King Saud University

College of Applied Medical Sciences

Rehabilitation of Health Sciences Department

Association Between Cognitive Impairment and Motor Dysfunction Among Patients with Multiple Sclerosis in Saudi Arabia: A Cross-Sectional Study

الإرتباط بين ضعف الإدراك والإختلال الحركي لدى مرضى التصلب العصبي المتعدد في المملكة العربية السعودية: دراسة عرضيه مستقطعه

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IV. Abstract

Introduction: Multiple sclerosis (MS) contributes to various signs and symptoms, particularly physical and cognitive impairments that negatively impact the quality of life. Previous studies found that motor impairment relates to mild cognitive impairment in some neurological diseases. The association between cognitive impairment and motor dysfunction in patients with MS was not addressed.

Aim: To address the association between cognitive impairment (CI) and motor dysfunction (MD) among patients with MS.

Methods: Sixty-eight patients with multiple sclerosis aged between (18 and 65 years) were included in this study to find the association between CI and MD. Cognitive impairment was assessed by using the Montreal Cognitive Assessment Scale. Motor dysfunction was assessed using the Handheld dynamometer for muscle strength, while postural balance, gait, and risk of fall have been assessed using Tinetti scale. Also, motor coordination was assessed in both upper and lower extremities through the Timed Rapid Alternating Movement for Upper Extremity and Timed Alternate Heel-to-Knee Test for lower extremity.

Results: Significant association was found between cognitive impairment presented by MoCA score and the scores of motor coordination, balance, gait, and risk of fall ($p < 0.005$) except muscle strength. Also, MoCA has shown significant, but weak correlations with all gait parameters (step length, foot clearance, step symmetry, step continuity, path deviation, trunk sway, walk stance) (p

< 0.005) apart from gait initiation. Stepwise multiple linear regression showed that the risk of fall may be considered as a predictor of cognitive impairment among patients with multiple sclerosis.

Conclusion: Overall, this study concludes that cognitive impairment is significantly associated with motor coordination, balance, gait, and risk of fall. Also, the risk of fall emerged as the best predictor of cognitive impairment among MS population.

Keywords: multiple sclerosis, motor dysfunction, cognitive impairment

الملخص

المقدمة: يساهم التصلب العصبي في ظهور عدة علامات وأعراض مختلفة منها ضعف الإدراك واختلال الحركة مما يؤثر سلباً على جودة الحياة لدى المرضى المصابين به. أثبتت الدراسات السابقة وجود علاقة بين الإختلال الحركي وضعف الإدراك البسيط لدى المرضى المصابين ببعض الأمراض العصبية ولكن لم تثبت الدراسات حتى الآن وجود علاقة بينهما لدى مرضى التصلب العصبي المتعدد.

أهداف البحث: لدراسة العلاقة بين ضعف الإدراك والإختلال الحركي لدى مرضى التصلب العصبي المتعدد الإنتكاسي.

منهجية البحث: دراسة مستقطعة لبحث الإرتباط بين الضعف الإدراكي والإختلال الحركي لدى 68 مريض بالتصلب العصبي المتعدد من عمر 18 إلى 65 سنه. تم تقييم ضعف الإدراك باستخدام مقياس مونتريال لتقييم الإدراك، في حين تم تقييم قوة العضلات باستخدام جهاز الديناموميتر، تقييم التوازن والمشي وخطر السقوط باستخدام مقياس تينتي، وتقييم التناسق الحركي للأطراف العلوية والسفلية.

النتائج: أظهرت النتائج وجود ارتباط ذو أهمية إحصائية بين ضعف الإدراك والمتمثل في نتيجة اختبار المونتريال والإختلال الحركي المتمثل بنتائج الإختبارات الحركية ($p < 0.005$) باستثناء اختبار قوة العضلات. كذلك أظهرت النتائج ارتباطات لكن ضعيفة بين اختبار المونتريال وخصائص المشي ($p < 0.005$) باستثناء خاصية التردد عند بدء المشي والتي لم تظهر أي ارتباط. بالإضافة أظهر الإنحدار الخطي المتعدد التدريجي خطر السقوط كمؤشر للضعف الإدراكي لدى مرضى التصلب العصبي المتعدد.

الخلاصة: توصلت هذه الدراسة إلى أن ضعف الإدراك مرتبط بشكل كبير بالتناسق الحركي والتوازن والمشي وخطر السقوط. أيضًا ، ظهر خطر السقوط كأفضل مؤشر للضعف الإدراكي بين المصابين بمرض التصلب العصبي المتعدد.

الكلمات المفتاحية: التصلب العصبي المتعدد، الإختلال الحركي، ضعف الإدراك

V. List of Abbreviations

MS	Multiple Sclerosis
CNS	Central Nervous System
KSA	Kingdom of Saudi Arabia
RRMS	Relapse Remitting Multiple Sclerosis
SPMS	Secondary Progressive Multiple Sclerosis
PPMS	Primary Progressive Multiple Sclerosis
PRMS	Progressive Relapsing Multiple Sclerosis
CI	Cognitive Impairment
MI	Motor Impairment
QOL	Quality of Life
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
BICAMs	a Brief International Assessment of Cognition for MS
MACFIMS	90-min Minimal Assessment of Cognitive Function in MS
UVB	Ultraviolet B Radiation
HHD	Handheld dynamometry
naMCI	Non-amnestic MCI
mdMCI	Multi-domain MCI
no-MCI	Individuals without MCI
APAs	Anticipatory postural adjustments
WHO	World Health Organization
POMA	Tinetti Performance Oriented Mobility Assessment
BPOMA	Balance Performance Oriented Mobility Assessment
GPOMA	Gait Performance Oriented Mobility Assessment
BBS	Berg Balance Scale
IRB	Institutional Review Board

VI. Definition of Terms

Executive Functioning: "A set of general-purpose control mechanisms, often linked to the prefrontal cortex of the brain, that regulate the dynamics of human cognition and action" (Miyake & Friedman, 2012).

Attention: "It is the taking possession by the mind in clear and vivid form of one out of what seem several simultaneous objects or trains of thought" (Posner, 1994).

Visuospatial skills: "Ability in manipulating visual patterns, as indicated by level of difficulty and complexity in visual stimulus material that can be handled successful, without regard to the speed of task solution" (Lohman, 1979).

Working memory: "The capacity to hold information briefly in memory while performing other mental operations on the information" (Mirsky, Fantie, & Tatman, 1995).

