INVESTIGATING PAIN PERCEPTION IN SOMATOSENSORY CORTEX FOR HEALTHY AND FIBROMYALGIA PATIENT POPULATIONS BY USING fNIRS

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INVESTIGATING PAIN PERCEPTION IN SOMATOSENSORY CORTEX FOR HEALTHY AND FIBROMYALGIA PATIENT POPULATIONS BY USING fNIRS

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I hereby declare that all information in this document has been obtained and presented in accordance with academic rules and ethical conduct. I also declare that, as required by these rules and conduct, I have fully cited and referenced all material and results that are not original to this work.

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ABSTRACT

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In this study, we investigated the difference in hemodynamic responses between fibromyalgia (FM) and healthy controls via functional near infrared spectroscopy (fNIRS) during application of painful stimulus and transcutaneous electrical nerve stimulation (TENS). We collected several clinical data (pain threshold, Beck Depression Inventory (BDI) score, Fibromyalgia Impact Questionnaire (FIQ) score, pain ratings) before and during the experiment. After data collection, we analyzed it using general linear model (GLM) and we applied classification methods to determine which cortical structures are important in discriminating healthy and patient groups. Our study showed that TENS effect was observed in both hands of healthy controls, but only left hand of FM patients. However, there is an opposite effect observed when the right hand of FM patients is stimulated. These findings indicate that the pain perception mechanism in FM syndrome needs further investigation since the outcome of the TENS treatment differs with respect to hands. When classification is done using SVM using features from the painful stimulation experiment, an accuracy of %90 is observed in distinguishing patients from healthy controls.

Keywords : Fibromyalgia, fNIRS, Classification, Pain, TENS

ÖZ

AĞRI ALGISININ SOMATOSENSÖRİYEL KORTEKSTE fNIRS KULLANILARAK SAĞLIKLI VE FİBROMİYALJİ HASTA POPÜLASYONLARINDA İNCELENMESİ

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Bu çalışmada, işlevsel yakın kızıl altı spekstroskopisi (fNIRS) aracılığı ile ağrılı uyaran ve deri üstü elektriksel sinir uyarımı (TENS) uygulayarak fibromiyalji (FM) hastaları ve sağlıklı kontroller arasındaki hemodinamik tepki farkı inceledik. Deney öncesi ve deney boyunca bir çok klinik veri elde ettik (ağrı eşiği, Beck Depresyon Envanteri (BDI) skoru, Fibromiyalji Etki Anketi (FIQ) skoru, ağrı notlandırması). Veri toplanmasından sonra, genel doğrusal model (GLM) uygulayarak analizini yaptık ve hasta ve kontrol gruplarının ayırımında hangi kortikal yapıların önemli olduğuna karar vermek için sınıflandırma metodları uyguladık. Çalışmamız TENS etkisinin sağlıklı kontrollerde her iki elde de gözlemlendiğini ancak fibromiyalji hastalarında sadece sol elde gözlemlendiğini göstermiştir. Ancak, FM hastalarının sağ eli uyarıldığında, ters bir etki gözlemlendiğini göstermiştir. Bu bulgular, TENS tedavisinin çıktıları ellere göre farklılık gösterdiğinden, fibromiyalji sendromundaki ağrı algı mekanizmasının daha ileri araştırmalara ihtiyacı olduğunu göstermektedir. SVM ile ağrı uyaran deneyinden gelen özniteliklerle sınıflandırma yapıldığında, %90 gibi bir doğruluk hastaların sağıklı kontrollerden ayrılmasında gözlemlenmektedir.

Anahtar Kelimeler: Fibromiyalji, fNIRS, Sınıflandırma, Ağrı, TENS

To my dear father Hasan Eken … Rest In Peace

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This thesis is more than a research assignment for me. In fact, it is a brief story of 7 years spent during my PhD studies. Naturally, there are several people that I would like to thank.

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LIST OF ABBREVIATIONS

ACC	Anterior Cingulate Cortex
ACR	American College of Rheumatology
ACTH	Adrenocorticotrophic hormone
ALE	Activation Likelihood Estimation
ANOVA	Analysis of Variance
AVP	Argininevasopressin
BA	Broadmann Area
BDI	Beck Depression Inventory
BOLD	Blood-Oxygen-Level Dependent
CBF	Cerebral Blood Flow
CBV	Cerebral Blood Volume
CC	Cingulate Cortex
CES-D	Center for Epidemiologic Studies Depression Scale
CLBP	Chronic Low Back Pain
CNS	Central Nervous System
CRH	Corticotrophin-releasing hormone
CSQ	Coping Strategies Questionnaire
CTS	Carpal Tunnel Syndrome
CW	Continuous Wave
DLPFC	Dorsolateral Pre Frontal Cortex
DMN	Default Mode Network
DPF	Differential Path Factor
DTI	Diffusion Tensor Imaging
DTW	Dynamic Time Warping
EAN	Executive Attention Network
EEG	Electroencephalography
EHI	Edinburgh Handedness Inventory
eVF	Electronic Von Frey
FFbH	Hannover Functional Disability Questionnaire
FIQ	Fibromyalgia Impact Questionnaire
FIR	Finite Impulse Response
FM	Fibromyalgia
fMRI	Functional Magnetic Resonance Imaging
fNIRS	Functional Near Infrared Spectroscopy
GABA	Gamma Amino Butyric Acid
GLM	General Linear Model
HADS	Hospital Anxiety and Depression Scale
HB	Deoxy- hemoglobin
HBO2	Oxy- hemoglobin
HC	Healthy Controls
HDR	Hemodynamic Response
HRF	Hemodynamic Response Function
IASP	International Association for the Study of Pain
IC	Insular Cortex
ICA	Independent Component Analysis
IFG	Inferior Frontal Gyrus
IPL	Inferior Parietal Lobe
k-nn	K- Nearest Neighborhood

KRS	Kohn Reactivity Scale
LEP	Laser Evoked Potentials
LONI	Laboratory of Neuroimaging
LPP	Late Positive Potential
MDD	Major Depressive Disorder
MDL	Minimum Description Length
MFC	Middle Frontal Cortex
MFG	Middle Frontal Gyrus
MI	Primary Motor Cortex
MNI	Montreal Neurological Institute
MPQ	MC-Gill Pain Questionnaire
MRI	Magnetic Resonance Imaging
MVN	Medial Visual Network
MVPA	Multi Voxel Pattern Analysis
OD	Optical Density
OFC	Orbito Frontal Cortex
PAG	Periaqueductal Gray
PCA	Principal Component Analysis
PCG	Posterior Cingulate Gyrus
PCS	Pain Catastrophizing Scale
PDI	Pain Disability Index
PET	Positron Emission Tomography
PFC	Pre Frontal Cortex
PPC	Posterior Parietal Cortex
QST	Quantitative Sensory Testing
SF	Short Form
SFG	Superior Frontal Gyrus
SG	Substantia Gelatinosa
SI	Primary Somatosensory Cortex
SII	Secondary Somatosensory Cortex
SIS	Subacromial Impingement Syndrome
SMA	Supplementary Motor Area
SN	Saliency Network
SPL	Superior Parietal Lobe
SS	Severity of Symptoms
STAI	State Trait Anxiety Inventory
STG	Superior Temporal Gyrus
STPI	State-Trait Personality Inventory
STS	Superior Temporal Sulcus
SVM	Support Vector Machine
TENS	Transcutaneous Electrical Nerve Stimulation
TP	Tender Points
TPJ	Temporo-Parietal Junction
TSSP	Temporal Summation of Second Pain
VAS	Visual Analogue Scale
VIP	Vasoactive Intestinal Peptide
VMPFC	Ventro Medial Pre Frontal Cortex
WPI	Wide Pain Index

CHAPTER 1

INTRODUCTION

If little labor, little are our gains:
Man's fate is according to his pain.

Robert Herrick (Hesperides 752.)

Pain perception is a complicated function and its mechanism includes affective, sensory and cognitive processing networks in brain. According to the International Association for the Study of Pain (IASP), pain is "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" and chronic pain has been classified for 5 different classes (Merskey & Bogduk, 1994). This classification was done according to ;1. the region of the body, 2. the system whose dysfunction may be causing the pain, 3. The duration and pattern of occurrence, 4. The intensity and time since onset and 5. etiology. However, in 1998 Woolf and his colleagues rejected this approach and suggested that pain can be identified in 3 different classes; 1. nociceptive pain, 2. inflammatory pain, 3. pathological pain (Woolf et al., 1998).

Pain is generally considered as a vital function of body due to its warning feature of several problems. Physiological sense of pain perception is called "Nociception", which is a subjective experience. This subjective experience depends on individual's personal psychological mood, having cognitive disorder or not, pain belief or expectations (Tracey & Mantyh, 2007). In 1965 Melzcak and Wall proposed a new theory about pain mechanism and perception in the nervous system based on a gate control model (Melzack & Wall, 1965). In this approach, spinal cord includes a neurological gate that prevents painful stimuli from reaching the brain. Nociceptive stimuli carried by small nerve fibers are enabled to pass through while stimuli sent by large fibers are prevented. Therefore, while nociceptive stimuli are being carried by small nerve fibers, inhibitory neurons do not block the gate and the nociceptive stimuli reaches over the brain. However, while non-nociceptive stimuli are being carried by large nerve fibers, inhibitory neurons prevent them to reach the brain by blocking the gate.

Nevertheless, since this theory was proposed, there has been no common agreement about the mechanism of pain perception. Researchers could not describe the specific cerebral regions that were involved in pain perception. After proposing gate control theory, Melzcak proposed a new approach about mechanism of pain perception in the brain called "Neuromatrix" (Melzack, 1989). In this approach, it is asserted that several brain parts including supplementary motor area (SMA), primary somatosensory cortex (SI), secondary somatosensory cortex (SII), anterior cingulate cortex (ACC), amygdala, prefrontal cortex (PFC), thalamus, insula and posterior

parietal cortex (PPC) are related with processing and perception of pain. Neuromatrix was considered as not pain specific, because it includes several brain regions that are also related with several cognitive processes. According to the Melzcak, Neuromatrix was dispersed over the brain and also includes a distributed neuronal network that creates patterns and handles information that streams through it (Melzack, 2001). Figure 1. shows the mechanism that was proposed by Melzcak in details. After 90's, the term "Neuromatrix" has given its place to the term "Pain-Matrix" (J. Brooks & Tracey, 2005; Ingvar, 1999; A. Jones, 1998; Ploghaus et al., 1999; Talbot et al., 1991). This term emphasizes the regions over the brain that are activated during pain perception and processing when nociceptive stimuli are used (J. Brooks & Tracey, 2005). However, the Pain Matrix is still under elaboration by investigators regarding to its participation in cognitive, affective and emotional processing networks (Iannetti & Mouraux, 2010). The Pain Matrix has been investigated in several studies focusing on two main research areas. First, the regions with significant activity after applying nociceptive stimuli are studied (Garcia-Larrea et al., 2003). Second, associations and statistical relationships between applied stimuli and Hemodynamic Response (HDR) magnitudes are investigated (Coghill et al., 1999; Derbyshire et al., 1997). These relationships have proven that Pain Matrix functions to perceive nociception intensity (Porro et al., 2003; Rainville, 2002).

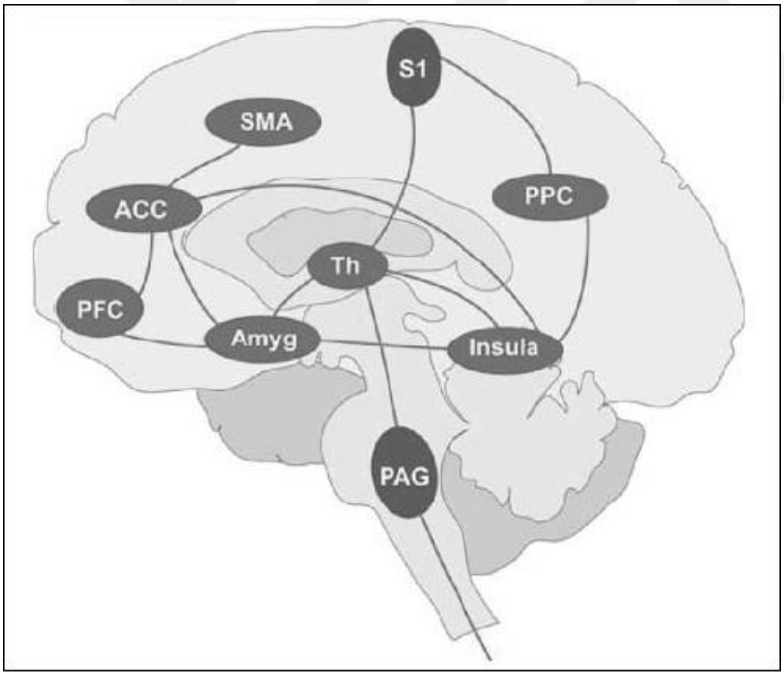


Figure 1.Pain Matrix (May, 2006)

On the other hand, regions that comprise the Pain Matrix are extremely important for patients that have chronic pain diseases. Because these patients are extremely sensible to even small amounts of nociceptive input, the pain mechanism is easily activated (Moseley, 2003). In this thesis, we focused on pain perception of Fibromyalgia (FM) patients with has 2-8 % prevalence of the population (Clauw, 2014) as well as healthy controls. FM is a widely known disease that can be

identified by chronic and widespread pain, tenderness and several cognitive dysfunctions. There are several systemic conditions that have same symptoms with FM (Hochberg et al., 2003). Patients with FM can usually have irritable bowel syndrome, functional gastro intestinal disorders, chronic fatigue, somatoform disorders and other regional pain diseases (Clauw, 2014). Also, there are several types of FM treatment that can be divided into two groups as pharmacologic and non-pharmacologic ones (Forte et al., 2015). Transcutaneous Electrical Nerve Stimulation (TENS) is one of the most popular non-pharmacologic treatment methods that has several examples in literature (Carbonario et al., 2013; Lauretti et al., 2013; Lofgren & Norrbrink, 2009; Mutlu et al., 2013).

In this thesis, our primary motivation was to understand the hemodynamic effects of TENS treatment in FM patients. For this purpose, we used Functional Near Infrared Spectroscopy (fNIRS) and recruited matched healthy controls. Furthermore, we studied the hand dominance factor in pain perception, by applying painful stimuli to the left and right hands of strongly right handed subjects.

This thesis contains 6 chapters other than this introduction part. In Chapter 2, there is a general overview including physiological, methodological and technical background to clarify several aspects of this multidisciplinary study. Also, a detailed literature review including neuroimaging studies of FM, pain perception, TENS and handedness in pain perception is available along with some psychophysical studies including pain relief of TENS. In Chapter 3, neuroimaging and psychophysical methods and their analyses will be explained in detail. In Chapter 4, neuroimaging and psychophysical analysis results will be presented. In Chapter 5, results will be discussed and compared with literature. In Chapter 6, conclusions of our research will be interpreted.

CHAPTER 2

BACKGROUND AND LITERATURE REVIEW

2.1.Somatosensory System

Somatosensory system is a complicated mechanism that carries out sensation from the skin, muscles, tendons, bones and joints to the central nervous system. It has two important subsystems. One of them is for detection of mechanical stimuli such as pressure, light touch, cutaneous tension and vibration. The other mechanism is related with painful stimuli and temperature. This system includes thermo-receptors, nociceptive receptors and mechanoreceptors. These receptors can be grouped as free and encapsulated types. Among those receptors, nociceptive receptors and thermo-receptors can be called as “free nerve endings”.

After delivery of a peripheral stimulation is given, the afferent nerves from receptors initiate synaptic activity on neurons with specific ascending pathway formation based on the type stimulation. These pathways go directly to the somatosensory cortex via spinal cord, brainstem and thalamus. According to the type of stimulus two different pathways are available. Mechano-sensory afferent fiber and nociceptive afferent fiber that carries pain and temperature sensation information cross either in spinal cord or brain stem. These afferent fibers are connected to the skin receptors. There are 4 types of mechano-receptors that are specialized according to the information they carry. Except for these mechano-receptors there are several free nerve endings which will be discussed later in this chapter. The receptors shown in Figure 2. are;

- Meissner’s Corpuscles: They are located between the dermal papillae. They carry light touch information via low frequency vibrations (30-50 Hz).

- Pacinian Corpuscles: They are the large endings located in the subcutaneous tissue. They are different than Meissner’s corpuscles based on response threshold, distribution and morphology. They carry deep pressure information. They have an onion shaped capsule that works as a high pass filter. They just pass through the high frequency vibrations (250-350 Hz) to innervate the nerve endings. They act faster and its response threshold is lower than Meissner’s corpuscles

- Merkel’s Disks: They are in epidermis. %25 of the mechano-receptors are Merkel’s Disks and found in hand, external genitalia, fingertips and lips densely. They carry touch information and also distinguishes shapes, edges and rough surfaces of objects.

- Ruffini’s Corpuscles: They are generally similar with other mechano-

receptors. They are sensitive to skin stretch and helps to control finger position and movement. %20 of the mechano-receptors are Ruffini's Corpuscles.

All these mechano-receptors are stimulated by Aβ axons. These axons are large and myelinated axons. Due to myelination, they transmit tactile information rapidly.

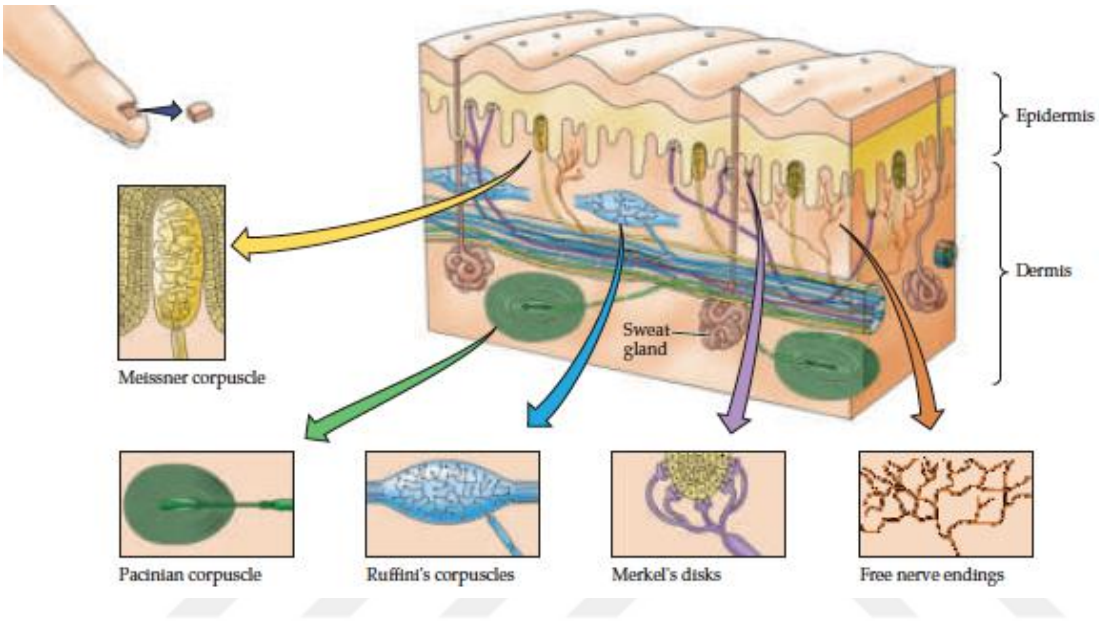


Figure 2. Details of Receptors onto a finger.
(taken from (Purves, 2004))

After nociceptive afferent fibers and mechanosensory afferent fibers are separated, mechanosensory afferent fibers pass through cuneate nucleus and medial leminiscus in medulla. Then they pass through midbrain together and reach to cerebrum. In cerebrum, sensory information directly reaches to thalamus, which is a quite important hub of brain network. Finally, the information goes to the somatosensory cortex of post central gyrus of cerebrum. A general view to somatosensory system can be seen in Figure 3.

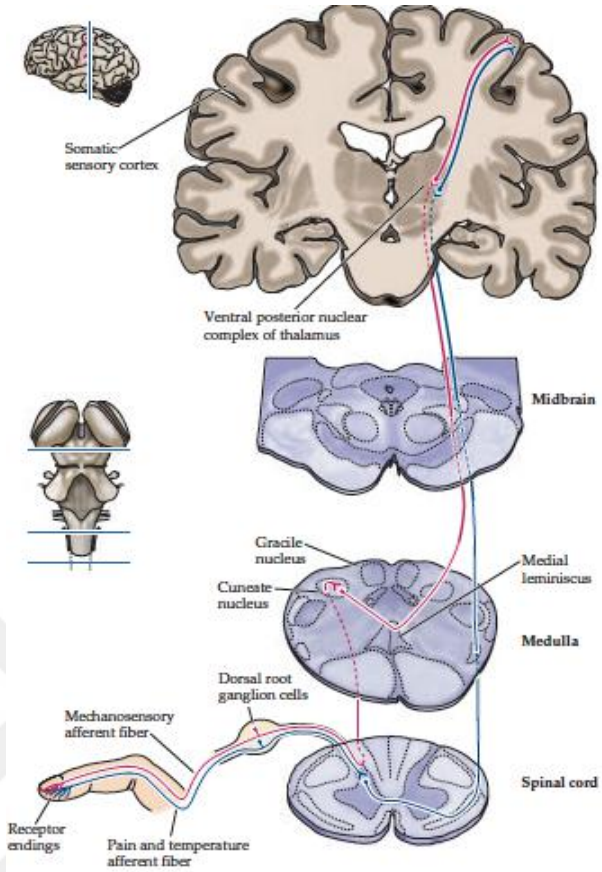


Figure 3. Somatosensory System.
(taken from (Purves, 2004))

2.2.Nerve Fibers (Axons)

There are 3 types of nerve fibers that innervate the mechano-receptors, nociceptors and thermoreceptors. These are;

- Aβ Sensory Fiber: They provide fast signal transmission due to having high myelination. They respond a very low threshold stimulus. They transmit the tactile stimuli like light touch. Their diameters are large, approximately 6-12 µm.
- Aδ Sensory Fiber: They provide slower signal transmission because of having a thin myelination. They show response against thermal and mechanical stimuli. Also carry fast and sharp pain.
- C Sensory Fiber: They are unmyelinated and have small diameter (approximately 0.5 – 2 µm). Their conduction is slower than the others. However, stimulus threshold of receptor activation is high. They respond thermal, chemical and mechanical stimuli.

Details for these fibers are shown in Table 1.

Table 1. Features of Nerve Fibers

Receptor Type	Connected Axons and Diameters	Conduction Speed of Axons	Location	Function	Adaptation	Activity Threshold
Free Nerve Endings	C (0.2 -1.5μm) , Aδ(1-5μm)	Aδ 3-30 m/s C, 0.5-2.0 m/s	All Skin	Pain, temperature	Slow	High
Meissner's Corpuscles	Aβ (6-12 μm)	80-120 m/s	Glabrous skin	Touch, pressure	Fast	Low
Pacinian Corpuscles	Aβ (6-12 μm)	80-120 m/s	Subcutaneous tissue	Deep pressure, vibration (dynamic)	Fast	Low
Merkel's Disks	Aβ(6-12 μm)	80-120 m/s	All Skin	Touch, pressure (static)	Slow	Low
Ruffini's Corpuscles	Aβ(6-12 μm)	80-120 m/s	All Skin	Skin strech	Slow	Low

In somatosensory cortex, somatic pathways are represented according to parts of the body. This visual representation of anatomical divisions in the somatosensory cortex is called Somatosensory Homunculus. Among these divisions, fingers and thumb which are the focus of our study have the greatest representation. Detailed structure of the Somatosensory Homunculus is shown in Figure 4.

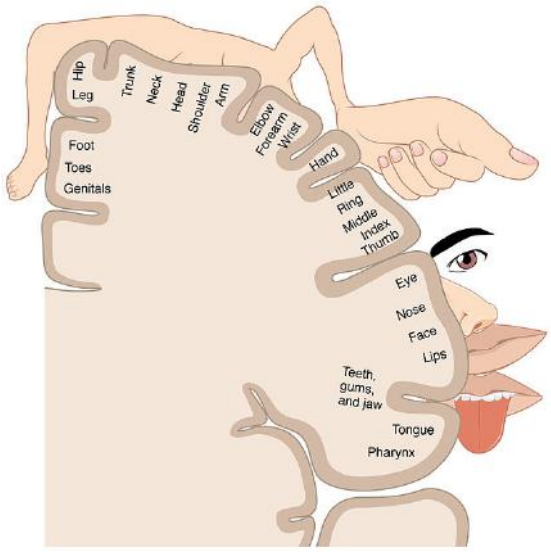


Figure 4. Somatosensory Homunculus

2.3.Pain Somatosensation

Stimulus that leads to tissue deformation generally triggers pain sensation. Pain sensation is generally acknowledged as the over-stimulation of same receptors in a specific part of body. Pain perception is also called “nociception”. In Latin “nocere” means “to hurt. Nociceptors exit from cell bodies in dorsal ganglia and convert various types of stimuli to receptor potentials. They transmit one nerve fiber activity to the periphery and the other to the brain stem and spinal cord. Nociceptive nerve fibers end up in “Free Nerve Endings”. Due to this, nociceptors can be grouped according to the specific features of axons related with them. Axons that carry the nociceptive stimulus information are conducted by either Aδ or C fibers. Aδ nociceptors are associated with conduction of mechanical or thermal stimuli. C nociceptors are associated with conduction of chemical stimuli in addition to mechanical and thermal stimuli. According to the properties of both of these axons shown in Table 1, although this process is slower than tactile stimulus conduction.

There are two nociception pathways. These are fast pain and slow pain pathways. Stimulation of these nociceptors causes pain perception in two categories. First pain and Second pain. First pain is the result of fast conduction of Aδ fiber. There is a slight latency between first pain and second pain. Also, second pain sensation is more spread over and lasts longer than first pain. Stimulus that triggers Aδ fibers causes a light prickling sensation. If the stimulus intensity is high enough, sharp pain is sensed. Besides, if this intensity shows an increasing trend, C fibers engage into this process and cause a pain sensation that lasts long. First and second pain illustrations are shown in Figure 5.

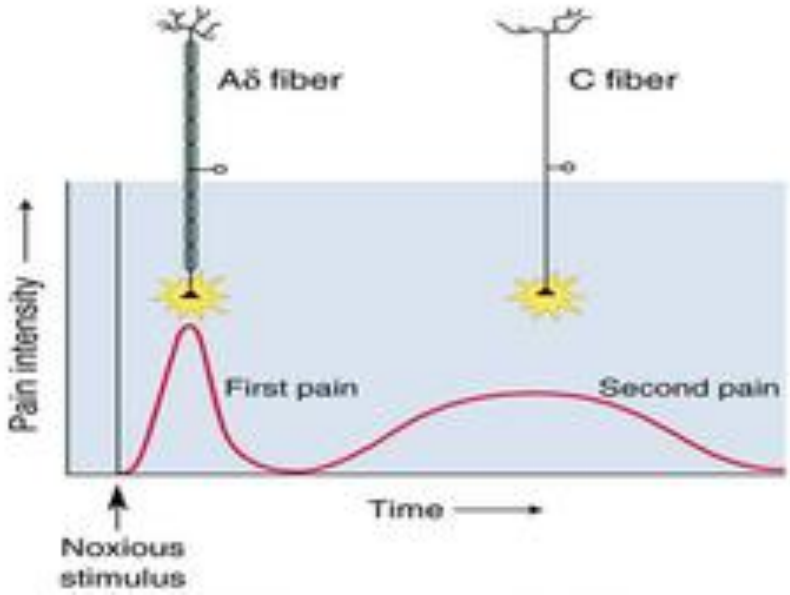


Figure 5. First pain and second pain.
(taken from quizlet.com).

2.4.Neuroimaging Studies of Pain Perception in Healthy Subjects

Pain perception and processing in the brain have been investigated for several years by using different kinds of neuroimaging modalities such as Functional Magnetic Resonance Imaging (fMRI) (Apkarian et al., 2005). Primary hemodynamic signatures of pain were analyzed in human brain as early as 1970s (Lassen et al., 1978). First fMRI study in literature was performed by using electric shock (Davis et al., 1995). Then neuroimaging of pain studies was generally carried out in terms of noxious and non-noxious stimuli comparison (Apkarian et al., 1999; L. R. Becerra et al., 1999; J. I. Chen et al., 2002; Lui et al., 2008). The main aim in these studies was the characterization of BOLD signal during noxious stimulus was application. When a noxious stimulus was applied to the participant, a double peak biphasic BOLD signal was observed in the hemodynamic response (Apkarian et al., 1999; L. Becerra et al., 2001; L. R. Becerra et al., 1999; J. I. Chen et al., 2002; Downar et al., 2003; Moulton et al., 2005; Ploner et al., 2002; Upadhyay et al., 2010). A popular explanation about initial peak of biphasic BOLD time course is, it might be related with threat detection mechanism of brain and the second peak might be represented as a response of pain processing (L. Becerra et al., 2001; J. I. Chen et al., 2002). In some studies, understanding the foundations of the biphasic double peak BOLD activity is the main goal. By analyzing the hemodynamic signal using two explanatory variables and between these two peaks the temporal difference was found to be 12.5 sec (Upadhyay et al., 2010).

There are several regions related with pain perception and processing which are mentioned in the “Pain Matrix”, such that SI, SII, ACC, anterior and posterior insular cortex (Bornhovd et al., 2002; Buchel et al., 2002; Bushnell et al., 1999; Coghill et al., 1999; Derbyshire et al., 1997; Johnstone et al., 2012; Moulton et al., 2005; Porro et al., 2003; Ringler et al., 2003). Also pre-frontal cortex is found to be closely related with pain processing (L. Becerra et al., 2008; L. R. Becerra et al., 1999; Derbyshire et al., 1997).

Some studies also demonstrated that the magnitude of HRF can be related with amount of pain perception for regions that are included in “Pain Matrix” (Bornhovd et al., 2002; Buchel et al., 2002; Coghill et al., 1999; Derbyshire et al., 1997; Porro et al., 1998). In light of this information, main function of Pain Matrix is intensity coding of perceived pain (Porro et al., 2003; Rainville, 2002).

Neuroimaging literature of experimental nociception shows that among 36 fMRI studies, some regions are consistently active (Apkarian et al., 2005);

- ACC (22 / 27 - % 81)
- SI (19 / 25 - % 76)
- SII (21 / 26 - % 81)
- Insula (23 / 23 - %100)
- Thalamus (13 / 16 - %81)
- PFC (14 / 20 - % 70)

According to fMRI studies in literature, four prominent regions of nociception are: SI, SII, ACC and insula. Results suggest that SI and SII are related with perception of sensory features of pain (Bushnell et al., 1999; J. I. Chen et al., 2002; Coghill et al., 1999). ACC and insula are generally involved in affective network of pain processing (Apkarian et al., 2005). Prefrontal and parietal cortices are generally related to memory, evaluation or stimulus perception (Coghill et al., 1999). Amygdala and nucleus accumbens (L. Becerra et al., 2001) were activated by painful stimulus through spinoparabrachial- amygdala connections Also, periaqueductal grey (PAG) plays an important role (Bushnell et al., 2013). In Figure 6. afferent pain pathways that includes these regions are shown. Afferent painful stimulus goes into brain via spinal cord and it follows three pathways. These are spinothalamic (spinal cord – thalamus), spinoparabrachio-amygdaloid (spinal cord – parabrachial nucleus – amygdala) and spinoreticulo-thalamic (spinal cord – reticular formation – thalamus) pathways. Painful stimulus that comes from thalamus is directly transmitted to insula, SII, SI and ACC. Also from spinoparabrachio-amygdaloid tract, painful stimulus directly comes to amygdala and it is transmitted to basal ganglia.

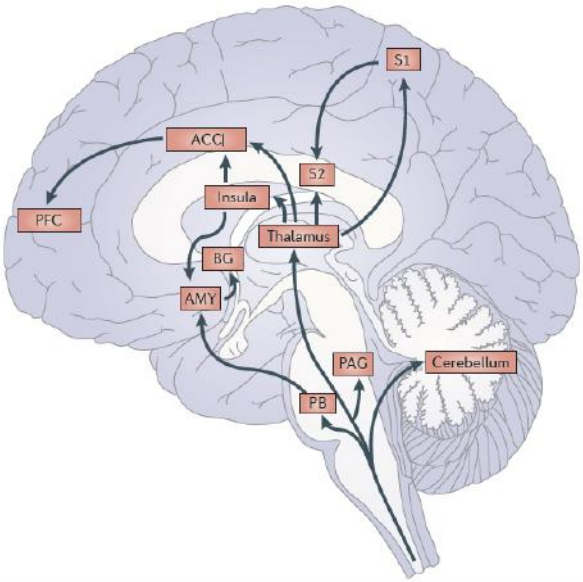


Figure 6. Afferent Pain Pathways (Bushnell et al., 2013).

Among neuroimaging modalities, Functional Near Infrared Spectroscopy (fNIRS) has recently become popular in order to analyze the pain perception in the brain. This is because of two main reasons. First, fNIRS has less limitations than fMRI: less stressful environment, less possibility of daydreaming. The other reason is primary somatosensory cortex is a close structure to the scalp and its activity can be observed by fNIRS efficiently (L. Becerra et al., 2009; L. Becerra et al., 2008; Franceschini et al., 2003; Koch et al., 2010). Using fNIRS, mechanisms that were considered in "Pain-Matrix" were analyzed but due to the physical restrictions, only somatosensory cortex and pre-frontal cortex were investigated (L. Becerra et al., 2008). Studies that focus on noxious and non-noxious stimuli comparison show that there are significant contralateral and ipsilateral S1 activation and contralateral activation has greater amplitude than ipsilateral activation (L. Becerra et al., 2009; L. Becerra et al., 2008;

Franceschini et al., 2003). A recent study also focuses on observing this comparison by using fNIRS on 11 healthy participants and the responses for both stimuli were easily discriminated (Yucel et al., 2015).

2.5.Diagnostic Measures in Fibromyalgia Syndrome

Fibromyalgia (FM) is a complicated widespread pain syndrome that appears during physical examination on several tender points of body. Prevalence of FM is generally %2-8 in population (Clauw, 2014). In Turkey, its prevalence is reported as 3.6 % (Topbas et al., 2005).

Smythe and Moldofsky have identified FM syndrome in 1970s (Smythe & Moldofsky, 1977). Initially, it was defined as inflammation of tissue and called "fibrositis". However, after there was clear evidence that this was not a tissue inflammation, its name changed as "fibromyalgia". After this relabeling, tender points of body were identified and accepted as a one of the primary diagnosis criteria by American College of Rheumatology (ACR) in 1990 (Wolfe et al., 1990). According to these criteria, patients feel intense pain sensation at least 11 of 18 tender points and complaints for more than 3 months. Tender points to be used for diagnosing FM are; Back of neck, Front of neck, Elbows, Hips, Lower back, Knees, Upper back, Shoulders, Chest.

In 2010, ACR updated the diagnosis criteria of Fibromyalgia (Wolfe et al., 2010). According to these criteria, symptoms should still be present for at least 3 months Patient should not have any other disorder that is possible to trigger pain syndrome. Pain in FM is quantized by two measures called Widespread Pain Index (WPI) and Symptom Severity (SS) scale. Patient WPI score should be $\geq$ 7 and SS scale score should be $\geq$ 5 for diagnosis. An alternative option is; WPI score should be between 3 and 6 and SS scale score should be $\geq$ 9. Before 2010 ACR criteria, all FM patients were women due to women having more tender points than men. Therefore, women are diagnosed as FM more than men -with a ratio of 9:1 (Firestein & Kelley, 2013). After 2010 ACR criteria, ratio of women to men became 2:1 (Clauw, 2014).

2.6.Background of Fibromyalgia

Despite the underlying reasons that cause FM being unknown, widespread pain that is because of the dysregulations in CNS is the core symptom of this syndrome. These dysregulations are more effective to increase pain sensation than peripheral nociception. This is called "Centralization Phenomenon". In this phenomenon, when a peripheral stimulus is applied to patient, pain sensation is observed more than expected. This centralization can be triggered by several factors like stress, excessive cognitive fatigue, insufficient sleep and mood changes (Phillips & Clauw, 2013). Patients that have FM generally suffer from chronic pain spread over their body. They have also another complaints such as headache, dysmenorrhea, chronic fatigue, irritable bowel syndrome, insomnia and other pain syndromes (Hudson & Pope, 1994). While determining FM, these symptoms should be considered.

Moreover, relatives of FM patients have also chronic pain history. First – degree relatives of FM patients have generally either FM or chronic pain syndrome (Arnold et al., 2004). Genetic factors are assumed to trigger FM and chronic pain syndrome (Holliday & McBeth, 2011). Genes related with pain syndromes arrange the binding of efficient neurotransmitters in pain sensation. Pain sensitivity is regulated by several genes (Clauw, 2014). Altered activity of these neurotransmitters causes significant change in pain sensitivity.

On the other hand, environmental factors with genetic factors are also effective in developing a pain syndrome. Factors that create stress on patients can generally trigger FM or chronic pain syndrome. Furthermore, several infections (like Epstein-Barr virus, Lyme disease, Q-fever) can cause chronic fatigue, which is a classical condition in both FM and chronic pain syndrome (Buskila et al., 2008).

As well as these factors, FM can also appear jointly with another chronic pain syndrome in 10-30 % of FM patients (Phillips & Clauw, 2013).

2.7.Fibromyalgia and Depression

FM patients generally tend to have depressive symptoms. 90 % of FM patients also show depressive symptoms and 62-86 % show major depressive disorder (MDD) (Aguglia et al., 2011; Arnold et al., 2006; Marangell et al., 2011; Wilke et al., 2010). There is a growing interest to associate depression with FM and pharmacological treatment of both syndromes consists of the same active serotoninergic and noradrenergic ingredients such as, amitriptyline, duloxetine and milnacipran (Gracely et al., 2012).

2.8.Functional Neuroimaging Studies of Fibromyalgia

There are several neural evidences of FM in functional neuroimaging literature (see reviews (Cagnie et al., 2014; Gracely & Ambrose, 2011; Jorge & Amaro, 2012; Staud, 2011)). This literature can also be divided in five different subtitles. These are;

- Painful stimulation studies
- Non-painful stimulation studies
- Resting-state functional connectivity studies
- FM - Depression association studies
- FM treatment studies

We evaluated studies related with depression and pain relationship in FM patients. FM. Also, we investigated the studies about the treatment methods and its functional results because in our study we are interested in the effects of TENS onto the FM patients. Among these studies, active regions that were found and pioneering studies are listed in Table 2 and Table 3 respectively.

2.8.1. Painful Stimulation Studies

Neuroimaging literature of FM generally focuses on painful stimulation studies using fMRI. In these studies, painful stimulation was generally applied to thumb. The main idea to focus on the thumb is tenderness. Tenderness was shown by deep tissue receptors found in muscular and non-muscular tissue. Also, the thumb has a great area of representation in both somatosensory and motor homunculi. Activations were generally observed in pain related regions such as SI, SII, ACC (sensory processing), STG, IPL (sensory association), putamen, cerebellum (motor activity) and DLPFC, VMPFC, insula, ACC, caudate, PAG (affective, emotional and cognitive processing) (see review (Jorge & Amaro, 2012)).

Painful stimulation studies generally focus on neural effects of subjectively equal painful stimulation (Cook et al., 2004; Craggs et al., 2012; Giesecke et al., 2005; Gracely et al., 2002; K. B. Jensen et al., 2009; K. B. Jensen et al., 2012; Pujol et al., 2009; Staud et al., 2008) and equal amount of painful stimulation (Cook et al., 2004; Giesecke et al., 2004; Gracely et al., 2002; Pujol et al., 2009). In stimulation studies, with equal amount of pain, the same stimulus intensity is applied to all subjects. In "subjectively equal pain", stimulus intensity for control group is larger so that pain sensation is equated for both groups. (i.e. Stimulation of FM patients and healthy controls were adjusted to obtain perceptually equal stimulus to accommodate for increased pain sensitivity of FM patients. This adjustment resulted in lower painful pressure stimulus applied to FM patients than applied to healthy controls).

Stimulation studies with subjectively equal amount of pain

Increased BOLD activation was found in FM patient group compared with healthy controls. In these studies, increased activation was observed in contralateral SI, SII, IPL, insula and cerebellum as shown in Figure 7. On the other hand, deactivations were found in ipsilateral SI (Gracely et al., 2002), thalamus and right ACC (K. B. Jensen et al., 2009; K. B. Jensen et al., 2012). All these regions are known regions from the definition of "Pain – Matrix". Another important finding in these studies is the activity differences between FM patients and healthy controls. FM patients generally showed higher activation in commonly activated regions (Cook et al., 2004; Giesecke et al., 2004; Gracely et al., 2002; K. B. Jensen et al., 2012; Pujol et al., 2009). In addition to these findings, time series of hemodynamic activation showed a prolonged insula activity. Also, hemodynamic activity was correlated with subjective pain sensation ratings of applied stimulus. It is suggested that painful stimulus enables common active regions in "Pain-Matrix" have higher levels in FM patients than healthy controls due to excessive tenderness of their body. This may be the result of changes in CNS that causes failure of processing afferences and stimulus was ended at spinal cord nociceptive neurons (Cook et al., 2007).

