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Social Cognition in Multiple Sclerosis: An Empirical Investigation

Supervisor
Prof. Mario Bonato

Co-supervisor
Prof. Murat Kürtüncü (Istanbul University, Istanbul Medical Faculty, Division of Medical Sciences)

Candidate: Dalya Eda Akbalık
Student ID number: 2081330

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Contents

List of Abbreviations

Abbreviation	Definition
AIC	Akaike Information Criterion
EDSS	Expanded Disability Status Scale
FED	Facial Emotion Discrimination
FEI	Facial Emotion Identification
FPRT	Faux Pas Recognition Test
HC	Healthy Control
MoCA	Montreal Cognitive Assessment
RMET	Reading the Mind in the Eyes Test
RRMS	Relapsing Remitting Multiple Sclerosis
ToM	Theory of Mind

Abstract

Despite extensive research on cognitive functioning in Multiple Sclerosis, there is a significant gap in understanding social cognitive deficits experienced by people with MS, particularly those with Relapsing-Remitting Multiple Sclerosis. Thirty RRMS and thirty healthy control (HC) participants were recruited and underwent several neuropsychological tests to assess Social Cognition. In order to test the affective component of Theory of Mind (ToM), the Reading the Mind in the Eyes Test (RMET) was applied, while to assess the cognitive component of ToM, the short version of the Faux-Pas Recognition Test (FPRT) was administered. For assessing Emotion Recognition, the Facial Emotion Identification (FEI) and Facial Emotion Discrimination (FED) tests were used. The RRMS group scored significantly lower in both ToM and Emotion Recognition Tests compared to the HCs, whereas performance for the two groups did not differ in the FED test. In addition, regression analyses revealed that only the FED test showed significant negative linear relationship with both EDSS and Disease Duration (in years). Finally, the RRMS group scored significantly lower in recognizing negative emotions of the FEI test compared to the HC group, while no significant difference was found in recognizing positive emotions between the two groups.

Keywords: Social Cognition, Theory of Mind, Emotion Recognition, RRMS

Introduction

Multiple Sclerosis (MS) is an inflammatory and degenerative neurological disorder which affects the humans 'central nervous system (Campbell-Lendrum & Prüss-Ustün, 2019). It is characterized by multifocal destruction of myelin sheaths and axonal loss in the brain. The course of MS is generally unpredictable, leading a significant burden on patients with motor impairment and cognitive dysfunction (Henry et al, 2011). The exact reasons for the rise in MS and the fundamental factors driving it are not fully understood. However, it is widely acknowledged that intricate interactions between genes and the environment are likely major contributors. Epidemiological insights into MS suggest that factors such as insufficient levels of vitamin D in the bloodstream, smoking, childhood obesity, and infection with the Epstein–Barr virus are probable influencers in the progression of the disease (Dobson & Giovannoni 2019). Multiple Sclerosis affects women more than men, with twice as many reported cases. Furthermore, people of Northern European descent appear to have a higher risk of developing MS. Clinical observations and supporting evidence from supplementary assessments, such as magnetic resonance imaging (MRI) of the brain and cerebrospinal fluid (CSF) examination, are used to make the diagnosis (Goldenberg, 2012).MS typically affects young adults and can result in severe disabilities that have significant adverse effects on quality of life. Between 30 and 70 percent of MS patients have cognitive impairment, which leads to problems in memory, attention, and information processing (Doğan & Ünlü Demirci, 2022). According to previous studies, people with MS may experience impairments in social cognitive functions in addition to the well-known cognitive impairments too (Neuhaus et al., 2018).

Social cognition is related to the mental processes that support social interactions, including the perception, interpretation, and response to other people's intentions, tendencies, and behaviours (Bora et al., 2015). Understanding emotional states is one domain of social

cognition that requires an ability to distinguish facial expressions and emotions (Callahan et al, 2011). Theory of Mind (ToM) is another domain of social cognition that refers to the ability to attribute the mental states of other people and use these attributions to understand and predict human behaviour (McDonald and Flanagan, 2004). There is an interaction between emotional recognition and ToM which improves interpersonal skills, and has a remarkable impact on social functioning (Krause et al, 2009).

In recent years, the relationship between social cognition and MS has been the subject of several articles; however, the consistency of these findings remains debatable (Lin X et al, 2020). Some studies have observed differences only in negative emotions when comparing HCs with MS patients. For instance, the study by Pitteri et al. revealed that MS patients may have selective difficulty in discriminating negative emotions like anger and fear in facial emotion recognition (Pitteri et al, 2019). In another study, Prochnow and colleagues found impairment in the recognition of facial expressions in all basic emotions except happiness and disgust for MS patients compared to the HC group (Prochnow et al, 2019). When it comes to ToM, while some studies found a significant impairment in the Faux Pas Test when comparing MS patients to HCs, others reported no differences in Faux Pas Test results between these two groups (Ouellet et al, 2010). While the relationship between MS and social cognitive functions remains unclear, there is also lack of research conducted on this topic with Turkish population. This study is designed to address this gap in the literature. I am going to explain each variable and domain of this study in detail in the following sections to make the study clearer for the audience.

Scope

This thesis project focused on examining the social cognitive functions of individuals who have Relapsing-Remitting Multiple Sclerosis compared to healthy controls who were matched with a RRMS group in terms of age, sex, and education. To be more specific, I assessed emotion recognition (particularly facial emotion recognition) and ToM abilities in order to evaluate both RRMS and HC group social cognitive functioning. The data collection has been conducted with a cross-sectional design for a period of 2 months at the Multiple Sclerosis and Myelin Disorders Clinic, Faculty of Medicine Istanbul University, Turkey. A total of 60 participants participated in the study (30 RRMS, 30 HC), with an age range between 18 and 65 years. Detailed information will be provided in the methodology section.

Goal

The primary goal of this thesis project is to examine social cognitive functioning in people with RRMS compared to healthy controls. To be more specific, the project aimed to;

- Assess emotion recognition (particularly facial emotion recognition) skills in both RRMS and HC groups.
- Assess ToM (both affective and cognitive components) in RRMS and HC groups.
- Assess whether other confounding variables such as disease duration, disability level, MoCA scores are interfering with social cognitive functioning in RRMS groups.
- Use collected data to support the development of new interventions aimed at improving the quality of life for people with MS and to further our understanding of how social cognition is altered or impaired in MS patients.

Research Questions

- Are there significant differences in facial emotion recognition scores between individuals with RRMS and the HC group on the Facial Emotion Identification (FEI) Test?
- Are there significant differences in facial emotion recognition scores between individuals with RRMS and the HC group on the Facial Emotion Discrimination (FED) Test?
- Is there a significant difference in ToM abilities between individuals with RRMS and the HC group as assessed by the Faux Pas Recognition Test (FPRT)?
- Are individuals with RRMS more likely to experience difficulties in recognizing negative emotions (like; anger, fear) compared to positive emotions (like; happiness, surprise) in facial expressions on the Facial Emotion Identification (FEI) Test?
- Is there a significant linear relationship between the duration of RRMS (measured in years) and social cognitive functions, including facial emotion recognition and ToM abilities?
- Is there a significant linear relationship between the Expanded Disability Status Scale (EDSS) scores, reflecting the level of disability in RRMS, and social cognitive functions, including facial emotion recognition and ToM abilities?
- Is there a positive linear relationship between MoCA scores and facial emotion recognition (FEI and FED) and ToM abilities (FPRT, RMET) in individuals with RRMS?

Research Hypotheses

All research hypotheses were preregistered in OSF (Open Science Framework). The link can be found below;

https://osf.io/7umfe/?view_only=d4c151a10f164d80914a28bcb243a009

H1: Individuals with RRMS will exhibit significant deficits in facial emotion recognition compared to the HC group.

H2: ToM abilities, as assessed by the FPRT and RMET, will be impaired in individuals with RRMS compared to the HC group.

H3: Individuals with RRMS will demonstrate specific difficulties in recognizing negative emotions (e.g., anger, fear) compared to positive emotions (e.g., happiness, surprise) in facial expressions that will be assessed by Facial Emotion Identification Test.

H4: There will be a significant linear relationship between the duration of RRMS (measured in years) and social cognitive functions, indicating that as the disease duration increases, social cognitive abilities will decline.

H5: There will be a significant linear relationship between the Expanded Disability Status Scale scores, reflecting the level of disability in RRMS, and social cognitive functions. Higher EDSS scores will be associated with poorer social cognitive performance in both ToM tests and facial emotion recognition tests.

H6: There will be a positive linear relationship between Facial Emotion Identification and Discrimination Tests scores; and MoCA scores in individuals with RRMS, indicating that better facial emotion recognition is associated with higher cognitive function as measured by the MoCA.

H7: There will be a positive linear relationship between Faux-Pas Recognition Test and Reading the Mind in the Eyes Test scores; and MoCA scores in individuals with RRMS, suggesting that better ToM abilities are associated with higher cognitive function as measured by the MoCA.

Literature Review

In this section, I will introduce key concepts for this thesis project, which are ToM and Emotion Recognition. Most importantly, I will provide papers that examine the relationship between Social Cognition and Multiple Sclerosis, but I will first provide some information about papers that investigated the relationship between various neurodegenerative disorders and Social Cognition in order to gain a general understanding of how social cognitive functioning changes during neurodegeneration. Finally, I will mention the Neural Correlates of Social Cognitive Functioning in MS. I believe that emphasising existing literature on this topic will enhance the readers understanding on social cognition as a neural mechanism and on how we observe changes in the brains of MS patients.

Theory of Mind (ToM)

Before giving conventional definition of Theory of Mind, I want to mention why it is so important for this thesis project. ToM is one of the critical parts of social cognition and enabling us to understand and infer the mental states of others, is essential to the normal development of social relationships (Mukerji et al, 2019). In this study, I wanted to assess ToM with Faux-Pas Recognition Test (FPRT) and Reading the Mind in the Eyes Test

(RMET) which are well designed standardized neuropsychological tests to measure level of impairment in healthy people and people with pathological diseases.

ToM is basically encompassing the ability to understand and attribute mental states (also known as mentalization) to one-self and others (Turkstra et al, 2020). This ability allows individuals to interpret and predict the behaviour of other people based on their beliefs, intentions, emotions, and feelings (Baron-Cohen et al, 1997). ToM includes cognitive and affective domains. The cognitive aspect is the ability to reason and understand other individuals' beliefs and intentions; on the other hand, the affective aspect is the understanding and interpreting these individuals' emotions and feelings (Shamay-Tsoory, 2009). Everyday social interplays depend on the ToM ability to negotiate and control complex social circumstances, including understanding social cues, interpreting non-verbal communication, and predicting other people's behaviour. To achieve these skills listed above, individuals gain from a combination of implicit and explicit mechanisms to be able to understand the thoughts and emotions of themselves and other people (Heyes &Frith, 2014).

Foremost, the ToM does not entirely depend on inferential processes but also involves simulation processes. These simulation processes, specifically the self-projection process, allow people to mentally simulate or imagine themselves in the place of others and, as a result, perceive these people's perspective and emotional state (Mitchell et al, 2006). Overall, ToM plays a critical role in human social interrelations and communication, making possible to understanding, empathy, and effective interpersonal relationships. That’s why our goal is to assess ToM ability in Relapsing-Remitting Multiple Sclerosis patients and healthy people who is matched in age, sex, and education level with the RRMS group to see if there is a difference in their ToM ability but most importantly whether MS leads some impairment in ToM ability (eventually in social cognitive functioning) in RRMS group. In the following

subsection, I will explain another important component of social cognition which is being able to recognize other people's emotions and facial expressions.

Emotion Recognition

The capacity to identify and understand emotions is crucial for effective human social interaction. It can offer us valuable insights into the mental states and possible intentions of other people and enabling individuals to navigate social situations more effectively (Cannolly et al, 2020). Facial emotion recognition (FER) plays an important role in social cognition and is crucial for interpersonal relationships. As a result, various tasks have been created to evaluate this ability across different populations, including patients with neurological and neurodegenerative disorders (Ferreira et al, 2021). When administering neuropsychological tests to evaluate facial emotion recognition, participants are usually shown pictures of faces expressing a range of emotions, including fear, disgust, surprise, anger, sadness, and happiness. Participants in these tasks are frequently asked to name or identify the emotion displayed on each face. The following are a few typical examples of neuropsychological tests used to assess facial emotion recognition: The Ekman Faces Test (Ekman & Friesen, 1976), The Reading the Mind in the Eyes Test (RMET) (Baron-Cohen et al, 2001), The Facial Emotion Recognition Task (FERT) (Kessels et al, 2014), and The Penn Emotion Recognition Test (PERT) (Gur et al, 2002). In this study, I measured emotion recognition ability through Facial Emotion Identification and Facial Emotion Discrimination Test. When it's come to Reading the Mind in the Eyes Test, majority of studies suggests that it is an advanced ToM test to measure individual differences and their social cognitive functions (Olderbak et al, 2015). On the other hand, some researchers advocate it is actually one of the simplest and popular neuropsychological tests to measure emotion recognition ability of individuals which

includes unconscious pairing of previous memories that have similar component of expressions with a vocabulary of mental state terms (Vellante et al, 2013). In this study I investigated the RMET under the ToM domain. Following subsection will cover the relationship between social cognitive functions and some of the most common neurodegenerative disorders including Multiple Sclerosis.

Social Cognition and Neurodegenerative Disorders

There are numerous definitions of social cognition in literature, with various approaches. If we want to explain this concept from cognitive psychology perspective, it would be as follows; the foundation of social cognition lies in a conceptual orientation rooted in the information processing perspective within cognitive psychology, which has more recently broadened to encompass cognitive science. This approach to social cognition is grounded in the belief that constructs pertaining to cognitive representation and processes are essential for comprehending all human responses, irrespective of whether they occur in social or non-social contexts (Augoustinos et al, 2014). What we understand from this is deeply connected to cognitive psychology and has expanded to incorporate insights from cognitive science. It highlights the role of cognitive processes and representations in shaping human responses across different contexts, including social interactions. On the other hand, from a social psychology perspective, researchers suggest that social cognition is inevitably social and it includes interpersonal and intersubjective aspect of cognition (Higgins, 2000). According to the social psychology perspective, we should also ask ‘How does someone thinks and feels affect how they interact with others?’ Social cognition is about how our thoughts and feelings mix with social situations, and social-cognitive principles help us understand how these two things influence each other (Higgins, 2000).