Verbal fluency: "A cognitive function that facilitates information retrieval from memory" (Mapstone, 2005).

Amnestic mild cognitive impairment (aMCI): "The memory loss is predominant, and it is associated with high risk to further conversion to AD" (Grundman et al., 2004).

Non-amnestic mild cognitive impairment (naMCI): "Individuals with naMCI have impairments in other domains than memory and have a higher risk to convert to other dementia forms such as diffuse Lewy body dementia" (Csukly et al., 2016).

Anticipatory postural adjustments: "The activation of postural muscles in a feedforward manner before a voluntary movement begins, in anticipation of the destabilizing forces caused by the movement" (Woollacott, 2009).

Information processing: "The ability to maintain and manipulate information in the brain for short time period and to the speed with which one can process that information" (Guimarães & Sá, 2012).

Abstract/conceptual reasoning: "The ability of information analysis, detecting pattern and relation, and solving problems on complex level (Datta & Roy, 2015).

Spatial orientation: "The process of integrating and interpreting sensory information to estimate one's orientation and self-motion" (Clark, Newman, Karmali, Oman, & Merfeld, 2019).

1. Introduction

1.1 Background

Multiple sclerosis (MS) is an inflammatory immune-mediated disease of the central nervous system (CNS) (Dobson & Giovannoni, 2019; Frohman, Racke, & Raine, 2006; Gelfand, 2014). It affects about 2.8 million people worldwide (Walton et al., 2020) and 40.4/100,000 at KSA in 2018 (AlJumah et al., 2020). It is common in young adults and in females more than males approximately (3:1) in most developed countries (Dobson & Giovannoni, 2019).

The pathological sign of MS is demyelinating plaques located in the grey and white matter of the brain and spinal cord that lead to neuronal demyelination (Karussis, 2014; Popescu, Pirko, & Lucchinetti, 2013). These plaques result when T cells enter the CNS and react with myelin antigens, leading to inflammatory demyelination, axonal loss, increase lymphocytes and macrophages infiltration, reduction of oligodendrocytes, and astrocytes proliferation and gliosis (Frohman et al., 2006; Huang, Chen, & Zhang, 2017).

The course of MS is characterized by intermittent episodes of neurological dysfunction and vary into different forms such as Relapse-Remitting (RRMS), Secondary Progressive (SPMS), Primary Progressive (PPMS), and Progressive Relapsing (PRMS) (Dobson & Giovannoni, 2019; F. D. Lublin, 2005; Fred D. Lublin & Reingold, 1996). The neurodegenerative nature of the disease contributes to various signs and symptoms that are differ from patient to patient and result from sensory, motor, and autonomic dysfunctions (Doshi & Chataway, 2016; Huang et al., 2017).

The clinical manifestations of MS may involve numbness, urinary/bowel problems, ataxia, tremor or dysmetria, vision disturbance, cognitive impairments (CI), and motor impairments (MI)

(Gelfand, 2014; Huang et al., 2017; Kurtzke, 1983). Motor and cognitive problems are the most common symptoms in patients with MS that negatively impact their quality of life (QOL) (Amato, Prestipino, & Bellinvia, 2019).

Motor dysfunction is one of the most important primary symptoms in patients with MS resulting from demyelination of central nervous system (CNS) (Schapiro, 1994). These symptoms include mobility problems, muscle weakness, spasticity, incoordination, and balance dysfunction (Huang et al., 2017; Schapiro, 1994). Subsequently, about 41% of patients with MS have walking disturbances that increase the chance of the risk of fall (M. L. Finlayson, Peterson, & Cho, 2006) and affect their daily living (N. G. Larocca, 2011). Approximately, 45% of patients with MS may use assistive equipment among their lives, such as cane, crutches, walker, and wheelchairs to facilitate their mobility (M. Finlayson, Guglielmello, & Liefer, 2001).

Cognitive impairment is another most common problem that may occur in patients with MS, its prevalence was ranged from 43% to 65% (S. M. Rao, G. J. Leo, L. Bernardin, & F. Unverzagt, 1991). It varies in severity between mild to severe and often present in all types of MS (Bagert, Camplair, & Bourdette, 2002). Furthermore, the most affected domains are executive dysfunction, lack of attention, loss of memory, and slow information processing (Chiaravalloti & DeLuca, 2008). Cognitive impairment may disturb social interactions, work participation and activity daily living in patients with MS (Schiavolin et al., 2013). Moreover, cognitive impairments in MS patients could be assessed by different instruments like Mini-Mental State Examination (Rao, 2004), Montreal Cognitive Assessment (MoCA) (S. Freitas et al., 2018), a Brief International Assessment of Cognition for MS (BICAMS) (Sandra Freitas et al., 2018), and 90-min Minimal Assessment of Cognitive Function in MS (MACFIMS) (Sandra Freitas et al., 2018). In this study,

MoCA was used to assess the patients' cognitive function, it is sensitive among patients with MS, easy to administer, and covers all domains of cognitive functions that we need to assess.

1.2 Statement of the Problem

Multiple sclerosis is one of the main factors that have been associated with cognitive impairment. (Bagert et al., 2002; Chiaravalloti & DeLuca, 2008; Rao, 2004). Previous studies found that motor impairment relates to mild cognitive impairment in some neurological diseases (Aggarwal, Wilson, Beck, Bienias, & Bennett, 2006; Franssen, Souren, Torossian, & Reisberg, 1999). According to the best of our knowledge, the association between cognitive impairment and motor dysfunction such as motor incoordination, poor balance, risk of fall, muscle weakness, and abnormal gait pattern in patients with MS was not addressed.

1.3 Aim of the study

To examine the association between cognitive impairment and motor dysfunction among patients with MS in Saudi Arabia.

1.4 Research hypothesis

There is a likelihood that cognitive impairment will be positively correlated with motor dysfunction in patient with MS.

1.5 Significance of the study

Cognitive impairment may disturb motor function in patients with MS, thus understanding the association between them helps clinicians to develop their health care program and plan a beneficial intervention. Clinical assessment of cognitive functions helps to determine the site of impairment and its effect on physical abilities (Benedict et al., 2011; Macias Islas & Ciampi, 2019). For example, executive functions are highly relevant in daily activities as motor performance needs adequate attention, decision making, and visuospatial skills (Benedict et al., 2011; D'Orio et al., 2012).