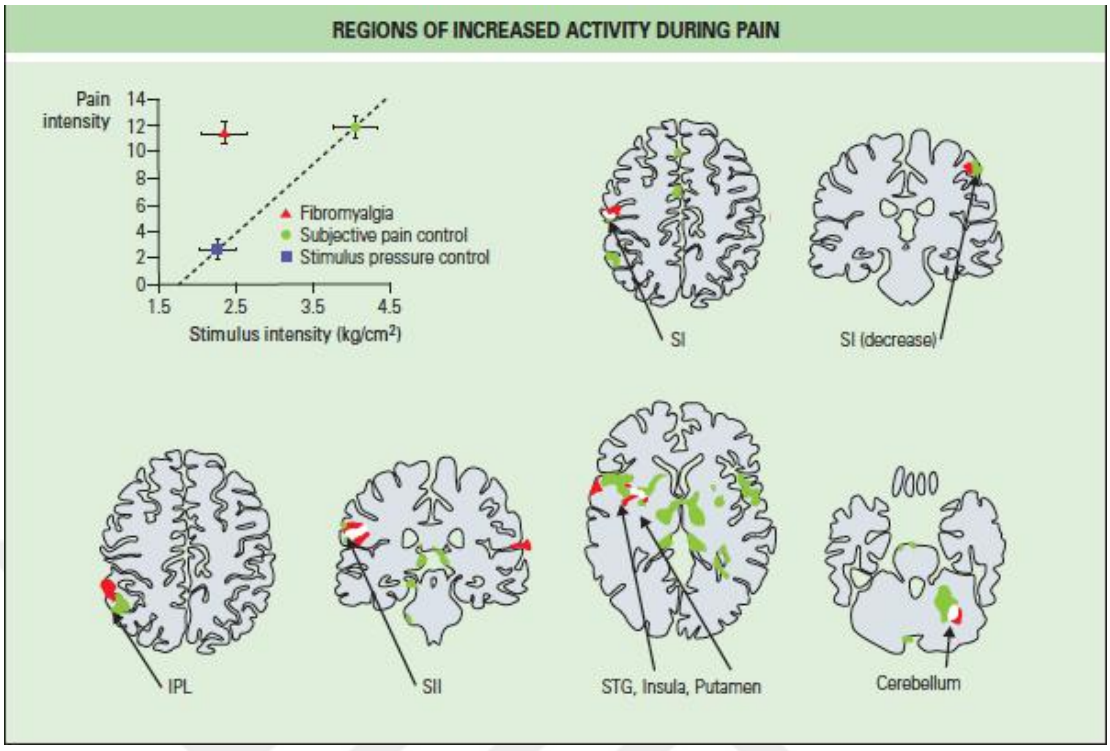


Figure 7. Activated regions and relationship between stimulus intensity and pain intensity (Gracely et al., 2002).

Stimulation studies with equal amount of pain

Activations were observed in pain related regions such as SI, SII, insula, ACC, IPL, cerebellum (Giesecke et al., 2005; Gracely et al., 2002; Pujol et al., 2009). Increased activation in contralateral SI, SII, IPL were found in FM group compared to healthy controls (Giesecke et al., 2005; Gracely et al., 2002). In Figure 7 it is shown that FM patients showed higher activity in SI, SII, ACC and insula than healthy controls. However, healthy controls also showed higher activations than FM patients in these regions (Pujol et al., 2009).

For both conditions above, FM patients showed activity in similar regions with magnitude than healthy controls, while painful stimuli were applied for equal amount of pain sensation. When same amount of painful stimuli was applied, FM patients show wider activation patterns than the other condition.

Another phenomenon in painful stimulation is temporal summation of "second pain" (TSSP), which is also called "wind up", is the addition of hemodynamic response caused by "second pain" after the activity for the initial stimulus as an impulse response (Figure 8). This is clinically important and relevant for chronic pain syndrome (Price et al., 1977). This phenomenon is thought as result of C-fibers' evoked responses of dorsal horn neurons. Also, it was associated with hemodynamic activity in several brain areas which is related with receiving input from spinal pathways and regions related with pain perception. Repetitive heat pulse stimulation showed that frequency of stimulus $\geq$ 0.33 Hz causes activation in SI, SII, insula,

ACC in both groups with no difference in activation and connectivity (Craggs et al., 2012; Staud et al., 2008). However, participants with FM syndrome required lower painful stimulus intensity for TSSP due to their excessive tenderness. These results may indicate an increased sensitivity to pain in FM patients that is not related with dysfunction of cerebral mechanisms. However, it might be related with excessive sensitivity of spinal cord neurons.

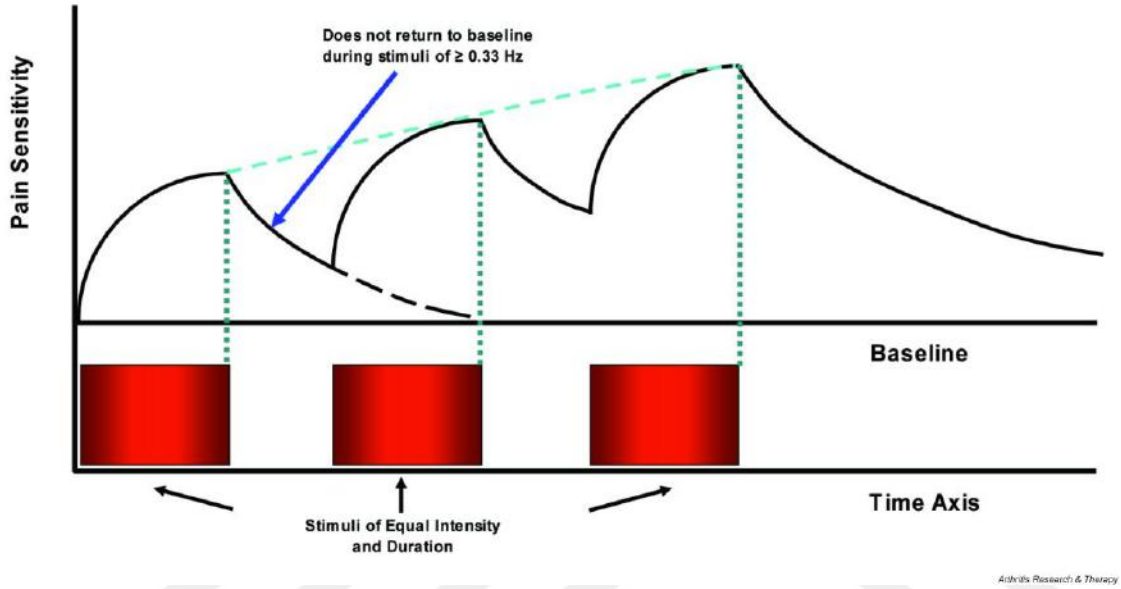


Figure 8. Representation of temporal summation of second pain on pain sensitivity. (Staud, 2006).

Moreover, incision studies measured the hemodynamic activity by applying an incision to right forearm in FM patients (Burgmer, Gaubitz, et al., 2009; Burgmer et al., 2012; Burgmer et al., 2010; Burgmer, Pogatzki-Zahn, et al., 2009). Frontal (Burgmer, Gaubitz, et al., 2009; Burgmer et al., 2010; Burgmer, Pogatzki-Zahn, et al., 2009), cingulate, SMA and thalamic activity (Burgmer, Gaubitz, et al., 2009; Burgmer, Pogatzki-Zahn, et al., 2009) were found in these studies. In some studies activations were found higher in FM patients (Burgmer, Gaubitz, et al., 2009; Burgmer, Pogatzki-Zahn, et al., 2009), in some not (Burgmer et al., 2010). In addition to these findings, pain anticipation was observable without painful stimulation (Burgmer, Pogatzki-Zahn, et al., 2009). These studies showed a significant alteration in hemodynamic activity after the incision in FM patients compared with healthy controls.

A very recent and unique fNIRS study has focused on cerebral signatures of FM syndrome (Uceyler et al., 2015). In this study, painful stimulation and non-painful stimulation (verbal fluency test) were performed to FM patients, Major depression patients and healthy controls. Results showed that painful stimulation experiment caused an increased bilateral activation in FM patients than healthy controls. DLPFC activation was higher in contralateral side in FM patients than major depression patients. Verbal fluency test results showed that all groups have similar activity.

2.8.2. Non-painful Stimulation Studies

In the literature, there exists few studies related with non-nociceptive sensory responses of FM patients. These suggest that FM patients show higher sensitivity not only to painful stimulation but also to non-painful stimulation such as tactile (Cook et al., 2004; Lopez-Sola et al., 2014), auditory and visual (Lopez-Sola et al., 2014) . In 2004 Cook and his colleagues tried to analyze the nociceptive system in patients with FM by fMRI (Cook et al., 2004). According to (Lopez-Sola et al., 2014)) in fMRI scans FM group has greater activity than controls for non-painful stimuli over several brain regions: PFC, SMA, Insular Cortex and ACC.

It was thought that FM syndrome can affect the sensory systems. A recent study also found differences for auditory, visual and tactile motor stimulation responses between healthy controls and FM patients (Lopez-Sola et al., 2014). Patients showed increased sensitivity to the multisensory stimulation in, SI/SII, insular cortex and medial / lateral frontal areas. Also, increased responses in the insula and anterior lingual gyrus were observed. fMRI results indicate that, hemodynamic response of patients is significantly reduced at the visual and auditory regions. Brain activity results of these regions were associated with subjective sensory hypersensitivity and clinical measures. This study showed that FM might cause perception abnormalities in several sensory systems.

Table 2. Activated regions in fMRI studies in FM.

In this table; FM: FM group, HC: Healthy controls, P : Painful stimuli study, NP : Non-painful stimuli study, RS : Resting state study. ACC : Anterior Cingulate Cortex, PCC : Posterior Cingulate Cortex, SI : Primary Somatosensory Cortex, SII : Secondary Somatosensory Cortex, Ins. : Insular Cortex, Amyg. : Amygdala, IPL : Inferior Parietal Lobe, SPL : Superior Parietal Lobe, PPC : Posterior parietal cortex, Cer. : Cerebellum, Thal. : Thalamus, PFC : Pre Frontal Cortex, FG : Frontal Gyrus, SMA : Supplementary Motor Area, MI : Motor Cortex, STG : Superior Temporal Gyrus. Uppercase (X) : shows activity in a region is greater in a group than the other one. Lowercase (x): shows activity in a region is lower in a group than the other one. M : Middle, I : Inferior, S : Superior. ICA : Independent Component Analysis, GLM : General Linear Model. * In Gracely et al., 2004 study, only FM patient group.

Activated Regions / Studies		ACC		SI		SII		Ins.		Amyg.		IPL		Cer.		Thal.		PCC		PFC		FG		SMA		MI		STG	
		FM	HC	FM	HC	FM	HC	FM	HC	FM	HC	FM	HC	FM	HC	FM	HC	FM	HC	FM	HC	FM	HC	FM	HC	FM	HC	FM	HC
Gracely et al., 2002 (P)		**X**	**x**	**X**	**x**	**X**	**x**	**X**	**x**			**X**	**x**	**X**	**x**			**X**	**x**			**x (M)**	**X (M)**					**X**	**x**
Cook et al., 2004 (P &NP)	P							**X**	**x**																				
	NP	**X**	**x**					**X**	**x**											**X**	**x**			**X**	**x**				
Gracely et al., 2004 *(P)		**X**		**X**		**X**		**X**				**X**		**X**		**X**		**X**				**X (I,S)**							
Giesecke et al., 2005 (P)								**X**	**x**	**X**	**x**																		
Pujol et al., 2009 (P) (ICA &GLM)	ICA	**X**	**x**	**X**	**x**	**X**	**x**	**X**	**x**			**X**	**x**											**X**	**x**	**X**	**x**		
	GLM			**X**	**x**	**X**	**x**	**X**	**x**			**X**	**x**													**X**	**x**		
Jensen et al., 2010 (P & NP)		**X**		**X**		**X**		**X**						**X**		**X**													
Napadow et al., 2010 (RS)						**X**	**x**	**X**	**x**																				
Lopez- Sola et al., 2014 (NP)								X	x					x	X													x	X

2.8.3. Functional Neuroimaging Studies of Pain and Depression in FM Syndrome

Effects of depression on neural mechanisms are quite related with FM syndrome. In 2005 Giesecke and his colleagues investigated the relationship between depression, clinical pain and experimental pain by using fMRI (Giesecke et al., 2005). In this study, contribution of depression to the pain perception in FM patients is evaulated. A 25 sec subjective nociceptive stimuli and 25 sec resting period is applied to participants 12 times during fMRI scan. Randomly varying intensities of nociceptive stimuli is used. In this study, depression and co-morbid major depression disorder (MDD) was found to be uncorrelated with the results of QST and hemodynamic activity in SI and SII. However, same factors were associated with magnitude of hemodynamic activity in amygdala and contralateral anterior insula. Clinical pain intensity was related with QST and hemodynamic activity of bilateral insula, contralateral ACC, PFC, which are regions of importance in affective processing. The most important result of this study is; sensory dimension of pain perception is not related to depression nor MDD.

The relationship between cognitive disorders and fibromyalgia is another topic of importance. According to Jensen and her colleagues, anxiety and depression caused poor perception of health and there was no relationship between these cognitive disorders and pain sensitivity or pain processing in brain in FM patients (K. B. Jensen et al., 2010). Depressive symptoms, anxiety and catastrophizing scores showed higher correlation coefficient with each other, but did not correlate with clinical pain ratings or pain sensitivity. SF-36 scores were correlated with BDI and State-Trait Anxiety Inventory. fMRI results showed that cerebral activity was not modulated by BDI, State-Trait Anxiety Inventory and Coping Strategies Questionnaire. This study showed that negative emotional state in FM patients could cause poor health perception. However, it does not affect the clinical and experimental pain experience of FM patients.

Another indicator to explain the severity of FM syndrome is catastrophizing. Catastrophizing is a collection of negative emotional processes and irrational thoughts which can be seen in several chronic painful diseases. Patients generally tend to exaggerate pain-related symptoms; they feel helplessness related to their disease. Higher levels of this problem is strongly related with increased pain intensity in FM patients (Hassett et al., 2000). Catastrophizing has been known to increase pain perception through increased attention to nociceptive stimuli and increased emotional reactions to pain. A painful stimulation study showed that hemodynamic activity is strongly related with catastrophizing in FM patients (Gracely et al., 2004). In this study, it was hypothesized that catastrophizing is strongly related with activation in brain regions associated with pain processing. Scores of catastrophizing were correlated with the activation in ipsilateral claustrum, cerebellum, DLPFC, parietal cortex, contralateral dorsal, DLPFC, MFC, and lentiform nuclei. Also, subjects were discriminated as high and low catastrophizing groups by dividing the patient group considering the median value of catastrophizing ratings. Both groups demonstrated increasing activity in ipsilateral SII, ipsilateral SI, contralateral insula, SI, inferior parietal lobule (IPL), PCG, SFG, IFG and thalamus.

High catastrophizers also showed activation in contralateral ACC and bilateral lentiform. In this study, it was shown that pain catastrophizing is significantly related with anticipation of nociception (MFC, cerebellum), attention to nociception (ACC, DLPFC), emotional effects of nociception (claustrum) and motor activity. Pain anticipation is a reflection of catastrophizing with augmented activation in frontal cortex, cingulate cortex and SMA before and after incision based stimulation with higher pain ratings as shown in Figure 9 &

Figure 10. This mechanism might be specific to FM, because other rheumatic diseases do not reflect such a mechanism (Burgmer et al., 2010; Burgmer, Pogatzki-Zahn, et al., 2009).

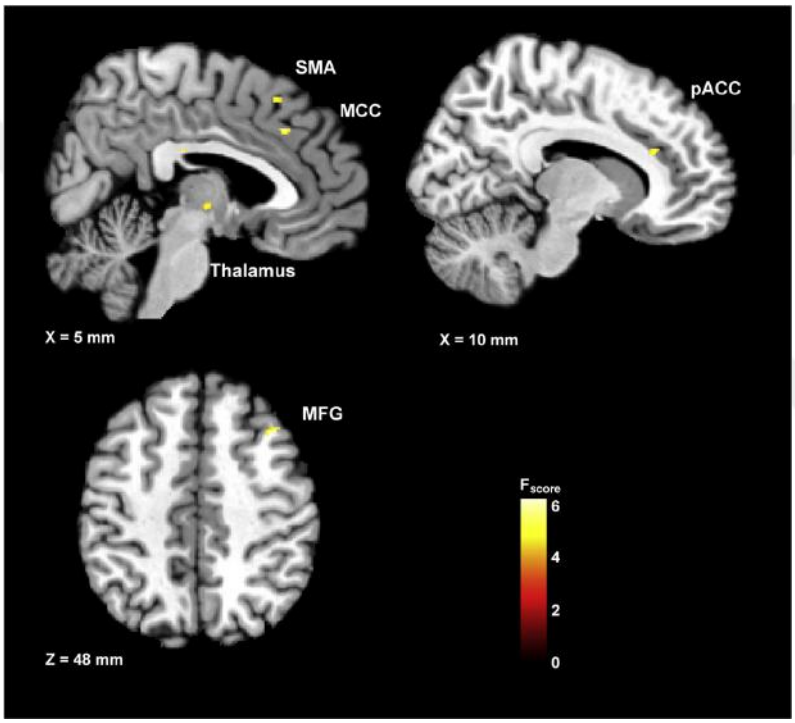


Figure 9. Significant brain activity in catastrophizing.
Significant differences between FM patients and healthy controls were observed in SMA, MCC, ACC and MFG(Burgmer, Pogatzki-Zahn, et al., 2009)

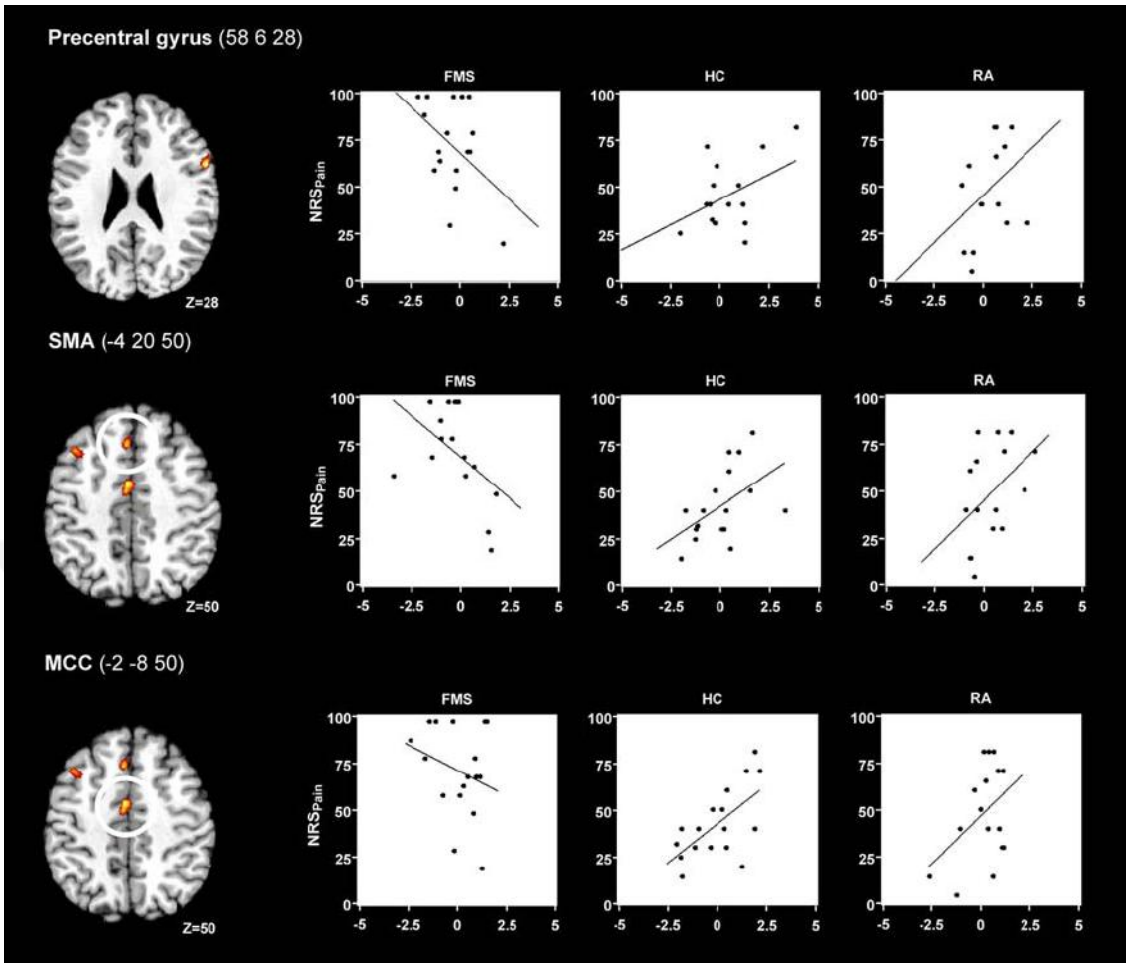


Figure 10. Correlations between pain ratings and BOLD activity
during incision in FM, RA (Rheumatoid Arthritis) and healthy control participants.
Multiple regression was done and HADS, pre-anxiety and clinical pain were used as covariates
(Burgmer et al., 2010)

2.8.4. FM Treatment Studies

Functional neuroimaging methods have also been used to observe the efficacy of pharmacologic and non-pharmacologic treatment methods in FM. Among pharmacologic treatments, effects of milnacipran which is a noradrenaline reuptake inhibitor were observed in fMRI. Decreased pain sensitivity and increased activity is observed in PCC and precuneus, which are parts of the descending inhibitory system (Mainguy, 2009).

fMRI studies showed that non-pharmacologic treatment methods were also effective in treatment of FM. A study protocol focused on effects of visuals of albeit exercises on pain catastrophizing (Morris et al., 2011). Also, real-time fMRI was used for FM patients to guide themselves for controlling the pain modulation system in especially rostral ACC (rostral ACC is a region that is strongly involved in pain perception and regulation). When FM patients were able to decrease or increase the rostral ACC

activation, their pain perception caused by a nociceptive stimulus also changed (deCharms et al., 2005).

Table 3. Summary of important studies in FM literature.
(LH: Left Hand, RH: Right Hand)

Study	FM Patients / Controls	Experimental Design	Results	Conclusions
Gracely et al., 2002 (fMRI)	n=16 (right handed 15 female, 1 male age = 52.6 ± 12.3 range 19-69 non-clinically depressed) / n=16 (right handed, 15 female, 1 male, age : 45.8 ± 10.5, range 22-61) (LH)	Two conditions. 1st same amount of pressure was given. 2nd different amount of pressure that causes same amount of pain rating was given. For every experiment 10 cycles including 30 sec painful stimuli 30 sec non-painful stimuli was applied.	2nd experiment causes activity in 19 regions for HC and 12 regions for FM. 7 regions were activated in common. 1st experiment caused only 2 regions of activity increase that none of them is common with FM group. Statistical comparison shows that 13 region has greater activity in FM group than HC group. Only one region is greater in HC group than FM group.	FM is identified by cortical or subcortical increased pain processing.
Cook et al., 2004 (fMRI)	n=9 (right handed female age 18-45 years) / n=9 (right handed female age 18-45 years) (LH)	5 run including practice, warm heat, 47 C, Pain of 5 and warm heat. Every run lasts 230 sec including 5 times 10 sec ON 30 sec off period with a final 30 sec.	PP results show that FM patients were sensitive to experimental heat than controls. Functional results show that painful (contralateral insula) and non – painful (PFC, SMA, insula, ACC) stimuli causes higher activity in FM patients than HC controls.	These results provide evidence to further explanation of FM.
Gracely et al., 2004 (fMRI)	15 High catastrophizing patients / 14 Low catastrophizing patients (LH)	25 sec pressure stimuli 25 sec rest x 12 times. Different intensities were applied in random sequence.	Twice activation in ipsilateral SII in high catastrophizers. Both groups → SII, Cont. insula, SI, IPL, thalamus. High cat. → Cont. Ant. ACC, bilateral lentiform. Both groups → ipsilateral SI, ant. and post. Cerebellum. PCC, SFG and IFG.	Pain catastrophizing is related with increased brain activation, independent of depression effect.
Giesecke et al., 2005 (fMRI)	11 CLBP patients (age 44 ± 13, 3 male , 8 female) , 16 FM patients (age 45 ± 12 , 4 male , 12 female) / 11 Healthy Controls (age 41 ± 7, 7 male, 4 female) (LH)	Same with Gracely et al., 2004	Common regions for equal amount of pressure (CLBP & FM) → Cont. SI & SII, IPL, Cerebellum and ipsi. SII. Commonn regions for equal pain sensation (FM, HC & CLBP) → Cont SI, SII, IPL, Insula, ACC & ipsi. SII, cerebellum.	Equal pain intensity causes more pain sensation in CLBP and FM patients. Equally pain sensation causes neuronal activations were similar in all groups.

Pujol et al., 2009 (fMRI)	9 right handed Female FM patients (age: 47.9 ± 9.4) / 18 Female Healthy Controls in 2 groups. Group 1 (9 right handed age: 47.2 ± 8.9) and group 2 (9 right handed age: 48.2 ± 5.5) (RH)	9 sec painful stimuli 21 sec resting period x 12 times. 2 different experiments. 6.8 kg /cm2 (same pain rating) and 4kg/cm2 (same amount of pain).	ICA and GLM were done. For same amount of pain, ICA results shows activation in both groups SI, SII, MI, IPL and insula. FM patients also show activation in ACC, SMA, Basal ganglia, Ang. Gyrus, Visual Cortex, and Frontal Operculum. FM group shows greater activation than HC group. GLM results shows that FM patients shows activation in SI, MI, IPL, SII, insula, frontal operculum. HC only shows activation in SI, MI and insula. FM also shows greater activation than HC. For same sensation of pain, pain-related regions were activated but FM patients show greater activation in anterior insula, basal ganglia and cingulate cortex.	ICA method can be applicable for analyzing pain responses and increased brain activation in FM patients can be related with emotional process.
Burgmer et al., 2009 (fMRI)	18 Female FM patients (age: 52.6 ± 7.9) / 18 Female Healthy Controls (49.5 ± 8.9) (RH)	4 sessions were carried out only first and second sessions were analyzed. In 1st session a 5 min baseline were scanned then a 5 min no scanning period. In 2nd session, after a 1-min pre-incision period, incision was performed and after the period of this incision there are 3 periods of post-incision that have durations of 2, 2,5 and 5,5 mins.	Activation differences were found in fronto-cingulate cortex, supplementary motor area and thalamus between both groups in not only pain stimulation but also pain anticipation period.	These results shows that central pain processing, cognitive and affective systems during pain anticipation can be effective in pain processing for FM patients.
Jensen et al., 2010 (fMRI)	83 female patients (43,8 ± 8,1 years) / No healthy controls	An event-related study. Painful stimulation was carried out with a mean stimulus onset of 15 seconds (btw. 10-20 sec). 4 different random sequences were applied for every patient but patients received sequences in different order.	Depressive symptoms, anxiety and catastrophizing scores were correlated with each other ($P<0.001$). No correlation between clinical pain ratings or sensitivity of pressure pain. General health rating was correlated with depressive symptoms and anxiety. Bilateral PAG, Amygdala, ACC and insula were activated. Contralateral SI and SII were activated. Cerebellum and thalamus were also activated. None of these regions were modulated by depressive symptoms, anxiety or catastrophizing.	Depression, anxiety or catastrophizing can cause a physical health perception in lower levels. However, these factors do not affect performance on clinical and experimental pain assessments.

Lopez- Sola et al., 2014 (fMRI)	35 female subjects (46,55 ± 5,94 years) / 25 female subjects (44,64, ± 5,94 years)	30 second rest, 30 second stimulation (visual, auditory and tactile motor stimulation) in 4 rest activation cycles. Visual stimulation is 3 Hz full field flashing checkerboard. Auditory stimulation is a series of 15 tones in different frequencies. Motor stimulation is the finger opposition task.	Patients shows increased unpleasantness to stimulations. fMRI showed that patients demonstrated reduced activity in primary and secondary visual and auditory cortices. These areas were highly correlated with subjective sensory sensitivity and clinical measures. Also increased responses were observed in insula and anterior lingual gyrus.	FM patients shows increased sensitivity to non nociceptive inputs in sensory cortices.

2.9. Transcutaneous Electrical Nerve Stimulation

TENS is a non-pharmacologic and core treatment method for inflammatory, neuropathic and musculoskeletal pain. It is generally used standalone among patients with mild to moderate pain but used jointly with medications for patients with moderate to severe pain. It is non-invasive, inexpensive, safe and easy to apply. Its purpose is to stimulate nerves to decrease transmission of painful stimulation (M. I. Johnson & Bjordal, 2011).

There are two types of TENS techniques that are generally used ;

- Conventional TENS: In this technique, high frequency and low intensity electrical nerve stimulation is applied to patients. It causes a strong and non-painful TENS sensation. This type of stimulation does not trigger muscle contraction on the painful region in body.
- Acupunctrure-like TENS: This technique uses low frequency and high intensity electrical nerve stimulation that causes non-painful muscle contractions in the painful region of the body.

Conventional TENS is the most commonly used technique for treatment at the site of pain. Only extra-ordinary conditions might require application of Acupuncture-like TENS such as change in skin sensitivity, widespread or multi-regional pain or availability of pain in deep structures (M. Johnson, 2014).

For conventional TENS, strong electrical stimulation is quite important (Moran et al., 2011). By considering the “gate control theory” mechanism, Aβ fibers that are also known as “large nerve fibers” are activated by using TENS and Aδ and C-fibers that are also known as “small nerve fibers” that carry nociceptive stimulus to brain regions.

Conventional TENS analgesic effect is shown in Figure 11. Nociceptive activity in Aδ and C fibers causes a triggering effect of interneurons in substantia gelationosa (SG) in spinal cord. This effect appears via neurotransmitters substance P (SP) or vasoactive intestinal peptide (VIP). Central nociceptor transmission T neurons excites somatosensory cortex of brain via spinoreticular and spinothalamic pathway.

In contrast, TENS stimulation in Aβ fibers cause an inhibitory activity in SG and T cells via the secretion of gamma amino butyric acid (GABA). Paraesthesia related with TENS is produced by stimulus going through to the brain by dorsal columns.

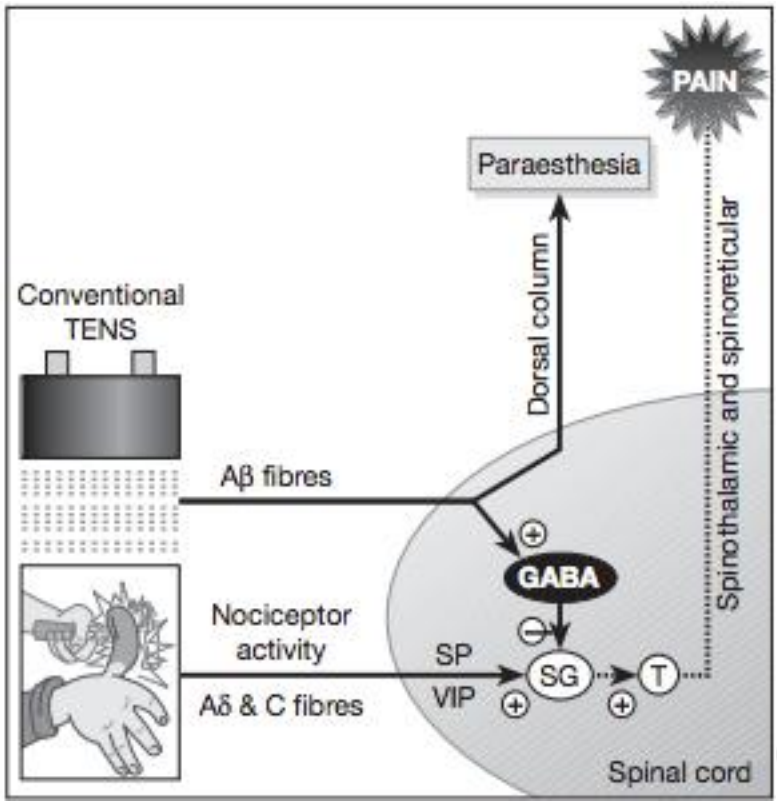


Figure 11. Neurophysiology of Conventional TENS analgesia
(Mark I. Johnson, 2001).

TENS application is performed by an adjustable pulse generator and conducting pads. One of these pads is used as anode and the other is used as cathode. Cathode directly stimulates the axon. This pad is directly placed to the proximal of the anode to not to block nerve transmission caused by hyperpolarization shown in Figure 12. When positive or negative direct current (DC) is applied, cathode directly triggers the axon and the impulses carried by nerve move in both directions. This is called depolarization of axon. Then, anode inhibits the axon to suppress nerve impulse. This is called hyperpolarization of axon.

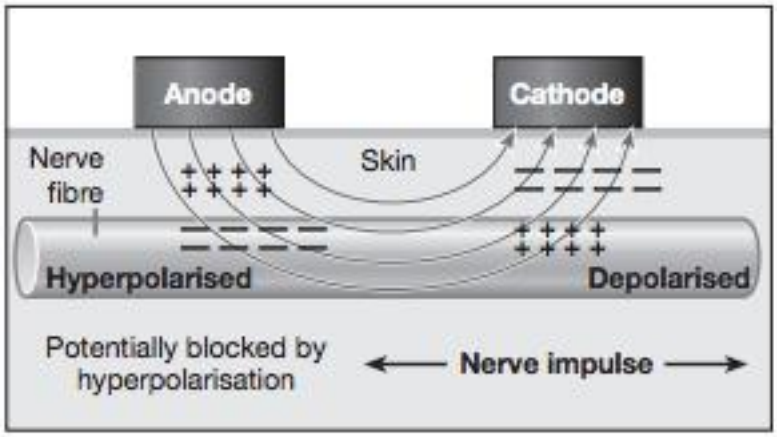


Figure 12. TENS application onto skin and stimulation of nerve fibre (Mark I. Johnson, 2001).

2.10. TENS Effects Based Functional Neuroimaging Studies

Despite the uncertainty of the exact mechanism of TENS, it is a widely known pain treatment and relief method. There are few neuroimaging studies that focus on demonstrating treatment effects of TENS. One of these studies investigates the effect of TENS in Carpal Tunnel Syndrome (CTS) patients by using fMRI (Kara et al., 2010). In this double blind randomized placebo-controlled study, it was aimed to observe the effects of TENS by using fMRI in CTS patients. 20 Female patients were randomly grouped into groups. One of these groups (n=10) received TENS and the other group (n=10) received sham-TENS treatment. For both groups, first an initial fMRI scan was carried out by stimulation of digits 2, 5 and 3. After that TENS was applied to the treatment group and sham-TENS was applied to placebo group. Then a second fMRI session was carried out after 20 minutes. 2nd finger stimulation fMRI scan started on 20th minute, 5th finger stimulation fMRI scan started on 25th minute and 3rd finger stimulation fMRI scan started on the 30th minute. fMRI activations were analyzed between TENS and sham-TENS groups. Results showed that TENS treatment caused a BOLD response decrease significantly for digit 2 in SII, ipsilateral MI, contralateral SMA, contralateral parahippocampal gyrus, contralateral lingual gyrus and bilateral STG. 25th and 30th min scans for digit 5 were observed similar between groups. After the TENS treatment, significant BOLD response decrease was observed in contralateral MI and contralateral SMA 30 to 35 minutes for digit 3. This study supports the effectiveness of TENS treatment by showing that in pain-related regions, stimulation of fingers which median nerve directly innervates causes a decrease in the BOLD signal, valid up to 35 minutes after treatment.

Another study by Klingner and his colleagues showed that ipsilateral brain activity is effective for somatosensation (Klingner et al., 2011). In this study, 12 healthy subjects were stimulated by electrical median nerve stimulation using block and event-related design. The data was analyzed by data-driven (ICA) and model-driven (GLM) methods considering both negative and positive BOLD responses. Results of both analysis methods showed that negative BOLD responses were observed??? in ipsilateral SI, insula, SMA, dorsal PCC and contralateral cerebellum. Also, negative

BOLD activation shows a delay of 2.4 sec and peak delay of 0.7 sec which may be related to different physiological basis of positive BOLD responses.

Another important by Kocyigit and her colleagues aimed to observe the effectiveness of TENS in subacromial impingement syndrome (SIS) (Kocyigit et al., 2012). 20 SIS patients attended this study and randomized into low-frequency TENS and sham-TENS groups. In this study, nociceptive stimuli were applied during fMRI scans before and after treatment. 10 ROI that were published to act in pain processing, were selected and analyzed in both hemispheres. Pain intensity was evaluated by VAS. Results demonstrated that low frequency TENS group gave significantly less VAS scores compared with sham-TENS group. Also, TENS group showed significant BOLD response decrease in SI, bilateral caudal ACC, and ipsilateral SMA. Significant correlation was found between VAS scores and activity changes in contralateral thalamus, PFC and ipsilateral PPC. Sham-TENS group did not show a significant change in VAS scores and activities in pain related regions. This study suggests that low frequency TENS may affect affective and motor aspects of pain perception.

TENS treatment literature does not only consist of fMRI based studies but also electrophysiological ones. Vassal and his colleagues analyzed TENS effect on nociceptive brain responses and pain processing on brain (Vassal et al., 2013). In this study, nociceptive laser pulses were applied onto dorsum of both feet of 20 healthy subjects. Laser evoked potentials (LEPs) and pain thresholds were acquired in 3 respective conditions. These are sham-TENS (2 Hz/ low intensity) onto left thigh, TENS (120 Hz / low-intensity) onto peroneal nerve and sham-TENS as replication of first condition. Results suggest that TENS condition shows a reduction in LEPs amplitude when TENS stimulation was performed ipsilaterally to the stimulation site. Pain threshold increase were observed in both limbs after TENS and sham-TENS sessions. However, TENS condition related amplitude increase was significantly greater than 3rd condition of TENS on the foot ipsilateral to TENS. This study shows that, high frequency and low intensity TENS caused a significant weakening effect on pain sensation and LEPs caused by painful stimuli.

Another TENS cooperated pain inhibition study was published by Choi and his colleagues (Choi et al., 2015). In this study, it was hypothesized that pain sensation caused by painful stimuli, hemodynamic responses, temporal summation and functional connectivity are weakened by TENS. Also pain relief is different between men and women. Pain only and pain + TENS conditions were applied to 24 healthy controls (12 men and 12 women). In pain only condition, nociceptive stimuli were delivered without applying TENS. In pain + TENS condition, nociceptive stimuli and TENS application were carried out simultaneously. TENS intensity that causes disturbance was applied to participants below a determined threshold. TENS intensity was applied in an increasing trend to overcome temporal summation from painful stimuli delivered in a repetitive order. Results show that ratings collected after the application of pain-only condition were significantly greater than ratings of pain + TENS condition. SI, SII and parietal cortices were found active with non-painful TENS stimulation. TENS augmented PAG and lateral PFC functional

connectivity. Women gave higher pain ratings than men during TENS and showed higher activation in TPJ and augmented PAG functional connectivity with the OFC. This study showed that, TENS is effective in pain reduction because of activation in the descending pain inhibition pathway. This indicates that TENS can be applicable in clinics.

2.11. TENS Effect on Fibromyalgia Syndrome

TENS effect on FM patients was investigated in small sample sizes in several studies. In general, according to the literature there is a common agreement about significant pain relief effect due to TENS in FM syndrome.

For example, Löfgren and her colleagues carried out this study over 32 FM patients (Lofgren & Norrbrink, 2009). Patients were randomly divided into two groups. One group of patients treated themselves via applying 42 °C superficial warmth and others applied TENS themselves. After 3 weeks they are required to give pain rating after each treatment and are asked about their treatment preference. Results suggest that there was no difference between two treatment modes for pain relief levels. Patients that used warmth therapy changed their median pain rating from 77.5 to 62.5. Other group changed their median pain rating from 80 to 62.5. 17 of 32 patients chose warmth therapy, 10 of them chose TENS. According to results of these treatment methods, pain reduction was observed in both methods.

Carbonario and his colleagues carried out another study over 28 women with FM (Carbonario et al., 2013). In this study, all participants attended 8-week aerobic exercises program and half of the participants took TENS treatment in addition to this program. Also the participants gave pain intensity by using visual analogue scale (VAS). Results show that TENS group performed a decrease in pain relatively non-TENS group.

Lauretti and her colleagues, applied two TENS systems at the lower back and the region between C7 and T1 vertebral regions simultaneously to FM patients (Lauretti et al., 2013). 39 patients attended to this study and were divided into three groups; placebo group, single active TENS group and double active TENS group. Single active TENS was applied to worst area of pain chosen between these two regions. Double active was applied both regions. Also, diclofenac was given to patients as analgesic. Among these groups, placebo group reported no pain reduction compared with previous VAS pain score. Single TENS group patients reported reduction of 2.5cm in VAS rating (drop from 8.5 to 6) and DTG patients reported reduction of 4.2 cm in VAS score (drop from 8.5 to 4.3 cm). There was a reduction in analgesic tablet usage in both single TENS group and double TENS group. Among groups amount of analgesia with quality of sleep and disposition was ordered as follows: Double TENS group >Single TENS group >Placebo group. TENS system was found effective and useful subjectively.