Whether it is manifesting itself in social or non-social contexts, social cognition encompasses domains beyond cognitive processes and gives us social skills, including communication skills such as the pragmatics of communication and prosody, as well as the ability to resolve social problems (Maresca et al, 2020). Social skills are essential for both initiating and sustaining interactions with others, and facilitating the accomplishment of interpersonal objectives, such as forming friendships or acquiring social assistance (Morgan, 1980). Social skills are dynamic and responsive to feedback from others, creating a continuous loop of perception and behaviour adjustment. According to researchers who work on social cognition, socially appropriate behaviour encompasses multiple processes, including perceptual abilities (like recognizing emotions and showing empathy), cognitive functions (like ToM), behavioural execution, problem-solving, and action evaluation (Tse & Bond, 2004). Impairments in social skills may drastically impact people negatively, resulting in difficulties with achieving personal goals or displaying abnormal or inappropriate social behaviours. Shamay-Tsoory and colleagues found that individuals that acquired frontal brain injuries had changes in social skills correlated with impairments in executive functioning, ToM, and empathy (Shamay-Tsoory et al, 2005).

Quite a few studies in the existing literature have investigated the impact of neurodegenerative disorders on social cognition. These investigations analyse how conditions like Alzheimer's disease, Parkinson's disease, Huntington's disease, Frontotemporal dementia (FTD), Multiple Sclerosis, and many others affect various aspects of social cognition, including emotion recognition, empathy, ToM, and social behaviour (Elamin et al, 2012). In the following paragraphs, I am going to provide several articles that explore the impact of neurodegeneration on social cognitive functioning, and how the disease course reflects changes or impairment in the ToM and emotion recognition skills.

The first study that I am going to mention was conducted by Dodich and her colleagues and included 112 subjects; 65 health participants and 47 participants with neurodegenerative disorders (these are 20 behavioural-variant frontotemporal dementia (bvFTD), 12 Alzheimer's Disease (AD), and 15 amnestic mild cognitive impairment (aMCI)). In the study all participants underwent a standardized non-verbal cartoon task known as the Social Attribution Task - Cartoon Version (SAT-C), which comprises two main experimental conditions: intention attribution and emotion attribution. Furthermore, there was a control condition focusing on comprehension of causality based on knowledge about the physical properties of objects or human bodies, termed causal inference (CI). Participants' tasks involved selecting the correct ending of a comic strip from three different possible endings (Dodich et al, 2016). The study revealed that patients with dementia (AD and bvFTD) manifested impairment in the performance of the Social Attribution Task (SET) and this impairment were present in all sub conditions of the SET, whereas individuals with aMCI showed no significant differences from HCs (Dodich et al, 2016). As a result, patients with AD exhibited impairment in ToM, deficiency in empathy, and difficulty recognizing facial emotions. Additionally, they displayed poor self-criticism and altered social behaviour, characterized by disinhibition, irritability, anger, and apathy.

In another study Bora and his colleagues conducted a meta-analysis of 30 studies comparing ToM performance in individuals with bvFTD and AD. They found that ToM impairment was more pronounced in bvFTD compared to AD. For bvFTD patients, ToM deficits were particularly evident in advanced tasks, such as recognizing faux pas and sarcasm. In contrast, ToM deficits in AD were relatively modest. The severity of ToM deficits was associated with longer disease duration and greater general cognitive impairment in both disorders. These findings suggest that assessing ToM could aid in the early identification of bvFTD (Bora, Walterfang & Velakoulis, 2015).

A different neurodegenerative disorder that has been explored in this topic is Amyotrophic Lateral Sclerosis (ALS). Notable researchers who worked on social cognition and ALS are Aho-Özhan and her colleagues; they investigated the perception of emotional facial expressions in ALS patients. Thirty ALS patients and twenty-nine HCs, matched for age, gender, and education, underwent a behavioural test involving Ekman faces expressing six basic emotions in their study. Moreover, a subgroup of fifteen ALS patients and fourteen HCs also matched and viewed these faces during functional magnetic resonance imaging (fMRI). They found that ALS patients manifested decreased accuracy in recognizing disgust and fear compared to HCs. fMRI scans also revealed reduced brain activity in regions associated with processing negative emotions, which is consistent with previous findings. Furthermore, ALS patients showed increased activity in the right inferior frontal gyrus, linked to social emotions, and decreased activity in the hippocampus bilaterally when they processed sad faces during the test. However, they did not find significant differences in brain activity for other emotional expressions. (Aho-Özhan et al, 2016).

I want to mention another ALS and Social Cognition studies because their test batteries match this thesis project. Burke and his colleagues investigated executive functions and social cognition in ALS patients who were categorized by disease onset which is bulbar or spinal. They found that ALS patients performed significantly worse than controls in executive function tests. When comparing bulbar-onset and spinal-onset patients, significant differences were found in social cognitive tests, specifically in the Reading the Mind in the Eyes Test, but not in the executive function tests. As a result, they concluded that ALS patients' exhibit deficits in executive function compared to controls, and bulbar-onset patients may experience more pronounced social-affective deficits than spinal-onset patients, despite executive function performance when we compare these two groups (Burke et al, 2016).

Lin et al., on the other hand, conducted a study to see if Parkinson's disease (PD) patients with more advanced motor symptoms had a more difficult time recognizing emotional facial expressions than a control group. The study included twenty-nine PD patients and twenty-nine HCs of similar age. They conducted two experiments; in the first one, participants were tasked with discriminating emotions, while the second experiment required gender identification. Their results revealed that PD patients had difficulty recognizing both negative (sadness and anger) and positive facial expressions in the first experiment. Their further analysis revealed that only PD patients with high motor dysfunction performed poorly in recognizing happy faces. In the second experiment, PD patients showed unimpaired gender identification abilities. As a result, they concluded that PD patients' ability to recognize emotions deteriorated with disease progression, starting with impaired recognition of negative emotions, which later extended to positive emotions (Lin et al, 2016).

Social Cognition and Multiple Sclerosis

Examining the relationship between social cognitive functioning and MS is the main goal of this thesis project. Particularly, the goal is to identify possible differences in ToM and Emotional Recognition abilities between people with MS and healthy group. To achieve this aim, I will present more academic articles that cover related topics. This will enable a thorough analysis of previous research results and provide a well-grounded basis for this study.

Emotion Recognition and MS

Emerging evidence suggests that individuals with MS frequently exhibit changes not only in traditional cognitive functions but also in social cognition, particularly concerning emotional processing (Maresca et al, 2020).

One of the first studies on this subject was conducted in 1989 by Beatty and colleagues (Chalah & Ayache, 2017). The Benton Facial Recognition Test (BFRT) for facial identity discrimination (Benton, Sivan, Hamsher, Varney, & Spreen, 1994) and an affective judgment task, which assesses the ability to recognize the six basic facial emotions; these are happiness, sadness, anger, fear, disgust, and surprise (Ekman & Friesen, 1976), were completed by patients with chronic progressive MS and HCs who were matched for age and education level. Patients performed poorly in cognitive tasks and were less accurate in distinguishing between facial emotions and identities than HC group (Beatty et al, 1989).

Another similar study was conducted by Phillips and her colleagues aimed to assess the impact of multiple sclerosis (MS) on the ability to identify emotional and non-emotional information from both static images and dynamic videos, and to examine whether difficulties in emotion perception were associated with quality of life. Thirty-two MS participants and thirty-three control participants matched for age and education completed tasks involving the identification of emotions and non-emotional information from faces and videos. The MS group performed more faultily than the control group on emotion perception tasks for both static images and dynamic videos, but not on identity perception tasks. Also, results revealed that ratings of social and psychological aspects of quality of life in MS were related to emotion perception scores, even after controlling for disease severity, duration, age, depression, and cognitive function.

These findings suggest that MS patients may have specific deficits in decoding emotional information from both static and dynamic stimuli and that addressing emotional skills could be important for evaluating functioning and quality of life in MS (Phillips et al, 2011).

In addition to the previous two studies, Prochnow et al. wanted to assess emotion processing levels in MS patients, using both facial affect recognition performance tests and self-report measures of emotion. They hypothesized that MS patients would have difficulty recognizing emotions from human facial expressions. Moreover, researchers aimed to determine whether this socially relevant deficit is associated with alexithymia in MS patients. The study included thirty-five MS patients who tested with a neuropsychological assessment which focused on emotion processing through two facial affect recognition tasks, as well as self-report measures to assess alexithymia. Sixty-one healthy participants were used as controls for comparison. According to self-reported measures, the study discovered that MS patients had higher levels of alexithymia than HCs (Prochnow et al, 2011). Furthermore, the Perceptual Competence of Facial Affect Recognition (PCFAE; as Prochnow et al. mentioned in their article, this test was developed by Ingenhag, Schäfer, and Franz in 2007 but is unpublished) and Ekman-60-Faces tests (Ekman, 1976), which measure facial affect recognition, showed higher error rates among MS patients. When it came to identifying emotions on the PCFAE, MS patients did worse than HCs in terms of fear, surprise, anger, and sadness, but not disgust or happiness (Prochnow et al, 2011).

Theory of Mind and MS

Considering that both cognitive and affective elements form the ToM (Shamay-Tsoory et al, 2007), it is unclear if and how these components are impaired in MS. While a number of studies revealed that MS patients had a ToM deficit, some of them revealed incongruent

results (Isernia et al, 2019). I will present several studies to see and understand the impairment in the ToM ability during the course of MS.

Roca and colleagues wanted to search for potential dissociations between cognitive and affective ToM abilities. 18 patients with mild RRMS and 16 control volunteers went through separate analyses. RRMS patients' ability to figure out the intentions of others was significantly lower than that of the control group, indicating deficits in cognitive ToM (Roca et al, 2014). Their affective ToM remained intact, allowing them to determine the emotions of others. They could not find a correlation between RRMS patients' executive function and the cognitive aspect of ToM, nor between their cognitive ToM and their depression or fatigue scores. However, executive function correlated with RRMS patients' overall score on the ToM task and with their ability to identify a social faux pas (Roca et al, 2014).

Another study on the affective and cognitive aspects of ToM and MS was conducted by Montembeault and colleagues who recruited 15 elderly pwMS (people with MS), 14 young pwMS, 14 elderly HC, and 13 young HC. They used an adaptation of the Conversations and Insinuations task (Ouellet et al, 2010) to measure ToM. During the study, participants watched four two-minute videos of social interactions. The videos were intercut with multiple-choice questions concerning the characters' intentions (for cognitive ToM, there are 14 questions) or emotional states (for affective ToM, there are 14 questions). Additionally, participants completed a brief neuropsychological battery that included cognitive tests such as the DKEFS Colour-Word Interference Test, the Montreal Cognitive Assessment (MoCA), and an experimental multimodal emotion recognition task in their study. The results of the study showed that in the ToM task, they observed significant impairment in cognitive ToM compared to affective ToM, older participants manifested more impairment than younger ones, and lastly, as expected, people with MS scored more faultily in the ToM tests compared

to the HC group. In addition, both in MS and HC participants, ToM and MoCA had a significant correlation (Montembeault et al, 2023).

Pöttgen et al. also wanted to assess social cognitive functions in MS patients to see if the disease can lead to some impairment in ToM. They applied a video-based test to measure ToM for 45 outpatient and 45 HC participants who were matched with the MS group in terms of age, sex, and education. MS patients demonstrated significantly impaired ToM compared to the HC group. Impairments were more pronounced in identifying emotions than in thoughts or intentions. During the early stages of MS, patients with limited disability and no significant neuropsychological deficits had significantly lower ToM than the HC group (Pöttgen et al, 2013). Since Pöttgen et al worked with patients who are in their early stages of MS, they observed impairments mainly in the affective component of ToM instead of the cognitive aspect. However, in the next article, we will see that more disabled patients (who have high scores of EDSS) may demonstrate impairment both in affective and cognitive components of ToM ability.

Banati et al., used verbal and nonverbal ToM tests (Faux Pas, Baron-Cohen's Adult Eyes and Faces test), as well as the Baron-Cohen's Empathy questionnaire (Baron-Cohen, 1999), to investigate social cognition in 40 mobile MS patients and 35 HCs. They used multiple logistic regression analysis to examine the effect of disability and disease duration on social cognition after adjusting for confounding factors such as age, gender, intelligence, depression, and anxiety. Even though they controlled several of these factors, patients with MS performed more faultily in nonverbal tests (like; adult Eyes Test), and patients with higher EDSS score performed worse in both verbal and nonverbal ToM tests (both in Eyes Test and Faux Pas) than the HC group (Banati et al, 2010). They concluded that early stages of MS patients showed impairment in affective ToM, but in the later stages they outperformed both in affective and cognitive aspects of the ToM ability.

In addition to the traditional static tasks used in the previously mentioned works, some authors also used dynamic videotaped tasks that showed social interactions, with comparable outcomes. One of these innovative studies was conducted by Kraemer and colleagues who used the assessment tool of the Movie for the Assessment of Social Cognition (MASC) test to measure both affective and cognitive aspects of the ToM. During the assessment, participants in the MASC test are required to conclude the mental states of video characters. The test was realized by writing a screenplay, filming the actual film with actors and a team of experts, and post-processing the footage before test-formatting it (Dziobek, 2006). To investigate ToM and empathy Kraemer et al worked with 25 young adult patients at an early stage of RRMS and 25 HCs, and participants underwent assessments of executive functions, including working memory (with Wechsler Memory Scale; Benson et al, 2010), set-shifting (with the Trail Making Test; Reitan & Wolfson, 1992) and inhibition (Kraemer et al, 2013). Additionally, instruments measuring ToM with the MASC test and empathy with Baron-Cohen's Empathy Quotient (Baron-Cohen & Wheelwright, 2004) were administered (Kraemer et al, 2013). In the result section of their article, they did not mention the affective and cognitive aspects of the ToM; most likely due to the MASC test covering both aspects of the ToM. However, they found that patients with early-stage relapsing-remitting multiple sclerosis (RRMS) exhibited significantly more incorrect responses in ToM tasks compared to HCs. Additionally, patients showed a significantly lower level of empathy based on self-rating questionnaires. Among the cognitive tests and measures of depression, ToM and Empathy Quotient (EQ) scores were only significantly correlated with the interference score of the Stroop test. These findings suggest that deficits in ToM and empathy are present even in the early stages of RRMS and may have a negative impact on interpersonal relationships for patients with the condition (Kraemer et al, 2013). Unlike Roca et al who found impairment in cognitive ToM but intact

affective ToM abilities, Kraemer et al find impairment in both aspects of the ToM skills even though both of the studies worked with mild RRMS patients.