2. Literature Review

2.1 Definition and Prevalence of Multiple Sclerosis

Multiple sclerosis (MS) is an inflammatory immune-mediated disease targeting the central nervous system (CNS) (Dobson & Giovannoni, 2019; Frohman et al., 2006; Gelfand, 2014). It affects about 2.8 million people worldwide (Walton et al., 2020) and 40.4/100,000 in 2018 at KSA (AlJumah et al., 2020). It is common in young adults aged between 20 and 40 years (Koch-Henriksen & Sorensen, 2010) and in females more than males approximately (3:1) in most developed countries (Dobson & Giovannoni, 2019).

2.2 Aetiology

The precise aetiology of multiple sclerosis is unknown (Bishop & Rumrill, 2015; Lassmann, 2011). However, there are many risk factors like smoking, Vitamin D, Ultraviolet B radiation (UVB) exposure, and previous Epstein–Barr virus infection, in combination with genetic factors can play important roles in developing multiple sclerosis (Bishop & Rumrill, 2015; Dobson & Giovannoni, 2019). In addition, migrant studies shown that those who migrated to a high-risk area before the age of 15, obtain the risk of their new country, whilst those who migrated after age 15 retained the risk of their previous country (Gale & Martyn, 1995; Ramagopalan & Sadovnick, 2011).

2.3 Pathology

The pathological hallmark of MS is focal demyelinating plaques in the grey and white matter of the brain and spinal cord that result in neuronal demyelination (Karussis, 2014; Popescu et al., 2013). These plaques result when T cells enter the CNS and react with myelin antigens, leading to inflammatory demyelination, axonal loss, increase lymphocytes and macrophages infiltration, reduction of oligodendrocytes, and astrocytes proliferation and gliosis (Frohman et al., 2006; Huang et al., 2017). Clinically, the course of MS is characterized by intermittent episodes of neurological dysfunction and vary into different forms such as Relapse-Remitting (RRMS), Secondary Progressive (SPMS), Primary Progressive (PPMS), and Progressive Relapsing (PRMS) (Dobson & Giovannoni, 2019; F. D. Lublin, 2005; Fred D. Lublin & Reingold, 1996). The neurodegenerative nature of the disease contributes to various signs and symptoms that are quite variable from patient to patient and result from sensory, motor, and autonomic dysfunctions (Doshi & Chataway, 2016; Huang et al., 2017). The clinical manifestations of MS may involve numbness, urinary/bowel problems, ataxia, tremor or dysmetria, vision disturbance, cognitive impairments (CI), and motor dysfunction (MD) (Gelfand, 2014; Huang et al., 2017; Kurtzke, 1983). In particular, Physical and cognitive problems are the most common symptoms in patients with MS that negatively impact their quality of life (QOL) (Amato et al., 2019).

2.4 Signs and Symptoms

Multiple sclerosis is classified into four clinical subtypes: (a) relapsing remitting (RRMS), (b) secondary progressive (SPMS), (c) primary progressive (PPMS), and (d) progressive relapsing (PRMS) (Bishop & Rumrill, 2015). Specifically, RRMS is the most common type and

characterized by multiple attacks of neurological function's deterioration followed by period of complete or incomplete recovery (F. D. Lublin, 2005). SPMS is characterized initially by the same course of RRMS followed by gradual progressive worsening of symptoms (F. D. Lublin, 2005). About 50% of RRMS patients develop SPMS after 10 to 15 years (Bishop & Rumrill, 2015; F. D. Lublin, 2005). PPMS affects about 10% of MS patients and characterized by the slow deterioration of neurological functions with no distinct attacks or recovery periods but occasional stability period and minor improvement (Bishop & Rumrill, 2015; F. D. Lublin, 2005). PRMS is comparatively rare, affecting about 6% of MS patients and characterized by a steady progression of the disease from onset with frequent exacerbation of symptoms (Bishop & Rumrill, 2015; F. D. Lublin, 2005).

The symptoms of MS differ noticeably between patients and depends on the site and size of lesions in the CNS (Gelfand, 2014). Further, the most frequent manifestations of MS affect sensory, motor, brain stem, cerebellar, and autonomic functions (Bishop & Rumrill, 2015; F. D. Lublin, 2005). For example, sensory dysfunction may appear as a tingling sensation, painful burning sensation, numbness, reduced sensation, or even loss of sensation (Files, Jausurawong, Katrajian, & Danoff, 2015). Moreover, bladder dysfunction accounts more than 90 percent of MS patients and incontinence episodes occur in one-third of them and affect their social life (Files et al., 2015). Also, the brain stem is usually affected and its most common manifestations include: vertigo (cranial nerve VIII), double vision (cranial nerves III, IV, VI), facial weakness (cranial nerve VII), and bulbar symptoms like dysphagia, dysarthria, and tongue paresis (cranial nerves IX, X, XII) (Gelfand, 2014).

Patients with MS commonly exhibit symptoms like (dysmetria, dysdiadochokinesia, tremor, ataxic gait, and nystagmus) as a result of cerebellar dysfunction (Gelfand, 2014). Although

symptoms like mobility problems, muscle weakness, spasticity, incoordination, and balance dysfunction affect patients with MS at some point in the disease course as a result of motor impairment (Huang et al., 2017; Schapiro, 1994). In addition to the physical impairments, MS patients often experience cognitive decline which negatively affect their social life and employment status (Bishop & Rumrill, 2015; D'Orio et al., 2012).

2.5 Motor Dysfunction

In patients with multiple sclerosis, motor impairments have a wide array of symptoms like muscle weakness, incoordination, tremor, and spasticity that negatively impact their daily life (Heremans, D'Hooge A, De Bondt, Helsen, & Feys, 2012; Johansson et al., 2007; Schapiro, 1994). Particularly, muscle weakness is considered as the most prevalent complaint among MS patients and influences their endurance, functional capacity, and quality of life (QOL) (Kent-Braun et al., 1997). Moreover, it's estimated that muscle weakness occurs in approximately 42% of MS patients at the onset of the disease and rise about 88% during the course of the disease (F. D. Lublin, 2005). Further, muscle weakness in MS resulting from corticospinal tract involvement or due to general deconditioning (Al Wutayd, Mohamed, Saeedi, Al Otaibi, & Al Jumah, 2018; Gelfand, 2014). Therefore, it's often appear along with other signs of upper motor neuron lesion like a positive Babinski sign, hyperreflexia, and hypertonicity (Gelfand, 2014).