Among these studies, the greatest number of participants is 66 FM patients that attended the study of Mutlu and her colleagues (Mutlu et al., 2013). In this study,

TENS effect with exercise was investigated over 66 women FM patients similar to Carbonario's study. They were treated after dividing into two groups randomly. Both groups were admitted into an exercise program for 12 weeks. In addition to exercise program, first group had also been treated via TENS during the first 3 weeks since the study began. Number of tender points, myalgic pain score, FIQ and short form-36 evaluations were done after the end of 3rd and 12th weeks. According to the results of these evaluations, both groups showed important progress in these evaluations. Progress in myalgic pain score was significantly greater than in the first group ($p=0.01$) at the 3rd week. But there was no significant difference at the end of 12th week ($p=0.87$). According to these results, exercise program was effective to treat myalgic pain and quality of life for women with FM. Exercising and TENS application can be effective to relieve pain for treatment of FM.

2.12. Handedness and Its Effect on Pain Sensitivity

Handedness or hand dominancy is an active research area in pain perception studies. There is no common agreement about the effect of handedness on pain perception. Some studies show that pain perception is different between hands (Chandramouli et al., 1993; Friedli et al., 1987; Ozcan et al., 2004; Pauli et al., 1999). Some does not agree about this difference (Neri & Agazzani, 1984; Newton & Mumford, 1972; Pud et al., 2009; Taylor et al., 1993). However if there is a difference between hands, non-dominant hand shows a higher sensitivity to nociceptive stimulus (Brennum et al., 1989; Buchanan & Midgley, 1987; R. Jensen et al., 1992; Murray & Safferstone, 1970; Petersen et al., 1992; Sarlani et al., 2003; Schiff & Gagliese, 1994). This conflict shows that while analyzing pain perception on either psychophysical studies or neuroimaging studies, handedness effect should be considered as effective factor. Moreover, some studies shows that pain threshold measured by a pressure algometer is greater in dominant hand than non-dominant hand of right-hand dominant participants (Brennum et al., 1989; Buchanan & Midgley, 1987; R. Jensen et al., 1992; Ozcan et al., 2004; Pauli et al., 1999; Petersen et al., 1992; Pud et al., 2009). When pressure pain threshold results show consistency about effect of laterality, on the other hand other types of stimulus such as heat (Bingel et al., 2003; Coghill et al., 2001; Long, 1994; Sarlani et al., 2003; Taylor et al., 1993), mechanical stimulation (Greenspan & McGillis, 1994) or electrical stimulation (Friedli et al., 1987; Neri & Agazzani, 1984; Newton & Mumford, 1972) does not give consistent results.

2.13. Functional Neuroimaging of Hand Preference in Pain Perception

There are several neuroimaging studies that include painful stimulation to both hands (Bingel et al., 2002, 2003; J. C. Brooks et al., 2002; Symonds et al., 2006).These studies were performed by using noxious laser(Bingel et al., 2002, 2003), electrical (Symonds et al., 2006) and heat stimulation (J. C. Brooks et al., 2002). Results of these studies showed that, there is bilateral activation and contralateral bias in SI, SII, insula and thalamus (Bingel et al., 2003; J. C. Brooks et al., 2002) and also motor output related structures such as putamen and cerebellum (Bingel et al., 2002). Also, these studies suggested pain processing was strongly lateralized to the right hemisphere especially in MFG, ACC, IFG, medial / superior FG and IPL (Symonds et al., 2006).

In addition to these results, a meta-analysis was performed by using activation likelihood estimate (ALE) method (Duerden & Albanese, 2013). In this meta-analysis, hemispheric lateralization of pain perception was analyzed by comparing two groups of studies on right hand and left hand stimulation. Results showed that without considering the left or right stimulation, insular cortex and right ACC showed the most significant probabilistic values which is generally observed in several pain studies (see review (Apkarian et al., 2005)). For left-side stimulation, likelihood of activation were found significant in right SI, MI, PPC and SFG and left SI, ACC, MI, IPL and MFG for right-side stimulation. Likelihood of activation in ipsilateral side was found significant in mid-brain for left-side stimulation. For right side stimulation, ACC, IPL and MFG showed the significant likelihood activation.

2.14. Classification of Fibromyalgia by Using Machine Learning

Classification of FM and healthy controls was performed using resting state functional (Sundermann et al., 2014) and structural MRI (Robinson et al., 2015) data. These studies indicated that accuracy of resting state functional data was found up to %73.5 by using support vector clustering and %53-76 accuracy was found for structural data using different classification algorithms such as multilayer perceptron, SVM, Naïve Bayes, J48 etc. Robinson and his colleagues used structural neuroimaging data obtained from 55 different regions and self report data including mood and pain intensity from 26 (14 FM, 12 HC, Age- Gender matched) participants was used in classification. Accuracy results of neural data based classification could not outperform self-report based classification (Robinson et al., 2015). Self- report data that includes mood and pain intensity, were used as input for classification. For mood %96.17 and pain intensity %95.83 accuracies were found which are higher than accuracies obtained from neuroimaging data (%76). Sundermann and his colleagues used Resting state functional connectivity data obtained from 50 participants (17 FM, 16 RA, 17 HC). MVPA was used as extracting models to discriminate SN and DMN. Highest accuracy result was %73.5 for FM vs HC (Sundermann et al., 2014).

2.15. Motivation and Hypothesis

Our primary motivation to carry out this study is to observe the effects of TENS in FM syndrome by using a recently popular functional neuroimaging method fNIRS. TENS is generally used in pain relief and treatment of chronic pain patients. But its hemodynamic features on FM patients are unknown. In this study, we aim to activate Aδ and C-fibers that carries nociceptive stimulus information by using painful stimulus and block by activating Aβ fibers using TENS. We decided to compare the resulting effects of TENS in the hemodynamic activity with the condition when TENS was absent. Our expectation is to see a higher hemodynamic activity in the “Pain only” condition than the “Pain + TENS” condition. Because, we are expecting TENS to decrease the activity during the application of painful stimuli.

2.16. Research Questions

Our primary research question is “is there a pain relief effect of TENS in FM patients while applying painful stimulus and can we observe this in the hemodynamic activity?”. We also investigate whether we can observe a difference between FM patients and healthy controls. Earlier, several studies were carried out by fMRI to understand the FM syndrome. But fMRI is an expensive method with low mobility when compared with fNIRS, making its application in clinic difficult. Our hypotheses for this research question are;

- Hypothesis 1: There exists a significant activity decrease in painful stimulation with TENS compared to painful stimulation without TENS in healthy controls. This activity decrease might reflect that TENS might block painful stimulus transmission to that region by activating Aβ fibers.

- Hypothesis 2: For FM patients, we are expecting to as in hypothesis 1. Because several studies indicated that TENS treatment shows a significant pain relief in these patients.

Hypotheses 1 and 2 are studied on both hands of strongly right-handed subjects.

Another important research question is “Can we distinguish FM patients and healthy controls using brain activity patterns during painful stimulation?”. Classification of FM disease was generally carried out using self-reports such as pain thresholds, mood information or structural neuroimaging (Robinson et al., 2015) and resting state functional connectivity data (Sundermann et al., 2014). We are expecting to see a higher accuracy using functional neuroimaging data collected after our painful stimulation experiment.

Hypothesis 3: Classification accuracy between then FM and HC groups will be larger than 80 %. For this purpose, we performed classification for every channel in order to understand which channels discriminate the FM patients and healthy controls.

CHAPTER 3

METHODOLOGY

Ankara University Faculty of Medicine Ethical Review Board committee approved our study and we were allowed to carry out this study using the fNIRS system at the Ankara University Brain Research and Application Center (AÜBAUM). Ethical Board Approval is provided in APPENDIX A.

3.1.Data Collection Before The Experiment

All participants signed written informed consent shown in APPENDIX B. Before the experiment, the subjects filled Beck Depression Inventory (BDI), and Edinburgh Handedness Inventory (EHI). For patients Fibromyalgia Impact Questionnaire (FIQ) is also filled. For female participants, menstruation cycle information was also collected. The subjects were told that they will feel experimental pain in their thumbs and they can stop participating in the study during any part of procedure. Pain threshold values were collected for both thumbs by using electronic Von Frey (eVF) anesthesiometer. For patients, number of tender points (TP) was measured by medical experts (M.K & A.B).

This information, as well as pain ratings during the experiment were recorded to "Participant Information and fNIRS Experiment Report Form" shown in APPENDIX C.

3.1.1. Beck Depression Inventory

Beck Depression Inventory (BDI) is a self-report inventory that includes 21 multiple-choice questions for determination of severity of depression (Beck & Beamesderfer, 1974). Subjects are required to fill this inventory according to their mood in past two weeks including the day they fill this inventory. Every question in this inventory correspond to the 21 different symptoms of depression including sadness, pessimism, past failure, loss of pleasure, guilty feelings etc.

BDI score is the sum of all scores over the 21 questions. According to the score ranges of BDI, after the revision in 1996 (Beck et al., 1996), severity of depression is categorized as;

- 0-13 is minimal depression.
- 14-19 is mild depression.
- 20-28 is moderate depression.
- 29-63 is severe depression.

3.1.2. Fibromyalgia Impact Questionnaire

Fibromyalgia Impact Questionnaire (FIQ) (Burckhardt et al., 1991), is a measure to observe the general health of FM patients for clinical and research purposes. Burckhardt and her colleagues (1991) developed FIQ by considering the information taken from patient reports, functional status of patients and clinical investigations. FIQ measures the effects on FM in daily life activities, depression, anxiety, pain, stiffness and fatigue.

FIQ includes 20 questions, first 11 questions are related with physical impairment. 12^{th} question is about physical and psychological mood of patient in the past week. 13^{th} question is related with missing work due to FM. $14\text{-}20^{th}$ questions are related with pain, fatigue, rested, stiffness, anxiety and depression respectively. Evaluation of this questionnaire is as follows.

- First 11 questions have a score range between 0-4 (0 - always, 1 –most, 2- occasionally, 3- never, 4- I don't). Among these questions, sum of all scores of questions except for answers "4- I don't" are considered and averaged and the result is multiplied with 3.33. For example, if a participant doesn't do 2 activities among 11 activities, the sum of scores is divided into 9.
- For 12^{th} question, the result is found by subtracting the score from 7 and (e.g. if the score is 3 days. The answer of this question is 7-3=4)
- Score of 13^{th} question is multiplied with 1.43.
- Scores of questions from 14-20 are directly considered without any additional operation.
- Sum of all scores gives us final FIQ score.

3.1.3. Edinburgh Handedness Inventory

Edinburgh Handedness Inventory (EHI) is used to determine the dominance of a person's hand during carrying out daily activities. It was developed by Oldfield in 1971 (Oldfield, 1971). In this inventory, there are 12 questions. 10 of this 12 questions are directly associated with hand preference and last two questions are related foot and eye preference. First 10 questions ask the hand preference while writing, drawing, throwing, using scissors, knife, spoon, broom and toothbrush, striking a match and opening a lid.

3.1.4. Quantitative Sensory Testing

For our painful stimuli experiment, we obtained individual pain thresholds for every participant. To obtain this value we applied Quantitative Sensory Testing (QST) method. In this method, stimulus is applied to the participant unless he/she gives a verbal sign to show their pain feelings. There are several types of measuring this value such as Staircase method, 4-2-1 Stepping algorithm, Multiple Random

Staircase method (see review (Yarnitsky, 1997)). We used electronic Von Frey anesthesiometer (eVF) (Ugo Basile Co., Varese, Italy) to carry this out. eVF is an precise and accurate method for measuring pressure pain threshold that has a standard usage to measure pain threshold that is mentioned in several studies (Ambalavanar et al., 2006; KuKanich et al., 2005; Tena et al., 2012; Vivancos et al., 2004). The eVF pressure pin has a 0.5 mm diameter and the measurement range of system is 1 to 1000 gram force with 0.1 gram force increments.

In this method, while the stimulation was being applied in linearly increasing intensity trend, participants gave the verbal sign when the stimulation caused an unpleasant feeling. This procedure was applied five times in order to obtain an accurate threshold value. The mean result of five measurements was considered as individual pain threshold value. Between every measurement, there is a 20 second interval to prevent habituation. Instead of a discrete measurement, continuous measurement gives a higher resolution of response to painful stimuli.

All measurements were taken from the dip joint between distal and proximal phalanx as shown in Figure 13. This region does not include a fatty area. Measurements from distal phalanx can vary and causes extreme results due to tissue flexibility. In Figure 14. it is shown that branch of median nerve is close to skin in dip joint.

Figure 13. Location of painful stimuli application onto the thumb.

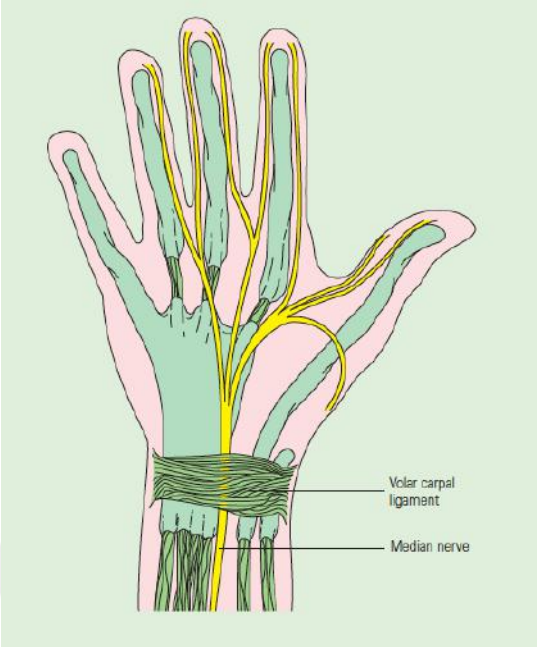


Figure 14. Median Nerve and its branches.
In this figure it is clear that our application points onto the thumb corresponds to the path that median nerve passes. (Hochberg et al., 2010)

3.2.Participants

3.2.1. Healthy Participants

17 healthy controls attended our study (15 female and 2 male participants; age: 36,2 ± 9,01, BDI score: 9,17 ± 8,78, education years: 16,7 ± 7,85). The inclusion and exclusion criteria were as follows.

Subject inclusion Criteria: Subjects with ages between 20-49, right hand dominant, no ongoing psychiatric or physical disorder.

Subject exclusion Criteria: Participants with psychiatric or nervous system disorder or other significant clinical conditions that cause chronic pain.

Some participants were disqualified during the setup because of excessive amount of hair which prohibited fNIRS signal collection.

3.2.2. Fibromyalgia Patients

19 FM patients attended (17 female and 2 male participants; age: 37,7 ± 5,86, BDI score: 19,63 ± 10,05, education years: 11,21 ± 6,07, FIQ : 61,31± 13,88, TP : 13,42 ± 2, Duration of illness: 4,32 ± 5,93).

- All methods and procedure were explained in details.
- They will feel experimental pain in their thumbs.
- Neither fNIRS system nor experimental pain will be harmful for them.
- They will give up participating study in any part of procedure.

Inclusion Criteria: Participants with age between 20-49 years, right handed, having more than 11 tender points for at least 3 months according to the ACR criteria (Wolfe et al., 1990) were included in this study.

Exclusion Criteria: Participants with psychiatric or nervous system disorder and that have other significant clinical conditions and who were taking their medications less than 12 hours ago, were excluded. Some patients were excluded from study because of less gain caused by excessive amount of hair while setting up probes.

3.3. Experiment Flow

After setting up 24-channel fNIRS cap to all participants, TENS stimulation and painful stimulation experiment were performed respectively to right and left hand.

3.3.1. Channel Positioning by EEG 10-20 System

fNIRS scans were carried out Using Hitachi ETG 4000 Continuous Wave Near Infrared Spectroscopy system. In this system 680 and 830 nm of near infrared wavelengths are used to observe the hemodynamic activity by considering Δc_{HBO2} and Δc_{HB}. Sampling frequency is 10 Hz. Optical light is sent to the head surface via a source optode and captured by a detector optode attached to a cap or grid. Optical light signals are converted to Δc_{HBO2} and Δc_{HB} by using Modified Beer Lambert Law (Cope & Delpy, 1988).

To maximize spatial accuracy, we utilized the EEG 10-20 electrode positioning system (Jasper, 1958) to position the source and detectors on to the head surface. In Figure 15. this system is shown in detail. In this positioning system, half of the distance from nasion to inion (Nz-Iz) corresponds to the channel Cz. After defining the position of Cz, we set the 3 x 3 probe holders for both hemispheres over the line of right ear and left ear.

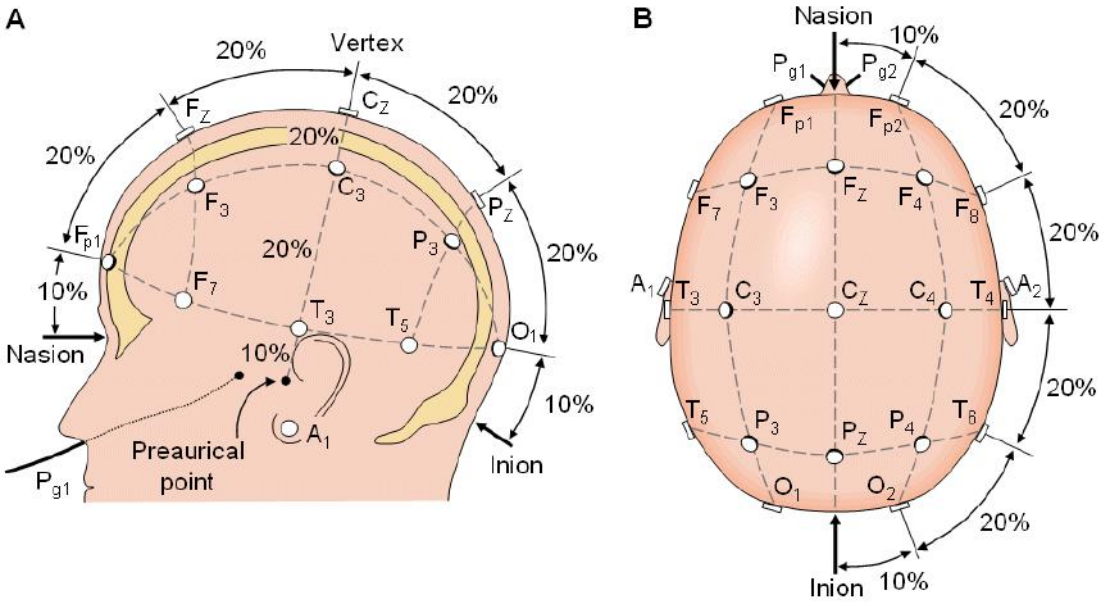
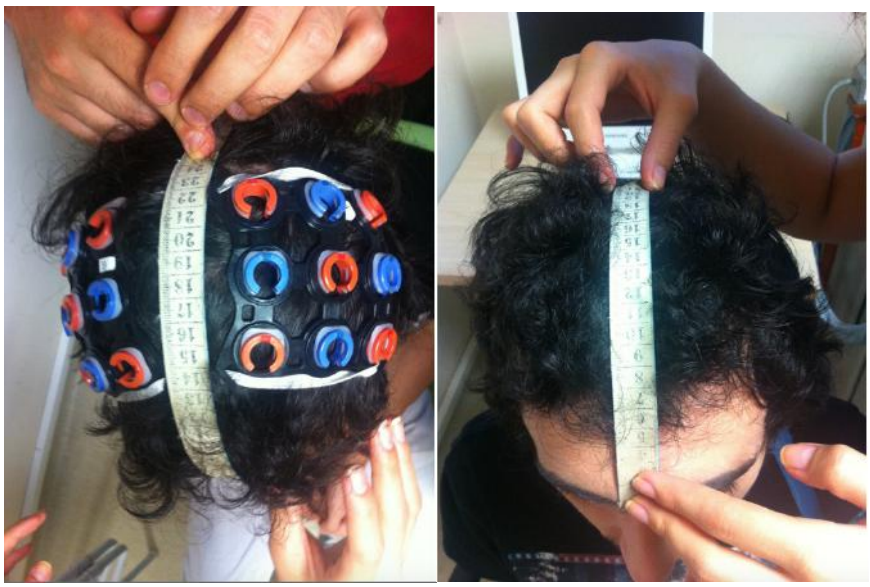


Figure 15. 10-20 System over the scalp from axial and sagittal view.
Distance is divided over 100 and 30 % from left tragus to right tragus corresponds to the C3 and opposite direction provides us to reach C4. 50 % of Nasion to Inion distance gives us Cz.

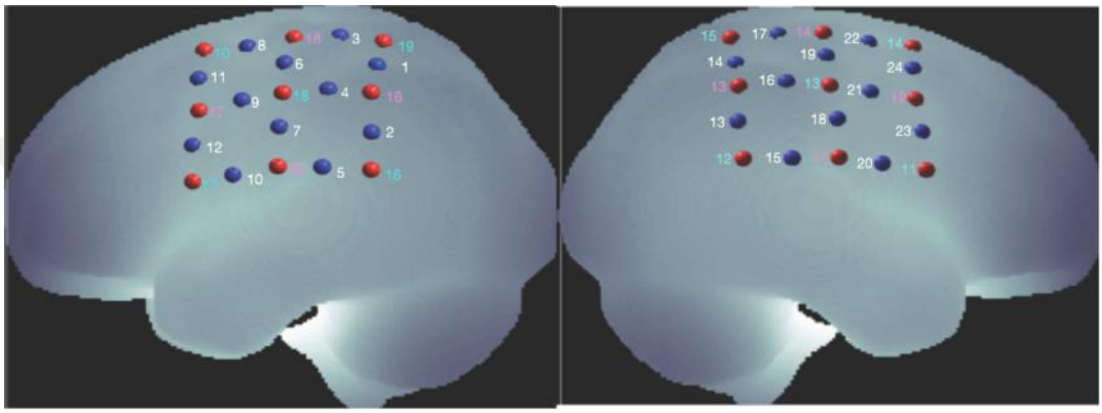
We defined the positions of C3 and C4 by measuring the distance between right tragus and left tragus as shown in Figure 16. 30 % of this distance give us the position of C3 from left tragus and C3 from the right tragus. According to several studies, C3 and C4 correspond to the left and right post-central gyrus respectively (Koessler et al., 2009; Okamoto et al., 2004). In light of this information, we set the center of 3 x 3 probe holder at these points as shown in Figure 16.



a) b)

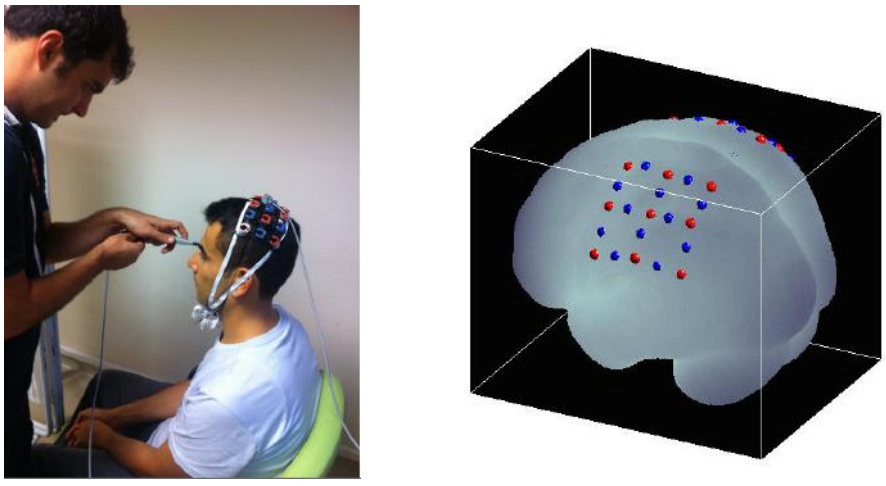
Figure 16. Probe Registration and Channel Position Measurements
a) Probe holder placement over the scalp. b) Distance from nasion to inion was measured.

We used the 2 x 3 x 3 optode configuration that includes 10 sources and 8 detectors and 24 channels as shown in Figure 17. In Figure 17, every channel is shown between one source and one detector. Channels 1-12 and 13-24 are located in left and right hemispheres respectively. Optode number 18 and 13 shown in red were placed onto the point C3 and C4 in left and right hemisphere respectively. After that probe holder placement, we marked optode positions by using 3D digitizer (Polhemus Co., Vermont, USA) to determine the exact position of every channel. Therefore we obtained the position file to use it for registering a MNI space to determine the landmarks that correspond to every channel position by using fNIRS Analysis Package (NAP) (Fekete et al., 2011a). An example is provided in Figure 18.



a) b)

Figure 17. Channel and probe positioning
(a) Left (b) Right view. Blue dots: locations of channels. Red dots: locations of the probes, White numbers : Channels, Pink numbers : Detectors, Cyan : Sources.



a) b)

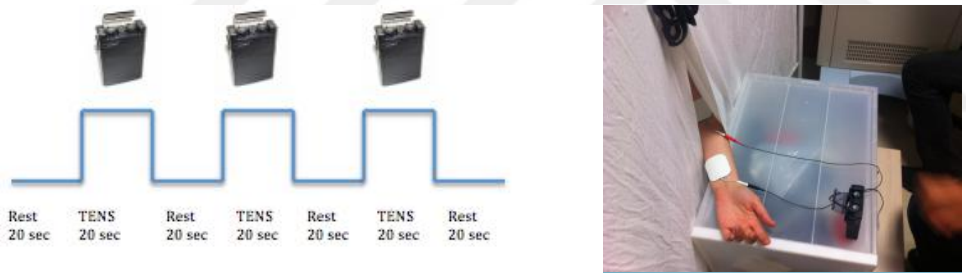
Figure 18. Probe positioning and registration in the MNI space.
a) 3D digitizer. b) MNI space.

3.4.Experimental Design

In our study, two experimental paradigms were used: One is for localizing the SI and the second one is our main experimental paradigm to study the effect of TENS in pain perception. Our experiments were applied initially for the dominant right and then to the non-dominant left hand. Between every experiment, participants were required to take a breath and relax.

3.4.1. Median Nerve TENS Stimulation Paradigm

In this experiment, we aimed to stimulate the median nerve to observe baseline TENS activity. While determining the TENS intensity, we first tested the intensity in every individual's forearm. We determined the TENS intensity threshold by asking them whether TENS causes a tingling effect in the forearm or not. We determined the actual intensity threshold as 30 mA which is almost similar in every individual. We used Intelect TENS (Chattanoga Co.) device with pulse width 60 μs, frequency 115 Hz and 30 mA current in asymmetric biphasic square wave waveform. We applied three blocks for 20 sec TENS stimulation and 20 sec resting state period. Marking the time blocks in the data were done by using E-prime 2.0 software (Psychology Software Tools, Pittsburgh, PA, USA). Experimental paradigm and application are shown in Figure 19.



a) b)

Figure 19. Median Nerve Stimulation paradigm via using TENS.
a) Task Design b) An application of TENS to left forearm

When a warning for TENS stimulation appeared on the screen the investigator initiated applying TENS stimulation. After the warning disappeared, a fixation appeared on the screen and so the investigator turned off the TENS device.

3.4.2. Pain and TENS Effect Paradigm

Our painful stimuli experiment consists of 6 blocks that includes 3 painful stimuli and 3 painful stimuli with TENS trial. Accordingly, the conditions in the experiment are named as 'Pain' and 'Pain+TENS'. Both blocks have 20 sec. stimulation and 40 sec resting period. While applying painful stimuli in 20 sec., 4 times eVF was applied on the dip joint of thumb. In every trial, after 4 sec. painful stimuli, there is 1 sec. of waiting period to prevent tissue deformation. Painful stimulation experiment design is shown in Figure 20 &Figure 21 respectively.

The amount of painful stimulation is set to the pain threshold of participant for related hand. For Pain + TENS block, TENS stimulation was applied with the same parameters as in TENS baseline experiment.

Before starting the painful stimuli experiment, participants were informed that after each block they will be asked to estimate the pain with a rating within a scale of 0 – 100 (No pain – Extreme pain). After every block, during resting period, participants gave a score based on their pain experience in the preceding block. Every score was recorded to the fNIRS Pain Experiment Report form.

TENS baseline and Painful stimuli experiments were carried out consequently for right hand and then left hand with the same order.

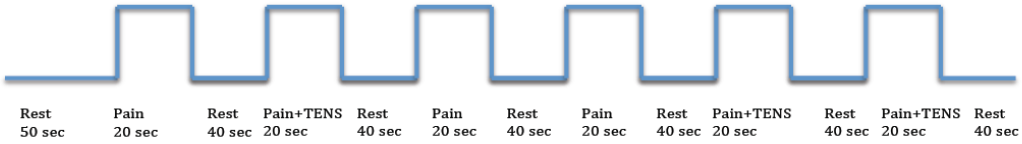


Figure 20. Pain and TENS effect experiment design

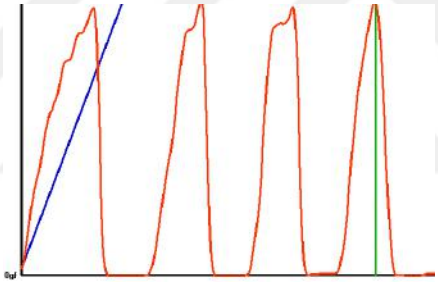


Figure 21. Painful stimulation trend in one trial.
X-axis: time (sec), y-axis : applied painful stimuli (gram force)
While applying painful stimuli, it is quite important to not to cause tissue deformation.
Red: Force applied to thumb, Green : Peak value of stimulation for a single pressure
Blue: Slope for initial pressure application.

3.5.Functional Near Infrared Spectroscopy Imaging Data Collection

Hemodynamic response is represented in fNIRS as increase in Δc_{HBO2} and decrease in Δc_{HB}. Because HBO2 concentration is directly associated with cerebral blood flow (CBF) and cerebral blood volume (CBV). This is called “Neurovascular Coupling” (Ferrari & Quaresima, 2012). In Figure 22. Relationship between $\Delta c_{HBO2}$and Δc_{HB} is shown. The generation of fNIRS signal from optical density is presented in APPENDIX D.

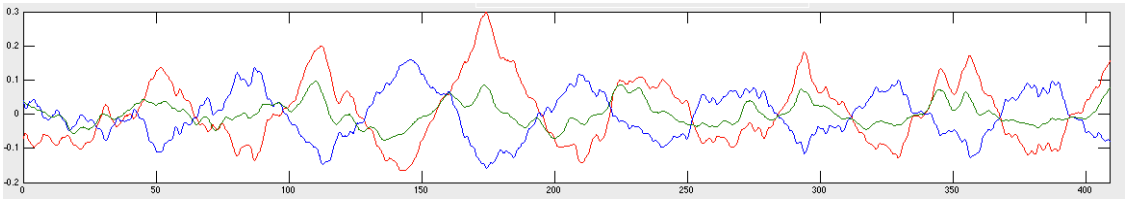


Figure 22. fNIRS time series.
Red: Δc_{HBO2}, Blue: $\Delta c_{HB}$and Green: total hemoglobin concentration change.

Near Infrared Spectroscopy signals include several types of artifacts introduced by experimental and subjective conditions. These artifacts can be grouped into 3 categories: Physiological artifacts, instrumental artifacts and experimental artifacts.

Generally, three types of physiological artifacts are available in literature. These are breathing artifact, cardiac pulsation and Mayer waves. Breathing artifact is generally observed approximately between 0.15-0.4 Hz while Mayer waves occur in approximately 0.05-0.2 Hz for adults. Heart pulsation is observed between 0.6- 2.0 Hz (Fekete et al., 2011a) as shown on Figure 23. This band consists high frequency noise components for hemodynamic response. A low pass filter, with has a cut off frequency at 0.05 Hz will be enough to remove out these artifacts.

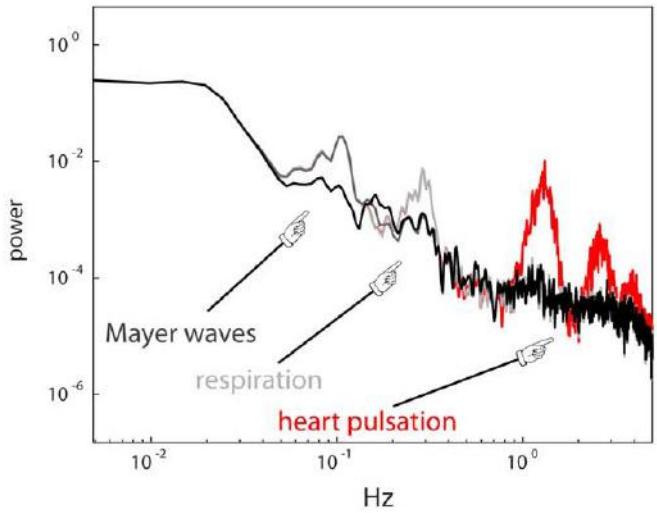


Figure 23. Power spectrum of physiological noises in fNIRS signals.
(Fekete et al., 2011a).

Instrumental artifacts generally demonstrate a Gaussian behavior. They are high frequency artifacts caused by sensors or an electrical interference from device. To remove such artifacts, a low pass time or frequency domain filter will be enough. Experimental artifacts generally occur in block- design studies due to cumulative activity trend caused by consecutive stimulation. In this activity trend, it is shown that, activity includes a linear drift with a constant slope as shown in Figure 24. To remove this artifact, a basic detrending function can be enough. However, there

might be losses from hemodynamic activity while removing out this artifact, so wavelet based minimum description length detrending method is an ideal method to remove it (Jang et al., 2009).

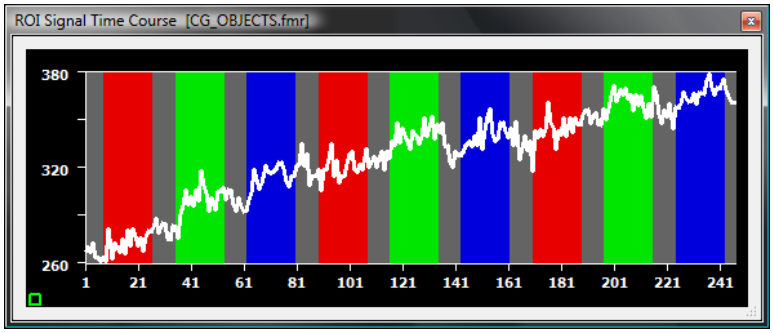


Figure 24. Linear trend in an fMRI signal.
(taken from www.brainvoyager.com)

Experimental artifacts are mostly presented in terms of head motion in fNIRS studies. These head movements can occur suddenly during experiment because participants may need to move their body. Head motion artifact generally seems to have an oscillatory behavior with frequency depending on speed of motion. To remove this artifact, different types of filters were used such as Principal Component Analysis (PCA) (Zhang et al., 2005), Wiener filtering (Izzetoglu et al., 2005), Kalman filtering (Izzetoglu et al., 2010), correlation based signal improvement (Cui et al., 2010), spline interpolation (Scholkmann et al., 2010) and wavelet filtering (Molavi & Dumont, 2012). In Figure 25. results of wiener filter onto fNIRS data with motion artifact was observed.

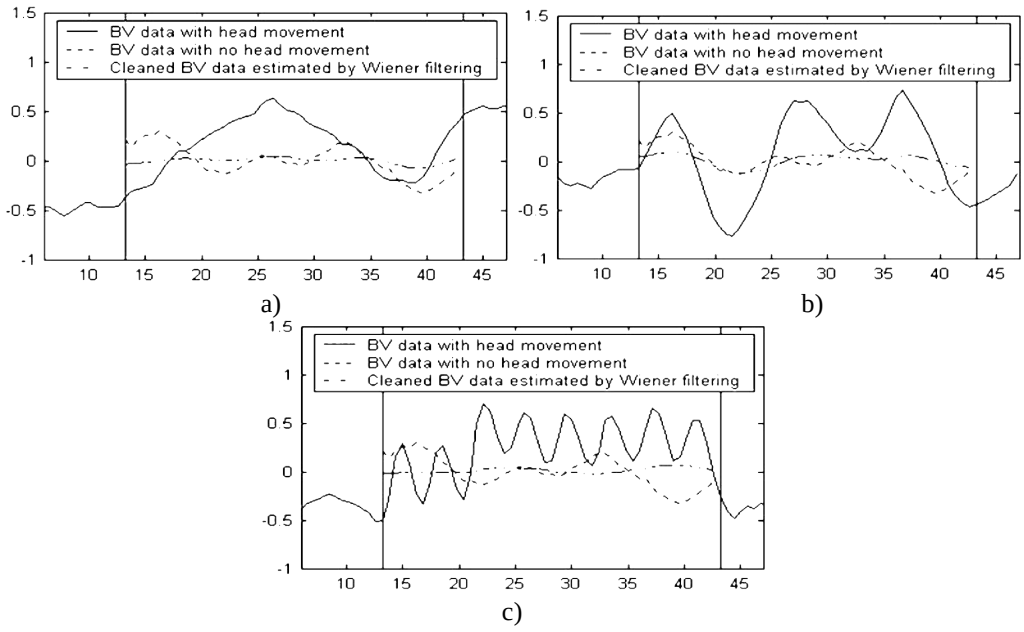


Figure 25. Motion artifact reduction by using Wiener filter
a) low head motion, b) medium head motion c) high head motion (Izzetoglu et al., 2005).

3.6.Data Analysis

Our data analysis pipeline includes pre-processing, identification of anatomical position of channels, generation of fNIRS activity profiles using the experimental conditions and classification of healthy controls versus FM patients. The entire data analysis pipeline was carried out using MATLAB (The MathWorks, Inc., Natick, MA, USA). We directly obtained the raw Δc_{HBO2} and Δc_{HB} data from fNIRS system without applying any filter or correction method.

3.6.1. Pre- processing Steps

Δc_{HBO2} and Δc_{HB} signals include several types of artifacts explained above. Before applying any noise removal filter, baseline correction was applied to detect the activity trend by observing negative peaks in Δc_{HB} and positive peaks Δc_{HBO2} during activity blocks. The baseline correction method eliminates the DC component from physiological signal. To observe the signal in a standard baseline pattern, average of pre-stimulus value in a defined amount of time is subtracted from the response data.

Wavelet Based De-trending filter was used to remove the signal drifts (Jang et al., 2009) using Minimum Description Length (MDL) (Rissanen, 1978) method. Details of this filter are shown in APPENDIX E. In Figure 26. Raw data and baseline corrected, low pass filtered (0.05 Hz cut off frequency) and wavelet based linear detrended data are shown.

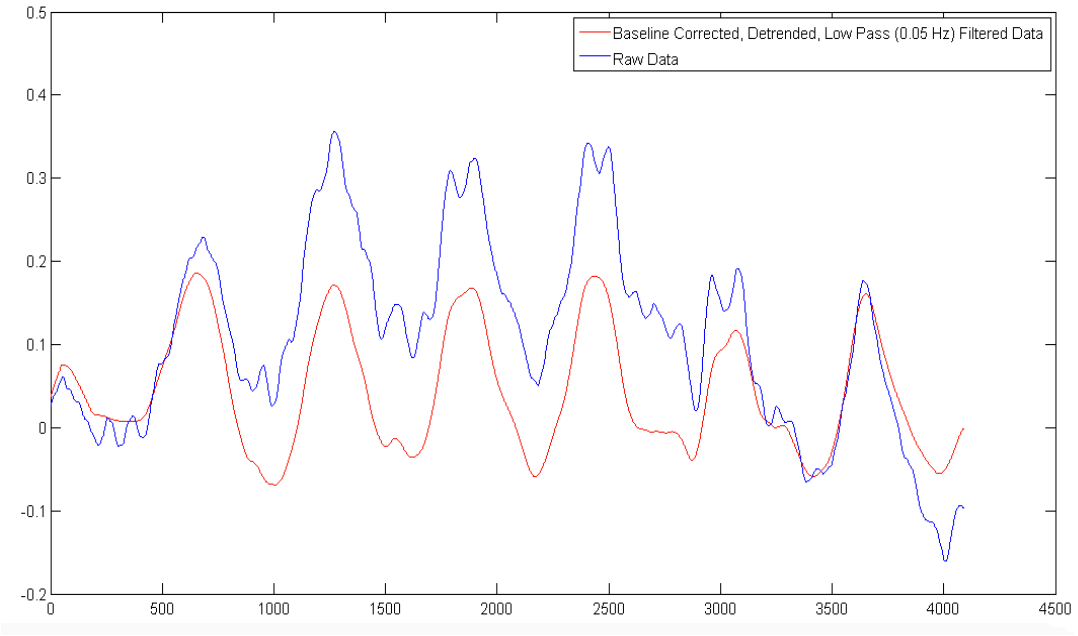


Figure 26. Filtering fNIRS signals. Blue : Raw data, Red : Baseline corrected, detrended and low pass filtered (0.05 Hz) data.

We designed this filter that has a cut-off frequency at 0.05 Hz as a FIR filter that corresponds to the 0.31 rad/sec and its stop-band frequency is 0.052 Hz that

corresponds to the 0.33 rad/ sec. Its stopband attenuation is -65 dB and Kaiser window was used to model the filter. In Figure 27. magnitude response of designed filter is shown.

