RESTING STATE NETWORK DISORGANIZATION AS NEURAL CORRELATE OF COGNITIVE DYSFUNCTION IN MULTIPLE SCLEROSIS

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INDEX

Abbreviations

HC: Healthy Control

fMRI: functional Magnetic Resonance Imaging

ICA: Independent Component Analysis

MRI: Magnetic Resonance Imaging

MiniSEA: Social Cognition and Emotional Assessment, brief version.

MS: Multiple Sclerosis

ROI: Regions of Interest

RR: Relapsing-Remitting

RR-MS: Relapsing-Remitting Multiple Sclerosus

RS: Resting State

RS-fMRI: resting state functional Magnetic Resonance Imaging

SIENAX: Structural Image Evaluation using Normalization of Atrophy

SPM: Statistical Parametric Mapping

ToM: Theory of Mind

VBM: Voxel-Based Morphometry

Resumen

La Esclerosis Múltiple, una enfermedad neurodegenerativa e inflamatoria crónica que afecta al sistema nervioso central, produce compromiso estructural y funcional del cerebro humano que ha sido bien descrito tanto desde el tipo de daño específico que genera a nivel de la sustancia gris y blanca, como los respectivos cambios en la conectividad que involucran desconexión y aumentos compensatorios de la conectividad funcional. Estas alteraciones generan, a lo largo de la historia natural de la enfermedad, niveles significativos de discapacidad tanto física como cognitiva.

En este último dominio, se ha descrito que hasta el 70% de los pacientes desarrollarán deterioro cognitivo afectando principalmente a funciones mentales como la velocidad de procesamiento, memoria de trabajo, aprendizaje y memoria verbal y visual, entre otros. Sin embargo, existe menos evidencia respecto al patrón en que se compromete la Cognición Social, un dominio cognitivo que ha motivado creciente interés en los últimos años y que podría tener un gran impacto en la calidad de vida de las personas afectadas.

Se entiende por cognición social a los procesos mentales involucrados en la decodificación de información sensorial de relevancia para la interacción con otros sujetos, su interpretación en el amplio sentido y la producción de los sustratos mentales para la conducta social. Aunque existen múltiples definiciones y su funcionamiento se ha conceptualizado a través de la identificación de diversos dominios, en la presente investigación nos centramos específicamente el las funciones de Percepción Social y Teoría de la Mente.

En primer lugar, la Percepción Social se relaciona con la adecuada capacidad de los sujetos de identificar los componentes emocionales contenidos, por ejemplo en la información visual. De esta forma, ante la observación de una cara con una tensa contracción de la frente y una particular disposición de los labios y dientes, es posible identificar esa expresión como enojo. Por otro lado, la Teoría de la Mente se relaciona con la capacidad de los sujetos de atribuir estados mentales a las personas con quienes interactúan en base a elementos del discurso, el contexto o bien de la expresión facial y corporal.

Así, los componentes de la cognición social le permiten a las personas adaptarse adecuadamente a las situaciones, interactuar con el entorno social y generar respuestas conductuales adaptativas.

El objetivo del presente estudio fue identificar los cambios estructurales y funcionales que se relacionan con alteraciones de la cognición social en pacientes con Esclerosis Múltiple.

Se realizaron pruebas cognitivas y adquisiciones de resonancia magnética estructural y funcional en 50 sujetos controles sanos y 68 pacientes con Esclerosis Múltiple Recurrente-Remitente. Estos últimos tenían una edad media cercana a 37 años y bajos niveles de discapacidad física (medidos por EDSS). A nivel clínico, fue posible objetivar menor rendimiento en las pruebas de cognición social en pacientes comparados con sujetos controles sanos. Esta alteración se dio de manera más significativa en el dominio de la Percepción Social que en el de Teoría de la Mente.

Además de la atrofia cerebral generalizada en los pacientes también fue posible identificar diversas regiones que mostraron significativas reducciones del volumen local, así como cambios en la conectividad funcional del cerebro completo en estado de reposo tanto con pares de regiones con aumento como disminución en la conectividad funcional.

Específicamente, el compromiso estructural de la ínsula y estructuras frontales mediales bilaterales se correlacionó significativamente con el nivel de deterioro de los procesos de la cognición social. Así también, a nivel funcional, cambios en la conectividad de la amígdala y de la corteza fusiforme se vieron involucrados en el deterioro de este dominio cognitivo, particularmente de la Percepción Social.

Abstract

Multiple Sclerosis is a chronic neurodegenerative and inflammatory disease that affects the central nervous system. It produces structural and functional compromise of the human brain that has been well described both from the type of specific damage it generates at the level of the gray and white matter, as well as the respective changes in connectivity that involve disconnection and compensatory increases in functional connectivity. These alterations generate, during the natural history of the disease, significant levels of both physical and cognitive disability.

In this last domain, it has been described that up to 70% of patients will develop cognitive impairment mainly affecting mental functions such as processing speed, working memory, verbal and visual memory, and learning, among others. However, there is less evidence regarding the pattern in which Social Cognition is committed, a cognitive domain that has motivated growing interest in recent years and that could have a significant impact on the quality of life of the people affected.

Social cognition is understood as the mental processes involved in the decoding of sensory information of relevance for interaction with other subjects, its interpretation in the broadest sense and the production of mental substrates for social behavior. Although there are multiple definitions and their functioning has been conceptualized through the identification of various domains, in this research, we specifically focus on the functions of Social Perception and Theory of Mind.

In the first place, Social Perception is related to the adequate capacity of the subjects to identify the emotional components contained, for example in visual information. In this way, before the observation of a face with a tense contraction of the forehead and a particular disposition of the lips and teeth, it is possible to identify that expression as anger.

On the other hand, the Theory of Mind is related to the capacity of the subjects to attribute mental states to the people with whom they interact based on elements of the discourse, the context or of the facial and corporal expression.

Thus, the components of social cognition allow people to adapt appropriately to situations, interact with the social environment and generate adaptive behavioral responses.

The objective of the present study was to identify the structural and functional changes that are related to alterations in social cognition in patients with Multiple Sclerosis.

Cognitive tests and acquisitions of structural and functional magnetic resonance were performed in 50 healthy controls and 68 patients with Multiple Recurrent-Remitting Sclerosis. The latter had an average age close to 37 years and low levels of physical disability (measured by EDSS). At a clinical level, it was possible to objectify lower performance in social cognition tests in patients compared with healthy control subjects. This alteration occurred more significantly in the domain of Social Perception than in the Theory of Mind.

In addition to the generalized cerebral atrophy in the patients, it was also possible to identify several regions that showed significant reductions in local volume, as well as changes in the functional connectivity of the whole brain at rest with both pairs of regions with increased and decreased functional connectivity.

Specifically, the structural involvement of the insula and bilateral medial frontal structures was significantly correlated with the level of impairment of the processes of social cognition.

Likewise, at the functional level, changes in the connectivity of the amygdala and fusiform cortex were involved in the deterioration of this cognitive domain, particularly of Social Perception.

I. Introduction

Chapter 1. Multiple Sclerosis Overview

Multiple Sclerosis (MS) has been characterized by inflammation, demyelination and neurodegeneration within the Central Nervous System (Dendrou, 2015; Friese, 2014) in the context of an autoimmune disease initiated by T cells (Dos Passos, 2016; Domingues, 2010). It represents the first cause of non-traumatic disability in the young-adult population with the striking potential of generating high degrees of disability in the third and fourth decade of life (Hohlfeld, 2009;Cristiano 2008, Eskandarieh, 2016, Benamer, 2009). Almost any motor, sensorial and cognitive domain has shown to be compromised during the disease evolution, caused by genetic and environmental factors such as infections or low vitamin D levels (Sadovnick, 1996). The main biological facts are well correlated to radiological findings. White matter lesions considered as typical of MS in distribution, morphology and evolution are the most characteristic kind of damage (Filippi, 2015). Figure 1 shows examples of Images fulfilling common diagnostic criteria.(McDonald, 2001, Polman, 2010).

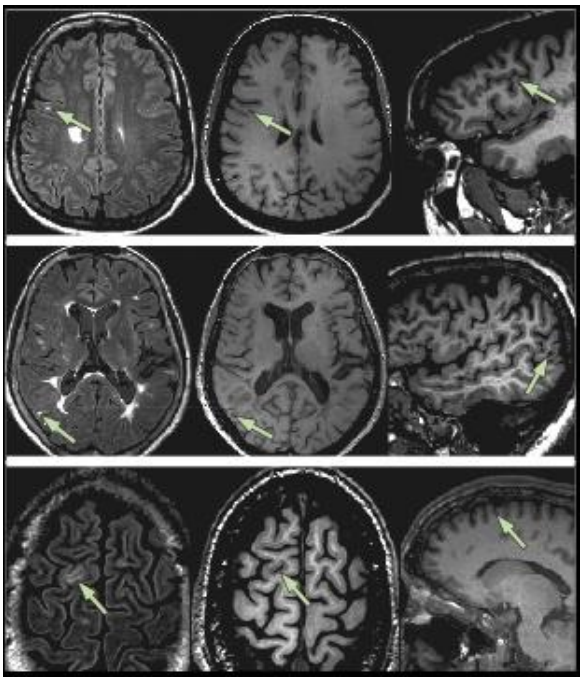

Figure 1. Cortical and juxtacortical lesion detection with MRI. Taken from “MRI criteria for the diagnosis of multiple sclerosis: MAGNIMS consensus guidelines” (Filippi, 2015)

At the same time, an important economic burden has been detected, including family and social costs affecting close to 2 million patients worldwide, with a women/men ratio of 2 to 3:1 and an estimated world prevalence of 30 per 100.000 inhabitants (Compston, 2002; Compston ,2008). Despite the existence of estimations reporting a prevalence of 14.3 per 100.000 habitants (Fernandez, 2008) and an incidence of 0.9 per 100.000 habitants for the period 2000-2006 in a hospital-based study (Diaz 2012), there are not accurate data describing the chilean reality regarding MS.

It exhibits high heterogeneity of manifestations, but most of patients initiate with a first episode of focal neurological deficit known as Clinical Isolated Syndrome (CIS) (Miller, 2005a; Miller, 2005B; Fisniku, 2008). In following years, 85% of the patients will develop Relapsing-Remitting MS (RR), which consists in neurological alterations (relapses), followed by periods of total or partial recovery between episodes. In the course of 10-15 years, about 40-50% of the patients will develop a Secondary Progressive disease (SP) accumulating disability, with identifiable episodes or even in absence of relapses. On the other hand, about 15% patients exhibit clinical evolution of a Primary Progressive (PP) phenotype characterized by accumulation of disability in absence of relapses (Miller, 2007).

It has been reported that 40–70% of the MS patients develop clinically relevant cognitive impairment (Achiron, 2006; Huijbregts, 2006; Potagas 2008). As in other neurodegenerative conditions, the MS cognitive dysfunction pattern is relatively well known and affects specially working memory, attention, processing speed (Katsari, 2016), verbal fluency and executive functions (Rao, 1991) compromising daily living skills (Bobholz, 2003) and social performance (Rao, 1991b). Interestingly, recent evidence links limitations in social functioning of patients with very specific cognitive alterations compromising primarily social-cognitive abilities, as decoding of facial emotions or mental states (Jenha, 2010; Henry, 2009;Phillips, 2011;Henry, 2011).

Given the wide impact of MS over the neural networks and the increasing interest on the social cognition domain, this work will focus on the findings on structural and functional acquisitions and its relations with this specific target of cognitive impairment. Technical and neuropsychological basis are described ahead.

Chapter 2. Social Cognition: Basic concepts and Neural basis for clinical practice.

Abstract:

The growing interest in the mechanisms determining the social functioning of human beings has raised the challenge of obtaining an accurate concept of social cognition and its related mechanisms, because several neurologic and psychiatric diseases exhibit related impairments since earliest stages. Social Cognition is defined as the integration of mental processes allowing the interaction among subjects and it includes phenomena as Social Perception, Theory of Mind and Empathy (or the affective response to the mental state of other people). In this article, as the primary aim, we expose the main concepts and neural basis in order to make easier the first approach for those who are looking for an application in the research with clinical populations.

Keywords: Social Cognition, Theory of Mind, Social Perception, Empathy.

Resumen: El creciente interés en los mecanismos que determinan el funcionamiento social en humanos ha levantado el desafío de obtener un concepto específico de cognición social y sus mecanismos relacionados, ya que varias enfermedades neurológicas y psiquiátricas muestran compromiso de este dominio desde etapas tempranas. Cognición Social se define como la integración de procesos mentales que permiten la interacción entre los sujetos e incluye fenómenos como la percepción social, teoría de la mente y empatía (o la respuesta afectiva a los estados mentales de otras personas). En este artículo, como principal objetivo, exponemos los principales conceptos y sus bases neurales para facilitar una primera aproximación a aquellos lectores que estén en busca de una aplicación en poblaciones clínicas.

Palabras Clave: Cognición Social, Teoría de la Mente, Percepción Social, Empatía.

Introduction:

Different cognitive abilities have been related to the successful development of social interactions. This phenomenon is explained by the existence of mechanisms to select environmental cues that require certain reactions of the involved subject(1). These notions establish the existence of both cognitive and behavioral components of social interaction.

Even if social cognition and social behavior have been present in relevant facts of the history of Neurology as in the Phineas Gage case, its importance as an independent source of cognitive declining has been relegated to a lower level of attention. The importance of clinical measurement of Social Cognition has been recently recognized, being included in the Fifth edition of Diagnostic and Statistical Manual of Mental Diseases (DSM-V) where is considered as one of the six fundamental neurocognitive domains(2, 3). This emphasis emerges from the experience of well-studied pathologies. For example, patients with schizophrenia chronically exclude themselves from socially

relevant activities as work and school and exhibit low personal care and difficulties in establishing relations with family and friends(4). This has been attributed to impairment in the identification of their own actions' inconvenience in human social environment or failure when attributing intentionality to others. These abilities are directly related to grey matter atrophy(5-9). This example provides an initial idea of the interaction and dependency between internally and externally directed functions.

On the other hand, the compromise of social performance responds to a central fact in Autism Spectrum Disorder. Its definition considers the presence of a persistent deficit in interaction, communication, and emotional reciprocity, causing significant impairments in social and occupational functioning(2). Available evidence suggests decoupling of different brain regions during development(10). This should explain why patients exhibit lower performance in Empathy tasks(11), which is strongly correlated with the functional compromise of related neural networks(12). Interestingly, diseases apparently exhibit specific clinical phenotypes of Social Cognition related to specific structural or functional changes. This notion has been supported by the identification of brain networks consistently involved in theoretical subsystems of social cognition(4).

The previous examples make it easier to establish a didactic view of social interaction. In the first place, we distinguish a behavioral and cognitive phenomenon. Figure 1 shows a schematic representation of social cognition, despite its dynamic nature is recognized. In this review, by the feasibility of the measurements, and because of the importance of its compromise also at the society's function level, we focus on cognitive components of social interaction: Theory of the Mind, Social Perception, and Empathy.

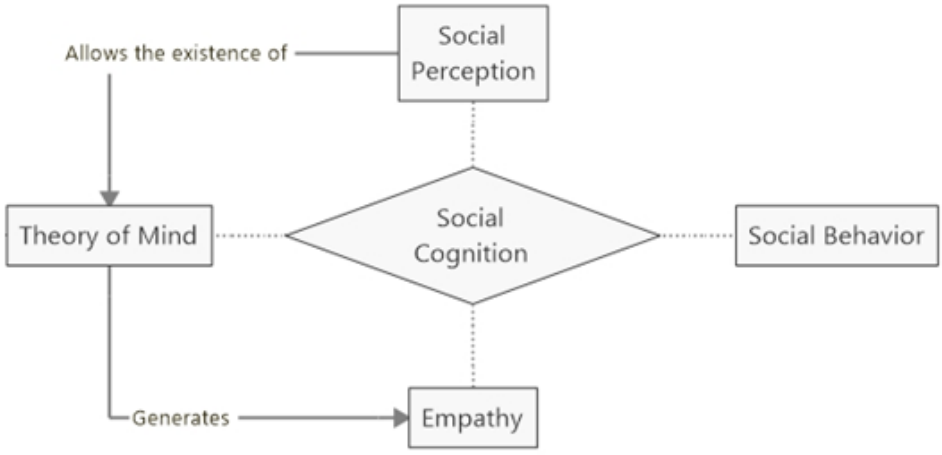

Figure 1. Social Cognition as a global concept unifies the operation of internally and externally directed processes. There are dependency and complementarity relationships among sun-domains.

The main objective of this article is to provide an introduction to the concept of Social Cognition and its subsystems, also reviewing some evidence regarding their neural correlate.

Social Cognition:

We understand Social Cognition as the integration of the processes that allow subjects of the same species to interact. This is as an essential process for the survival of individuals and species. It depends on the exchange of social signals that allow obtaining information about other subjects, and learning about environment based on those signals. Starting from basic phenomenon as the attribution of intention, Social Cognition allows the generation of a shared reality among persons (13, 14).

For the current models, human brain operates as a probabilistic inference system hierarchically organized to constantly anticipate input and infer possible causes(15). In this line, the main outcome of Social Cognition should be top-down predictions with the objective to diminish the difference between predicted and real input(16). For example, a correct interpretation of faces, words and body postures should lead to an accurate prediction of others subjects response and to an adequate preparation for generating a correct reaction.

In disease models, social cognition tends to fail, appearing clinically as an alteration of the following components: Decrease in Theory of Mind tasks, reduced emotional Empathy, and poor Social Perception(4). In the following paragraphs, we analyze those concepts separately. Table 1 provides an overview of cognitive domains, clinical situations, and available tests.

Theory of Mind:

For a successful socialization, we need to recognize other persons experiences and intentions as an independent factor. This ability to represent the psychological perspective of other subjects has been called mentalization and it requires theorizing about their thoughts. This phenomenon is known as Theory of Mind (ToM)(17).

This concept has been frequently defined as the capacity to infer mental states of individuals (for example beliefs or intentions)(4, 18) and has been measured by different experimental paradigms as those based on pictures, short stories, and animations. It must not be considered as a monolithic ability used only on certain occasions because the mere presence of a subject in a scene has shown to trigger processes computing possible thoughts or intentions(19). This also recognizes the existence of more primitive levels of intersubjectivity operating even at a perceptual and attentional level(20).

Generally, ToM tasks evaluate this function from two different angles: “Perspective Take”, in which inferring about the mental state is required, and “Decoding” in which mental states must be identified as it is expressed by eyes(21).

From a neuroanatomic perspective, there is strong evidence supporting the existence of a network underlying these functions. Medial Prefrontal Cortex (mPFC) has been associated with the initiating mechanism of beliefs and wishes attribution(22) and the processing of relevant social or emotional information regarding other subjects(23). It also participates in later reflections and complex mental elaborations regarding inferred mental states(24).

Superior Temporal Sulcus (STS) has also been involved in others' actions representation(25). It has been systematically demonstrated by its activation during actions interpretation and social animations observation(26).

