factors for the development of FMS. Recent studies have underlined a possible role for physical precipitating events in the aetiology of FMS, and in some cases clear connections have been made between the type of physical precipitant factor and the phenomenology of the resulting functional symptom (Stone et al., 2009). However, the physical precipitant events identified (e.g. minor injury, flu-like illness or headache) are very common in the general population, and therefore why they should provoke FMS in only a small proportion of individuals still remains unclear.

One clue to this question has been the clinical observation that physiological markers of panic or anxiety are often reported at onset of FMS (e.g. in association with a physical precipitating event), but that patients do not feel and do not report a concurrent psychological state of anxiety (Kranick et al., 2011). These studies in patients with FMS link to previous studies on psychogenic non-epileptic seizures (PNES) where patients presented physiological changes seen in panic attacks but generally do not feel "panicked". This phenomenon has been called "non-fearful panic" (Chen et al., 2011).

Failure to identify and describe emotions in oneself and a difficulty in distinguishing and appreciating the emotions of others is named alexithymia, a term introduced by Peter Sifneos in 1973 to define certain clinical features seen in patients affected by psychosomatic disorders who had difficulty engaging in psychoanalysis (Sifneos, 1973). Previous studies of alexithymia in patients with conversion disorders have been limited to psychogenic non-epileptic seizures (Myers et al.,

2013; Bewley et al., 2005), In these studies both patients with epilepsy and those with PNES presented high levels of alexithymia. Only one recent study assessed the prevalence of alexithymia in a general group of patients affected by conversion disorders and this found higher rates in patients compared to healthy subjects (Gulpek et al., 2013). No studies up to date have assessed the prevalence of alexithymia in a population of patients with FMS. We were specifically interested in evaluating this, as high levels of alexithymia could help give an interpretation for the clinical observation of a dissociation between patients' endorsement of physiological markers of panic/anxiety and their denial of the psychological experience of panic/anxiety.

The aim of this study was to assess the prevalence of alexithymia in patients with FMS and to study its pathophysiological role. In addition, we evaluated the presence of other mental states that may act as a confounding factor in the interpretation of alexithymia (personality disorders, depressive disorders and impaired social cognition). To this aim, we conducted a cross-sectional study in a population of patients with FMS and in two control groups [patients with organic movement disorders (OMD) and healthy subjects].

3.2 Materials and Methods

3.2.1 Subjects

Patients affected by FMS and OMD were recruited from neuropsychiatry and neurology outpatient clinics at the National Hospital for Neurology and Neurosurgery (NHNN), London, UK, between November 2014 and May 2015. Two patients refused to take part in the study.

Fifty-five consecutive patients affected by FMS, 33 age- and sex-matched patients with an organic movement disorder and 34 age- and sex-matched healthy subjects were included in the study. Patients with FMS were included if they had "clinically established and documented" diagnostic criteria for FMS according to Fahn & Williams criteria (Williams et al., 1995). The diagnosis was made by a neurologist specialized in movement disorders according to clinical presentation and proper investigations. Patients with OMD were included after the diagnosis made by a

neurologist expert in movement disorders. Healthy controls were visitors to the hospital and hospital staff. All participants gave informed consent for the study. UCL Institute of Neurology and National Hospital for Neurology Joint Ethics Committee reviewed and approved the study protocol.

3.2.2 Exclusion criteria

Exclusion criteria for all subjects were: (a) age less than 18 years; (b) inability to communicate with the researcher or complete questionnaires due to language difficulties, severe learning disabilities or dementia; (c) any other serious neurological or medical diseases; (d) the presence of an overlap between functional and organic movement disorders.

3.2.3 Assessment

- The 20-item Toronto Alexithymia Scale (TAS-20). This is a well-validated and commonly used tool to assess alexithymia (Bagby et al., 1994); it is a multi-dimensional self-report scale with a three-factor structure: difficulty identifying feelings (DIF), difficulty describing feelings (DDF), and externally orientated thinking (EOT). As well as comparing TAS scores across the groups, we took the suggested TAS criterion score of ≥ 61 as categorically denoting alexithymia.
- The Montgomery-Asberg Depression Rating Scale (MADRS). This is a 10-item semi-structured clinician rated scale widely used to assess degree of depression; it yields reliable and internally consistent scores and demonstrates criterion-related validity (Davidson et al., 1986).
- The Reading the Mind in the Eyes Test (Eyes). This is an advanced test of theory of mind. It is widely used to study individual differences in social cognition and emotion recognition across different groups and cultures. Although it is not a diagnostic tool, several studies indicate that the Eyes is a reliable instrument for evaluating social cognition in adults (Vellante et al., 2012).

- The Structured Clinical Interview for Personality Disorders (SCID II). This is a semi-structured assessment tool for personality disorders (PD). It has been shown to be reliable, internally consistent and valid (Lobbestael et al., 2011).

3.2.4 Statistical analysis

Statistical analysis was performed using SPSS version 21 (Statistical Package for Social Science). The variables were first tested for normality using the Shapiro-Wilks test. The variables that were not normally distributed ($p<0.05$) were log10-transformed. For continuous data, a one-way analysis of variance (ANOVA) was used to test for differences across the three groups with post-hoc Bonferroni pairwise comparisons when significant. The X square test was used for categorical data. Bonferroni correction was applied to correct for multiple comparisons. Analyses of covariance (ANCOVA) were carried out using scores from the MADRS and the Eyes as covariates where adequate.

3.3 Results

Fifty-five FMS patients (42 of 55 females [76%]; mean age 43 years [SD, 10.55 years], 33 patients with OMD (23 of 33 females [70%]; mean age 45.70 years [SD, 14.64 years], and 34 healthy controls (23 of 34 females [68%]; mean age 42.18 years [SD, 11.32 years] were included in the study. Patients' clinical features are shown in Table 3.1.

SYMPTOM	Patients with FMS (N=55) n (%)	Patients with OMD (N=33) n (%)
Tremor	12(21.8%)	2 (6.1%) *2 essential tremor*
Myoclonus	12 (21.8%)	2 (6.1%) *2 cortical myoclonus*
Dystonia	12 (21.8%)	27 (81.8%) *15 cervical dystonia* *12 focal hand dystonia*
Weakness	16 (29.1%)	2 (6.1%) *1 transverse myelitis* *1 motor neuron disease*
Gait	1 (1.8%)	
Tic	2(3.6%)	

Table 3.1 Motor symptoms in functional and organic patient groups. FMS = functional motor symptoms; OMD = organic movement disorders.

There was a significant difference in TAS-20 scores between the three groups ($F(2, 119) = 20.467$, $p<0.001$), as shown in Table 3.2.

Post hoc analysis showed that each pairwise comparison was significant (FMS versus OMD: $p = 0.031$; FMS versus healthy subjects: $p < 0.001$; OMD versus healthy controls: $p = 0.003$). Alexithymia was present in 34.5%, 9.1% and 5.9% of the FMS, OMD and healthy subjects respectively. The proportions of alexithymic patients (TAS-20 > /= 61) differed significantly between groups (χ square (2) = 14.129, $p < 0.001$). Comparisons between groups showed a significantly increased proportion of high-alexithymic subjects in FMS patients (34.5%) as compared to OMD patients (9.1%; χ square (1) = 7.127, $p = 0.08$) and healthy individuals (5.9%; χ square (2) = 89.000, $p < 0.001$).

SCALES	Patients with FMS (N=55)	Patients with OMD (N=33)	Healthy controls (N=34)	p
TAS-20 score mean (SD)	55.38(12.12)	49.19 (9.13)	40.79 (8.54)	**0.0002**
TAS-20 < 51 n (%)	24 (43.6)	19 (57.6)	31 (91.2)	**0.0002**
TAS-20 = 52-60 n (%)	12 (21.8)	11 (33.3)	1 (2.9)	**0.0003**
TAS-20 > 61 n (%)	19 (34.5)	3 (9.1)	2 (5.9)	**0.0001**
DIF Mean (SD)	14.42 (4.5)	12.06 (3.8)	9.97 (3.1)	**0.0003**
DDF Mean (SD)	21.22 (5.8)	17.48 (5.4)	12.74 (4.4)	**0.0002**
EOT Mean (SD)	19.76 (4.6)	19.85 (3.6)	18.06 (4.0)	0.128

Table 3.2 Toronto Alexithymia Scale (TAS-20) total scores, percentage reaching criteria for presence of alexithymia (> 60), and subscale scores for: difficulty identifying feelings (DIF), difficulty describing feelings (DDF), and externally orientated thinking (EOT). FMS = functional motor symptoms; OMD = organic movement disorders.

Mean scores on the Eyes test and MADRS are shown in Table 3.3.

SCALES	Patients with FMS (N=55)	Patients with OMS (N=33)	Healthy controls (N=34)	p
MADRS score Mean (SD)	10.65 (7.5)	6.27 (5.8)	4.32 (4.59)	**0.0002**
Eyes score Mean (SD)	23.38 (4.3)	22.73 (4.1)	24.21 (3.9)	0.353

Table 3.3 Montgomery-Asberg Depression Rating Scale (MADRS), Reading the Mind in the Eyes' Test (Eyes) scores. SD = standard deviation; FMS = functional motor symptoms; OMD = organic movement disorder.

One-way ANOVA on the Eyes test did not show a significant effect of group ($F(2, 119) = 1.052$, $p=0.353$). For the MADRS, there was a significant main effect of group ($F(2, 119) = 11.455$, $p < 0.001$). Post hoc pairwise comparisons revealed significant differences between FMS patients and OMD patients ($p = 0.007$) and

FMS patients and healthy subjects ($p < 0.001$). Significant differences on total alexithymia scores remained when MADRS score was entered as a co-variate using ANCOVA ($F (3, 121) = 26.636$; $p < 0.001$).

Group differences were observed in both the DIF and DDF dimensions of the TAS-20, whereas the EOT subscale appeared relatively consistent across the three groups as shown in Table 2. One-way ANOVA on the DIF subscale scores showed a significant main effect of group ($F (2, 119) = 13.383$; $p < 0.001$). Post hoc pairwise comparisons revealed significant differences between FMS patients and OMD patients ($p = 0.025$) and between FMS patients and healthy subjects ($p < 0.001$). However, no significant difference was observed between OMD patients and healthy controls ($p = 0.102$). One-way ANOVA on the DDF subscale also demonstrated a significant main effect of group ($F (2, 119) = 26.281$; $p < 0.001$). Pairwise comparisons revealed significant differences between FMS patients and OMD patients ($p = 0.006$), FMS patients and healthy individuals ($p < 0.001$), and OMD patients and healthy controls ($p = 0.001$). With respect to the EOT dimension, one away ANOVA revealed a non-significant effect of group ($F (2, 119) = 2.088$ $p = 0.128$). ANCOVA with MADRS score as a co-variate was performed in order to detect any effect of depression on the DIF and DDF subscales, with results showing that depression did not act as a significant confounding factor ($F (3, 121) = 18.549$, $p < 0.001$ for DIF; $F (3, 121) = 33.727$, $p < 0.001$ for DDF).

Correlations between TAS-20 total score, TAS-20 subscores and the Eyes score were not significant (range of $r = -0.126$-0.006).

Regarding personality disorders, the prevalence of each subtype is shown in Table 3.4. There was no overlapping between different personality disorders in the same patient.

PD SUBTYPE	FMS patients n (%) (N=55)	OMD patients n (%) (N=33)	Healthy controls n (%) (N=34)	P
Avoidant	2 (3.6)	0 (0)	0 (0)	0.290
Dependent	2 (3.6)	0 (0)	0 (0)	0.290
Obsess-comp.	14 (25.4)	0 (0)	1 (2.9)	**0.0001**
Passive-aggres.	2 (3.6)	0 (0)	1 (2.9)	0.554
Depressive	3 (5.4)	0 (0)	0 (0)	0.154
Paranoid	3 (5.4)	0 (0)	0 (0)	0.154
Schizotypal	0 (0)	1 (3)	0 (0)	0.257
Schizoid	2 (3.6)	1 (3)	0 (0)	0.543
Histrionic	0 (0)	1 (3)	0 (0)	0.257
Narcissistic	2 (3.6)	0 (0)	0 (0)	0.290
Borderline	3 (5.4)	1 (3)	0 (0)	0.372
Antisocial	1 (1.8)	0 (0)	0 (0)	0.541

Table 3.4 Structured Clinical Interview for Personality Disorders (SCID II) scores. FMS = functional motor symptoms; OMD = organic movement disorder.

X square analysis showed a significant difference only in the distribution of OCPD (χ square (2) = 16.217, $p < 0.001$) within the three groups. The presence of OCPD was found to strongly correlate with the presence of alexithymia ($r = 0.283$ $p = 0.002$); in fact, 71.4% of patients who had OCPD were also alexithymic. Comparisons between groups showed a significantly increased proportion of OCPD in FMS patients as compared to OMD patients (χ square (1) = 9.989, $p=0.02$) and healthy controls (χ square (1) = 7.600, $p = 0.006$).

3.4 Discussion

3.4.1 Alexithymia

My results show that patients affected by FMS presented significantly higher rates of alexithymia than patients affected by OMD and healthy individuals, with a third of patients with FMS reaching full criteria for alexithymia (TAS > 61). The rates of alexithymia still remained significantly higher in patients affected by FMS even after controlling for depressive symptoms. The link between alexithymic features and depressive symptoms has been widely studied and it is well known that alexithymia is a risk factor for the development of depression (Saarijavi et al., 2011). Nevertheless, we found alexithymia to be a significant marker for FMS, independent of the presence of depressive symptoms. With respect to the three subscales of the TAS-20, patients affected by FMS were significantly more alexithymic on factor I (difficulty identifying feelings) and factor II (difficulty describing feelings), but not on factor III (externally orientated thinking). According to the study by De Gucht et al (De Gucht et al., 2003) the internal consistency of the EOT subscale is significantly lower than that of factor I and factor II, suggesting that a two-factor approach, could be more adequate to assess alexithymia. It may also be the case that for patients affected FMS, difficulty in identifying and explaining feelings relates only to the self, and not to the understanding of the emotions of other people. As additional evidence for this interpretation, patients with FMS were not significantly different from healthy subjects on the Eyes test, suggesting that the ability to recognise emotional expressions and mental states of individuals based on a partial facial expression (measures of social cognition) are not impaired in patients with FMS. Similar data with respect to the Theory of Mind have been found by Stonnington et al in patients affected by conversion disorders (Stonnington et al., 2013).