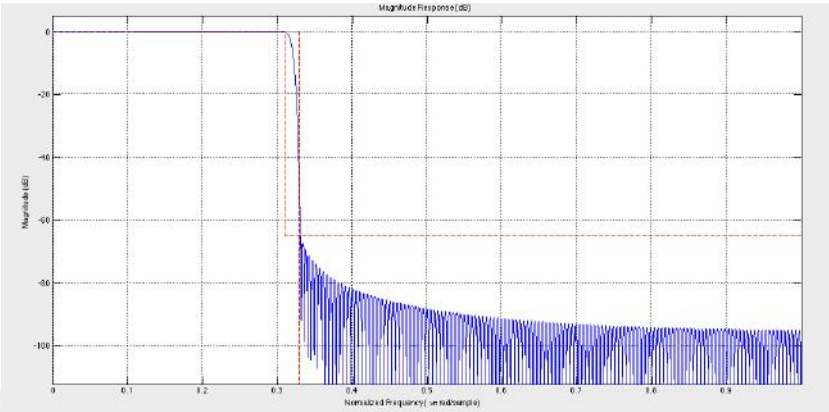


Figure 27. Magnitude response of FIR filter that was used to remove out physiological artifacts

After filtering, we applied amplitude thresholding method either for Δc_{HBO2} and Δc_{HB} data in order to remove out channels with excessive noise. In Δc_{HBO2} data we adjusted amplitude threshold for maximum value to 1 and minimum value to -1. If amplitude exceeds this value, related Δc_{HBO2} and Δc_{HB} channel is removed.

3.6.2. Probe Position Registration and Association with Cortical Structures

For every participant, we obtained fNIRS probe positions and registered to the MNI space via an algorithm embedded in fNIRS Analysis Package (Fekete et al., 2011b). After obtaining coordinate values for every participant, we averaged the coordinate values (Okamoto et al., 2004; Tsuzuki & Dan, 2014). To obtain brain regions that correspond to the average MNI coordinates; we used LONI Probabilistic Brain Atlas (LPBA40) (Shattuck et al., 2008) . In Table 4, channel numbers with corresponding cortical structures are shown with the mean ± cumulative standard deviation coordinate values we obtained from our participants.

Table 4. Channel numbers and average coordinate positions.
Corresponding cortical structures registered onto MNI space after using LPBA 40 cortical atlas.
Probability values were obtained from LPBA 40 cortical atlas.(L : Left, R: Right)

Channel Number	Mean X	Mean Y	Mean Z	SD	Probability	Corresponding Cortical Structure
1	-40,77	-48,77	64,97	10,48	0,86	L Superior Parietal Gyrus
2	-59,55	-49,44	44,52	9,41	0,71	L Angular Gyrus
3	-31,02	-35,25	72,91	10,9	0,52	L Superior Parietal Gyrus
4	-53,88	-33,41	56,97	9,99	0,70	L Supramarginal Gyrus
5	67,22	-34,77	30,55	8,70	0,92	L Supramarginal Gyrus
6	-44,22	-20	65,22	11,12	0,82	L Post Central Gyrus
7	-62,38	-19,16	43,66	9,33	0,50	L Post Central Gyrus
8	-29,55	-5,38	70,33	11,96	0,45	L Pre Central Gyrus
9	-52,63	-5,02	52,94	10,42	0,73	L Pre Central Gyrus
10	-65,38	-5,44	25,66	9,43	0,78	L Post Central Gyrus

11	-39,11	9,83	59,52	11,66	0,97	L Middle Frontal Gyrus
12	-57,27	9,75	35,80	10,00	0,75	L Pre Central Gyrus
13	61,02	-50,91	43,69	8,30	0,93	R Angular Gyrus
14	42,13	-49,30	64,44	9,31	0,54	R Superior Parietal Gyrus
15	69	-36,58	30,69	7,94	0,65	R Supramarginal Gyrus
16	56,25	-34,80	56,77	9,40	0,83	R Supramarginal Gyrus
17	32,63	-34,97	72,94	10,31	0,52	R Superior Parietal Gyrus
18	64,94	-20,97	44,27	9,36	0,98	R Supramarginal Gyrus
19	46,36	-20,33	65,16	10,88	0,85	R Post Central Gyrus
20	68,02	-6,55	27,5	8,55	0,90	R Post Central Gyrus
21	55,50	-6	53,02	10,47	0,57	R Post Central Gyrus
22	31,94	-5,11	69,75	11,50	0,69	R Pre Central Gyrus
23	59,86	8,86	37,05	9,54	0,93	R Pre Central Gyrus
24	42,13	9,97	59,02	10,95	0,81	R Middle Frontal Gyrus

3.6.3. Patient and Healthy Control Classification

In this study, after preprocessing steps, we carried out classification between conditions and groups. Among several types of classification methods, we applied Support Vector Machine (SVM) method. We used Dynamic Time Warping (DTW) method to extract a new feature in order to increase accuracy of classification. DTW distance can be measured between the hemodynamic response and Δc_{HBO2} response obtained from each participant.

DTW measures the similarity between two time series that can change in time. This similiarity metric is DTW distance which is between hemodynamic response (HDR) that we obtained from our experiment and hemodynamic response function (HRF) that we created via spm_hrf function in Statistical Parametric Mapping (SPM) (Friston, 2007). Hemodynamic response (HDR) and hemodynamic response function (HRF) are different terms. Hemodynamic response (HDR) is the response that we obtained during experimentally stimulated participant via fNIRS. Hemodynamic response function (HRF) can be explained as “modeled hemodynamic response” by several parameters such as;

- delay of response : time that peak value of signal was reached.
- delay of undershoot : time that hemodynamic response goes under baseline and then fits to baseline.
- dispersion of response : width of hemodynamic response from initial dip to undershoot.
- dispersion of undershoot : width of hemodynamic response from undershoot to end of kernel.
- ratio of response to undershoot : time ratio between response and undershoot for scaling.
- onset : time between the end of applied stimulus and initial dip of hemodynamic response.
- length of kernel : duration for hemodynamic response function.

Parameters of a HRF function are shown in Figure 28.

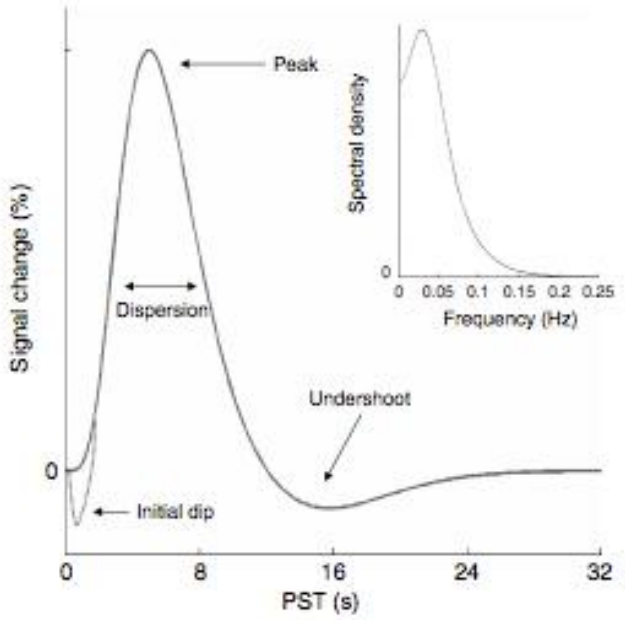


Figure 28. Typical BOLD impulse response and its power spectrum. (Friston, 2007).

HRF is generally used in GLM analysis to obtain more accurate β values which indicate the similarity between the HRF and HDR. We used both these data by finding DTW distance between them to create a significant feature for our classification. Because, as we mentioned above, if there is a significant difference between hemodynamic responses of FM and healthy control groups, DTW distance will also be different.

To create the feature vector, we used 6 different features obtained from stimulation of right and left hand (6 x 2 = 12 features). These are;

- Peak Δc_{HBO2} value of hemodynamic response during the pain-only condition stimulation.
- Peak Δc_{HBO2} value of hemodynamic response during the pain + TENS condition stimulation.
- Mean Δc_{HBO2} value of hemodynamic response during the pain-only condition stimulation.
- Mean Δc_{HBO2} value of hemodynamic response during the pain + TENS condition.
- Dynamic Time Warping (DTW) distance between the boxcar function convolved with Hemodynamic Response Function (HRF) signal and the Δc_{HBO2} signal during the pain only condition.
- Dynamic Time Warping (DTW) distance between the boxcar function convolved with Hemodynamic Response Function (HRF) signal and the Δc_{HBO2} signal during the pain + TENS condition.

While selecting these features to classify patient and healthy controls, a common finding in several painful stimulation fMRI studies was considered. Painful stimulation causes a higher activity in FM patients than healthy controls (Cook et al., 2004; Giesecke et al., 2004; Gracely et al., 2002; K. B. Jensen et al., 2012; Pujol et al., 2009). Due to having performed a similar experiment, we thought that we can use this significant difference as a discriminating feature for classification of FM and healthy controls. Mean or maximum peak value of hemodynamic response can be an ideal discriminative feature for those two groups. Parameters of HRF function are (in secs) ;

- Delay of response : 16
- Delay of undershoot : 30
- Dispersion of response : 4
- Dispersion of undershoot : 4
- Ratio of response to undershoot : 10
- Onset : 6
- Length of kernel : 40

Choosing DTW similarity metric as a discriminative feature was also relevant with the same common finding mentioned above. By using similar HRF, we can compare both groups by using hemodynamic responses of “Pain only” and “Pain + TENS” condition. A graph between a “Pain only” trial and HRF function that with the parameters as above is shown in Figure 29.

We chose length of kernel as 40 sec. Because despite having a 20 sec ON period in our experiment, hemodynamic response also needs an extra time for refractory and resting state period, after applying painful stimulation. By using these features, we created a hemodynamic response function which we assumed as ideal. Then we measured the distance between this hemodynamic response and single block averaged hemodynamic response for both conditions (“Pain only” & “Pain +TENS” in both hand (Right & Left) separately.

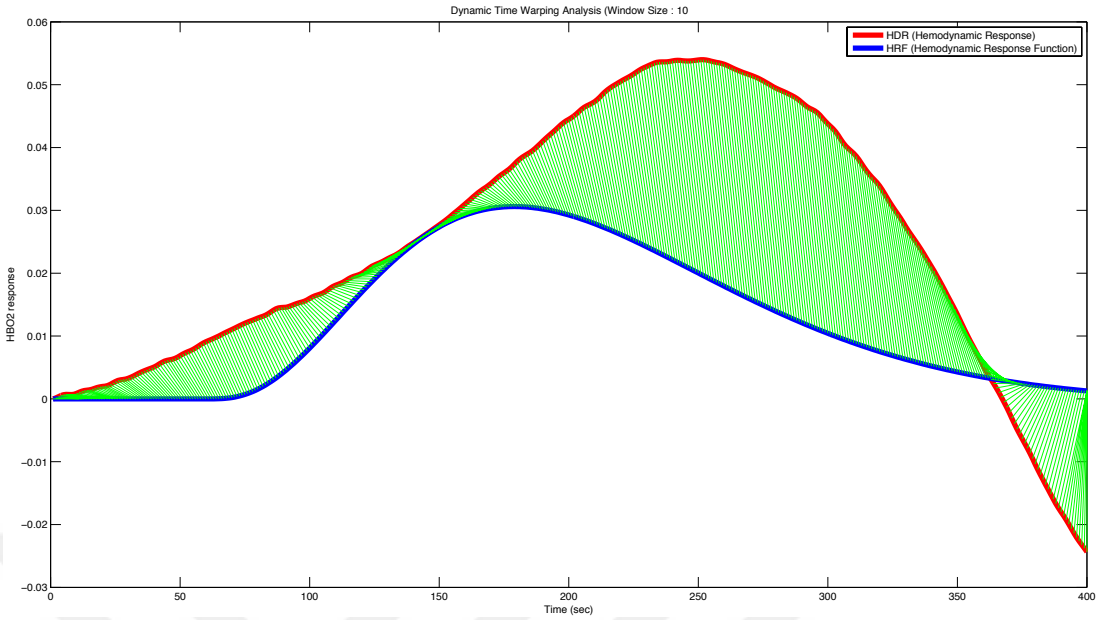


Figure 29. DTW Distance between Hemodynamic Response Function (HRF) and HBO2 data for one block. (window length =10).

During these analyses, we chose DTW window length as 10 after several trials. After creating feature vector for each subject for every 24 channels, in order to not to encounter a curse of dimensionality problem, we reduced the dimensions to 4, making sure that carry at least % 80 variances of features by using Principal Component Analysis (PCA). We created classification maps for SVM using sensitivity, specificity, accuracy and precision results.

We also analyzed the FM and healthy control classification by using self-reports (BDI score, Pain threshold of both hands). We did not use pain ratings because there is no significant difference found between groups, hands and conditions, which will be mentioned in Chapter 5. We applied the same procedure that we used for hemodynamic data. However, we only performed SVM classification by using different kernels (linear, polynomial (2-10th order), radial basis function).

In order to find brain activation differences between experimental conditions, we used the widely known General Linear Model (GLM) Analysis.

3.6.4. Post- Processing Steps

3.6.4.1.Dynamic Time Warping

Dynamic Time Warping (DTW) distance between the boxcar function convolved with Hemodynamic Response Function (HRF) signal and the BOLD response during the stimulation time, depicted as HDR is computed as follows.

Dynamic time warping (DTW) is a similarity measurement algorithm that is generally used for two time series that varies in time or speed. It was developed by

Sakoe and Chiba in 1978 (Sakoe & Chiba, 1978) for speech recognition. It finds an optimal match between two time series that might include stretched and compressed parts. To achieve this, it minimizes the total distance between these two time series. For time series, $X = [x_0, x_1, x_2 \dots \dots . x_{N-1}]$ and $Y = [y_0, y_1, y_2 \dots \dots . y_{N-1}]$ that have the same length N, a distance matrix A is constructed that has NxN dimensions. We can assume X as hemodynamic response function (HRF) that is a template function that we created for and assumed as ideal hemodynamic response for our further analysis and Y as hemodynamic response obtained from our experiment.. For every index of A ;

$$A_{ij=}d(x_i, y_j) \text{ (1)}$$

show the Euclidean distance between x_i and h_j. Primary objective of this method is to find the path that minimizes between two time series that starts from the index (0,0) to (N-1,N-1). This way is called Warping path.

$$W = [w_0, w_1, \dots \dots . . w_k] \text{ (2)}$$

If we assume time indices a and c for one time series and b and d for other time series, k^{th} and $k\text{-}1^{th}$ point in our warping path can be identified as $w_k = (a, b)$ and $w_{k-1} = (c, d)$ and this warping path should provide following conditions ;

Monotonic condition : In warping path indices does not go back in time domain. This provides that time points are not repeated in warping path. Indices can stay same or increase. These points ensures that

$$a - c \geq 0 \ \& \ b - d \geq 0 \text{ (3)}$$

Continuity condition : Warping path advances one step at a time. Index change between a-c and b-d can be less or equal to one. Equation $a - c \leq 1 \ \& \ b - d \leq 1$ (4) shows this condition.

$$a - c \leq 1 \ \& \ b - d \leq 1 \text{ (4)}$$

Boundary condition : The path should start from A(0,0) and finish A(N-1,N-1). Because, path should follow

Warping window condition : An ideal alignment path onto distance matrix A can not be too far from the diagonal of this matrix. For warping window length r,

$$|\text{a} - \text{b}| > \text{r} \ \& \ |\text{c} - \text{d}| > \text{r}. \text{ (5)}$$

In DTW, warping matrix is created by using linear programming. To find the minimum distance between two time series, first Euclidean distance $d(x_i, y_j)$ should be found and defined as cost value. Then, to proceed in the warping matrix, minimum value of the neighboring cells (D (i-1,j-1), D(i-1,j) , D(i,j-1)) is chosen and

the D(i,j) can be found by the following formula. In Figure 30, proceeding of warping path is shown on the a distance matrix.

$$D(i,j) = \mathrm{d}(x_i, y_j) + \min\left(D(i-1,j-1), D(i-1,j), D(i,j-1)\right) \quad (6)$$

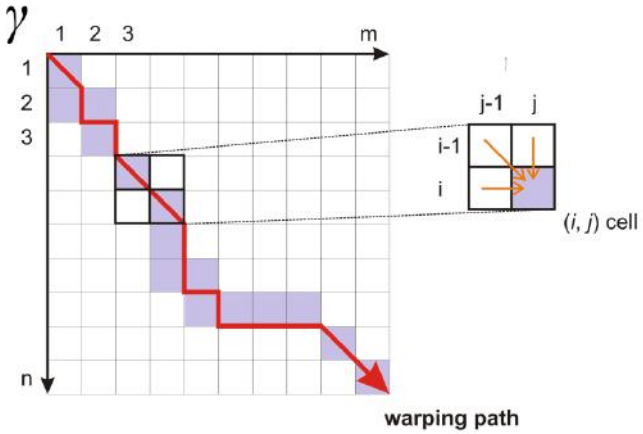
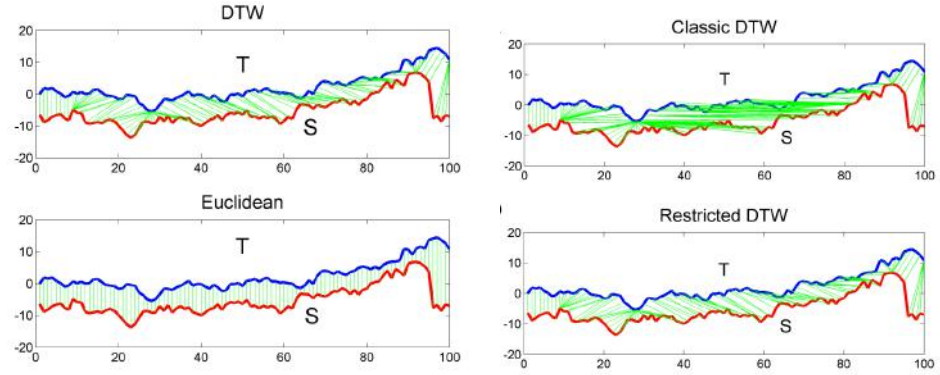


Figure 30. A distance matrix and warping path on it using Dynamic Time Warping. (Taken from (Cassisi C., 2012))

In this method, time dependency of both time series is eliminated. Since the BOLD response usually shows a significant delay after stimulus onset and by defining the delay time and related time points we find the similarity distance between fNIRS time series and hemodynamic response function convolved with boxcar function.

In Classic DTW, every point of a time series can be mapped to other time series. So this causes unexpected results as shown in Figure 31.a. To overcome this problem we used a window parameter to restrict the analysis part. We found the Euclidean distance between HDR function inside window length that we defined and every time point of fNIRS data. In Figure 31.a, difference between Dynamic Time Warping and Euclidean distance two graphs shows the distance mismatches between two time series when one of the time series was shifted in time. In Figure 31.b. the difference between classic DTW and restricted (windowed) DTW is shown. In classic DTW, even distance of furthest indices can be measured and added to distance value. But, in restricted DTW, if the restriction parameter is known, maximum similarity –means minimum distance- can be measured between both time series. Time delay between BOLD response and boxcar function can vary according to the experimental conditions.



(a) (b)

Figure 31.Comparison of Dynamic Time Warping and Euclidean Distance. (Cassisi C., 2012)
a) Differences between Dynamic Time Warping and Euclidean Distance
b) Differences between Classic DTW and Restricted (Windowed) DTW.

In Figure 32, we detected the warps in a block between the hemodynamic response function and BOLD signal for window length 5 time points that corresponds to the 0.5 sec for 10 Hz sampling rate of fNIRS system. To maximize the similarity, we empirically decided about this window that corresponds to the delay between hemodynamic response function (HRF) and BOLD signal (HDR).

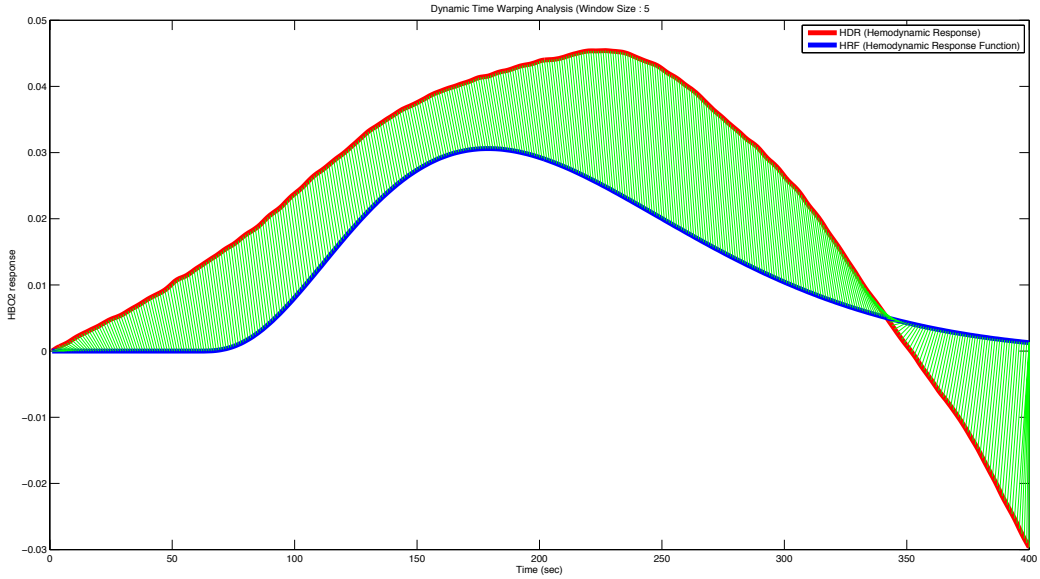


Figure 32. DTW results of Hemodynamic response and Hemodynamic Response Function that we created (Red : Hemodynamic response we obtained from our experiment, Blue : Hemodynamic response function, Green : lines that shows the warps between two time series. Window length=5).

3.6.4.2.1st Level General Linear Model (GLM) Analysis

GLM analysis is used to obtain functional maps of individual subjects. GLM uses least squares estimation to obtain experimental β coefficients that represent a fit to the ideal HRF waveform generated from the flow of the experimental task for each specific condition. 1st level GLM analysis was carried out by using fNIRS Analysis Package (NAP). We obtain β coefficients of Pain and Pain + TENS related activations in Painful Stimuli experiment.

$$Y_{i,k} = X\beta_{i,k} + \varepsilon_{i,k} \quad (7)$$

$$\beta_{i,k} = (X^T X)^{-1} X^T Y_{i,k} \quad (8)$$

Such that X represents the regressors generated from HRFs, ε is the assumed zero mean Gaussian noise N (0, σ). i represents the channel and k represents the subject.

By using β values, we directly estimate the F maps for 24 channels that represents the difference between Pain / rest, Pain / Pain + TENS and Pain + TENS / rest.

3.6.4.3.2nd Level GLM Analysis

In 2nd level GLM analysis, we also analyzed the all data for every group and every hand by using Beta values. Therefore, we obtained 4 different estimates for median nerve TENS stimulation paradigms as well as Pain and TENS effects.

- FM group for left hand
- FM group for right hand
- HC group for left hand
- HC group for right hand

For our median nerve TENS stimulation we have only “TENS” condition. So, we just did “TENS / rest” paradigm. In Pain and TENS effect paradigm, we have two conditions “Pain only” and “Pain + TENS”. We did “Pain / rest”, “Pain + TENS / rest” and “Pain / Pain + TENS” comparisons for this paradigm.

3.6.4.4.Group Comparison

To compare FM patients and healthy controls for Pain only and Pain +Tens conditions, we performed a 2 x 2 (Group x Condition) between – within design repeated measures ANOVA. This statistical analysis is done for every channel and both hands (right & left) separately using either beta values obtained from GLM estimation or mean Δc_{HBO2}. We compared the means of significantly different factors for every channel to observe which group, hand or condition was differentiable.

CHAPTER 4

RESULTS

In this part, we performed all analyses by using SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.) and MATLAB (The Math Works, Inc., Natick, MA, USA). Shapiro- Wilk test was applied to all data to determine whether the data distribution is normal or not. Based on this result, we applied parametric or non-parametric tests. When we observed a group of data is normally distributed and the other is skewed, we applied Box-Cox transformation to transform the data into a normal distribution.

4.1.Clinical and Demographic Information of Patient and Control Groups

36 participants attended our study. In fibromyalgia (FM) group, 19 patients that includes 17 female and 2 male participants and in healthy control (HC) group 17 healthy controls that includes 15 female and 2 male participants were recruited. Clinical and demographic information of participants and statistical results are shown in Table 5.

Table 5. Clinical and Demographic Information of Participants

Variable	FM patients (n=19)	Healthy Controls (n=17)	Statistical significance between FM and HC
Age	37.7 ± 5.8	36.2 ±9.0	p=0.538
Gender (M/F)	2/17	2/15	p=1.000
Education Level (years)	11,21 ± 6,07	16,7 ± 7,85	p=0.021
Menstrual Phase[1]	1/8/8	1/8/6	p=1.000
BDI score	19,63 ± 10,05	9,17 ± 8,78	p=0.002
FIQ score	61,31± 13,88	-	-
Number of Tender Points	13,42 ± 2	-	
Disease Duration (years)	4,32 ± 5,93	-	
Right Hand Pain Threshold (gramforce) Left Hand Pain Threshold (gramforce)	208.9 ± 54.0 183.3 ± 56.7	244.8 ± 46.8 242.5 ± 41.7	Group (p=0.009), Hand (p=0.025), Group x Hand (p=0.072)
Pain Ratings Right Hand Pain only Right Hand Pain + TENS Left Hand Pain only Left Hand Pain + TENS	 70.75±20.50 69.47±22.86 67.89±24.51 72.91±24.68	 64.27 ± 25.33 67.27 ± 24.86 64.84 ± 28.63 70.23 ± 28.38	Group (p=0.733), Hand (p=0.549), Condition (p=0.002) Group x Hand (p=0.648) Group x Condition (p=0.256) Hand x Condition (p=0.061) Group x Hand x Condition (p=0.372)

[1] Menstruation cycle information obtained from female participants is quantized according to the day they attended to experiment. Female participants were classified in menstrual cycle period as; post-menopause, Luteal or Follicular phases and these phases were quantized as 1,2 and 3 respectively.

Student's t-test showed that there is no difference between age values. Mann-Whitney U test shows that healthy controls are more educated than FM patients. There is only one participant in post-menopause period in both groups. When both groups were compared, Fisher's test shows that there is no significant difference between them.

On the other hand, Student's t-test showed that BDI scores between both groups differ. According to the BDI scores, FM patients show more tendencies to depressive symptoms.

A 2x2 (Group x Hand) one between and one within subject design Analysis of Variance (ANOVA) was applied on pain threshold results. As expected a significant difference between FM patients and healthy controls is found. Also, there is a significant difference between hands. Group and Hand interaction also show a marginally significant difference between hands. Post hoc analysis using Bonferroni adjustment showed that healthy controls showed higher pain threshold than FM patients. Also, right hand showed higher pain threshold than left hand.

Post hoc analysis using Bonferroni adjustment showed that healthy controls showed higher pain threshold than FM patients. Also, right hand showed higher pain threshold than left hand.

Mean and standard deviation values of subjective pain ratings for every experiment is shown in Table 6. for left hand and right hand pain stimulation. A 2x2x2 (Group x Hand x Condition) one-between and two-within factor design ANOVA was applied to the pain ratings collected after every painful stimuli application (where group: FM patients and Healthy Controls, hand: left and right, condition: "Pain only" and "Pain + TENS"). There is no significant difference between groups, hands, hand and group interaction, group and condition interaction and group, hand and condition interaction. But there is a significant difference between condition and marginally significant difference between hand and condition. Post hoc test using Bonferroni adjustment showed that ratings of "Pain+TENS" was significantly higher than "Pain only" ratings.

Table 6. Mean and standard deviation of pain ratings for two condition, two hand and two groups.

Hand & Condition / Group	Left Hand Pain	Left Hand "Pain + TENS"	Right Hand Pain	Right Hand "Pain + TENS"
FM patients	68,00 ± 24,48	73,00 ± 24,72	71,00 ± 20,52	69,00 ± 22,82
HC	66,12 ± 28,22	71,09 ± 27,71	65,09 ± 24,76	67,92 ± 24,22

4.2.Correlation Analysis of Psychophysical Results

Correlation analysis was applied to observe the statistical relationship between the psychophysiological measures. The correlation results can be found in Table 7.

4.2.1. BDI and FIQ Correlation

In the previous section, we showed that FM patients show higher depression levels compared with healthy controls. In order to observe the relationship between FM severity and BDI we estimated the Pearson's correlation coefficient between FIQ and BDI scores of FM patients. According to the results, there is a significant correlation between FIQ and BDI in FM patients (r=0.545, p =0.016).

4.2.2. BDI and Pain Threshold Results

BDI and Pain Threshold results analysis were done for both hands and both groups. Pearson's correlation results showed that; for FM patients, there is no significant correlation for left (r = -0.004, p= 0.986) and right hand (r= 0.245, p=0.312). Similarly, in healthy control groups, BDI scores are not correlated with pain thresholds in left (r=0.449, p = 0.070), however not in right (r =0.388, p = 0.123) hands.

4.2.3. BDI and Pain Rating Results

For FM patients none of the left and right hand pain ratings in the "Pain only" or "Pain + TENS" conditions were correlated with the BDI scores[2]. Also for healthy controls, none of the left and right hand pain ratings in the "Pain only" or "Pain + TENS" conditions were correlated with the BDI scores[3].

4.2.4. FIQ and Pain Thresholds with Pain Ratings

There are no significant correlations between FIQ score and pain thresholds of FM patients (Left hand: r= 0.272, p= 0.259; right hand: r= 0.109, p= 0.657).

For pain ratings, "Pain only" condition for left hand is marginally significant correlated with FIQ (r= 0.417, p=0.075), as well as "Pain + TENS" condition (r= 0.428, p= 0.067). For right hand, there is a significant correlation between "Pain only" condition and FIQ scores (r= 0.485, p=0.035). However, no significant correlation is found with "Pain + TENS" condition for right hand (r= 0.382, p= 0.106).

[2] For FM, correlation between BDI and Pain rating: Left hand "Pain Only" (r =0.408, p=0.083) and "Pain + TENS" (r=0.290, p =0.229) not significant. Right hand "Pain Only" (r=0.296, p =0.217) and "Pain + TENS" (r=0.246, p= 0.309) not significant.

[3] For HC, correlation between BDI and Pain rating: 1. "Pain only" condition for both hands (Left hand, r =0.143, p= 0.584; right hand, r= -0.016, p= 0.951) 2. "Pain + TENS" condition for both hands (Left hand, r = 0.197, p= 0.447; right hand, r= 0.003, p= 0.991).

Table 7. Correlation results between psychophysical measures.
** represents the significant values * represents the marginally significant values.
PPT : Pressure Pain Threshold, LH : Left hand, RH : Right hand.

	Fibromyalgia Patients						
Psychophysical Measures	BDI	PPT (LH)	PPT (RH)	Rating ("Pain only")		Rating (Pain +TENS)	
				Left	Right	Left	Right
FIQ	0,545**	0,272	0.109	0,417*	0,485**	0,428*	0,382
BDI	-	-0,004	0,245	0,408*	0,296	0,289	0,246

	Healthy Controls					
Psychophysical Measures	PPT (LH)	PPT (RH)	Rating ("Pain only")		Rating ("Pain + TENS")	
			Left	Right	Left	Right
FIQ	-	-	-		-	
BDI	0,448*	0,388	0.292	-0.030	0,227	0,090

4.3.fNIRS Data Analysis Results

In our study, we used only Δc_{HBO2} data for 1st and 2nd order GLM analysis, because increase in Δc_{HBO2} data shows us an increase in cerebral blood flow (CBF) and cerebral blood volume (Ferrari & Quaresima, 2012). This is an indicator of the hemodynamic activity in related channel and corresponding cortical region.

4.3.1. Individual Subject Analysis

After performing pre-processing steps mentioned in methods section manually, we used NAP to perform GLM analysis. We directly estimated the F maps by using β values obtained from GLM for individual analysis.

For median nerve TENS stimulation paradigm, we have only one condition. Hence GLM provides us one activation map for each hand. These maps are;

- Left hand "TENS" / rest
- Right hand "TENS" / rest

For painful stimuli paradigm, GLM provides us three activation maps for both hands. These maps are;

- Left hand "Pain only" / rest
- Left hand "Pain + TENS" / rest
- Left hand "Pain only" / "Pain + TENS"
- Right hand "Pain only" / rest
- Right hand "Pain + TENS" / rest
- Right hand "Pain only" / "Pain + TENS"

4.3.2. 2nd Level GLM Group Analysis Results

4.3.2.1.Group Analysis Results of Median Nerve TENS Stimulation

For both groups, TENS stimulation results for both hands were shown in APPENDIX G Table 19 and Figure 33. For FM patients, TENS stimulation to non-dominant hand showed us a significant activity in ipsilateral angular, bilateral superior parietal, bilateral post central, contralateral supramarginal and bilateral middle frontal gyri. Dominant hand TENS stimulation of FM patients results showed us significant activity in contralateral angular, bilateral post central, bilateral pre central, contralateral supramarginal, bilateral middle frontal gyri.

For healthy controls, non-dominant hand TENS stimulation showed us significant activity in bilateral superior parietal, ipsilateral angular, ipsilateral pre central, contralateral post central, contralateral supramarginal and contralateral middle frontal gyri. Dominant hand stimulation for healthy controls showed significant activity in ipsilateral angular, bilateral superior parietal, bilateral post central, ipsilateral supramarginal and contralateral pre central gyri.

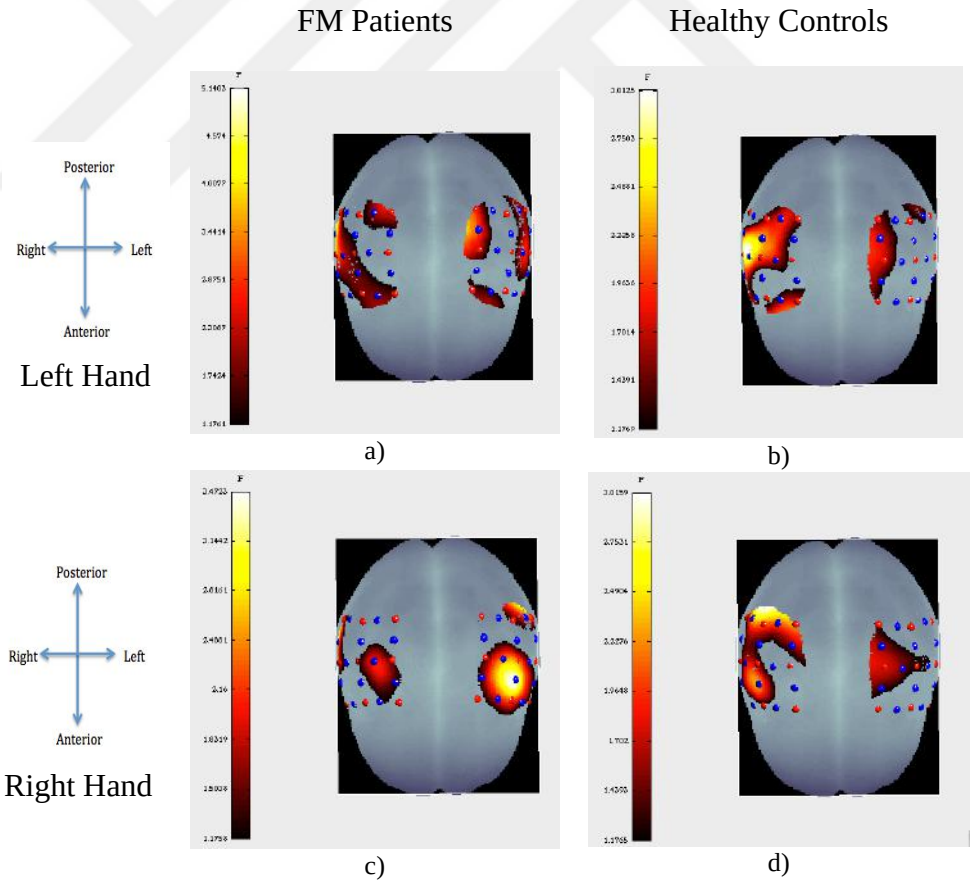


Figure 33. Results of Median Nerve Stimulation Experiment.
a) Left hand stimulation for FM patients b) Left Hand Stimulation for healthy controls
c) Right hand stimulation for FM patients d) Right hand stimulation for healthy controls.

Single block averages for all channels of left and right hand TENS stimulation for both groups were shown in Figure 34-Figure 37.

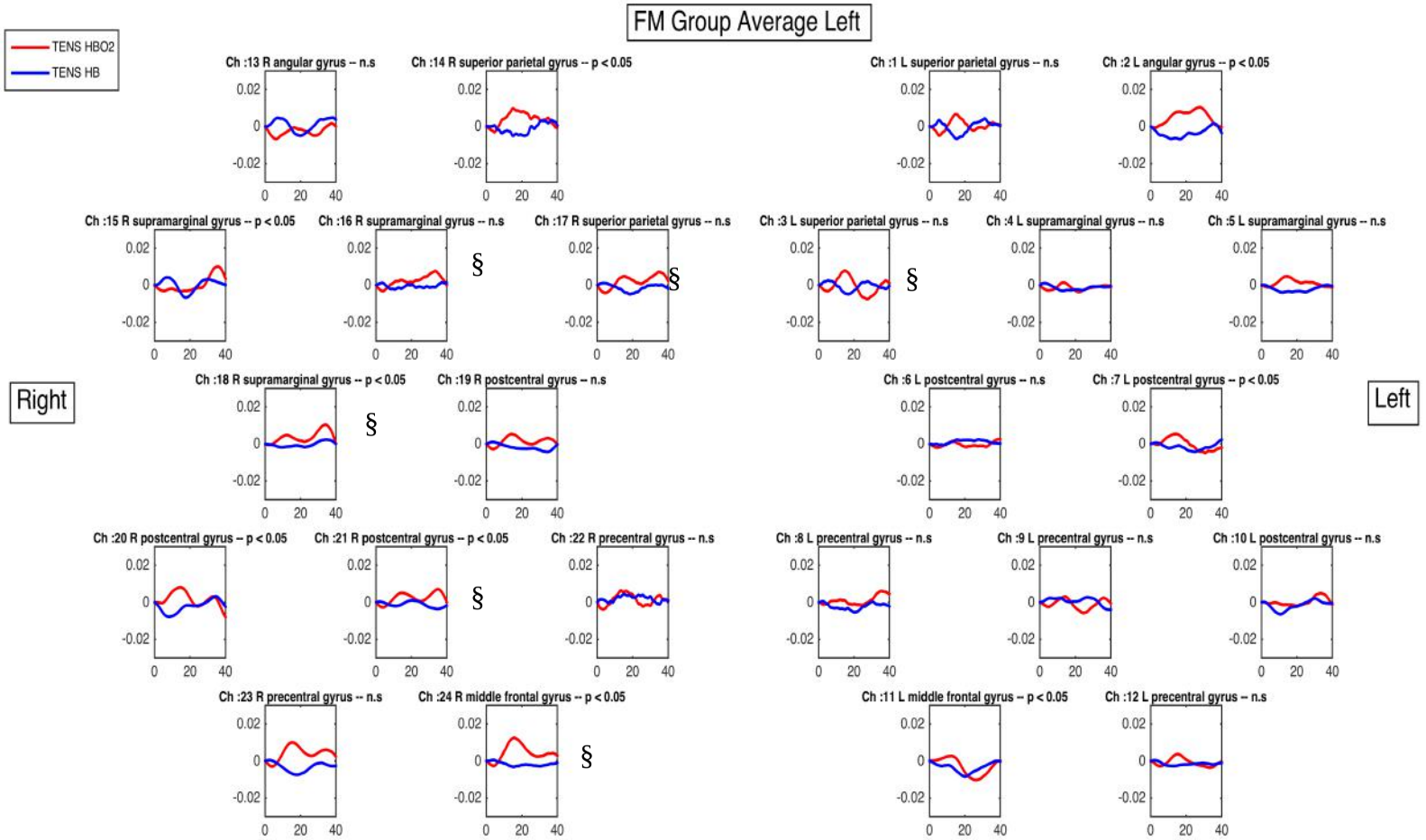


Figure 34. Left Hand Median Nerve Stimulation Group Block Average Results for FM patients.
In this Figure, Red represents Δc_{HBO2} and blue represents Δc_{HB}. y- axis shows the concentration change (mili molar, mM and x axis shows the time (sec). Significance shown on every graph is for 2nd llevel group analysis. n.s : Not significant, § : channels that show significant group (FM & HC) difference. ** : channels that show significant group (FM & HC) and hand (right & left) interaction.