In the same line, Temporal-Parietal Junction(TPJ) has been related to the representation of thoughts or beliefs of other subjects but not it other mental states as feelings or body sensations(27, 28). This notion has received additional support by using tasks based on social animation or associated with intention inference(26). Furthermore, it is important to recognize that ToM functions can't be reduced to a unique processing level. For example, while TPJ has been related to explicit detection and processing of mental states, STS has been involved in the implicit management of this information, both components being necessary for behavior predictions(29).

These accurate conceptual distinctions, so commonly used, could partially explain the wide variability of available evidence. Also, the overlap among regional functions should implicate a higher potential of the functional and neurodynamic approach rather than structural localizationism.

Figure 2 shows a schematic simplification of how individual cognitive variables influence the interpretation of social information during the process of ToM.

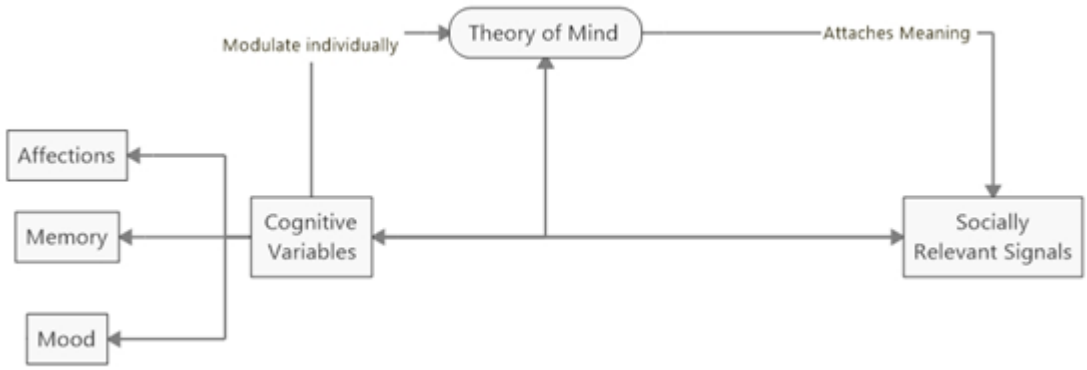

Figure 2. Theory of Mind Process attributes meaning to social signals and it`s modulated by individual cognitive variables.

Empathy:

It refers to the generation of an emotional response in the observer to situations affecting other subjects. This may correspond to the same emotion; in this case, the phenomenon is known as Affective Resonance, or correspond to a different one, as being angry when public humiliation of a person is seen(4, 30). It is an essential component of human emotional experience and social interaction because when an observed mental state is understood and affective responses are generated, prosocial and cooperative behaviors can exist(31).

When studying this kind of behavior, mimicking of body posture and movements (Chameleon Effect) has been demonstrated in performing a collaborative task with a stranger, improving quality of interaction. Indeed, a stronger chameleon effect has been demonstrated in more emphatic subjects(32). It was early intuited, since the definition of the concept by Theodore Lipps, that "internal imitation" of actions has a relevant role in Empathy(33).

When looking for neural correlates of previously described processes, recent studies have shown that performance in tasks related to the consciousness of own and other's feeling and actions is related to the activity of different brain regions as Somatosensorial, Insular, Cingulate and Visual Cortices(34), providing an initial notion of the wide diversity of involved neural resources.

Also, the Amygdala has an important role in the central processes involved in Empathy. Beyond its relation with emotive responses, long-term memory, identification of affective content of a stimulus and perception of gaze orientation(31) it probably exerts a systemic neuromodulating function, because its activation precedes the involving of other areas during the observation of expressive faces(35). Given the great relevance of this region in social cognition and Empathy, its role in conditions as Autism Spectrum Disorder has been studied, showing compensatory activation of non-related cortical areas during the processing of face images(36) while local activity of the Amygdala during this kind of task has shown to be increased(37). Considering the evidence, some authors have proposed amygdalin developmental alterations as a neuroanatomical and functional substrate of socio-cognitive impairment in those patients(38).

Mirror Neurons System (MNS) is another concept commonly used to understand the neural mechanism underlying Empathy. This term arose from the observation of certain neurons in the Premotor Cortex of monkey that discharge when observing an action performed by another monkey or by the experimenter, corresponding to the neural representation of observed behavior(39). Then, in the initial conceptualization, MNS links observation and execution of motor acts(40), but further studies using Functional Magnetic Resonance Imaging (fMRI) have shown that those properties are not exclusively present in visual systems but also in auditory and language functions(41). Interestingly, when observing other people being subjected to pain, Insular and Cingulate cortex activation have been registered, but this activation is modulated by negative perceptions about the affected person(42). Then, a complex mix of factors determines Empathy as a process, and the

activity of different brain regions are involved in the performance in Empathy tasks(43, 44) providing a neurodynamic explanation for behavioral variability.

Figure 3 schematizes the flow from social clues to mental state inference and the generation of a related emotion response.

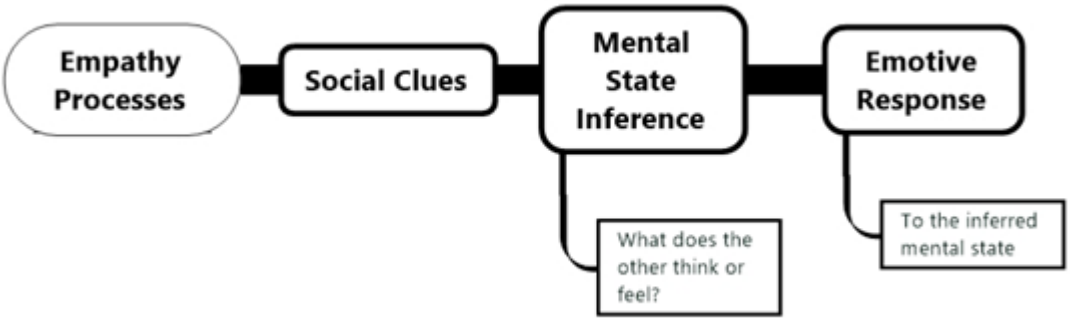

Figure 3. Empathy, as the process by which an affective response is generated, requires the identification of social clues and the inference of mental states in the interacting subjects.

Social Perception:

Social Perception has been defined as the ability to perceive mental states of others based on behavioral signals(45) and it's considered to proceed to more complex processes that emerge more lately in the human development(46). The perception of expressive actions of movements is an important element for the comprehension of the social environment(47) and it modulates the human behavior. Indeed, the mere observation of an action in other person triggers anticipated action in the observer based on the inference of desire and intentions(48).

For a long time, the study of this concept has been driven by the following axiom: we can't directly perceive mental states of other persons and we must execute several mental abilities to infer them (mind-reading). But recently, this notion has been challenged by Direct Social Perception Theory which has been supported by models as Bayesian Predictive Coding, suggesting a probabilistic inference involving different levels(15, 16).

The role of the Amygdala has enticed particular interest given its participation in the discrete neural representation of certain emotions(49). When a fast processing is required(50), sight is oriented to facial points with social relevance, as eyes(51, 52). Then, this region codifies emotional salience of social information(53). In the same line, Orbito-Frontal Cortex has shown to participate in the

perception of reward associated with environmental clues, participating in relevant aspects of planning and modulation of behavior in human and primates(54).

In the other hand, Fusiform Gyrus includes several areas involved particularly in visual aspects of Social Perception(55). Certain regions are related to a selective response to the body or facial stimuli(56) participating in complex processes as identity or intentions recognition(57). Nevertheless, codifying social information must not be understood as a static and anatomically circumscribed phenomenon. STS has shown to receive auditory and visual afferences to extract and represent dynamically socially relevant information(58, 59).

In the same line, neural networks perspective has provided additional information about the role of limbic lobe and other subcortical structures in the interpretations of facial expressions. A meta-analysis considering 105 original articles and 1600 subjects concluded that processing of faces with emotional expressions is related to the activation of visual, limbic, temporoparietal and prefrontal cortices and also with putamen and cerebellar activity. While cerebellum and visual cortex are involved in the processing of all expressions, happiness, fear and sadness recruit amygdala and anger and disgust expressions recruit insula selectively(60). One more time, it provides evidence regarding diversity and complexity of neural resources involved in Social Perception.

From the perspective of disease, Frontal-Temporal Dementia constitutes a well-studied example. In those patients, detection and categorization of emotions have been related to grey matter volume in Anterior Temporal lobe and Inferior Frontal gyrus. Also, when compared with healthy controls, patients exhibit higher functional connectivity among mentioned regions of interest(61), suggesting the existence of functional compensatory changes.

Figure 4 shows selection and categorization of environmental information as critical steps in Social Perception.

Conclusions:

The study of Social Cognition implicates a challenge at the conceptual level. In this article, we have proposed Social Cognition as an integration of processes by which subjects perceive social cues (Social Perception), infer psychological states of other persons (Theory of the Mind) and finally generate emotional responses to motivate and modulate behavior (Empathy). Even if this schematization may be conceptually improved, we propose it as a starting point to evaluate these cognitive functions in clinical populations.

In this review we have intentionally omitted a deeper characterization of Social Behavior in order to focus attention on those domains whose clinical evaluation is more practical, even recognizing an additional effort to provide an operational description of the behavioral domain should be done.

The growing interest in establishing this domain as a focus of research opens a high amount of opportunities to generate evidence regarding specific disease patterns both in relation to natural story and therapeutics.

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Chapter 3. Social Cognition: Concepts, Neural Basis and its role in Multiple Sclerosis.

Abstract:

Social Cognition, including Social Perception, Empathy and Theory of the Mind, focuses on how people process, store, and apply information about other people and social situations guiding social interactions. Specific patterns have been described in patients affected by different pathologies such as Alzheimer's, Autism and Schizophrenia. Multiple Sclerosis (MS), an immune-mediated neurodegenerative disease, can affect global cognition in 40-70% of the patients, with an impact on work and family status. MS patients have shown a decrease in performance of tasks related to Social Cognition, and reflect changes in structure and activity of specific brain areas. In this article, we propose an operational definition of Social Cognition and its subdomains and a comprehensive overview of how Social Perception, Empathy, and Theory of the Mind are decreased in MS patients. Finally, we discuss its relationship with neuropsychiatric disorders and expose some questions that remain unanswered.

Keywords: Cognitive Neurosciences, MS and related diseases, Neuropsychology, Biological Psychiatry.

Introduction:

The importance of the clinical assessment of cognitive abilities involved in social functioning has been recently recognized in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders which includes Social Cognition as one of the six core neurocognitive domains[1].

Social Cognition abilities in different levels, as inclusive fitness and reciprocal altruism, have been related correlated to the capability for developing deep social interactions. The existence of this kind

of interactions has been explained by recognizing the existence of mechanisms by which perception selects elements in the environment that require a reaction of the involved subject[2]. The previous sentence requires further analysis to understand the clinical relevance of Social Cognition: the environment provide an extensive amount of information, but people don't produce an interactive or social reaction to all of them. Then, the recognition and processing of social information are occurring continuously in the human brain and a specific system for decoding and generating social reactions must underlie to these functions. Also, its integrity is required and its disorganization must produce clinical manifestations.

Both in healthy subjects and in disease populations, specific social cognition domains and its related neural networks have been described. For example, schizophrenic patients experience severe impairments of social interactions as a significant difficulty in maintaining relationships with family and friends, disengagement from socially important activities, such as work and study, and poor self-care[3]. The inability to identify social inconvenience in the patient's environment or even in their own actions and speech[4] may be a possible cause of the clinical manifestations or their poor performance in related tasks as the "Faux-pas test"[5] which exhibit a significant correlation with grey matter atrophy[6]. Those social inconveniences may be detected as a complex interpretation of the situation or emerge from a simpler process as the decoding of emotions contained in a face. In the case of Alzheimer's Disease, the identification of, anger, fear, surprise, sadness and happiness has been shown to be impaired, but the recognition of disgust resulted selectively preserved[7].

On the other hand, the definition of Autism Spectrum Disorder includes the presence of persistent deficits in social interaction, communication and reciprocity, generating a significant impairment in social and occupational functioning[1] with difficulties in generating an adequate emotional response to other's behavior[8] and implicating developmental alterations and specific neurodynamic changes.

Taken together, these disease examples allow us the identification of the main three domains included in Social Cognition: Social Perception, Empathy, and Theory of the Mind.

Cognitive impairment in Multiple Sclerosis (MS) has been described as involving primarily processing speed and working memory, but a more widespread involvement has also been described[9]. The specific pattern in which Social Cognition is affected in MS patients still remains undefined, despite the early recognition of the existence of mood disorders and its impact in the quality of life [10].

The objective of this article is to provide a practical characterization of Social Cognition and its subdomains and describe an initial overview of Social Cognition impairment in MS.

Social Cognition:

The Human Brain is always trying to reduce the difference between its top-down predictions and the actual input[11]. For the modern theoretical approaches, it works as a probabilistic inference system hierarchically organized to get this objective and also generate an interpretation of possible causes[12]. In this theoretical frame, Social Cognition is defined as the sum of processes that allow to subjects of the same species to interact as an indispensable ability for surviving. It depends on the exchange of social codes to obtain information about other's behavior and about environment[13]. It starts by basic phenomena as intentions attribution and heads towards higher complexities as the creation of a shared reality. Those processes are compromised in different diseases under the conceptualizations of Social Perception, Empathy, and Theory of the Mind[4]. Figure 1 shows interaction among domains of social cognition. In the following paragraphs, we will expose these concepts.

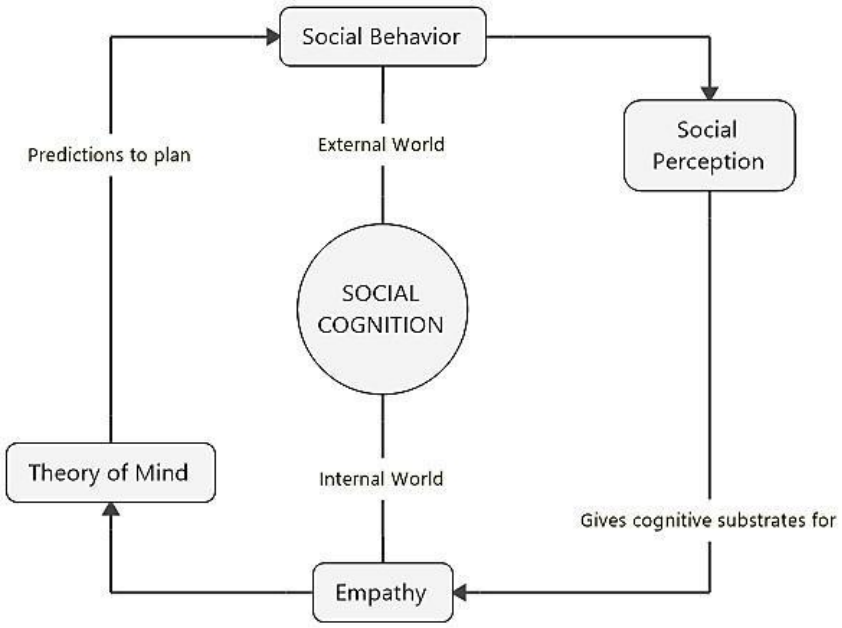

Figure 1: Social Cognition has expressions both in External and Internal World. Out-comes of each domain may constitute substrate or modulate other domain's manifestations

Social Perception:

Human beings need to perceive actions and movements to understand the social environment[14]. This perception modulates the behavior because the observation of a specific act by itself may trigger the anticipated action in the observer based on an automatic inference of intention[15]. In this context, the social perception has been defined as the ability to perceive information about the mental state of other subjects based on behavioral signals[16] and it's often considered as a basic phenomenon that precedes to more complex and taking time processes.

The study of Social Perception has been directed for many years by the axiom of indirect Social Perception, but in recent years this notion has been challenged by models of Direct Social Perception

in which humans can primary perceive the mental state of others before the subsequent processing of the social information[11; 12].

Theory of Mind:

To recognize the existence of another person's experiences and intentions is a necessary step for obtaining a successful socialization and it requires the observer attributes to others an independent mind. This ability to represent the psychological perspective of interacting subjects has been defined as mentalization and requires an internal theorization about their thoughts and beliefs. This concept has been called Theory of Mind (ToM)[17].

ToM has been identified as the act of inferring mental states as beliefs, thoughts and intentions requiring the comprehension of the implied emotions, affective states and feelings[3]. It must not be considered as an ability used on selective occasions because there is evidence suggesting the mere presence of subjects in the scene triggers process to compute their possible beliefs or thinking[18]. This kind of evidence recognizes the existence of earlier levels of inter-subjectivity that operates at the perceptual and of shared attention level.

At the clinical level, ToM tasks evaluate this function from the approaches of Taking Perspective or Decoding. In the first case, subjects are required to reason about the mental state of a different person, as measured by short stories of Mini-SEA test, a useful tool for differentiating disease patterns related to social cognition based on medial and orbital-frontal functions[19]. In the second cases, subjects must infer thoughts or feelings based on expression, for example, by the eyes (Mind in the eyes)[20].

Neural Correlates (NC) of Social Cognition:

There is a wide range of studies looking for neural correlates of social cognition, but the significant differences between definitions of the constructs of empathy, social perception and ToM have generated high complexity in determining which brain areas are involved in each function. In the following paragraphs we propose an integrative view of evidence supporting theoretical mechanisms underlying social cognition sub-components, recognizing that the complex nature of those functions may imply parallelism and superposition of some brain regions and processes.

NC of Empathy:

In the case of Empathy, several cortices, as Anterior Cingulate, Somatosensorial, Visual and Insular Cortex and Amygdala[21] have shown to be related to the awareness of one's own and others' actions.Amygdala has also a role in the generation of emotional responses, decoding the affective content of a stimulus, long term memory and orientation of visual attention[22] , contributing to modulate the whole brain activity because its activation precedes to the involvement of other areas during the observation of faces with an emotional expression[23]. All these functions explain its structural and functional relation with Autism Spectrum Disorder [24]and its developmental changes has been proposed as the underlying mechanism to the socio-cognitive impairment in this disease[25].

On the other hand, Mirror Neurons System (MNS) was described by the observation of neurons in the Pre-Motor Cortex of monkeys which trigger action potential when the animal observes a movement developed by other monkey or by the experimenter. This activity has been interpreted as a neural representation of the observed behavior[26] by linking observation to the execution of motor actions[27] but also involving auditory and language systems[28]. Interestingly, neural representation by MNS is a multifactorial phenomenon influenced by subjective factors as positive or negative judgmentsabout the involved subjects[29] and codifies such an important information as the

qualification of an object as desirable based on its perception as the focus of interest for other persons. This process is mediated by a network involving Striatal and Prefrontal regions[30], probably underlying certain kinds of learning particularly dependent on social interaction.

NC of ToM:

Temporal-Parietal junction(TPJ) has been related to the neural representation of thoughts and beliefs[31]. The use of social animation or predicting behavior tasks has supported the involvement of this area[32] but it's important to recognize that functions involved in ToM are not related exclusively to specific regions. While TPJ has been related to the detection and explicit processing of mental states, other cortical areas, as STS has been related to the implicit processing of this information. Both, explicit and implicit mechanism are involved in the prediction of human behavior[33]. Interestingly, other studies have proposed STS cortex to be responsible for the representation of other people actions[34,35]. Medial Prefrontal Cortex (mPFC) has also shown to be related to mechanisms responsible of desire and beliefs attribution[36], to the processing of emotional or socially relevant information regarding interacting persons[37] and reflection about their possible state of mind[15].