Recently several studies have assessed the link between alexithymia and conversion disorders, mainly concentrating on PNES. The main result is that patients with PNES are no more likely to be alexithymic than individuals with epileptic seizures (Myers et al., 2013; Bewley et al., 2005; Tojek et al, 2000); one study found an increased prevalence in PNES (Kaplan et al., 2013) although

another shows that alexithymia may be a feature only of a small subgroup (Brown et al., 2013). Only one study evaluated alexithymia in other conversion disorders (Gulpek et al., 2013). This study is deeply different from ours: first, they put together all kinds of conversion disorder; they used only healthy subjects as a control group; and they did not consider co-morbidities. However, they found a higher level of alexithymia in patients than healthy subjects, although this was higher than ours (74.5%), and they also found that this pertained only to factor I and II.

According to several studies, the prevalence of alexithymia in the general population is approximately 10% (Taylor et al., 1997). This prevalence in is line with that of our OMD group (9.1%) but is higher than our healthy subjects (5.9%). The discrepancy in the prevalence of alexithymia between our control sample and the control samples of previous studies could be due to the relatively small size of our group.

3.4.2 Personality disorders

Our data also demonstrate a significantly higher proportion of obsessive-compulsive personality disorder in patients affected by FMS as compared to patients with OMD and healthy controls. Previous studies have already highlighted the role of personality disorders as a risk factor for the development of both FMS (Feinstein et al., 2001; Binzer et al., 1998) and PNES (Howarka et al., 2007; Reuber et al., 2004) but no studies up to date have found increased prevalence specifically of OCPD in patients with functional neurological symptoms. Feinstein et al (Feinstein et al., 2001) found a prevalence of personality disorder of 42% in their sample of patients affected by FMS (mainly antisocial, borderline and dependent personality disorders). Similar data were pointed out by Howarka et al (Howarka et al., 2007) and by Reuber et al (Reuber et al., 2004) in patients with PNES: they found high prevalence of borderline personality disorders. On the other hand, Kranick et al (Kranick et al., 2011), who evaluated personality disorders in patients affected by FMS using the Revised Neuroticism-Extroversion-Openness Personality Inventory (NEO-PI-R), a dimensional tool, did not find any significant

difference in their group of patients compared to healthy volunteers. This difference might be in line with the observation that different forms of functional neurological symptoms (PNES, functional weakness or motor symptoms) might be associated with different personality traits (assessed by categorical tools).

Our data, showing a higher prevalence of OCPD in patients affected by FMS, are in contrast with the results of the studies described above. Although our study has been conducted with a relatively small sample of patients, it differs significantly from that of Feinstein et al (Feinstein et al., 2001), which has no comparative control group and from that of Kranick at al (Kranick et al., 2011) which has used only a dimensional tool. Nevertheless, further studies are needed to clarify the prevalence of each subtype of personality disorder in a bigger population of patients affected FMS.

In our study we observed a significant overlap between OCPD and alexithymia with 10 of 14 OCPD patients also meeting full criteria for alexithymia. This suggests that both scales may be assessing similar traits. However, this is unlikely to be the unique interpretation since the TAS-20 asks almost exclusively about feelings whereas the SCID II mainly concentrates on thoughts and behaviour. Nevertheless, alexithymia as a construct does include characteristics overlapping with those of OCPD. For example, several studies reported patients affected by psychosomatic symptoms developing compulsive behaviours and “a life guided by rules and regulations” as well as emotional disconnection (Taylor et al., 1997). Nemiah et al (Nemiah et al., 1976) showed that alexithymia is characterised by: (a) difficulty identifying emotions, differentiating among the range of common affects, and distinguishing between feelings and the bodily sensations of emotional arousal; (b) difficulty finding words to describe emotions to other people; (c) constricted imaginal processes; and (d) a thought content characterized by a preoccupation with the minute details of external events. This therefore suggests that OCPD may not be an independent risk factor for the development of FMS and that alexithymia is a more relevant personality construct for understanding the mechanism underlying FMS. However, of relevance is that Kang et al have recently found an overlap between alexithymia and obsessive-compulsive

disorder, with 41% comorbidity (Kang et al., 2002). To clarify this, further studies should include an assessment of obsessive-compulsive disorder as well as obsessive-compulsive personality disorder.

3.4.3 Integration with current neurobiological models

How might alexithymia be a significant mechanistic factor for the development and maintenance of FMS? I have already discussed the clinical evidence that patients with FMS often present physiological markers of panic and anxiety, without a psychological counterpart. These results are reinforced by the evidence that patients with FMS have greater arousal as indicated by galvanic skin response, higher baseline cortisol, reduced heart rate variability, greater threat vigilance and greater startle response to arousing stimuli (Bakvis et al., 2009; Seignourel et al., 2007; Maurer et al., 2015). I speculate that the autonomic arousal occurring during a physical precipitating event fails to be interpreted correctly as anxiety/panic in alexithymic patients. These sensations may instead be misinterpreted as symptoms of physical diseases, because of an attribution of sensations to organic rather than psychological factors. This vicious cycle might be further fostered in patients with obsessive-compulsive personality traits or disorders. In fact, the pervasive pattern of mental controlling and checking, at the expense of flexibility and openness might reinforce the patient's belief of illness and exaggerated focus on physical symptoms.

This interpretation, shown in Figure 3.1, perfectly fits with the neurobiological model proposed by Edwards et al according to which abnormal attention, abnormal beliefs/expectations and abnormalities in the sense of agency are three key concepts in the neurobiology of FMS (Edwards et al., 2013).

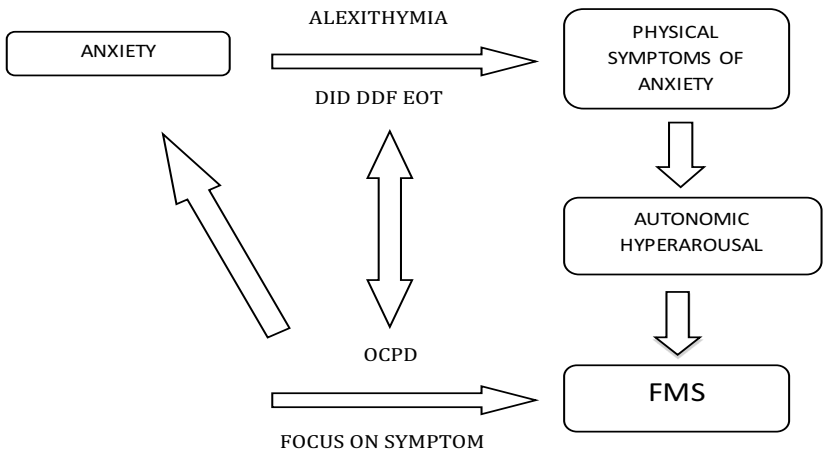


Figure 3.1 Integration with current neurobiological models. DIF = difficulty identifying feelings; DDF = difficulty describing feelings; EOT = externally orientated thinking; OCPD = obsessive-compulsive personality disorder; FMS = functional motor symptoms.

We acknowledge the limits of our study. First, we did not conduct a systematic interview for Axis I psychiatric disorders to establish diagnoses of affective and anxiety disorders. In particular, we did not assess the prevalence of anxiety symptoms in our samples - anxiety might be a confounding factor for alexithymia which we were unable to address. Second, this study is limited by the lack of a disability-matched OMD control group as 81 % of patients had a diagnosis of dystonia which is not representative of all movement disorders. Third, the choice of some scales might be criticized: although the TAS-20 is the most widely used instrument for assessing alexithymia, the use of a self-reported scale might be not appropriate, as alexithymic patients are not very self-reflective; with respect to the assessment of PD, it might have been more appropriate using a double instrument (categorical and dimensional approach), rather than just a categorical one.

Chapter 4:
The role of interoception in the development of functional motor symptoms

4.1 Introduction

We have already seen in Chapter 1 the crucial role of attention in the development and maintenance of FMS. Nevertheless, previous studies regarding the allocation and maintenance of attention in FMS concentrated only on how attention is allocated to exteroceptive signals about the state of the body, such as visual stimuli or tactile stimuli (Edwards et al., 2013). To the best of our knowledge, to date no studies have been conducted in order to evaluate how attention is allocated to interoceptive signals of the state of the body. Interoception is defined as the perception of sensations from inside the body, including those related to the function of internal organs, such as heart beat, respiration, satiety (Mehling et al., 2009). It has already been demonstrated that interoception plays an important role in many theories of emotion (Craig et al., 2002; Damasio et al., 1994) and a strong relationship has been suggested between sensitivity to internal bodily signals, namely interoceptive sensitivity (IS) and emotional experience. Therefore, the assessment of interoceptive awareness in patients affected by FMS might represent a fundamental mechanistic link between studies concentrating only on psychological and emotional factors in FMS, and those focusing on specific sensorimotor or cognitive abnormalities.

Several methods for assessing interoceptive awareness have been described, including gastrointestinal distension, adrenergic stimulation, and heart beat detection task. The latter is the most frequently used method (Schandry, 1981). Recent studies using heart beat detection task have showed that interoceptive awareness is positively correlated with intensity of emotional experience (Critchley et al., 2004; Pollatos et al., 2007) and with activation of brain areas thought to play a key role in emotional processing (insula, anterior cingulate cortex, ventro-medial and dorsolateral prefrontal cortex, somatosensory cortex) (Critchley et al., 2004).

The aim of this study was to explore interoceptive awareness in patients with FMS and to correlate this with levels of alexithymia. This could give us further insight into emotional processing of patients with FMS at a broader and more mechanistic level than studies focusing on specific potentially traumatic life events. Our hypothesis was that patients with FMS would have lower interoceptive awareness than healthy controls and that lower interoceptive awareness would be negatively correlated with degree of alexithymia. In addition, given recent suggestions that interoceptive awareness, as measure of sensory perception of the body from within, is negatively correlated to the sensory perception of the body from the outside (self-objectification) (Ainley et al., 2013). we aimed to evaluate the relationship between interoceptive awareness and self-objectification in patients with FMS and healthy subjects.

4.2 Materials and Methods

4.2.1 Subjects

We recruited 17 consecutive patients with FMS from the movement disorder outpatient clinics at National Hospital for Neurology and Neurosurgery, between May 2015 and November 2015. Inclusion criteria were age > 18 years, a diagnosis of clinically established and documented FMS according to Fahn and Williams criteria (Williams et al., 1995). Patients with any major concurrent neurological disorder were excluded. No patients refused to take part in the study. One patient was excluded as an outlier since he scored more than 2 SD above the groups mean on the heart beat detection task and there were cues that he did not follow instructions during the task. Eighteen healthy subjects (visitors to hospital and hospital staff), matched for age, gender and Body Mass Index (BMI), were recruited and served as a control group. Individuals with a history of any major concurrent neurological, cardiac or psychiatric disorders were excluded. One individual was excluded as she failed to comply with the instructions of the main heart beat detection task. All participants gave informed consent for the study. UCL Institute of Neurology and National Hospital for Neurology Joint Ethics Committee

reviewed and approved the study protocol. Clinical characteristics for the two groups are given in table 4.1.

ID	Age	Gender	Abnormal movement	Medications	Disease duration (years)
1	37	F	functional neck dystonia	Citalopram Mirtazapine Pregabalin Quetiapine	8
2	61	F	functional tics, tremor and jerks	Citalopram	10
3	46	M	right foot fixed dystonia	Mirtazapine	6
4	30	F	functional right arm spasms	None	10
5	40	M	functional tics	None	4
6	43	F	functional tremor	None	3
7	34	F	functional tremor	Fluoxetine Cocodamol	5
8	18	F	right hand fixed dystonia	None	9
9	36	F	functional weakness	None	5
10	47	F	bilateral feet fixed dystonia	Trihexyphenidyl	4
11	45	F	functional tremor	None	3
12	56	F	functional weakness	Citalopram Gabapentin Diazepam Codeine phosphate	31
13	34	M	functional spasms of the right arm	None	3
14	50	M	functional tremor	Venlafaxine Quetiapine Tramadol	7
15	52	F	functional spasms	Pregabalin	2
16	22	F	functional spasms	None	2

Table 4.1 Patient's characteristics. F = female; M = male.

4.2.2 Clinical assessment

Clinical and demographical data were collected as well as a full description of movement disorder onset, evolution and current phenomenology.

Patients and healthy subjects were asked to complete the 20-item Toronto Alexithymia Scale (Bagby et al., 1994). See Chapter 3 for details.

Depression was evaluated using the Montgomery Asberg Depression Rating Scale (MADRS) and the subscore "inner tension" was evaluated as a measure of anxiety (Montgomery & Asberg, 1979). See Chapter 3 for details. We then assessed in all participants "self-objectification", defined as the tendency to experience one's body principally as an object, evaluating it for its appearance rather than for its effectiveness, using the Self-Objectification Questionnaire (SOQ) (Fredrickson et al., 1998).

The SOQ evaluates the extent to which individuals view their bodies in observable, appearance-based terms, versus non-observable competence-based terms. Participants are required to rank 10 body attributes by how important each is to their own physical self-concept, from 0 (for least impact) to 9 (greatest impact). Scores range from 225 to 25, with higher scores indicating greater emphasis on appearance, which is interpreted as greater self-objectification.