2.5.1 Muscle Weakness

Up to 89% of patients with multiple sclerosis have muscle weakness that is more pronounced in the lower extremities than the upper extremities (Chung, 2015; Hoang, Gandevia, & Herbert, 2014; Swingler & Compston, 1992). It can occur in any disease stage and associated with the

disease progression regardless the type of MS (Hoang et al., 2014). Moreover, decreased muscle strength can be attributed to corticospinal tract lesions (Reich et al., 2008), or volume loss of the brain, brain stem or spinal cord (D. H. Miller, Barkhof, Frank, Parker, & Thompson, 2002). In addition, reduced motor unit firing rates could play a primary role in skeletal muscle characteristics changes (Alon Kalron, Achiron, & Dvir, 2011).

2.5.1.1 Muscle Strength Assessment

2.5.1.1.1 Handheld dynamometry (HHD)

It is an instrument that widely used to assess muscle strength for both clinical and research settings (Schwartz, Cohen, Herbison, & Shah, 1992). In terms of psychometric properties, test-retest reliability was good to excellent and statistically significant in patients with MS for both weaker and stronger sides (ICCs = 0.81–0.96, 0.83–0.97), respectively (Mañago, Hebert, & Schenkman, 2017). While, inter-rater reliability was very good for upper limbs ranged from 0.85 to 0.95 and poor for lower limbs ranged from (-0.20 to 0.96) (Agre et al., 1987). In contrast, the interrater reliability of HHD was good in neurological patients ranging from 0.84 to 0.94 (R. W. Bohannon, 1986). Furthermore, the discriminative validity of HHD was proved by significant difference between MS group and healthy control group for all muscle groups ($P < 0.001$–0.003) (Mañago et al., 2017).

2.5.1.1.2 Handgrip Dynamometry (HGD)

The interclass correlation coefficient (ICC) of HGD was .98 for both interrater and test-retest reliabilities (Lamers, Kelchtermans, Baert, & Feys, 2014; Paltamaa, West, Sarasoja, Wikström, &

Mälkiä, 2005). Also, it has a significant but low correlation with the Manual Ability Measure (MAM-36) ($\rho = .36$ (Rt-grip), $\rho = .33$ (Lt-grip)) (Chen, Kasven, Karpatkin, & Sylvester, 2007) and ($\rho = -.33$) with Tremor Severity Scale (TSS) (Alusi, Worthington, Glickman, & Bain, 2001). Specifically, several studies reported that there was association between handgrip strength and physical fitness, length of hospital stay (Kerr et al., 2006; Roberts, Syddall, Cooper, & Aihie Sayer, 2012; Shyam Kumar et al., 2013), functional limitations (Morey, Pieper, & Cornoni-Huntley, 1998), and morbidity and mortality rates (Celis-Morales et al., 2017; Celis-Morales et al., 2018; Morey et al., 1998). Moreover, a significant association between handgrip strength and knee extensors strength and back strength in healthy women (Wang, Leger, & Dumas, 2005). In addition, the strength of handgrip found to be a useful tool to predict the overall muscular strength and endurance either for healthy people or with special populations (Trosclair et al., 2011; Wind, Takken, Helders, & Engelbert, 2010).

2.5.2 Motor Incoordination

It is defined as the ability to execute smooth, efficient, controlled, and accurate movements (Byl, 2002). Incoordination occurs in about 80% of MS patient during the disease course which increases the risk of disability and worse prognosis (F. D. Lublin, 2005; Mills, Yap, & Young, 2007; Wilkins, 2017). It occurs primarily as a result of lesions within the cerebellum or in its connections such as proprioceptive afferent inputs (Wilkins, 2017). Moreover, the cerebellum is connected to the cortical areas by cortico-ponto-cerebellar or cerebello-thalamo-cortical tracts which are the main cerebellar pathways responsible for movement coordination (Bergman & Afifi, 2005; Grothe, Lotze, Langner, & Dressel, 2017). Along with the motor function of the cerebellum, recent studies shown a critical role of cerebellum in cognitive processing such as working memory,

verbal fluency, and attention (D'Ambrosio et al., 2017; Grothe et al., 2017; Middleton & Strick, 1994; Ruet et al., 2014). Additionally, the presence of cerebellar motor signs is associated with the severity of cognitive decline in MS patients (Valentino et al., 2009).

2.5.2.1 Coordination Assessment

2.5.2.1.1 Timed Alternate Heel-to-Knee Test

Coordination test is considered as a standard part of the neurological examination (Lanzino, Rabinstein, et al., 2012; Rogers, 1988). Movement coordination can be evaluated by assessing the speed and quality of movement or a combination of both (Desrosiers, Rochette, & Corriveau, 2005; Lanzino, Rabinstein, et al., 2012). It has an excellent agreement among raters (mean kappa > 0.8038 or ICC > 0.9039) (Lanzino, Rabinstein, et al., 2012). It can be used as a valid and reliable coordination test in acute patient with CNS pathology as it can discriminate incoordination from normal performance (Lanzino, Rabinstein, et al., 2012).

2.5.2.1.2 Timed Rapid Alternating Movement for Upper Extremity

Rapid alternating movement is considered as a coordination test for upper extremity and frequently used clinically among practitioners (Andrews, Folger, Norbet, & Swift, 2008). It has shown fair to moderate intrarater and inter rater reliabilities (κ = 0.47–0.59; κ = 0.33–0.58, respectively) (Alusi, Worthington, Glickman, Findley, & Bain, 2000). Moreover, timed rapid alternating movement had moderate (mean kappa > 0.60) or good (mean ICC > 0.75) levels of agreement, and differentiate impaired from unimpaired movements (Lanzino, Rabinstein, et al.,

2012). In acute patients with CNS pathology, it can be utilized as a valid and reliable coordination measure (Lanzino, Rabinstein, et al., 2012). Rycroft (2019) found that individuals with non-amnestic MCI (naMCI) or multi-domain MCI (mdMCI) showed poorer hands pronation-supination test compared to individuals without MCI (no-MCI) (Rycroft et al., 2019).

2.5.3 Balance Impairment

Balance is defined as “the ability to maintain the body’s center of mass over its base of support” (Vander Linden, 1996). It mainly requires a coordination of 3 sensorimotor systems that include proprioception, Vision, and vestibular apparatus (Speers, Kuo, & Horak, 2002; Stevens, Goodman, Rough, & Kraft, 2013). These integrated systems can be interrupted by the demyelinating process of MS disease leading to balance deficits (Stevens et al., 2013). In comparison with healthy control, MS patients demonstrate slowed and declined anticipatory postural adjustments (APAs) plus increased sway variability (Krishnan, Kanekar, & Aruin, 2012; Stevens et al., 2013).