Why Social Cognition in MS?

Multiple Sclerosis (MS) is an autoimmune disease characterized by inflammation and neurodegeneration within the Central Nervous System[38,39]. It has been related to genetic and environmental factors[40] and it represents the first cause of non-traumatic disability in the young-adult population (20-40 years)[41].

MS exhibits high heterogeneity of clinical presentations, most patients presenting with the first episode of focal neurological deficit known as Clinical Isolated Syndrome[42,43,44], but 85% of the

patients will develop Relapsing-Remitting MS, which consists in neurological alterations (relapses), followed by periods of total or partial recovery between episodes (remissions). If untreated, in the course of 10-15 years, about 40-50% of the patients will develop a Secondary Progressive disease accumulating disability even in the absence of identifiable relapses. On the other hand, about 15% patients exhibit clinical evolution of a Primary Progressive phenotype characterized by the accumulation of disability in absence of relapses[45].

In the current management of MS, cognitive dysfunction represents a major therapeutic challenge and a source of anxiety among patients since the earliest stages of the disease. It is estimated that 40–70% of the MS patients develop clinically relevant cognitive impairment[46,47,48]. As in other neurodegenerative conditions, MS cognitive dysfunction pattern has been described as affecting especially working memory, attention, processing speed[9], verbal fluency and executive functions[49]. The impact of this kind of dysfunction in global social functioning are also associated with declining in daily living skills[50] and it has been demonstrated that MS patients with cognitive impairment are less likely to have a job and participate in recreational and social activities, than those without cognitive impairment[51].

Social cognition has not been systematically considered as part of the common clinical evaluation, but its impact on the quality of life should ensure its inclusion as an important outcome for the therapeutical success of disease modifying therapies clinical trials in the last years. Nevertheless, a limited number of articles refer to the impact of cognitive rehabilitation in socio-cognitive abilities and outcomes commonly consider just conventional domains of cognitive evaluation[52].

Social Cognition in Multiple Sclerosis:

Initially, Social Cognition impairment was considered as entirely dependent and parallel to the general cognitive dysfunction. Even if this parallelism is currently under review, the.notion of a global decrease in cognitive function causing alterations in facial emotion recognition, empathy and ToM performance is still valid.

Recent evidence has shown 20% of social cognition impairment among MS patients[53]. The larges deficit has been found for ToM tasks and for the recognition of certain negative facial emotion expressions[54,55]. Social cognition deficits show a significant correlation with the performance in other cognitive domains[56,57,58]and also exhibit behavioral impact affecting moral evaluation of others actions[59]. Figure 2 shows a schematic progression and clinical manifestations of social cognition impairment.

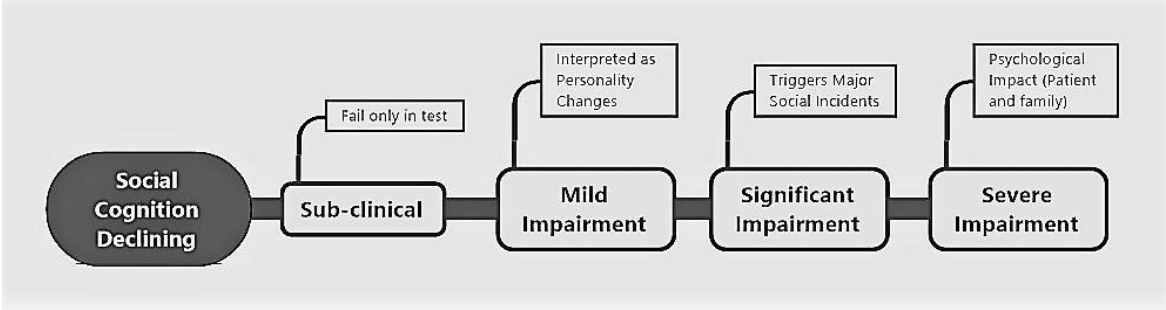

Figure 2: Social Cognition Declining starts in a sub-clinical state (detectable only by directed tasks). The appearance of mild, significant and severe manifestations produces difficulties in social performance of patients.

MS & Social Perception:

Social perception has been studied since the earliest stages of the disease. When 20 patients with a Clinical Isolated Syndrome or MS and 23 healthy controls were evaluated for the ability to differ between emotional facial stimuli, the patients demonstrated significantly decreased reaction times and accuracy in emotion recognition tests compared to healthy controls. However, the results also suggested worse cognitive abilities in the patients with a significant relationship with socio-cognitive performance[60]. Supporting the same notion of parallelism between general cognitive performance and social cognition, there is some evidence regarding the correlation of ToM and affect recognition with executive dysfunction and information processing speed[61].

In a different way of interpreting the origin of social cognition impairment, some experiments introduce the possibility of this dysfunction as being separated from general cognitive state. In a study with 32 MS and 33 healthy control participants, matched for age and education, evaluating the ability to identify emotions and non-emotional information from static images of faces and videos of interacting people, participants with MS performed more poorly than healthy controls on emotion perception, but not identity perception. Interestingly, for the dynamic tasks, the MS group were impaired on emotion perception, but not age and gender perception[62]. These results indicate a specific deficit in decoding static and dynamic information about emotions in MS patients in the context of preserved non-emotional processing.

When looking for neural correlates of social perception impairment in MS, increased activation in the Posterior Cingulate Cortex and Precuneus for the identification of anger and disgust faces, and greater activity in the Occipital Fusiform Gyri, the Anterior Cingulate and in the Inferior Frontal Cortex for the recognition of neutral faces have been reported[63]. Those network activity changes have a substrate in anatomical damage because increases in lesion volume have been reported to correlate with lower success in face emotion recognition[64].

MS & ToM:

When ToM has been separately evaluated in MS patients they performed significantly worse than controls in all tasks, but these deficits were not correlated to demographic variables or neuropsychological test performance and the performance in Faux-Pas test has been correlated to the lesion load in specific tracts[64,65], considering disconnection by white matter damage as one of the possible underlying mechanism of ToM impairment[66,67]. The previous evidence supports the notion of considering ToM impairments as due to the disconnection mechanism characterizing this disease in which white matter damage and its impact on the neural connectivity is a major issue.

An interesting approach considers ToM as divided into two components: cognitive ToM and affective ToM, the first related to the inference of intentions and the second to emotional states. Under this paradigm, eighteen patients and sixteen healthy controls performed Faux-Pas Test. The patients showed deficits in cognitive ToM with a preserved affective ToM performance. Those deficits were not related to executive dysfunction, depression, or fatigue[68]. One more time, the evidence supports the existence of independent and specific socio-cognitive impairments without relation to decrease in memory or processing speed.

Discussion and Conclusions:

The impact of MS in the global functionality is well understood in the clinical environment. Its relation with psychiatric disorders is also well documented. For example, dysregulation of the affective processes has been consistently reported, even preceding the disease onset, and cases in which the

first episode follows a maniac or post-partum depressive episode have also been reported. Globally, neuropsychiatric abnormalities related to MS consider disorders of mood, affect and behavior, and abnormalities disturbing cognition[69]. Those possibilities add complexity to the mental and cognitive evolution of these patients, considering that the appearance of an incurable disease implicates changes in the way of understanding their own lives and self-transcendence[70].

Given that cognitive status influence family and work performance[50,51] we recognize that socio-cognitive impairment exerts a key role in determining the quality of life.

More than a definitive answer, the evidence exposed in this article proposes several questions in which further research must focus. Is there an independent socio-cognitive impairment? Could we find it in the absence of conventional cognitive impairment? We think that investigations as those developed by Rocca et al. support the existence of an independent way of compromising specifically Social Cognition in the subjects who are still "cognitively preserved" from the traditional perspective. This idea implicates the acceptance of a significant possibility: there are some patients experiencing disorganization of their social life before a significant or detectable decrease in working memory or processing speed. Then, the changes in the behavior in those apparently normal subjects may be interpreted in different and often negative ways in their social environment.

Even if most of the research regarding social cognition and MS avoid to explicitly mention the theoretical controversies about concepts, components and specific landmarks between them, different theoretical approaches to these concepts are implicit in the experimental design and data analysis. Probably, this might explain a significant percentage of variability among studies.

Despite the contribution of studying Social Cognition to the understanding of MS and the evidence supporting the idea of socio-cognitive impairment as a clinical manifestation of disconnection syndrome we must recognize the wide variability in the relationship of Social Perception, Empathy and ToM of with neuroanatomical findings (general or regional brain atrophy, functional or non-conventional structural approaches). This inconsistency in structural and functional correlates may also be due to the lack of a unique operative definition of these cognitive domains.

Finally, decrease in the performance of Social Perception, Empathy, and ToM tasks are already defined as a fact in the natural history of MS, but the existence of a primary socio-cognitive impairment - in absence of global cognitive compromise-, the biological markers preceding its appearance, and its evolution in relation to the different pharmacological treatments, still represent a challenge for the future comprehension of this disease.

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Chapter 4. Functional Magnetic Resonance Imaging(fMRI): basic principles and applications to Neurosciences.

Abstract:

Functional Magnetic Resonance Imaging(fMRI) has become an advanced tool in the research of brain functions, both in healthy subjects and in patients with neuropsychiatric diseases, achieving identification and localization of the neural activity and brain metabolism. Since the earliest approach to the study of brain function by MRI, more advanced techniques have been developed to consider the neural dynamics. In both resting and task-related modalities, evidence has been provided regarding the initiation, evolution or response to treatment of different disease models. The diversity of possible artifacts associated with the acquisition of the images and complexity of experimental designs and data analysis have generated a great debate about the technique. The main focus of this article is to provide an introduction to the basis of fMRI, its interpretation and contribution to the study of the mechanisms underlying neurological disorders.

Keywords: Functional Magnetic Resonance Imaging, Neural Networks, Mental Disorders, Neurological Disorders.

Introduction:

The interest on attributing specific functions to brain regions have diminished with the fall into disrepute of the Gall's Phrenology. Nevertheless, pathologists as Broca and Wernicke exposed cases of patients in which local brain lesions produced specific functional impairments(1). Even if those cases of regional syndromes still remain valid, they have contributed to the permanence of localization notions in the mind of physicians and researchers. Today, it has been recognized that the attribution of high complexity functions to a brain area is difficult or even inappropriate because brain activity depends on the structural connections among different regions. Also, the lesion models, when being interpreted from the functional disconnection perspective contribute to refute localizationism as a sufficient explanation of the brain cortex organization.

Given the need of an approach providing more integrative explanations of the neural resources involved in the execution of certain cognitive functions or its disintegration in neurodegenerative disorders, the functional Magnetic Resonance Imaging (fMRI) can be used to identify brain areas related to specific functions and other that, despite they are anatomically separated, are functionally connected establishing networks(2). Figure 1 shows examples of neural networks recruited during the performance of different cognitive tasks.

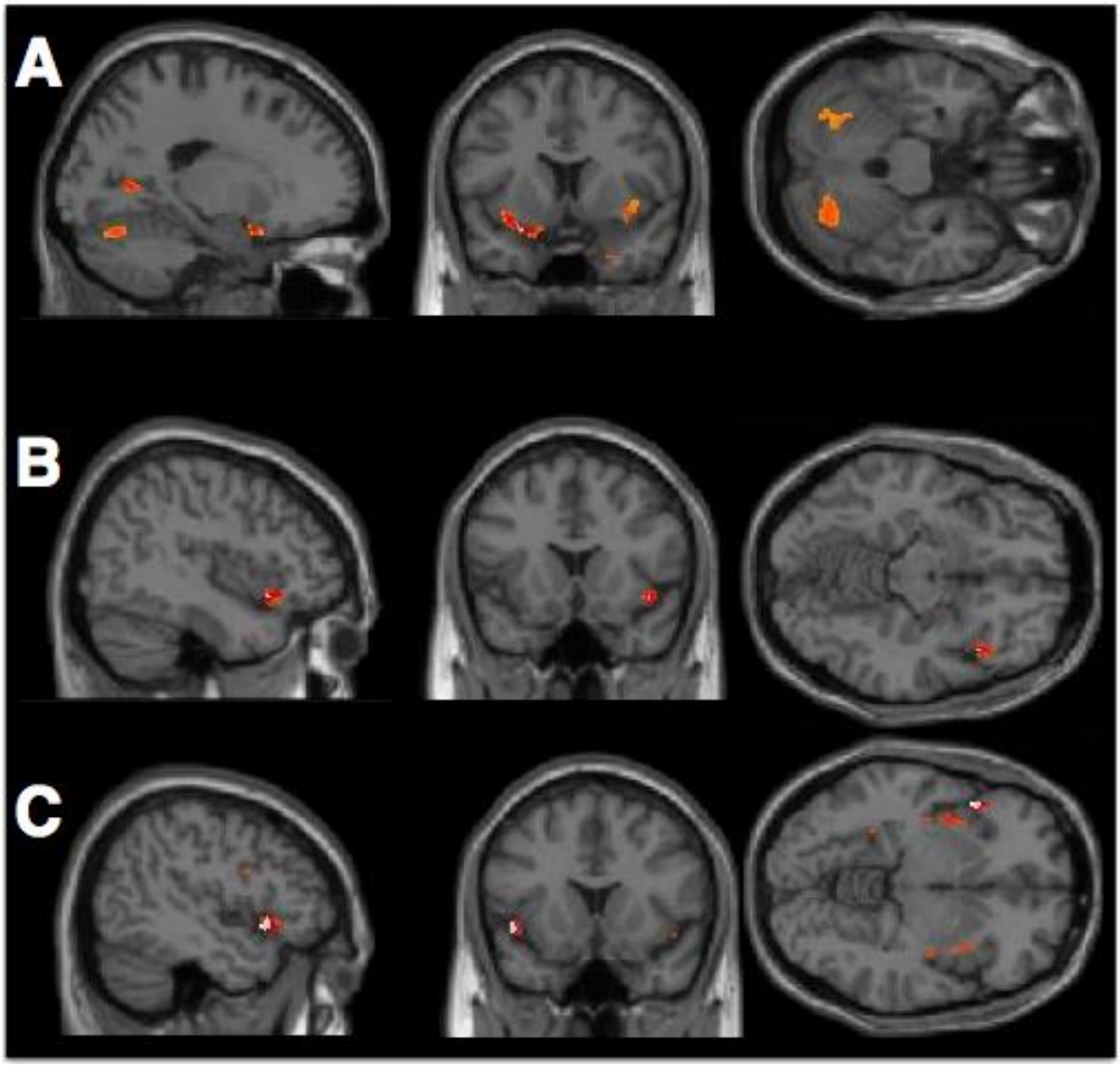

Figure 1. Brain Cortices activated during the performance of cognitive tasks. It shows significant changes in BOLD signal during different cognitive tests. A) Theory of Mind Task, B) Visual Learning Task, C) Verbal Fluency task

The aim of this article is to introduce to the reader on the basis of fMRI and its interpretation and, at

the same time, give an account of its contribution to the understanding of the underlying mechanisms of several diseases affecting the central nervous system. Also, we propose this technique offer different opportunities in research for radiology, neurology, and neurosciences that could be taken based on interest, need and local reality of each researcher. An experimental paradigm based on fMRI offers a high degree of adaptation to the specific research question. Indeed, a resting state fMRI may have a duration of 5 minutes (or much longer) and requires a standardized acquisition protocol considering technical details and decisions regarding accurate definitions and instructions of the mental resting condition, eyes position and strict movement control. In the other hand, more complex experimental designs can include the performing of motor or cognitive tasks and need the use of electronic devices compatible with the magnetic field and also require a longer acquisition time with a slower learning curve both for the researcher and the experimental subject.

Origin of the BOLD signal:

fMRI studies are based fundamentally on the acquisition of the BOLD (Blood Oxygen Level Dependent) signal. The initial articles describe changes in the signal depending on the apparent transversal relaxation time T2* in a visual stimulation experimental paradigm. Those changes found at the primary visual cortex were concordant with the idea of neural activity increasing regional blood flow and venous blood oxygenation, generating a diminish in the local deoxyhemoglobin, a molecule with paramagnetic properties(3, 4).

In recent years, the knowledge regarding this neurovascular coupling has increased. The current theoretical model considers the generation of action potentials, synaptic activity, neuromodulators and neurotransmitters release and astrocytic activity among other factors that contribute to

increasing the brain blood flux and volume and also the metabolic rate of the involved nervous tissue. Nevertheless, the increase of blood flux is higher than the increase of metabolic rate, generating an increase in the oxygen availability and diminishing the deoxyhemoglobin, implicating an increase in the BOLD signal of the involved region compared to the baseline (5, 6).(figure 2)

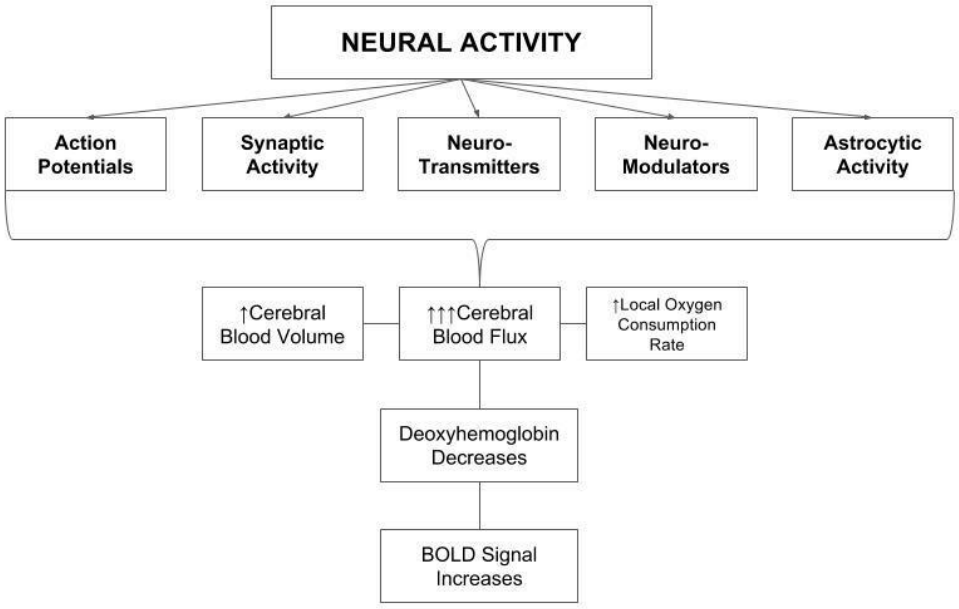

Figure 2. Neural Events related with changes in BOLD signal. When a brain region in involved in the development of an activity or in the processing of some kind of information, electrical, chemical and cellular phenomena are triggered. It modulates the blood supply and the metabolic rate of involved cortices, changing the balance between oxyhemoglobin, affecting the bOLD signal, which is the main target of the fMRI.

fMRI Data Analysis:

The analysis of data derived from fMRI experiments requires domain over theoretical concepts often excluded the contents of traditional medical teaching. In order to make easier this approach, we define basic concepts to understand how different encephalic regions are functionally related and we describe two methods frequently used in the interpretation of data, Independent Component Analysis and Graph Theory.