4.2.3 Heart beat detection task

Patients and healthy subjects took part in a single 15-min testing session. Heart rate was recorded with a Polar wrist worn heart rate monitor (model RS 800 CX).

Figure 4.1 Polar watch model RS 880 CX.

Participants were seated, with their wrists gently resting on the band for the heart rate monitor, which was located on a table in front of them. They were asked to silently count their own heartbeats by concentrating on their heart activity. During heart beat counting, participants were instructed to count their heartbeats by concentrating on bodily feelings without taking their own pulse or trying other physical manipulations.

A 3-minutes baseline heart beat recording was performed after which the perception task was performed three times, for time intervals lasting 25, 45 and 65 seconds. In between one interval time and the next one the subject rested for 30 seconds, so that the testing followed this sequence: perception (25 sec) – rest (30 sec) - perception (45 sec) - rest (30 sec) - perception (65 sec).

4.2.4 Statistical analysis

The accuracy of heartbeat perception was calculated as the mean score of three heartbeat perception interval according to the following transformation (Schandry, 1981):

1/3 ∑ [(1- (|recorded heartbeats – counted heartbeats| / recorded heartbeats)]. With this formula, the IS score can vary between 0 and 1, with higher scores

suggesting smaller differences between recorded and perceived heartbeats (e.g. or higher IS).

All analyses were conducted in Stata 13 (StataCorp, 2013). All analyses were conducted using non-parametric tests, corrected for multiple comparisons using the Bonferroni method, as the data were not normally distributed. All reported results are based on two-tailed p values. Correlations were conducted using Spearman bivariate correlations, corrected for multiple comparisons with the Bonferroni method.

To investigate the relationship between group classification and IS, we conducted a simple linear regression on the IS scores with group (dummy-coded) as the regressor. To investigate which facets of FMS symptomatology were explained by the relation between IS and group, we conducted separate multiple linear regressions on MADRS depression scores, TAS-20 alexithymia scores and SOQ self-objectification scores. IS and group were the regressors, and we included the IS by group interaction term in each model. Interactions were followed up by examining the significance of the slopes within each group. Given correlations among psychometric variables, we controlled for TAS-20 scores in the analyses on MADRS depression scores and for MADRS scores in the analyses on TAS-20 and SOQ scores. Continuous variables were centred to avoid multicollinearity issues otherwise inherent in regression models. Finally, due to the aforementioned distribution issues we conducted these multiple regressions using non-parametric bootstrapping estimation (1000 repetitions), which does not make distributional assumptions on the data. We thus report bootstrapped standard errors and confidence intervals below.

4.3 Results

4.3.1 Group Characteristics

The FMS patients were older than the control individuals, with a higher BMI, but non-parametric Mann-Whitney U tests revealed that age and BMI did not differ significantly between the groups (see Table 4.2). Gender ratio was also not significantly different between the groups, as tested by the X square test

(categorical data). The FMS patients were significantly more depressed than the control group, although no patient scored above the cut-off (total score of 30) for severe, clinical depression. The FMS patients were also more alexithymic than the control group, with six FMS patients and two healthy controls scoring above the cut-off (total score of 61), but the difference between the groups showed only a trend towards significance. Finally, no significant differences were observed between the groups in self-rated, body objectification.

	Patients with FMS (N = 16)		HC (N = 17)		p value (corrected)	Test
Gender (F/M)	12/4		12/5		1.0	X sq
	Median	IQR	Median	IQR		
Age	41.5	14.5	33	13	1.0	Mann-Whitney U
BMI (kg/m²)	27	8.5	21	5	0.18	Mann-Whitney U
TAS-20 Total	55.5	26	38	19	0.06	Mann-Whitney U
MADRS	12	16	1	3	**0.006**	Mann-Whitney U
SOQ	-12.5	-19	-11	-20	1.0	Mann-Whitney U
	Mean	SE	Mean	SE	P value	
IS	0.50	0.05	0.65	0.04	0.026	**Regression**

Table 4.2 Demographic and psychometric characteristics of the two groups. FMS = functional movement disorders; HC = healthy controls; IS = interoceptive sensitivity; F = female; M = Male; BMI = body mass index; TAS-20 =Toronto Alexithymia Scale; MADRS = Montgomery Asberg Depression Rating Scale; SD = standard deviation; SOQ = Self-Objectification Questionnaire.

4.3.2 Correlations between interoceptive awareness and other variables

Spearman's bivariate correlations, corrected for multiple comparisons using the Bonferroni method, were conducted in each group separately to examine the relation between interoceptive sensitivity and the other psychometric variables in our samples, i.e., MADRS depression scores, TAS-20 alexithymia scores and SOQ self-objectification scores. These analyses revealed no significant

correlations. Results are depicted in Table 4.3. However, when pooling participants across groups (N = 33) to increase statistical power, we observed a significant correlation between interoceptive sensitivity and MADRS depression scores (see Table 4.3).

	Patients with FMS (N =16)		Healthy controls (N = 17)		Combined	
	Interoceptive sensitivity					
	Rho	*P*	Rho	*P*	Rho	*P*
TAS-20 tot (%)	-0.38	0.44	0.02	1.0	-0.30	0.28
MADRS	-0.51	0.13	-0.30	0.74	-0.47	**0.02**
SOQ	-0.40	0.37	-0.16	1.0	-0.29	0.29

*All *ps Bonferroni adjusted*

Table 4.3 Correlations between IS and other trait variables in each of the two groups and overall. TAS-20 = Toronto Alexithymia Scale; MADRS = Montgomery Asberg Depression Rating Scale; SOQ = Self-Objectification Questionnaire

4.3.3 Regression Analyses

When investigating the relationship between group classification and IS, Group was a significant predictor of IS (b = .15, SE = .07, p = .026, 95% CI [.02, .27]). As expected, patients showed lower IS (M = .50, SE = .05) than healthy controls (M = .65, SE = .04).

When investigating whether IS in interaction with group, and controlling for MADRS depression scores, predicted TAS-20 scores, we found that scores on the TAS-20 were not explained by IS (b = 10.50, SE = 22.18, p = .636, 95% CI [-32.98, 53.98]), group (b = .49, SE = 4.87, p = .919, 95% CI [-9.06, 10.05]) or their interaction (b = -11.22, SE = 28.16, p = .690, 95% CI [-66.41, 43.97]), while MADRS scores significantly predicted TAS-20 scores; the higher the depression score, the higher the alexithymia score (b = 1.41, SE = .37, p < .001, 95% CI [.69, 2.15]).

When investigating whether IS in interaction with group, and controlling for TAS-20 scores, predicted MADRS depression scores, IS and group emerged as significant predictors of MADRS depression scores (b = -21.40, SE = 9.17, p = .020, 95% CI [-39.37, -3.44] and b = -5.92, SE = 2.17, p = .006, 95% CI [-10.18, -

1.67], respectively). In addition, there was a marginally significant interaction of interoceptive awareness and group on MADRS depression scores (b = 19.32, SE = 10.30, p = .061, 95% CI [-.87, 39.50]), although confidence intervals included zero. Following up this effect revealed that for patients (p = .020) but not for controls (p = .640), lower IS predicted higher depression scores. Lastly, TAS-20 scores also significantly predicted MADRS scores (b = .19, SE = .07, p = .005, 95% CI [.06, .33]).

Finally, when investigating whether interoceptive awareness in interaction with group, controlling for MADRS depression scores, predicted SOQ self-objectification scores, IS emerged as a significant predictor (b = -44.46, SE = 16.94, p = .009, 95% CI [-77.66, -11.26]), while group did not (b = -1.18, SE = 4.74, p = .803, 95% CI [-10.48, 8.12]). However, there was a significant interaction between Group and IS, (b = 38.98, SE = 19.45, p = .045, 95% CI [.85, 77.11]). Following up this interaction, it was found that for patients (p = .009), but not for controls (p = .611), lower IS predicted higher self-objectification. Lastly, MADRS scores did not predict SOQ scores, (b = -.38, SE = .35, p = .273, 95% CI [-1.07, .30]).

4.4 Discussion

The main finding of this study is that patients affected by FMS presented lower IS compared to an age, gender and BMI matched group of healthy volunteers.

We also found that patients with FMS showed higher rates of depressive symptoms and higher levels of alexithymia than healthy subjects. Nevertheless, interoceptive sensitivity was not correlated with alexithymia scores within or across groups, even after controlling for depressive symptoms. On the other hand, MADRS scores showed an overall negative correlation with IS across groups, and IS was a predictor of depressive symptoms in patients with FMS, but not in healthy subjects. Finally, although self-objectification and IS scores did not show an overall association between or within groups, IS was a predictor of self-objectification in the FMS but not the healthy control group in regression analyses.

Our data suggest that patients with FMS demonstrated reduced interoceptive awareness but this is a trait that may be linked to some of their concomitant, non-motor symptoms, e.g. depressive symptoms and self-objectification tendencies. In the last few years many studies have shown a correlation between IS and depressive symptoms (Dunn et al., 2010; Terahhar et al., 2012; Furmar et al., 2013; Dunn et al., 2007). For example, recent studies have underlined that patients affected by major depression disorder present reduced IS, even after controlling for anxiety (Dunn et al., 2010). In addition, reduced IS has been linked to lower heart beat evoked potentials (HEPs) in depressed patients, an EEG measure able to provide an objective correlate of interoceptive processing (Terhaar et al., 2010). Our data are in line with these studies, demonstrating that reduced performance on the heart beat detection task was a predictor of sub-clinical depressive symptoms in patients with FMS, but not healthy individuals. Therefore, we speculate that IS may contribute to deficits in emotional processing, known to be associated with depressive symptoms and other related psychopathologies (Dunn et al., 2007). Nevertheless, these findings do not answer the question of how these emotional deficits are specifically linked to the development and maintenance of FMS.

In this respect, it is significant that our results show that even after controlling for depressive symptoms, IS still remains a predictor of self-objectification, particularly in patients affected by FMS. To the best of our knowledge, no study has assessed self-objectification in FMS. Nevertheless, a negative correlation between interoceptive sensitivity and self-objectification has been shown in a group of healthy subjects (Ainley et al., 2013) and in a group of patients affected by anorexia nervosa (Pollatos et al., 2008). More broadly, authors suggested that self-objectification may be considered as a risk factor for the development of eating disorders; the worry with the exterior appearance of the body might dissipate many valuable resources needed for interoceptive sensitivity, so that patients suffering from eating disorders become less aware of their internal signals, such as emotional bodily states (e.g. hunger and satiety) (Fredrickson et al., 1997). Many other studies have shown a significant correlation between self-objectification and

eating disorders and recently, interoceptive awareness has been shown to directly mediate the relationship between self-objectification and eating disorders (Myers et al., 2008; Peat et al., 2011).

In the light of previous data in patients affected by FMS regarding the excessive attentional focus on exteroceptive signals (e.g. visual or tactile signals), our findings warrant further investigation of the relationship between interoceptive awareness, self-objectification and functional symptoms.

We also shown that IS in patients with FMS does not correlate to the level of alexithymia, even after controlling for depression. This result is quite surprising, as previous studies have demonstrate IS to negatively correlate with alexithymia (Herbert et al., 2011) and patients with FMS to have high rates of alexithymic features. In this respect, we should replicate our study in a larger group of patients affected by FMS with higher levels of alexithymia, and greater gender balance (Herbert et al., 2011), before defining conclusions. Nevertheless, a possible explanation for our results might be that in patients with FMS alexithymia is not caused by reduced awareness into one's inner signals, but may be caused by other general factors such as depressive symptoms (depression and alexithymia were found to predict each other in our whole sample) or anxiety symptoms (see Chapter 3).

In conclusion, our study show that patients affected by FMS have reduced interoceptive sensitivity than healthy controls, and such lower interoceptive sensitivity may predict depression and self-objectification. Our findings warrant further investigation of interoceptive awareness in patients with FMS, as a key to study emotional impairment at a more mechanistic level than focusing only on psychological factors such as traumatic life events.

Chapter 5:
The role of mild cognitive impairment in the development of functional motor symptoms

5.1 Introduction

As already highlighted in Chapter 1, the aetiology of FMS still remains unknown. In Chapter 3 and 4 we have seen the potential role for emotional factors in the development and maintenance of FMS. Nevertheless, there is some evidence that also cognitive factors, such as memory and attention, might play a crucial role in determining FMS.

At the beginning of the 19th century, Janet was the first to conceptualize hysteria as presenting also a neurocognitive component – in particular, as an impairment of memory processing arising during a traumatic event. Later aetiopathological models concentrated on deficits in both memory and attention, and postulated that these deficits would be more evident during the presence of symptoms and during testing conditions that were stressful or that induced anxious symptoms (Ludwig et al., 1972; Whitlock et al., 1967). Recent studies have been interpreted as supporting these hypotheses according to which patients with active FMS are mildly cognitively impaired and that they are even further compromised when subjected to additional stress during testing conditions. A few studies have been conducted assessing neurocognitive function in patients with FMS and results have been quite controversial. In all these studies a traditional neurocognitive battery has been used (Reuber et al., 2008; Brown et al., 2014; Duncan et al., 2008; Kozlowska et al., 2015).

The Guilty Knowledge Task (GKT) is a simple, fast, computerised paradigm specifically assessing deception ability (Mameli et al., 2010; Priori et al., 2008). We already known that the process of lying is under regulation by complex, multifacet cognitive mechanisms, including attention, memory, set shifting, inhibition and conflict monitoring (conflict between the automatic truthful and the lie response) (Mameli et al., 2010; Priori et al., 2008; Spence et al., 2004). Neuroimaging studies

(mainly using fMRI) have demonstrate that the process of lying demands additional cognitive processing, which engages different areas of the brain including frontal and parietal cortex, cerebellum, striatum, insula and thalamus (Elble et al., 2000; Higginson et al., 2008). This additional effort leads to longer reaction times (RTs) for lying responses than for true responses and primarily involves prefrontal cortex areas.