2.5.4 Gait Impairment

The WHO/International Classification of Disability, Functioning, and Health defines walking as ‘‘moving along a surface on foot, step by step, so that one foot is always on the ground, such as when strolling, sauntering, walking forwards, backwards, or sideways’’(N. Larocca, 2011; "WHO/International Classification of Functioning: Walking,"). Gait pattern functions are defined as ‘‘movement patterns associated with walking, running or other whole body movements,’’ and gait impairments may include ‘‘spastic gait, hemiplegic gait, paraplegic gait, asymmetric gait,

limping, and stiff gait pattern'' (N. Larocca, 2011; "WHO/International Classification of Functioning: Walking,"). Gait abnormalities are common among MS patients and their characteristics depend on the site of lesions within the CNS (Stevens et al., 2013). For example, reduce step length, reduce cadence, reduce joints movement and increase changes in gait parameters (Stevens et al., 2013) that negatively impact their quality of life (Zwibel, 2009). Moreover, individuals with MS increase the variability of gait and reduce their walking velocity when they perform cognitive tasks while walking compared with healthy controls (Hamilton et al., 2009). On the other hand, about 50% of MS patients require an assistive device with walking within 15 years of disease onset (Myhr et al., 2001; Weinshenker et al., 1989).

2.5.5 Risk of Fall

MS patients vary at high risk of fall with an incidence between 31% to 63% over a period between 3 to 6 months (M. L. Finlayson et al., 2006; Matsuda et al., 2011; Nilsagard, Lundholm, Denison, & Gunnarsson, 2009). Further, many factors related to an increased fall risk in the MS population like gait abnormalities (Nilsagard, Denison, Gunnarsson, & Bostrom, 2009; Nilsagard, Lundholm, et al., 2009), proprioception impairment (Nilsagard, Denison, et al., 2009), diminished balance (M. L. Finlayson et al., 2006; Matsuda et al., 2011; Sosnoff et al., 2011), use of an assistive device, spasticity, vision problems, low endurance of muscles, fatigue, and heat sensitivity (Nilsagard, Denison, et al., 2009). Moreover, osteoporosis and fear of falling are associated with increase fall-related injury specially to individuals aged 55 years and older (Peterson, Cho, von Koch, & Finlayson, 2008). In addition, cognitive problems like forgetfulness and poor concentration are associated with frequent falls in MS patients (M. L. Finlayson et al., 2006; Nilsagard, Denison, et al., 2009).

2.5.5.1 Balance, Gait, and Risk of Fall Assessment

2.5.5.1.1 Tinetti Performance Oriented Mobility Assessment (POMA)

It is a performance-based measure and composed of two subscales: Balance (BPOMA) and gait (GPOMA) (Hayes & Johnson, 2003) (Appendix A). The test-retest reliability for POMA varied between (.72 and .86) and the inter-rater reliability varied between (.80 and .93) in elderly people (Raiche, Hebert, Prince, & Corriveau, 2000) and shown excellent reliability in multiple sclerosis individuals (ICC > 0,936) (Besios, Nikolaos, Vassilios, & Giorgos, 2019). In terms of concurrent validity, GPOMA has a moderate correlation with the 9-item Physical Performance Test and high correlation of BPOMA with the Berg Balance Scale (BBS) (Hayes & Johnson, 2003). In addition, GPOMA shown a moderate correlation with Gait Assessment and Intervention Tool (GAIT) (r = .62) in people with multiple sclerosis (Gor-García-Fogeda, Cano-de-la-Cuerda, Daly, & Molina-Rueda, 2021).

2.5.6 Spasticity

2.5.6.1 Modified Ashworth Scale (MAS)

It is the most common scale to examine spasticity and widely applied in the clinical field (Balci, 2018). It is easy to use, and does not require equipment to apply it (Balci, 2018; Richard W. Bohannon & Smith, 1987). The inter-rater reliability of MAS was agreed on 86.7% between assessors and Kendall's tau correlation between two experienced raters was 0.847 ($p < .001$) (Richard W. Bohannon & Smith, 1987). While Intrarater reliability was 58% agreement ($\rho = 0.821$; $\tau = 0.739$; κ 0.422) in head injury patients (S. C. Allison, Abraham, & Petersen, 1996). Furthermore, MAS shown good internal consistency (Cronbach's alpha: 0.78) but poor intrarater reliability (ICC: 0.49) (Rasova, Martinkova, Vyskotova, & Sedova, 2012). In contrast, Inter-rater

and intrarater reliability were found fair to moderate with lower limbs in MS patients ($\kappa = 0.360$ and 0.488, respectively), and good to moderate for upper limbs ($\kappa = 0.625$ and 0.593, respectively) (Ansari, Naghdi, Arab, & Jalaie, 2008). In addition, MAS is very sensitive to changes after treatment ($p < .001$) (Rasova et al., 2012) (Appendix B).

2.6 Cognitive Impairment

Cognitive deficit is a common manifestation of multiple sclerosis, with a prevalence rate of up to 65% (Chiaravalloti & DeLuca, 2008; Piras et al., 2003; Rao, 2004; Stephen M Rao, Gary J Leo, Linda Bernardin, & Frederick Unverzagt, 1991). Cognitive impairment has been found across the disease courses either at earlier or later stages and can range from mild to severe impairment (Chiaravalloti & DeLuca, 2008; Rao, 2004). In particular, the main domains of cognitive functions that often affected adversely by MS include attention, executive functioning, information processing, visuospatial skill, abstract/conceptual reasoning and memory (Chiaravalloti & DeLuca, 2008; Rao, 2004). Whereas, cognitive domains that are not usually impaired by MS are essential verbal skills (e.g. word naming), simple attention (e.g. repeating digits) (Stephen M Rao et al., 1991), and general intelligence (Macniven et al., 2008).