Before the description of the analysis methods, we must define the concepts of functional and effective connectivity because both of them are essential to the comprehension of this information. A basic approach to the study of the BOLD signal is related to the observation of regions with increases and decreases in signal intensity during the performance of certain motor or cognitive task. However, the brain functioning depends both on the local processing of information and on interacting patterns widely distributed over the entire neural network. Hereby, the current emphasis in the systematization of the study of brain function considers the concept of Connectome as a representation of the functional structure allowing the integration of information and that provides an integrative map of neural connections among distant regions underlying brain functions. This is based on the quantification of the interactions among a great amount of cortical region(7, 8), without the limitations of studying changes in the regional signal which by itself support localizationist approach and result insufficient to understand brain dynamics.

Several methods are focused on the study of the structural or anatomical connectivity of the human brain, but most of the articles using fMRI are based on connectivity concepts surpassing the strictly anatomical way. Then, it is necessary to understand the definitions of functional and effective connectivity.

A. Functional Connectivity: an Observable phenomenon that is quantified through measures of statistical dependence or correlation (positive or negative) between the signals measured in different regions of the brain (7, 9). In figure 3, the curves B and C schematize the neural activity of two separated regions. We assume the existence of functional connectivity after statistical processing because increases or decreases in the signal of one region are correlated with similar changes in the other studied region.

B. Effective Connectivity: Gives an account of the causal effect that the activity of one neural system exerts over other through synaptic influence at the individual level or considering multiple synapses (7). It corresponds to a construct trying to explain correlations previously described by the functional connectivity measures(9). In this case, the existence of effective connectivity implies that changes in some of the regions represented in figure 3 cause modifications on neural activity and on the BOLD signal of the other regions.

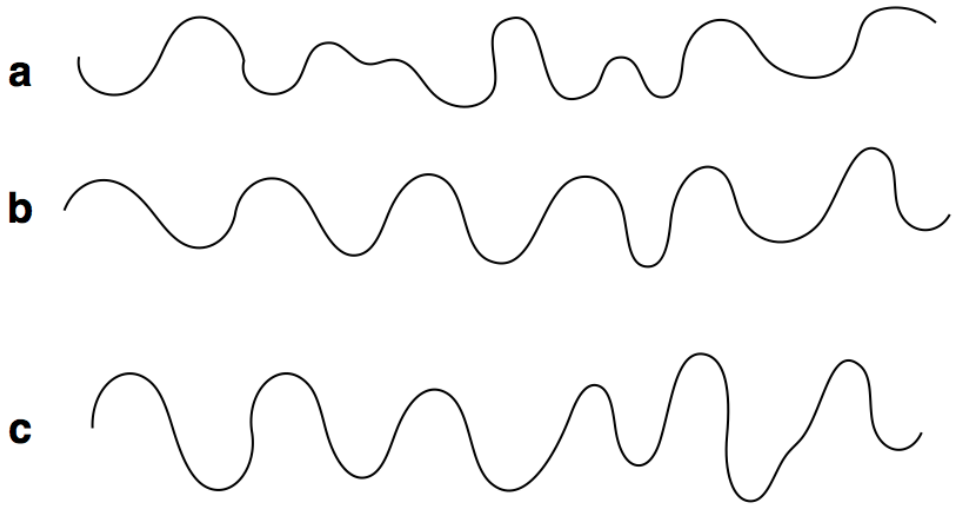

Figure 3. Functional and Effective Connectivity. Figura 3. Conectividad Funcional y Efectiva. Curves **a**, **b** and **c** are BOLD signal variations in three different and anatomically separated regions of brain cortex. Given that increases in curve **b** temporally coexist with increases in **c** signal and decreases in **a** curve, we assume the existence of a positive correlation and anticorrelation respectively, among the studied areas. We speak about Effective Connectivity when statistical processing allows establishing that fluctuation in a certain area are causally related with signal changes in other regions.

In the following paragraphs, we describe the methods used in the analysis of the fMRI data through theoretical approaches to the study of brain connectivity:
A. Independent Component Analysis (ICA): ICA is a technique which decomposes a matrix of 2D data (Time x Voxels) in a series of temporal courses and associated spatial maps describing the behavior of the underlying signals(2,10). It is an approach to study the whole brain and it was designed to separate a multivariant signal into subcomponents. It is used without an a priori hypothesis but assuming the statistical independence of the variability sources. The entire brain network is decomposed into spatial and temporal maps with a specific signal course. Each map is interpreted as a network of brain areas with similar fluctuations of the BOLD signal during the acquisition(2,11).

In operative terms, an approach like this will take all fMRI data derived from one or several brains and it will group the regions with similar temporal courses of the BOLD signal, assuming that by activate or deactivate together, they are an identifiable network. Figure 4 schematizes this processing of fMRI data.

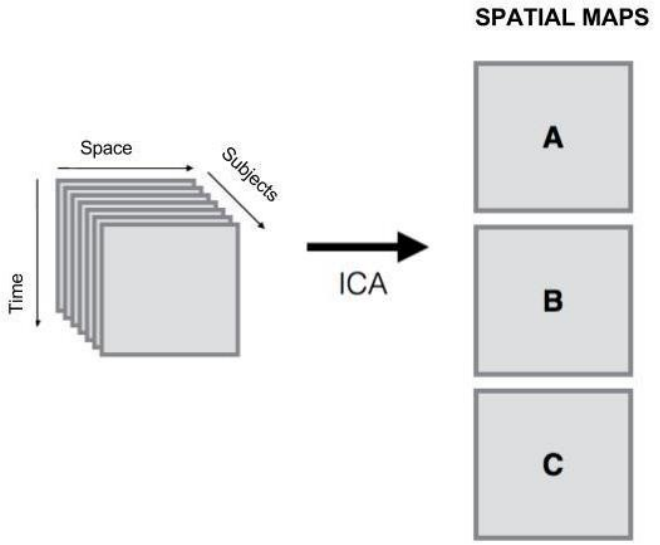

Figure 4. Independent Component Analysis. Systematically, this approach process the spatial-temporal data obtained from the fMRI acquisition of different subjects and it identifies as independent components of the neural network to the group of regions which signal varies in a similar way through the time. A, B and C represent maps or neural networks considering different involved areas with different contribution to the variability of the whole brain signal.

B. Graph Theory: The analysis based on this approach consider the relationships among nodes and edges. The first corresponds to the cellular components of a certain brain region, differentiable and with functional homogeneity. In the other hand, the edges describe the degree of functional or structural connectivity among nodes of a network(8). Figure 5 shows an example of a hypothetical network constituted by nodes and edges.

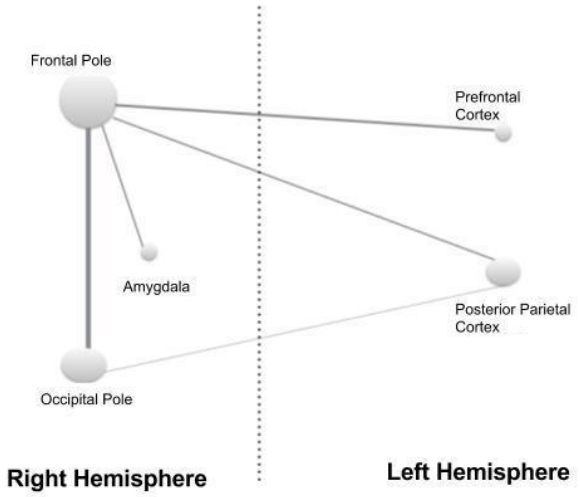

Figure 5. Neural Network represented by Nodes and Edges. Hypothetical schematization of the dynamic behavior of BOLD signal. It could be observed both under a cognitive experimental paradigm or in resting state. Brain regions are represented by spheres which size is related to the amount of connections and the edges show the strength of the interaction between areas.

The Graph Theory, as a theoretical approach to fMRI analysis, propose some metrics frequently considered in those studies:(7)

The degree of a Node: It is related to the number of connections of the node in question, it provides a measure of its effect on the functioning and structure of the neural network. High-degree nodes, with a central position in brain function, are often referred as "hubs" or activity centers. 2. Clustering: Measurement of the local efficiency of a node. Express the level of local connectivity of a network. High levels of grouping are interpreted as high levels of complexity of the local organization. In other words, this index shows the level of interconnection of the cerebral cortex segment with its neighboring regions.

3. Modular Organization Level: Frequently interpreted as a measure of the segregation of information in neural networks. It is related to the level of specialization of an area in the processing of a certain type of information.

4. Global Efficiency: It is calculated as the inverse of the number of steps necessary to travel between each pair of nodes in the network. Informs about the effectiveness of networks to communicate information between their remote parts.

In a more specific application of the previous observations, it has been described that a small number of highly connected and centrally located regions have a fundamental role in the topology or global function of the brain network and are highly connected to each other, constituting an organization that has been known as Rich Club(12, 13). The study of the connectivity of this group of brain regions could provide important information on the mechanisms underlying the cognitive alterations observed in the different neuropsychiatric pathologies.

Applications:

There is more than one way to use fMRI as a tool to study brain function. Next, we describe the use of rest fMRI, especially in neurodegenerative or psychiatric pathology. In addition, an outline of the role of simultaneous registration with functional tests of the motor or cognitive activation in the understanding of neurodegenerative pathologies is presented. Both modalities have allowed a great advance in the identification of markers and patterns of each disease.

Resting State fMRI:

Advances in fMRI have allowed researchers to sketch the architecture of a network of intrinsic activity in the human brain(14). Some studies have shown that, during periods free of the motor or cognitive

tests, spontaneous neuronal activity occurs in groups of cortical and subcortical regions with different locations, but functionally related. In this phenomenon, visual, motor and cognitive control areas would be involved(15, 16).

Likewise, in a study including healthy subjects, Fox et al. described the interactions at rest between certain cortical regions. Among other results this study indicates that, when using the posterior cingulate cortex as the focus of the analysis it is possible to find regions whose signal is positively correlated, as the medial prefrontal cortex, while the activity of other regions, such as the intraparietal sulcus region, the fields frontal ocular and medial temporal region, shows a strong negative correlation(17), showing that the dynamics of the brain at rest, which accounts for the conditions for the flow of information between regions, is a fundamental factor for the normal functioning of the human brain. Taken together, the above evidence exhibits fMRI as a potential tool not only in the study of resting activity in specific regions of the cerebral cortex but also its levels of correlation with the activity variations of other areas under study.

Task-Related fMRI:

From the first experiences in the application of this technique to the study of the functioning of the central nervous system, there has been accumulated increasing evidence from experimental models that imply the performance of a certain task during the fMRI registry. In this way, starting with simple designs that allowed detecting the activation of areas different from the primary motor cortex during the movement of the fingers(18), or the participation of the somatosensory and cingulate cortices in the perception of pain(19), the foundations were laid for its application in other functional systems under the premise that motor or cognitive acts modify the activity of the cerebral cortex and that this change can be measured by fMRI. When studying more complex processes such as the recovery of semantic information(20) or

the accomplishment of cognitive tests of high complexity, changes of 2-5% are observed in the basal signal -which accounts for resting metabolism- of specific regions during tasks(21). These variations, although apparently minor, have been statistically significant and have allowed expanding this methodology to the study of neuropsychiatric diseases during the last two decades. Currently, relevant examples of the clinical application of fMRI associated with tasks correspond to the pre-surgical identification of epileptogenic foci, whose anomalous increase in neuronal activity can be identified through this technique(22) or the identification of eloquent areas neighboring or affected by tumoral lesions(23) whose commitment could compromise the production and understanding of language (24) or other clinically relevant functions(25).

Association between Rest and Active Signal:

It is important to define the relationship between the phenomena observed at rest and those of a brain that is performing tasks. In this line, when performing a motor test during a fMRI recording, it has been shown that 74% of the variability in cortical activation is attributable to fluctuations inherent in the activity of intrinsic networks.
This finding is important because: (a) It provides evidence that spontaneous fluctuations in the BOLD signal correspond to more than physiological noise and (b) Proposes that the intrinsic variations of the BOLD signal correlate with the variability of normal human behavior (26). In the same way, functional connectivity in the resting state has shown to be a good predictor of individual differences in the neuronal response in disease models (27), so that both modalities -resting state and related to tasks- will contribute to the study of different pathological conditions as detailed below.

Disease Models:

Experimental data from different disease models support the hypothesis of network degeneration as the functional basis of related clinical manifestations. The confirmation of this postulate offers clinical opportunities by the possibility of diagnosis based on the degeneration of neural networks, as well as the monitoring of the evolution of the disease and response to treatment(14).

The analysis of certain specific disease models under a connectomics-based approach using fMRI has provided evidence to the approach of schizophrenia as a disconnection syndrome(8,28), in which alterations in thalamocortical connectivity have been studied (29) or regarding to other regions that seem to be affected from early stages of development or even in relatives at high risk of developing the disease(30). The study of other developmental disorders has reinforced the notion of alterations in large-scale connectivity as the mechanism underlying their clinical manifestations. Thus, in Autistic Spectrum Disorder (ASD), recent studies using this technique have published decreases in global, intra and interhemispheric functional connectivity as being well-correlated with clinical scores(31), probably due to the commitment of critical areas for social communication(32). This has shown how the measures of interest obtained in fMRI studies show alterations in the connectivity and information flow between regions and cerebral hemispheres in patients with ASD, which can be closely related to the deterioration of behavior and social cognition proper to the disease.

In the case of dementia, Alzheimer's disease is characterized by neurodegeneration and dysfunction of the neuronal network at different levels(33), increases in the excitability of cortical regions and compensatory inhibitory mechanisms in the hippocampus(34), as well as atrophy and deposit of amyloid beta in areas related to the recovery of memories(35). In the other hand, Frontotemporal

Dementia with its varied clinical manifestations has been linked to alterations of the large-scale neuronal network(36). In this way, the use of fMRI in dementia has shown how changes in the activity and connectivity of regions and networks involved in cognitive deterioration are related to alterations ranging from the histological level to clinical manifestations.

In the case of mood disorders, they have also been widely studied under this paradigm of neural networks using fMRI. In this regard, has progress been made not only in the design of diagnostic tools(37,38), but markers of complications such as the appearance of psychosis in depressive disorders have also been identified and structural or functional alterations in frontal and insular associative cortices are related to the appearance of depressive psychosis (39). Likewise, the validation of the pharmacological therapeutic effect in the functional connectivity of these patients has been sought(40). Other examples are Epilepsy and Parkinson's disease, where the pharmacological effect over the cortical activity has been well documented (41-43). For the reader interested in the study of neurodegenerative and neuropsychiatric diseases, it is important to keep in mind that fMRI has constituted an objective way to evaluate the impact of cognitive rehabilitation in models of disease such as Multiple Sclerosis, where subjects under this type of rehabilitation showed greater activity in different regions of the cerebellum (44). Likewise, the measures derived from the resting state fMRI have allowed identifying to the subjects suffering from Obsessive Compulsive Disorder with high specificity, only based on measurements of the neural network and widely used statistical methods such as the Pearson correlation(45). All these publications demonstrate that this methodology can provide concrete and manageable measures that can be used by clinical and research teams.

Discussion:

The contributions and opportunities described in the previous paragraphs have been limited on their massive application because significant differences on the quality of the images, their levels of error and given that the meaning of their results is subject to the influence of multiple factors that must be considered when working under this type of paradigm.
In this regard, it is known that the choice of hardware, particularly the number of channels of the coil, as well as the choice of acquisition parameters are critical for the relationship between signal and noise(46). Although one of the most important characteristics of magnetic resonance is its good spatial resolution, this parameter is affected by including the entire brain, as well as considerably increasing the time of acquisition of the images(47). Many of the current approaches have a complete view of the brain dynamics of neural networks, so it must be taken into account at the time of acquisition of the images, as well as to propose an experimental design in order to optimize the acquisition time(48)

On the other hand, cephalic movement can be a source of significant noise, especially considering that the studied response in the fMRI is based on a small percentage of signal changes. It has been described that the movement of the head varies for different clinical groups (49), and also differs according to whether the recording is performed at rest or associated with tasks, affecting more significantly the acquisition in task-free paradigms(50). The importance of this source of artifacts in the registry has led to the creation of various methods for correction of head motion or breathing and its inclusion as part of the preprocessing of these images(51-54).

It has been described that the experimental design for the realization of tasks, whether these are developed in blocks or continuously, can influence the observed results(55). The fact that different statistical approaches can lead to different levels of error in the characterization or detection of

responses in the BOLD signal is well documented(56). The existence of this type of errors has recently motivated the article by Eklund et al, 2016. It achieved some notoriety even at the level of the media, who in the most extreme cases, have pointed out that all the available scientific evidence under the experimental paradigm of fMRI (40,000 articles as indicated) corresponds to false results. In summary, this research uses 1484 records of fMRI in the resting state and submits them to analysis protocols designed for records associated with tests. Although the researchers expected to get 5% false positives, they reached around 70%(57). Despite the impact that those declarations can produce, it must be taken into account that the article raises a criticism of the statistical approaches used in the interpretation of the data, but it does not constitute by itself a criticism of the use of fMRI as a tool and neither it questions the relationship between the BOLD signal and the neuronal dynamics.

Beyond the difficulties in the implementation and analysis of fMRI images, this technique offers several opportunities in the understanding of different pathologies of the neuropsychiatric sphere. For example, it is currently understood that biological systems, at various levels, tolerate disturbances to which they respond in an adaptive way until a certain level of disturbance in which the functional dynamics cannot be recovered and permanent changes are triggered(58). This principle could lead to the identification of biological markers based on fMRI that allow the identification or prediction of the onset of a disease or the appearance of its cognitive manifestations.

Finally, the weight of the study contribution of networks based on fMRI will be determined by the capacity of the research teams to standardize the registration and analysis techniques, as well as the willingness and feasibility of the clinical teams to include these types of sequences in the usual monitoring of their patients.

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Chapter 5: Functional Magnetic Resonance Imaging in the study of Multiple Sclerosis.

Abstract:

Introduction: Multiple Sclerosis(MS), a neuroinflammatory and demyelinating disease, modifies the normal connectivity among different brain regions involved in specific functions. Functional Magnetic Resonance Imaging(fMRI), based on local changes in oxygen level as a response to the increase in neural activity, provides an approach to neural connectivity and brain dynamics which give us an overview on visual, motor and cognitive dysfunction and their mechanisms

Aim: to give an insight into multiple sclerosis functional alterations studied using fMRI.

Methods: an advanced search was performed using PubMed. Terms “fMRI", “visual”, “motor”, “cognitive” and “Multiple Sclerosis” included in title and abstract were considered. We focus on original articles available in English. Articles were included based on their abstracts, looking for those potentially useful for understanding functional changes in MS.

Results: an important amount of studies have used fMRI as a complementary tool in the study of MS and clinically relevant alterations compromising visual, motor and cognitive domains. Since the earliest stages of the disease, local activity, and global neural dynamics appear to be compromised. Even when functional performance is still preserved, a different recruitment of neural resources arises as a compensatory response to disconnection observed in the disease.