In this view, deception might be impaired in those clinical conditions characterized by complex attention and memory deficits. Recent studies have found patients affected by Parkinson's disease and patients affected by essential tremor to have greater difficulty than healthy controls in making deceptive responses (Abe et al., 2013; Mameli et al., 2013).

The aim of our study was to investigate whether deceptive responses are impaired in patients affected by functional motor symptoms, using the Guilty Knowledge Task. We also tested patients with FMS for the moral sense, a philosophical and psychological aspect, traditionally linked to deception, using a computer-controlled procedure, the moral judgment task, testing non moral (NM), impersonal moral (IM) and personal moral (PM) dilemmas (Fumagalli et al., 2010). A group of healthy subjects (HS) was used as a control group.

5.2 Materials and Methods

5.2.1 Subjects

Thirteen consecutive patients affected by FMS were recruited via neuropsychiatric clinic at San Paolo Hospital, Milano, Italy, between November 2015 and May 2016, and they were compared to 14 healthy subjects (visitors to hospital and hospital staff), matched for age, gender and score on the Mini-Mental State Examination (MMSE) (Folstein et al., 1975), as a control group. No patients refused to take part in the study.

Patients were included if they had "clinically established and documented" (Williams et al., 1995) FMS according to Fahn & Williams criteria. The diagnosis of FMS was made by a neurologist and a psychiatrist on the basis of clinical presentation and proper investigations. All patients with FMS had symptoms at the

time of the examination. We decided to select only patients with non-remittent symptoms in order to have a more homogeneous group. The specific functional symptoms were gait disorders (30%), tremor (20%), dystonia (40%), and myoclonus (10%).

All participants gave informed consent for the study. The Ethics Committee of San Paolo Hospital reviewed and approved the study protocol.

5.2.2 Exclusion Criteria

See Exclusion Criteria Chapter 3.

5.2.3 Experimental Protocol

All subjects participated in an experimental session lasting about 80 min during which they underwent a psychological assessment and an experimental evaluation.

5.2.3.1 Psychological evaluation

All patients and controls underwent the following assessment:

- 20 item-Toronto Alexithymia Scale (TAS-20). See Chapter 3 for description.
- Hamilton Rating Scale for Depression (HAM-D). This is the one of the most widely used clinician-administered depression assessment scale. Each item on the questionnaire is scored on a 3 or 5-point scale, depending on the item, and the total score is compared to the corresponding descriptor; it has been showed to yield reliable and internally consistent scores and to demonstrate criterion-related validity (Hamilton, 1960).
- Hamilton Rating Scale for Anxiety (HAM-A). The HAM-A is the first rating scales developed to measure the severity of anxiety symptoms, and is still widely used today in both clinical and research settings. The scale consists of 14 items, each defined by a series of symptoms, and measures both psychic anxiety and somatic anxiety. Several studies have shown that it is reliable, internally consistent and valid (Maier et al., 1980).

5.2.3.2 Guilty Knowledge Task

Truthful and deceptive responses were evaluated using a computer-controlled procedure (E-Prime-Psychology Software Tools, Inc.), a simplified version of the GKT used by Mameli et al. (Mameli et al., 2010). Subjects were first required to select 5 pictures (i.e., selected pictures) from a set of 10. They were then requested to answer truthfully or to lie to the question ‘‘do you have this picture?’’ referring to a picture randomly presented on the computer screen: 50% of the times the picture was one of those selected and 50% of the times it was one of those not selected, with a total of 80 trials. Twenty stimuli required a truthful response to selected pictures (TS: responding truthfully to a selected picture) and 20 to unselected pictures (TU: responding truthfully to an unselected picture); 20 stimuli required to lie to selected pictures (LS: lying to a selected picture) and 20 to unselected pictures (LU: lying to an unselected picture). Hence, before each picture was presented, the participant was instructed by the computer to lie or to respond truthfully (Figure 5.1a).

5.2.3.3 Moral Judgement Task

We used the moral judgment task proposed by Fumagalli et al. (Fumagalli et al., 1997). We used a battery of 30 practical dilemmas randomly extracted from 60 scenarios (Greene et al., 2004) translated into Italian. The task consisted of 20 Non moral dilemmas (NM) and two classes of “moral” scenarios subdivided into Impersonal Moral (IM, 18 scenarios) and Personal Moral (PM, 22 scenarios) dilemmas. In agreement with the utilitarian theory, we distinguished utilitarian and non-utilitarian responses. Each dilemma was presented in a series of three screens of text. The first two screens each presented a paragraph describing the context and details of the dilemma. The third screen posed a question about a hypothetical action related to the scenario (“Would you…in order to…?”). Participants were allowed to read through screens 1 and 2 at their own pace, pressing the space bar to advance to the next screen. In the third screen, participants had a maximum of 25 s to read the final question and press the left

(YES) or the right (NO) mouse button (Figure 5.1b). Stimuli were presented on a personal computer screen using E-Prime Version 1.1 (Psychology Software Tools, Inc, Pittsburgh, USA).

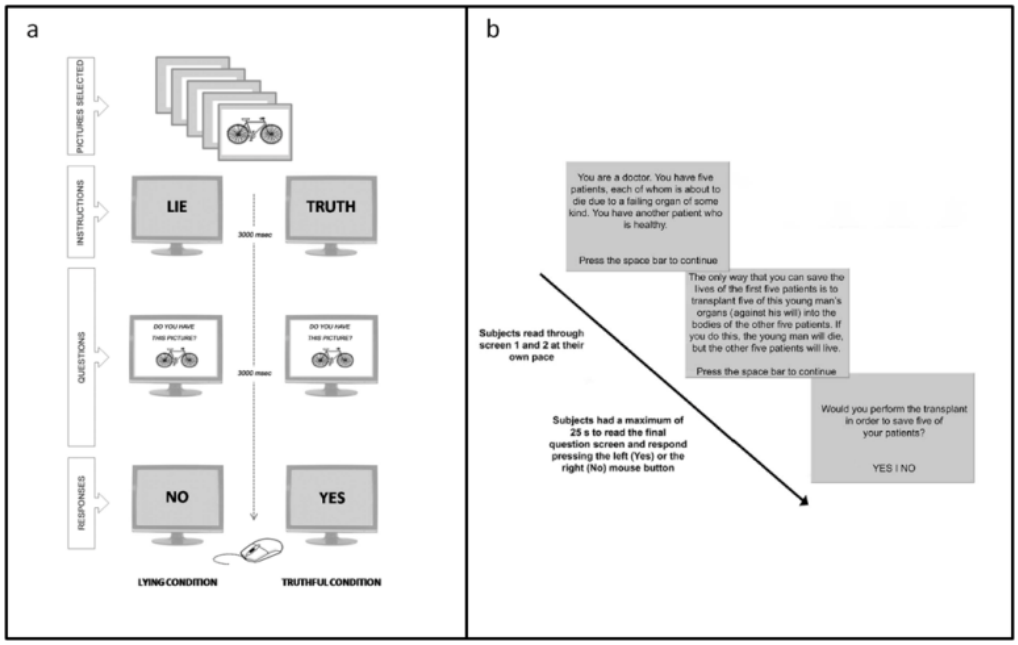


Figure 5.1a The modified version of the Guilty Knowledge Task
Figure 5.1b The Moral Judgement Task

5.2.4 Statistical analysis

To compare the two groups (FMS patients, HS) a one-way analysis of variance (ANOVA) with between factor 'group' was run for all tests used in screening evaluation (MMSE, HAM-D, HAM-A, TAS-20), for Deception Assessment (Total Truth, Total Lie, TS, LS, TU, LU) and in Moral Sense Assessment (Total NM, Total IM, Total PM, NMu, IMu, PMu, NMnu, IMnu, PMnu).

For psychological screening, we analysed the scores in all single tests (HAM-D, HAM-A, TAS-20), whereas for the deception task we analysed RTs and response accuracy and RTs for moral task. Tukey Post hoc test was used to assess differences between the variables measured for each task. Pearson's correlation coefficient was calculated to check the correlation between continuous variables

and lie performance in the GKT/moral sense in the moral task. All statistical data were analysed with STATISTICA V.5.5 (Statistica, StatSoft. Inc, Italy). Unless otherwise indicated all values are expressed a means±SD.

5.3 Results

Data for 13 FNS patients and 14 HS were entered into the statistical analysis.

5.3.1 Psychological assessment

No significant differences were found between the two groups for age (F (1,25) = 0.406; p = 0.530), gender (X^2 (1,25) = 0.466; p = 0.496), education (F (1,25) = 0.000; p = 0.984) and MMSE (F (1,25) = 0.078; p = 0.782). No significant difference was found in the TAS-20 score (F (1,25) = 0.718; p = 0.407). Patients affected by FMS scored higher than HS at HAM-D score (F (1,25) = 3.568; p = 0.044) and HAM-A score (F (1,25) = 5.424; p = 0.031). For details see Table 5.1.

	Patients with FMS (N = 13)	HS (N = 14)	p
Gender, female n (%)	11 (84.6)	13 (92.9)	0.496
Age, years (SD)	49.7 (17.1)	45.6 (15.9)	0.530
Educational level, Years (SD)	12.6 (3.9)	12.6 (3.1)	0.984
MMSE mean score (SD)	28.3 (2.3)	28.5 (2.1)	0.782
TAS-20 mean score (SD)	46.9(14.7)	42.1 (10.7)	0.407
HAM-D mean score (SD)	8.2 (6.6)	3.4 (4.2)	**0.044**
HAM-A mean score (SD)	10.1 (8.4)	3.1 (3.5)	**0.031**

Table 5.1 Demographic variables and psychometric assessment. SD = standard deviation; FMS = functional motor symptoms; HS = healthy subjects; MMSE = Mini Mental State Examination; TAS-20 = Toronto Alexithymia Scale; HAM-D = Hamilton Rating Scale for Depression; HAM-A = Hamilton Rating Scale for Anxiety.

5.3.2 Deception task

5.3.2.1 Total score comparison between the two study groups

The RTs were significantly longer for lie responses than for true responses ($F(1,26) = 50.47$; $p < 0.001$) in the two groups.

ANOVA showed that total RTs were significantly longer for patients with FMS than for HS, in true responses ($F(1,25) = 4,36$; $p = 0.047$, post hoc: $p = 0.047$) and lie responses ($F(1,25) = 4.26$; $p=0.05$, post hoc: $p = 0.05$) (Figure 5.2)

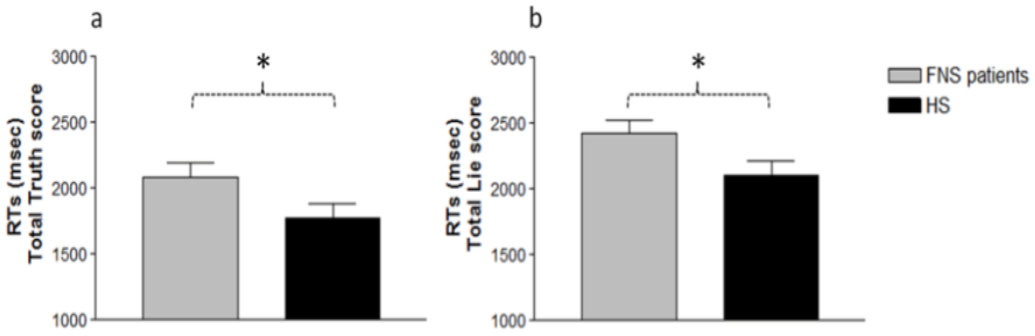


Figure 5.2 Reaction times for total truth scores and for total lie scores for FNS patients and healthy controls

No differences were found between the two groups for accuracy in producing true responses ($F(1,25) = 0.09$, $p = 0.77$), and for lying responses ($F(1,25) = 0,12$, $p = 0.73$) (Table 5.2).

	Patients with FMS (N = 13)	HS (N = 14)
Reaction times (ms)		
True responses	2089 (106.9)	1774 (106.2)
Lie responses	2425 (103.2)	2103 (115.9)
True Selected responses	1915 (117)	1647 (101.2)
Lie Selected responses	2469 (88.05)	2081 (135.4)
True Unselected responses	2281 (112.6)	1965 (113.8)
Lie Unselected responses	2416 (124.1)	2084 (131.6)
Accuracy		
True responses	35.92 (2.1)	36.64 (1.2)
Lie responses	30.92 (2.5)	32.07 (2.1)
True Selected responses	18.46 (1.1)	18.21 (0.64)
Lie Selected responses	15.38 (1.4)	16.50 (1.2)
True Unselected responses	17.46 (1.2)	18.43 (0.73)
Lie Unselected responses	15.54 (1.3)	15.57 (1)

Table 5.2 Reaction times and accuracy for the Deception task. FMS = functional motor symptoms; HS = healthy subjects

All results are expressed as mean±(SEM). ms, milliseconds.

All results are expressed as mean±(SEM). ms, milliseconds.

5.3.2.2 Comparison between the two study groups: Selected Response

No differences were found in RTs for patients with FMS than HS, in TS responses ($F(1,25) = 3.03$; $p = 0.09$), conversely ANOVA showed significantly longer RTs for patients with FMS than HS, in LS responses ($F(1,25) = 5,6$; $p = 0.026$, post hoc: $p = 0.026$). (Figure 5.3 a, b)

No differences were found in accuracy for TS responses ($F(1,25) = 0.036$, $p = 0.85$), and for LS responses ($F(1,25) = 0.35$, $p = 0.56$). (Table 5.2).