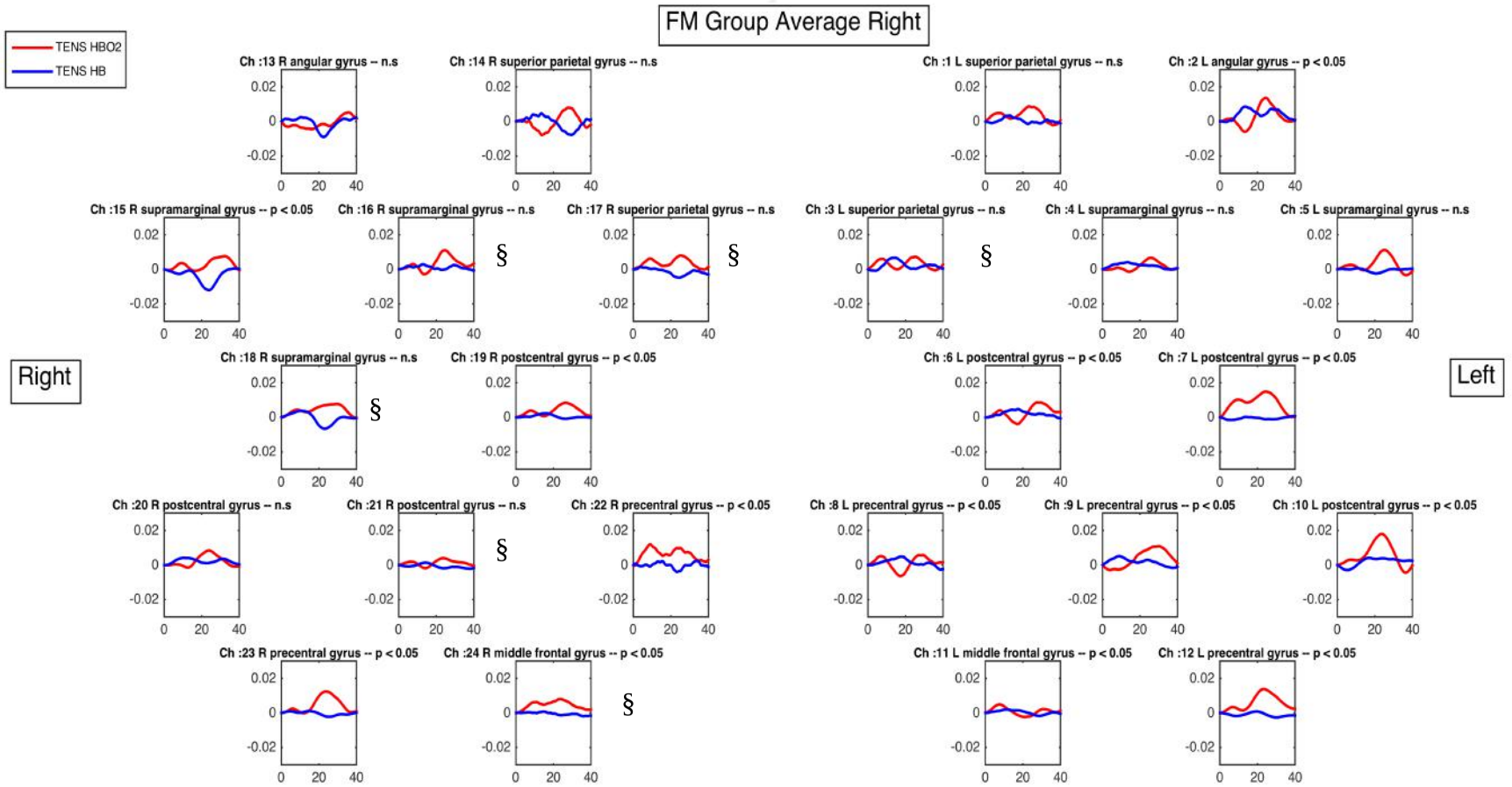


Figure 35. Right Hand Median Nerve Stimulation Group Block Average Results for FM patients.
In this Figure, Red represents Δc_{HBO2} and blue represents Δc_{HB}. y- axis shows the concentration change (mili molar, mM and x axis shows the time (sec).
Significance shown on every graph is for 2nd llevel group analysis. n.s : Not significant, .§ : channels that show significant group (FM & HC) difference.
** : channels that show significant group (FM & HC) and hand (right & left) interaction

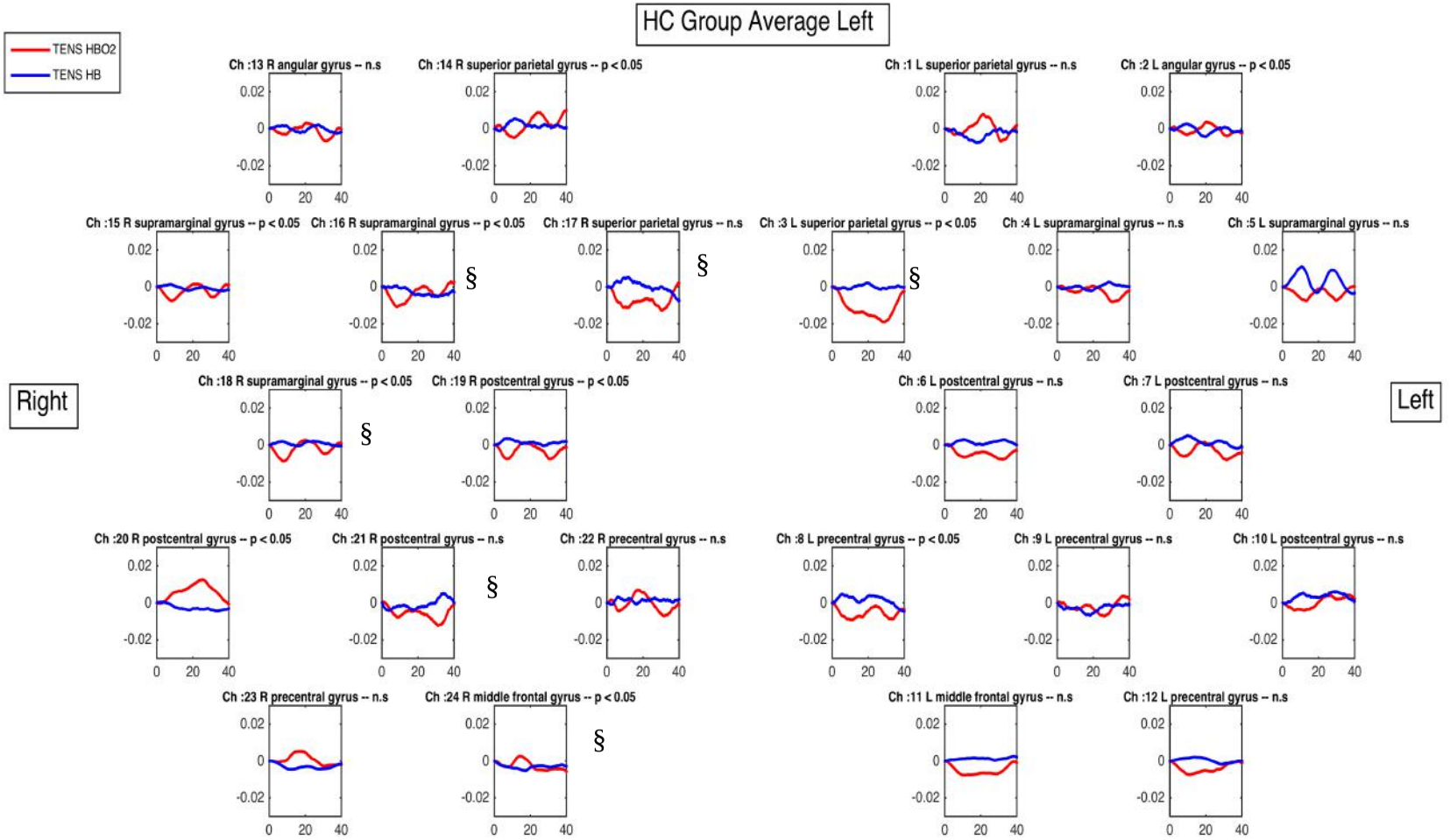


Figure 36. Left Hand Median Nerve Stimulation Group Block Average Results for Healthy controls.
In this Figure, Red represents Δc_{HBO2} and blue represents Δc_{HB}. y- axis shows the concentration change (mili molar, mM and x axis shows the time (sec).
Signifiance shown on every graph is for 2nd llevel group analysis. n.s : Not significant, § : channels that show significant group (FM & HC) difference.
** : channels that show significant group (FM & HC) and hand (right & left) interaction.

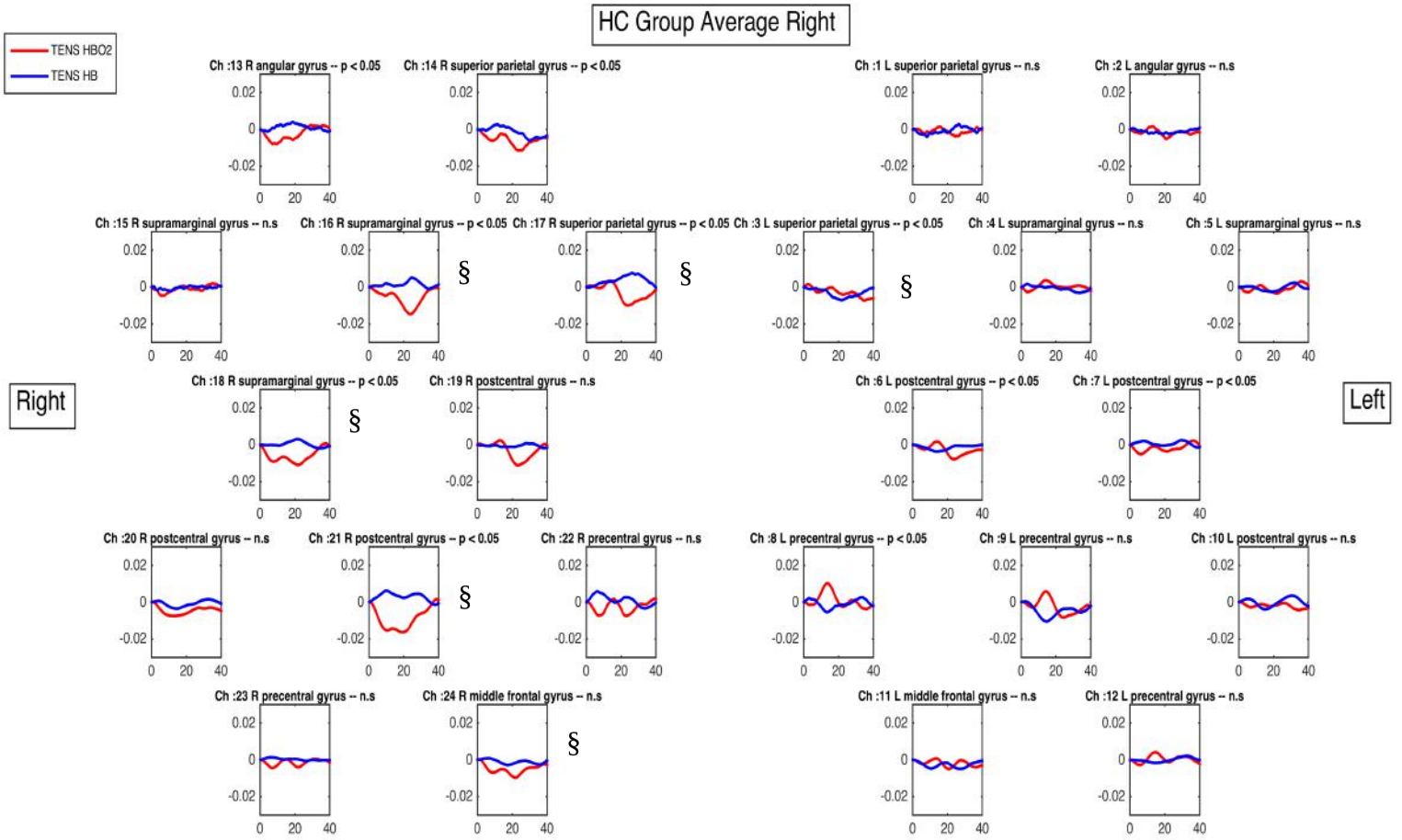


Figure 37. Left Hand Median Nerve Stimulation Group Block Average Results for Healthy controls.
In this Figure, Red represents Δc_{HBO2} and blue represents Δc_{HB}. y- axis shows the concentration change (mili molar, mM and x axis shows the time (sec).
Signifiance shown on every graph is for 2nd llevel group analysis. n.s : Not significant, § : channels that show significant group (FM & HC) difference.
** : channels that show significant group (FM & HC) and hand (right & left) interaction.

For group comparison, we applied a 2 x 2 (Group (FM & Healthy controls) x Hand (Right & Left)) between within design repeated measures ANOVA on the mean Δc_{HBO2} measurements. Results showed that there is a significant group difference in right and left superior parietal gyrus, right supramarginal, post central and middle frontal gyri. Pairwise comparison showed that FM patients showed higher activity than healthy controls. None of these regions showed significant difference in Hand main effect and Group x Hand interaction. All results are shown in Table 8.

Table 8. Group comparison of Median Nerve TENS Stimulation Experiment.
A 2 x 2 between-within design (Group (FM & HC) x Hand (Right & Left)) repeated measures ANOVA was perfomed by using mean Δc_{HBO2} values.
** and bold highlighted values represents statistically significant P values ($p<0.05$).

Channel	Region	Group	Hand	Group x Hand
1	Superior Parietal Gyrus	0,474	0,782	0,523
2	Angular Gyrus	0,153	0,658	0,845
3	Superior Parietal Gyrus	**0,031****	0,085	0,450
4	Supramarginal Gyrus	0,702	0,294	0,999
5	Supramarginal Gyrus	0,220	0,609	0,713
6	Post Central Gyrus	0,145	0,449	0,830
7	Post Central Gyrus	0,102	0,222	0,405
8	Pre Central Gyrus	0,296	0,238	0,264
9	Pre Central Gyrus	0,302	0,453	0,386
10	Post Central Gyrus	0,297	0,806	0,559
11	Middle Frontal Gyrus	0,523	0,201	0,897
12	Pre Central Gyrus	0,119	0,198	0,783
13	Angular Gyrus	0,993	0,938	0,562
14	Superior Parietal Gyrus	0,456	0,197	0,684
15	Supramarginal Gyrus	0,851	0,792	0,231
16	Supramarginal Gyrus	**0,021****	0,891	0,722
17	Superior Parietal Gyrus	**0,010****	0,291	0,611
18	Supramarginal Gyrus	**0,012****	0,544	0,434
19	Post Central Gyrus	0,065	0,690	0,594
20	Post Central Gyrus	0,744	0,168	0,133
21	Post Central Gyrus	**0,022****	0,398	0,704
22	Pre Central Gyrus	0,104	0,725	0,407
23	Pre Central Gyrus	0,153	0,803	0,725
24	Middle Frontal Gyrus	**0,007****	0,575	0,566

4.3.2.2.Group Analysis and Group Comparison of Painful Stimuli Experiment for Both Hand

We performed GLM analysis for FM and healthy control groups for right and left hands.

Left Hand Painful Stimulation Experiment Results

For non-dominant (left) hand of FM patients, three conditions ("Pain only" / rest, "Pain + TENS", rest and "Pain only"/ "Pain + TENS") are shown in Figure 38 and F values for every channel are shown in APPENDIX G Table 20.

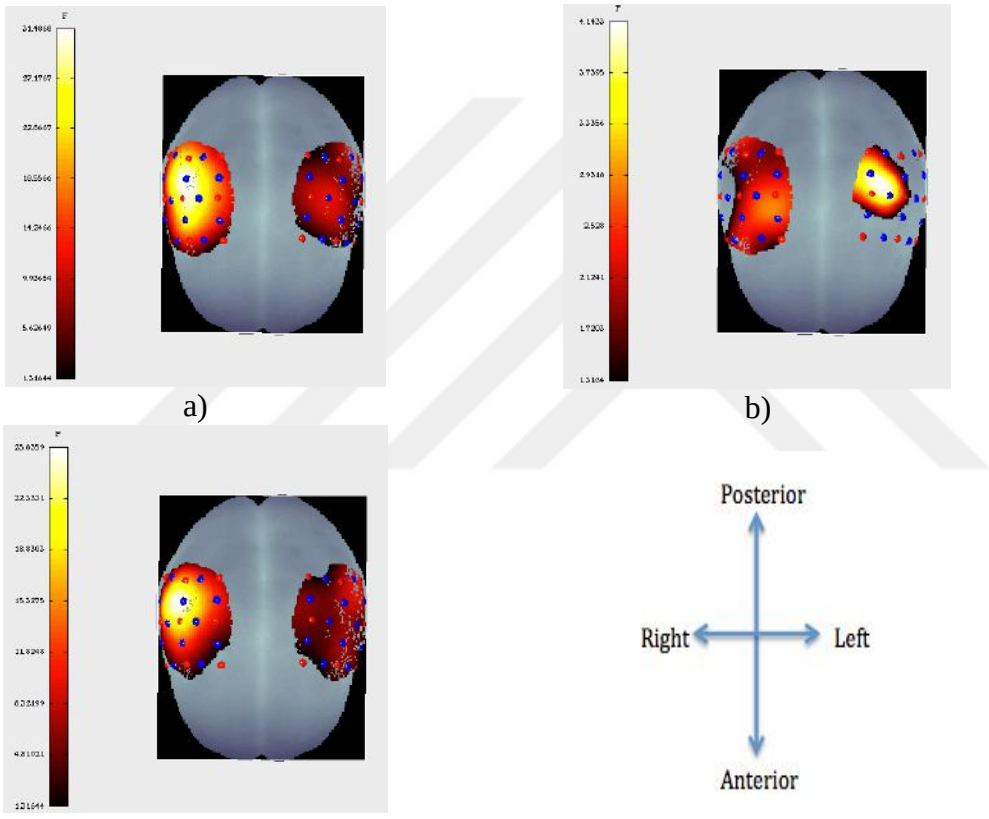


Figure 38. Left hand painful stimuli experiment results for FM patients.
Comparison of a) Only "Pain only" / rest condition b) "Pain only" / "Pain + TENS" conditions c) "Pain + TENS" / rest condition

In Figure 38.a. higher F values in contralateral than ipsilateral were observed in "Pain only" condition without using TENS. Bilateral superior parietal, Supramarginal, Post central, Middle Frontal and Pre central gyri showed a significant activity. These results show that higher contralateral activities were observed in post-central, supramarginal, superior parietal, pre-central, middle frontal and angular gyri.

Similar type of activity was observed in both hemispheres for "Pain + TENS" condition compared with only "rest" condition shown in Figure 38.c. Higher F values in contralateral than ipsilateral side were also observed. But F values decreased in all

contralateral regions and some regions in ipsilateral side like Supramarginal, post central, pre central and middle frontal gyri compared to only “Pain only” condition. In “Pain + TENS” condition, bilateral superior parietal, angular, supramarginal, pre central, post central and middle frontal gyri were activated.

In Figure 38.b. we compared “Pain only” and “Pain + TENS” conditions. Significant ipsilateral activity was observed in Superior Parietal and Post Central gyri. Also, significant contralateral difference was observed in angular, superior parietal, supramarginal, post central, pre central and middle frontal gyri. Block averages of all channels for left hand stimulation of FM patients are shown in Figure 39.

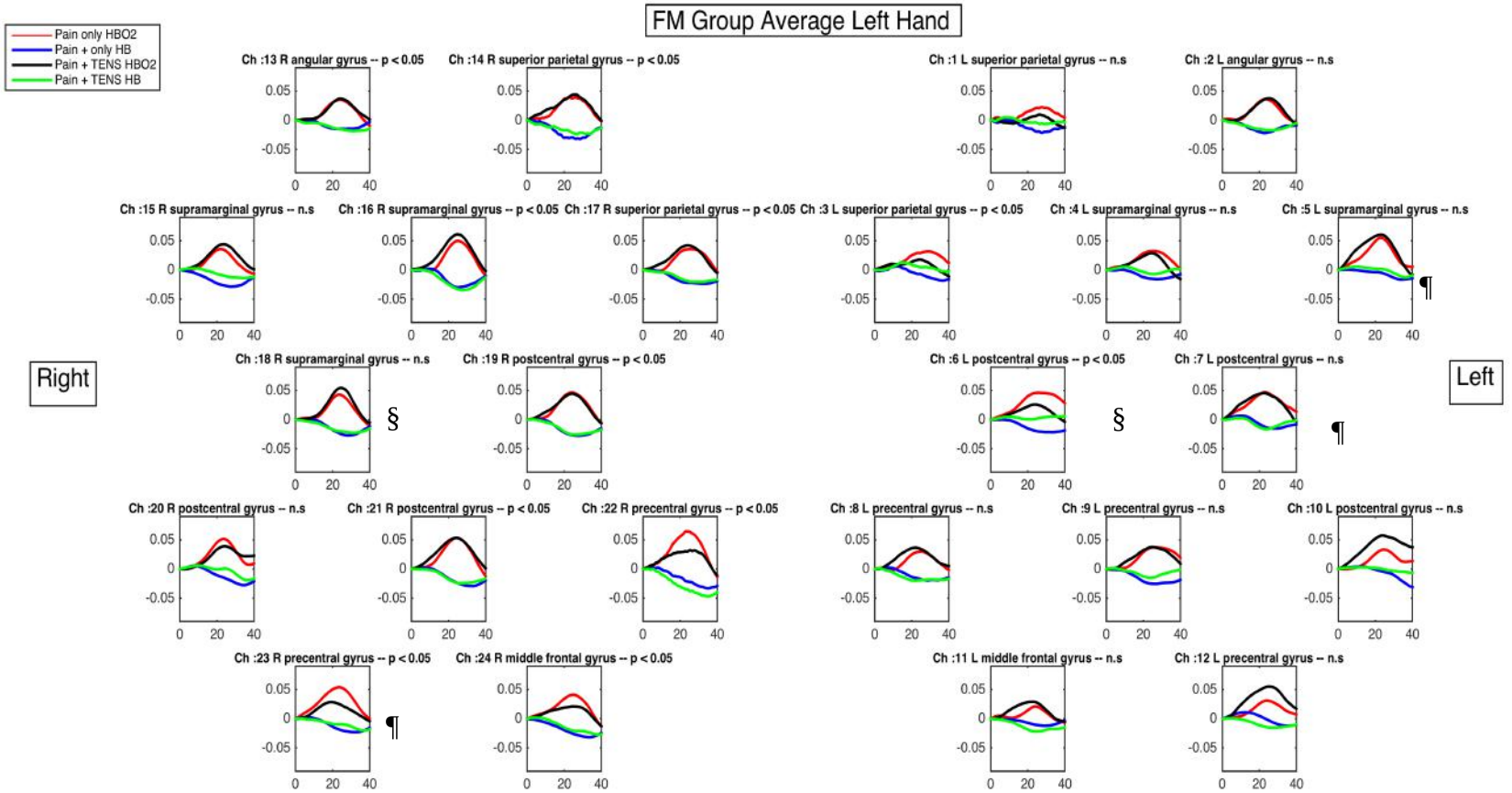


Figure 39. Group single block averages in for all channels of FM patients for left hand stimulation.
Red : “Pain only” HBO2 response, Blue : “Pain only” HB response, Black : “Pain + TENS” HBO2 response, Green : “Pain + TENS” HB response.
p <0.05 ; shows the significant channels between Pain / Pain + TENS conditions.
n.s : not significant.** represents the group (FM & HC) and condition (“Pain only & “Pain+ TENS”) interaction, § : shows group (FM & HC) main effect, ¶ shows condition (“Pain only & Pain + TENS) main effect.

In left hand stimulation of healthy controls, we had to remove one participant (Healthy control no : 5) because the activity profile was not correlated with the task waveform. For left hand, three conditions (“Pain only” / rest, “Pain + TENS”, rest and “Pain only” / “Pain + TENS”) are shown in Figure 40. and F values for every channel are shown in APPENDIX G Table 22. Significant activations are $p < 0.05$, for F values and p-values were corrected by channel number.

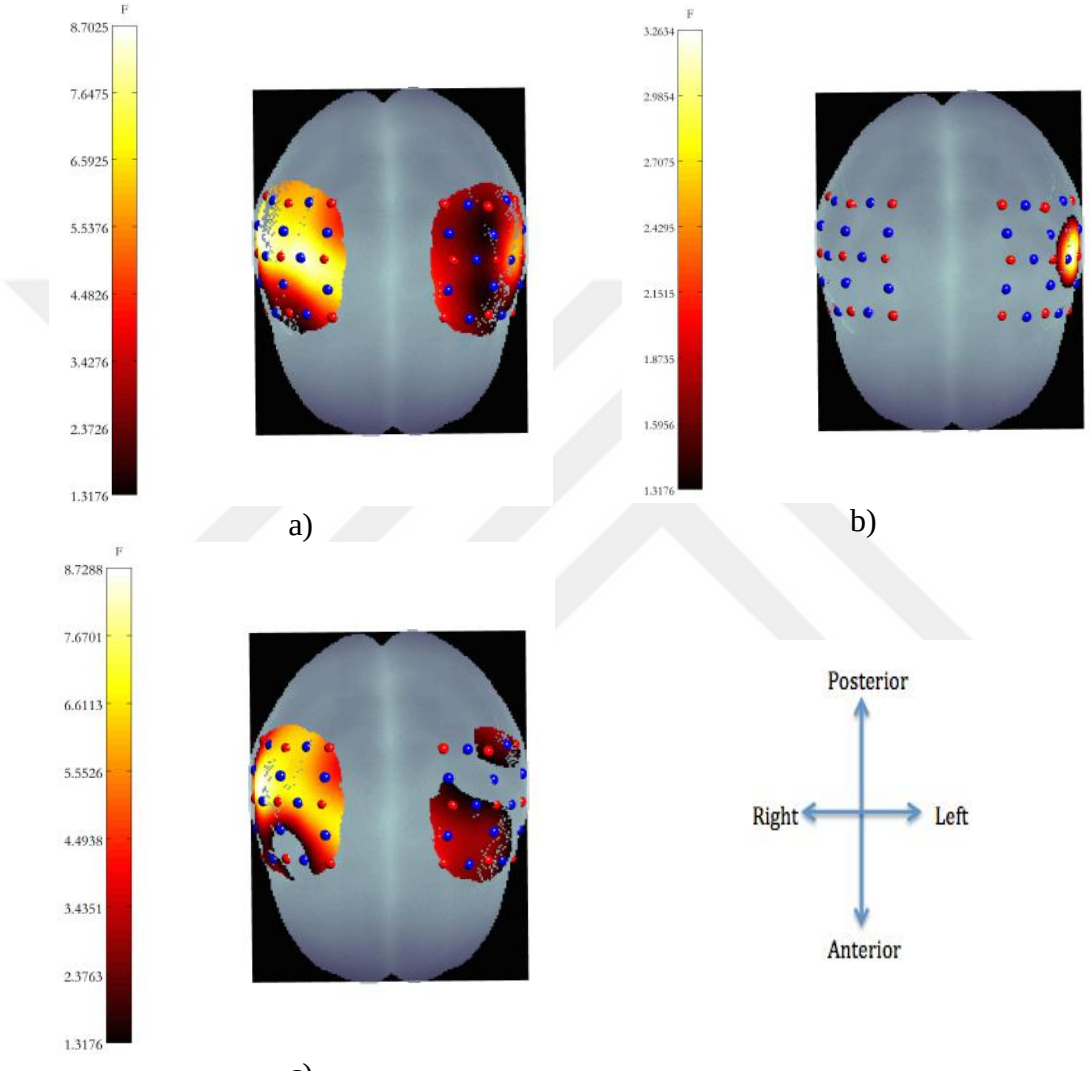


Figure 40. Left hand painful stimuli experiment results for healthy controls.
Comparison of a) Only “Pain only” / rest condition b) “Pain only” / “Pain + TENS” conditions
c) “Pain + TENS” / rest condition.

For non-dominant hand in healthy controls, “Pain only” condition create a higher contralateral activity than ipsilateral as it is shown in Figure 40. a. Significant bilateral post central gyrus activation -except for channels 10 and 20- supramarginal, superior parietal, pre central and middle frontal gyri were observed in “Pain only” condition. In Figure 40.c. “Pain + TENS” activation also show higher contralateral activation than ipsilateral side. All channels were activated except for channels

1,3,4,5,7,10,20,21 and 24. Bilateral superior parietal, angular, contralateral supramarginal, pre central, post central and ipsilateral middle frontal gyri. In Figure 40.b. “Pain only” and “Pain + TENS” comparison shows that significant difference is shown in ipsilateral post central and ipsilateral supramarginal gyri. Block averages of all channels for left hand stimulation of healthy controls are shown in Figure 41.

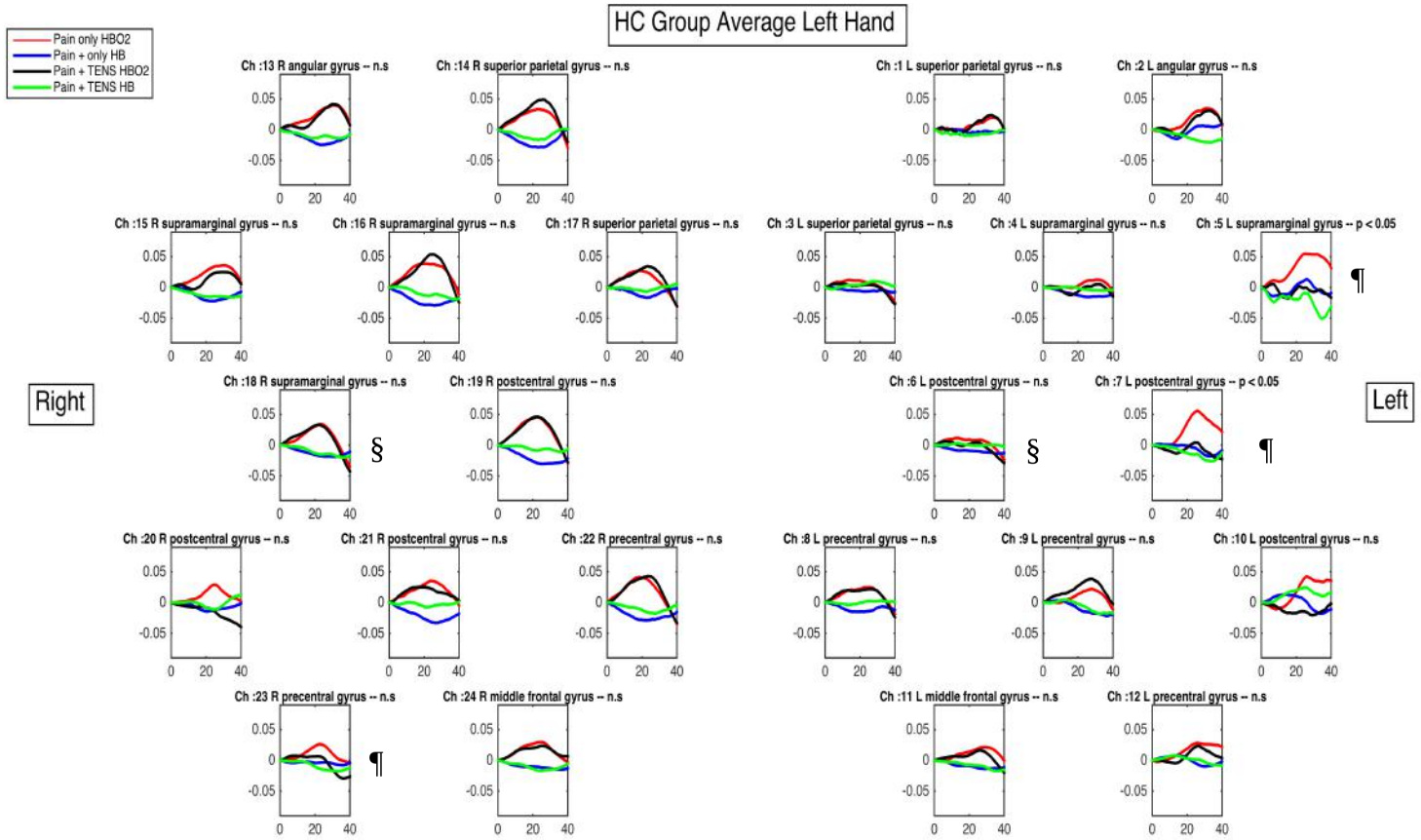


Figure 41. Group single block average of left hand stimulation of healthy controls.
Red: “Pain only” HBO2 response, Blue: “Pain only” HB response, Black: “Pain + TENS” HBO2 response, Green: “Pain + TENS” HB response.
p <0.05 ; shows the significant channels between Pain / Pain + TENS conditions.
n.s : not significant. .** represents the group (FM & HC) and condition (“Pain only & “Pain+ TENS”) interaction, § : shows group (FM & HC) main effect,¶ shows condition (“Pain only & Pain + TENS) main effect.

We performed 2 x 2 (Group (FM patients & Healthy controls) x Condition ("Pain only" & "Pain + TENS)) repeated measures design ANOVA analysis by using mean Δc_{HBO2} values for left hand.

For left hand stimulation, significant difference was observed only in group and condition main effects. Contalateral supramarginal and ipsilateral post central gyri showed a significant group main effect. Post hoc analysis using bonferroni correction revealed that FM group showed higher activity than healthy controls.

Condition main effect was observed in ipsilateral supramarginal, ipsilateral post central and contralateral pre central. Post hoc analysis using bonferroni correction revealed that "Pain only" condition was found higher than "Pain + TENS" condition in ipsilateral supramarginal (Channel 5), ipsilateral post central (Channel 7) contralateral pre central gyri (Channel 23) for mean values. There is no significant interaction between group and condition. Results are shown in Table 9.

Table 9. P values of 2 way repeated measures ANOVA for left hand (Group (FM,HC) x Condition (Pain only , Pain + TENS)) using mean Δc_{HBO2}. Bold highlights represent the statistically significant p- values ($p<0.05$). Unhighlighted p-values represent the marginally significant values. Degrees of freedom is (1,34). (C : Contralateral, I : Ipsilateral)

Channels	Regions	Side	Group effect p values	Condition effect p values	Interaction p values
1	Superior Parietal Gyrus	I	n.s	n.s	n.s
2	Angular Gyrus	I	n.s	n.s	n.s
3	Superior Parietal Gyrus	I	n.s	n.s	n.s
4	Supramarginal Gyrus	I	n.s	n.s	n.s
5	Supramarginal Gyrus	I	n.s	**0,004**	n.s
6	Post Central Gyrus	I	**0,014**	n.s	n.s
7	Post Central Gyrus	I	n.s	**0,006**	n.s
8	Pre Central Gyrus	I	n.s	n.s	n.s
9	Pre Central Gyrus	I	n.s	n.s	n.s
10	Post Central Gyrus	I	n.s	n.s	n.s
11	Middle Frontal Gyrus	I	n.s	n.s	n.s
12	Pre Central Gyrus	I	n.s	n.s	n.s
13	Angular Gyrus	C	n.s	n.s	n.s
14	Superior Parietal Gyrus	C	n.s	n.s	n.s
15	Supramarginal Gyrus	C	n.s	n.s	n.s
16	Supramarginal Gyrus	C	n.s	n.s	n.s
17	Superior Parietal Gyrus	C	n.s	n.s	n.s
18	Supramarginal Gyrus	C	**0,041**	n.s	n.s
19	Post Central Gyrus	C	n.s	n.s	n.s

20	Post Central Gyrus	C	n.s	n.s	n.s
21	Post Central Gyrus	C	n.s	n.s	n.s
22	Pre Central Gyrus	C	n.s	n.s	n.s
23	Pre Central Gyrus	C	n.s	**0,042**	n.s
24	Middle Frontal Gyrus	C	n.s	n.s	n.s

Right Hand Painful Stimulation Experiment Results

For right hand stimulation of FM patients, F values of three conditions ("Pain only" / rest, "Pain + TENS" / rest and "Pain only" / "Pain + TENS") are shown in APPENDIX G Table 21. In this table channels from 1-12 is labeled as contralateral. F maps of three conditions are shown in Figure 42.

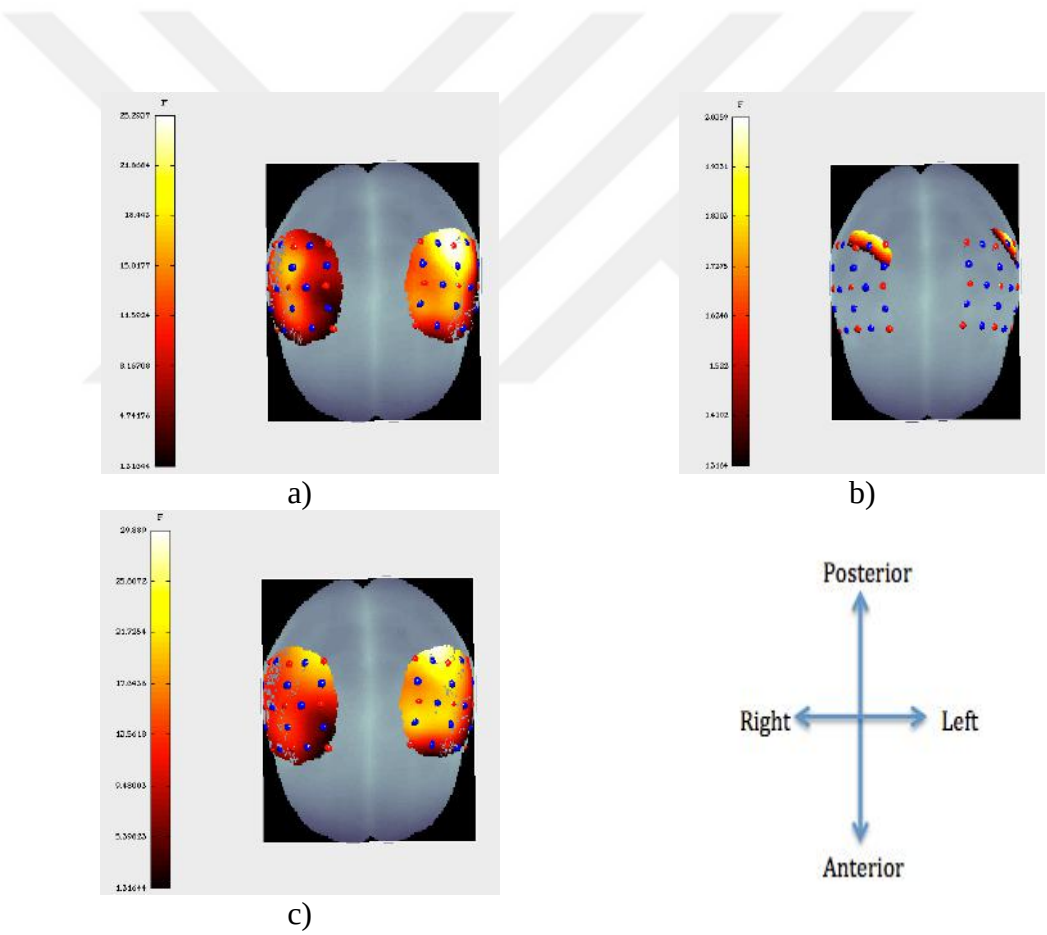


Figure 42. Right hand painful stimuli experiment results for FM patients.
Comparison of a) Only "Pain only" / rest condition b) "Pain only" / "Pain + TENS" conditions c) "Pain + TENS" / rest condition

For dominant hand, "Pain only" condition causes a bilateral activation, which is stronger in contralateral side as shown in Figure 42.a. Painful stimuli effect was strongly observed in Angular, Supramarginal, Superior parietal, Pre Central and Post

Central gyri. “Pain + TENS” is shown in Figure 42.c. Higher F values observed in contralateral than ipsilateral similar to the “Pain only” condition. In “Pain + TENS” condition, bilateral superior parietal, angular, supramarginal, pre central, post central and middle frontal gyri were activated. In “Pain + TENS” condition, bilateral superior parietal, angular, supramarginal, pre central, post central and middle frontal gyri were activated. In Figure 42.b. “Pain only” and “Pain + TENS” comparison shows us a significant difference in bilateral angular gyrus, contralateral supramarginal and ipsilateral superior parietal gyrus. In Figure 43. block averages of all channels for right hand stimulation of FM patients are shown.