Conclusions: the main findings of fMRI applied to MS are strongly related to the demyelinating nature of the disease and provide an adequate insight into the mechanisms that underlie functional alterations reported in this disease. fMRI also appears to be useful for studying disease evolution and response to treatment in MS and other disorders.

Keywords: Neuroimaging; fMRI; Multiple Sclerosis; Functional neuroimaging; Nervous system disease; Neurodegenerative diseases.

Introduction:

When a brain region is involved in the performance of a specific task, its neuronal activity generates changes in the Blood Oxygen Level Dependent(BOLD) signal. These changes are measurable under specific sequences of Magnetic Resonance Imaging[1, 2].This kind of acquisitions are known as Functional Magnetic Resonance Imaging(fMRI) and the variations in the intensity of their signal are due to the changes in the relation between oxygenated and deoxygenated hemoglobin in the brain blood vessels as a consequence of the increase in oxygen income triggered by different metabolic mechanisms both of neuronal and astrocytic origin[3, 4]. Neural activity can be studied both in resting state and during motor or cognitive tasks. Despite the existence of certain agreement regarding the BOLD signal basis, there rare different approaches to the analysis of the fMRI data. In these approaches, the concepts of functional and effective connectivity are frequently applied. The first is related to the correlation measures between the variations in BOLD signal taken from different brain regions and the second one is related to the causal effect of a cortical region over another[5, 6]. In the same line, the brain activity can be decomposed into a series of independent components determined by activity changes in a coordinated shape across the time[7-9] or as a sum of nodes interconnected by axis[*5*]. Some of them are so highly connected and influential over the brain dynamic that has been called as "Rich Club" organization[10, 11].

Under the theoretical construct previously shown, fMRI has provided abundant evidence regarding the underlying mechanisms of neurologic and neuropsychiatric diseases as depression[12] or schizophrenia[13], and the neural mechanisms related to their response to treatment[14].

Multiple Sclerosis(MS) is an inflammatory and neurodegenerative disease characterized by the loss of myelin in the white matter and eventually axonal loss[15, 16]. So, many of its manifestations have been attributed to the development of a disconnection syndrome. Indeed, from the neuroimaging perspective, both structural (Diffusion Tensor Imaging, DTI) and functional connectivity approaches have shown to coexist and give a report of disconnection underlying disability and cognitive changes[17]. Beyond its potential to generate disability in young people, one of the most interesting issues in MS is that 40-70% of patients develop some level of cognitive impairment[18] despite de wide variability in lesion load and brain atrophy.

Aim: The main objective of this article is to provide an insight on how fMRI has contributed to the understanding of the impact of MS in different functional systems and how it could be useful for being applied to the study of other diseases.

Methods: an advanced search was performed using PubMed web platform. The terms “fMRI", “Multiple” and “Sclerosis” as included in title and abstract were considered to perform the search. Only articles published during the last ten years were considered. Nevertheless, some older articles regarding Multiple Sclerosis or fMRI technique are mentioned in order to provide conceptual context. A list of 200 articles was initially obtained. All of them were classified as potentially relevant or irrelevant for this systematic review based on its Title and Abstract. 71 potentially relevant articles were analyzed (considering full text) and finally 50 articles were included. After full text analysis, we included 30 articles evaluating clinically relevant functions (as visual, motor and cognitive abilities) through an experimental design based on fMRI acquisitions. We also included resting state studies in MS patients. Articles not including fMRI, or those developed in other clinical populations were

excluded. Figure 1 shows the flowchart of the strategy for search and include articles. A considerable amount of additional articles are cited in the text with explanatory purposes, most frequently in the introductory paragraphs and in the contextualization of resting state fMRI.

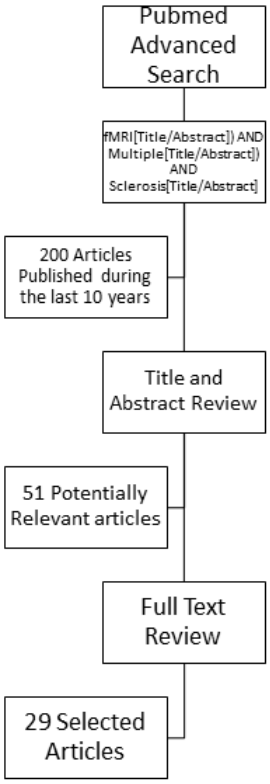

Figure 1. Flowchart of the search strategy.

Task-related fMRI:

Probably, the most solid conclusion derived from fMRI studies in MS is related to the existence of cortical reorganization occurring in patients[19]. Nevertheless, as clinical and structural findings differ among MS subtypes, the related fMRI findings must variate between Relapsing Remitting (RR) and Progressive forms of the disease. Even if counterintuitive, cortical plasticity is not always related

to good news. In the following paragraphs, we discuss evidence regarding neural plasticity responses in neural systems commonly affected in MS patients.

Visual System:

One of the first protocols investigating changes in the visual system in MS using fMRI applied a monocular photic stimulation to seven patients who had recovered from a unique episode of unilateral Optic Neuritis. They showed higher activation of the visual network including claustrum, posterior and lateral parietal cortex and thalamus besides the activation of primary visual cortex when stimulating the affected eye. Interestingly, when stimulating the unaffected eye, only insula, claustrum and primary visual cortex were activated. These findings were strongly related to the latency of visually evoked potentials, suggesting cortical reorganization may represent an adaptation to permanently abnormal input[20]. Additional research has supported this idea[21] and supplemented the whole picture by reporting a decrease in the activation of the primary visual cortex[22]. Taken together, this evidence establishes a general mechanism by which brains react to a demyelinating lesion to compensate functional alterations: a decrease in the participation of primarily involved brain areas and a compensatory increase in the recruitment of non-related regions.

The dynamic functional recovery after an episode of Optic Neuritis has been also studied. Korsholm *et al*, followed 19 patients during six months after the first clinical episode of MS, and reported significantly lower activation of the lateral cingulate nucleus in the acute phase when visual stimulation was applied. Furthermore, this difference between eyes decreased during recovery and finally disappeared during the follow-up[23]. This has been interpreted as early plasticity phenomena. Even if a dynamic behavior of neural plasticity event has been established, its temporal profile during the disease evolution and its contribution to preservation or impairment in different

functions still remain undefined. Figure 2 shows a schematic representation of both normal and abnormal processing of visual input in MS.

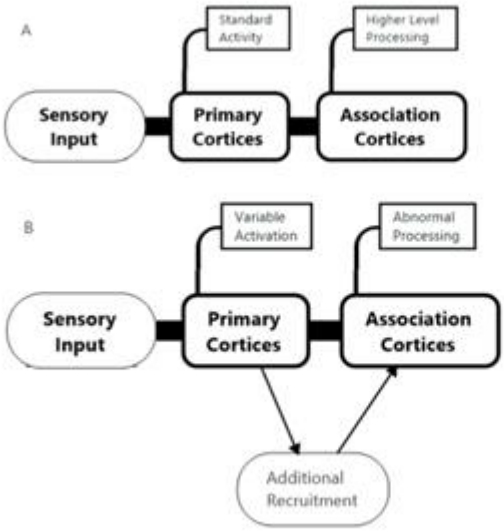

Figure 2. Schematic comparison of input processing A. Normal Sensory Input processing involving primary and association cortices in a well limited way. B. In a lesioned brain as in MS, a sensory input generates variable activation of primary cortices and then abnormal recruitment of association cortices leading to abnormal perception or interpretation of input.

Motor System:

When considering the motor system, the notion of adaptive or maladaptive plasticity arises again. When comparing Motor-impaired MS patients with those Motor-preserved groups, both considering RR and progressive patients, fMRI has allowed establishing differences from the perspective of neural networks. Those patients with preservation of motor skills have shown higher functional

connectivity in visual processing areas and patients with motor impairment show lower levels of functional connectivity in somatosensory association cortices, even in the absence of significant differences in lesion load[24].

On the other hand, the study of motor functions during fMRI recordings has provided evidence of disorganization in brain cortex since the earliest stages of the disease. A group of patients with Clinically Isolated Syndrome(CIS) was followed during a year in order to compare cortical activity patterns in those who remain under the diagnosis of CIS and those who progress to MS. Non progressive subjects showed higher activation of areas integrating motor network while the progressive group showed higher activity in several frontal, parietal, temporal and occipital areas[25]. Even if a higher recruitment of cortical surface can contribute to limit the impact of structural damage during the MS natural history, the early activation of those mechanisms could produce an early consumption of the brain's adaptive properties[19], commonly observed in patients with a more progressive phenotype.

The fatigue, a major clinical event in MS[26], has been also evaluated under fMRI paradigms. The subjective levels of fatigue have been related to changes in the cortical activity of certain areas as caudate, putamen, pallidum, thalamus and amygdala during demanding motor tasks and in relation with rest periods in RR with minimal levels of disability as measured by EDSS[27]. In the same line, it has been demonstrated that in fatigued patients, executive and motor areas exhibit abnormal activation during motor tasks requiring prolonged effort[28]. These findings suggest that alterations in the activity of motor and non-motor areas are related with the appearance of fatigue as an

important symptom of MS, identifying it as a complex phenomenon with a basis in the neural dynamics.

Figure 3 shows a schematization of normal and abnormal motor process since planning to execution.

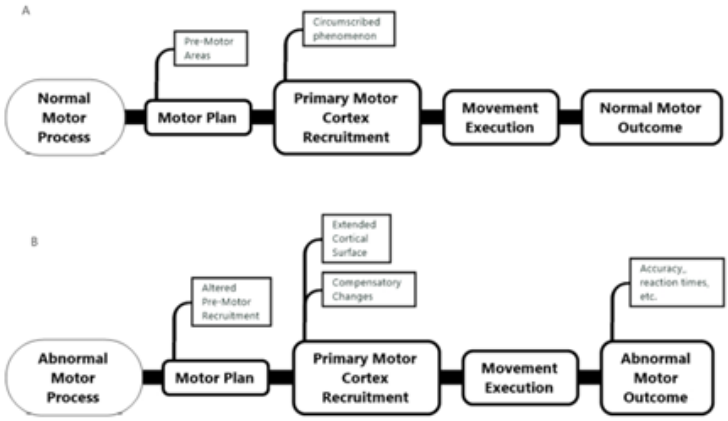

Figure 3. Schematic comparison of normal and abnormal motor processes. A. In a healthy brain, after a specific motor planning, a circumscribed participation of motor cortices leads to an accurate motor performance. B. In a brain with altered networks all steps, since planning to execution of movement can lead to an abnormal motor outcome.

Cognitive Functions:

In the current management of the disease, cognitive dysfunction represents a big therapeutic challenge, especially considering that in early stages of the disease, more than 50% of patients will exhibit some significant cognitive dysfunction[29-31]. As in other neurodegenerative diseases, the

pattern of cognitive decrease in MS is relatively well known and affects specifically working memory, processing speed[32], verbal fluency and executive functions[33]. The compromise of these functions directly affects daily living skills[34] and social functioning[35].

Considering this profile, studies using fMRI and Paced Auditory Serial Addition Test(PASAT) working memory test in early stages of the disease have shown that a preserved performance in the task is related to a higher activation of frontopolar, prefrontal and cerebellar cortices[36] and Brodmann areas 44 and 45[37]. This provides evidence about how, even in cognitively preserved subjects, changes in neural resources involved in specific functions can be found[38], both by the higher recruitment of non-related areas, as supplementary motor cortex during working memory tasks[39] or by changes in activity properties of regions highly related to cognitive functions, as centrality measures of Default-Mode Network(DMN) regions[40]. In the same line, since early stages of the disease alterations in how brain answer to an increase in cognitive demands has been demonstrated[41, 42]. It adds complexity to the cognitive study of those patients because some alterations may remain at a subclinical level depending on cognitive demands of the environment.

Additionally, the impact of cognitive rehabilitation on the functioning of neural networks has also been studied using fMRI. Subjects included in this kind of management have reported improvement in processing speed performance and higher activation of prefrontal and temporoparietal regions[43], providing an objective neurodynamic basis to evaluate the response to this or another kind of treatments.

Social Cognition Domain has recently become a focus of interest for MS teams and fMRI has been a useful tool in this area. When face expressions recognition tasks have been applied, differences in cortical recruitment have been found among disease phenotypes[44].

Resting-State fMRI in MS:

The study of the BOLD signal in absence of cognitive or motor tasks has allowed obtaining a view of the intrinsic functional architecture of human brain. Interestingly, some studies in free task conditions have reported that spontaneous neural activity does exist in a group of cortical and subcortical regions in different locations but functionally related, including visual, motor and cognitive control areas[45, 46]. If we pay attention to this last group, using posterior Cingulate Cortex as a region of interest, there are regions in which resting state signal is positively correlated, as medial Prefrontal Cortex, and negatively correlated as Intraparietal Sulcus, Frontal Orbital fields and medial Temporal regions[47]. Thus, the brain is intrinsically organized into networks operating even in absence of an overt cognitive or motor behavior. Table 1[48-55] summarizes some of the most commonly considered Resting State Networks both in the study of healthy and disease populations. Figure 4 shows examples of Resting State Networks on healthy subjects.

Commonly Studied Resting State Networks
1. Auditory and Language Processing
2. Visual Processing
3. Executive Functioning
4. Sensorimotor
5. Attentional
6. Default Mode
7. Right Frontoparietal
8. Left Frontoparietal

Table 1. Commonly identified resting state networks in fMRI studies. They are strongly related to functional systems including motor and cognitive abilities.

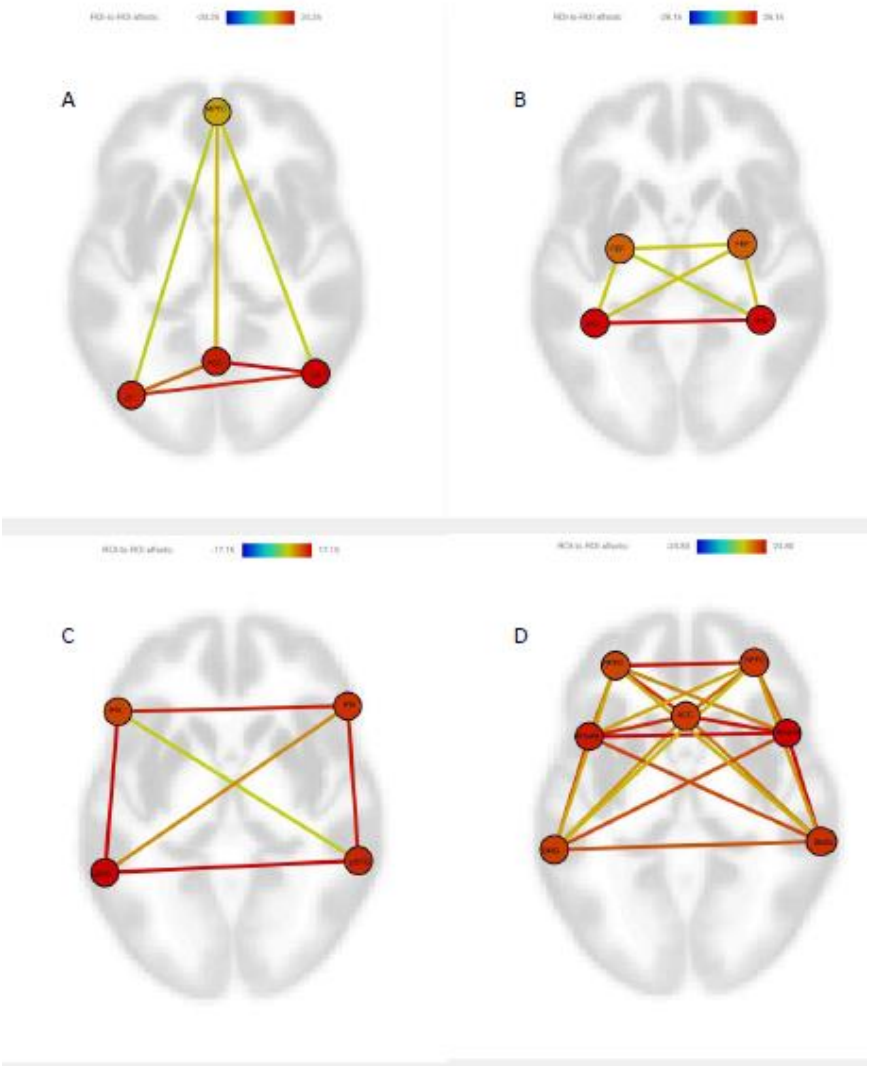

Figure 4. Resting State Networks. During Mental Rest, some brain areas exhibit correlated changes in their neural activity constituting well-differentiated functional units. (Here some examples) A. Default Mode Network: Medial Prefrontal Cortex (MPFC), Posterior Cingulate Cortex (PCC) and Lateral Parietal (LP). B. Dorsal Attentional Network: Frontal Eye Fields (FEF), Inferior Parietal Sulcus (IPS). C. Language Network: Inferior Frontal Gyrus (IFG), posterior Superior Temporal Gyrus. D. Salience Network: rostral Prefrontal Cortex (RPFC), Anterior Cingulate Cortex (ACC), Anterior Insula (Ainsula) and Supramarginal Gyrus (SMG)

Despite the big amount of information derived from fMRI acquisitions, the accuracy of its interpretations depends on an adequate data processing and analysis. Two of the most frequent approaches to the study of brain connectivity beyond the local changes in BOLD signal are Independent Component Analysis (ICA) and Graph Theory. In the first case, ICA decomposes the brain dynamics into spatial maps of regions with correlated changes in neural activity during the time[7]. In the other hand, Graph Theory evaluates the influence of brain regions over other areas or over the entire brain and describe each region of interest -or nodes- using terms as the degree of a node, clustering, Modular Organization and Global Efficiency to characterize the influence of each node on close and distant regions[5].

In the specific case of MS, resting state fMRI(rs-fMRI) has provided a higher degree characterization of correlation between structural disconnection, as measured by DTI and functional changes[17]. Also, it has contributed to understanding the network reorganization following the initial appearance of an acute lesion[56]. When considering temporal evolution of functional connectivity compensations, a global pattern has been established. An initial enhancement of brain connectivity decreases during the disease course and this decrease is related to disability progression[57]. Also, some specific functional connectivity patterns, as those alterations in Anterior Cingulate Cortex, often characterize CIS patients who progress to RR MS[58]. As a view to the different stages of the illness, 14 patients with CIS, 31 patients with RR MS and 41 healthy controls were studied. CIS patients showed increased synchronization in six of the eight identified resting state networks, including the DMN and sensorimotor network, compared to controls or RR MS patients. When the disease progresses, no significant resting state synchronization differences were found between patients and controls, suggesting that this specific cortical reorganization of resting state networks is an early and finite phenomenon in MS[59].