Moreover, Genova et al developed a dynamic task which is called the Awareness of Social Inference Test (TASIT) which measures affective and cognitive ToM to assess people with MS's ability to understand and interpret lies and sarcasm. Fifteen people with MS and 15 HCs took the TASIT's Social Inference-Enriched subtest, which involved watching videotapes of social interactions that included lies and sarcasm. Additionally, cognitive tests were given to better understand the relationship between specific cognitive abilities and the ability to understand lies and sarcasm. In comparison to HCs, the MS group demonstrated impaired ability to interpret and understand lies and sarcasm. These impairments were associated with a variety of cognitive abilities, including processing speed, working memory, learning and memory, and premorbid IQ (Genova et al, 2016).

Papers on Neural Correlates of ToM in MS

Prior to talking about studies that use fMRI images of patients with Multiple Sclerosis to assess their ToM abilities, I want to quickly discuss the affected regions in ToM to get a general sense of the neural correlates of this skill.

The ACC, OFC, amygdala, and numerous regions of the temporal lobe, such as the posterior STS, temporal pole, and temporoparietal junction, are among the complex neural networks that ToM targets (Schulte-Rüther et al, 2011). Surprisingly, available data indicate that ToM is not just limited with the areas I listed above; different frontal circuits may also modulate ToM subcomponents. According to Shamay-Tsoory and Aharon-Peretz, the ventromedial prefrontal cortex (VMPFC) appears to be especially involved in processing

affective to memory (ToM); however, the ventrolateral prefrontal (VLPFC) and dorsolateral prefrontal cortices (DLPFC) appear to be primarily involved in mediating cognitive ToM (Shamay-Tsoory & Aharon-Peretz, 2007). In the upcoming paragraphs, I will list some research that investigates these brain regions listed above and also correlates findings from neuropsychological examination and fMRI images in MS populations.

Mike et al looked at how disconnection mechanisms and regional cortical atrophy affected facial expression processing and ToM in MS. The researchers wanted to look into how brain pathology affected mentalization performance in people with MS. They compared the mentalization performance of 49 MS patients with 24 age and gender-matched HCs. Additionally, T1- and T2-weighted three-dimensional brain MRI images were obtained from the MS patients and 18 age- and gender-matched HCs.

Total and regional T1 and T2 white matter lesion volumes were measured in MS patients, as well as the overall thickness of the brain cortical in both the disease and the HCs. The study discovered a correlation between the total T1 lesion load and the regional T1 lesion load of association fibre tracts connecting cortical regions related to visual and emotion processing, and the performance on tests measuring mental states and emotions from facial expressions and eye gazes.

Furthermore, these tests showed correlations with specific cortical areas involved in emotion recognition from facial expressions (such as the right and left fusiform face area, frontal eye field), processing of emotions (such as the right entorhinal cortex), and socially relevant information (such as the left temporal pole). The findings suggest that both disconnection mechanisms due to white matter lesions and cortical thinning of specific brain areas may result in cognitive deficits in MS, affecting emotion and mental state processing

from facial expressions and contributing to everyday and social life difficulties of these patients (Mike et al, 2013).

In order to evaluate the relationship between resting-state functional alterations in patients with relapsing-remitting MS and social cognition, Labbe and colleagues conducted fMRI study. They worked with 45 RRMS and 47 HC subjects to test their hypotheses. First of all, they started with neuropsychological evaluation with the Mini-Social Cognition and Emotional Assessment (MiniSEA) (Maxime-Louis Bertoux, 2014) to assess social cognition. It consists of two distinct items: the Face Emotion Recognition to assess Social Perception and ToM, and a shortened version of the Faux-Pas (FP) to assess social cognition. Also, ten short stories in the ToM section featuring characters that unintentionally hurt or offend someone else were presented to the participants. After neuropsychological assessment, both functional and structural images were maintained from the participants. Their results revealed that participants performed worse on social cognition tests, primarily those that involved identifying facial emotions. When it comes to RRMS group, their right anterior insula, middle frontal, and occipital regions show decreased functional connectivity, whereas the occipital and visual areas show increased connectivity. They also found that the ability to recognize emotions and perform ToM tasks is correlated with the fusiform cortex and amygdala's connectivity (Labbe et al, 2020). As a result, they concluded that RRMS patients' changes in social cognition were found to be correlated with changes in functional connectivity during resting state.

The last study I am going to present in this subsection was conducted by Ciampi et al. to investigate the relationship between Social Cognitive performance and its correlations with traditional cognitive domains, brain atrophy, and quality of life in primary and secondary Progressive MS patients. In their study, the mini-Social Cognition and Emotional Assessment (mini-SEA) (Bertoux et al, 2012, Bertoux et al, 2014) was used to assess social cognition.

This 30-minute composite battery is a simplified version of the Social Emotional Assessment test (Funkiewiez et al., 2012). It consists of two separate tests: a shortened version of the Faux-Pas (FP) and the Face Emotion Recognition (FER). They also wanted to assess general cognitive functioning through various neuropsychological tests. These are: Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS) (Benedict et al, 2006), processing speed with Symbol Digit Modality Test (SDMT) (Smith, 2002), Verbal and Visual Episodic memory: including the Spanish version of the California Verbal Learning Test (CVLT) (Ponton et al, 1996), and the Brief Visuospatial Memory Test-Revised (BVMT-R) (Benedict, 1997). For assessing executive functions, they used the Paced Auditory Serial Addition Test (PASAT) (Gronwall, 1977), the Stroop test Spanish version (Golden, 1994) and cognitive shifts with flexibility categorical and lexical fluency and control of interference (FAS) from the D-KEFS (Delis et al., 2001). Lastly, quality of life is measured through the Spanish version of the Multiple Sclerosis Impact Scale (Hobart et al, 2001). They worked with 43 MS patients in total; 23 were primary and 20 were secondary progressive. Their mean age and length of disease were 57.2 and 15.7 years, respectively. They had a median EDSS of 6.0, indicating a high degree of disability, and a widespread impairment in traditional domains, primarily episodic verbal/visual and working memories. They found that the Mini-SEA score showed a correlation with executive functions, and in the primary Progressive MS group it showed a correlation with visual episodic memory. They found a correlation between the Mini-SEA score and the total normalized grey matter volume. Specifically, there was a significant correlation found between increased impairment in Social Cognition and atrophy in the right regions of the fusiform gyrus and praecuneus, as well as the bilateral cortical regions of the orbitofrontal, insula, and cerebellum. QOL and Social Cognition were uncorrelated in their sample (Ciampi et al, 2018).

Hence, as we can see from the articles that are mentioned in this subsection, there are specific brain regions and neural networks which showed activation during the situations that required ToM abilities, and these activated areas and observable atrophy in the cortical regions when there is malfunctioning in social cognition give us better understanding how crucial it is for daily healthy functioning. Most importantly, these findings may show us critical consequences of impaired social cognition in MS and how detrimental it can be for people with neurodegenerative disorders (Duclos et al, 2018).

In the upcoming chapter, I will go over this thesis project's methodology section. I will go into detail about the population, the sampling criteria, the participants, and every neuropsychological test and test that I used to rule out confounding variables (like EDSS scores, anxiety, and depression). Lastly, I will go over the data collection and analysis section and how this thesis project's hypotheses are tested.

Method

This thesis project was approved by the ethics committee of the Istanbul University, Faculty of Medicine; Clinical Studies Ethics Committee. All subjects (both RRMS and HC groups) gave their informed consent. A total of 60 participants were included in this study, with 30 individuals in the RRMS group and 30 in the HC group. RRMS patients who are under clinical follow-up at Istanbul University Hospital, Multiple Sclerosis and Movement Disorder clinic were invited to participate in a Neuropsychological evaluation. They had been diagnosed and were being followed up every 3 or 6 months by Prof. Dr. Murat Kürtüncü at the same hospital. Other medications, including antidepressants, were allowed as long as they were prescribed by a physician and taken at a consistent dosage for the previous six months. However, patients with major psychiatric illnesses (such as substance abuse or schizophrenia)

were excluded. Also, patients with Montreal Cognitive Assessment Battery (MoCA) scores less than 21 points, which is a cut off determined by validation study of Turkish version of MoCA (Ozdilek & Kenangil, 2014), were excluded. Furthermore, RRMS patients who experience an attack in the last 3 months and who received high-dose steroid treatment in the last 3 months before the administration of neuropsychological tests were excluded. Lastly, patients who scored 17 or above in Beck Depression Scale and who scored 16 or above in Beck Anxiety Scale I were excluded in order to control effects of psychological symptoms on Social Cognition tests. Healthy volunteers were recruited from the stuff who worked in the same hospital. Healthy volunteer subjects were chosen to match the patients' age, educational level, and gender.

On the other hand, inclusion criteria for this project were being between 18 to 65 years old for both the experimental and control group. Also, for the RRMS group, patients' EDSS (Expanded Disability Status Scale) score was required to be between 0 to 6. The Expanded Disability Status Scale (EDSS) is the most widely used scale among patients with multiple sclerosis. The EDSS is a highly effective method for reflecting disability (Noseworthy et al., 1990). It is a scoring system ranging from 0 to 10 and reveals the patient's morbidity (Şen, 2018). Also, willingness to participate in the study and proficiency in writing and speaking Turkish were essential.

Participants

Originally, a total of 67 participants were recruited for this study. However, because of insufficient scores in MoCA or high scores in Beck Depression or Beck Anxiety Inventory, seven participants were excluded. All participants (both RRMS and HC) match in their age, years of education, gender (22 female and 8 males in each group), and MoCA scores.

Descriptive Statistics	RRMS (n=30) Mean (SD)	HC (n=30) Mean (SD)
AGE	45.33 (10.69)	44.83 (14.46)
YEARS OF EDUCATION	12.03 (4.68)	11.7 (3.92)
EDSS SCORE	2.45 (1.3)	-
DISEASE DURATION (YEARS)	16.26 (8.09)	-
MoCA (max. 30)	26.03 (2.12)	26.03 (1.96)
FPRT (max. 30)	13.53 (6.85)	26.43 (2.63)
RMET (max. 32)	20.76 (4.75)	24.5 (3.08)
FEI (max. 19)	11.83 (2.26)	14.33 (2.12)
FED (max. 30)	25.3 (2.34)	26.33 (2.8)

Table 1: Demographic Characteristics and Group Comparison Results.

Neuropsychological Tests

MoCA-TR (Montreal Cognitive Assessment Scale in Turkish):

MoCA-TR is a 10-minute screening test developed to briefly assess seven cognitive domains on a single page, specifically designed for mild cognitive impairment. The test includes the following components: trail making test (1 point), cube copying (1 point), clock drawing (3 points), naming: (lion, rhinoceros, and camel) (3 points), counting forward and backward (2 points), vigilance (1 point), serial 7s (3 points), sentence repetition (2 points) and verbal fluency (1 point), abstract thinking (2 points), delayed recall (5 points), and orientation (6 points).

The maximum score on the MoCA-TR is 30. Scores of 21 and above are considered normal. The Turkish validity and reliability study was conducted by Ozdilek and Kenangil in 2014, using patients with Parkinson's disease for testing (Ozdilek & Kenangil, 2014).

Faux Pas Recognition Test (FPRT):

The FPRT is designed to assess individuals' ability to interpret the thoughts and feelings of others in a Faux Pas situation. The adult version of the test was developed by Baron-Cohen and colleagues in 1999 (Baron-Cohen, 1999). Faux pas refers to the inadvertent or unknowing utterance of something one should not say. The test comprises a total of 10 Faux Pas stories and 10 control stories, numbered 2, 4, 7, 11, 12, 13, 14, 15, 16, 18, and 1, 3, 5, 6, 8, 9, 10, 17, 19, 20 respectively. Each story is read to the participant, who is then asked four questions per story. Participants are scored based on their responses. The test takes approximately 30-40 minutes, and each story is worth 1 point, with a maximum possible score of 20 (Şandor & İşcen, 2021). In this study, the short version consisting of 10 stories were used. A Turkish adaptation study was done by Şandor and İşcen in 2021 where they tested both short and long version of the FPRT test on Turkish population. The short version of the test has three subsections; total scores for the correct detection of Faux Pas situations in FP stories (FPS) ranged between 0 to 5, total scores for answers to all questions in 5 FP stories (TFPS) ranged between 0 to 30, and total scores for the 5 control stories (TCS) ranged between 0 to 10 (Şandor & İşcen, 2021).

Reading the Mind in the Eyes Test:

The original version of the test includes 37 questions which have 36 actual questions and 1 test question. Each picture presents one correct and three incorrect options to the participant. Throughout the test, participants are expected to choose the option that best describes what the person in each pair of eye pictures is thinking or feeling. A dictionary containing 93 words, including expressions used in the test and words with similar meanings is provided to participants during the test. The dictionary includes meanings and usage examples of the

expressions (Baron-Cohen et al., 1999). In 2011, a Turkish validation and reliability study was conducted by Yıldırım and his colleagues. They excluded some of the items because of the lack of reliability based on the results. At the end, they concluded that for clinical or non-clinical samples, the 32-item Turkish version of the Eyes Test can be useful in neuroscience research examining areas like ToM and emotion regulation (Yıldırım et al., 2011).

Facial Emotion Identification Test (FEI):

Kerr and Neale developed two tests in 1993 to assess the perception of emotion expression in schizophrenia: the Facial Emotion Identification Test and the Facial Emotion Discrimination Test (Kerr and Neale, 1993). The Facial Emotion Identification Test is presented as a slide show containing 19 black-and-white facial photographs depicting different emotional expressions. The photographs include six primary emotions (these are; happiness, sadness, anger, fear, surprise, and shame). The test is arranged to display each photograph for fifteen seconds, with a ten-second interval between them. Participants are provided with a response key containing six basic emotions for each of the 19 items. As participants view each photograph, they are asked to mark which of the six basic emotions best describes what the person in the photo is feeling. A correct answer earns 1 point, and the maximum score for the test is 19 (Erol et al., 2009). The Turkish validation and reliability study was done by Erol et al and her colleagues in 2009 on schizophrenic patients and they found a significant difference between HCs and schizophrenic patients where the patient group outperformed the HC group (Erol et al., 2009).