5.3.2.3 Comparison between the two study groups: Unselected Response

No differences were found in RTs for patients with FMS than HS, in TU responses (F(1,25) = 3.88; p=0.06) and for LU responses (F (1,25) = 3.34; p = 0.08). (Figure 5.3 c, d).

No differences were found in accuracy for TU responses (F (1,25) = 0.48, p = 0.50), and for LU responses (F (1,25) = 0.0004, p = 0.98). (Table 5.2).

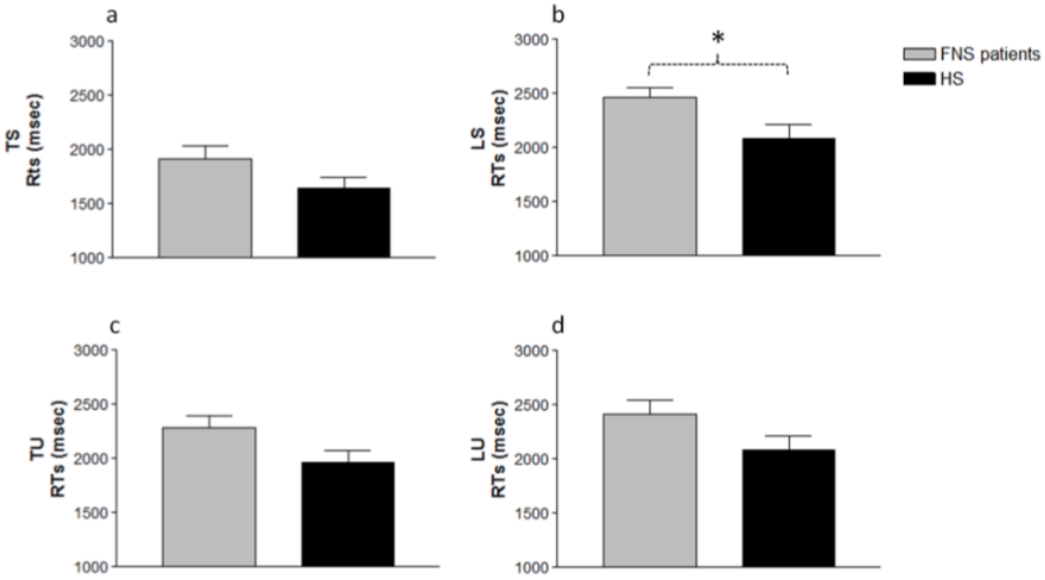


Figure 5.3 Reaction times for FMS patients and healthy controls

5.3.2.4 Correlation

No significant correlation was found either between deception ability and demographic variables or between deception ability and MMSE score/psychological scales' score.

5.3.3 Moral Judgement Task

5.3.3.1 Total score comparison between the two study groups: non moral, impersonal moral, personal moral responses

No differences were found in RTs for patients with FMS than HS, in NM responses ($F(1,25) = 0.33$; $p = 0.6$) in IM responses ($F(1,25) = 0.43$; $p = 0.51$) and in PM responses ($F(1,25) = 0.15$; $p = 0.7$).

5.3.3.2 Comparison between the two study groups: utilitarian, non utilitarian responses

No differences were found in RTs for patients with FMS than HS, in NMu responses ($F(1,25) = 0.24$; $p = 0.6$) in IMu responses ($F(1,25) = 0.20$; $p = 0.67$), in PMu responses ($F(1,23) = 0.04$; $p = 0.8$), in NMnu responses ($F(1,21) = 0.13$; $p = 0.7$) in IMnu responses ($F(1,25) = 2,07$; $p = 0.16$), in PMnu responses ($F(1,25) = 0.27$; $p = 0.6$).

5.3.3.3 Correlation

No significant correlation was found either between moral sense and demographic variables or between moral sense and MMSE score/psychological scales' score.

5.4 Discussion

The main finding of our study is that when tested with the GKT, a procedure assessing deception ability, patients with FMS were slower than healthy controls in producing both truthful and lying responses. The accuracy in producing both truthful and lying responses did not differ between the two groups. These results are reinforced by the fact that MMSE score, depression, anxiety and alexithymia did not correlate with the GKT responses, excluding they might represent confounding factors. In addition, the moral sense, studied with moral judgement task proposed by Fumagalli et al (Fumagalli et al., 1997), did not differ between patients with FMS and HS and did not correlate with the GKT responses.

To the best of our knowledge, this is the first study assessing deception in patients affected by FMS. In the light of these findings, we might formulate a possible

interpretation, in order to consider the aetiology of these disorders at a more mechanistic level than concentrating on traumatic life events and related risk factors.

According to recent neurobiological studies, the longer RTs at the GKT seen in our patients, reinforced by the fact that it did not correlate with depression and anxiety levels, might represent a non-specific cognitive feature, such as previously reported in other movement disorders (e.g. Parkinson's disease or essential tremor) (Abe et al., 2013; Mameli et al., 2013). Previous studies assessing cognitive functions in conversion disorders have been conducted but results have been controversial. The study by Brown et al investigated neuropsychological functioning in patients with conversion disorders, concentrating on executive and memory function (Brown et al., 2014). A directed forgetting task (DFT) using words with variable emotional valence was also used to investigate memory suppression. Twenty-one patients affected by conversion disorders and 36 healthy subjects completed a battery of traditional neuropsychological tests; results showed patients to have deficits in executive function and auditory-verbal memory. Nevertheless, the executive deficits were mainly caused by differences in anxiety and mood between the groups, suggesting that cognitive deficits might not be key features of the disorder itself but consequences of depressive or anxious symptoms. Other studies of cognitive functioning in patients with conversion disorders suggested, at baseline, reduced performance on tasks of attention, processing speed, verbal fluency, verbal and visual memory, and motor skills (Reuber et al., 2008; Brown et al., 2014; Duncan et al. 2008). In these studies, cognitive deficits were explained as representing a key aspect of the disorder itself; brain disease and associated deficits in neurocognitive function were viewed as risk factors for the development and maintenance of functional neurological symptoms (Reuber et al., 2008; Brown et al., 2014; Duncan et al., 2008). Neurocognitive functions have been studied also in children and adolescents with conversion disorders: the study by Kozlowska et al demonstrated patients aged 8-18 years affected by acute conversion disorders to have a lower ability to manipulate and retain information, to block interfering information, and to inhibit

responses, all of which are needed for effective attention, executive function, and memory (Kozlowska et al., 2015). Nevertheless, other studies using traditional tests of neurocognitive batteries found no impairment in cognitive functions in patients with conversion disorders. The novelty of our study resides in the fact that we showed a specific impairment in the ability to produce lies (in terms of longer RTs at the GKT), which might reflect the specific intense cognitive load required by the deception task. Complex experimental paradigms, such as those we administered in our study (GKT), can detect alterations in cognitive functioning or even subclinical deficiencies. Computerised tasks that test several cognitive functions simultaneously also allow evaluating patients' cognitive capacities, simulating a real-life situation in which the environment issues multiple requests and requires fast responses. The GKT concentrates exactly on these cognitive processes and requires the subject to make an intense cognitive effort to overcome the high cognitive load the task demands. The cognitive complexity related to the deception task may help to explain the GKT abnormality in patients with FMS, in whom mild, subtle cognitive dysfunctions - per se clinically irrelevant - may serially cumulate, ultimately resulting in impaired lying.

Current knowledge along with our new data in patients with FMS - possibly arising from individually unrecognised extremely mild, cognitive impairment - should help in designing specific rehabilitative programmes to improve cognitive and behavioural disturbances in these patients.

Chapter 6:
The neuromodulatory effect of tDCS in functional motor symptoms

6.1 Introduction

We have already widely discussed in previous chapters how emotional and cognitive factors might combine together in order to determine the onset and maintenance of FMS. We have also seen in Chapter 1 how neuroimaging studies (fMRI studies) have provided first evidences that emotional brain circuits (mainly involving the amygdala and the cingulate cortex region) might be differentially activated in individuals affected by FMS and interact with their motor symptom (Kanaan et al., 2007). Nevertheless, no studies up to date have never assessed whether these emotional factors and emotional brain circuits might be influenced or modified by the effect of neuromodulation.

Transcranial Direct-Current Stimulation (tDCS) is a non-invasive neuro-stimulation technique based on a weak electric stimulation (1-2 mA for 5 to 30 minutes) able to modulate the neural activity. The increase or decrease in neuronal excitability causes an alteration of the cerebral function that can be exploited for therapeutic purposes or to improve our knowledge of the functioning of the central nervous system (Nitsche et al., 2008). Positive stimulation (anodic tDCS) results in a depolarization of the neuronal membrane potential that facilitates the start of spontaneous action potentials. Negative stimulation (cathodic tDCS) leads to a hyperpolarization with inhibitory effect on the excitability. The effects persist according to the duration of the stimulation: a ten-minutes session generates one hour long results. The mechanism underlying the operation is not completely understood: according to Monai et al. (Monai et al., 2016) tDCS would act by altering synaptic transmission through modifications of intracellular levels of cAMP and calcium and the activation of glial elements, which depend on protein synthesis. These events are similar to those of neuroplasticity and in particular to Long Term Potentiation (LTP) and Long Term Depression (LTD).

Given its mechanism of action, tDCS has been used therapeutically for a wide range of psychiatric and neurologic conditions, such as Major Depressive Disorder, Schizophrenia and memory problems. (Brunoni et al., 2016; Bennabi et al., 2014; Agarwal et al., 2013). As yet there are no reports of its use for functional neurological symptoms, but it has been used for fibromyalgia (Marlow et al., 2013), complex regional pain syndrome (Dufka et al., 2015) and chronic pain more widely. The main purpose of the present study was to evaluate the neuromodulatory effect of a single anodic tDCS session over the right posterior parietal cortex in subjects with FMS and in age and gender-matched healthy individuals. Recent models of human posterior parietal cortex have variously emphasized its role in spatial perception, visuomotor control and directing attention (Malhotra et al., 2009). As outcome measures, we decided to choose the heart beat detection task as a measure of interoceptive awareness (already showed to be reduced in patients with FMS, see Chapter 4) and the Posner paradigm for the assessment of spatial attention, which has never been tested in patients affected by FMS.

6.2 Materials and Methods

6.2.1Subjects

Nine consecutive patients with a diagnosis of FMS were recruited from the outpatient unit of the San Paolo Hospital in Milan, Italy, between June 2016 and November 2016. Two patients refused to take part in the study. Patients were included only in the case of a clinically established and documented diagnosis of FMS according to Fahn and Williams criteria (Williams et al.,1995). The diagnosis was made by a neurologist and a psychiatrist on the basis of clinical presentation and appropriate investigations. A sample of 7 age-matched and sex-matched healthy subjects was recruited among members of the hospital staff and their relatives.

All participants gave informed consent for the study. The Ethics Committee of San Paolo Hospital reviewed and approved the study protocol.

6.2.2 Exclusion Criteria

See Chapter 3 for details.

6.2.3 Assessment

The presence of depressive and anxiety symptoms was evaluated at baseline respectively with the Hamilton Rating Scale for Depression (HAM-D) and the Hamilton Rating Scale for Anxiety (HAM-A). The self-assessment questionnaires 20-item Toronto Alexithymia Scale (TAS-20) and Self-Objectification Questionnaire (SOQ) were then administered at T0. See Chapter 3, 4 and 5 for details about the scales.

6.2.4 tDCS

All participants underwent two sessions of tDCS (one real and one sham) at T0 and at T1 (at least two days after T0, in order to avoid carry-over effect). All subjects underwent the two conditions in a randomized order.

tDCS was administered through a battery-driven, constant current stimulator (neuroConn GmbH, Illmenau, Germany) using a pair of saline-soaked sponge rubber electrodes. Stimulation was applied over the right PPC (P4, according to international 10–20 EEG system). Electrode size of the anode was 25 cm² (leading to 0.06 mA/cm2 current density in the real tDCS conditions), while the size of the reference electrode/cathode was 35cm² (leading to 0.04mA/cm2 current density in the real tDCS conditions). To allow a double-blinded study design, where both the experimenter and participant were blinded for the sham (control) condition, the latter was performed in the same way as active stimulation but with the instrument set in the "study mode": an initial 30s real stimulation ensured that participants felt the itching or tingling sensation at the beginning of the stimulation.

6.2.5 Outcome measures: heart beat detection task and Posner paradigm

At the end of each tDCS session all participants underwent the following outcome measures:

- Heart beat detection task. See Chapter 4 for full description.

- Posner paradigm. In order to exclude an unspecific effect of tDCS on arousal, an external cueing visual paradigm (Posner et al., 1984; Posner et al., 1987; Posner et al., 1988) was administered, including 60 trials. At the beginning of each trial, a fixation cross appeared for 2000 ms on the center of the screen. Then, two rectangles appeared at the left and right of the fixation cross and, after a further random range of 200-700 ms, one of the two perimeters blinked for 200 ms (cue). After 100 ms, a small square appeared inside one of the two shapes (target). Subjects had to indicate as quickly and accurately as possible where the target appeared by pressing the left or right index finger one of the assigned keys on a qwerty keyboard: "F" when the target appeared to the left and "J" when to the right. Catch trials in which no target appeared were also included (12 trials). Accuracy (ACC) and response time (RTs) were then collected (Figure 6.1).