Even if the previously described study reported that RSN changes were limited to the CIS stage, in a different experimental design including 13 patients with RR MS patients and 14 matched healthy controls, independent component analysis(ICA) provided eight consistent neuronal networks involved in motor, sensory and cognitive processes and for seven resting state networks, the global level of connectivity was significantly increased in patients compared with controls. Interestingly, no significant decrease in connectivity measures was found in early multiple sclerosis patients. Given the relevance of well-validated scores to measure disability in the clinical follow-up of MS the correlation among those scales and resting state connectivity has been studied. The disability level as measured by the Multiple Sclerosis Functional Composite Score(MSFCS) values were negatively correlated with increased connectivity within the dorsal frontoparietal network, the right ventral frontoparietal network and the prefrontal-insular network[60]. Also, connectivity has reported being shifted toward the DMN in cognitively less-efficient participants(anticorrelation), whereas it was shifted toward the Control Network in cognitively efficient participants(positive correlation)[61].

This evidence shows that it is possible to identify resting state change patterns with both an adaptive and maladaptive role in cognitive functioning.

Considering that clinical and anatomic features exhibit considerable variances between disease phenotypes, group differences in DMN activity were found in the left medial Prefrontal Cortex, left Precentral Gyrus, and Anterior Cingulate Cortex, exhibiting different patterns for each group also related to cognitive performance[62]. That evidence must be interpreted as related to the role of spontaneous regional brain activity as an insight into the mechanisms underlying of behavioral impairment in MS[63].

When more subjective symptoms often reported in MS are studied under a rs-fMRI paradigm, interesting findings have also been reported. In sleep-disturbed patients, decreased functional connectivity between cognitively relevant areas as the thalamus, superior frontal gyrus, opercular

cortex, cingulate, parietal cortex and precuneus have been shown, providing a neurodynamic explanation for some severe sleep disturbances in MS[64]. In the case of fatigue, neurodynamic properties of the insula, caudate[65] and motor and executive network are contributing to the occurrence of centrally produced and persistent fatigue while hippocampal functional connectivity has reported being strongly correlated with severity of depressive symptoms and disability levels[66].

Also, rs-fMRI has reported being a useful tool for monitoring the therapeutic response based on functional reorganization[67, 68], proposing an interesting role in the follow-up of these patients.

Conclusions:

fMRI has strongly contributed to understanding neural mechanism underlying motor, visual and cognitive alterations in MS. Today, Neural Plasticity is a well-documented phenomenon occurring after an inflammatory and demyelinating lesion in the central nervous system. Despite the initially adaptive role of both structural and neurodynamic compensations during the early stages of the diseases, its prognostic utility and the potential for predicting phenotypes and evolution ways still remain unresolved. We consider fMRI contributions will increase when local clinical teams involved in the management of MS patients consider fMRI as a permanent part of the follow up of patients. At the same time, correlating fMRI findings with clinical performance in standardized neuropsychological evaluations will provide interesting additional evidence both in MS and in other neurological and neuropsychiatric diseases.

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II. Objectives:

General Objective:

To identify networks underlying to the global and social cognitive impairment in patients with Relapsing- Remitting Multiple Sclerosis (RR-MS).

Specific Objectives:

To describe the prevalence and pattern of social cognitive impairment in a local cohort of RR-MS patients.

To Identify structural patterns of brain atrophy underlying social cognitive impairment in RR-MS patients.

To compare brain connectivity patterns among social-cognitively preserved and impaired subjects.

III. Hypothesis:

There is a specific pattern of socio-cognitive impairment related to the structural and functional compromise of limbic structures in patients with Relapsing-Remitting Multiple Sclerosis.

IV. Methods

Bioethics:

The present investigation was approved by the ethics committee of the medical school of the Pontifical Catholic University of Chile as an extension of the previously approved project "National registry of patients with Multiple Sclerosis", and all subjects gave informed consent. Recruitment:

Patients with Relapsing-Remitting Multiple Sclerosis under control at Hospital Clinico Pontificia Universidad Católica, Chile, were invited to participate in a full Neuropsychological evaluation when concomitant to their routine radiological control.

Healthy volunteers, education and age-matched, were included to perform the same neuropsychological examination, and structural/functional images were acquired using the same protocol.

Neuropsychological Evaluation:

Conventional Cognitive evaluations were based on the Minimal Assessment of Cognitive Function in Multiple Sclerosis(Benedict, 2006; Benedict, 2002; Benedict, 2012). It evaluates domains as Processing Speed (SDMT test)(Smith, 2002), Verbal and Visual Episodic memory(CVLT and BVMT-R tests)(Benedict, 1997; Ponton, 1996), Working Memory (PASAT)(Gronwall, 1977), Inhibitory control (Stroop test, Spanish version)(Golden, 1994) and Verbal Fluency (FAS test)(Delis, 2001). All the cognitive tasks were performed in Spanish by a trained evaluator as detailed in a previous article(Ciampi, 2018). Performance in each of these cognitive tasks is expressed as a z-score.

Depression, Fatigue, and Mental Status were evaluated by applying Beck Depression Inventory II,(Melipillán, 2008 ; Sanz, 2003), Fatigue Severity Scale-FSS(Krupp, 1995) and Mini-Mental Status Examination (MMSE) respectively. Only subjects with a MMSE score higher than 24(González-Hernández, 2009), according to the local regulatory law for clinical research.

Social Cognition was evaluated using the Mini-Social Cognition and Emotional Assessment (MiniSEA)(Bertoux, 2014; Bertoux, 2012), a 30 min composite battery which is the reduced version of the Social Emotional Assessment test(Funkiewiez, 2012). It consists of two different items including a shortened version of the Faux-Pas (FP) and the Face Emotion Recognition to evaluate Theory of Mind and Social Perception subdomains respectively. Theory of Mind section includes ten short stories in which a character inadvertently hurts or offends another. Then, the subject needs to infer another's mental state making attributions to their knowledge, beliefs, and emotions. Half of the vignettes are control stories, and the other half includes a principal character who inadvertently offends another. The subject is expected to recognize the situations in which a FP is committed, why the leading subject did it (cognitive theory of mind) and how the victim must have felt (affective theory of mind). Social Perception item consists of 35 pictures for face affect recognition of basic emotions among a list presented at the bottom of the screen including happiness, sadness, anger, surprise, fear, disgust and neutral. A global MiniSEA score and individual performances on Social Perception and Theory of Mind task were obtained separately. Given the absence of a locally validated version of MiniSEA, results are expressed as absolute scores.

Magnetic Resonance Imaging Parameters:

Both structural and functional images were acquired in a Philips Ingenia 3 T device. T1W-3D and resting-state fMRI acquisition parameters are detailed in Table 1. During resting-state acquisition, patients and healthy control subjects were instructed to maintain their eyes opened, fixed on a point in front of their faces and avoid thinking.

A FLAIR sequence was also acquired for the segmentation of brain lesions as detailed below.

MRI Acquisition Parameters	T1W-3D	rsfMRI
TR (ms)	7.8	2500
TE (ms)	3.6	35
Matrix (mm)	240 x 240	80 x 80
Field of view (mm)	240 x 240 x 164	220 x 220 x 132
Acquisition resolution (mm_3)	1.00 / 1.00 / 1.00	2.75 / 2.75 / 3.00
Reconstructed resolution (mm_3)	0.50 / 0.50 / 0.50	2.75 / 2.75 / 3.00
Flip angle (º)	8	82
Inversion time (ms)	977	-
Number of signal averages	1	1
Bandwidth (Hz)	191.5	35.9
SENSE factor	2.5	1.8
Slices	327	40
Acquisition time	4 min 8 s	8 min 27 s
Dynamic scan volumes	-	200

Table 1. Acquisition Parameters for structural and functional sequences. MRI: Magnetic Resonance Imaging; T1W-3D: T1 weighted 3D image; rsfMRI: resting-state functional Magnetic Resonance Imaging; TR: repetition time; TE: echo time; SENSE: sensitivity encoding.

Structural Study:

Structural Image Evaluation using Normalization of Atrophy (SIENAX): Brain tissue volume, normalized for subject head size, was estimated with SIENAX(S. M. Smith, 2002), part of FSL(S. M. Smith, 2004), (Fmrib, Oxford, UK, available at http://www.fmrib.ox.ac.uk/). SIENAX starts by extracting brain and skull images from the single whole-head input data. The brain image is then affine-registered to MNI152 space (using the skull image to determine the registration scaling); this is primarily to obtain the volumetric scaling factor, to be used as a normalization for head size. Next, tissue-type segmentation with partial volume estimation is carried out to calculate the total volume of brain tissue (including separate estimates of volumes of grey matter, white matter, peripheral grey matter and ventricular CSF).

Voxel-Based Morphometry (VBM): Lesions were segmented by the lesion growth algorithm(Schmidt, 2012) as implemented in the LST toolbox version 1.2.3 (www. statisticalmodelling.de/lst.html) for SPM. The algorithm first segments the T1 images into the cerebrospinal fluid, grey matter and white matter. This information is then combined with the co-registered FLAIR intensities to calculate lesion belief maps. By thresholding these maps with a pre-chosen initial threshold (k) an initial binary lesion map is obtained which is subsequently grown along voxels that appear hyperintense in the FLAIR. The outcome, a lesion probability map, in alignment with a T1 volume, creates a filled image in native space. Then, volumes based on a voxel-wise comparison of grey and white matter volumes were applied to T1 filled images by using SPM8. (Statistical Parametric Mapping 8; Functional Imaging Laboratory, Wellcome Department of Imaging Neuroscience, Institute of Neurology, London, UK; http:// www.fil.ion.ucl.ac.uk/spm) It runs on Matlab 2015b (Mathworks, Natick, MA, USA). T1 filled images were Segmented, Replaced to a DARTEL template and then normalized to MNI space using VBM8 preprocessing in SPM8(Ashburner, 2007). A two-sample t-test was selected as a factorial design to perform a regional comparison between control subjects and patients. Multiple regression was chosen as the factorial design using MiniSEA, Social Perception, and Theory of Mind scores. Interaction analysis was performed to look for differences in the association of

regional brain volume and cognitive performance between groups. Significance was assessed using a family-wise error (FWE) corrected of p-value<0.05 and Cluster size>20 voxels. The cluster size was selected considering the main size of the regions included in the Harvard-Oxford Atlas(Desikan, 2006) to avoid the over-representation of small clusters mostly related to noise(Woo, 2014).

Functional Study

Raw images obtained from rsfMRI scans underwent realignment, slice timing correction, coregistration with the T1W-3D acquisitions, and normalization to the MNI space using SPM12. The resulting images were processed with the CONN toolbox (www.nitrc.org/projects/conn) to perform a ROI-to-ROI resting-state connectivity analysis. It considers a 91 cortical areas and 15 subcortical areas from the FSL Harvard-Oxford Atlas, 26 cerebellar areas of the Automated Anatomical Labeling (AAL) Atlas and 32 regions commonly used for investigating resting-state connectivity (including DMN, Dorsal attention Network Executive Control Network, etc.)(Nieto-Castanon, 2012; Whitfield-Gabrieli, 2012). A two-sample t-test was performed to look for differences in resting state connectivity between groups. One way ANCOVA-interaction analysis was performed to detect differences between groups in the association of resting-state functional connectivity and social cognition performance. A FDR-corrected p-value<0.05 was considered significant for functional analysis.

Statistical Analysis:

Statistics were performed using Minitab 17 Statistical Software (2010). [Computer software]. State College, PA: Minitab, Inc. (www.minitab.com). Correlation between continuous variables was assessed using Spearman Correlation. Differences between groups were assessed using the Mann-Withney test. The interaction of potential confounders as depression and fatigue scores with traditional and social cognitive domains was assessed by using Analysis of Covariance (ANCOVA). The result was considered as significant with a p-value<0.05.

Specific statistical parameters for Structural and Functional analysis are specified in their respective subheadings.

V. Results

Study population:

We included 68 Relapsing-Remitting Multiple Sclerosis Patients and 50 healthy control subjects. All of them underwent full neuropsychological evaluation and Magnetic Resonance Imaging including both structural and resting-state functional sequences, but only 45 Patients and 47 healthy control subjects were included in the functional analysis. See Figure 1.

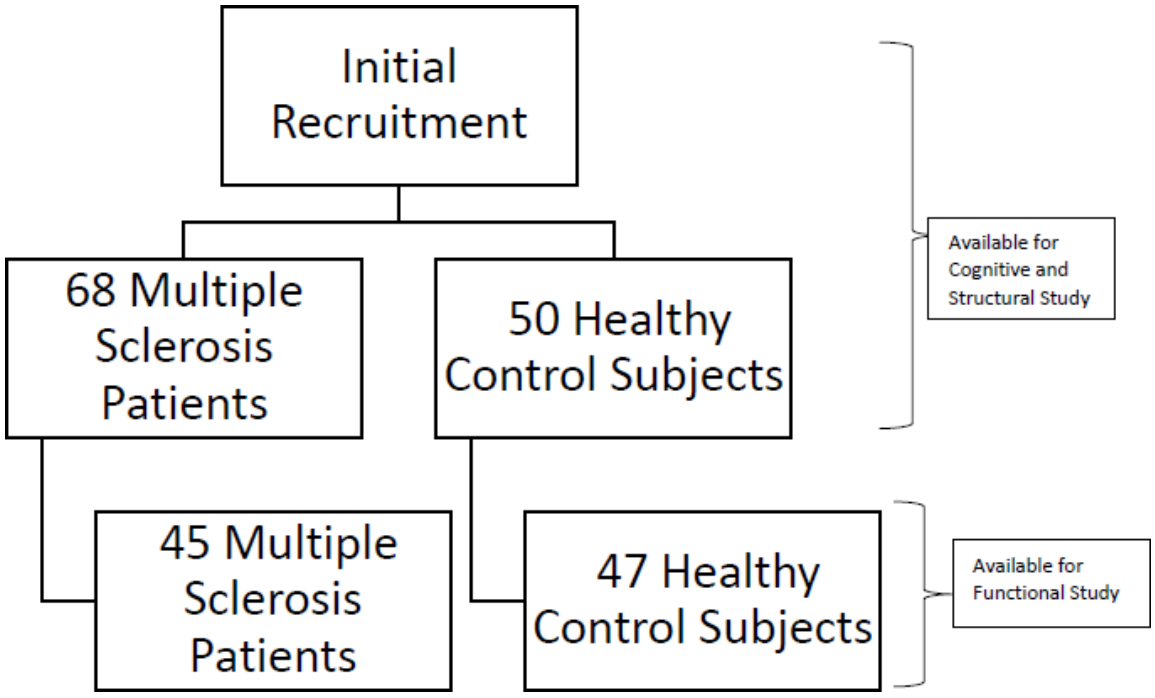


Figure 1. Flowchart detailing Recruitment of Patients and Control Subjects.

Demographical and clinical characteristics of patients included in the functional and structural analysis are shown in Supplementary Table 1.

General Characterization:

The present study focuses on a relatively young sample of patients (37,43 + 11,2 years old versus 37,97 + 10,76 years in control group, p-value=0,765). The mean disease duration is 5,052 + 3,649 years and median EDSS (Expanded Disability Status Scale) is 1 (range 1-4,5).

94,3% of patients have a university or technical career compared to 98% in the control group(p-value=0.098). Employability level is 91,5% in patients and 94% in control subjects, (p-value=0,731). See Tables 2 and 3.

	Healthy Control	Patients	p- value
Age (Mean + SD)	37,43 ± 11,20	37,97 + 10,76	0,765
Gender (Male/Female)	26/24	48/20	0,039
Job Status (%)			
Unemployed	2	2,8	1
Student	4	5,7	1
Employed	94	91,5	0,731
Educational Level (%)			
Secondary	2	5,7	0,394
Technical	2	10	0,136
Professional	96	84,3	0,041

Table 2. Demographic comparison between Healthy subjects (n=50) and Patients(n=68).

	Healthy Control	Patients	p- value
Beck (Mean ± SD)	15,50 ± 7,4	21 ± 15,38	0,001
Krupp (Mean + SD)	1,951 ± 0,823	2,915 ± 1,708	0,009
Minimental Status Examination (Mean + SD)	29,58 ± 0,6	29,64 ± 0,7	0,374
Disability Level by EDSS (Median [Min,Max,IQR])	-	1[0,5,2]	
Disease's Evolution time (Mean + SD)	-	5,052 ± 3,649	

Table 3. Health comparison between Control Subjects (n=50) and Patients(n=68). Depression (Beck), Fatigue (Krupp) and Mental Status are shown. Also Disability Level and disease's evolution time are shown for patients group.

No significant difference in Mental Status was found in comparison with healthy subjects (p- value= 0,374), while significantly higher scores in fatigue and depression questionnaires were obtained for the patient's group (p-value= 0,001 and 0,001 respectively).

Neuropsychological assessment:

Significantly lower scores were obtained for the patient's groups in Processing Speed, Verbal Fluency and Verbal and Visual Memories compared to healthy controls (p-value<0,05). No significant difference was found between the patients and control group when performances in Working Memory and Cognitive Interference tests were compared. No traditional cognitive domains exhibited mean Z scores lower than -1,5 (threshold for cognitive impairment). See Table 4.

	Group*	Media	Desv. Est	p-value
Processing Speed	0	0,403	0,882	0,005
	1	-0,03	1,141	
Working Memory	0	-0,123	0,97	0,094
	1	-0,52	1,381	
Verbal Memory	0	-0,569	1,455	0,029
	1	-1.298	2,027	
Visual Memory	0	0,611	0,911	<0,001
	1	-0,166	1,38	
Verbal Fluency	0	1,348	1,49	0,001
	1	0,335	1,163	
Cognitive Interference	0	-0,69	7,36	0,773
	1	0,929	0,929	

Table 4. Differences in Cognitive performance considering conventional domains. * O= Healthy Control Group (n=50), 1= Multiple Sclerosis Patients (n=68)

As shown in Table 5, patients exhibit a lower global Social Cognition performance, as measured by Mini-SEA score, than healthy subjects (p-value= 0,046), mainly influenced by the social perception score (p-value=0,015).

	Group*	Median	IQR	p-value
MiniSEA	0	26,106	3,96	0,046
	1	25,26	3,033	
Social Perception	0	12,82	2,09	0,015
	1	11,83	1,738	
Theory of Mind	0	14,625	2,25	0,153
	1	13,725	2,7	

Table 5. Social Cognition Comparison between groups. * O= Healthy Control Group (n=50), 1= Multiple Sclerosis Patients (n=68).

To describe the relationship between traditional cognitive domains and Social Cognition, Supplementary Table 2 shows a Spearman Correlation Matrix considering those values.

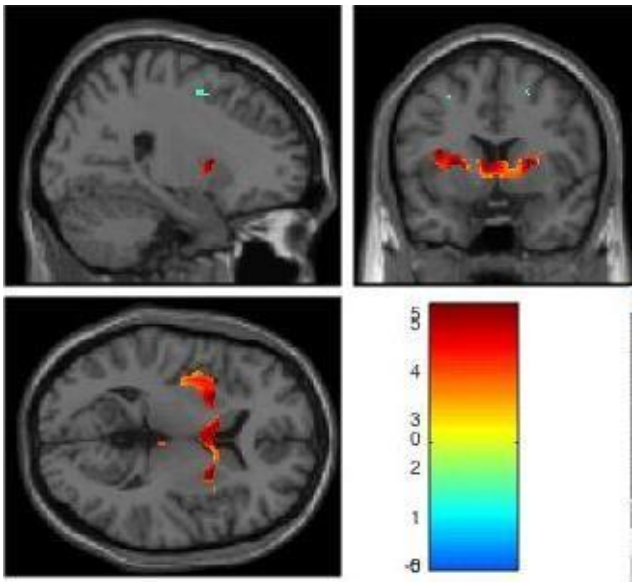
Structural Analysis:

Patients exhibit significant lower whole brain and white matter volumes compared to healthy controls. See Table 6. No significant correlation between those global or regional volumes and Social Cognition performance was found.