Facial Emotion Discrimination Test (FED):

This test comprises of 30 pairs of black-and-white photographs, each pair either displaying the same or different emotional expressions. Similar to FEI, the test is presented as a slide show, with each pair shown for fifteen seconds and a ten-second interval between them. Participants are asked, for each photograph pair, whether the two faces show the same or different emotions. The response key for each question includes the options 'different' and 'same.' Participants indicate their choice for each photograph pair, and 1 point is awarded for a correct answer. The maximum score for the test is 30 (Erol et al., 2009).

Beck Depression Inventory:

It was developed by Beck and colleagues in 1961, and the scale comprises 21 multiple-choice questions designed to identify depressive symptoms. The test, lasting a total of 10 minutes, features responses ranging from 0 to 3, with the highest score being 63 and the lowest 0. Based on the resulting score, depressive symptoms can be categorized into four levels: none-mild, mild-moderate, moderate-severe, or severe. Participants are expected to respond based on their mood over the past week. Validity and reliability of Beck Depression Inventory for Turkish population was conducted by Nesrin Hisli in 1989 (Hisli, 1989).

Beck Anxiety Inventory:

It is a screening inventory consisting of 21 questions, with each question offering a total of 4 options: none (0 points), mild (1 point), moderate (2 points), and severe (3 points). Scores from 8 to 15 indicate mild anxiety symptoms, 16-25 suggest moderate anxiety symptoms, and 26-63 imply severe anxiety symptoms. Participants are expected to respond based on their

mood over the past week. Validity and reliability of Beck Anxiety Inventory for Turkish population is conducted by Meral Gümüş Avcı in 1995 (Avcı, 1995).

Expanded Disability Status Scale

The Disability Status Scale (DSS), which was developed in 1983 and later evolved into the Expanded DSS (EDSS), is the initial scale used to evaluate physical disability in MS cases. One of its biggest benefits is that it hasn't changed much since it was first used in 1983. It is highly valuable as it represents the clinical status as a number and encompasses all functional systems that may be affected by MS, like Pyramidal (P), Cerebellar (Cll), Brain Stem (BS), Sensory (S), Bladder-Bowel (BB), Visual (V), Cerebral or Mental (Cb), and Other (O) (Çinar & Yorgun, 2018). The EDSS has 20 steps with 0.5 increments."0" denotes a normal neurological examination, and "10" denotes an MS-related death. The EDSS score rises in proportion to the decline in MS, and the first score after 0 is 1, not 0.5. Following 1, the score rises in 0.5-point increments to indicate the clinical decline (Kurtzke, 1983). For this thesis project, I only included RRMS patients who scored from 0 to 6 in EDSS and the test was applied to the patients by Prof. Dr. Murat Kürtüncü.

Data Collection Procedure

The data collection sessions were carefully structured to ensure consistency and reliability. Each session was begun with a brief introduction (explaining that they are about to voluntarily participate to a master’s thesis project) and consent process, followed by a series of neuropsychological test administered in a standardized order. The sessions were started with the Beck Depression Inventory (BDI) and the Beck Anxiety Inventory (BAI), each taking

about approximately 10 minutes. After that, Montreal Cognitive Assessment (MoCA) is administered to assess overall cognitive function, taking approximately 10-15 minutes. These screening tools I mentioned above were helping us to exclude RRMS or HC participants who are not eligible for inclusion criteria of the study. Right after scoring selection tests, I scored all three of them (MoCA, BDI, and BAI) and then decided whether proceed with participant or not. Right after that, I administered Participants will then proceed to the Faux Pas Recognition Test (FPRT), which was required approximately 15-20 minutes. Then, Reading the Eyes in the Mind Test (REM), which lasted about 10-15 minutes. Finally, Facial Emotion Identification Test (FEI) and the Facial Emotion Discrimination Test (FED) were administered; each lasted around 10-15 minutes. The total duration of each session was approximately about 75-90 minutes.

Data collection did take place in a quiet, comfortable room within the Istanbul University Hospital/MS clinic setting to minimize distractions and ensure a controlled environment. This setting is provided access to necessary equipment and allow for proper administration of neuropsychological tests.

All tests were administered by myself (except EDSS) to ensure standardized delivery and to assist participants with any questions. I followed a scripted protocol for each assessment to maintain consistency across sessions. Participants (especially RRMS patients and patients with age above 60) were given short breaks as needed to reduce fatigue and maintain concentration throughout the session.

Data Analysis

The statistical analysis for this study involves a comprehensive approach to assess social cognitive functions in individuals with Relapsing-Remitting Multiple Sclerosis (RRMS) compared to a HC group. Independent samples t-tests were employed to compare mean scores of facial emotion recognition, measured by tests such as Facial Emotion Identification (max. score is 19) and Discrimination Tests (max. score is 30) as well as mean scores of ToM, assessed using the Faux-Pas Recognition Test (max score is 30 for the short version) and Reading the Eyes in the Mind Test (mean score 23.64 out of 32 in the validation study), between the RRMS group and the control group (H1 and H2). Multivariate Analysis of variance (MANOVA) was utilized to explore differences in recognition accuracy for positive and negative emotions within each group, focusing on the Facial Emotion Identification Test (H3). Linear Regression Analysis was conducted to investigate the relationship between the severity of RRMS symptoms (through disease duration in years, and EDSS score) and social cognitive functions (H4 and H5). Furthermore, linear regression models were constructed to examine the associations between MoCA scores (>21) and Facial Emotion Identification and Discrimination Tests (H6), as well as between MoCA scores and Faux-Pas Recognition Test and Reading the Eyes in the Mind Test (H7). All statistical analysis were originally planned to conduct using R programming, but since result illustration and tables are clearer and more understandable in JASP, independent sample T-test and ANOVA tests were conducted through JASP. On the other hand, regression analyses were performed only in R.

Hypothesis Testing;

Independent Samples t-Tests for Hypothesis 1 and Hypothesis 2:

To compare the social cognitive functions between individuals with RRMS and HCs, independent samples t-tests were conducted using JASP. Specifically, t-tests were used to compare scores on the Facial Emotion Identification Test (FEI), Facial Emotion Discrimination Test (FED), Reading the Eyes in the Mind Test (RMET), and the Faux Pas Recognition Test (FPRT) between the two groups. In JASP, each test's scores were specified as dependent variables and group membership (RRMS vs. HCs) as the independent variable. The purpose of these t-tests was to determine if there are significant differences in social cognitive functions between the two groups.

MANOVA for Hypothesis 3:

Multivariate Analysis of Variance (MANOVA) was used to explore differences in emotion recognition accuracy for positive and negative emotions within each group using JASP. The FEI scores for six different emotions (Fear, Anger, Sadness, Shame for negative emotions, and Surprise, Happiness for positive emotions) were analyzed and two MANOVA analyses were conducted; one for positive emotions with two dependent variables (Surprise and Happiness, and another for negative emotions with four dependent variables (Fear, Anger, Sadness, Shame). For the fixed factors, I inserted groups (RRMS vs HC).

Linear Regression Analysis for Hypothesis 4:

To examine the relationship between the duration of RRMS (measured in years) and social cognitive functions, linear regression analyses were performed using the `lm()` function in R. The dependent variables in these analyses were the social cognitive function scores, specifically the Facial Emotion Identification Test (FEI), Facial Emotion Discrimination Test (FED), Reading the Eyes in the Mind Test (RMET), and the Faux Pas Recognition Test (FPRT). The independent variable was disease duration as a continuous variable (from 1 to 29 years). The variable names in R were `disease duration` for the independent variable and `FEI`, `FED`, `RMET`, and `FPRT` for the dependent variables. Each social cognitive function score was tested with the disease duration variable using different regression models to determine if there is a significant linear relationship, indicating that as the disease duration increases, social cognitive abilities decline.

Linear Regression Analysis for Hypothesis 5:

To investigate the relationship between the Expanded Disability Status Scale (EDSS) scores, which reflect the level of disability in RRMS, and social cognitive functions, linear regression analyses were conducted using the same procedure as in H4. The dependent variables will be the social cognitive function scores: Facial Emotion Identification Test (FEI), Facial Emotion Discrimination Test (FED), Reading the Eyes in the Mind Test (RMET), and the Faux Pas Recognition Test (FPRT). The independent variable will be the EDSS scores, ranging from 0 to 6. Each social cognitive function score will be tested separately with the EDSS variable in different regression models.

Linear Regression Analysis for Hypothesis 6 and Hypothesis 7:

To examine the relationship between cognitive function, as measured by the Montreal Cognitive Assessment (MoCA) scores, and social cognitive functions in individuals with RRMS, linear regression analyses were conducted. First, the relationship between MoCA scores and facial emotion recognition was analyzed. The dependent variables were the scores from the Facial Emotion Identification Test (FEI) and Facial Emotion Discrimination Test (FED). The independent variable was the MoCA score, ranging from 21 to 30 (as scores below 21 was not included). This analysis aimed to determine if there is a positive linear relationship, indicating that higher MoCA scores are associated with better facial emotion recognition.

Similarly, the relationship between MoCA scores and ToM abilities was explored using the Faux Pas Recognition Test (FPRT) and Reading the Mind in the Eyes Test as the dependent variables and MoCA scores as the independent variable. The aim of the analysis was if higher MoCA scores correlate with better ToM performance.

As with the previous analyses, the regression coefficient for Faux Pas Recognition was examined to ensure it is significantly different from zero. The same regression procedure was applied across these models, testing each dependent variable separately with the MoCA scores to validate the hypotheses.

Results

Results of Independent T-test for Hypothesis 1 and Hypothesis 2

Independent Samples T-Test

	Test	Statistic	df	p	Cohen's d	SE Cohen's d
FPRT	Student	9.457	58.000	< .001	2.442	0.407
	Welch	9.457	37.341	< .001	2.442	0.407
RMET	Student	3.549	58.000	< .001	0.916	0.284
	Welch	3.549	49.758	< .001	0.916	0.284
FEI	Student	4.339	58.000	< .001	1.120	0.296
	Welch	4.339	57.737	< .001	1.120	0.296
FED	Student	1.913	58.000	0.061	0.494	0.266
	Welch	1.913	56.209	0.061	0.494	0.266

Table 2

The table points out the independent samples t-test results which compare the scores of social cognition tests between the RRMS group and the HC group. These tests are the Faux Pas Recognition Test (FPRT or FPRT total), Reading the Eyes in the Mind Test (RMET), Facial Emotion Identification Test (FEI), and Facial Emotion Discrimination Test (FED). Student's t-test and Welch's t-test results are shown, together with the degrees of freedom (df), p-values, Cohen's d, and the standard error of Cohen's d.

Group Descriptives

	Group	N	Mean	SD	SE	Coefficient of variation
FPRT	HC	30	26.433	2.674	0.488	0.101
	RRMS	30	13.533	6.976	1.274	0.516
RMET	HC	30	24.500	3.138	0.573	0.128
	RRMS	30	20.767	4.833	0.882	0.233
FEI	HC	30	14.333	2.155	0.393	0.150
	RRMS	30	11.833	2.306	0.421	0.195
FED	HC	30	26.333	2.857	0.522	0.108
	RRMS	30	25.033	2.385	0.435	0.095

Table 3

The table shows HC and RRMS groups descriptive. These are number of participants in each group (N), average (Mean), Standard Deviation (SD), Standard Error (SE), and Coefficient of Variation.

Results of Table 2 and 3:

When we look at Tables 2 and 3, we can see that differences between HC and RRMS are remarkable. In the FPRT test, the HC group's mean score is 26.43 (*SD*=2.67) while the RRMS group scored significantly lower with a mean of 13.53 (*SD*=6.97). When it comes to the Reading the Eyes in the Mind Test (RMET), the HC group's mean score is 24.50 (*SD* = 3.138) and the RRMS group's mean is 20.77 (*SD* = 4.833). Also, the Facial Emotion Identification Test (FEI) shows significant differences, with the HC group's mean score being 14.33 (*SD* = 2.15) and the RRMS group's mean score being 11.83 (*SD* = 2.30). On the other hand, in the Facial Emotion Discrimination Test (FED), the HC group has the mean score of

26.33 (*SD* = 2.86) compared to 25.03 (*SD* = 2.38) for the RRMS group, so no significant difference can be found in FED scores between two groups.

When it comes to independent sample t-test results, we can see two versions of the test (one is with Student t-test, and the other one is Welch t-test). Since there is a difference between variances of two groups (HC and RRMS), I will mention Welch t-test in detail.

Firstly, in the Faux Pas Recognition Test (FPRT), there is a significant difference between the HC group and the RRMS group, with the RRMS group significantly outperformed, t (37) = 9.46, $p < .001$, (Cohen's d = 2.42). Similarly, for the Reading the Mind in the Eyes Test (RMET), the t-test reveals a significant difference between the two groups, t (49) = 3.55, $p < .001$, (Cohen's d = 0.92). Also, in the Facial Emotion Identification Test (FEI), the RRMS group also scored significantly lower revealed by the t-test results indicating a significant difference, t (57) = 4.34, $p < .001$, (Cohen's d = 1.12). However, the results for the Facial Emotion Discrimination Test (FED) do not show a significant difference between the HC and RRMS groups, t (56) = 1.91, $p = .061$, (Cohen's d = 0.49).

Test of Normality for Independent Sample T-test (Hypothesis 1 and 2):

Test of Normality (Shapiro-Wilk)

		W	p
FPRT	HC	0.898	0.007
	RRMS	0.971	0.559
RMET	HC	0.936	0.071
	RRMS	0.969	0.518
FEI	HC	0.944	0.116
	RRMS	0.961	0.321
FED	HC	0.919	0.026
	RRMS	0.969	0.515

Note. Significant results suggest a deviation from normality.
Table 4

Results of Table 4:

The Shapiro-Wilk test for normality showed that the FPRT and FED data for the HC group deviate significantly from normality ($W = 0.89$, $p = .007$) and ($W = 0.92$, $p = .03$), respectively), indicating that this data is not normally distributed. On the other hand, the RRMS group's FPRT ($W = 0.97$, $p = .56$) and FED ($W = 0.96$, $p = .51$) data does not show significant deviations from normality. The same case can be seen in the RMET and FEI data where the HC and RRMS groups don't deviate significantly from normality (p-values > 0.05), indicating that this data is normally distributed.

Results of MANOVA for Hypothesis 3

MANOVA Results for Negative Emotions in FEI test:

MANOVA: Pillai Test

Cases	**df**	**Approx. F**	**Trace $_{Pillai}$**	**Num df**	**Den df**	**p**
(Intercept)	1	363.339	0.964	4	55.000	< .001
Groups	1	5.790	0.296	4	55.000	< .001
Residuals	58					

Table 5

Note: Results maintained by using accuracy scores for each emotion.