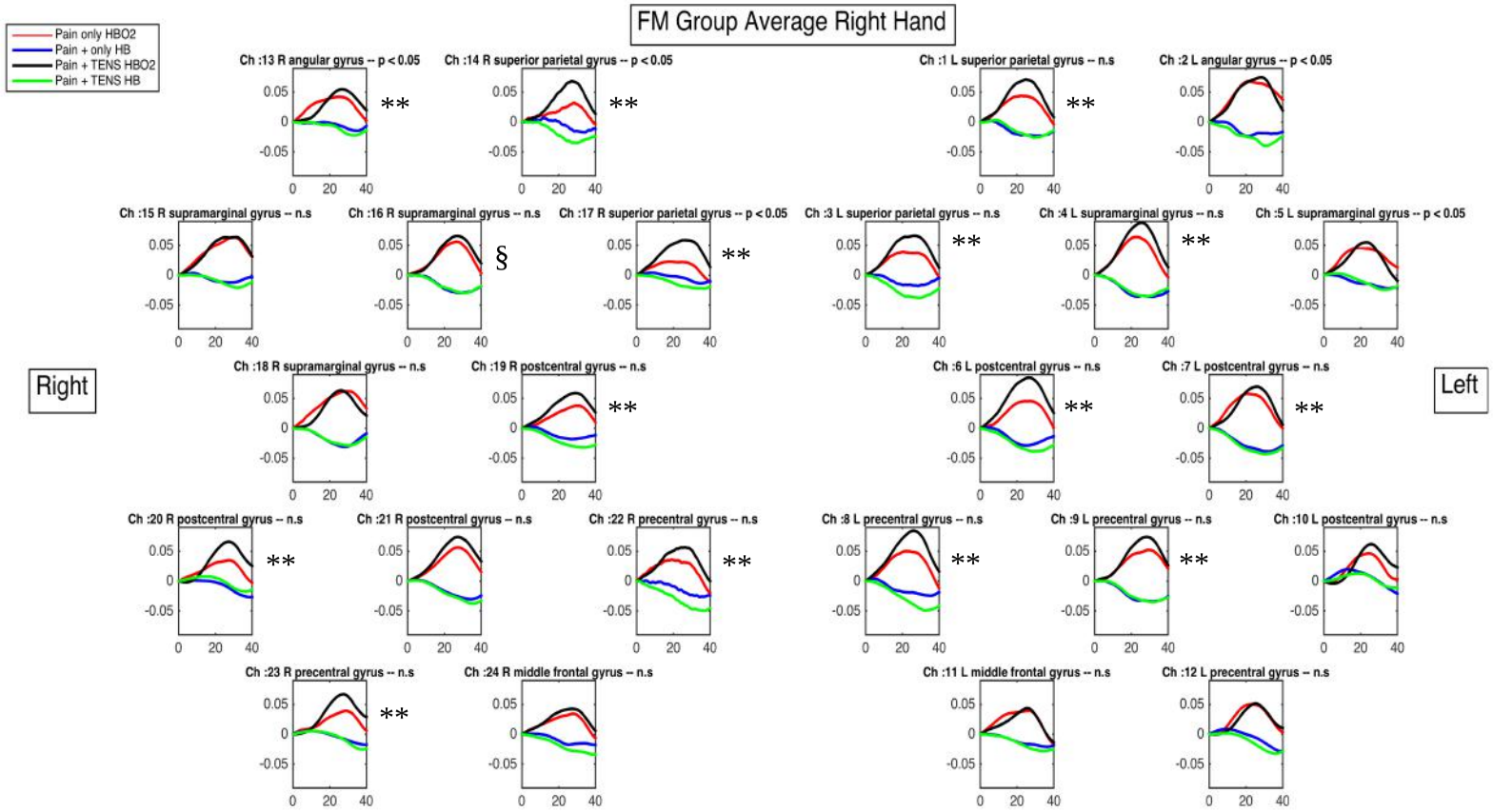


Figure 43. Group single block averages right hand stimulation of FM patients
Red: “Pain only” HBO2 response, Blue : “Pain only” HB response, Black : “Pain + TENS” HBO2 response, Green : “Pain + TENS” HB response.
p <0.05 ; shows the significant channels between Pain / Pain + TENS conditions.
n.s : not significant. .** represents the group (FM & HC) and condition (“Pain only & “Pain+ TENS”) interaction, § : shows group (FM & HC) main effect,¶ shows condition (“Pain only & Pain + TENS) main effect.

For right hand stimulation of healthy controls we had to remove out one participant due to no correlation of the brain activity profile with the task waveform (Heathy control no : 5). F maps of three conditions (“Pain only” / rest, “Pain + TENS” / rest and “Pain only” / “Pain + TENS”) are shown in Figure 44 and F values for every channel are shown in APPENDIX G Table 23. Significant activations are $p < 0.05$, and all p-values were corrected by channel number.

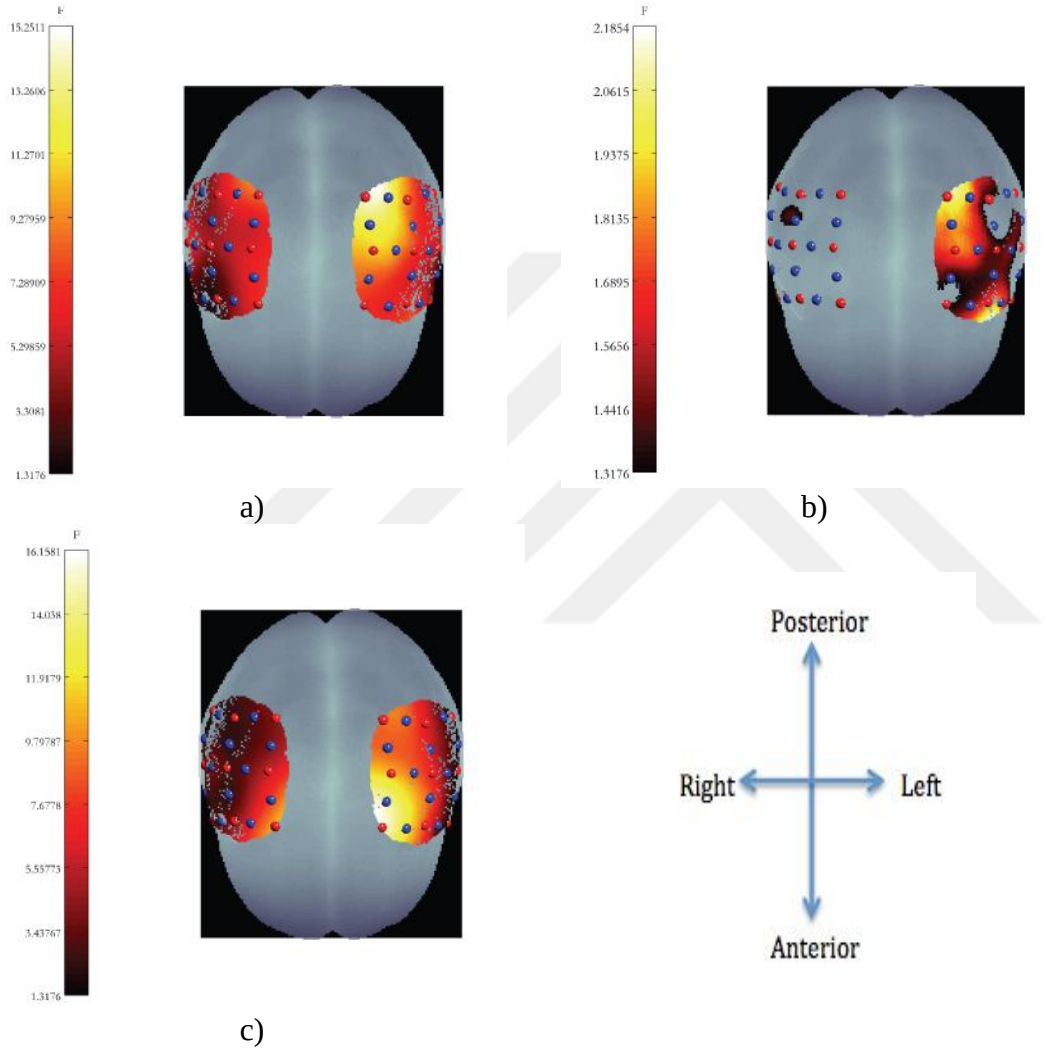


Figure 44. Right hand painful stimuli experiment results for healthy controls.
Comparison of a) Only “Pain only” / rest condition b) “Pain only” / “Pain + TENS” conditions c) “Pain + TENS” / rest condition

For dominant hand of healthy controls, we observed a higher contralateral activity than ipsilateral activity in both “Pain only” and “Pain + TENS” conditions. “Pain only” condition mostly shows significant activity in posterior regions compared with “Pain + TENS” condition. In Figure 44.a. “Pain only” condition causes activity in bilateral superior parietal, angular, supramarginal, pre central, post central and middle frontal gyri. Figure 44.c. shows the activity in “Pain + TENS” condition. As expected a higher contralateral activity than ipsilateral was observed. Except for

channel 10, all channels were significantly active. Regions including bilateral superior parietal, angular, supramarginal, pre central, post central and middle frontal gyri were found as active.

Figure 44.b. shows that “Pain only” and “Pain + TENS” comparison showed significant difference in contralateral region. Regions including, contralateral superior parietal gyrus(Channel 1&3), angular gyrus (Channel 2), post central gyrus (Channel 6 & 7), pre-central gyrus (Channel 8,9 & 12) and middle frontal gyrus (Channel 11) was found significant. Block averages of all channels for left hand stimulation of FM patients are shown in Figure 45.

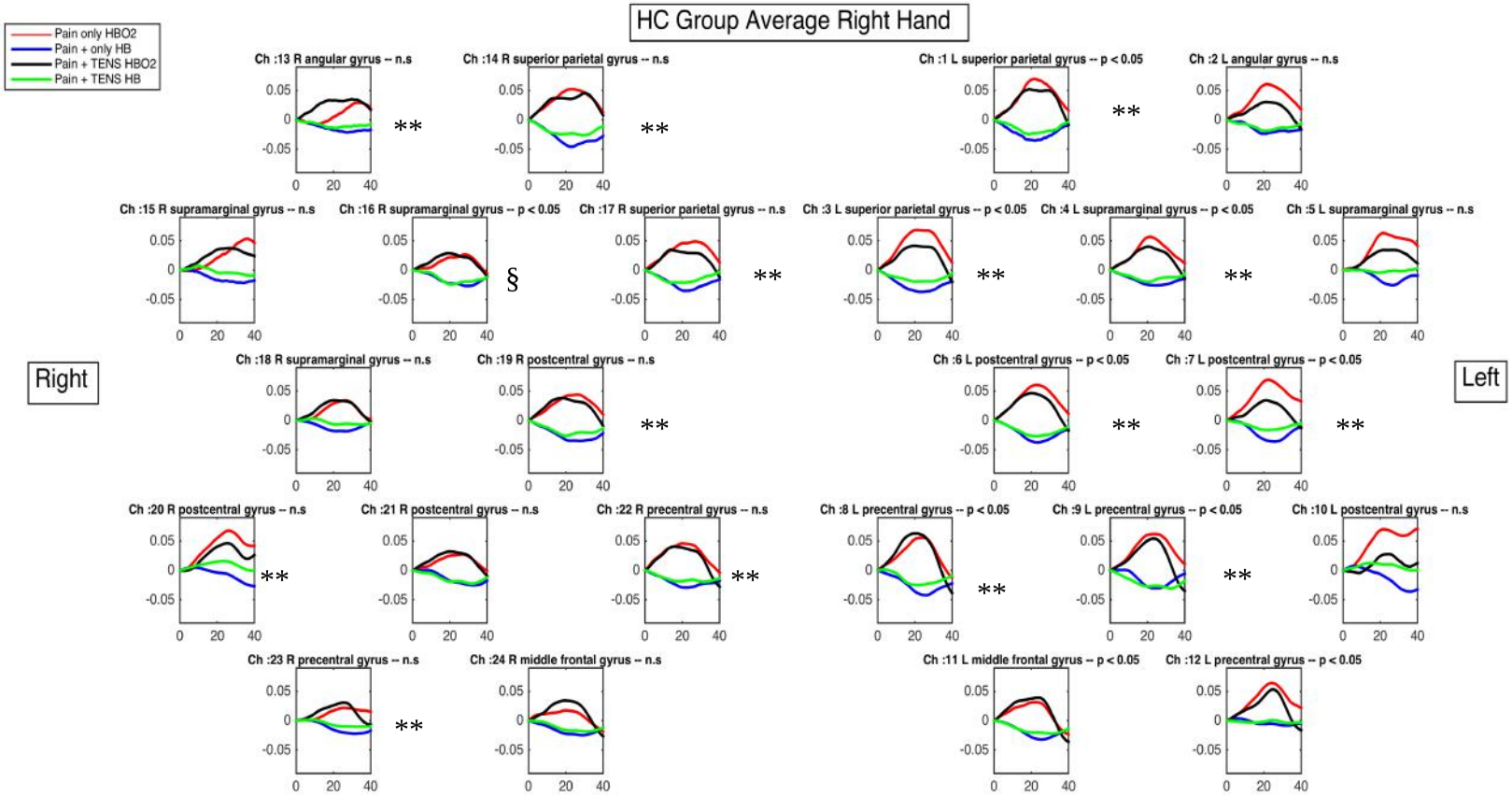


Figure 45. Group block trial average of right hand stimulation of healthy controls.
Red: “Pain only” HBO2 response, Blue: “Pain only” HB response, Black: “Pain + TENS” HBO2 response, Green: “Pain + TENS” HB response.
p <0.05 ; shows the significant channels between Pain / Pain + TENS conditions.
n.s : not significant.** represents the group (FM & HC(and condition (“Pain only & “Pain+ TENS”) interaction, § : shows group (FM & HC) main effect,¶ shows condition (“Pain only & Pain + TENS) main effect.

We performed 2 x 2 (Group (FM patients & Healthy controls) x Condition ("Pain only" & "Pain + TENS")) repeated measures design ANOVA analysis by using mean Δc_{HBO2} values for right hand.

For right hand stimulation, significant main effect between groups was observed in ipsilateral supramarginal gyrus. Pairwise comparison showed that cortical activity was greater in FM patients than healthy controls in the ipsilateral supramarginal gyrus.

Widespreade significant Group x Condition interactions were found in the bilateral superior parietal, contralateral supramarginal, bilateral post central, ipsilateral angular, bilateral pre central gyri for mean values and ipsilateral superior parietal gyrus for beta values. Post hoc analysis using bonferroni correction revealed that "Pain + TENS" activity was found higher in FM patients than healthy controls and "Pain only" activity was found higher in healthy controls than FM patients. Results are shown Table 10.

Table 10. P values of 2 way repeated measures ANOVA for right hand (Group (FM & HC) x Condition (Pain only & Pain + TENS)) using mean Δc_{HBO2} values. Bold highlights represent the statistically significant p- values ($p<0.05$). Unhighlighted values represent the marginally significant values. Degrees of freedom is (1,34) (C : Contralateral, I : Ipsilateral).

Channels	Regions	C/I	Group effect p values	Condition effect p values	Interaction p values
1	Superior Parietal Gyrus	C	n.s.	n.s.	**0,019**
2	Angular Gyrus	C	n.s.	n.s.	n.s.
3	Superior Parietal Gyrus	C	n.s.	n.s.	**0,009**
4	Supramarginal Gyrus	C	n.s.	n.s.	**0,016**
5	Supramarginal Gyrus	C	n.s.	n.s.	n.s.
6	Post Central Gyrus	C	n.s	n.s.	**0,011**
7	Post Central Gyrus	C	n.s.	n.s.	**0,036**
8	Pre Central Gyrus	C	n.s.	n.s.	**0,010**
9	Pre Central Gyrus	C	n.s.	n.s.	**0,037**
10	Post Central Gyrus	C	n.s.	n.s.	n.s.
11	Middle Frontal Gyrus	C	n.s.	n.s.	n.s.
12	Pre Central Gyrus	C	n.s.	n.s.	n.s.
13	Angular Gyrus	I	n.s.	n.s.	**0,023**
14	Superior Parietal Gyrus	I	n.s.	n.s.	**0,005**
15	Supramarginal Gyrus	I	n.s.	n.s.	n.s.
16	Supramarginal Gyrus	I	**0,044**	n.s.	n.s.
17	Superior Parietal Gyrus	I	n.s.	n.s.	**0,003**
18	Supramarginal Gyrus	I	n.s.	n.s.	n.s.
19	Post Central Gyrus	I	n.s.	n.s.	**0,038**

20	Post Central Gyrus	I	n.s.	n.s.	**0,048**
21	Post Central Gyrus	I	n.s	n.s.	n.s.
22	Pre Central Gyrus	I	n.s.	n.s.	**0,025**
23	Pre Central Gyrus	I	n.s.	n.s.	**0,037**
24	Middle Frontal Gyrus	I	n.s.	n.s.	n.s.

2 x 2 repeated measures fNIRS results of TENS and painful stimulation experiment results are shown in APPENDIX G
Table 24.

4.4.Correlation Analysis Between Psychophysical Data and Neural Data

4.4.1. Pain Ratings – fNIRS Data Correlation

We analyzed the Pearson's correlation coefficient between the pain ratings and brain activation mean hemodynamic Δc_{HBO2} response. We computed the correlation coefficients separately for the channels, conditions and hands while we merged the HC and FM group data. Only significant results are shown in Table 11 while all correlations are attached to APPENDIX F Table 17. For all correlation values significance level is $p < 0.05$.

Table 11. Significant Correlations between Pain Ratings and fNIRS Data

Stimulated Hand	Channel	Structure	Condition	Pearson's Correlation (r)
Left	2	Left Angular Gyrus	"Pain only"	0.338
Left	13	Right Angular Gyrus	"Pain only"	0.462
			"Pain + TENS"	0.325
Left	14	Right Superior Parietal Gyrus	"Pain only"	0.387
Right	3	Left Superior Parietal Gyrus	"Pain only"	-0.363
Right	5	Left Supramarginal Gyrus	"Pain only"	-0.355

According to these results, significant correlations in left hand stimulation for "Pain only" and "Pain + TENS" condition were observed in right superior parietal gyrus and bilateral angular gyri. For right hand and "Pain only" condition, left supramarginal gyrus and superior parietal activity were found significantly correlated negatively with corresponding pain ratings.

4.4.2. Pain Threshold - fNIRS Data Correlation

We analyzed the Pearson's correlation coefficient between the pain thresholds and brain activation mean hemodynamic Δc_{HBO2} response. We computed the correlation coefficients separately for the channels, conditions and hands while we merged the HC and FM group data. Only significant results are shown in Table 12. While all correlations are attached to APPENDIX F Table 18. For all correlation values significance level is $p < 0.05$.

Table 12. Significant Correlations between Pain Thresholds and fNIRS Data

Stimulated Hand and Pain Threshold	Channel	Structure	Condition	Pearson's Correlation (r)
Left	1	Left Superior Parietal Gyrus	"Pain + TENS"	0.352
Right	12	Left Pre Central Gyrus	"Pain+TENS"	-0.369
Right	16	Right Supramarginal Gyrus	"Pain + TENS"	-0.332
Right	18	Right Supramarginal Gyrus	"Pain + TENS"	-0.443
Right	19	Right Post Central Gyrus	"Pain + TENS"	-0.450
Right	20	Right Post Central Gyrus	"Pain + TENS"	-0.359
Right	21	Right Post Central Gyrus	"Pain + TENS"	-0.348

"Pain +TENS" condition of left hand stimulation revealed significant positive correlation at the left superior parietal gyrus. For right hand stimulation, "Pain +TENS" condition revealed significant negative correlation in left pre central, right supramarginal and right post central gyri.

4.5.Classification Analysis

As mentioned in Chapter 3, we performed classification by using Support Vector Machine to classify our fNIRS data. First, we extracted maximum and mean Δc_{HBO2} value for every "Pain only" and "Pain + TENS" block. Then we found the Dynamic Time Warping alignment distance between Δc_{HBO2} response and our hemodynamic response function convolved with experimental boxcar function.

We used 6 different features for both right and left hand (6 x 2 = 12 features) as explained in Chapter 3.7.3. However, we reduced the dimension to 4 in order to get rid of curse of dimensionality problem. We have 12 features and 35 observations. We accepted rule of thumb for optimum observation and dimension relationship as

$n \geq d^2$ (where n= number of observations, d= number of dimensions). So according to this relationship, if we reduce the number of dimension to 4, the total number of observations (i.e.35, 17 FM patients and 18 healthy controls) will be greater than 16. In order to reduce the feature vector to 4 dimensions, we need to make sure that a significant amount of the variance (eg. 80%) is represented. PCA is suitable for this purpose. We used 10-fold cross validation to obtain a generalized performance of SVM classifier. We used k as k=2…10 for 11 different kernels. These kernels are ;

- Linear
- Polynomial degree (2-10th order)
- Radial Basis Function

In Figure 46. Classification process flow chart for fNIRS data is shown.

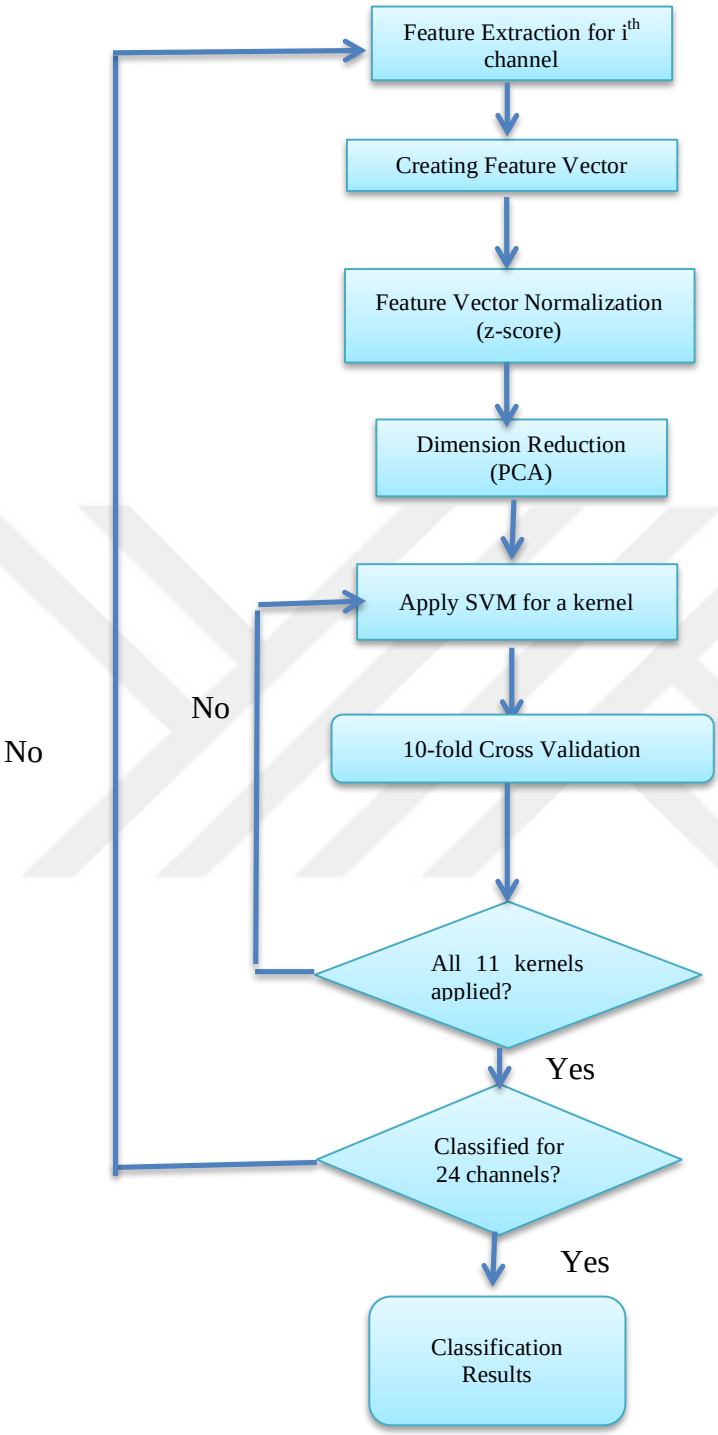


Figure 46. Classification process flow chart for fNIRS data.

Among these classification results we obtained higher accuracy results from Linear Kernel, 2nd order, 5th order and 10th order polynomial kernels. Channel positions are shown in Figure 47 for ease of interpretation.

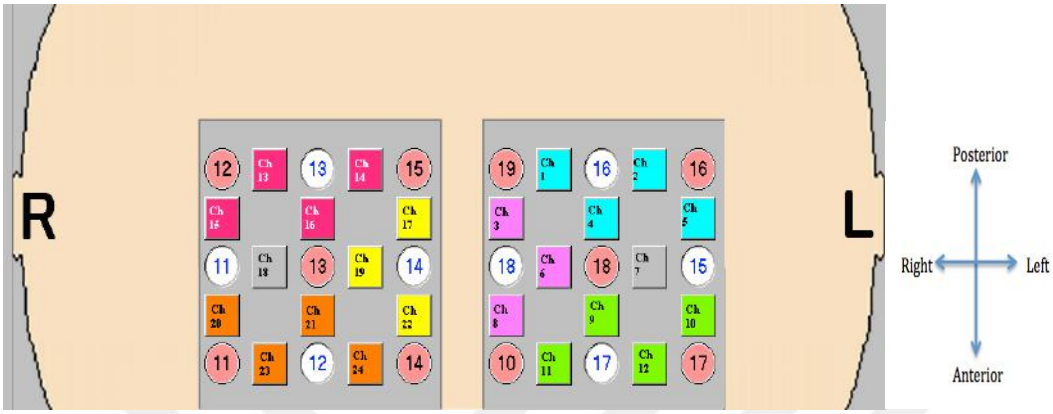


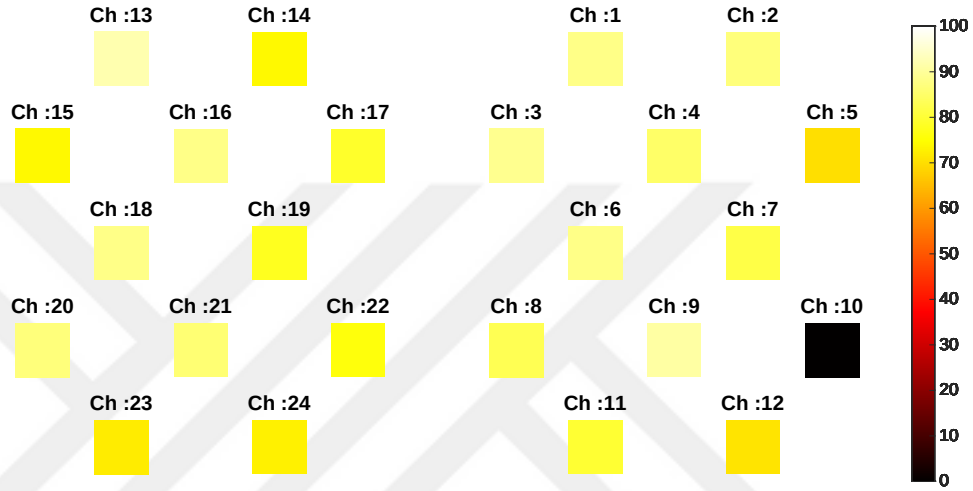
Figure 47. Channel Configuration of our experiment.

SVM classification was performed by using "ClassificationSVM" class in MATLAB. For every fold of 10-fold cross validation, we partitioned 32 of 35 samples as training dataset and 3 of 35 samples as test datasets. Our observations from each channel are used as separate classifiers. SVM classification results performed by using Linear, 2nd order, 5th order and 10th order polynomial kernels as shown in Table 13. In addition, in Figure 48, SVM accuracy results are shown as classification maps for linear, 2nd order, 5th order and 10th order polynomial kernels.

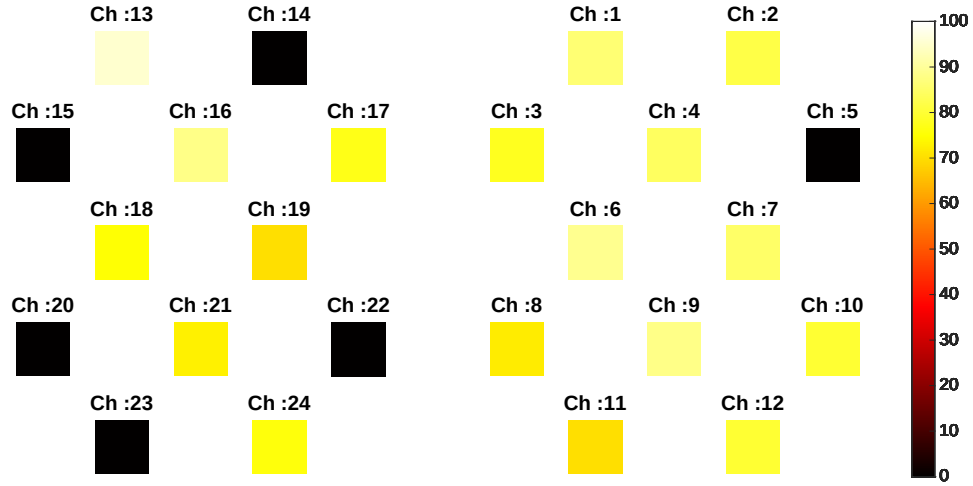
Table 13. SVM classification accuracies based on brain activity data for Linear Kernel, 2nd order, 5th order and 10th order polynomial kernel.

Channel	Structure	Linear Kernel	2nd Order Polynomial	5th Order Polynomial	10th Order Polynomial
1	Superior Parietal Gyrus	88.33 ± 21.94	85.83 ± 24.86	80.00 ± 14.27	75.83 ± 22.38
2	Angular Gyrus	86.66 ± 18.51	81.66 ± 21.09	70.00 ± 21.94	62.50 ± 18.11
3	Superior Parietal Gyrus	89.16 ± 14.19	77.50 ± 24.86	72.50 ± 18.86	64.16 ± 25.17
4	Supramarginal Gyrus	85.00 ± 16.10	84.16 ± 32.02	80.83 ± 18.02	68.33 ± 26.29
5	Supramarginal Gyrus	70.00 ± 31.72	62.50 ± 24.61	68.33 ± 17.48	54.16 ± 28.93
6	Post Central Gyrus	88.33 ± 15.32	89.16 ± 14.19	83.33 ± 14.70	79.16 ± 14.83
7	Post Central Gyrus	81.66 ± 22.50	85.00 ± 16.10	71.66 ± 28.65	70.00± 25.52
8	Pre Central Gyrus	82.50 ± 15.44	71.66 ± 17.21	85.00 ± 16.10	76.66 ± 23.51
9	Pre Central Gyrus	90.83 ± 14.93	88.33 ± 15.32	74.16 ± 30.54	74.16 ± 19.42
10	Post Central Gyrus	67.50 ± 17.32	80.00 ± 14.27	85.00 ± 22.49	67.50 ± 19.42
11	Middle Frontal Gyrus	80.00 ± 14.27	70.00 ± 28.10	70.83 ± 24.92	63.33 ± 18.51
12	Pre Central Gyrus	70.83 ± 23.32	80.00 ± 24.91	80.00 ± 21.94	67.50 ± 23.38
13	Angular Gyrus	91.66 ± 13.61	95.00 ± 10.54	91.66 ± 13.60	67.50 ± 28.72
14	Superior Parietal Gyrus	74.16 ± 22.03	66.66 ± 15.21	53.33 ± 31.96	50.00 ± 23.89
15	Supramarginal Gyrus	74.16 ± 24.98	55.83 ± 24.55	66.66 ± 24.84	60.83 ± 40.45
16	Supramarginal Gyrus	88.33 ± 15.32	88.33 ± 15.32	65.00 ± 28.54	63.33 ± 9.78
17	Superior Parietal	79.16 ± 21.61	76.66 ± 26.29	73.33 ± 24.47	67.50 ± 20.95

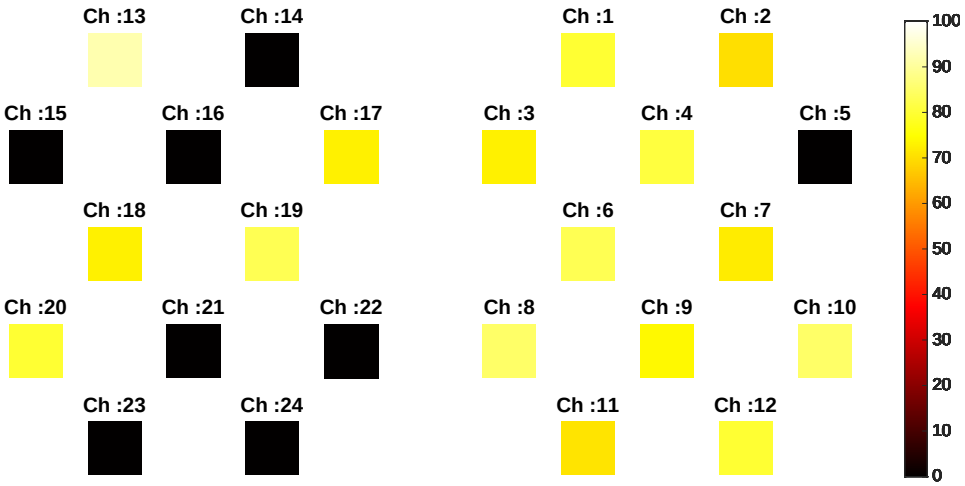
	Gyrus				
18	Supramarginal Gyrus	88.33 ± 15.31	75.00 ± 25.46	73.33 ± 24.47	62.50 ± 30.50
19	Post Central Gyrus	77.50 ± 26.07	70.00 ± 25.52	82.50 ± 15.44	60.00 ± 17.92
20	Post Central Gyrus	86.66 ± 18.51	66.66 ± 27.49	80.00 ± 24.28	69.16 ± 26.95
21	Post Central Gyrus	85.83 ± 15.24	73.33 ± 22.15	61.66 ± 32.44	64.16 ± 32.41
22	Pre Central Gyrus	75.83 ± 19.02	65.83 ± 29.77	66.66 ± 24.84	65.00 ± 26.58
23	Pre Central Gyrus	71.66 ± 17.21	66.66 ± 29.92	67.50 ± 23.39	57.50 ± 23.39
24	Middle Frontal Gyrus	72.50 ± 26.07	75.83 ± 24.67	59.16 ± 20.20	48.33 ± 23.17



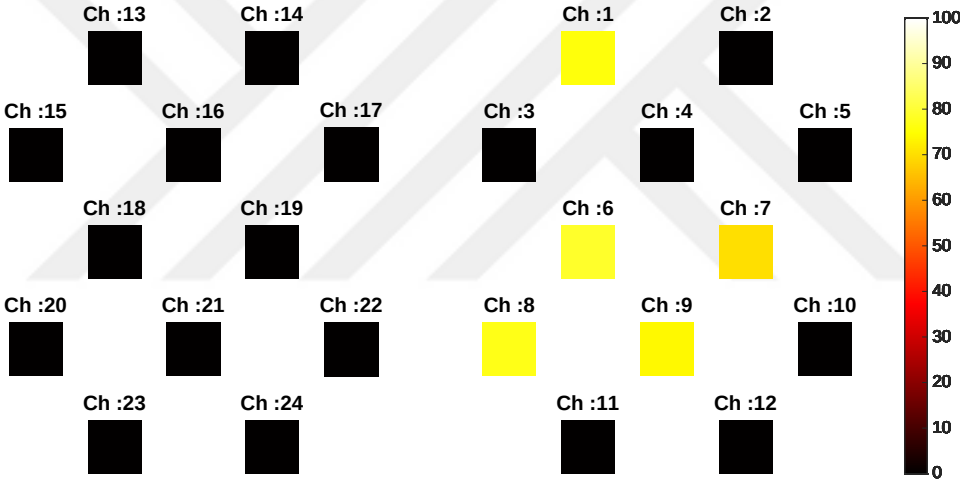
a)



b)



c)



d)

Figure 48. SVM accuracy results for all channels to classify FM patients and healthy controls a) Linear, b) 2nd order, c)5th order d) 10th order.
Colorbar shown in right side of the figure represents the accuracy values as a color.
Channels that has accuracy lower than %70 are darkened as black.

According to the classification results, linear kernel SVM showed greatest performance among all kernels. Except for channel 10 all channels showed higher classification rates than %70. The 2nd order kernel SVM classifier showed highest accuracy performance specific to channel 13 with 95%. 5th and 10th degree polynomial kernel SVM classifiers showed acceptable accuracy values if not best.

4.5.1. Self- Report Based Classification Results

We used three features to construct our feature vector, based on subjective reports obtained from patients: BDI score, left and right hand pain threshold values. We used SVM as classifier, while linear, polynomial (2-10th degree) and radial basis functions are tested as kernels. A 10 –fold cross validation was applied to generalize accuracy results. Results are shown in Table 14.

Table 14. SVM classification accuracy for Self-Report data with different kernels and parameters

SVM Classification Kernel and Parameters	Accuracy (Mean ± Std)
Linear	88,33±21,94
Polynomial (2nd degree)	74,17±22,03
Polynomial (3rd degree)	74,17±22,03
Polynomial (4th degree)	74,17±23,72
Polynomial (5th degree)	69,17±21,17
Polynomial (6th degree)	66,67±29,92
Polynomial (7th degree)	73,33±23,17
Polynomial (8th degree)	74,17±18,61
Polynomial (9th degree)	72,50±20,05
Polynomial (10th degree)	70,00±26,99
Radial Basis Function	87,50±21,25

In differentiating patients versus controls based on subjective reports, we obtained highest accuracy (%88.33) by using Linear kernel.

CHAPTER 5

DISCUSSION

The main purpose of this thesis is to understand neural signatures of TENS with respect to the stimulated hand. We also investigated associations between psychophysical data and experimental hemodynamic data.

5.1.Summary of Research Questions and Related Findings

We had two research questions. These are;

1. “While applying painful stimulus, is there a pain relief effect of TENS in FM patients while applying painful stimulus and can we observe this in the hemodynamic activity?”

2. “Can we distinguish FM patients and healthy controls using brain activity patterns during painful stimulation?”

For the first question we had two hypotheses tested separately for FM and HC groups;

- Hypothesis 1: Hemodynamic activity in “Pain +TENS” condition will be significantly less than “Pain only” condition in healthy controls.
- Hypothesis 2: Hemodynamic activity in “Pain +TENS” condition will be significantly less than “Pain only” condition in FM patients.

According to the right hand stimulation results, our first hypothesis for healthy controls was accepted. However, our second hypothesis for FM patients was rejected due to significant increase in “Pain + TENS” condition compared to “Pain only” condition. This result might be explained as a malfunctioning in gate control mechanism in FM patients. Because, FM patients show hypersensitivity to sensory stimulation due to central sensitization and dysfunction in pain inhibition mechanism.

Our left hand stimulation results indicated that our hypotheses for both groups were accepted. Because for both groups a significant hemodynamic reduction was observed in “Pain + TENS” condition compared to “Pain only” condition. Moreover, FM patients showed higher activity than healthy controls and “Pain only” condition. These results are replications from literature.

For our second research question, we hypothesized that we can obtain classification accuracy greater than 80 %. Our results indicated that this prediction was satisfied because we obtained more than 90 % accuracy from classification of FM patients and healthy controls.

In order to explain our findings by comparing with literature in a clear way, we created Table 15 and focused on what the other studies found. In this table, studies that carry similar methodology with our study are considered and the corresponding results are compared.

Table 15. Our main findings and comparison with the literature

Finding	Study	Similarity with our study	Related Information
After painful stimulation experiment to both hands, FM patients showed higher hemodynamic activity than healthy controls.	(Gracely et al., 2002)	Painful stimulation study to left hand with equal amount of pain sensation.	FM patients showed increased activation was observed in right SI, SII, IPL.
	(Cook et al., 2004)	Painful stimulation study to left hand with equal amount of pain sensation.	There is no significant difference in any region between both groups.
	(Staud et al., 2008)	Painful stimulation study to right foot with equal amount of painful sensation.	No significant difference in any region between FM patients and healthy controls.
	(Pujol et al., 2009)	Painful stimulation study to right hand with equal amount of painful sensation.	FM patients showed higher activity in anterior cingulate, basal ganglia and insula which are unreachable regions to obtain information by using fNIRS.
	(Uceyler et al., 2015)	Right hand painful stimulation study with fNIRS to compare activity between FM patients and healthy controls.	Results showed that painful stimulation applied to right hand caused an increased bilateral activation in FM patients than healthy controls.
After painful stimulation to left hand, TENS efficiency in hemodynamic response was observed in left post central gyrus and supramarginal gyrus healthy controls.	(Choi et al., 2015)	Painful stimulation (16 mA) without TENS in healthy controls.	In this study, 24 participants participated TENS efficiency was observed in right middle frontal cortex and right inferior partietal cortex (supmarginal gyrus is a part of inferior parietal cortex). We applied 30 mA and painful stimulation in levels of pain threshold and observed ipsilateral activity.
Negative BOLD activation was observed in TENS stimulation onto healthy controls.	(Klingner et al., 2011)	Similar conventional median nerve stimulation application on the right wrist of healthy controls.	40 Hz frequency, 5mA, 200 μs pulse duration, median nerve stimulation caused ipsilateral SI, SMA, insula, PCC and contralateral cerebellum.

5.2.fNIRS Data Analysis

5.2.1. Median Nerve TENS Stimulation

We performed this median nerve stimulation experiment to observe the baseline effects of TENS in both groups. Stimulation intensity was tested before the experiment and applied to everyone at 30 mA to cause a non-nociceptive tingling effect. Such low intensity and high frequency application type of TENS is called "Conventional TENS" (I. Jones & Johnson, 2009) which is used for pain relief.

We observed group difference in left and right superior parietal, right supramarginal, right post central and right middle frontal gyri. Post hoc analysis revealed that FM patients showed higher activation than healthy controls. Similar non-painful stimulation study showed that FM patients showed greater activity than healthy controls in prefrontal, supplementary motor area, insular and anterior cingulate cortex by using non-painful warm stimuli using a thermal stimulator(Cook et al., 2004). On the other hand, another study revealed that non-painful stimulation study initiated that higher activation in FM patients compared to healthy controls for visual, auditory and tactile (finger tapping) stimulation in insula and lingual gyrus (Lopez-Sola et al., 2014). Compared with our study, these different results might be related with stimulation type and intensity. However, increased activation in FM patients compared with healthy controls is a general pattern which indicates that TENS related activity in FM patients might increase due to central sensitization. Because stimulated large Aβ nerve fibers that carries non-nociceptive stimulation causes allodynia in FM patients (Woolf, 2011). According to Cook and his colleagues (Cook et al., 2004) central nervous system dysregulation was found independent of stimulus type in FM patients. FM patients may consider TENS stimulation as a nociceptive stimulation which may have introduced additive effect to hemodynamic activation. Lopez-Sola and her colleagues (Lopez-Sola et al., 2014) explains this condition that may be a part of pathology in FM.