	Healthy Control (Median)	Patients (Median)	p- value
Normalised Brain Volume	1556749	1525070	0,001
Grey Matter Volume	781920	773392	0,162
White Matter Volume	777425	752897	<0,001

Table 6. Brain Volumes comparison. Median of all volumes measured by SIENAX algorithm are higher in Control Group (Control group, n=50; Patients n=68).

When looking for differences in regional atrophy between groups, we found significant clusters of voxels in both hemispheres compromising Insula, Caudate, Cingulate Gyrus and Medial Frontal Gyrus among others. See Figure 2 and Supplementary Table 3.



p <0.05 FWE: 0.05 Cluster Size>20voxeles

Figure 2. Voxel Based Morphometry. A. Voxels with significant differences between healthy control group (n=50) and Multiple Sclerosis Patients (n=68).

When the correlation between Regional Volume and Social Cognition Performance was analyzed, specific areas as Insula, Medial Frontal Cortex, Cingulate Cortex appear to be significantly correlated to the cognitive processes of social perception and theory of mind.See Supplementary Table 4 and Figure 3.

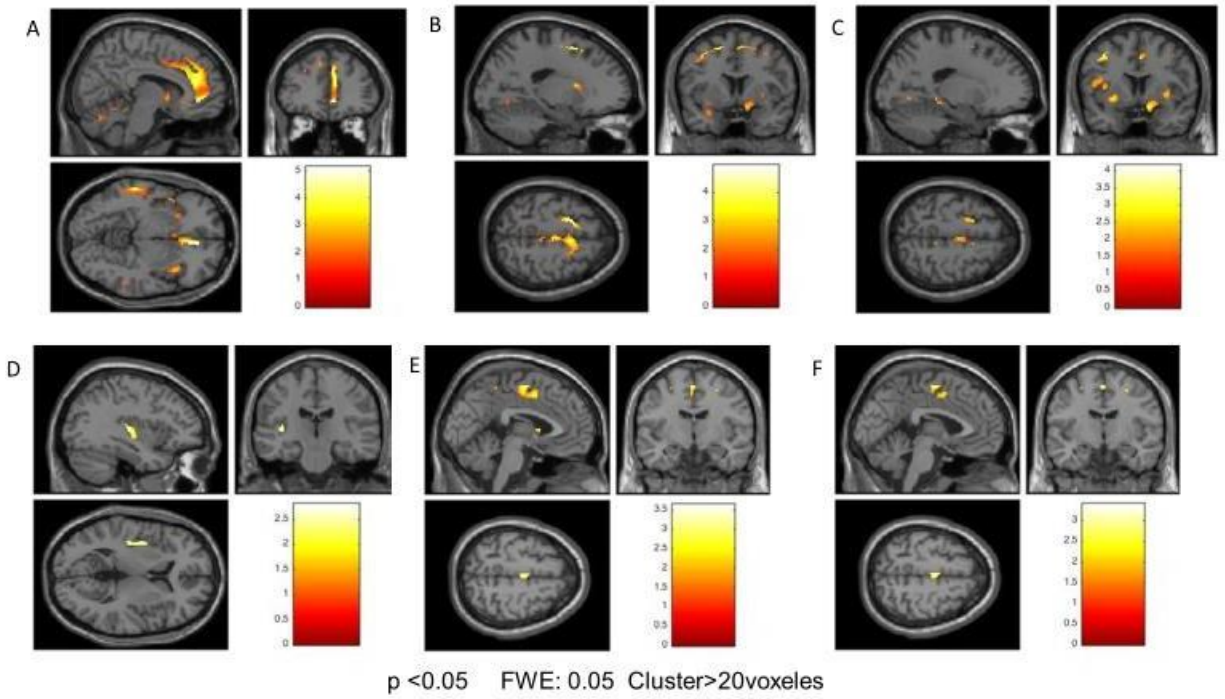


Figure 3. Brain Areas showing significant association between regional volume and Social Cognition performance. A. MiniSE, B. Social Perception and C. Theory of Mind in Healthy Control Subjects (n=50); D. MiniSEA, E. Social Perception and F. Theory of Mind in Multiple Sclerosis Patients (n=68).

The interaction analysis shows that left Insula and bilateral Medial Frontal Regions exhibit significantly different levels of association with the theory of mind and social perception scores See Figure 4 and Table 6.

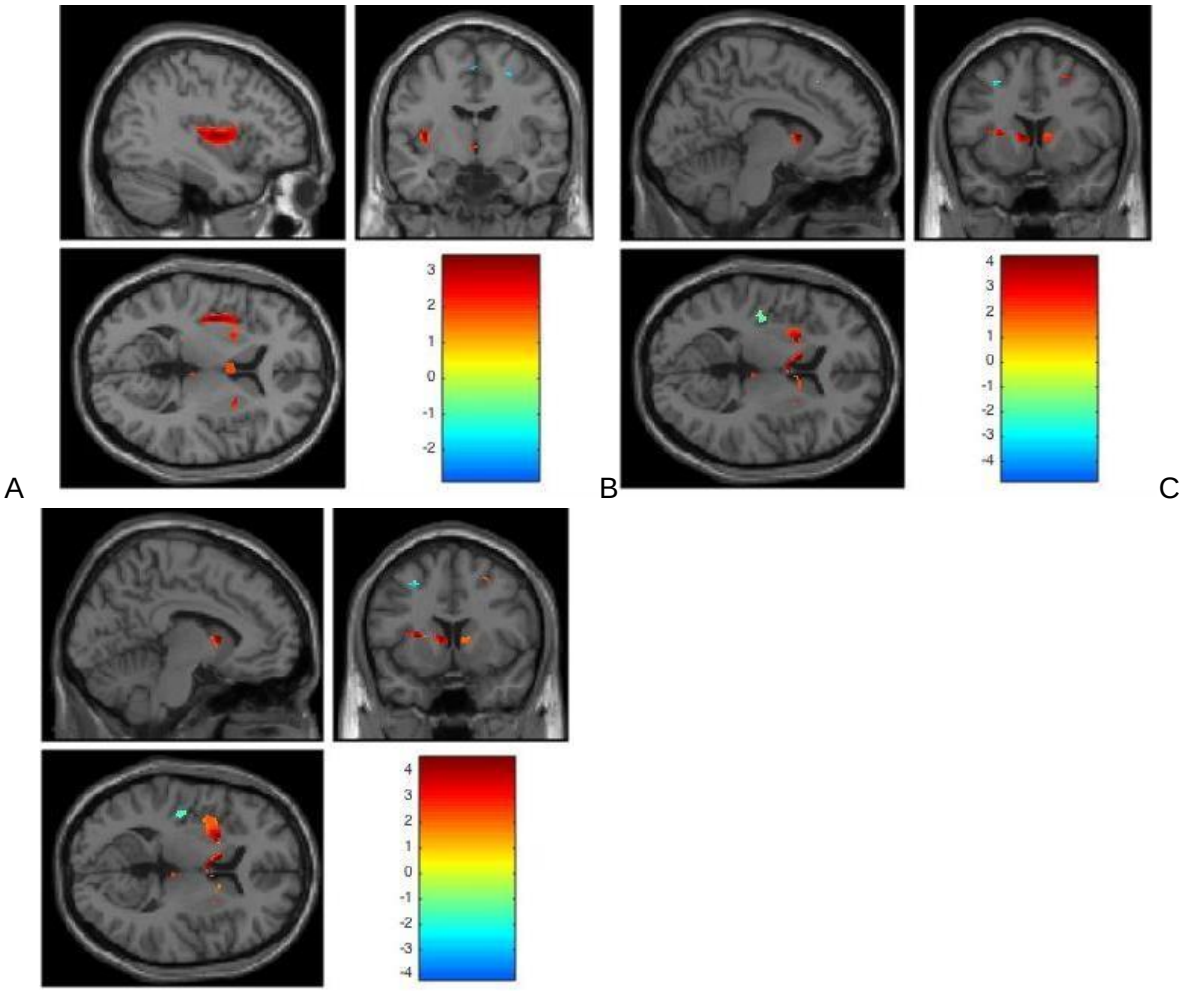


Figure 4. Clusters which level of association with social cognition performance are significantly different in Healthy Control (n=50) and MS Patients (n=68) (Interaction Analysis). A. MiniSEA B. Social Perception C. Theory of Mind.

Task	hemisphere	Brain Region	Cluster Size	Peak MNI Coordinates X	Y	Z	Peak Intensity (t value)
MiniSEA	L	Insula	556	-37,5	-7,5	6	3,4151
	R	Putamen	52	25,5	7,5	6	2,5131
	L	Putamen	55	-25,5	6	6	2,282
	R	Thalamus	22	3	-24	9	2,6437
	L	Precuneus	200	-6	-66	28,5	2,3188
	R	Precuneus	22	15	-55,5	51	-2,6159
	R	Middle Frontal Gyrus	54	28,5	-6	52,5	-2,1859
	R	Superior Frontal Gyrus	42	22,5	10,5	52,5	-2,2862
	L	Medial Frontal Gyrus	39	0	-9	58,5	-2,8403
Social Perception							
	L	Insula	169	-36	-18	3	-2,8699
	L	Insula	393	-36	9	15	4,2085
	L	Caudate	401	-7,5	10,5	7,5	4,2433
	R	Thalamus	22	3	-25,5	7,5	2,3914
	L	Medial Frontal Gyrus	167	-12	16,5	48	-3,3116
	R	Medial Frontal Gyrus	946	3	-15	57	3,8668
	L	Parietal Lobe	66	-31,5	-52,5	-40,5	-2,4902
	R	Medial Frontal Gyrus	34	12	34,5	39	-4,3898
	L	Middle Frontal Gyrus	52	-28,5	13,5	43,5	-4,7525
	L	Parietal Lobe	25	-37,5	-30	48	2,9788
	R	Middle Frontal Gyrus	116	27	19,5	48	3,0708
	L	Middle Frontal Gyrus	20	-30	-4,5	54	2,3153
Theory of Mind							
	L	Insula	604	-34	9	14	4,4925
	L	Insula	169	-37,5	-18	1,5	-2,3379
	R	Caudate	508	-7,5	10,5	7,5	5,5474
	R	Thalamus	21	3	-24	9	2,8925
	L	Posterior Cingulate	50	-3	-61,5	22,5	2,0879

L	Medial Frontal Gyrus	204	-12	34,5	40,5	-3,91898
L	Parietal Lobe	50	1,5	-69	37,5	2,9298
R	Cingualte Gyrus	1326	-1,5	-1,5	46,5	3,7867
L	Parietal Lobe	120	-36	-46,5	40,5	-2,427
R	Medial Frontal Gyrus	36	12	34,5	40,5	-3,9899
L	Middle Frontal Gyrus	60	-28,5	13,5	43,5	-4,1395
R	Middle Frontal Gyrus	54	27	19,5	48	2,8369
R	Parietal Lobe	27	15	-55,5	51	-2,9776
L	Medial Frontal Gyrus	26	-10,5	6	55,5	-3,2675
R	Middle Frontal Gyrus	30	28,5	-4,5	54	3,1619

Table 6. Voxel Based Morphometry comparison of association between social cognition performance and regional brain volume in control (n=50) versus patients (n=68) (Interaction Analysis)

Functional Analysis:

To look for differences in functional connectivity between the groups, we performed an analysis based on Regions of Interest (ROIs) including the commonly described components of Resting State Networks. 74 pairs or ROIs have shown significantly higher resting state functional connectivity in patients and 69 pair exhibit significantly higher connectivity in patients (See Table 7 and Supplementary Table 5 and Figure 5).

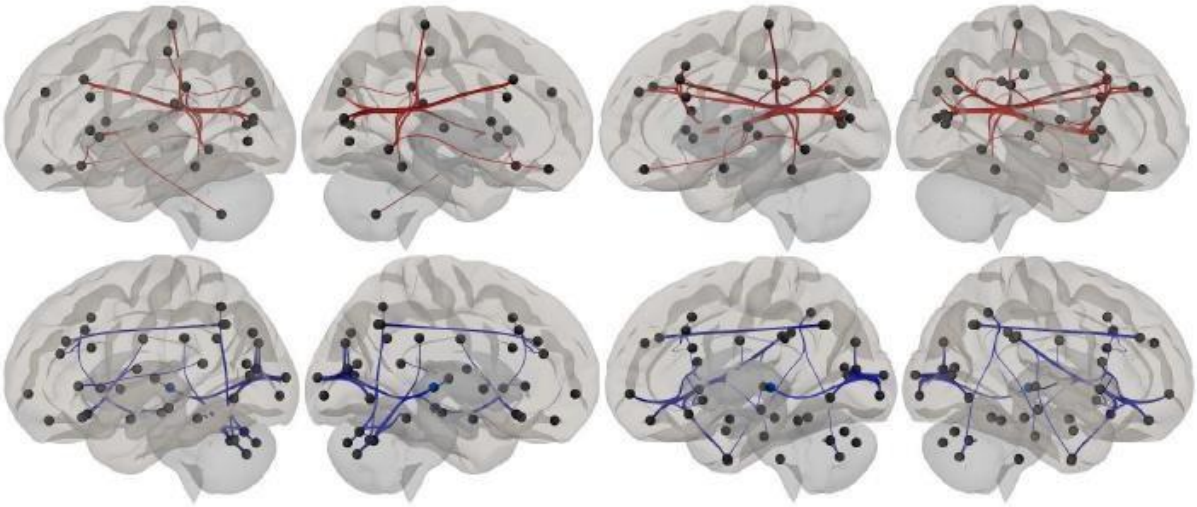


Figure 5. Default Connectivity exhibit changes in cognitively preserved Multiple Sclerosis Patients. Schematization of Significant differences in functional connectivity between Multiple Sclerosis Patients (n=45) and Healthy Control Subjects(n=47). Black spheres are Regions of Interest participating in commonly described Resting State Networks. Blue Lines represent regions with increased functional connectivity in patients during rest.
Red lines represent connections with significantly decreased connectivity levels at rest.

ROI to ROI	t - value	p-unc	p-FDR
Occipital Pole r -Isthmus of the Cingulate Cortex r	-5,62	<0,0001	0,0014
Posterior Cingulate Cortex-Lateral Prefrontal Cortex r	-5,12	<0,0001	0,0076
Occipital Pole l -Lingual Gyrus r	-5	<0,0001	0,0079
Occipital Pole l -Isthmus of the Cingulate Cortex r	-4,94	<0,0001	0,0079
Occipital Pole r -Lingual Gyrus r	-4,88	<0,0001	0,0085
Precuneous -Lateral Prefrontal Cortex r	-4,79	<0,0001	0,0085
Cuneal l -Occipital Pole r	-4,78	<0,0001	0,0085
Occipital Pole r -Medial Visual Cortex	-4,74	<0,0001	0,009
Occipital Pole l -Medial Visual Cortex	-4,57	<0,0001	0,012
Amygdala l-Frontal Operculum l	-4,5	<0,0001	0,015
Rostral Prefrontal Cortex l-Inferior Frontal Gyrus opercularis r	4,44	<0,0001	0,0168
Anterior Insula r-Cerebellum Region 7 l	4,48	<0,0001	0,0151
Anterior Cingulate Cortex-Medial Visual Cortex	4,59	<0,0001	0,012
Middle Frontal Gyrus r -Frontal Operculum r	4,62	<0,0001	0,0114
Anterior Insula r-superior Lateral Occipital Cortex r	4,64	<0,0001	0,0112
Anterior Insula l-superior Lateral Occipital Cortex r	4,66	<0,0001	0,0111
Anterior Insula r-Medial Visual Cortex	4,77	<0,0001	0,0085
Anterior Cingulate Cortex-Isthmus of the Cingulate Cortex l	4,78	<0,0001	0,0085
Anterior Insula r-posterior Supramarginal Gyrus r	4,98	<0,0001	0,0079

Anterior Cingulate Cortex-Isthmus of the Cingulate Cortex r	5,63	<0,0001	0,0014	

Table 7. Resting State Differences between Healthy Control Group (n=47) and Patients (n=45). Selected pairs of Regions of Interest in which functional connectivity levels are significantly different between patients and healthy control subjects. Negative T-values mean higher connectivity in patients and positive t-values show stronger functional connectivity in control subjects.

At the same time, the functional connectivity of several pairs or regions exhibits a significantly different association with the performance Social Cognition tasks. As shown in Table 8, the interaction of the left posterior segment of the temporal Fusiform Cortex appears to be correlated to the social perception performance, and the right Amygdala with contralateral Occipital cortices appears to be involved in theory of mind subdomain.

Task	ROI to ROI	t-value	p-unc	p-FDR
MiniSEA	Heschl's Gyrus l -posterior Middle Temporal Gyrus r	-4,13	0,0001	0,0135
	Subcallosal Cortex -posterior Superior Temporal Gyrus	-3,79	0,0003	0,0454
	posterior Superior Temporal Gyrus-Heschl's Gyrus l	-3,55	0,0006	0,0354
	posterior Superior Temporal Gyrus-Orbitofrontal Cortex r	-3,54	0,0007	0,0354
	posterior Superior Temporal Gyrus-Orbitofrontal Cortex l	-3,35	0,0012	0,0493
	Rostral Prefrontal Cortex-Inferior Frontal Gyrus r	3,44	0,0009	0,0287
	Rostral Prefrontal Cortex-anterior Medial Temporal Gyrus r	3,45	0,0009	0,0287
	Rostral Prefrontal Cortex-posterior Superior Temporal Gyrus r	3,61	0,0005	0,0278
	Rostral Prefrontal Cortex-anterior Superior Temporal Gyrus l	3,81	0,0003	0,0208
	Rostral Prefrontal Cortex-posterior Middle Temporal Gyrus r	3,83	0,0002	0,0208
Social Perception	Orbitofrontal Cortex l -posterior Superior Temporal Gyrus R	-4,07	0,0001	0,0167
	Temporal Fusiform Cortex anterior seg, l -posterior Superior Temporal Gyrus l	-4,02	0,0001	0,0203
	Fusiform Gyrus Occipital r -Planum Polare l	-3,93	0,0002	0,0271
	Subcallosal Cortex -Visual Lateral Cortex	-3,82	0,0002	0,0406
	Medial Frontal Cortex -Central Operculum r	-3,81	0,0003	0,0417
	Temporal Fusiform Cortex anterior seg, l -Temporal Pole r	-3,79	0,0003	0,0225
	Fusiform Cortex Temporal posterior seg, l -Fusiform Gyrus Occipital r	-3,4	0,001	0,042
	Fusiform Cortex Temporal posterior seg, l -Planum Temporale r	-3,27	0,0015	0,042
	Fusiform Cortex Temporal posterior seg, l -Postcentral Gyrus r	-3,27	0,0015	0,042
	Fusiform Cortex Temporal posterior seg, l -Fusiform Cortex Temporoccipital seg, r	-3,25	0,0016	0,042
	Fusiform Cortex Temporal posterior seg, l -Precentral Gyrus l	-3,24	0,0017	0,042
	Fusiform Cortex Temporal posterior seg, l -Postcentral Gyrus l	-3,18	0,0021	0,042

	Fusiform Cortex Temporal posterior seg, l -Inferior Temporal Gyrus anterior seg, r	-3,12	0,0025	0,042
	Fusiform Cortex Temporal posterior seg, l -Accumbens r	-3,11	0,0025	0,042
	Fusiform Cortex Temporal posterior seg, l -Middle Temporal Gyrus anterior seg, r	-3,1	0,0026	0,042
	Fusiform Cortex Temporal posterior seg, l -Lateral Occipital Cortex inferior seg, r	-3,04	0,0031	0,0434
	Fusiform Cortex Temporal posterior seg, l -Heschl's Gyrus r	-2,95	0,0041	0,05
	Fusiform Cortex Temporal posterior seg, l -Inferior Frontal Gyrus triangularis l	-2,93	0,0043	0,05
Theory of Mind	Cerebellum region 3 l -Lateral Occipital Cortex inferior seg r	3,6	0,0005	0,0452
	Cerebellum region 3 l -LG r	3,51	0,0007	0,0452
	Cerebellum region 3 l -Visual Lateral r	3,46	0,0008	0,0452
	Amygdala r-Lateral Occipital Cortex inferior seg l	4,42	<0,0001	0,0046
	Amygdala r-Visual Lateral Cortex l	3,6	0,0005	0,0425

Table 8. Pairs of Brain Regions with significant differences in the level of association of resting state connectivity and social cognition performance between Healthy Controls (n=47) and Multiple Sclerosis Patients(n=45) (Interaction Analysis).