The MANOVA results showed that there is a statistically significant difference between the groups on the combined dependent variables (sadness, fear, shamed, anger), as indicated by Pillai's trace $V = 0.29$, F (4,55) = 5.79, $p < .001$. The effect size is considerable, with Pillai's trace value of 0.296 suggesting a moderate to large effect. This significant result indicates that

the group (RRMS and HC) has a significant impact on the combined set of negative emotions in FEI test being tested.

Assumption Checks

Box's M-test for Homogeneity of Covariance Matrices

χ^2	df	p
21.030	10	0.021

Shapiro-Wilk Test for Multivariate Normality

Shapiro-Wilk	p
0.979	0.379

Table 6

Since the p value is less than the significance level of 0.05 in the Box's M-test, the assumption of homogeneity of covariance matrices is violated. However, the Shapiro-Wilk test with a p-value greater than 0.05 indicates that the assumption of multivariate normality is satisfied.

ANOVA Results (analyzing negative emotions individually):

ANOVA: Sadness

Cases	Sum of Squares	df	Mean Square	F	p
(Intercept)	35.313	1	35.313	628.028	< .001
Groups	0.602	1	0.602	10.706	0.002
Residuals	3.261	58	0.056		

Table 7

The ANOVA results for the Sadness variable showed significant differences between RRMS and HC. The analysis shows a significant effect of the groups on the accuracy of Sadness, F (1,58) = 10.706, p = .002. These findings indicate that the groups differ significantly in their Sadness scores, and this difference is statistically significant.

ANOVA: Fear

Cases	Sum of Squares	df	Mean Square	F	p
(Intercept)	20.045	1	20.045	446.034	< .001
Groups	0.420	1	0.420	9.346	0.003
Residuals	2.607	58	0.045		

Table 8

Also, the ANOVA results for the Fear as a dependent variable showed significant differences between RRMS and HC. The analysis shows a significant effect of the groups on the accuracy of Fear, F (1,58) = 9.346, p = .003. These findings indicate that the groups differ significantly in their Fear scores.

ANOVA: Shame

Cases	Sum of Squares	df	Mean Square	F	p
(Intercept)	14.017	1	14.017	152.431	< .001
Groups	0.150	1	0.150	1.631	0.207
Residuals	5.333	58	0.092		

Table 9

On the other hand, ANOVA results for the Shame variable showed nonsignificant differences between RRMS and HC. The analysis shows a nonsignificant effect of the groups on the accuracy of Shame, F (1,58) = 1.631, p = .207. These findings indicate that the groups are not differ significantly in their Shame scores.

ANOVA: Anger

Cases	Sum of Squares	df	Mean Square	F	p
(Intercept)	28.704	1	28.704	633.220	< .001
Groups	0.417	1	0.417	9.192	0.004
Residuals	2.629	58	0.045		

Table 10

Like in sadness and fear, also ANOVA results for the Anger variable showed significant differences between RRMS and HC. The analysis shows a significant effect of the groups on the accuracy of Anger, F (1,58) = 9.192, p = .004. These findings indicate that the groups differ significantly in their Anger scores.

MANOVA Results for Positive Emotions in FEI test:

MANOVA: Pillai Test

Cases	df	Approx. F	Trace Pillai	Num df	Den df	p
(Intercept)	1	6977.594	0.996	2	57.000	< .001
Groups	1	0.680	0.023	2	57.000	0.511
Residuals	58					

Table 11

Note: Results maintained by using accuracy scores for each emotion.

The MANOVA test shows that there is no significant difference between the groups on the combined dependent variables (happiness and surprised), as indicated by Pillai's trace V = 0.02), F (2,57) = 0.68, p = .511. The effect size is considerable, with Pillai's trace value of 0.02 suggesting a small effect. This significant result indicates that the group (RRMS and HC) does not have significant impact on the combined set of positive emotions in FEI test being tested. However, the intercept is significant F (2,57) = 6977.594, p < .001, reflecting the overall variance in the dependent variables not attributable to the group differences. These findings support the conclusion that RRMS patients do not exhibit significantly different patterns in identification of positive emotions compared to HCs.

Box's M-test for Homogeneity of Covariance Matrices

χ^2	df	p
180.236	3	< .001

Shapiro-Wilk Test for Multivariate Normality

Shapiro-Wilk	p
0.114	< .001

Table 12

Since the p value is less than the significance level of 0.05, the assumption of homogeneity of covariance matrices is violated. Also, the Shapiro-Wilk test with the p-value less than 0.05 indicates that the assumption of multivariate normality is violated.

ANOVA: Surprise

Cases	Sum of Squares	df	Mean Square	F	p
(Intercept)	40.838	1	40.838	701.800	< .001
Groups	0.037	1	0.037	0.644	0.425
Residuals	3.375	58	0.058		

Table 13

The ANOVA results for the Surprise variable did not show significant differences between RRMS and HC. The analysis does not show a significant effect of the groups on the accuracy of Surprise, F (1,58) = 0.644, p = .425.

ANOVA: Happiness

Cases	Sum of Squares	df	Mean Square	F	p
(Intercept)	58.984	1	58.984	14150.580	< .001
Groups	0.004	1	0.004	0.960	0.331
Residuals	0.242	58	0.004		

Table 14

The ANOVA results for the Happiness variable did not show significant differences between RRMS and HC. The analysis does not show a significant effect of the groups on the accuracy of Happiness, F (1,58) = 0.960, p = .331. These findings indicate that the groups do not differ significantly in their Happiness scores.

Results of Linear Regression Analysis for Hypothesis 4

In order to test hypothesis 4, linear regression analyses were conducted to evaluate the relationship between the duration of the RRMS (disease duration in years) and performance

on social cognition tests (FPRT, RMET, FEI, FED). However, only the FED test revealed a significant linear relationship with disease duration.

A regression analysis did not reveal a significant relationship between FPRT and disease duration, F (1,28) = 0.915, p = .347. Also, no significant relationship was found between RMET and disease duration, F (1,28) = 3.23, p = .083. The same results occurred when testing the relationship between the FEI test and disease duration, F (1,28) = 0.584, p = .451. Since only the FED test revealed a significant relationship with disease duration, a regression table and scatter plot are provided in the below for these two variables.

	Dependent variable:
	FED
Duration	−0.118*
	(0.050)
Constant	26.947***
	(0.909)
Observations	30
R^2	0.165
Adjusted R^2	0.135
Residual Std. Error	2.218 (df = 28)
F Statistic	5.530** (df = 1; 28)
p-value (overall model)	0.026
Note:	*p<0.05; **p<0.01; ***p<0.001

Table 15 (Note: unstandardized beta is represented under "Dependent variable" and standard error is inside the parentheses)

The overall model is statistically significant so we can reject the null hypothesis which states there is a no relationship between disease duration and FED scores. F (1,28) = 5.53, p = .026. The adjusted r square is 0.13 so it explains %13 of variance, that's why we can say that model does not fit well with the data but it's improvable. Also, regression coefficient (the intercept

only model) is statistically significant when the predictor variable is set to zero. This indicates that for each additional year of disease duration, FED scores decrease by approximately 0.117 points, and this decrease is statistically significant. Hence, results indicate that the duration of the disease has a significant effect on FED scores among the participants for this study. The significant regression coefficient suggests that there is meaningful linear relationship between disease duration and performance on the FED.

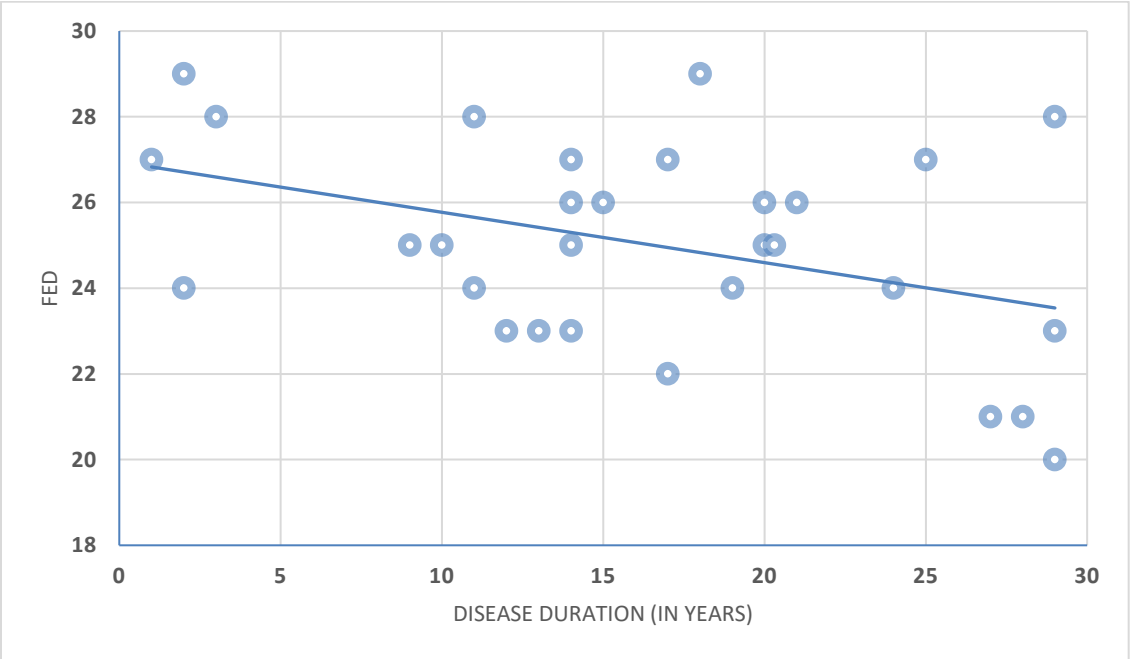

Figure 1: The figure illustrates the relationship between disease duration and facial emotion discrimination (FED) scores. The x-axis represents the duration of the disease (in years), and the y-axis shows the FED scores. The central blue line indicates a negative linear trend, suggesting that FED scores decrease as disease duration increases. The shaded area represents the confidence interval, which broadens with longer disease durations, indicating increased variability.

Results of Linear Regression Analysis for Hypothesis 5

In order to test hypothesis 5, linear regression analyses were conducted to evaluate the relationship between the disability level of RRMS patients (EDSS scores) and performance on social cognition tests (FPRT, RMET, FEI, FED). However, only the FED test revealed a significant linear relationship with EDSS scores.

A regression analysis did not reveal significant relationship between FPRT and EDSS scores, F (1,28) = 0.562, p = .459. Also, no significant relationship was found between RMET and EDSS scores, F (1,28) = 3.73, p = .06. The same results occurred when testing the relationship between the FEI test and EDSS scores, F (1,28) = 0.739, p = .397. Since only the FED test revealed significant relationship with EDSS scores, a regression table and scatter plot are provided in the below for these two variables.

	Dependent variable:
	FED
EDSS.scores	−0.712*
	(0.311)
Constant	26.778***
	(0.865)
Observations	30
R^2	0.157
Adjusted R^2	0.127
Residual Std. Error	2.228 (df = 28)
F Statistic	5.230* (df = 1; 28)
p-value (overall model)	0.03
Note:	*p<0.05; **p<0.01; ***p<0.001

Table 16

The overall model is statistically significant so we can reject the null hypothesis which states there is no relationship between EDSS and FED scores. F (1,28) = 5.23, p = .029. The adjusted r square is 0.12 so it explains %12 of the variance, that's why we can say that the model does not fit well with the data but it's improvable. Also, the regression coefficient (the intercept-only model) is statistically significant when the predictor variable is set to zero. This indicates that for each unit increase in EDSS score, FED scores decrease by approximately 0.71 points, and this decrease is statistically significant. Hence, results indicate that EDSS scores (disability level) significantly affect FED scores among this study's participants. The significant regression coefficient suggests a meaningful linear relationship between EDSS scores and performance on the FED.

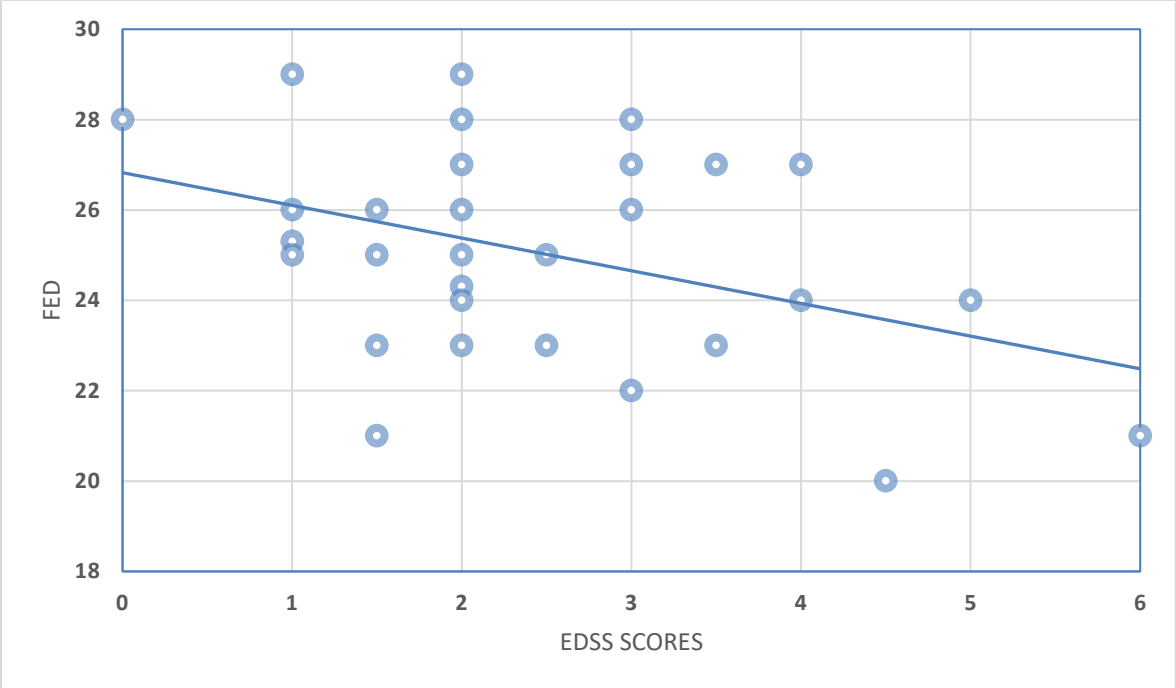

Figure 2: shows effect pilot created using R. The x-axis represents the EDSS (disability level), and the y-axis shows the FED scores. The central blue line indicates a negative linear trend, suggesting that FED scores decrease as EDSS score increases. The shaded area represents the confidence interval, which broadens with higher EDSS score, indicating increased variability.