Superior parietal gyrus, located in posterior parietal cortex, is known as sensory association area and it is found to be significantly active in median nerve stimulation studies (Boakye et al., 2000; Klingner et al., 2011). Boakye and his colleagues performed median nerve stimulation to both hands of healthy participants and analyzed brain activity by using fMRI (Boakye et al., 2000). They showed that sensorimotor cortex, SII, insula, SMA, frontal cortex and posterior parietal cortices (BA 7: superior parietal gyrus, BA 40: supramarginal gyrus) were activated. Also post central gyrus was found significantly active in several median nerve stimulation studies (Boakye et al., 2000; Klingner et al., 2011; Spiegel et al., 1999) of healthy controls.

Another important point in these analysis is the hemodynamic deactivation observed in healthy controls. In FM patients, positive activation was observed that might be related with hypersensitivity to sensory stimulation. However, activity decrease is observed in right hemisphere of healthy controls. This decrease in consistent with the

recent studies in the literature. Ipsilateral activity decrease by median nerve stimulation of dominant hands of right handed healthy controls is reported for 40 Hz frequency which is accepted as a Conventional TENS frequency (Kampe et al., 2000; Kastrup et al., 2008; Klingner et al., 2010; Mullinger et al., 2014). We also observed significant activity decrease in right hemisphere for both hand stimulations. Furthermore, a combined study that uses fMRI-EEG and CBF data revealed that negative BOLD signal and negative CBF was associated in increase of mu power in EEG signal which is known as an electrophysiological signature to neural inhibition (Mullinger et al., 2014). Recent findings indicated that activity decrease in ipsilateral primary somatosensory cortex might be related with applied stimulus intensity (Klingner et al., 2010), augmentation in sensory threshold (Kastrup et al., 2008) or transcallosal inhibition (Hlushchuk & Hari, 2006). Hence we arrive at the conclusion that, in healthy controls, but not in FM patients, median nerve TENS stimulation invoked inhibitory activity in the parietal cortex.

5.2.2. Painful Stimulation with TENS

In this study, our primary objective was to observe whether TENS has any effect on the perception and brain activity patterns during the application of painful stimuli to FM patients as well as healthy subjects. We also investigated hand differences, by applying the same experiment to both left and right hands. For both groups and stimulation of both hands, bilateral activation was observed in both “Pain only / rest” and “Pain + TENS / rest” comparisons. Differences was observed in “Pain only / Pain + TENS” comparison.

For left hand stimulation of FM patients, “Pain only” and “Pain + TENS” conditions were found significantly different in bilateral superior parietal and post central gyri, contralateral angular, supramarginal, pre central and middle frontal gyri. When we focused on trial averages of both conditions for active channels, we see that “Pain only” condition causes a higher activation than “Pain + TENS” conditions, supporting the expected pain relief effect of TENS intervention.

When we compared “Pain only” condition with “Pain + TENS” condition for right hand stimulation of FM patients, significant bilateral differences were observed in angular gyri, contralateral supramarginal gyrus and ipsilateral activities in superior parietal gyri. Contrary to the left hand though, the “Pain + TENS” condition initiated more brain activity than the “Pain only” condition. Hence the therapeutic effects of TENS was nor observed.

“Pain only” and “Pain + TENS” comparison of left hand stimulation of healthy controls showed that significant difference was observed in ipsilateral post central and supramarginal gyri. Single trial averages of left hand stimulation of healthy controls for these channels also indicate that “Pain only” condition has a higher activation than “Pain + TENS” condition, supporting the expected effects of TENS treatment.

For right hand stimulation of healthy controls, single trial averages in active channels indicated that “Pain only” condition initiated more brain activity than the “Pain + TENS” condition validating the effect of TENS treatment. This observation was valid for all channels in left hemisphere except for channels 4 & 5 (supramarginal gyrus) and 10 (postcentral gyrus). A general view to results for group analysis for painful stimuli experiment for both hands is shown in Table 16.

Table 16. Summary of the results of the painful stimuli experiment for both hands.

Conditions	Pain / “Pain + TENS” Comparison		Pain / rest Comparison		“Pain + TENS” / rest Comparison	
Hand / Groups	Left Hand Exp.	Right Hand Exp.	Left Hand Exp.	Right Hand Exp.	Left Hand Exp.	Right Hand Exp.
FM patients	TENS causes a significant decrease in ipsilateral Post Central and Superior Parietal gyri.	TENS causes a significant increase in ipsilateral angular and superior parietal gyri.	All regions were bilaterally activated. Regions in contralateral generally show higher activity than ipsilateral ones.	All regions were bilaterally activated. Regions in contralateral generally show higher activity than ipsilateral ones.	All regions were bilaterally activated. Regions in contralateral generally show higher activity than ipsilateral ones.	All regions were bilaterally activated. Regions in contralateral generally show higher activity than ipsilateral ones.
Healthy Controls	TENS causes a significant decrease in ipsilateral Post Central and Supramarginal Gyri.	TENS causes a significant decrease in contralateral post central gyrus.	All channels except 10 & 20 (corresponding region post central gyrus) shows significant activity. Regions in contralateral show higher activity than ipsilateral ones.	All regions were bilaterally activated. Regions in contralateral generally show higher activity than ipsilateral ones.	All channels except 4,5,7,10,20 and 24 shows significant activity. Regions in contralateral generally show higher activity than ipsilateral ones.	All regions were bilaterally activated. Regions in contralateral generally show higher activity than ipsilateral ones.

For right hand stimulation, 2 x 2 (Group (FM patients vs. Healthy Controls) x Condition (“Pain only” vs “Pain + TENS”)) repeated measures ANOVA showed that significant interaction was found between Group and Condition.

TENS effect for healthy controls was observed as decreased signal for “Pain + TENS” condition compared to “Pain only” condition, especially in ipsilateral supramarginal gyrus (BA40) located in IPL, and ipsilateral superior parietal (BA7) gyri. Activity decrease in IPL is an replication with a previous fMRI study that showed the TENS effect in IPL while applying painful stimuli in healthy controls (Choi et al., 2015). Superior parietal gyri plays an important role in attention network, which is also strongly associated with SI (Bushnell et al., 2013). IPL was found active when a nociceptive stimulus was applied both in healthy controls and FM patients (Gracely et al., 2004; Gracely et al., 2002; Pujol et al., 2009). Our results suggested that, TENS showed pain relief effect in superior parietal gyrus and IPL (supramarginal gyrus – BA40) in healthy controls. Parietal cortex is generally related with spatial perception of non-nociceptive and nociceptive stimulus (Porro et al., 2007). Inferior parietal (supramarginal (BA40) and angular (BA39)) gyri have

important role in attention to the noxious stimuli. Also, superior parietal gyrus is known as sensory association cortex. Decrease of hemodynamic activity in "Pain+TENS" condition might be related with decrease hypervigilance to the painful stimuli because of decrease in painful stimuli sensation compared with "Pain only" condition.

In FM patients, in terms of the response to painful stimuli applied to the right hand, use of TENS caused an increase in hemodynamic response compared to the condition when TENS was not applied. This is in contradiction to the decrease we expected due to the use of TENS in FM patients. These results might reflect a malfunctioning in gate control mechanism in FM patients. Woolf (Woolf, 2011) suggests that non-nociceptive stimulation causes allodynia and secondary hyperalgesia that might occur due to peripheric sensitization in individuals who have central sensitization. According to Cook et al.,(Cook et al., 2004) central nervous system dysregulation was found independent of stimulus type in FM patients. FM patients may consider TENS stimulation as a nociceptive stimulation which may have introduced additive effect to hemodynamic activation. Lopez-Sola et al., (Lopez-Sola et al., 2014) explains this condition as a part of pathology in FM. Staud (Staud, 2006) suggests that after central sensitization appeared in FM syndrome, Aβ fibers that carry non-nociceptive input information to spinal cord, starts to transmit nociceptive input. TENS impulses that are transmitted to spinal cord by Aβ fibers may be determined as nociceptive information in addition to nociceptive stimulation for "Pain + TENS" condition in FM patients. Such alteration in pain perception mechanism due to changes in peripheral and central nervous systems is addressed in the work of Pogatzki-Zahn and her colleagues (Pogatzki-Zahn et al., 2009). Increased hemodynamic activity was found in FM group compared with healthy controls in the ipsilateral angular and supramarginal gyri. Several studies showed that higher hemodynamic activities were observed in FM patients when compared with healthy controls (Cook et al., 2004; Giesecke et al., 2004; Gracely et al., 2002; K. B. Jensen et al., 2012; Pujol et al., 2009). This might be related with excessive sensitivity to painful stimuli.

By assessing an equal pain sensation experiment, we observed significant activities in ipsilateral angular and supramarginal gyri, which are the two main subcomponents of IPL. IPL was found active in pain processing when equal pain sensation experiment was assessed in the recent studies (Gracely et al., 2002; Pujol et al., 2009). Activity differences in both groups in ipsilateral supramarginal and angular gyri, which are the two subcomponents of IPL, might be related with augmented pain processing in these regions. Excessive pain sensation and higher attention that was paid to the painful stimuli might cause higher activity in FM patients. This higher activity may indeed be associated with different pain threshold levels in the FM and the control groups.

For left hand stimulation, 2 x 2 repeated measures design ANOVA results indicated that significant differences was found in only condition main effect. Post hoc analysis showed that "Pain only" condition showed increased hemodynamic activity than "Pain + TENS" condition, an expected result due to the effect of TENS

treatment. A similar study performed to left legs of healthy controls showed that painful stimulation showed higher activation than painful stimulation with TENS in right middle frontal and right inferior parietal gyri of healthy subjects (Choi et al., 2015). We found “Pain only” activity higher than “Pain + TENS” activity in right middle frontal gyrus and left supramarginal gyrus which is the part of inferior parietal gyrus. In addition to these findings, we also observed TENS effect in right post central, right pre central and left superior parietal gyri. Compared to the ANOVA done on the right hand data presented above, these results on the left hand may reflect that TENS effect can change according stimulation side.

Condition main effect was observed in ipsilateral supramarginal gyrus located in IPL, ipsilateral post central gyrus and contralateral pre central gyrus. Post hoc results showed that “Pain only” activity was found higher than “Pain + TENS” activity. Recent studies on FM patients demonstrated that TENS causes a significant pain reduction (Carbonario et al., 2013; Dailey et al., 2013; Lofgren & Norrbrink, 2009; Mutlu et al., 2013). Activity reduction via TENS was found in right supramarginal gyrus located in inferior parietal lobe. Such a reduction in inferior parietal lobe was found in a recent study performed on healthy participants (Choi et al., 2015). This may indicate that TENS efficiency can be represented both in healthy controls and FM patients in parietal cortex which has an important role in pain perception.

When median nerve TENS stimulation and painful stimulation experiment results are merged for the right hand, we encountered a very important finding in bilateral superior parietal gyrus (Channel 3 and Channel 17). In these regions, while TENS activity in FM patients was found higher than healthy controls in TENS experiment, right hand painful stimulation experiment showed that “Pain + TENS” activity was found higher in FM patients than healthy controls, although there is no significant group difference in pain ratings. Therefore, this activity difference in both groups might be related with an unexpected contribution of TENS, causing allodynia in FM patients, which results in an activity increase due to hypersensitivity. At the same time, an activity decrease in healthy controls is observed because of expected results due to the “Gate Control Theory of Pain”. Such a striking result is not present in the left hand stimulation experiments we performed. There is not enough knowledge in FM literature that explains such a dichotomy between the right versus left hands.

On the other hand, Choi and his colleagues found that “Pain + TENS ” activity was higher than “Pain only” condition in post central gyrus of healthy participants (Choi et al., 2015), a finding similar to ours. Such an increase might be associated with TENS parameters, menstrual phase condition of female participants, pain threshold and amount of painful stimulation. A recent review including 20 studies performed with healthy participants revealed that frequency change in TENS, while keeping constant other parameters, does not cause any significant positive outcome (C.-C. Chen et al., 2008). But a recent study in 130 healthy participants showed that TENS efficiency at the pain site might be related with stimulation intensity (Moran et al., 2011). So, while Choi and his colleagues were applying an

average 16 mA TENS intensity, we applied 30 mA and this difference might cause a deactivation in BOLD signal. Another possible factor in this difference is amount of painful stimulation. Choi and his colleagues applied 45°C heat stimulation to all participants, while we were applying painful stimulation in levels of individual pain threshold. Also, due to desiring to create gender balanced groups, most of the participants were females.

A recent fNIRS study that focuses on significant differences between FM patients, FM patients with MDD and healthy controls revealed that FM patients showed higher bilateral activity than healthy controls (Uceyler et al., 2015). In this study, painful stimulation was performed onto the muscle bulk of the finger extensors of the right hand. So, in this case when we compared our right hand stimulation results with this study, we observed bilateral increased hemodynamic activation in FM patients compared with healthy controls. This is an important replication for reliability of our study.

Pain threshold of individuals might have been effective in such a difference in hemodynamic responses. Due to being a subjective measure, pain threshold may manipulate the cerebral signatures of pain perception. Moreover, menstrual phase of female participants might cause a significant change in pain threshold. Also, this may trigger sudden changes pain threshold. In our study, we applied painful stimulation at the level of individual pain threshold of participants.

5.3.Neural and Psychophysical Data Correlation

In this analysis, we used clinical information to correlate with fNIRS data: Pain threshold of both hands and Pain ratings of both hand and conditions.

Significant correlation between pain ratings and mean value of trial averaged hemodynamic response are generally observed in angular (BA 39) and superior parietal gyri. Angular gyrus is one of the main components of IPL which is involved in attentional network and strongly related region in pain perception (Porro et al., 2007). Correlations in IPL and angular gyrus are consistent with a previous study that includes right hand painful stimulation to FM and healthy controls (Pujol et al., 2009). These correlations indicate that pain ratings might be related with paid attention to the levels of painful stimuli in both groups. Superior parietal gyrus is generally known as somatosensory association area and strong correlation might indicate that this association is strongly related with pain perception. Also, superior parietal gyrus is related with attentional network of pain perception (Bushnell et al., 2013).

On the other hand, the nature of the correlations reveal a dichotomy related to the stimulated hand. For “Pain only” condition, the significant correlations between the pain ratings an mean brain activity in the contralateral superior parietal and angular –or supramarginal- gyri are positive for the left hand but negative for the right hand. The effect sizes vary between 0.35 to 0.45. This is an important finding which is not reported elsewhere until now, and it warrants further investigation.

Pain threshold and neural data correlation results indicate that a similar finding for the “Pain + TENS” condition as far as right hand stimulation is concerned. Right hand stimulation causes negative significant correlation in contralateral pre-central, and ipsilateral supramarginal, and post-central gyri. Negative correlation in these regions might indicate that hyperalgesia and allodynia causes excessive amount of pain sensation in patients that have low pain threshold. Due to malfunctioning in gate control theory peripheral and central sensitization causes lower pain threshold and excessive hyperalgesia and allodynia (Woolf, 2011). However in order to interpret these correlations faithfully, new experiments are warranted such that the intensity of pain stimulus is manipulated around individual pain threshold of each subject by delivering lower and higher intensities compared to the individual pain threshold.

5.4.Classification Analysis

Classification of FM patients and healthy controls was performed using SVM. Results indicated that linear and 2nd order degree polynomial kernel returned best classification performance, an accuracy of 90 %. Several functional neuroimaging studies with painful stimulation indicated that FM patients showed higher hemodynamic activity than healthy controls (Burgmer et al., 2010; Giesecke et al., 2005; Gracely et al., 2004; Gracely et al., 2002; Pujol et al., 2009). We thought that this difference might be a discriminative feature to classify the patients and healthy controls. We also used DTW as a feature to indicate similarity of the HRF and the HDR. These measures helped the SVM achieve a high accuracy.

We compared our classification results with classification based on self-report data (Pain-threshold, BDI score). However, our classification based on neuroimaging data outperformed the classification based on self-report data. This might indicate that subjective painful stimulation experiment contains features that might be considered as important biomarkers for classifying FM patients and healthy controls.

5.5.Demographic, Clinical and Psychophysical Data Analysis

In our study, we focused on handedness and effects of TENS in pain perception of FM syndrome patients and healthy controls. So, before our experiment we collected some clinical (BDI, FIQ) and psychophysical (Pain threshold, pain ratings) measures. We collected BDI values to measure the psychological mood of the patient or healthy participant. So, we found that BDI values of FM patients are significantly higher than healthy controls. This was expected case, because there are several evidences in literature that FM and psychological mood has a strong relationship (see review (Gracely et al., 2012)).

Another important parameter was pain threshold. In several studies, pain threshold of FM patients are significantly lower than healthy controls (Cook et al., 2004; Giesecke et al., 2004; Gracely et al., 2002; Pujol et al., 2009). Lower pain threshold

in FM patients was associated with abnormalities caudate and thalamus (Mountz et al., 1995) and increase of glutamate and glutamate + glutamine in insula (Harris et al., 2009). When pain threshold is measured from both hands, results showed that pain thresholds of FM patients are significantly lower than healthy controls and pain threshold of non-dominant (left) hand is significantly lower than dominant (right) hand. In literature, there are several explanations regarding hand differences in healthy controls: focusing on repulsive emotional component of pain rather than sensory one (Schiff & Gagliese, 1994), being fast and accurate using dominant hand which is strongly related with cerebral laterality (Ozcan et al., 2004). Same approaches may be considered for FM patients in to explain such laterality difference.

We collected pain ratings to observe the psychophysical effects of. As we expected there is no significant difference between groups and hands also no interaction between them. Because, we applied painful stimulation to every participant at the level of individual pain threshold to observe similar pain sensation. In terms of pain ratings, there is a significant difference between conditions “Pain only” and “Pain + TENS” conditions. Methodologically similar study showed that there is a significant difference between these conditions (Choi et al., 2015). However, while we were expecting a lower rating in “Pain + TENS” condition compared with “Pain only” condition, surprisingly we found the just the opposite result. This may be the result of being sensed an additive pain due to TENS.

5.6.Correlation Analysis of Psychophysical Results

Significantly positive correlation between BDI and FIQ scores indicated that there is strong association between psychological mood and severity of FM disease. There are several studies in which %90 of FM patients that had depressive symptoms and 62-86 % of them were also diagnosed as major depressive disorder (MDD) (Aguglia et al., 2011; Arnold et al., 2006; Marangell et al., 2011; Wilke et al., 2010). Co-occurence of depression and FM is generally thought as a combination of environmental and genetic factors. Triggering genetic factors by environmental factors such as stressful events causes Corticotrophin-releasing hormone (CRH), argininevasopressin (AVP), adrenocorticotrophic hormone (ACTH) and cortisol increase (Gracely et al., 2012).

There is no significant correlation between BDI score and pain threshold of both hands for both groups. Also, BDI did not show any significant association with Pain ratings collected during the painful stimulation with or without TENS. Some evidences in literature shows that some FM patients could show extreme pain sensitivity but this could not be associated with any psychological and cognitive factors (Giesecke et al., 2003). Positive correlation between Pain ratings and FIQ scores showed that severity of FM is strongly related with pain sensation.

5.7.Limitations of the Thesis

Our primary difficulty was the application of optical brain imaging to the female participants. Although, Hitachi ETG-4000 CW fNIRS system can work over the hairy skin, excessive amount of hair sometimes prevented us to complete the experiment and we had to discard some participants.

We did not counterbalance the right and left hand stimulation experiments. We always followed the experiment order by performing right hand stimulation experiment than left hand stimulation experiment both in TENS and painful stimulation experiment. That might have affected the results of left hand stimulation.

We applied painful stimulation and TENS manually. Therefore, during the application process, user-centric errors might have occurred such as timing of stimulation. An automated system might give more accurate results. Furthermore, the environmental setting of the experiment might have caused a threatening effect in the patients.

Due to insufficient number of participants, we could not apply several features in order to not to cause a curse of dimensionality problem. If we had larger data size, other classifiers could be used.

We could not create groups which are balanced in terms of education. We had to recruit that are educated less. This might be also an effective factor for our results because a recent study revealed that FM patients that have low socioeconomic level have more symptom severity (Fitzcharles et al., 2014). Also, we did not measure the pain sensation levels of FM patients before beginning the experiment and accepted FIQ score as the major indicator for severity of FM syndrome.

5.8.Future Work and Implications

Fibromyalgia is the one of the most popular research topics in rheumatology. It also has direct relationship with several psychiatric disorders such as depression, anxiety. Therefore, underlying reasons that cause FM should be investigated in advanced brain imaging studies. A recent review about central sensitization of FM patients using structural MRI and fMRI (Cagnie et al., 2014) addressed that cause and effect relationship should be investigated in further studies in different chronic pain groups. Central sensitization is not only observed in FM but also available in rheumatoid arthritis, osteoarthritis, temporomandibular disorders, headache, neuropathic pain, complex regional pain syndrome etc. (Woolf, 2011). One of the further studies should be focused on common main effects of central sensitization in different chronic pain patients. A resting state fMRI study on different groups can be performed to understand the common factors in central sensitization of these patients or a DTI study can enable to understanding the significant changes in white matter tract in the groups.

On the other hand, our findings from by stimulating both hands in FM group revealed that hand dominancy affects pain perception in FM patients. Especially, significant difference between pain thresholds of both hands and experimentally induced pain stimulation caused functional activation maps to reveal that handedness is a significant factor in pain perception in FM patients. More detailed neuroimaging studies might be performed to understand the causality of this effect.

Another significant question is the difference between FM and depression. There are several evidences that FM and depression shows the similar neurologic signatures (see review (Gracely et al., 2012)). Also, it was reported that 62-86 % of FM patients also show depressive symptoms (Aguglia et al., 2011; Arnold et al., 2006; Marangell et al., 2011; Wilke et al., 2010). But to understand the central sensitization mechanism in FM patients, differences between FM and depression should be noted.

In addition to the questions mentioned above, multimodal neuroimaging (fMRI-EEG or fNIRS-EEG) approaches might give us more accurate information about functional changes in FM patients during painful or non-painful stimulation studies. Especially, hypersensitivity to painful and non-painful stimulation can be explained in details by associating neural and hemodynamic responses from different domains.

CHAPTER 6

CONCLUSION

There is a growing interest for brain imaging in FM syndrome. Evidences that are found in neuroimaging studies addressed that FM causes structural and functional changes in brain. This study is one of the few studies that focus on FM syndrome by using fNIRS. fNIRS is a recently popular neuroimaging method that has several advantages compared with other modalities.

Our study consists of several important findings in fibromyalgia.

According to our findings from the brain activity patterns, pain perception in FM syndrome differs with respect to the dominant hand. Our primary objective was to understand whether TENS was effective in FM patients or not. Our findings supported that the gate control theory of pain malfunctions in FM syndrome in the dominant hand of strongly right handed subjects. This finding validates a new discussion about TENS efficiency in FM patients.

Classification of FM syndrome is an open problem in literature, since its diagnosis is being done based on verbal reports. We performed classification tests by considering features based on the fundamental differences between groups such as: hemodynamic activity during painful stimulation and change in hemodynamic activity during TENS application. In FM versus HC classification, we obtained higher accuracy compared to other structural and functional neuroimaging studies in the literature.

This thesis is a pioneering study in investigation of pain responses from both dominant and non-dominant hands in FM. The efficiency of TENS in pain perception in FM patients is found to be different based on the stimulated hand. Further studies will use this information and improve the methodology to understand the mechanism of pain perception in FM.

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APPENDIX A

ETHICAL BOARD APPROVAL FORM

KLİNİK ARAŞTIRMALAR ETİK KURULU KARAR FORMU

ARAŞTIRMANIN AÇIK ADI	Ağrı olgusunun somatosensöriyel ve pre frontal korteklerde sağlıklı ve fibromiyalji hastalığı olan bireylerde f NIRS kullanılarak araştırılması
VARSA ARAŞTIRMANIN PROTOKOL KODU	

ETİK KURUL BİLGİLERİ	ETİK KURULUN ADI	Ankara Üniversitesi Tıp Fakültesi Klinik Araştırmalar Etik Kurulu
	AÇIK ADRESİ:	Ankara Üniversitesi Tıp Fakültesi Morfoloji Binası 06100 Sıhhıye/ANKARA
	TELEFON	0312 595 82 27
	FAKS	0312 310 63 70
	E-POSTA	etik@medicine.ankara.edu.tr

BAŞVURU BİLGİLERİ	KOORDİNATÖR/SORUMLU ARAŞTIRMACI UNVANI/ADI/SOYADI	Yrd.Doç.Dr.Didem GÖKÇAY			
	KOORDİNATÖR/SORUMLU ARAŞTIRMACININ UZMANLIK ALANI				
	KOORDİNATÖR/SORUMLU ARAŞTIRMACININ BULUNDUĞU MERKEZ	Orta Doğu Teknik Üniversitesi Enformatik Enstitüsü			
	DESTEKLEYİCİ				
	DESTEKLEYİCİNİN YASAL TEMSİLCİSİ				
	ARAŞTIRMANIN FAZI VE TÜRÜ	FAZ 1	☐		
		FAZ 2	☐		
		FAZ 3	☐		
		FAZ 4	☐		
		Gözlemsel ilaç çalışması	☐		
		İlaç dışı klinik araştırma	☐		
		Diğer ise belirtiniz: Laboratuvar çalışması			
	ARAŞTIRMAYA KATILAN MERKEZLER	TEK MERKEZ ☒	ÇOK MERKEZLİ ☐	ULUSAL ☒	ULUSLARARASI ☐

ASLI GIBIDIR
10 Şubat 2016

Etik Kurul Başkanının
Unvanı/Adı/Soyadı: Prof. Dr. Mehmet MEMİ
İmza:

KLİNİK ARAŞTIRMALAR ETİK KURULU KARAR FORMU

ARAŞTIRMANIN AÇIK ADI	Ağrı olgusunun somatosensöriyel ve pre frontal korteklerde sağlıklı ve fibromiyalji hastalığı olan bireylerde f NIRS kullanılarak araştırılması
VARSA ARAŞTIRMANIN PROTOKOL KODU	

	Belge Adı	Tarihi	Versiyon Numarası	Dili
DEĞERLENDİRİLEN BELGELER	ARAŞTIRMA PROTOKOLÜ			Türkçe ☐ İngilizce ☐ Diğer ☐
	BİLGİLENDİRİLMİŞ GÖNÜLLÜ OLUR FORMU			Türkçe ☐ İngilizce ☐ Diğer ☐
	OLGU RAPOR FORMU			Türkçe ☐ İngilizce ☐ Diğer ☐
	ARAŞTIRMA BROŞÜRÜ			Türkçe ☐ İngilizce ☐ Diğer ☐

	Belge Adı		Açıklama
DEĞERLENDİRİLEN DİĞER BELGELER	SİGORTA	☐	
	ARAŞTIRMA BÜTÇESİ	☐	
	BİYOLOJİK MATERYEL TRANSFER FORMU	☐	
	İLAN	☐	
	YILLIK BİLDİRİM	☐	
	SONUÇ RAPORU	☐	
	GÜVENLİLİK BİLDİRİMLERİ	☐	
	DİĞER:	☐	

KARAR BİLGİLERİ		
	Karar No:04-178-14	**Tarih: 10 Mart 2014**
	Yukarıda bilgileri verilen başvuru dosyası ile ilgili belgeler araştırmanın/çalışmanın gerekçe, amaç, yaklaşım ve yöntemleri dikkate alınarak incelenmiş ve uygun bulunmuş olup araştırmanın/çalışmanın başvuru dosyasında belirtilen merkezlerde gerçekleştirilmesinde etik ve bilimsel sakınca bulunmadığına toplantıya katılan etik kurul üye tam sayısının salt çoğunluğu ile karar verilmiştir. NOT: Ağrı veren cihazın alkol yerine batikonla temizlenmesi önerilir.	

KLİNİK ARAŞTIRMALAR ETİK KURULU	
ETİK KURULUN ÇALIŞMA ESASI	Klinik Araştırmalar Hakkında Yönetmelik, İyi Klinik Uygulamaları Kılavuzu
BAŞKANIN UNVANI / ADI / SOYADI:	Prof.Dr.Mehmet MELLİ

Unvanı/Adı/Soyadı	Uzmanlık Alanı	Kurumu	Cinsiyet		Araştırma ile ilişki		Katılım *		İmza
Prof.Dr.Mehmet MELLİ	Farmakoloji	A.Ü.Tıp Fakültesi	E ☒	K ☐	E ☐	H ☒	E ☒	H ☐	
Prof.Dr.Cihan YURDAYDIN	Gastroenteroloji	A.Ü. Tıp Fakültesi	E ☒	K ☐	E ☐	H ☒	E ☐	H ☒	
Prof.Dr.Mehmet GÜREL	Genel Cerrahi	A.Ü. Tıp Fakültesi	E ☒	K ☐	E ☐	H ☒	E ☒	H ☐	
Prof.Dr.Tanju ÖZÇELİKAY	Farmakoloji	A.Ü.Eczacılık Fakültesi	E ☒	K ☐	E ☐	H ☒	E ☒	H ☐	
Doç.Dr.A. Ruhi SOYLU	Biyofizik	H.Ü. Tıp Fakültesi	E ☒	K ☐	E ☐	H ☒	E ☒	H ☐	
Prof.Dr.Cem ATBAŞOĞLU	Ruh Sağlığı ve Hastalıkları	A.Ü. Tıp Fakültesi	E ☒	K ☐	E ☐	H ☒	E ☐	H ☒	
Prof.Dr.Serdar ÖZTÜRK	Biyokimya	A.Ü. Tıp Fakültesi	E ☒	K ☐	E ☐	H ☒	E ☒	H ☐	
Prof.Dr.Serap SİVRİ	Çocuk Sağlığı ve Hastalıkları	H.Ü. Tıp Fakültesi	E ☐	K ☒	E ☐	H ☒	E ☒	H ☐	
Prof.Dr.Zarife ŞENOCAK	Hukuk	A.Ü.Hukuk Fakültesi	E ☐	K ☒	E ☐	H ☒	E ☐	H ☒	
Prof.Dr.Banu ÇAKIR	Halk Sağlığı	H.Ü. Tıp Fakültesi	E ☐	K ☒	E ☐	H ☒	E ☐	H ☒	
Prof.Dr.Güngör UTKAN	Tıbbi Onkoloji	A.Ü. Tıp Fakültesi	E ☒	K ☐	E ☐	H ☒	E ☒	H ☐	
Doç.Dr.Derya ÖZTUNA	Biyoistatistik	A.Ü. Tıp Fakültesi	E ☐	K ☒	E ☐	H ☒	E ☒	H ☐	
Yrd.Doç.Dr.Nüket KUTLAY	Tıbbi Genetik	A.Ü. Tıp Fakültesi	E ☐	K ☒	E ☐	H ☒	E ☒	H ☐	
Uz.Dr.Önder İLGİLİ	Tıp Tarihi ve Etik	A.Ü.Tıp Fakültesi	E ☒	K ☐	E ☐	H ☒	E ☒	H ☐	
Gülsüm ASLAN	Arkeoloji	-	E ☐	K ☒	E ☐	H ☒	E ☐	H ☒	

*:Toplantıda Bulunma

ASLI GİBİDİR

10 Şubat 2016

Etik Kurul Başkanının
Unvanı/Adı/Soyadı: Prof. Dr. Mehmet Melli
İmza:

APPENDIX B

INFORMED CONSENT FORM

Araştırmanın adı: Ağrı Olgusunun Somatosensöriyel ve Pre Frontal Kortekslerde Sağlıklı ve Fibromiyalji Hastalığı Olan Bireylerde fNIRS Kullanılarak Araştırılması

Sorumlu araştırmacı: Yrd. Doç. Dr. Didem Gökçay
Araştırmanın yapılacağı yer: ODTÜ Enformatik Enstitüsü, Ankara Üniversitesi Beyin Araştırma ve Uygulama Merkezi

Orta Doğu Teknik Üniversitesi Medikal Enfomatik bölümü Doktora öğrencisi Aykut EKEN tarafından, Orta doğu Teknik Üniversitesi Enformatik Enstitüsü Öğretim Üyelerinden Yrd. Doç. Dr. Didem Gökçay'ın danışmanlığında ve yine Ankara Fizik Tedavi ve Rehabilitasyon Hastanesi Uzman Doktorlarından Uzm. Dr. Murat Kara'nın ortak danışmanlığında, Doktora tezi kapsamında fibromiyalji tanısı alan hasta popülasyonlarında ağrı olgusunun araştırılması olarak planlanan bu araştırma projesine katılmak için davet edilmektesiniz. Çalışma sağlıklı ve hasta yetişkinleri kapsamaktadır ve çalışmaya 40 gönüllü katılacaktır.

Beyin görüntülemesi Ankara Üniversitesi Beyin Araştırma ve Uygulama Merkezinde bulunan ve beyin görüntülemeye yarayan fNIRS cihazı yardımıyla yapılacaktır ve herhangi bir potansiyel risk içermemektedir. fNIRS cihazında radyasyon veya tehlikeli bir dalgaboyunda herhangi bir ışın kullanılmaz klinik ve deneysel olarak pek çok uygulamaları vardır.

fNIRS çekimi öncesinde katılımcıların ağrı eşiklerini belirlemek için toplamda yaklaşık 2 dakika sürecek olan sayısal sensöriyel test von frey filamanı ile parmağa uygulanacaktır. Daha sonra katılımcılar bir koltuğa oturtularak başlarına fNIRS cihazının problarının bağlı olduğu kepler giydirilecek ve deney esnasında, önceden belirlenen ağrı eşiğinin yüzde 10 oranında arttırılmış bir hali parmağınıza uygulanacaktır. Aynı anda fizik tedavi işlemlerinde kullanılan TENS (Transkütan Elektriksel Sinir Uyarımı) ile rahatsız etmeyecek düzeyde elektriksel uyarım uygulanacaktır. Bu iki uyarı kesinlikle kalıcı bir fiziksel zarar vermeyecek olup sadece geçici ve kabul edilebilir rahatsızlığa neden olacak bir uyarılardır.

fNIRS çekimi tamamen zararsız bir işlemdir. Çekim süresince hiçbir kafa hareketi olmaması gerekmektedir. Öksürme, kafa sallama gibi hareketler sinyalde beklenmedik değişiklikler oluşturduğundan, bazı çekimlerin tekrarlanması gerekebilir. Bu nedenle mümkün olduğunca kafanızı kıpırdatmamanız gerekmektedir. Bu uygulama yaklaşık olarak 5 dakika sürecek olup, kesinlikle size herhangi bir fiziksel zarar vermeyecektir.

Bu çalışmada hakkınızda edinilen tüm bilgiler gizli tutulacak ve sadece araştırmacıların bilgisine sunulacaktır. Bu çalışmadan herhangi bir rapor veya yayın yapılması halinde okuyucuların sizleri tanımasına yol açacak hiçbir kişisel bilgi bulunmayacaktır.

Deney, genel olarak kişisel rahatsızlık verecek unsurlar içermemektedir. Ancak, katılım sırasında herhangi bir nedenden ötürü kendinizi rahatsız hissederseniz yanınızda duracak olan araştırıcıya söyleyerek yarıda bırakıp çıkmakta serbestsiniz. Araştırmaya katılımınız tamamıyla gönüllülük çerçevesinde olup, istediğiniz zaman, hiçbir yaptırım veya cezaya maruz kalmadan, hiçbir hak kaybetmeksizin araştırmaya katılmayı reddedebilir veya araştırmadan çekilebilirsiniz. Çalışmaya katılmamayı da seçebilirsiniz.

Deney sonunda, bu çalışmayla ilgili sorularınız cevaplanacaktır. Bu çalışmaya katıldığınız için şimdiden teşekkür ederiz. Çalışma hakkında daha fazla bilgi almak için veya herhangi bir sorunuz olduğunda, Orta Doğu Teknik Üniversitesi Medikal Enformatik Doktora öğrencisi Aykut EKEN (Tel: 0536 677 73 64, E-posta: aeken@metu.edu.tr), ODTÜ Enformatik Enstitüsü Öğretim Üyesi Yrd. Doç. Dr. Didem Gökçay (Oda: A-216, Tel: 03122103750, E-posta: dgokcay@metu.edu.tr ile iletişim kurabilirsiniz.

Bilgilendirilmiş Gönüllü Olur Formu'ndaki tüm açıklamaları okudum. Yukarıda konusu ve amacı belirtilen araştırma ile ilgili tüm yazılı ve sözlü açıklama aşağıda adı belirtilen araştırmacı tarafından yapıldı. Bu çalışmaya tamamen gönüllü olarak katılıyorum ve istediğim zaman gerekçeli veya gerekçesiz olarak yarıda kesip çıkabileceğimi veya kendi isteğime bakılmaksızın araştırmacı tarafından araştırma dışı bırakılabileceğimi biliyorum. Verdiğim bilgilerin bilimsel amaçlı yayınlarda isim bilgilerim olmadan kullanılmasını, görüntü kayıtlarıma sadece araştırmacı veya etik kurul tarafından gizli tutulmak kaydıyla erişilebilmesini kabul ediyorum. Kendi özgür irademle, hiçbir baskı ve zorlama olmadan "Ağrı Olgusunun Somatosensöriyel Kortekste ve Sağlıklı ve Fibromiyalji Hastalığı Olan Bireylerde fNIRS Kullanılarak Araştırılması" adlı çalışmaya katılmayı kabul ettiğimi ve bu formun bir kopyasının bana verildiğini aşağıdaki imzamla beyan ederim.

Gönüllü:

Adı Soyadı: Tarih İmza

----/----/-----

Adres ve telefon:

Tanıklık Eden Yardımcı Araştırmacı:

Adı Soyadı: Tarih İmza

----/----/----

APPENDIX C

PARTICIPANT INFORMATION AND fNIRS PAIN EXPERIMENT REPORT FORM

Kişisel Bilgiler **IDCODE :**

Adı:

Soyadı :

Yaşı :

Cinsiyeti :

Alınan Veriler

Kullandığı El (Edinburgh Handedness Test'e göre) : Sağ ❒ Sol ❒

BDI Score :

Dahil Olduğu Grup : Hasta ❒ Sağlıklı ❒

Yapılan Ölçümler

Ağrı Eşiği Ölçümleri

- Uygulanan Ağrı Şiddetleri :
- Elde edilen Ağrı Ratingleri :
- Ağrı Eşiği :

Probe Yerleşimi İçin Ölçümler

- Nasion – Inion (Nz-Iz) Dikey Mesafesi :
- Sağ kulak – Sol Kulak (AR-AL) Dikey Mesafesi :
- Nasion – Cz : Nz- IZ x 0.5 =
- Sağ kulak – C4 : AR-AL x 0.3 =
- Sol kulak – C3 : AR-AL x 0.3 =

TENS Eşiği :

TENS Esnasında Uygulanan Ağrı Şiddetleri : / /

TENS Yokken Uygulanan Ağrı Şiddetleri : / /

Deney Tarihi :

Deney ile ilgili diğer notlar :

APPENDIX D

FUNDAMENTALS OF FUNCTIONAL NEAR INFRARED SPECTROSCOPY

fNIRS is a non-invasive optical brain imaging technique that has been a recently popular in neuroimaging literature. From 1993 to 2014, several publications in different research areas have been published in PubMed by using fNIRS (Boas et al., 2014). Like Functional Magnetic Resonance Imaging (fMRI), fNIRS measures the cerebral hemodynamics While fMRI is using inhomogeneity of magnetic field caused by Deoxy-hemoglobin (HB) increase or decrease (Ogawa et al., 1990), fNIRS uses the light emission and scattering features of chromophores, Oxy-Hemoglobin (HBO2) and HB. Increase in deoxy-hemoglobin causes a decrease in fMRI intensity and vice versa. fNIRS measures concentration changes of Oxy- hemoglobin (Δc_{HBO2}) and Deoxy- hemoglobin (Δc_{HB}). Hemodynamic response is represented in fNIRS as increase in Δc_{HBO2} and decrease in Δc_{HB}. Hemodynamic response is an term related with the changes in MR signal caused by neural activity that are triggered by stimulation (Huettel et al., 2004). Relationship between neural activity and hemodynamic response is still unknown. Hemodynamic response is represented in fMRI and fNIRS in different ways. Hemodynamic response is represented in fMRI as decrease in HB and intensity changes in functional images caused by magnetic field inhomogeneity due to this decrease. However in fNIRS, both in HBO2 and HB changes are directly measured by light absorption and scattering. When compared this modality with other neuroimaging tools, it can be said that its portability and cost effectiveness are the greatest advantages of fNIRS. Also, it is a practical tool for measuring hemodynamic activity while performing static and dynamic motor activities (Perrey, 2008). Due to these advantages, its clinical and experimental applications have been increased recently.

Efficiency of a neuroimaging modality can be analyzed by considering two main features, spatial and temporal resolution. Spatial resolution in neuroimaging can be identified as the ability of discriminating signal alterations between different brain regions. Temporal resolution is the ability of detecting response of a stimulus as fast as possible in time domain. When compared with other modalities such as EEG, fMRI or PET, fNIRS has better temporal resolution and lower immobility than fMRI and better spatial resolution than EEG (Mehta & Parasuraman, 2013). In Figure 49. These comparisons are shown in a graphical representation.