VI. Discussion

In the present study, Multiple Sclerosis Patients with low levels of disability and preservation of traditional cognitive domains, exhibit a significantly lower social cognition performance compared to education and age-matched healthy controls, which is more evident in the social perception sub-domain. Despite the existence of global brain atrophy, this finding was not correlated with social cognition performance in this selected group of RRMS patients. Regional structural changes as measured by Voxel-Based Morphometry provide a more accurate notion of the structural correlates of social cognition declining in those patients involving Insula, Medial Frontal Regions and Cingulate Cortex. On the other hand,resting-state functional connectivity has shown how widespread changes in the interac tion of specific pairs of brain regions underly to alterations in social perception and theory of mind performance, exceeding the variability observed in healthy control subjects.

Interestingly, the mentioned changes in social cognition are observed in the context of a group with low disability measures, high educational and job status and a relatively short disease duration. This corroborates the existence of social cognition declining, since the earliest stages of the disease, including CIS (Clinically Isolated Syndrome)(Jehna, 2010). It constitutes a major challenge, considering that socio-cognitive declining has been related to job loss and divorce(Julian, 2008; Rao, Leo, Bernardin, , 1991; Rao, Leo, Ellington, , 1991).

In the other hand, despite the existence of a few significant correlations between social-cognition and traditional cognitive domains observed separately in control and patients groups, the theory of mind and social perception changes appears to be not dependent of commonly studied cognitive deficits.

Also, the presence of the disease has not shown to modify the association between socio-cognitive and traditional cognitive performances as working memory, processing speed, etc. This dependency has generated contradictory interpretations in the literature, with author concluding that social cognition declining is a product of global cognitive compromise(Genova, 2016; Jehna, 2010) or an independent domain(Ciampi, 2018; Roca, 2014). Given the relatively short disease duration, and the observed lower performance both in domains as processing speed, verbal fluency and memory and social cognition but the absence of interaction between domains, the studied group of RR-MS patients appears to exhibit Social Domain as an independent source of cognitive disability.

Interestingly, the results of the comparison between the control group and patients using VBM show a structural compromise of several regions. Some of them have been shown to participate in relevant modular functions involved in social cognition as Insula(R. Smith, 2017), Caudate(Hughes, 2013; Kemp, 2013) and Medial Frontal Gyrus(Baird, 2006). Then, even from the stage of structural comparison, the compromised brain regions may plausible a social cognition impairment.

In the case of resting-state functional analysis based on Regions of Interest, a global comparison between healthy subjects and MS patients shows the existence of pairs of regions with increased or decreased functional connectivity. Those connections with weaker connectivity correspond to the underlying disconnection syndrome of the MS(Zhou, 2014) while increased functional connectivity shows the presence of compensatory well-described changes(Patel, 2018). Interestingly, functional changes appear to exceed the changes detected by the regional structural approach, as suggested by recent studies in which functional modifications may occur even in the absence of structural changes at the beginning of the disease(Backner, 2018).

At the same time, changes in the information flow between brain regions could be understood under the paradigm of cognitive reserve and neural compensation(Stern, 2003; Stern, 2005; Stern, Zarahn, , 2003).

The observed functional changes and their relation to social perception and theory of mind performance provide an insight into the mechanisms underlying social cognition declining in multiple sclerosis. The correlation between Fusiform Cortex Connectivity and Social Perception performance is significantly different in patients. This fact is also supported by the evidence of the involvement of the fusiform region in facial emotion processing in healthy subjects(Utevsky, 2017) but also by its participation as the underlying neural correlate in social perception alterations of conditions as autism(Nomi, 2015) or Anxiety Disorder(Frick, 2013). At the same time, the observed participation of the amygdala's connectivity changes in the declining of the theory of mind performance has a robust amount of available evidence. Amygdala has been related to the codification of the emotional saliency of social information(Costafreda, 2008) and the awareness of self and others actions(Williams, 2016). The detailed analysis of those neural correlates also promotes the understanding of social perception as a critical component required for an adequate process of mentalization (or theory of mind). Limitations:

The present article exhibit certain limitations. In the first place, despite healthy control subjects were included to obtain a well matching for age and education level, gender composition significantly differs given the inclusion of men and women almost in the same proportion in the control group while the patient's groups exhibit a predominance of the female gender, as commonly seen in MS populations. Nevertheless, there was no significant interaction between gender and group (Control versus Patients) for the determination of social perception (t:-1,66 , p:0,100) or theory of mind(t:-0,97 , p:0,332).

In the other hand, a more detailed analysis the Social Cognition scores will also show that a short distance underlies to the significant difference in Social Perception as measured by face-emotion recognition test (corresponding to a successful emotion identification of 29,9 and 27,6 of the 35 pictures in healthy controls and MS patients respectively). This differences probably situates the social cognition impairment of the studied group at the subclinical level.

Nevertheless, for the present experimental design is not possible to estimate the functional impact of this difference in daily life activities.

Future Directions:

Additional research should explore several aspects not covered by the present study and which remain undefined in the specific field of social cognition in Multiple Sclerosis. One point of interest is to prospectively define the dependency of social perception and theory of mind performance on the cognitive declining of non-social domains.

On the other hand, the functional impact of the initial (and probably subclinical) socio-cognitive impairment should be evaluated by a more qualitative approach to estimate the actual disability produced by social cognition declining.

VII. Conclusions

The present study has allowed coming to the following conclusions (Derived from the results detailed in the previous chapter):

1. The MS patients studied group exhibit a significant level of brain atrophy and a related functional disconnection.
2. There are compensatory increases in resting-state functional connectivity between an identifiable amount of brain regions.
3. Significant impairment in Social-Cognitive function, mostly related to social perception domain, has been found in the MS patients.
4. Social Cognition impairment is significantly correlated with the regional atrophy of left Insula and fronto-medial bilateral structures.
5. The social cognitive changes in MS patients are significantly correlated with resting state connectivity of the Fusiform Gyrus, Amygdala and Frontal Structures.

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IX. Appendix

	MRI Group	Media	Desv.Est.	Q1	Mediana	Q3	p-Value
Age	0	37,97	10,76	29,25	36,00	46,50	0,417
	1	36,36	10,44	27,00	35,00	44,00	
EDSS	0	NA	1,294	0,000	0,000	2,000	0,756
	1	NA	1,197	0,000	0,000	1,500	
Evolution Time(years)	0	5,052	3,649	2,000	4,500	7,000	0,437
	1	4,289	2,609	2,000	4,000	6,250	
Krupp	0	26,23	15,38	14,00	21,00	38,50	0,706
	1	25,03	15,03	14,00	20,00	37,00	
Beck	0	7,79	7,96	2,00	6,00	10,00	0,613
	1	6,351	5,122	2,000	6,000	9,000	
MMSE	0	29,643	0,672	29,000	30,000	30,000	0,753
	1	29,595	0,725	29,000	30,000	30,000	

Supplementary Table 1. Comparison Between patients included in the structural and functional analysis. (EDSS= Expanded Disability Status Scale; MMSE= Mini Mental Status Examination)

Spearman Correlation	Group	Processing Speed (rho/p)	Working Memory (rho/p)	Verbal Fluency (rho/p)	Visual Memory (rho/p)	Verbal Memory (rho/p)
MiniSEA	control	0,016/0,911	0,293/0,039	0,211/0,185	0,095/0,519	0,130/0,370
	patients	-0,039/0,753	0,195/0,116	0,365/0,003	0,312/0,01	0,147/0,231
Social						
	control	-0,032/0,826	0,148/0,306	0,196/0,221	0,068/0,647	0,083/0,564
Perception						
	patients	-0,043/0,729	0,195/0,117	0,244/0,052	0,230/0,059	0,021/0,865
Theory of						
	control	0,130/0,369	0,373/0,008	0,196/0,221	0,089/0,581	0,160/0,266
Mind						
	patients	-0,039/0,75	0,203/0,102	0,209/0,083	0,193/0,115	0,184/0,133

Supplementary Table 2. Spearman Correlation between conventional and Social Cognition Domains.

Hemisphere	Brain Region	Cluster Size (voxels)	Peak MNI Coordinates x	y	z	Peak Intensity
Left	Insula	945	-25,5	7,5	7,5	5,3477
	Insula	34	-40,5	-13,5	-4,5	-2,2296
	Precuneus	320	-4,5	-61,5	22,5	3,0026
	Meddial Frontal Gyrus	216	12	34,5	40,5	-4,1697
	Superior Frontal Gyrus	-12	22,4	42	34,5	2,4814
	Cingulate Gyrus	1127	-3	-3	49,5	3,8899
	Inferior Parietal	30	-37,5	-43,5	40,5	-2,2525
	Meddial Frontal Gyrus	64	-28,5	13,5	43,5	-4,9715
Right	Caudate	900	24	7,5	6	5,4274
	Thalamus	23	3	-24	9	4,3259
	Meddial Frontal Gyrus	33	13,5	33	40,5	-3,8995
	Meddial Frontal Gyrus	40	28,5	28	48	3,0403
	Precuneus	52	15	-55,5	51	-4,3498
	Superior Frontal Gyrus	34	22,5	3	51	-2,9649

Supplementary Table 3. Clusters of voxels exhibiting significant difference between healthy control group (n=50) and Multiple Sclerosis Patients (n=68).

Group	Task	Hemisphere	Brain Region	Cluster Size (Voxels)	Peak MNI Coordinates x y z	Peak Intensity
Healthy Control	MiniSEA	Right	Anterior Cingulate	2696	9 40,5 -6	5,1444
		Left	Insula	1744	-34,5 -9 1,5	4,1002
		Right	Insula	1012	36 13,5 13,5	4,07
			Cerebellum Anterior Lobe	952	-27 -25,5 -18	3,9922
		Left	Middle Temporal Gyrus	663	-58,5 -30 -4,5	3,8528
		Right	Insula	433	52,5 -6 1,5	2,7931
		Left	Middle Frontal Gyrus	339	-7,5 46,5 34,5	4,0067
		Right	Middle Temporal Gyrus	156	55,5 -10,5 -15	3,4426
			Cerebellum Posterior Lobe	120	-10,5 -60 -18	2,5173
			Cerebellum Posterior Lobe	110	13,5 -70,5 -28,5	2,4472
			Posterior Cingulate Gyrus	107	1,5 -54 30	2,142
			Cerebellum Posterior Lobe	86	-27 -67,5 -36	2.2396
			Inferior Frontal			

Left	Gyrus	82	-39 18 25,5	2,6224
	Superior Temporal		-46,5 12 -	
Left	Gyrus	74	4,5	2,6956
	Supplementary		-4,5 -15	
Left	Motor Area	70	52,5	2,6401
	Middle Temporal		-48 -61,5 -	
Left	Gyrus	69	10,5	2,4671
Right	Precentral Gyrus	66	43,5 -3 39	2,4181
Right	Posterior Gingulate	49	13,5 -67,5 9	2,1349
			-55,5 -19,5	
Left	Postcentral Gyrus	48	15	2,3869
			37,5 36	
Right	Middle Frontal Gyrus	48	28,5	2,2605
	Middle Temporal		54 -43,5 -	
Right	Gyrus	44	4,5	2,1837
Left	Middle Frontal Gyrus	41	-22,5 51 12	2,3095
	Inferior Frontal		49,5 27	
Right	Gyrus	37	13,5	2,4714
	Middle Temporal		-52,5 -45	
Left	Gyrus	36	10,5	1,9508
	Parahippocampal		33 -25,5 -	
Right	Gyrus	35	19,5	2,1931
			-28,5 18	
Left	Middle Frontal Gyrus	32	43,5	2,3007
Right	Precentral Gyrus	27	52,5 -7,5 24	2,3074
			25,5 1,5 -	
Right	Amygdala	23	28,5	1,8836

Social Perception	Right	Middle Frontal Gyrus	630	6 3 58,5	4,9332
	Left	Middle Frontal Gyrus	552	-18 6 57	4,9542
	Left	Postcentral Gyrus	526	-48 -22,5 42	3,2088
	Left	Parahippocampal Gyrus	402	-31,5 3 -19,5	2,6517
	Left	Anterior Cingulate	289	-10,5 40,5 -3	2,3554
	Right	Frontal Lobe	277	15 9 -15	3,121
	Right	Superior Temporal Gyrus	193	54 -45 18	3,3569
	Right	Putamen	186	25,5 16,5 7,5	2,277
	Right	Postcentral Gyrus	178	54 -21 22,5	2,2012
	Right	Middle Frontal Gyrus	132	3 52,5 27	2,4664
	Left	Putamen	85	-18 9 12	3,178
	Left	Lingual Gyrus	79	-13,5 -76,5 -3	2,0737
	Right	Middle Frontal Gyrus	72	16,5 36 43,5	3,0067
	Left	Cingulate Gyrus	67	-6 -31,5 42	2,2805
	Right	Precuneus	59	15 -73,5 37,5	2,1102
	Left	Anterior Cingulate	48	-7,5 33 27	2,3225
		Cerebellum Anterior Lobe	43	-1,5 -61,5 -7,5	1,9534

		Inferior Frontal			
	Left	Gyrus	34	-45 33 9	2,607
		Supplementary			
	Right	Motor Area	30	4,5 -28,5 57	2,5549
	Right	Precentral Gyrus	29	49,5 -4,5 9	2,1702
		Inferior Frontal		-45 22,5 -	
	Left	Gyrus	26	4,5	2,3023
Theory				-36 -37,5	
of Mind	Left	Insula	1546	52,5	3,6791
		Inferior Frontal			
	Right	Gyrus	1524	15 9 -15	3,1416
				13,5 -72	
	Right	Precuneus	1295	37,5	4,1634
	Right	Precuneus	899	-3 -36 49,5	2,6663
	Left	Anterior Cingulate	764	-6 39 -3	2,5127
	Right	Cingulate Gyrus	543	4,5 7,5 43,5	2,7422
				10,5 -69 -	
	Right	Lingual Gyrus	493	4,5	3,0397
		Superior Temporal		52,5 -42	
	Right	Gyrus	478	16,5	3,215
	Left	Putamen	334	-25,5 3 -6	2,828
				40,5 21	
	Right	Middle Frontal Gyrus	297	31,5	2,857
	Left	Middle Frontal Gyrus	294	-36 7,5 46,5	3,4952
		Superior Temporal			
	Left	Gyrus	261	-54 -22,5 6	3,0127
		Middle Temporal		-40,5 -66	
	Left	Gyrus	177	28,5	2,8119

	Middle Temporal		-52,5 -48 -	
Left	Gyrus	147	4,5	2,6783
	Inferior Frontal		-29,5 15 -	
Left	Gyrus	123	13,5	2,3313
Right	Postcentral Gyrus	100	34,5 -36 51	2,9097
Right	Middle Frontal Gyrus	99	30 -4,5 52,5	2,9891
Left	Lingual Gyrus	96	-15 -76,5 -3	2,3739
Right	Putamen	86	21 16,5 -1	2,2828
	Parahippocampal		-16,5 -34,5	
Left	Gyrus	69	-7,5	2,1904
	Parahippocampal		18 -31,5 -	
Right	Gyrus	69	10,5	2,1575
			55,5 -28,5	
Right	Supramarginal Gyrus	46	25,5	2,0415
			46,5 -10,5	
Right	Insula	40	15	1,8986
	Cerebellum Anterior			
	Lobe	40	-1,5 -57 -30	1,871
Right	Middle Frontal Gyrus	35	1,5 39 33	2,0552
	Middle Occipital		-40,5 -72	
Left	Gyrus	34	7,5	2,1703
			28,5 -64,5	
Right	Precuneus	29	39	2,3236
			4,552,5	
Right	Middle Frontal Gyrus	27	28,5	2,0522
	Superior Frontal			

		Left	Gyrus	24	-19,5 1,5 57	2,6191
		Left	Middle Frontal Gyrus	24	-3 24 45	2,7308
Patients	MiniSEA	Left	Insula	283	-36 -21 6	2.8059
		Right	Hippocampus	12	33 -16,5 -7,5	2.2743
		Right	Superior Frontal Gyrus	15	16,5 21 46	1.8856
	Social Perception	Left	Putamen	90	-24 12 9	2.8248
		Left	Caudate	79	-4,5 9 6	2.9423
		Left	Parietal Lobe	11	-36 -33 46,5	2.152
		Left	Supplementary Motor Area	298	-1,5 -9 58,5	3.6418
		Left	Precentral Gyrus	17	-28,5 -10,5 54	2.098
		Left	Precuneus	18	0 43,5 57	2.0487
		Right	Caudate	62	10,5 9 -1,4	2.2716
		Right	Cingulum	88	6 34,5 39	2.2708
		Right	Middle Frontal Gyrus	47	24 7,5 54	2.2328
		Right	Middle Frontal Gyrus	65	25,5 -16,5 55,5	3.043
	Theory of Mind	Left	Cingulate Gyrus	71	0 1,5 48	2,342
		Left	Medial Frontal Gyrus	97	-1,5 -9 58,5	3,4064
		Left	Precentral Gyrus	13	-27 -10,5 54	1,9063
		Right	Middle Frontal Gyrus	29	24 7,5 34	2,0878
		Right	Middle Frontal Gyrus	94	27 -18 55,5	2,9645

Supplementary Table 4. Clusters of Voxels significantly correlated to MiniSEA, Social Perception and Theory of Mind Scores (p-value<0,05, FWE:0,05, Cluster Size>20) (Patients n=68; Control Group n=50)