Results of Linear Regression Analyses for Hypothesis 6 and Hypothesis 7

Linear Regression Results for MoCA and Emotion Recognition Tests (FEI and FED):

	Dependent variable:
	FEI
MoCA	0.475*
	(0.181)
Constant	−0.544
	(4.725)
Observations	30
R^2	0.198
Adjusted R^2	0.169
Residual Std. Error	2.102 (df = 28)
F Statistic	6.907* (df = 1; 28)
p-value (overall model)	0.014
Note:	*p<0.05; **p<0.01; ***p<0.001

Table 17

The overall model is statistically significant so we can reject the null hypothesis which states there is no relationship between MoCA and FEI scores. F (1,28) = 6.907, p = .013. The adjusted r square is 0.17 so it explains %17 of the variance, that's why we can say that the model does not fit well with the data but it's improvable. However, the regression coefficient (the intercept-only model) is not statistically significant when the predictor variable is set to zero (beta=-0.54, t=-0.11, p= .90) This indicates that for each unit increase in MoCA score, FEI scores increase by approximately 0.47 points, and this increase is statistically significant. Hence, results indicate that MoCA scores (general cognitive assessment) significantly affect FEI scores among this study's participants. The nonsignificant regression coefficient suggests there is no meaningful linear relationship between MoCA scores and performance on the FEI.

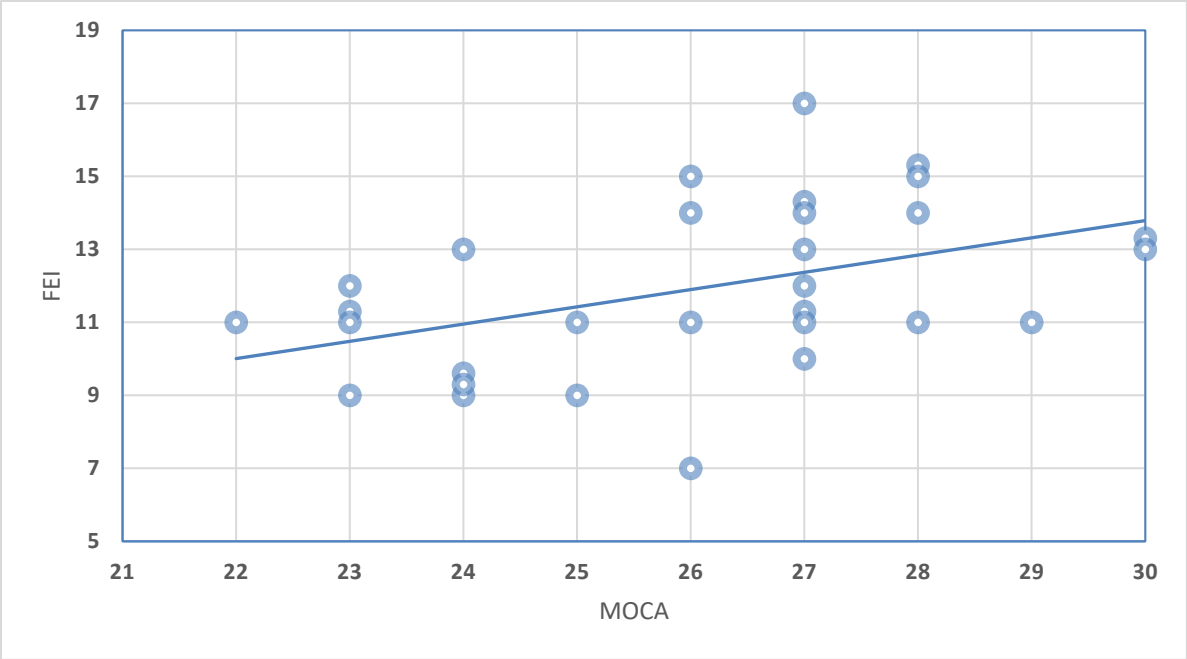

Figure 3: shows effect pilot created using R. The x-axis represents the MoCA (general cognitive screening tool), and the y-axis shows the FEI scores. The central blue line indicates a positive linear trend, suggesting that FEI scores increase as MoCA score increases.

	Dependent variable:
	FED
MoCA	0.429*
	(0.193)
Constant	13.852*
	(5.029)
Observations	30
R^2	0.151
Adjusted R^2	0.121
Residual Std. Error	2.237 (df = 28)
F Statistic	4.977** (df = 1; 28)
p-value (overall model)	0.03
Note:	*p<0.05; **p<0.01; ***p<0.001

Table 18

The overall model is statistically significant so we can reject the null hypothesis which states there is no relationship between MoCA and FED scores. F (1,28) = 4.97, p = .03. The adjusted r square is 0.12 so it explains %12 of the variance, that's why we can say that the model does not fit well with the data but it's improvable. Also, the regression coefficient (the intercept-only model) is statistically significant when the predictor variable is set to zero (beta= 13.85, t= 2.75, p=.01) This indicates that for each unit increase in MoCA score, FED scores increase by approximately 0.43 points, and this increase is statistically significant. Hence, results indicate that MoCA scores (general cognitive assessment) significantly affect FED scores among this study's participants. The significant regression coefficient suggests meaningful linear relationship between MoCA scores and performance on the FED.

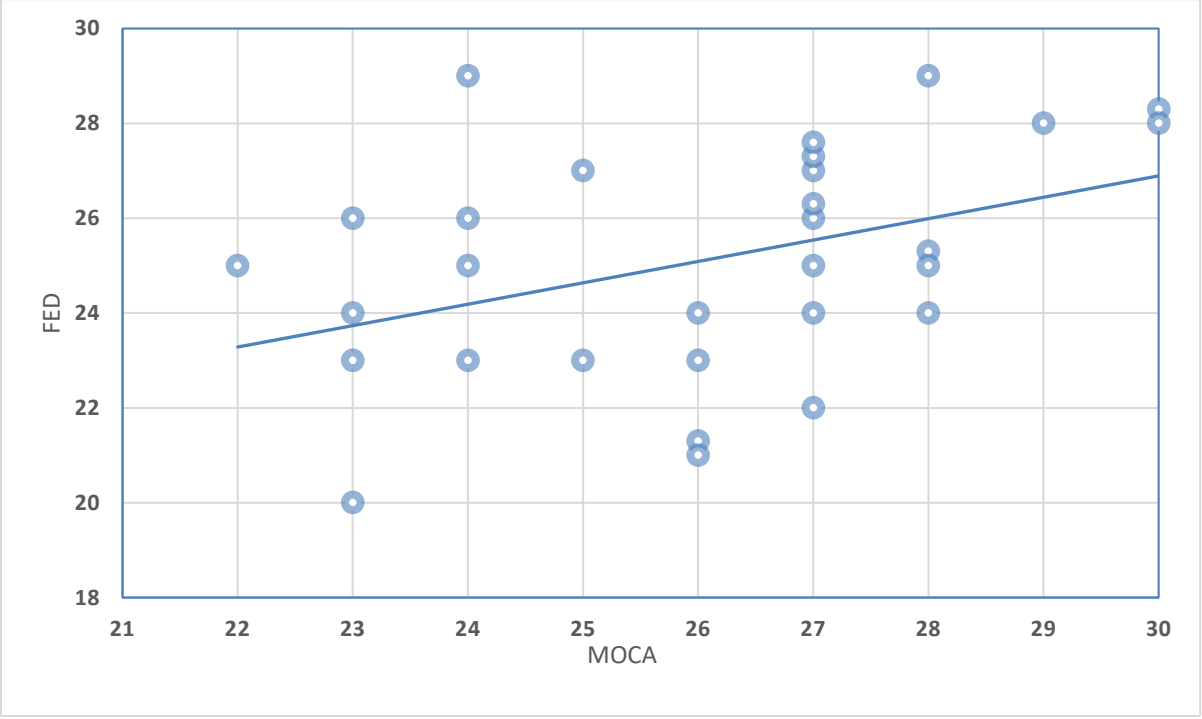

Figure 4: shows effect pilot created using R. The x-axis represents the MoCA (general cognitive screening tool), and the y-axis shows the FED scores. The central blue line indicates a positive linear trend, suggesting that FED scores increase as MoCA score increases.

Linear Regression Results for MoCA and ToM Tests (FPRT and RMET):

	Dependent variable:
	FPRT
MoCA	1.671**
	(0.523)
Constant	−29.956*
	(13.668)
Observations	30
R^2	0.267
Adjusted R^2	0.241
Residual Std. Error	6.079 (df = 28)
F Statistic	10.191*** (df = 1; 28)
p-value (overall model)	0.003
Note:	*p<0.05; **p<0.01; ***p<0.001

Table 19

The overall model is statistically significant so we can reject the null hypothesis which states there is no relationship between MoCA and FPRT scores. F (1,28) = 10.19, p = .003. The adjusted r square is 0.24 so it explains %24 of the variance, that's why we can say that the model does not fit well with the data but it's improvable. Also, the regression coefficient (the intercept-only model) is statistically significant when the predictor variable is set to zero (beta= -29.95, t= -2.19, p= .03) This indicates that for each unit increase in MoCA score, FPRT scores increase by approximately 1.67 points, and this increase is statistically

significant. Hence, results indicate that MoCA scores (general cognitive assessment) significantly affect FPRT scores among this study's participants. The significant regression coefficient suggests meaningful linear relationship between MoCA scores and performance on the FPRT.

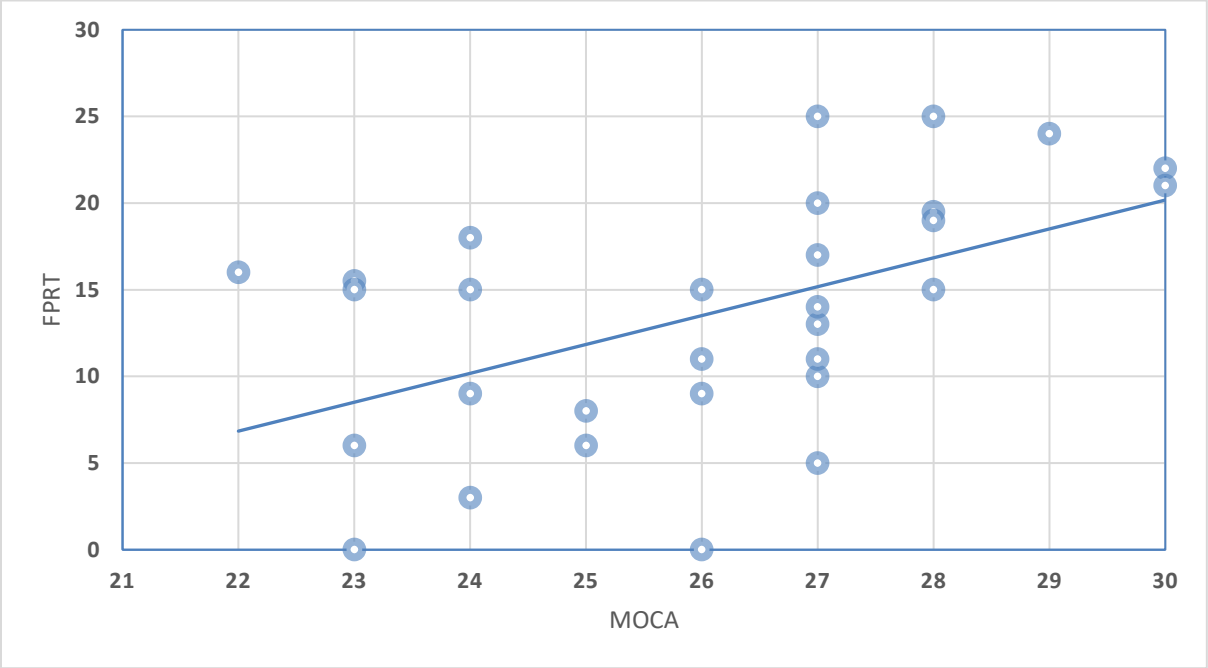

Figure 5: shows effect pilot created using R. The x-axis represents the MoCA (general cognitive screening tool), and the y-axis shows the FPRT scores. The central blue line indicates a positive linear trend, suggesting that FPRT scores increase as MoCA score increases.

	Dependent variable:
	RMET
MoCA	1.269**
	(0.349)
Constant	−12.262
	(9.114)
Observations	30
R^2	0.321
Adjusted R^2	0.296
Residual Std. Error	4.054 (df = 28)
F Statistic	13.220*** (df = 1; 28)
p-value (overall model)	0.0011
Note:	*p<0.05; **p<0.01; ***p<0.001

Table 20

The overall model is statistically significant so we can reject the null hypothesis which states there is no relationship between MoCA and RMET scores. F (1,28) = 13.22, p = .001. The adjusted r square is 0.29 so it explains %29 of the variance, that's why we can say that the model does not fit well with the data but it's improvable. However, the regression coefficient (the intercept-only model) is not statistically significant when the predictor variable is set to zero (beta= -12.26, t= -1.34, p= .19). For each unit increase in MoCA score, RMET scores increase by approximately 1.26 points, and this increase is statistically significant. Hence, results indicate that MoCA scores (general cognitive assessment) significantly affect RMET scores among this study's participants. The nonsignificant regression coefficient suggests there is no meaningful linear relationship between MoCA scores and performance on the RMET.