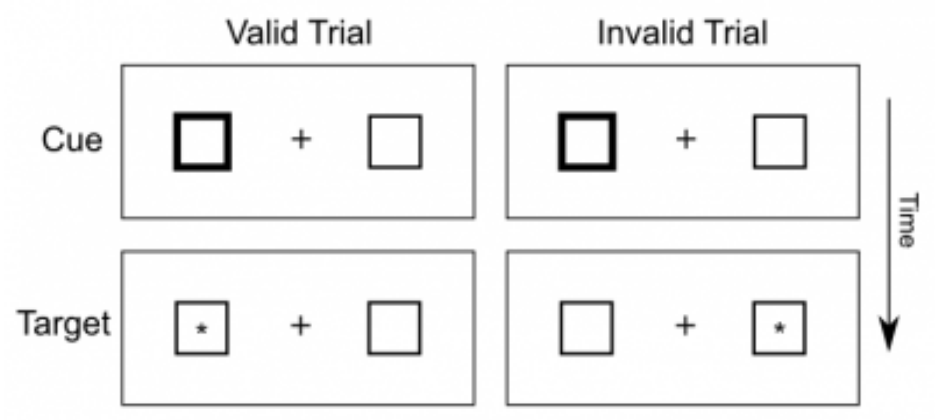


Figure 6.1 The Posner paradigm

After completion of the two tDCS sessions patients and controls completed a questionnaire for possible adverse reactions during or after tDCS. No adverse reactions have been reported. In addition, they were asked which stimulation condition they had perceived as (i) the weakest, and (ii) the strongest (if they answered to have perceived differences in the first place). Finally, we checked if individuals became aware of the sham stimulation and could guess it correctly.

80% of the subjects did not recognize the placebo session correctly when asked at the end of the experiment.

6.2.6 Statistical analysis

The collected data was exported to Microsoft Excel 2014®. Statistical analysis was performed using Statistical Package for Social Science (SPSS V.24). The variables were first tested for normality using the Shapiro–Wilks test. The variables that were not normally distributed ($p<0.05$) were log10-transformed. For continuous data, a one-way analysis of variance (ANOVA) was used to test for differences across the groups. The χ^2 test was used for categorical data. ANOVA for repeated measures was used for comparisons between real and sham interoceptive awareness. Correlations between values of interoceptive awareness and demographic and psychometric variables were calculated with Spearman bivariate correlation. The confidence interval considered for statistical significance was 5% ($p < 0.05$).

6.3 Results

Nine patients with FMS (8 out of 9 women [88,9%], average age 48.22 years [SD 17.54]) and seven healthy controls (6 out of 7 women [85.7%], average age 44.86 years [SD 18.76]) were included.

A lower level of education in patients was the only sociodemographic difference observed between the two groups ($F(1) = 6.112$, $p = 0.013$).

Patients with FMS presented the following symptoms: 1/9 (11.1%) functional tremor, 1/9 (11.1%) functional dystonia, 2/9 (22.2%) functional myoclonus, 4/9 (44.4%) functional weakness and 1/9 (11.1%) functional weakness associated to functional gait disturbances.

Two patients were excluded as outliers since they scored more than 2 SD above the groups mean on the heart beat detection task and there were cues that they did not follow instructions during the task. For socio-demographic variables and clinical scales scores see Table 6.1.

Patients obtained significantly higher scores than controls both at HAM-D (F (1,14) = 5.077, p = 0.041) and at HAM-A (F (1,14) = 4.588, p = 0.048) scales.

	Patients with FMS (N = 9)	HS (N = 7)	p
Gender, female n (%)	8 (88.9)	6 (85.7)	0.849
Age, years (SD)	48.22 (17.548)	44.86 (18.765)	0.717
Marital status Single Married Divorced Widowed n (%)	 1 (11.1) 7 (77.8) 0 (11.1) 1 (0.0)	 3 (42.9) 3 (42.9) 1 (14.3) 0 (0.0)	0.220
Educational level, years (SD) 13 years 18 years n (%)	 8 (88.9) 1 (11.1)	 2 (28.6) 5 (71.4)	**0.013**
Employment, Unemployed Student/Employed Retired n (%)	 0 (0.0) 5 (55.5) 4 (44.4)	 0 (0.0) 6 (85.7) 1 (14.3)	0.197
TAS-20, mean score (SD)	39.44 (10.91)	35.29 (3.95)	0.356
TAS-20 <51, n (%)	8 (88.9)	7 (100.0)	
TAS-20 52-60, n (%)	0 (0.0)	0 (0.0)	
TAS-20 >61, n (%)	1 (11.1)	0 (0.0)	
HAM-D, mean score (SD)	14.67 (9.27)	5.14 (7.03)	**0.041**
HAM-A, mean score (SD)	11.78 (7.95)	4.14 (5.70)	**0.048**
BAQ, mean score (SD)	63.56 (21.33)	75.71 (23.65)	0.299
SOQ, mean score (SD)	-11.33 (13.60)	-14.14 (8.07)	0.637

Table 6.1 Socio-demographic variables and clinical scales scores. SD = standard deviation; FMS = Functional Motor Symptoms; HS = healthy subjects; TAS-20 = Toronto Alexithymia Scale; HAM-D = Hamilton Depression Rating Scale; HAM-A = Hamilton Anxiety Rating Scale; BAQ = Body Awareness Questionnaire; SOQ = Self-Objectification Questionnaire.

Patients showed lower levels of interoceptive sensitivity than healthy controls [F (1,12) = 15.875, p = 0.002)] and longer reaction time in the spatial attention task [(F (1, 14) = 13.565, p = 0.001)] at baseline (after sham stimulation). No differences between patients and controls were found at baseline in terms of accuracy of the Posner paradigm (Table 6.2).

	Patients with FMS (N = 9)	HS (N = 7)	p
Interoceptive Sensitivity post tDCS sham - baseline (SD)	0.466 (0.132)	0.697 (0.078)	**0.002**
Reaction Time Posner paradigm post tDCS sham - baseline (SD)	143,70 (68,725)	41,81 (48,618)	**0.001**
Accuracy Posner paradigm post tDCS sham - baseline (SD)	-0,04 (0,081)	-0,04 (0,062)	0.654

Table 6.2 Mean scores of Interoceptive Sensitivity and reaction time of the Posner paradigm at baseline (after sham tDCS stimulation). tDCS = transcranial Direct-Current Stimulation; SD = standard deviation; FMS = Functional Motor Symptoms; HS = healthy subjects.

Our data showed a significant difference between the levels of interoceptive awareness after real and sham stimulation (F = 21.87, p = 0.001) in the whole group of participants. When considering the two groups separately, this difference still remains significance only in patients with FMS (F = 13.62, p = 0.001). With respect to the visual task, we did not find any significant difference between the performance after the real and the one after the sham stimulation, both in the group as a whole and in the groups considered separately (Table 6.3 and 6.4).

	Interoceptive Sensitivity post tDCS Sham (SD)	Interoceptive Sensitivity post tDCS Real (SD)	p
Patients with FMS (N = 9)	0.466 (0.132)	0.672 (0.151)	**0.001**
HS (N = 7)	0.697 (0.078)	0.810 (0.072)	0.231
Group as a whole	0.544 (0.111)	0.724 (0.083)	**0.001**

Table 6.3 Mean scores of Interoceptive sensitivity after sham and after real tDCS stimulation. tDCS = transcranial Direct-Current Stimulation; FMS = Functional Motor Symptoms; HS = healthy subjects; SD = standard deviation

	RT post tDCS Sham (SD)	RT post tDCS Real (SD)	p	Accuracy post tDCS Sham (SD)	Accuracy post tDCS Real (SD)	p
Patients with FMS (N = 9)	143.70 (68.72)	121.38 (67.15)	0.543	-0.04 (0.081)	-0.05 (0.071)	0.432
HS (N = 7)	41.81 (48.61)	45.18 (32.37)	0.231	-0.04 (0.062)	-0.01 (0.030)	0.653
Group as a whole	100,54 (54.12)	86.55 (44.43)	0.645	-0.04 (0.075)	-0.03 (0.064)	0.431

Table 6.4 Mean scores of reaction time of the Posner paradigm after sham and after real tDCS stimulation. RT = reaction time; tDCS = transcranial Direct-Current Stimulation; FMS = Functional Motor Symptoms; HS = healthy subjects; SD = standard deviation.

After the real stimulation we found a negative correlation between interoceptive sensitivity and (i) TAS-20 total score ($p = 0.024$, $\rho = -0.597$); (ii) HAM-D total score ($p = 0.015$, $\rho = -0.633$); (iii) HAM-A total score ($p = 0.029$, $\rho = -0.582$). In the same condition we also found a positive correlation between interoceptive sensitivity and the SOQ total score ($p = 0.010$, $\rho = 0.659$). No significant correlations have been found between visual attention and psychometric scales after real stimulation. No significant correlations have been found between interoceptive sensitivity or visual attention and psychometric scales after sham stimulation.

6.4 Discussion

In this study we evaluated the neuromodulatory effect of a single anodic tDCS session over the right posterior parietal cortex in subjects with FMS and in age and gender-matched healthy individuals, using the heart beat detection task and the Posner paradigm as outcome measures.

Our main results showed that:

-after sham stimulation patients with FMS showed significantly lower interoceptive sensitivity (heart beat detection task) and longer reaction times at the Posner paradigm than healthy controls.

-there was a significant difference between the levels of interoceptive awareness after real and sham stimulation in the whole group of participants. When considering the two groups separately, this difference still remains significance only in patients with FMS

6.4.1 Interoceptive sensitivity

In this study we first replicated our previous results with respect to interoceptive sensitivity in FMS (see Chapter 4 for a full discussion).

We further showed that interoceptive sensitivity might be influenced by a single anodic tDCS session over the right posterior parietal cortex in the group of FMS but not in healthy controls. Several complex neurobiological mechanisms that are still not well understood seem to be involved in the neuromodulatory effect of tDCS. A recent review by Medeiros et al pointed out that tDCS involves a cascade of events at the cellular and molecular levels. Moreover, tDCS seems to be associated with glutamatergic, GABAergic, dopaminergic, serotonergic, and cholinergic activity modulation (Medeiros et al., 2012).

Given the crucial role of interoceptive awareness in the pathophysiology of FMS and given the neuromodulatory effect of tDCS in patients with FMS (in terms of improvement of the performance on the heart beat detection task), we might hypothesize also a therapeutic effect of tDCS for FMS. Up to date no studies have been conducted exploring the therapeutic effect of tDCS in patients with conversion disorders. Nevertheless, over the last decade there has been a steady accumulation of evidence to support transcranial magnetic stimulation (TMS) as a treatment for functional neurological disorders (Chastan & Parain et al., 2010; Shah et al., 2015; Broersma et al., 2015; McWhirter et al, 2016; Garcin et al 2017). According to these studies, TMS seems to be a partially effective treatment for FMS; nevertheless, it is hard to interpret data from uncontrolled case series, especially when methodologic reporting is not optimal, as it is in the majority of these studies. In addition, given that one of the possible mechanism of action of TMS in FMS is the placebo effect, these results must be interpreted with particular caution. Future studies are needed to better investigate the role of tDCS in patients with FMS, both in terms of understanding etiological mechanisms and in terms of treatment implications.

6.4.2 Spatial attention

We have already discussed in Chapter 1 the crucial role of attention in the aetiopathology of FMS. However, no studies up to date have assessed spatial attention in patients affected by FMS.

According to several studies, the posterior parietal cortex plays a crucial role in visual attention control (Sparing et al., 2009). The spatial attention is fundamentally based on the activation of two distinct neuronal networks: the "top-down" dorsal system (including intraparietal and upper frontal cortex portions) is involved in the targeted selection of stimuli and responses; the “bottom-up” right-sided ventral system includes the temporoparietal cortex and the lower frontal cortex and it is supposed to act as a "switch" of the dorsal system by redirecting attention to major or unexpected events outside the attentional focus (Roy et al., 2015). Previous studies on healthy volunteers showed that a 1 mA intensity anodic stimulation on the PPC is able to influence spatial attention to the visual controlateral hemispace, while cathodic stimulation would have the opposite effect (Sparing et al., 2009).

In addition, Matthias et al established a connection between interoceptive awareness and attentive performance: healthy controls with higher levels of interoceptive sensitivity reported significantly higher scores to the visual attention task (Matthias et al., 2009). Thus, authors have hypothesized that the perception of the signals coming from within body is crucial for the processing of exogenous visual stimuli and that the processing pathways of these two different types of stimulation may be partially shared.

On these assumptions, we evaluated whether there was a significant difference between the attentional capacities of healthy controls and FMS patients and whether a single anodic tDCS session over the right posterior parietal cortex might influence the spatial attention in the two populations. As hypothesized, our results showed that patients with FMS had longer reaction times than healthy controls at the Posner paradigm, namely they were more influenced by exogenous cues than controls. Our results are in line with the data by Matthias et al, showing that interoceptive awareness is positively correlated to spatial attention.

However, our data did not show an effect of tDCS on spatial attention, either in patients with FMS and in controls. This might be due to the small number of subjects included. Further studied on bigger samples are needed to better clarify this aspect.

Chapter 7:
The definition of a biological marker in functional motor symptoms: a magnetic resonance spectroscopy study

7.1 Introduction

We have deeply analysed in previous chapters the role of emotional and cognitive abnormalities in the aetiopathology of FMS. Thus, we decided to further strengthen our results by using a safe, non-invasive neuroimaging technique, the magnetic resonance spectroscopy.