2.6.1 Cognitive Function Assessment

2.6.1.1 The Montreal Cognitive Assessment (MoCA)

The MoCA is a screening instrument that mainly used in both clinical and research settings to evaluate a wide range of cognitive functions like: executive functions, short-term memory, visuospatial abilities, attention, concentration and working memory, language, and temporal and spatial orientations (Charvet et al., 2015; Sandra Freitas et al., 2018) (Appendix C). In comparison

with Mini-Mental State Exam, MoCA assesses more cognitive domains and more sensitive in detecting mild cognitive impairment about 90% while that of MMSE is 18% (Charvet et al., 2015). In terms of psychometric properties, a significant correlation coefficient between the MoCA total scores and the scores in the neuropsychological battery assessment instruments ranging between 0.31 and 0.62 ($p < 0.01$) in the MS group (Sandra Freitas et al., 2018). The internal consistency of the MoCA was found a Cronbach's a of 0.61 for the MS group (Sandra Freitas et al., 2018). In addition, the domain-specific subscores of MoCA have a moderate to strong correlation with respective domain-specific criterion standards in which memory subscore demonstrated the highest correlation ($r = 0.73$, $p < .001$), while the language was shown the lowest ($r = 0.42$, $p < .001$) (Lam et al., 2013).

3. Methods

3.1 Study design

A cross-sectional study

3.2 Participants

A total of 68 MS patients of both genders was recruited in this study. The sample size was estimated based on the rule of thumb $N > 104 + m$ (where m is the number of independent variables) (Green, 1991) and 20-30% was added to the total for an anticipation of the drop out. The inclusion criteria were adults' participants aged between (18 and 65) of both genders, confirmed diagnosis of MS, not having receptive, expressive, or global aphasia, able to read and write, and able to walk with or without assistive devices. Patients with communication difficulties, muscle weakness less than (grade 3) in manual muscle testing, spasticity equal or more than (grade 3) according to Modified Ashworth Scale (MAS), vision and hearing problems, patients who have severe cognitive impairment (score less than 10) based on the MoCA total score, other neurological diseases rather than MS, and individuals with a history of psychiatric illness were excluded from this study.

3.3 Ethical Considerations

Ethical approvals were obtained from the Health Sciences Institutional Review Board (IRB) at King Saud University and Sultan Bin Abdulaziz Humanitarian City in Riyadh. A consent form was filled by the participant (Appendix D). The examiner completed training and certification program as well as permission was taken to administer and score MoCA scale (Appendix E).

3.4 Data collection method

The data were collected by a trained physical therapist after ethical approvals taken from the Health Sciences Institutional Review Board (IRB) at King Saud University and Sultan Bin Abdulaziz Humanitarian City. In addition, some participants were recruited through advertisement in the social media. The screening sheet was used for eligibility and to gather participants' demographic data either from their medical profile or directly from the participants. It includes participants' current age, gender, age at onset of symptoms, disease duration, and the ability to walk with or without assistive devices (Appendix F).

3.5 Outcome measures

3.5.1 Montreal Cognitive Assessment (MoCA)

MoCA is a brief, quick test, can be administered within 5 to 10 minutes and has a universal cut-off point of 26 to determine cognitive impairment. (Charvet et al., 2015; Dagenais et al., 2013). The eight domains of this test assess executive functions involve: alternating trial making task (1 point), verbal fluency task (2 points), and verbal abstracting task (2 points), short-term memory domains consist of: two trials of five words learning and recall them after about 5 minutes, visuospatial abilities include: drawing a clock (3 points) and copying a cube (1 point), language domain covers 3 items: naming (3 points), repetition of 2 sentences (2 points), and verbal fluency (1 point), attention comprises 3 items: read the list of digits forward and backward (2 points), a serial subtraction (3 points), and vigilance (1 point), abstraction domain (2 points), and orientation to time and place (6 points) (Charvet et al., 2015). In this study the Arabic version of MoCA was used by a trained and certified examiner in the Montreal Cognitive Assessment (MoCA) to assess the participant's cognitive function (Rahman & El Gaafary, 2009). The final score is the sum of

all earned points and additional point was given if the participant educational level was equal or less than 12 years (Charvet et al., 2015). Furthermore, if the participant is unable to hold a pen due to upper extremity impairment, the items making trial, drawing a clock, and a cube copy will be cancelled and 5 points will be given instead (Charvet et al., 2015).

3.5.2 Muscle strength: Handheld and Hand grip Dynamometers

Isometric muscle strength was measured by the examiner using a handheld dynamometer in kilogram 3 times for each muscle and the highest value was chosen as reported in a previous study (Trosclair et al., 2011). For handgrip strength, the participant was in a sitting position with shoulder adducted and the elbow was flexed in 90-degree, the instrument was squeezed by the participant's hand. While, for knee extensors the participant was in a short sitting position with knee in 90-degree flexion, the instrument was held by the examiner on the anterior lower third of the participant's leg.

3.5.3 Timed Alternate Heel-to-Knee Test

In alternate heel-to-knee test, the participant was in a supine position and was asked to bend the knee and drag the heel of the tested leg to reach the level of the contralateral knee then extend the tested knee completely and this was repeated ten times as fast and accurate as possible (Lanzino, Rabinstein, et al., 2012). The scoring was obtained by the examiner which was used stopwatch during the test to measure the time in seconds that required to finish ten repetitions for each side (Lanzino, Rabinstein, et al., 2012; Pinheiro, Menezes, & Teixeira-Salmela, 2014). Two trials were performed for each side and the faster one was selected based on a previous study found

that the second trial of coordination testing was faster in comparison with the third trial (Lanzino, Conner, et al., 2012).

3.5.4 Timed Rapid Alternating Movement for Upper Extremity

The participant was in a sitting position and asked to perform the test for each side separately after verbal instructions and visual demonstration by the examiner. The participant was asked to perform alternative supination-pronation movements for 10 times as fast and accurate as possible. The examiner used a stopwatch and counted the time duration in seconds from the beginning until the end of 10 repetitions. The participant was asked to perform two trials, the faster one has been selected (Lanzino, Conner, et al., 2012).

3.5.5 Tinetti Performance Oriented Mobility Assessment (POMA)

It is a performance-based test and assesses both balance (BPOMA) and gait (GPOMA) separately to indicate balance and gait impairments and their total score shows the risk of fall (Hayes & Johnson, 2003; Tinetti, 1986). It is composed of nine tasks for balance assessment and seven tasks for gait assessment in an ordinal scale for each task of 0, 1, and 2 (Tinetti, 1986). In addition, the risk of fall is high when the total score is equal or less than 18, moderate when the score between 19 to 23, and low when it is equal or more than 24 (Tinetti, 1986). In balance section, the subject sat on a hard-armless chair and obeyed the examiner instructions. It includes sitting balance, rising, attempts to rise, immediate standing balance within the first 5 seconds, standing balance, nudged, eyes closed in standing, turning 360 degrees, and sitting down (Tinetti, 1986). While in gait section the subject could use an assistive aid and walk at usual speed and back at

rapid and safe speed. It includes gait initiation, step length and height, step symmetry, step continuity, path, trunk sway, and walking distance (Hayes & Johnson, 2003).