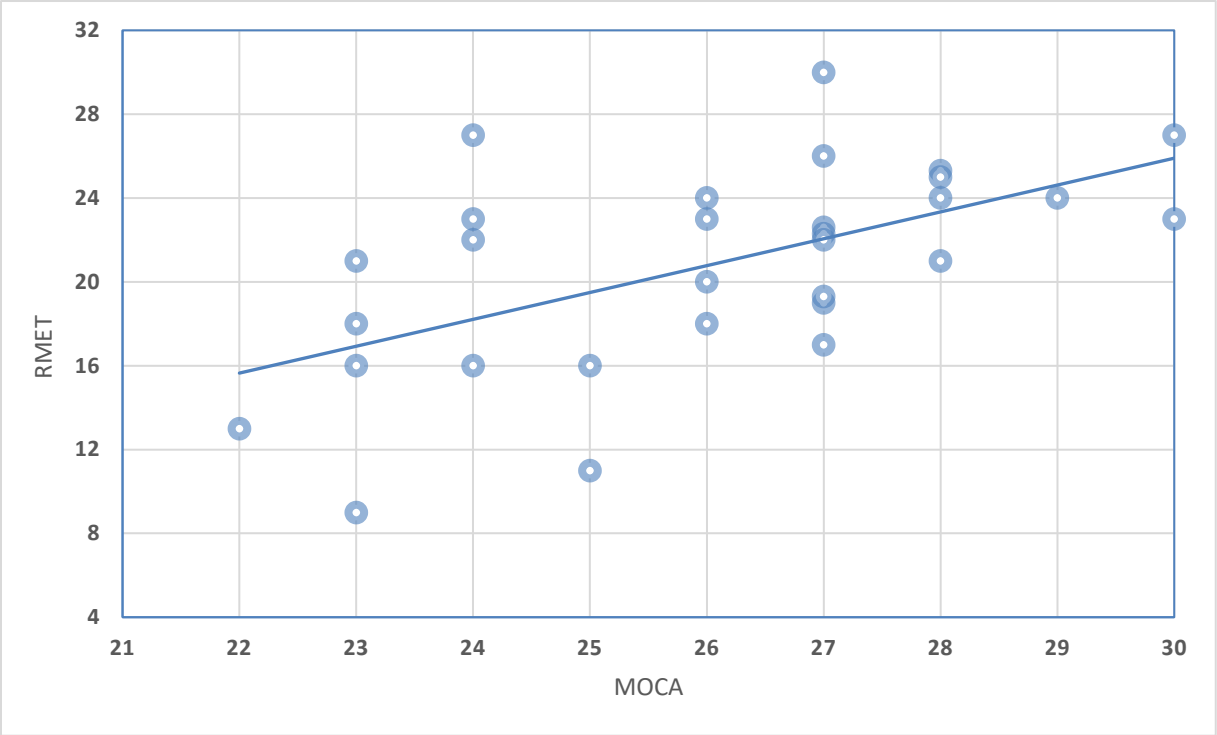

Figure 6: shows effect pilot created using R. The x-axis represents the MoCA (general cognitive screening tool), and the y-axis shows the RMET scores. The central blue line indicates a positive linear trend, suggesting that RMET scores increase as MoCA score increases.

Additional Analysis (Akaike Information Criterion (AIC) to choose the best model)

In order to apply AIC, I included intercept only model as a first model then disease duration, MoCA, and EDSS score as a single predictor in different models. In addition, I performed multiple regressions with and without interaction models where social cognition tests (FPRT, RMET, FEI, FED) were dependent variables and disease duration, MoCA, and EDSS scores were independent variables to see their joint effect on social cognition tests. Each social cognition test is tested separately with AIC analyses, I will mention each test one by one in the following paragraphs.

AIC Analysis for FPRT:

Model	Formula	df	AIC
m1	Intercept-only model	2	204.67
m2	FPRT ~ Duration	3	205.71
m3	FPRT ~ MoCA	3	197.36
m4	FPRT ~ EDSS scores	3	206.07
m5	FPRT ~ Duration + MoCA + EDSS scores	5	201.21
m6	FPRT~ Duration * MoCA * EDS scores	9	208.12

Note: AIC = Akaike's Information Criterion; df = degrees of freedom.

The Akaike Information Criterion (AIC) states that within a group of models the one with the lowest AIC value is the most accurate in representing the data among other models. It has the smallest entropy when we compared it to the unknown "true" model (Leitner & Turner, 2017). For this analysis, the AIC values revealed that m3 (MoCA only model) is the best model because it has the lowest value (AIC = 197.36). Since regression analysis of FPRT and MoCA is taking place in page 62, I will not present it in this section.

AIC Analysis for RMET:

Model	Formula	df	AIC
m7	Intercept-only model	2	182.65
m8	RMET ~ Duration	3	181.37
m9	RMET ~ MoCA	3	173.04
m10	RMET ~ EDSS scores	3	180.89
m11	RMET ~ Duration + MoCA + EDSS scores	5	175.45
m12	RMET~ Duration * MoCA * EDS scores	9	179.00

In this analysis, the AIC values revealed that m9 (MoCA only model) is the best model because it has the lowest value (AIC = 173.04). Since regression analysis of RMET and MoCA is also taking place in page 64, I will not present it in this section.

AIC Analysis for FEI:

Model	Formula	df	AIC
m13	Intercept-only model	2	138.24
m14	FEI~ Duration	3	139.62
m15	FEI ~ MoCA	3	133.63
m16	FEI ~ EDSS scores	3	139.46
m17	FEI ~ Duration + MoCA + EDSS scores	5	132.29
m18	FEI~ Duration * MoCA * EDS scores	9	131.86

In this analysis, the AIC values revealed that m18 (Multiple regression with interaction model) is the best model because it has the lowest value (AIC = 131.86). I will present the results of this regression model in the following paragraph in detail.

	Dependent variable:
	FEI
Duration	1.680
	(1.269)
MoCA	0.818
	(0.591)
EDSS.scores	−10.609
	(7.744)
Duration:MoCA	−0.068
	(0.049)
Duration:EDSS.scores	0.095
	(0.402)
MoCA:EDSS.scores	0.420
	(0.290)
Duration:MoCA:EDSS.scores	−0.003
	(0.015)
Constant	−10.015
	(16.259)
Observations	30
R^2	0.493
Adjusted R^2	0.332
Residual Std. Error	1.885 (df = 22)
F Statistic	3.056* (df = 7; 22)
p-value (overall model)	0.02
Note:	*p<0.05; **p<0.01; ***p<0.001

Table 21

The overall model is statistically significant so we can reject the null hypothesis which states there is no relationship between FEI and at least one of the predictors. F (3,06) = 7, 22, p = .02. The adjusted r square is 0.33 so it explains %33 of the variance, that's why we can say that the model fits well with the data but it's improvable. However, none of the individual predictors or interaction terms reached statistical significance. The coefficient for Duration was (beta= 1.68, t= 1.32, p=.19); for MoCA, (beta= 0.81, t= 1.38, p= .18); and for EDSS

scores, (beta= -10.61, *t*= -1.37, *p*=.18). The interaction between Duration and MoCA was (beta= -12.26, *t*= -1.34, *p*= .19); between Duration and EDSS scores, (beta= 0.09, *t*= .24, *p*=.81) between MoCA and EDSS scores, (beta= 0.42, *t*= 1.45, *p*= .16); and the three-way interaction between Duration, MoCA, and EDSS scores is (beta= -0.002, *t*= -0.17, *p*= .86).

AIC Analysis for FED:

Model	Formula	df	AIC
m19	Intercept-only model	2	140.27
m20	FED~ Duration	3	136.86
m21	FED ~ MoCA	3	137.36
m22	FED ~ EDSS scores	3	137.13
m23	FED ~ Duration + MoCA + EDSS scores	5	136.45
m24	FED~ Duration * MoCA * EDS scores	9	141.35

In this analysis, the AIC values revealed that m23 (Multiple regression without interaction model) is the best model because it has the lowest value (AIC = 136.45). I will present the results of this regression model in the following paragraph in detail.

	Dependent variable:
	FED
Duration	−0.073
	(0.053)
MoCA	0.256
	(0.202)
EDSS.scores	−0.393
	(0.336)
Constant	20.531**
	(5.738)
Observations	30
R^2	0.279
Adjusted R^2	0.196
Residual Std. Error	2.139 (df = 26)
F Statistic	3.354* (df = 3; 26)
p-value (overall model)	0.03
Note:	*p<0.05; **p<0.01; ***p<0.001

Table 22

The overall model is statistically significant so we can reject the null hypothesis which states there is no relationship between FED and at least one of the predictors. *F* (3,35) = 3, 26, *p* = .03. The adjusted r square is 0.19 so it explains %19 of the variance, that's why we can say that the model fits well with the data but it's improvable. Examining the individual predictors, the intercept was significantly different from zero (beta=20.53, *t*=3.58, *p*= .001). However, none of the predictors reached statistical significance. The coefficient for Duration was (beta= 0.07, *t*= -1.37, *p*= .18); for MoCA, (beta= 0.25, *t*= 1.27, *p*= .21); and for EDSS scores, (beta= -0.39, *t*= -1.17, *p*= .25).

Additional analysis of FPRT subsections

Independent Samples T-Test

	Test	Statistic	df	p	Cohen's d	SE Cohen's d
Intentionality Q.	Student	8.195	58.000	< .001	2.116	0.376
	Welch	8.195	41.289	< .001	2.116	0.376
FP Correct Detection	Student	6.036	58.000	< .001	1.558	0.327
	Welch	6.036	32.870	< .001	1.558	0.327
Control Stories (TCS)	Student	NaN	[a]			
	Welch	NaN	[a]			
Affective ToM Q.	Student	5.619	58.000	< .001	1.451	0.319
	Welch	5.619	38.488	< .001	1.451	0.319

[a] the variance in Control Stories (TCS) is equal to 0 after grouping on Groups

Table 23

Independent sample t-test was conducted to see is there a difference between RRMS and HC group in subsections of FPRT test. Firstly, in the Intentionality Question, there is a significant difference between the HC group and the RRMS group where RRMS group significantly outperformed, t (41) = 8.19, p < .001, (Cohen's d = 2.116). Similarly, for the FP Correct Detection, the t-test reveals a significant difference between the two groups, t (32) = 6.04, p < .001, (Cohen's d = 1.56). Also, in the Affective ToM Question, the RRMS group also scored significantly lower which is indicating a significant difference, t (38) = 5.62, p < .001, (Cohen's d = 1.45).

However, the results for the Control Stories (TCS) do not show a significant difference between the HC and RRMS groups, and since the variance in TCS us equal to 0, we are not able to display results for that subsection of the FPRT test.

Group Descriptives

	Group	N	Mean	SD	SE	Coefficient of variation
Intentionality Q.	HC	30	4.600	0.675	0.123	0.147
	RRMS	30	2.233	1.431	0.261	0.641
FP Correct Detection	HC	30	4.833	0.379	0.069	0.078
	RRMS	30	3.167	1.464	0.267	0.462
Control Stories (TCS)	HC	30	10.000	0.000	0.000	0.000
	RRMS	30	9.733	1.015	0.185	0.104
Affective ToM Q.	HC	30	4.533	0.629	0.115	0.139
	RRMS	30	2.833	1.533	0.280	0.541

Table 24

In the Intentionality Question, HC group's mean score is 4.6 (*SD*=0.675) while RRMS group scored significantly lower with a mean of 2.23 (*SD*=1.43). This difference is also can be seen when we look at the coefficient of variation scores for RRMS (0.641) compared to the HC group (0.147), so we can see that variation is higher in RRMS group. When it comes to the FP Correct Detection the HC group's mean score is 4.83 (*SD* = 0.379) and RRMS group's mean is 3.17 (*SD* = 1.46), with the RRMS group again displaying more variability (coefficient of variation of 0.462). On the other hand, Control Stories (TCS) did not show significant differences, with the HC group's mean score of 10.00 (*SD* = 0.000) and the RRMS group's mean score is 9.73 (*SD* =1.015). However, in the Affective ToM Question, the HC group has the mean score of 4.53 (*SD* = 0.629) compared to 2.83 (*SD* = 1.53) for the RRMS group, with the RRMS group again displaying more variability once again (coefficient of variation of 0.541).

Additional Correlation Analyses

Pearson's Correlations

Variable		Age_RRMS	Disease Duration	EDSS scores	MoCA
1. Age_RRMS	Pearson's r	—			
	p-value	—			
2. Disease Duration	Pearson's r	0.686	—		
	p-value	< .001	—		
3. EDSS scores	Pearson's r	0.352	0.375	—	
	p-value	0.057	0.041	—	
4. MoCA	Pearson's r	-0.372	-0.311	-0.360	—
	p-value	0.043	0.094	0.050	—

Table 25

Pearson's correlation analysis was conducted to see whether confounding variables such as age, disease duration (in years), disability levels (EDSS scores), and MoCA scores are correlated with each other. As we can see from *'Table 32'*, RRMS patients' age revealed strong positive correlation with disease duration (r=0.686, p<.001), and it also revealed negative correlation with MoCA scores of RRMS patients (r=0.372, p=.043). On the other hand, disease duration and disability level (EDSS scores) showed a significant moderate positive correlation (r=0.375, p=.041). Lastly, a significant negative correlation was found between MoCA and EDSS scores (r=0.360, p=.05).

Pearson's Correlations

Variable		MoCA_HC
1. MoCA_HC	Pearson's r	—
	p-value	—
2. FPRT	Pearson's r	0.023
	p-value	0.904
3. RMET	Pearson's r	0.604
	p-value	< .001
4. FEI	Pearson's r	0.070
	p-value	0.715
5. FED	Pearson's r	0.277
	p-value	0.139

Table 26

Pearson's correlation analysis was conducted to see the relationship between global cognitive functioning measured by MoCA and social cognitive functioning of HC group. As we can see from *'Table 33'*, only RMET and MoCA revealed strong positive correlation with each other (r=0.604, p<.001).

Discussion

The main aim of this thesis study is to investigate social cognitive functioning in adults with RRMS compared to HCs. To be more specific, the project sought to assess emotion recognition skills (particularly facial emotion recognition) in both RRMS and HC groups, ToM (both affective and cognitive components) in RRMS and HC groups, and whether other confounding variables such as disease duration, disability level, and MoCA scores interfere with social cognitive functioning in RRMS groups. Finally, one of the primary goals of this study is; providing data to support the development of new interventions aimed at improving the quality of life for people with MS, as well as to gain a better understanding of how social cognition is affected or damaged in MS patients.

When it comes to summarizing key findings, firstly; I stated in the first hypothesis individuals with RRMS will exhibit significant deficits in facial emotion recognition (which is assessed by FEI and FED tests) compared to the HC group. In order to test this hypothesis, independent sample t-test was conducted to assess differences between healthy and patient groups. Results revealed that there is a significant difference between RRMS and HC groups' FEI scores. As we can see in the *Table 3*, RRMS groups' mean score is 11.83, and HC groups' mean score is 14.33. When we look at the reliability and validation study of FEI and

FED tests on Turkish population by Erol et al., schizophrenia patients' mean score on FEI test was 10.3, and healthy groups' mean score was 12.9 (Erol et al., 2009). We need to take into account demographic features of these two cohorts where we can see the difference in terms of age, sex, education. Even though mean age is higher in this cohort (RRMS=45.33, HC=44.83) compared to the cohort in the study by Erol et al. (patient group=35.6, healthy group=35.9), there is a considerable difference in education years between the current study (RRMS=12.03, HC=11.07) and Erol et al.'s study (patient group=8.5, healthy group=8.6). It seems despite a difference in age among these two cohorts, higher education level in the current study may lead better performance in FEI compared to the cohort participated in Turkish reliability and validation study. This assumption can be supported by previous studies, like study by De Souza and colleagues. Their study results revealed that education appears to have an impact on facial recognition accuracy. They discovered that participants with higher levels of education outperformed those with lower levels (De Souza et al., 2018).