Neuroimaging provides the opportunity to study the neural mechanisms of FMS, to understand how these symptoms are produced and linked to potential psychologic or emotional risk/triggering factors. fMRI studies showed abnormal limbic regulation with elevated emotional arousal and amygdala activity (Kanaan et al., 2007; Voon et al., 2010a; Voon et al., 2011) and abnormal ventromedial prefrontal cortex (vmPFC) activation, a region known to regulate emotional appraisal, memory retrieval, and self-reflective representations (Vuilleumier et al., 2014; Cojan et al., 2009; Voon et al. 2011). The vmPFC might provide important modulatory signals to both cortical and subcortical sensorimotor, visual, and even memory circuits, promoting maladaptive self-protective behaviours based on personal affective appraisals of particular events. In other words, the vmPFC is a key limbic structure that may play an important role as a relay between emotional regulation and complex bodily function control. Despite these studies provided important clues about the clinical neuroanatomy of FMS, their neurochemical and molecular basis are still unknown. Glutamate is the major excitatory neurotransmitter in the mammalian brain. Limbic and paralimbic regions, including the vmPFC, are innervated by glutamatergic pyramidal cells (Cortese et al., 2005). Ernst et al found glutamate levels in the left insula and in the anterior cingulate cortex to be positively correlated with alexithymia and awareness of autonomic nervous system reactivity in healthy subjects (Ernst et al., 2014). High levels of

alexithymia and reduced interoceptive awareness have been found to be key features of patients with FMS, as described in previous chapters.

Magnetic resonance spectroscopy (MRS) non-invasively characterizes the chemical composition of tissues, defines tissue-specific metabolic processes and identifies chemical or metabolic pathophysiological factors in diseases (Jansen et al., 2006). In the brain, the concentrations and mobility of MRS-detectable low-molecular weight chemicals are measured as spectral peaks that can reveal neurochemical abnormalities in specific brain regions.

With the hypothesis that patients with FMS have increased glutamate-glutamine (Glx) in the anterior cingulate cortex/medial prefrontal cortex, this study aimed to assess by MRS several brain metabolites [N-Acetyl-aspartate (NAA) (a specific marker of neuronal viability), myo-inositol (MI) (a glial cell marker, increased in case of glial cells activation and proliferation, and an inflammatory marker), choline (Cho) (involved in cell membrane synthesis and degradation) and the sum of glutamate (the major excitatory neurotransmitter) and glutamine (Glx), and creatine (Cr) (an energy buffer and shuttle, used as a denominator for in vivo spectroscopy) in the anterior cingulate cortex (ACC)/medial prefrontal cortex (mPFC) and in the occipital cortex (OCC) (control region) of patients affected by FMS and healthy controls. The MRS peaks of brain metabolites were also correlated with rating scales for alexithymia, anxiety, depression and quality of life.

7.2 Materials and methods

7.2.1 Subjects

Ten consecutive patients affected by FMS were recruited via neuropsychiatric clinic at San Paolo hospital, Milano, Italy, between November 2016 and May 2017, and they were compared to 10 healthy individuals (visitors to hospital and hospital staff), matched for age, gender and MMSE (Folstein et al., 1975). Only one patient refused to take part in the study.

Patients were included if they had “clinically established and documented” (Williams et al., 1995) FMS according to Fahn & Williams criteria. The diagnosis of FMS was made by a neurologist and a psychiatrist on the basis of clinical

presentation and proper investigations. All patients with FMS had symptoms at the time of the examination. We decided to select only patients with non-remittent symptoms in order to have a more homogeneous group. The specific functional symptoms were gait disorders (50%), tremor (20%), dystonia (20%), and myoclonus (10%).

The assessment of the functional motor symptoms (in terms of phenomenology and function) was performed by means of the Psychogenic Movement Disorders Scale (PMD scale), which is the unique validated rating scale for functional movement disorders (Hinson et al., 2005). The PMD scale rates 10 phenomena (rest tremor, action tremor, dystonia, chorea, bradykinesia, myoclonus, tics, athetosis, ballism, cerebellar incoordination), 2 functions (gait, speech), and 14 body regions. In part 1 of the scale, each phenomenon is first rated as present or absent. If present, the phenomenon is given a severity grade and duration factor 0 (lowest) to 4 (highest) for each body region. Global Severity and Incapacitation are assessed for each phenomenon and also rated on a 0 to 4 scale. Part 2 of the PMD scale rates the presence, severity, duration, and incapacitation of two functions: gait and speech. Total scores for phenomena, functions, and their sum are calculated and documented in part 3 of the scale. The Total Phenomenology Score is calculated as the sum of all severity, duration, and incapacitation ratings of all phenomena across the body regions. The Total Function Score is the sum of severity, incapacitation, and duration ratings for the functions gait and speech. The Total Psychogenic Movement Disorder Score represents the sum of the Total Phenomenology Score and the Total Function Score.

All participants gave informed consent for the study. The Ethics Committee of San Paolo Hospital reviewed and approved the study protocol.

7.2.2 Exclusion Criteria

See Exclusion Criteria Chapter 3.

7.2.3 Experimental Protocol

All subjects participated in an experimental session lasting about 100 minutes during which they underwent a psychological assessment and a magnetic resonance spectroscopy.

7.2.3.1 Psychological evaluation

All patients and controls underwent the following assessment:

- The 20 item-Toronto Alexithymia Scale (TAS-20). See Chapter 3 for description.
- The Hamilton Rating Scale for Depression (HAM-D). See Chapter 5 for description.
- The Hamilton Rating Scale for Anxiety (HAM-A). See Chapter 5 for description.
- EuroQol 5D (EQ5D). This is a widely used instrument assessing the generic quality of life. The EQ-5D questionnaire is made up for two components: health state description and evaluation. In the description part, health status is measured in terms of five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. In the evaluation part, the respondents evaluate their overall health status using the visual analogue scale (EQ-VAS). It has been shown to have good validity and reliability (Rabin et al., 2001).

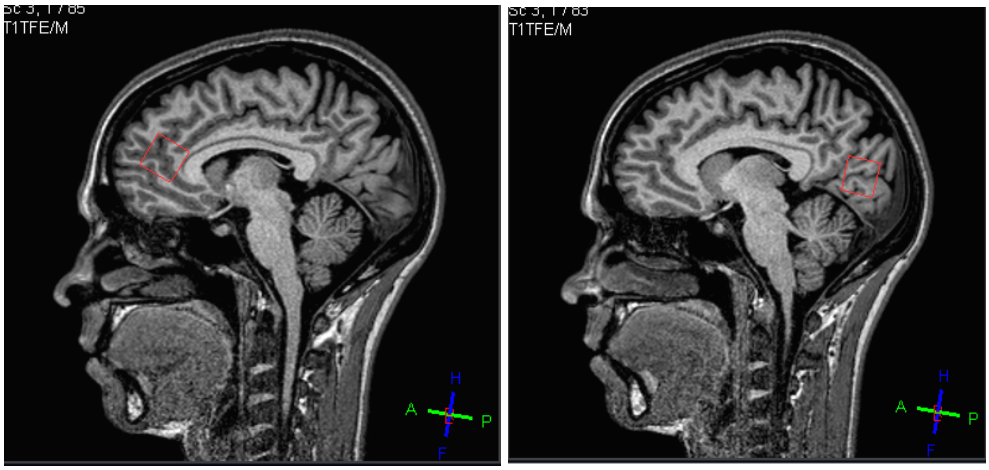
7.2.3.2 Magnetic Resonance Spectroscopy

MRI scans were performed on a MR Achieva 1.5 T scanner (Philips Healthcare, Best, The Netherlands), equipped with a 8 channels head coil. In addition to anatomical images (volumetric acquisition FFE T1 for positioning the voxel and TSE T2 to exclude brain diseases), short - TE spectra (TR/TE = 1700/8.8 msec) and medium - TE spectra (TR/TE = 2000/144 msec) were acquired in each subject from two volumes of interest (VOI) of 8 ml*; one in the ACC also containing portions of medial prefrontal cortex (mPFC), hence named ACC/mPFC, and a second in the OCC. For each MRS scan, a reference spectrum was acquired without water

suppression and used later for phase correction of the corresponding water-suppressed spectrum. We report metabolite concentrations as ratios with respect to the total creatine concentration (a commonly used denominator for in vivo spectroscopy).

We choose the occipital cortex as a control region because definitely out of interest from the brain circuits we wanted to study. In addition, from a technical angle, it is possible to set the voxel on the median line in a way very similar to the ACC.

* or cm3



a b

Figure 7.1 Placement of the magnetic resonance spectroscopic voxel (red frame) in (a) the ACC/mPFC and (b) the OCC in a representative patients/subject. Anatomical imaging was performed in all three orthogonal planes for positioning the MRS voxels.

7.2.4 Statistical analysis

To describe the quantitative variables, the means and standard deviations were calculated, since they were normally distributed. Sociodemographic variables were compared by group using the chi-square or Anova test, depending on whether the variable was qualitative or quantitative. To analyse possible

differences in brain metabolite levels between patients with FMS and healthy subjects, a one-factor Anova test was calculated. In addition, we used the parametric Pearson correlation in the FMS group, in the control group and in the group as a whole, to study the relationship between brain metabolites for which the levels were significantly different, and for which the clinical variables were studied. To determine the statistical significance in psychological tests between patients and controls, a one-factor Anova test was used. Statistical analyses were carried out using SPSS version 24 (Statistical Package for Social Science). P-value lower than 0.05 were considered statistically significant.

7.3 Results

7.3.1 Sociodemographic and psychological variables

No significant differences were found in terms of gender, age, marital status, educational level and MMSE among the two groups. In the control group, rating scores on the psychopathology questionnaires were within the normal range. Psychological ratings of the healthy control group were significantly different from the FMS group. The psychological profiles showed the usual psychological characteristics of FMS patients: high scores in depression and anxiety assessed respectively with the HAM-D and HAM-A; high scores on the TAS-20 and low quality of life as measured by the EQ5D. For demographic variables and psychometric assessment see Table 7.1. Table 7.2 shows the total scores of the PMD for each patient.

	Patients with FMS (N = 10)	HS (N = 10)	significance
Gender, female n (%)	9 (90)	9 (90)	Chi sq = 1.456, p = 0.867
Age, years (SD)	47.10 (17.00)	44.38 (14.57)	F = 0.765, p = 0.724
Educational level, Years (SD)	13.5 (3.68)	15.5 (2.67)	F = 6.223, p = 0.217
Marital status, n (%)			Chi sq = 5.453, p = 0.072
Single	2 (20)	1 (10)	
Married	8 (80)	9 (90)	
MMSE mean score (SD)	29.00 (1.41)	29.67 (0.57)	F = 14.654, p = 0.465
TAS-20 mean score (SD)	44.56 (9.68)	33 (4.24)	**F = 13.776, p = 0.044**
HAM-D mean score (SD)	9.11 (5.6)	1.33 (2.30)	**F = 4.765, p = 0.047**
HAM-A mean score (SD)	9.89 (2.67)	6.43 (2.51)	**F=5.875, 0.032**
EQ5D mean score (SD)	91.5 (6.5)	61.7 (8.3)	**F=35,641 0.041**

Table 7.1 Demographic variables and psychometric assessment. FMS = functional motor symptoms; HS = healthy subjects; SD = standard deviation; MMSE = Mini Mental State Examination; TAS-20 = 20-item Toronto Alexithymia Scale; HAM-D = Hamilton Rating Scale for Depression; HAM-D = Hamilton Rating Scale for Anxiety; EQ5D = EuroQol 5D.

Patient number	Total Phenomenology Score	Total Function Score	Total Psychogenic Movement Disorder (1+2)
1	3	3	6
2	3	3	6
3	2	1	3
4	3	3	6
5	4	4	8
6	4	3	7
7	4	2	6
8	3	2	5
9	2	1	3
10	3	3	6

Table 7.2 Total scores of the psychogenic movement disorders scale for each patient.

7.3.2 Spectroscopic results

7.3.2.1 Short TE spectra

A significant increase in Glx/Cr was found in the ACC/mPFC but not the OCC in patients with FMS (mean ± SD = 1.63 ± 1.11) compared to healthy controls (mean ± SD = 0.39 ± 0.30) (F = 6.386, p = 0.028). NAA/Cr, Cho/Cr, MI/Cr did not differ significantly between patients affected by FMS and healthy controls, both in the ACC/mPFC and in the OCC (See Table 7.3 and 7.4).

	Patients with FMS (N = 10)	HS (N = 10)	F	p
NAA/Cr (SD)	1.28 (0.21)	1.84 (1.02)	2.311	0.157
Cho/Cr (SD)	0.77 (0.19)	1.27 (0.83)	2.832	0.123
MI/Cr (SD)	0.25 (0.12)	0.40 (0.18)	2.452	0.152
Glx/Cr (SD)	1.63 (1.11)	0.39 (0.30)	6.386	**0.028**

Table 7.3 Relative values of neurochemicals for patients with FMS and healthy controls in the ACC/mPFC, obtained by short-TE spectra. SD = standard deviation; FMS = functional motor symptoms; HS = healthy subjects; NAA = N-Acetyl-aspartate; Cr = creatine; Cho = choline; MI = myo-inositol; Glx = glutamate+glutamine.

	Patients with FMS (N = 10)	HS (N = 10)	F	p
NAA/Cr (SD)	1.84 (0.15)	1.71 (0.35)	0.772	0.399
Cho/Cr (SD)	0.47 (0.07)	0.46 (0.07)	0.118	0.737
MI/Cr (SD)	0.40 (0.10)	0.29 (0.08)	4.115	0.067
Glx/Cr (SD)	1.20 (0.17)	1,39 (0.39)	1.253	0.287

Table 7.4 Relative values of neurochemicals for patients with FMS and healthy controls in the OCC, obtained by short-TE spectra. SD = standard deviation; FMS = functional motor symptoms; HS = healthy subjects; NAA = N-Acetyl-aspartate; Cr = creatine; Cho = choline; MI = myo-inositol; Glx = glutamate+glutamine.