3.6 Statistical analysis

All statistical analysis was performed by using SPSS (version-23). Participants' characteristics were presented by descriptive analysis. Pearson Correlation Coefficient analysis was used to assess the strength and direction of the association between cognitive and motor variables and Kendall's coefficient of rank correlation tau-sub-b, τb test was used to examine the association between MoCA and gait parameters (Parish & Guilford, 1957). After that, motor variables that were shown significant correlations with MoCA were used in a multiple linear regression to determine the predictor variables (Aristotelous et al., 2019; Gonzalez-Chica, Bastos, Duquia, Bonamigo, & Martínez-Mesa, 2015). All data were expressed as mean (M) ± standard deviation (SD), the significance level of the P value was <0.05 with 95% of confidence interval.

Table 3-1. Example of a Conventional Approach to Interpreting a Correlation Coefficient

Absolute Magnitude of the Observed Correlation Coefficient	**Interpretation**
.00 - .10	Negligible correlation
.10 - .39	Weak correlation
.40 - .69	Moderate correlation
.70 - .89	Strong correlation
.90 – 1.00	Very strong correlation

3.7 Timetable

Table 3-2 Timetable

Task \ Month	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Write a research proposal																				
Proposal submission & presentation																				
IRB process & approval																				
Data collection																				
Data analysis																				
Thesis Writing																				
Thesis Submission																				
Thesis Presentation																				

4. Results

4.1 Subjects and Demographic Data

The total number of the sample of the current study was sixty-eight subjects were enrolled in this study (53 females and 15 males, their mean age was 36.78 ± 9.32). 89.7% of the participants were right-handed, while only 10.3% of the participants were left-handed. 66.2% of the participants reported that they got bachelor's degree education, and almost half of them 48.5% had a normal body mass index (BMI) **Figure 4-1**. The disease duration and age at onset of symptoms were (10.65 ± 7.27; 26.24 ± 8.21) respectively. Participants' demographic characteristics are presented in **Table 4-1**.

Table 4-1. Participants' Demographic Characteristics

Characteristic	**MS (n=68)**
Age (Years) (mean ± SD)	36.78 ± 9.32
Handedness (mode ± SD) Right (%) Left (%)	1.00 ± .306 89.7 10.3
Gender (mode ± SD) Male [n (%)] Female [n (%)]	1.00 ± .418 15 (22.1) 53 (77.9)
Multiple Sclerosis Subtype RRMS [n (%)] SPMS [n (%)] PPMS [n (%)]	 63 (92.6) 2 (2.9) 3 (4.4)
Age at onset of symptoms (Years) (mean ± SD)	26.24 ± 8.21
Disease Duration (Years) (mean ± SD)	10.65 ± 7.27
Weight (Kg) (mean ± SD)	68.48 ± 15.37
Height (m) (mean ± SD)	1.63 ± .089
BMI ($Kg/m^{2)}$ (median ± SD) Underweight (%) Normal (%)	2.00 ± .936 1.5 48.5

Overweight (%)	29.4
Obese (%)	14.7
Extremely Obese (%)	5.9
Education Years (mean ± SD)	14.84 ± 2.62
Primary School (%)	2.9
Intermediate (%)	1.5
Secondary (%)	23.5
Bachelor (%)	66.2
Master (%)	4.4
PHD (%)	1.5

RRMS= Relapse-Remitting Multiple Sclerosis, SPMS= Secondary Progressive Multiple Sclerosis, PPMS= Primary Progressive Multiple Sclerosis, SD= Standard Deviation, BMI= Body Mass Index

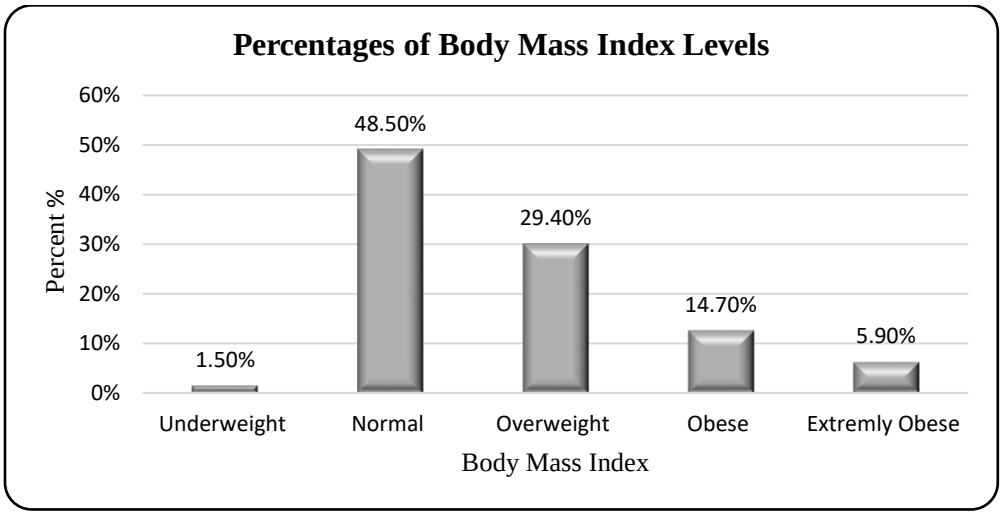


Figure 4-1. Body Mass Index of the Participants

4.2 Descriptive Statistics of Cognitive and Motor Variables

All data about cognitive function, muscle strength, coordination, balance, gait, and risk of fall are summarized in **Table 4-2**. The total score of Montreal Cognitive Assessment was 23.56 ± 3.57 and the participants were classified into three levels of cognitive status (27.9 % had no cognitive impairment, 66.2% had mild cognitive impairment, and 5.9% had moderate cognitive impairment) **Figure 4-2**. Specifically, memory was the most affected domain about 83.8%, followed by executive functions and visuospatial skills 75% and 72.1%, respectively. While language was the