When it comes to results of FED test, independent sample t-test results revealed that there is no significant difference on FED scores between RRMS and HC group. RRMS groups' mean score is 25.03, and HC groups' mean score is 26.33. When we look at the reliability and validation study of FEI and FED tests on Turkish population by Erol et al., schizophrenia patients' mean score on FEI test was 22.9, and healthy groups' mean score was 26. As we can see mean score of HC groups between two cohorts are almost same, while patient groups are not but since we are encountering completely two different diseases (RRMS vs. Schizophrenia) and education level is considerably higher in the cohort of the current study, we can pursue the difference between patients' groups FED scores as expectable.

Overall, we can partially accept the first hypothesis since RRMS group exhibited deficits only in FEI test where they need to identify six primary emotions (these are; joy, sadness, anger, fear, surprise, and shame). Similar results are maintained by other studies too; such as a

study by Berneiser et al. and colleagues investigated impaired recognition of emotional facial expressions in patients with MS and they found that MS group performed significantly worse than HC group in the task of naming five basic emotions. However, their cohort also revealed significant difference in facial emotion discrimination task where subjects were asked to indicate whether the faces presented on two cards depict the same or different emotions (Berneiser et al., 2014). Nevertheless, we need to take into account that different neuropsychological batteries were applied to assess facial emotion discrimination abilities between two groups and even though there is no significant difference, RRMS group performed slightly worse in FED test compared to HC group for the current cohort.

In the second hypothesis, I declared that ToM abilities, as assessed by the FPRT and RMET, will be impaired in individuals with RRMS compared to the HC group. In order to test this hypothesis, independent sample t-test was conducted again to see if there is any difference between RRMS and HC groups. Results for FPRT test revealed that RRMS group scored significantly lower with a mean of 13.53, while HC group mean was 26.43. When we look at the Turkish adaptation of FPRT, the mean score for the short version of the test was 21.87. The cohort's age range was 32.52 and the mean duration of education was 13.13 in year (Şandor & İşcen, 2021). Since their sample size is considerably higher (N=420) compared to the current study's sample size (N=30 for HC group), we may understand the relatively higher mean score in FPRT scores of HC group in the current study.

From the results we can see that RRMS group considerably outperformed in FPRT compared to HC group. However, in the analysis I measured total or global score of FPRT test and total score includes intentionality, affective ToM, Faux-Pas correct detection (FPS) questions, as well as total score of control stories (TCS). Several studies investigated detailed analysis of FPRT test for their own samples and most of them found impairment in one or more subsections of the test. For instance, Henry et al discovered that the patients performed

significantly worse only on the intention-related questions presented after the Faux Pas stories. This suggests that the MS patients correctly identified the faux pas but misinterpreted it as an intentional utterance (Henry et al., 2015). In the current study, intentionality question, affective ToM, FPS were revealed significant difference between RRMS and HC group, whereas TCS was not revealed any statistically significant difference.

When it comes to RMET test; independent sample t-test results revealed that there is a significant difference on RMET scores between RRMS and HC group. RRMS groups' mean score is 20.77, and HC groups' mean score is 24.50. In the Turkish validation of RMET test, their cohort's mean score was 23.64 (Yıldırım et al., 2011) so mean scores of RMET test for the current study (for HC) and validation study are considerably close to each other. When we take into account RRMS group's mean score, we can see that they performed worse than both current study's HC group and validation study. Hence, we can consider some impairment in the affective aspects of the ToM abilities which are assessed by RMET. Several studies maintained the results which supports the current study's findings; for instance, study by Garcia et al. used reduced version of RMET test on MS and HC and they found significant difference between MS and HC groups' RMET scores (Garcia et al., 2018). Other very similar results were maintained by Zahraie et al and colleagues in 2018 when they were investigating the relationship between RMET and executive functions between MS and healthy participants. They found significant difference between MS and control groups in RMET, as well as significant difference in executive functioning (Zahraie et al., 2018). Overall, we can say that, our findings for both FPRT and RMET are matching with studies conducting on this topic even though neuropsychological batteries are not complement each other fully because of language adaptation studies or different variations of the same tests.

In the third hypothesis I stated that individuals with RRMS will demonstrate specific difficulties in recognizing negative emotions (e.g., anger, fear) compared to positive emotions

(e.g., happiness, surprise) in facial expressions that will be assessed by FEI test. In order to test this hypothesis MANOVA was performed for negative and positive emotion categories. Also, ANOVA was performed to see the difference between RRMS and HC group for each specific basic emotion. Results revealed that there is significant difference in recognizing negative and positive emotions between RRMS and HC group where RRMS patients showed difficulties in identifying negative emotions. Significant difference was seen in fear, sadness and anger, whereas no significant results maintained for shame, surprised, and happiness between two groups. A study by Henry et al. revealed similar results to those of the current study; recognition of fear and anger were disrupted for their MS group while no significant differences were found for recognition of surprise, happiness, sadness, or disgust (Henry et al., 2009). These findings align with previous research indicating that white matter pathology (such as MS) can disrupt both cognitive function and social perceptual abilities.

Banati et al, declared that the duration of the disease, level of disability, and cognitive impairment in RRMS are all important variables to understand the MS. Furthermore, clinical characteristics such as disease duration or level of disability have only moderate correlation. Exploring the relationship between social cognition and other cognitive functions in MS, taking into account the clinical features of the disease, appears necessary to deepen our understanding of social cognition deficits in RRMS (Banati et al., 2010). That's why one of the crucial points for this study was investigating the impact of disease duration, EDSS scores, and MoCA on social cognitive functioning of RRMS patients. In the upcoming paragraphs I will provide the results maintained to prove following hypotheses.

Fourth hypothesis states that there will be a significant linear relationship between the duration of RRMS (measured in years) and social cognitive functions, indicating that as the disease duration increases, social cognitive abilities will decline. In order to test this hypothesis linear regression analyses were conducted and results revealed that there is no

significant relationship between disease duration and FPRT, RMET, and FEI tests, whereas results showed significant relationship between disease duration and FED scores, indicating that as disease duration increases, RRMS patients' performance on FED test deteriorates. A study conducted by Sonia Batista and colleagues also did not find significant relationship between disease duration and ToM test scores of MS patients (Batista et al., 2018). This might explain why current study also did not reveal significant results for ToM tests (FPRT, RMET) in RRMS group. Another study by Dulau et al. used Faux Pas task and RMET, facial emotion recognition, emotional awareness, emotional fluency, and alexithymia tests to measure social cognitive functions of RRMS, SPMS (secondary progressive MS), and PPMS (primary progressive MS). They found no significant correlation between disease duration and any of the social cognition tests listed above (Dulau et al., 2017). On the other hand, contradictory results are also existed in literature; for instance, a study by Banati et al. in 2010 found significant difference between disease duration and RMET test but this difference was found when they compared HC and Long-term MS patients (≥7 years of disease duration) (Banati et al., 2010). However, Faux Pas test and face test did not reveal significant relationship with disease duration in their study, so further analysis might be need in this aspect of the study.

When it comes to fifth hypothesis, I declared there will be a significant linear relationship between the Expanded Disability Status Scale scores, reflecting the level of disability in RRMS, and social cognitive functions. Higher EDSS scores will be associated with poorer social cognitive performance in both ToM tests and facial emotion recognition tests. In order to prove this hypothesis once again I conducted linear regression analysis with four models for four different tests (FPRT, RMET, FEI, and FED). The results showed that only the FED test had significant results with the EDSS score, indicating that as the EDSS score increases, the performance of RRMS patients on the FED test declines. There are several studies which found similar results with the current study.

For instance, a study by Neuhaus et al conducted a study with MS patients and they used Geneva Social Cognition scale (GeSoCS) (Martory et al., 2016) to measure social cognitive functioning of HC and MS groups. The test includes Faux Pas task, short version of RMET, facial affect recognition task and others. Their results revealed no significant relationship between any of the social cognition tasks in GeSoCS and EDSS scores of the MS patients (Neuhaus et al., 2018). Other related results were maintained by Henry et al. in 2017 when they found no significant correlations between social cognition measures (emotion recognition and ToM tasks) and clinical characteristics like disease duration and EDSS scores (Henry et al., 2017). As we can see, both of these studies did not measure discrimination abilities of emotions which is assessed by FED test in this study. However, other social cognition tests match with the current study and show complementary results with each other.

Two last hypothesis of this thesis project was mainly stated to investigate the relationship between social cognitive functions and overall cognitive functioning (measured with MoCA). Since social cognition tests has two categories in the current study: ToM tests (FPRT, RMET) and facial emotion recognition tests (FEI, FED), I formulized two separate hypotheses to understand this relationship between two main phenomena.

In the sixth hypothesis, I declare that there will be a positive linear relationship between FEI and FED; and MoCA scores in individuals with RRMS, indicating that better facial emotion recognition is associated with higher cognitive function as measured by the MoCA. In order to test this hypothesis linear regression analysis was conducted and results revealed that both FEI and FED test showed significant relationship with MoCA score of RRMS patients. Many studies in the literature found significant association between social cognition and MoCA with various neurodegenerative disorders including MS. For example; study by Carvalho et al. conducted a study to assess facial emotion recognition abilities of AD patients and they found that fear which is one of the most impaired basic emotions in almost all

neurodegenerative diseases showed significant positive correlation with AD patients' MoCA scores, in other way lower MoCA score indicates lower fear recognition ability among patients with Alzheimer disease. When it comes to MS population, quiet recent study published by Sever Aktuna et al in 2024 when they found significant positive correlation between FEI and FED tests and MoCA scores in RRMS patients (Sever Aktuna et al., 2024). Another complementary result was found by Montembeault et al in 2022 on MS population where they compared young and old MS population with HCs in order to investigate social cognition abilities. They found that multimodal emotion recognition (which includes facial emotion pictures and vocal emotional burst with to identify seven emotions) has significant positive relationship with MoCA scores of MS patients (Montembeault et al., 2022). Based on the previous and current study's findings we can conclude that there is a positive and significant relationship between facial emotion recognition abilities and global cognitive impairment assessed by MoCA.

Finally, in the last hypothesis I declared that there will be a positive linear relationship between Faux-Pas Recognition Test and Reading the Mind in the Eyes Test scores; and MoCA scores in individuals with RRMS, suggesting that better ToM abilities are associated with higher cognitive function as measured by the MoCA. For the purpose of prove the hypothesis, linear regression analysis was performed and results revealed that both FPRT and RMET tests showed significant and positive relationship with MoCA scores in the RRMS group. Findings indicate that RRMS patients who have some global cognitive impairment, performed poorly in both affective and cognitive ToM tests as stated in seventh hypothesis. Similar results are maintained by different studies conducted in this area; for instance, study by Isernia et al. examined the affective and cognitive ToM abilities on the patients with different MS phenotypes on 2019. Results of their study showed that both affective and cognitive ToM tests revealed significant relationship with MoCA and other cognitive

screening tools like Spatial Recall Test, Symbol Digit Modalities test and others (Isernia et al., 2019). Considerably recent study is conducted by Isernia et al once again in 2022 to investigate neuro correlates of ToM deficits. This time their MS cohort showed significant relationship between cognitive aspect of ToM and MoCA score, on the other hand affective ToM was not correlated with global cognitive impairment (Isernia et al., 2022). As a result, based on the findings of the previous studies and the current study, we can conclude that better cognitive functioning indicates better ToM abilities in the majority of the MS cohorts.

Conclusion

Despite the promising findings provided by this study, the current study has some limitations. Firstly, the relatively small sample size ($N = 30$ for each group) may limit the generalizability of the results, as a larger cohort would offer more statistical power, especially in the regression analysis to detect relationship between variables. Secondly, the cross-sectional design of the study can be another limitation even though it is useful for identifying correlations, does not allow for the establishment of causal relationships between disease progression and social cognitive decline in RRMS patients. Hence longitudinal studies are may be more accurate to assess the changes that might occur with disease progression over time. Moreover, although this study assessed key aspects of SC, it was limited to specific tests (FEI, FED, FPRT, RMET). Including other SC tests, particularly video based Faux-Pas tests could provide a more comprehensive understanding of these deficits in RRMS since written Faux Pas scenarios requires reading and working memory overload. Additionally, some other potential confounding variables such as fatigue and medication use which are very common in RRMS were not fully accounted for and they are potentially influencing social cognitive functions in RRMS patients. Also, the cultural and linguistic adaptations of SC tests like

RMET and FPRT may lead variations in performance, as cultural differences in interpreting facial expressions or Faux Pas scenarios could have influenced the findings and impacted reliability of the results. Lastly, some additional analysis might be needed to disentangle the role of general cognitive functioning (MoCA) since all SC tests revealed significant positive linear relationship with MoCA test results in the patient group (RRMS). Future studies may consider these limitations and try to improve study designs according to them.

In conclusion, the results of this study suggest that RRMS patients exhibited impairment in both affective and cognitive aspects of ToM, and impairment in emotion recognition abilities among RRMS patients, especially in emotion identification task (naming 6 primary emotions). Findings of this thesis project contribute the literature on social cognitive functions in MS and emphasizing the importance of ToM and emotion recognition deficits in RRMS patients. Although, only FED test showed association with disease related factors such as; disease duration and disability level of patients (EDDS score), we still need to consider them as important confounding variables which may have potential impact on social cognition abilities. Also, impairments observed in social cognition for this cohort were associated with general cognitive functioning of RRMS patients. These results align with existing studies and offering us valuable insights into the challenges faced by RRMS patients in social cognitive functioning which may impact their daily social interactions and overall quality of life. Moreover, the significant relationship between social cognitive functioning and global cognitive functioning suggest that interventions aimed at improving cognitive function may have a beneficial impact on the social cognitive abilities of individuals with RRMS. Future research should further explore these relationships and investigate potential interventions that can address impairment in both social cognition and global cognitive functioning.

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