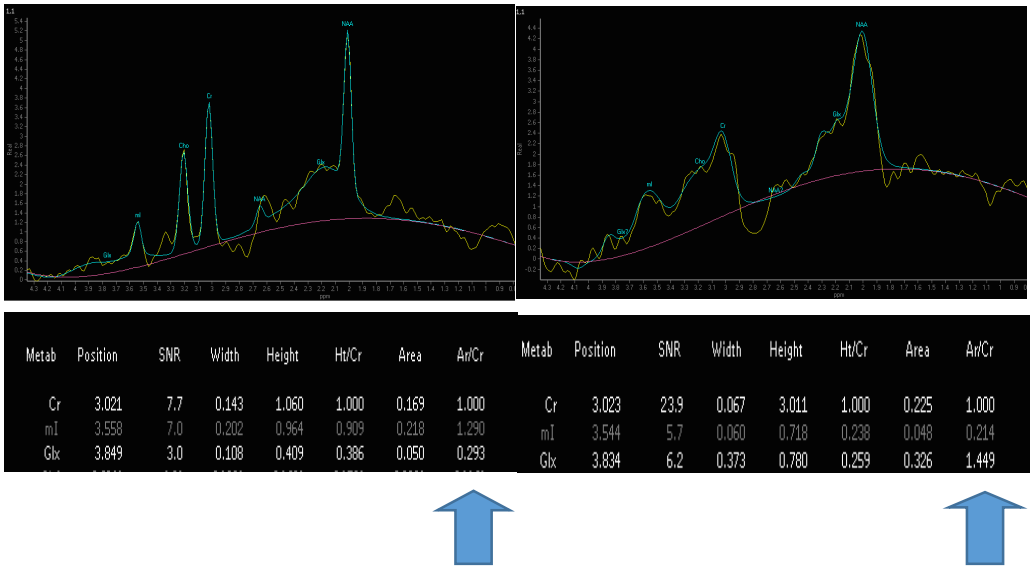


Figure 7.2 On the left side, short-TE spectrum acquired for the volume of interest ACC/mPFC of a patient with FMS. On the right side, short-TE spectrum acquired for the volume of interest ACC/mPFC of a healthy subject. Note that patient with FMS presents significantly higher Glx/Cr level than the healthy control.

7.3.2.2 Medium TE (144 msec) spectra

No significant differences between patients with FMS and healthy controls were found with respect to the level of any of the brain metabolites measured, obtained by medium-TE spectra.

	Patients with FMS (N = 10)	HS (N = 10)	F	p
NAA/Cr (SD)	1.50 (0.16)	1.52 (0.14)	0.121	0.734
Cho/Cr (SD)	1.15 (0.12)	1.09 (0.06)	1.081	0.312

Table 7.5 Relative values of neurochemicals for patients with FMS and healthy controls in the ACC/mPFC, obtained by medium-TE spectra. SD = standard deviation; FMS = functional motor symptoms; HS = healthy subjects; NAA= N-Acetyl-aspartate; Cr=creatine; Cho=choline.

7.3.2.3 Correlations

We found a significant positive correlation between the level of Glx/Cr in the ACC/mPFC obtained by short TE and (i) HAM-A score in the group as a whole (rho = 0.732, p = 0.003); (ii) TAS-20 score in the group as a whole (rho = 0.432, p = 0.023). We also found a positive correlation between the level of Glx/Cr in the ACC/mPFC obtained by short TE and the total score of the PMD scale). No other significant correlations were found between levels of brain metabolites and psychological scores.

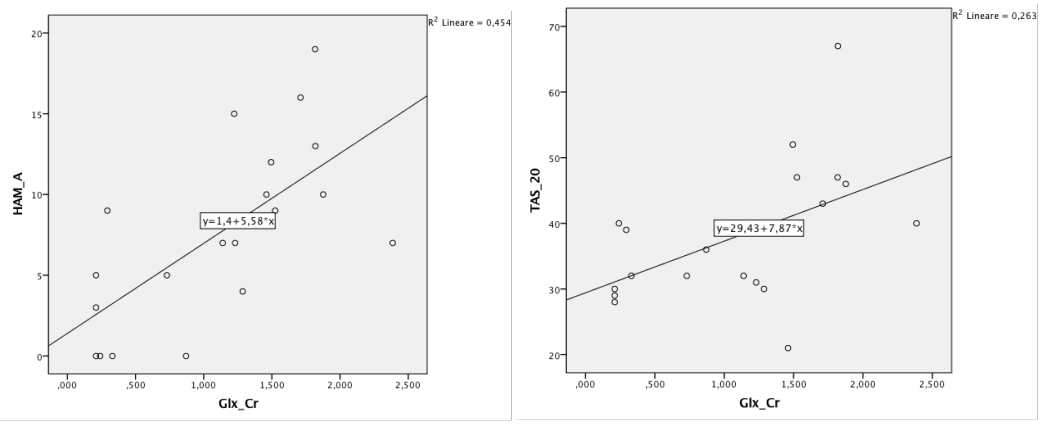


Figure 7.3 On the left side, positive correlation between Glx/Cr in the ACC/mPFC obtained by short TE and (i) HAM-A score in the group as a whole (rho = 0.732, p = 0.003). On the right side, positive correlation between Glx/Cr in the ACC/mPFC obtained by short TE and TAS-20 score in the group as a whole (rho = 0.432, p = 0.023).

7.4 Discussion

The main finding of this study is the increase level of Glx/Cr in the ACC/mPFC of patients affected by FMS. Glx/Cr increase correlated with TAS-20 and HAM-A score, suggesting that Glx levels in these brain regions in turn correlated with alexithymia and anxiety. Because spectral peaks did not differ between patients and healthy subjects in the OCC, the finding is topographically specific. This is the first MRS study on patients with FMS identifying a possible neurobiological marker

of this condition. Glutamate is the major excitatory neurotransmitter in the mammalian brain. Limbic and paralimbic regions receive a glutamatergic input from pyramidal cells (Cortese et al., 2005). In a recent study on a trait anxiety mouse model, the major excitatory neurotransmitter glutamate, which binds to the N-methyl-D-aspartate (NMDA) receptor, was found at higher levels in the plasma of a High Anxiety Behaviour mouse as compared with a Low Anxiety Behaviour mouse (Zhang et al., 2011). Several studies using MRS have shown that anxiety disorders are associated with alterations in the glutamatergic system also in humans. A study on social anxiety disorder (Phan et al., 2004) showed an increase in glutamate/Cr in the ACC of patients as compared with controls along with a correlation of glutamate/Cr with the intensity of social anxiety symptoms. The authors explained the findings on the basis of proposed models for glutamate's role in anxiety according to which an increased glutamatergic activity in the limbic system is associated with fear-related learning and reactivity (Walker & Davis, 2002). Further, the hyperresponsive limbic system in response to social threat/scrutiny and anxiety-provoking situations in patients with social anxiety, as well as its attenuation on successful treatment, suggests the functional significance of glutamate in anxiety disorders (Phan et al., 2004). Similarly, Grachev and Apkarian reported an increase in glutamate in the orbito-frontal cortex in healthy individuals with high state-trait anxiety (Grachev & Apkarian, 2000). Modi et al found increased levels of Glx/Cr in the ACC and hippocampus correlating with anxiety in healthy individuals, thereby suggesting that glutamate underlies anxiety even at sub-clinical level (Modi et al., 2014). Despite the well-studied association between anxiety and alexithymia and the role of the limbic system in the regulation of emotions, Ernst et al. was the first to investigate the relationship between alexithymic features, interoceptive awareness and glutamate and gamma-aminobutyric acid (GABA) concentrations in the left insula and the ACC in 18 healthy subjects, using 3T MRS. Behaviourally, they found a close association between alexithymia and interoceptive awareness; in addition they found glutamate levels in the left insula to be positively associated with both alexithymia and awareness of autonomic nervous system reactivity, while GABA

concentrations in ACC to be selectively associated with alexithymia (Earnst et al., 2014). Our results in patients with FMS are in line with the studies mentioned above. Given the proposed role for alexithymia and interoceptive awareness in FMS, we have already hypothesized patients with FMS to have difficulty in identifying their feeling and inner body states, including feelings of anxiety. Here we take our theory a step forward, confirming our hypothesis with respect to altered emotionality in patients with FMS (alexithymia) and providing a neurobiological counterpart to it, namely increased level of Glx/Cr.

Increased excitatory neurotransmitters lead to neuronal hyperexcitability. Glutamate is an excitatory amino acid, and excessive glutamate neurotransmission has been implicated in excitotoxic neuronal damage (Bleich et al., 2003). On the other hand, the mPCC is an area involved in memory and has been studied in mild cognitive impairment (Fayed et al., 2008). At this purpose, cognitive measures, e.g. the MMSE, have been found to correlate with posterior cingulate deactivation induced during an associative memory encoding task (Pihlajamaki & Sperling, 2009). This means that individuals with higher MMSE score showed greater task-induced deactivation in the posteromedial regions of the default network, and vice versa. Yet, recent studies reported a mild cognitive impairment (Reuber et al., 2008; Brown et al., 2014; Duncan & Oto, 2008) in patients with FMS.

Recently, the hypothesis that the brain has a default mode of functioning has received significant attention (Buckner et al., 2008). We hypothesize that high levels of Glx in certain areas of the brain (in this study we found elevated levels of Glx in the PCC, a key zone in the default network hypothesis) provoke cellular damage and disruptions in circuits involved in emotional and cognitive abnormalities, typically seen in patients affected by FMS.

Up to here, we have speculated about the role of potential upstream influences, such as limbic influences, in the pathogenesis of FMS. But how these influences might induce functional motor symptoms? Voon et al found patients with FMS to

have an abnormal activation of the amygdala, which is in line with our hypothesis of emotional dysregulation in patients with FMS (Voon et al., 2010). They also have demonstrated aberrant limbic-motor interactions in patients with motor conversion disorder that may underlie the influence of affect or arousal on motor function. Patients with motor conversion disorder had greater functional connectivity from the right amygdala to the right supplementary motor area. Although there are no direct neuroanatomical projections with the supplementary motor area, the amygdala projects to the nucleus accumbens and dorsal striatum, which have projections via the pallidum and thalamus to the supplementary motor area (Groenewegen et al., 1997). Alternatively, amygdala projections to the periacqueductal grey and midbrain cell bodies may also have downstream effects on supplementary motor area activity (Lang et al., 2010).

The crucial role of glutamate in FMS might also have some important implications not only from an aetiopathogical angle, but also from a therapeutic perspective. Numerous drugs have an effect on the glutamatergic system, both promoting the release and the inhibition of glutamate, acting on different kind of channels. Within these drugs, ketamine is surely of interest. Ketamine is a well-established anaesthetic drug that has been in use for around 50 years (Domino et al., 1965). It has been known since the mid 1980s that ketamine provokes use-dependent blockade of the N-methyl-D-aspartate (NMDA) receptor (Mc Donald et al., 2006); and that this blockade of excitatory synaptic activity probably causes the loss of responsiveness that is associated with clinical ketamine anaesthesia. However, in the last few years, subsequent work has demonstrated that ketamine exhibits a wide range of different molecular effects, and its clinical usefulness has expanded to include a role in the management of a wide range of conditions including chronic pain (Hirota et al., 2006) and depression (Duman et al., 2012). Recently Stan et al studied the effects of in vivo local application of the ketamine and of the N2B subunit-specific antagonist Ro25-6981 upon evoked glutamate release. Both ligands inhibit glutamate release in subregions of the hippocampus and prefrontal cortex. Likewise, acute systemic ketamine treatment caused a reduction in evoked

glutamate release in the subiculum (Stan et al., 2014). Thus, we might hypothesize a therapeutic effect of ketamine in patients affected FMS; further studies are needed to test this hypothesis.

7.4.1 Methodological considerations and limitations

From a technical point of view, the increased level of Glx/Cr was detected only when the short TE spectrum was acquired; this is in line with the well-known higher sensitivity of short spectra in the detection of brain metabolites. Glx rather than glutamate was measured. However, the pool of glutamate and glutamine is largely integrated over a timescale of minutes (Hertz et al., 2004).

One of the limitations of this exploratory research is the small sample size (N = 10) of each group of patients. However, this study has only proposed a new hypothesis; but larger replication studies are needed. Another limitation is the absence of measures of absolute concentrations of the neurochemicals.

Chapter 8:

Conclusions and future directions

In summary, this study provided high-impact data on the role of emotional and cognitive abnormalities in the aetiopathology of FMS. In particular, we found patients with FMS to be more alexithyimic and to have reduced interoceptive awareness when compared to healthy controls. Additionally, we found that the level of interoceptive awareness in patients affected by FMS might be modulated by a single anodic tDCS session over the right posterior parietal cortex. With respect to cognitive factors, patients with FMS showed an impairment in deception with respect to healthy controls, suggesting a mild multifacet cognitive impairment.

In addition, this is the first work showing alterations in ACC/mPFC neurochemistry in patients affected by functional motor symptoms, with significantly higher levels of Glx with respect to healthy subjects. This study thus contributes to the limited literature available on altered metabolism and neural mechanisms underlying FMS, providing a first indication of a possible biological marker.

Further studies on bigger samples are needed to confirm our data, in order to have an even better understanding of the aetiopathology of FMS and to open a new panorama also from a therapeutic point of view.

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Acknowledgements

The work presented here has been conducted in collaboration with the Sobell department of Motor Neuroscience and Movement Disorders, University College London, where I spent a part of my PhD program under the supervision of Dr Lucia Ricciardi. She was involved in the initial concept and supervision of the project. I am very much obliged to her for mentoring and supporting me not only during the time actually spent in London. Obviously, I am really grateful to Prof Orsola Gambini for tutoring me and for her non-stop teachings. I am also grateful to Dr Diana Goeta, Dr Laura Crucianelli, Dr Carla Uggetti, Dr Marcello Cadioli and Dr Roberto Volpe, who helped me in the laboratory sessions, analysis and interpretation of data, and to Prof Silvio Scarone, Prof Mark Edwards and Prof Alberto Priori for their invaluable inputs. Finally, I am very grateful to all subjects, who took part in this project with long sessions in the lab.