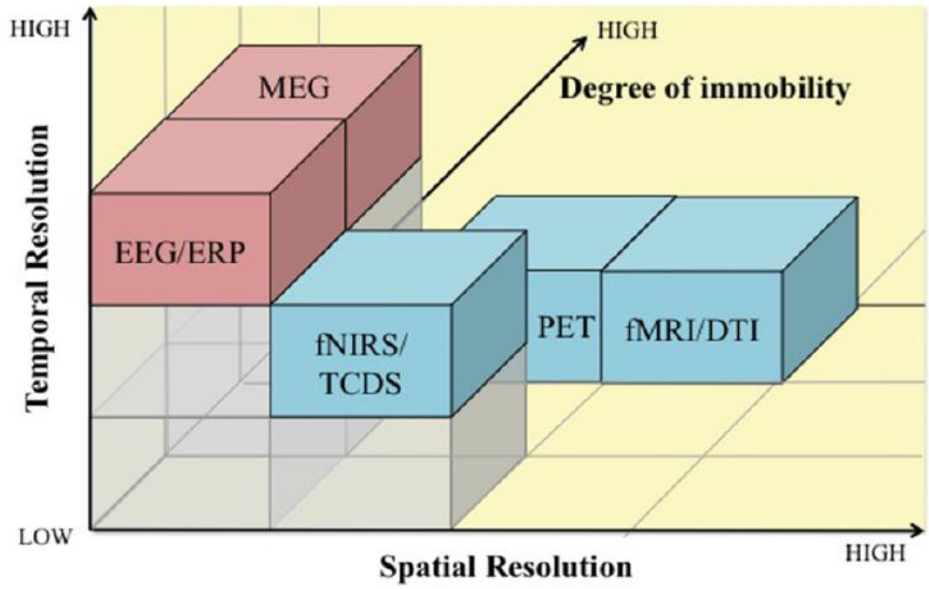

Figure 49. Degree of immobility, spatial and temporal resolutions of neuroimaging modalities (Mehta & Parasuraman, 2013)

On the other hand, the greatest disadvantage of fNIRS technology is the inability of measuring hemodynamic activity in deeper sub cortical structures. Near infrared light can only penetrate at most 3-4 cm, which prevents us to observe the hemodynamic activity in sub cortical regions.

Moreover, there are two types of optodes in fNIRS devices, sources and detectors. Near infrared light is sent from sources and captured by detectors. During this process, near infrared light travels by following a banana shape pathway due to potential absorption and scattering by tissues as shown in Figure 50.

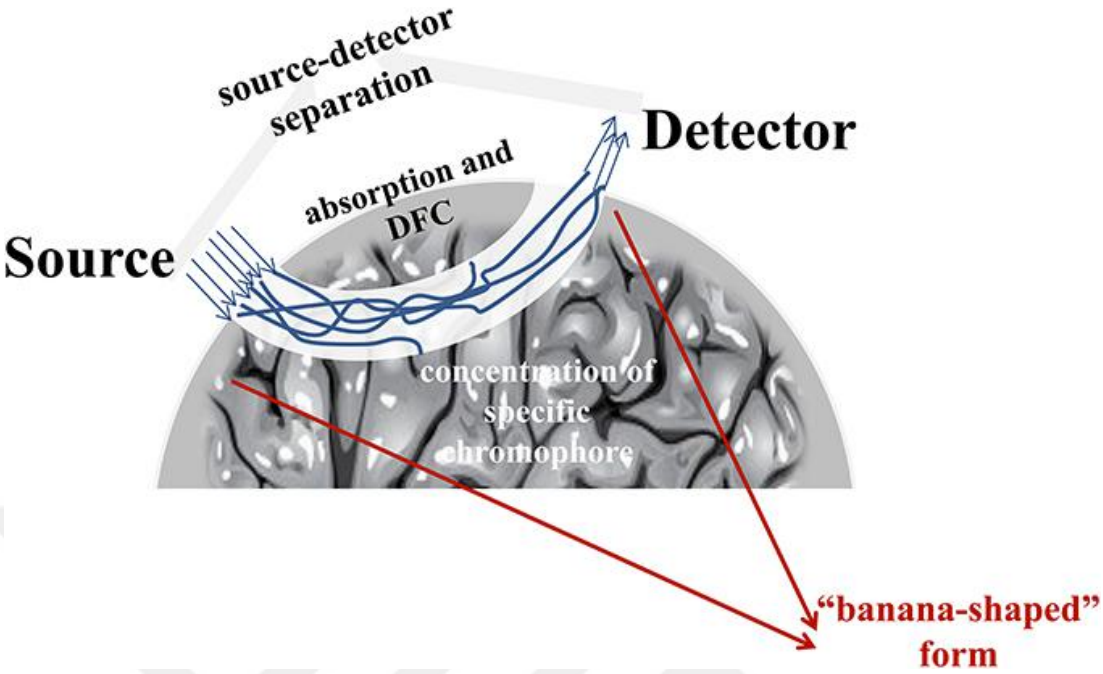

Figure 50. Penetration of near infrared light to the cortical tissue.
Near infrared light travels generally a banana shape pathway from source to detector. (Kopton & Kenning, 2014)

Hemodynamic activity measurement by fNIRS depends on Modified- Beer Lambert law (Cope & Delpy, 1988). When near infrared light penetrates to the tissue, it shows two types of behavior;

- Absorption by chromophores (HB, HBO2 and Water Molecules)
- Scattering by inhomogeneous medium (such as cell membrane)

Beer – Lambert law depends on a logarithmic ratio T, between the intensity of light that enters to a substance and leaves the substance. In this equation, intensity ratio is associated with concentration of chromophores c, distance between light enters and leaves the substance, d and absorption coefficient ε.

$$T = \frac{I_1}{I_0} = e^{-\varepsilon.c.d} \quad (9)$$

We find optical density (OD) by taking negative logarithm of T.

$$OD = -\log(T) \quad (10)$$

After, replacing intensity ratio of input and output lights, instead of T, we obtained that optical density equals to;

$$OD = -\log\left(\frac{I_1}{I_0}\right) = -\log\left(e^{-\varepsilon.c.d}\right)$$

$$OD = \log\left(\frac{I_0}{I_1}\right) = \varepsilon . c . d \ (11)$$

In this equation, I_1 is intensity of light that leaves the substance; I_0 is intensity of light that enters the substance. Near infrared light sent from a light source over the head surface is captured by detector as absorbed and scattered light. While analyzing optical density (OD) for different wavelengths, λ is used for different wavelengths of near infrared light.

$$OD(\lambda) = \varepsilon_\lambda . c . d = \log\left(\frac{I_{0\lambda}}{I_{1\lambda}}\right) \ (12)$$

The total optical density of light is sum of different wavelengths.

$$OD_{total}(\lambda) = \sum_{i=1}^{n} OD_n(\lambda) = \sum_{i=1}^{n} \varepsilon_{n,\lambda} . c_n . d \ (13)$$

In Equation 13, n represents the number of chromophores. For fNIRS, there are two chromophores. These are oxy-hemoglobin (HBO2) and deoxy-hemoglobin (HB). We find total optical density for a wavelength ($OD_{total}(\lambda)$) by adding optical densities of these chromophores for two wavelengths (for Hitachi ETG-4000, 680 and 900 nm).

In Modified Beer-Lambert law, some additive parameters were added to Beer-Lambert law such as differential path factor (DPF) and S_λ is the constant attenuation factor for wavelength λ and the equation 13 is modified as it is shown below;

$$OD_\lambda = \log\left(\frac{I_{0\lambda}}{I_{1\lambda}}\right) = \varepsilon_\lambda . \Delta c . d . DPF + S_\lambda \ (14)$$

To obtain the normalized optical density before beginning the experiment, a rest period is applied to obtain the reference optical density ($OD_{\lambda,rest}$) for wavelength λ. This is done for measuring the baseline near infrared light intensity. Then, it is removed from the optical density that is obtained during experiment ($OD_{\lambda,test}$) for wavelength λ. S_λ is removed in this equation.

$$\Delta OD_\lambda = OD_{\lambda,test} - OD_{\lambda,rest} \ (15)$$

We replaced optical density for both optical density of test and rest.

$$\Delta OD_\lambda = \log\left(\frac{I_{0\lambda}}{I_{test\lambda}}\right) - \log\left(\frac{I_{0\lambda}}{I_{rest\lambda}}\right) \ (16)$$

In Equation 16, $I_{test\lambda}$ is the intensity of light during test phase of experiment and $I_{rest\lambda}$ is the intensity of light during rest phase of experiment. Division in logarithm is converted to subtraction to remove out $log(I_{0\lambda})$.

$$\Delta OD_\lambda = \log(I_{0\lambda}) - \log(I_{test\lambda}) - \log(I_{0\lambda}) + \log(I_{rest\lambda}) \ (17)$$

Difference between optical density in during experiment and rest period is shown in Equation 18.

$$\Delta \mathrm{OD}_{\lambda} = \mathrm{OD}_{\lambda,\mathrm{test}} - \mathrm{OD}_{\lambda,\mathrm{rest}} = \log\left(\frac{\mathrm{I}_{\mathrm{rest}\lambda}}{\mathrm{I}_{\mathrm{test}\lambda}}\right) \quad (18)$$

To find the concentration changes in chromophores,

$$\Delta \mathrm{OD}_{\lambda} = \log\left(\frac{\mathrm{I}_{\mathrm{rest}\lambda}}{\mathrm{I}_{\mathrm{test}\lambda}}\right) = \sum_{i=1}^{n} \varepsilon_{\mathrm{i},\lambda}.\Delta \mathrm{c}_{\mathrm{i}}.\,\mathrm{d}.\,\mathrm{DPF} \quad (19)$$

In Equation 19, DPF is differential path factor that is used for scaling, related with source and detector seperations to path length that near infrared light follows between source and detector (Strangman et al., 2003), For both oxy-hemoglobin (HBO2) and deoxy- hemoglobin (HB), this summation is represented as ;

$$\Delta OD_{\lambda} = \varepsilon_{HBO2,\lambda}.\Delta c_{HBO2}.d.DPF + \varepsilon_{HB,\lambda}.\Delta c_{HB}.d.DPF \quad (20)$$

For two wavelengths $\lambda_1 = 680$ and $\lambda_2 = 900$, optical density changes are derived as ;

$$\begin{cases} \Delta OD_{\lambda_1} = \varepsilon_{HBO2,\lambda_1}.\Delta c_{HBO2}.d.DPF + \varepsilon_{HB,\lambda_1}.\Delta c_{HB}.d.DPF \\ \Delta OD_{\lambda_2} = \varepsilon_{HBO2,\lambda_2}.\Delta c_{HBO2}.d.DPF + \varepsilon_{HB,\lambda_2}.\Delta c_{HB}.d.DPF \end{cases} \quad (21)$$

These equations can be written as a linear system.

$$\begin{pmatrix} \Delta OD_{\lambda_1} \\ \Delta OD_{\lambda_2} \end{pmatrix} = \begin{bmatrix} \varepsilon_{HBO2,\lambda_1}.d.DPF & \varepsilon_{HB,\lambda_1}.d.DPF \\ \varepsilon_{HBO2,\lambda_2}.d.DPF & \varepsilon_{HB,\lambda_2}.d.DPF \end{bmatrix} \begin{pmatrix} \Delta c_{HBO2} \\ \Delta c_{HB} \end{pmatrix} \quad (22)$$

By solving this linear system for both Δc_{HB} and Δc_{HBO2}, we find the concentration changes of HB and HBO2.

In fNIRS systems, near infrared light in two types of wavelength are used. Lower wavelength near infrared light is generally between 680-730 nm. Higher one is 830-900 nm. This discrimination is necessary to maximize the measurement of related chromophore. As shown in Figure 51, absorption factor of HB is higher than HBO2 in range of 680-730 nm and vice versa between 830-900 nm.

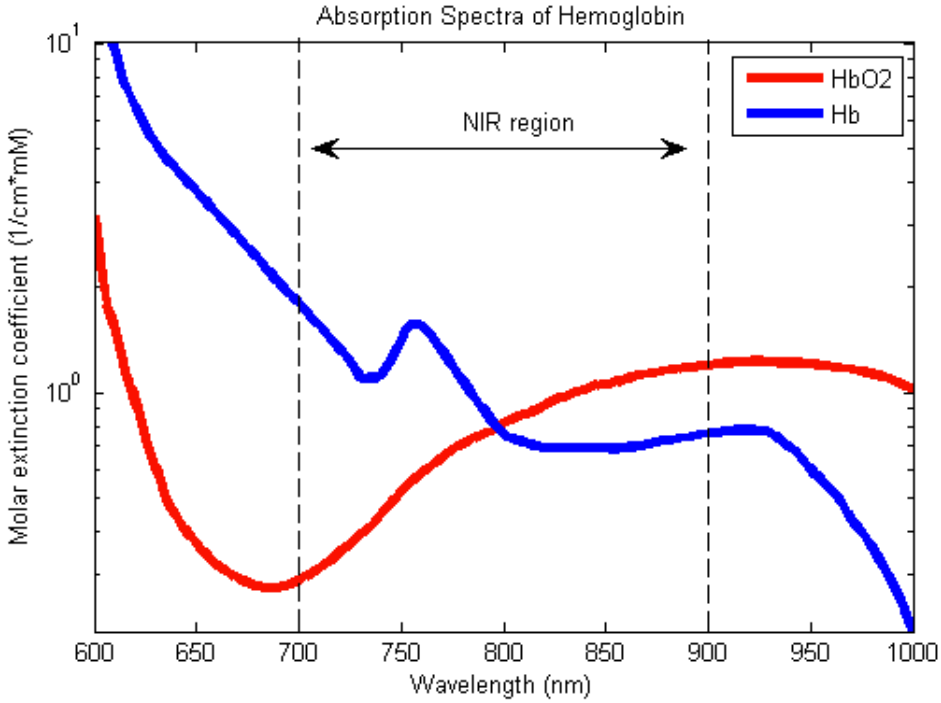

Figure 51. Relationship between absorption factor and wavelength for HBO2 and HB. (taken from https://en.wikipedia.org/wiki/Functional_near-infrared_spectroscopy).

APPENDIX E

WAVELET BASED MINIMUM DESCRIPTION LENGTH DETRENDING ALGORITHM (Jang et al., 2009)

In neuroimaging studies, there is significant difference between block and event-related BOLD results. Linear trend on BOLD response generally appears in block design studies due to cumulative effect of successive stimulation. To remove this effect, fitting a linearly increasing function onto the data and removing it from the data might be enough. However some extra low frequency artifacts, due to breathing or vaso-motion can appear during the experiment. These artifacts can significantly affect the results of General Linear Model (GLM) analysis of NIRS signals. To receive a reliable result from GLM analysis, these artifacts should be removed from data. However, while removing these low frequency artifacts, some low frequency hemodynamic activity related observations can be removed. Jang and his colleagues proposed this method to overcome these problems (Jang et al., 2009).

In this method, it is proposed that a wavelet function $\psi(t)$ which is associated with the multi-resolution analysis. $\Phi(t)$, h and g are respectively the functions of scaling, high pass filter and low pass filter related with this wavelet analysis. Besides, let θ be the continuous signal that has length N-1. So, J is the value that represents the number of maximum wavelet decomposition that satisfies the equation $N = 2^J$. Following recursive equations show extraction of the wavelet coefficients created by approximation coefficients $\{a\theta_j[k]\}_{j,k}$ and detail coefficients $\{d\theta_j[k]\}_{j,k}$.

$$a\theta_0[k] = \theta[k], \quad k = 0, \dots \dots . N-1. \text{ (23)}$$

$$a\theta_{j+1}[k] = \sum_n h[n-2k]a\theta_j[n], \quad k = 0, \dots, 2^{-j-1}N-1 \text{ (24)}$$

$$d\theta_{j+1}[k] = \sum_n g[n-2k]a\theta_j[n], \quad k = 0, \dots, 2^{-j-1}N-1 \text{ (25)}$$

In these equations, $j = 0 \dots J-1$. Then, a W matrix is introduced to show the discrete wavelet transform.

$$W\theta = (a\theta_j[0], d_j, d_{j-1}, \dots . , d_1)^T$$

In this vector,

$$d_j = (d\theta_j[0])$$

$$d_{j-1} = (d\theta_{J-1}[0], d\theta_{J-1}[1])^T$$

$$d_j = (d\theta_j[0], \dots, d\theta_j[2^{-J}N - 1])^T$$

$$\vdots$$

$$d_1 = (d\theta_1[0], \dots, d\theta_1[2^{-1}N - 1])^T \quad (26)$$

GLM of classical BOLD response can be shown as ;

$$y = X\beta + \varepsilon \quad (27)$$

In this equation, y is the BOLD response, X is the regressors, ϵ is the noise (assumed Gaussian behavior). If we add the linear trend bias θ to this model,

$$y = X\beta + \varepsilon + \theta \quad (28)$$

Except for θ, other components of this equation are almost known. In this point, linear trend can be modeled such that;

$$\theta(t) = \alpha\theta_j[0]\phi(2^{-J}t) + \sum_{j=J_0}^{J}\sum_{k=0}^{2^{-j}N-1} d\theta_j[k]\psi(2^{-j}t - k) \quad (29)$$

In this equation, J_0 is the best scale that identifies the smoothness of drift. Detail coefficients are all zero for best scales $1 \le j \le J_0 - 1$. Via discrete wavelet transform, linear trend can be shown

$$W\theta = [a\theta_J[0], d_J, \dots, d_{J_0}, 0, \dots, 0]^T$$

Maximum likelihood estimation of the linear trend and the unknown GLM coefficients β can be shown.

$$\xi = [A^T\Sigma^{-1}A]^{-1}A^T\Sigma^{-1}Wy. \quad (30)$$

In this equation, $\xi = (a\theta_J[0], d\theta_J[0], \dots, d\theta_{J_0}[2^{-J_0}N - 1], \beta)^T$ and A ;

$$A = \begin{bmatrix} I_{n_0 x n_0} & WX \\ 0_{(N-n_0)Xn_0} & \end{bmatrix}$$

In matrix A, $n_0 = 2^{-J_0+1}N$ shows the number of nonzero coefficients of trend function. $I_{n_0Xn_0}$ shows the identity matrix, $0_{(N-n_0)Xn_0}$ shows the zero matrix. A is a $N\ X\ (n_0 + L)$ matrix, Σ shows the noise covariance matrix that has $N\ X\ N$ dimensions. W is the discrete wavelet transform matrix and X is the wavelet coefficient matrix.

To obtain optimum result by using this algorithm, selection of J_0 is quite important. As mentioned above, J_0 specifies the number of wavelet coefficients n_0 that identifies the linear trend and naturally it influences the general form of the obtained linear trend signal θ. If n_0 is a large number, there will be an extreme loss in hemodynamic response signal. If it becomes smaller, then linear trend cannot be identified and removed clearly.

Selection of this parameter is carried out by model order selection methods. In this algorithm model order selection is done by Minimum Description Length method (Rissanen, 1978).

APPENDIX F

CORRELATION RESULTS BETWEEN fNIRS DATA and CLINICAL DATA

Table 17. Correlation between individual average trial mean HBO2 values and subjective pain ratings for both conditions and hands.
** and bold highlight represents significant correlations p<0.05

Channel	Region	Left Hand		Right Hand	
		"Pain only"	"Pain + TENS"	"Pain only"	"Pain + TENS"
1	Superior Parietal Gyrus	0,268	-0,056	-0,333	-0,297
2	Angular Gyrus	**0,338****	0,086	-0,296	0,005
3	Superior Parietal Gyrus	0,130	-0,129	**-0,363****	-0,189
4	Supramarginal Gyrus	0,180	-0,078	**-0,283****	-0,150
5	Supramarginal Gyrus	0,178	-0,063	-0,355	0,072
6	Post Central Gyrus	0,091	0,027	-0,205	-0,227
7	Post Central Gyrus	0,257	0,141	-0,170	-0,069
8	Pre Central Gyrus	0,158	-0,055	0,010	-0,155
9	Pre Central Gyrus	0,255	0,036	-0,126	0,037
10	Post Central Gyrus	0,126	-0,003	-0,257	-0,107
11	Middle Frontal Gyrus	-0,052	-0,233	0,009	-0,199
12	Pre Central Gyrus	0,102	0,001	-0,310	-0,122
13	Angular Gyrus	**0,462****	**0,325****	-0,086	0,187
14	Superior Parietal Gyrus	**0,387****	0,091	-0,038	-0,102
15	Supramarginal Gyrus	0,127	0,125	0,037	0,277
16	Supramarginal Gyrus	0,049	0,000	-0,166	-0,176
17	Superior Parietal Gyrus	0,310	-0,036	-0,242	-0,148
18	Supramarginal Gyrus	0,191	0,077	-0,167	0,031
19	Post Central Gyrus	0,162	0,111	-0,124	-0,127
20	Post Central Gyrus	0,169	0,235	-0,110	-0,089
21	Post Central Gyrus	0,186	0,075	-0,088	-0,080
22	Pre Central Gyrus	-0,088	-0,136	-0,053	-0,123
23	Pre Central Gyrus	0,181	0,135	0,057	0,039
24	Middle Frontal Gyrus	0,127	-0,095	-0,056	-0,182

Table 18. Correlation between individual average trial mean HBO2 values and Pain thresholds for both conditions and hands.
* and bold highlight represents the statistically significant results. (p<0.05).

Channel	Region	Left Hand		Right Hand	
		Pain	"Pain + TENS"	Pain	"Pain + TENS"
1	Superior Parietal Gyrus	0,114	**0,352****	0,198	-0,197
2	Angular Gyrus	0,085	0,239	-0,085	-0,114
3	Superior Parietal Gyrus	-0,159	0,166	0,197	-0,216
4	Supramarginal Gyrus	-0,085	0,243	-0,038	-0,202
5	Supramarginal Gyrus	0,162	0,103	0,116	-0,127
6	Post Central Gyrus	-0,213	0,127	0,080	-0,237
7	Post Central Gyrus	0,191	0,155	0,053	-0,129
8	Pre Central Gyrus	-0,082	-0,013	-0,066	-0,199
9	Pre Central Gyrus	-0,056	0,134	-0,124	-0,063
10	Post Central Gyrus	-0,052	-0,172	0,108	-0,066

11	Middle Frontal Gyrus	0,185	0,061	-0,127	-0,225
12	Pre Central Gyrus	-0,077	0,036	-0,037	**-0,369****
13	Angular Gyrus	-0,078	0,172	0,189	-0,223
14	Superior Parietal Gyrus	-0,110	0,243	-0,025	-0,175
15	Supramarginal Gyrus	-0,112	0,077	0,053	-0,302
16	Supramarginal Gyrus	-0,143	-0,025	-0,089	**-0,331****
17	Superior Parietal Gyrus	-0,149	0,151	-0,007	-0,196
18	Supramarginal Gyrus	-0,168	-0,166	-0,181	**-0,443****
19	Post Central Gyrus	-0,101	0,099	-0,073	**-0,450****
20	Post Central Gyrus	0,074	0,012	0,177	**-0,359****
21	Post Central Gyrus	0,021	0,001	-0,159	**-0,348****
22	Pre Central Gyrus	-0,028	0,039	0,037	-0,274
23	Pre Central Gyrus	0,053	-0,167	0,124	-0,240
24	Middle Frontal Gyrus	-0,019	0,027	-0,167	-0,186

APPENDIX G

TABLES OF STATISTICAL RESULTS

Table 19.Left and right hand TENS stimulation results of FM patients and healthy controls.
** represents the significant channels. All p values were corrected by channel number (p-val / 24).
Degrees of freedom for FM is 200, 3400 and for healthy controls 200,3000.
(C : Contralateral, I : Ipsilateral)

		FM Patients				Healthy Controls			
Channel	Region	Left Hand Median Nerve Stimulation		Right Hand Median Nerve Stimulation		Left Hand Median Nerve Stimulation		Right Hand Median Nerve Stimulation	
		C/I	F value of TENS / rest	C/I	F value of TENS / rest	C/I	F value of TENS / rest	C/I	F value of TENS / rest
1	Superior Parietal Gyrus	I	0,3803	C	0,7628	I	1,0293	C	0,6255
2	Angular Gyrus	I	2,0888**	C	2,1090**	I	1,3134**	C	0,3613
3	Superior Parietal Gyrus	I	2,9173**	C	0,1877	I	1,7732**	C	1,5645**
4	Supramarginal Gyrus	I	0,1010	C	0,7906	I	0,5954	C	0,9228
5	Supramarginal Gyrus	I	0,7290	C	0,5897	I	0,0932	C	0,4227
6	Post Central Gyrus	I	0,2681	C	2,4108**	I	0,8506	C	1,4615**
7	Post Central Gyrus	I	2,5557**	C	1,3198**	I	0,3973	C	1,1871**
8	Pre Central Gyrus	I	0,8059	C	1,4077**	I	1,3203**	C	1,3011**
9	Pre Central Gyrus	I	0,2658	C	3,4215**	I	0,4503	C	0,8054
10	Post Central Gyrus	I	0,7803	C	1,1716**	I	0,7502	C	0,2641
11	Middle Frontal Gyrus	I	1,3644**	C	1,8143**	I	0,7189	C	0,7996
12	Pre Central Gyrus	I	0,5389	C	1,5523**	I	1,0995	C	0,8861
13	Angular Gyrus	C	0,3610	I	0,4953	C	0,2289	I	2,2641**
14	Superior Parietal Gyrus	C	1,9889**	I	0,8181	C	1,8832**	I	2,0396**
15	Supramarginal Gyrus	C	4,4884**	I	2,4960**	C	1,7776**	I	0,3006
16	Supramarginal Gyrus	C	1,0823	I	0,5076	C	2,2724**	I	1,2046**
17	Superior Parietal Gyrus	C	0,7750	I	0,2787	C	0,9268	I	1,4810**
18	Supramarginal Gyrus	C	2,3774**	I	1,0291	C	2,7132**	I	1,6932**
19	Post Central Gyrus	C	0,4717	I	2,0098**	C	1,6241**	I	0,7814
20	Post Central Gyrus	C	1,5198**	I	1,0317	C	1,7639**	I	0,7077
21	Post Central Gyrus	C	1,7723**	I	0,7991	C	0,4512	I	2,2138**
22	Pre Central Gyrus	C	0,4884	I	1,3270**	C	0,8523	I	0,6913
23	Pre Central Gyrus	C	0,8715	I	1,1552**	C	1,1581	I	0,2743
24	Middle Frontal Gyrus	C	1,8542**	I	1,1114**	C	1,4867**	I	0,6945

Table 20. Activated Regions of FM patients in Left hand Painful Stimuli Experiment for 3 conditions. A corrected p value (0.05/24) is used as a threshold for statistical significance. ** represents significant activations. Degrees of freedom (df): 200, 7200.(C : Contralateral, I : Ipsilateral)

Channel	Region	C / I	F values of "Pain only" / rest	F values of "Pain + TENS" / rest	F values of "Pain only" / "Pain + TENS"
1	Superior Parietal Gyrus	I	3.6370**	2.1020**	1.2968
2	Angular Gyrus	I	10.8214**	9.5809**	1.2014
3	Superior Parietal Gyrus	I	7.5248**	5.5874**	3.8132**
4	Supramarginal Gyrus	I	7.3791**	7.7932**	1.4779
5	Supramarginal Gyrus	I	5.2602**	6.7028**	1.2572
6	Post Central Gyrus	I	11.6285**	4.6296**	3.6968**
7	Post Central Gyrus	I	4.2172**	5.1070**	0.5175
8	Pre Central Gyrus	I	5.7938**	3.3983**	0.7639
9	Pre Central Gyrus	I	9.2659**	7.1544**	0.7807
10	Post Central Gyrus	I	2.0162**	3.1472**	0.0536
11	Middle Frontal Gyrus	I	2.0727**	2.6972**	0.3228
12	Pre Central Gyrus	I	2.1741**	4.9760**	0.3332
13	Angular Gyrus	C	18.7958**	10.5509**	2.1199**
14	Superior Parietal Gyrus	C	17.5761**	12.1784**	1.8453**
15	Supramarginal Gyrus	C	9.2045**	7.9335**	0.7031
16	Supramarginal Gyrus	C	31.1577**	24.9681**	1.7327**
17	Superior Parietal Gyrus	C	16.2596**	11.4338**	2.1080**
18	Supramarginal Gyrus	C	19.3479**	16.9992**	0.6813
19	Post Central Gyrus	C	26.7581**	15.5732**	2.5450**
20	Post Central Gyrus	C	3.2866**	1.5918**	0.4529
21	Post Central Gyrus	C	24.7638**	12.4293**	2.2730**
22	Pre Central Gyrus	C	11.9837**	3.0677**	2.7144**
23	Pre Central Gyrus	C	9.2631**	3.1481**	2.1522**
24	Middle Frontal Gyrus	C	9.2378**	2.8482**	1.9326**

Table 21. Activated Regions of FM patients in Right hand Painful Stimuli Experiment for 3 conditions. A corrected p value (0.05/24) is used as a threshold for statistical significance. ** represents not significant activations (p>0.05). Degrees of freedom (df) :200, 7200. Highlighted values are the greater ones to compare with other condition. (C : Contralateral, I: Ipsilateral)

Channel	Region	C/I	F values of "Pain only" / rest	F values of "Pain + TENS" / rest	F values of "Pain only" / "Pain + TENS"
1	Superior Parietal Gyrus	C	21,8335**	26,3387**	0,6184
2	Angular Gyrus	C	19,9742**	20,3111**	1,6584**
3	Superior Parietal Gyrus	C	13,6590**	17,3804**	0,4317
4	Supramarginal Gyrus	C	22,7248**	21,5862**	0,7128
5	Supramarginal Gyrus	C	4,4552**	9,2849**	1,2879**
6	Post Central Gyrus	C	15,3423**	20,3569**	0,2429
7	Post Central Gyrus	C	9,2365**	14,2012**	0,7714
8	Pre Central Gyrus	C	15,8644**	21,5891**	0,3814
9	Pre Central Gyrus	C	16,2888**	19,2531**	0,7823
10	Post Central Gyrus	C	2,5251**	2,7339**	0,3380
11	Middle Frontal Gyrus	C	8,9244**	8,7622**	0,3618
12	Pre Central Gyrus	C	6,6662**	3,6519**	0,6458
13	Angular Gyrus	I	13,5222**	14,1847**	1,2494**
14	Superior Parietal Gyrus	I	8,7268**	20,1844**	1,5314**
15	Supramarginal Gyrus	I	10,6350**	13,4451**	0,4191
16	Supramarginal Gyrus	I	17,6590**	14,2801**	0,5656
17	Superior Parietal Gyrus	I	8,2136**	16,9426**	1,2751**
18	Supramarginal Gyrus	I	11,5371**	12,2384**	0,4760
19	Post Central Gyrus	I	9,3588**	11,5776**	0,0641
20	Post Central Gyrus	I	4,6347**	9,3031**	0,4806
21	Post Central Gyrus	I	15,1531**	14,6265**	0,1770
22	Pre Central Gyrus	I	3.8369**	4,3580**	0,1171
23	Pre Central Gyrus	I	4.7525**	8,8130**	0,3783
24	Middle Frontal Gyrus	I	6.6363**	6,8673**	0,0638

Table 22. .Activated Regions of healthy controls in Left hand Painful Stimuli Experiment for 3 conditions. A corrected p value (0.05/24) is used as a threshold for statistical significance. ** represents significant activations (p>0.05). Degrees of freedom (df) : 200, 6400. (C : Contralateral , I : Ipsilateral)

Channel	Region	C / I	F values of "Pain only" / rest	F values of "Pain + TENS" / rest	F values of "Pain only" / "Pain + TENS"
1	Superior Parietal Gyrus	I	2,54**	1,29	0,33
2	Angular Gyrus	I	3,35**	2,46**	0,16
3	Superior Parietal Gyrus	I	2,68**	1,31	0,31
4	Supramarginal Gyrus	I	1,79**	0,95	0,44
5	Supramarginal Gyrus	I	4,56**	0,44	1,68**
6	Post Central Gyrus	I	2,06**	1,60**	0,15
7	Post Central Gyrus	I	5,76**	0,87	2,93**
8	Pre Central Gyrus	I	3,55**	3,46**	0,08
9	Pre Central Gyrus	I	1,90**	2,67**	0,05
10	Post Central Gyrus	I	1,22	0,29	0,75
11	Middle Frontal Gyrus	I	2,44**	2,78**	0,48
12	Pre Central Gyrus	I	1,51**	1,84**	0,09
13	Angular Gyrus	C	6,24**	5,44**	0,17
14	Superior Parietal Gyrus	C	6,12**	6,33**	0,04
15	Supramarginal Gyrus	C	7,80**	4,50**	0,38
16	Supramarginal Gyrus	C	7,21**	6,96**	0,33
17	Superior Parietal Gyrus	C	5,28**	4,86**	0,28
18	Supramarginal Gyrus	C	7,76**	7,75**	1,28
19	Post Central Gyrus	C	8,38**	6,50**	0,47
20	Post Central Gyrus	C	0,59	0,95	0,57
21	Post Central Gyrus	C	4,26**	1,03	0,80
22	Pre Central Gyrus	C	6,80**	5,80**	0,26
23	Pre Central Gyrus	C	1,59**	2,06**	0,63
24	Middle Frontal Gyrus	C	2,65**	0,76	0,49

Table 23. Activated Regions of healthy controls in Right hand Painful Stimuli Experiment for 3 conditions. A corrected p value (0.05/24) is used as a threshold for statistical significance. ** represents significant activations (p>0.05). Degrees of freedom (df) : 200, 6400. (C : Contralateral, I: Ipsilateral)

Channel	Region	C / I	F values of "Pain only" / rest	F values of "Pain + TENS" / rest	F values of "Pain only" / "Pain + TENS"
1	Superior Parietal Gyrus	C	13,59**	9,10**	1,87**
2	Angular Gyrus	C	5,72**	3,06**	1,28
3	Superior Parietal Gyrus	C	12,26**	8,82**	1,85**
4	Supramarginal Gyrus	C	7,99**	6,32**	1,11
5	Supramarginal Gyrus	C	5,97**	2,01**	1,31**
6	Post Central Gyrus	C	9,85**	9,07**	1,64**
7	Post Central Gyrus	C	5,99**	3,74**	1,45**
8	Pre Central Gyrus	C	8,17**	14,65**	1,34**
9	Pre Central Gyrus	C	6,02**	8,58**	1,43**
10	Post Central Gyrus	C	2,71**	1,09	0,56
11	Middle Frontal Gyrus	C	6,58**	12,25**	1,45**
12	Pre Central Gyrus	C	6,66**	4,39**	1,80**
13	Angular Gyrus	I	3,67**	2,25**	0,92
14	Superior Parietal Gyrus	I	7,51**	3,25**	0,80
15	Supramarginal Gyrus	I	6,13**	2,39**	1,23
16	Supramarginal Gyrus	I	4,39**	2,46**	1,37**
17	Superior Parietal Gyrus	I	5,95**	4,21**	1,07
18	Supramarginal Gyrus	I	5,66**	3,84**	0,66
19	Post Central Gyrus	I	5,25**	3,59**	0,79
20	Post Central Gyrus	I	4,41**	2,30**	0,31
21	Post Central Gyrus	I	2,82**	2,38**	0,32
22	Pre Central Gyrus	I	6,63**	7,96**	0,93
23	Pre Central Gyrus	I	13,59**	9,10**	1,87**
24	Middle Frontal Gyrus	I	5,72**	3,06**	1,28

Table 24. All 2 x 2 repeated measures ANOVA results of TENS and Painful Stimulation Experiment by using mean HBO2 results.
For TENS stimulation we used Group (FM & HC) and Hand (Right & Hand) variables.
For painful stimulation experiment, we used right and left hand stimulation data separately for Group (FM & HC) and Condition ("Pain only" & "Pain + TENS").
Bold highlighted and underlined p values are statistically significant ($p < 0.05$). Bold highlighted and underlined explanations are post hoc comparison results shown below the p values.

		TENS Experiment			Painful Stimulation with TENS Experiment					
					Left Hand			Right Hand		
Channel	Region	Group	Hand	Group x Hand	Group	Condition	Group x Condition	Group	Condition	Group x Condition
1	Superior Parietal Gyrus	n.s	n.s	n.s	n.s	n.s	n.s	n.s.	n.s.	**0,019 Pain + TENS of FM > Pain + TENS of HC**
2	Angular Gyrus	n.s	n.s	n.s	n.s	n.s	n.s	n.s.	n.s.	n.s.
3	Superior Parietal Gyrus	**0,031 FM>HC**	n.s	n.s	n.s	n.s	n.s	n.s.	n.s.	**0,009 Pain + TENS of FM > Pain + TENS of HC**
4	Supramarginal Gyrus	n.s	n.s	n.s	n.s	n.s	n.s	n.s.	n.s.	**0,016 Pain + TENS of FM > Pain + TENS of HC**
5	Supramarginal Gyrus	n.s	n.s	n.s	n.s	**0,004 Pain only > Pain + TENS**	n.s	n.s.	n.s.	n.s.
6	Post Central Gyrus	n.s	n.s	n.s	**0,014 FM>HC**	n.s	n.s	n.s	n.s.	**0,011 Pain + TENS of FM > Pain + TENS of HC**
7	Post Central Gyrus	n.s	n.s	n.s	n.s	**0,006 Pain only > Pain + TENS**	n.s	n.s.	n.s.	**0,036 Pain + TENS of FM > Pain + TENS of HC**
8	Pre Central Gyrus	n.s	n.s	n.s	n.s	n.s	n.s	n.s.	n.s.	**0,010 Pain + TENS of FM > Pain + TENS of HC**
9	Pre Central Gyrus	n.s	n.s	n.s	n.s	n.s	n.s	n.s.	n.s.	**0,037 Pain + TENS of FM > Pain + TENS of HC**
10	Post Central Gyrus	n.s	n.s	n.s	n.s	n.s	n.s	n.s.	n.s.	n.s.

11	Middle Frontal Gyrus	n.s	n.s	n.s	n.s	n.s	n.s	n.s.	n.s.	n.s.
12	Pre Central Gyrus	n.s	n.s	n.s	n.s	n.s	n.s	n.s.	n.s.	n.s.
13	Angular Gyrus	n.s	n.s	n.s	n.s	n.s	n.s	n.s.	n.s.	**0,023 Pain + TENS of FM > Pain + TENS of HC**
14	Superior Parietal Gyrus	n.s	n.s	n.s	n.s	n.s	n.s	n.s.	n.s.	**0,005 Pain + TENS of FM > Pain + TENS of HC**
15	Supramargina l Gyrus	n.s	n.s	n.s	n.s	n.s	n.s	n.s.	n.s.	n.s.
16	Supramargina l Gyrus	**0,021 FM>H C**	n.s	n.s	n.s	n.s	n.s	**0,044 FM>H C**	n.s.	n.s.
17	Superior Parietal Gyrus	**0,010 FM>H C**	n.s	n.s	n.s	n.s	n.s	n.s.	n.s.	**0,003 Pain + TENS of FM > Pain + TENS of HC**
18	Supramargina l Gyrus	**0,012 FM>H C**	n.s	n.s	**0,041 FM>H C**	n.s	n.s	n.s.	n.s.	n.s.
19	Post Central Gyrus	n.s	n.s	n.s	n.s	n.s	n.s	n.s.	n.s.	**0,038 Pain + TENS of FM > Pain + TENS of HC**
20	Post Central Gyrus	n.s	n.s	n.s	n.s	n.s	n.s	n.s.	n.s.	**0,048 Pain + TENS of FM > Pain + TENS of HC**
21	Post Central Gyrus	**0,022 FM>H C**	n.s	n.s	n.s	n.s	n.s	n.s	n.s.	n.s.
22	Pre Central Gyrus	n.s	n.s	n.s	n.s	n.s	n.s	n.s.	n.s.	**0,025 Pain + TENS of FM > Pain + TENS of HC**
23	Pre Central Gyrus	n.s	n.s	n.s	n.s	**0,042 Pain only > Pain + TENS**	n.s	n.s.	n.s.	**0,037 Pain + TENS of FM > Pain + TENS of HC**
24	Middle Frontal Gyrus	**0,007 FM>H C**	n.s	n.s	n.s	n.s	n.s	n.s.	n.s.	n.s.

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MS	Başkent University Biomedical Engineering	2009
BS	Başkent University Biomedical Engineering	2006
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WORK EXPERIENCE

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2016-	Düzce University	Research Assistant
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2007 December- 2008 April	Penta Electronic Medical Systems (Ultrasound Distributor of GE)	Sales Specialist
2006 December- 2007 December	Turkish Armed Forces Health Commandership	Medical Lieutenant
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FOREIGN LANGUAGES

English (TOEFL : 83 (2011), ÜDS : 76.25 (2011)), Spanish (Active English A1+A2 certificate and B1 class)

ABSTRACTS

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HOBBIES

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Operating Systems: Windows, OS X
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Language, LaTeX
Neuroimaging Softwares : AFNI, SPM, FSL (fMRI & MRI analysis), NIRS-SPM, NAP, POTATo (fNIRS analysis), EEGLAB, Fieldtrip (EEG-ERP Analysis).

VITA

Aykut Eken was born in Ankara on August 17, 1984. He received his B.S and MSc. degree in Biomedical Engineering from the Başkent University in July 2006 and February 2009 respectively. He worked in private companies as sales specialist, product specialist of medical devices, researcher in Middle East Technical University and research assistant in same institution since then. He started his PhD studies in the same university in 2009 Medical Informatics department. His main areas of interest in academics are functional neuroimaging, signal processing and pattern classification in neurological signals.