lowest domain approximately 24% **Figure 4-3**. The mean of the heel to knee test was lower on the left side (00:00:15.26 ± 00:00:05.71) than on the right side (00:00:17.15 ± 00:00:06.81) with a significant average difference (t_{67} = 3.647, p = 0.001). While, no significant differences were found between the mean of the right and left sides of handgrip strength (23.46 ± 6.59 for the right hand and 22.68 ± 7.51 for the left hand) (t_{67} = 1.389, p = .169), knee extension strength (26.67 ± 8.52 for the right leg and 26.08 ± 8.29 for the left leg) (t_{67} = .981, p = .330), and pronation/supination coordination test (00:00:06.87 ± 00:00:01.81 for the right side and 00:00:07.03 ± 00:00:01.63 for the left side) (t_{67} = -.967, p = .337). Therefore, the average of both sides and paired sample t-test were analysed for all variables that examined bilaterally as illustrated in **Table 4-3**. Moreover, the mean of balance and gait scores were 13.06 ± 3.69 and 8.82 ± 3.28, respectively. In addition, the mean of the risk of fall was 21.94 ± 6.80 which indicates moderate risk of fall **Figure 4-4**.

Table 4-2. Participants' Scores (mean and Standard deviation) per parameter.

Parameters	**MS (n=68)**
MoCA (Total) (mean ± SD)	23.56 ± 3.57
MoCA Levels (%)	
Normal (26-30)	27.9
Mild CI (18-25)	66.2
Moderate CI (10-17)	5.9
MoCA Domains (%)	
Executive Functions	75
Visuospatial Skills	72.1
Memory	83.8
Attention	64.7
Language	24
Orientation	41.2
RT-Handgrip strength (Kg) (mean ± SD)	23.46 ± 6.59
LT-Handgrip strength (Kg) (mean ± SD)	22.68 ± 7.51

RT-Knee Extension strength (Kg) (mean ± SD)	26.67 ± 8.52
LT-Knee Extension strength (Kg) (mean ± SD)	26.08 ± 8.29
RT-Supination/Pronation (sec) (mean ± SD)	00:00:06.87 ± 00:00:01.81
LT-Supination/Pronation (sec) (mean ± SD)	00:00:07.03 ± 00:00:01.63
RT-Heel to Knee (sec) (mean ± SD)	00:00:17.15 ± 00:00:06.81
LT-Heel to Knee (sec) (mean ± SD)	00:00:15.26 ± 00:00:05.71
Balance (mean ± SD)	13.06 ± 3.69
Gait (mean ± SD) Gait Initiation Step Length Foot Clearance Step Symmetry Step Continuity Path Excursion Trunk Sway Base of Support	8.82 ± 3.28 .868 ± .341 1.897 ± .352 1.632 ± .731 .353 ± .481 .691 ± .465 1.294 ± .624 1.515 ± .782 .508 ± .504
Risk of Fall (mean ± SD) Low Risk of Fall (%) Moderate Risk of Fall (%) High Risk of Fall (%)	21.94 ± 6.71 58.8 14.7 26.5

MoCA= Montreal Cognitive Assessment, Mild CI= Mild Cognitive Impairment, Moderate CI= Moderate Cognitive Impairment, p-value is significant at the 0.05 level (2-tailed).

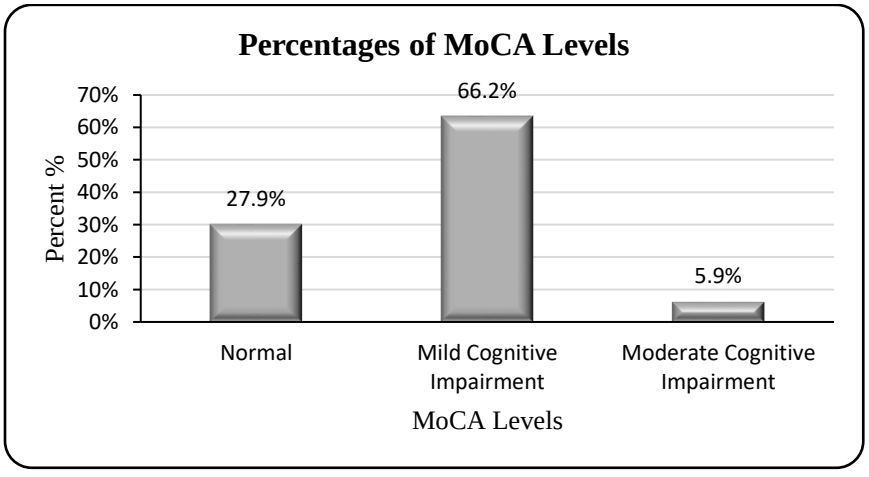


Figure 4-2.Cognitive Status of the included MS

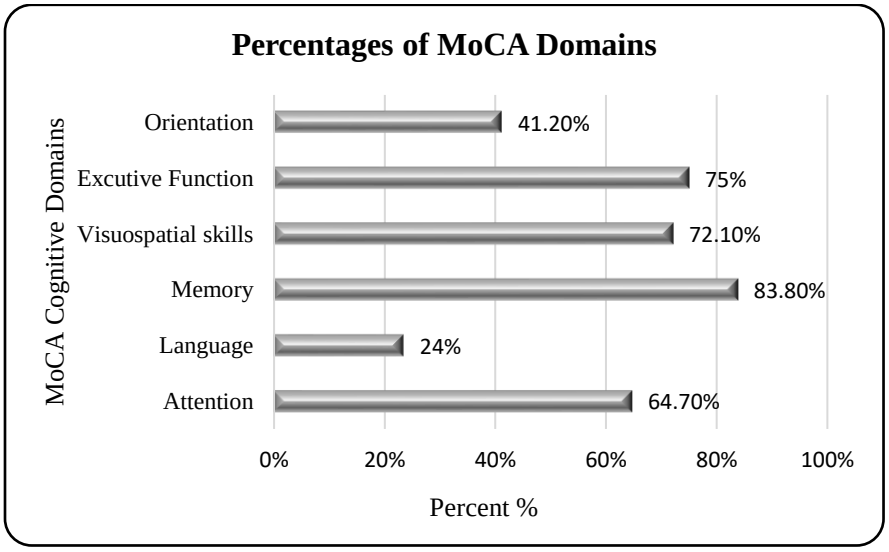


Figure 4-3. Percentages of MoCA Domains among MS Patients with Cognitive Impairment

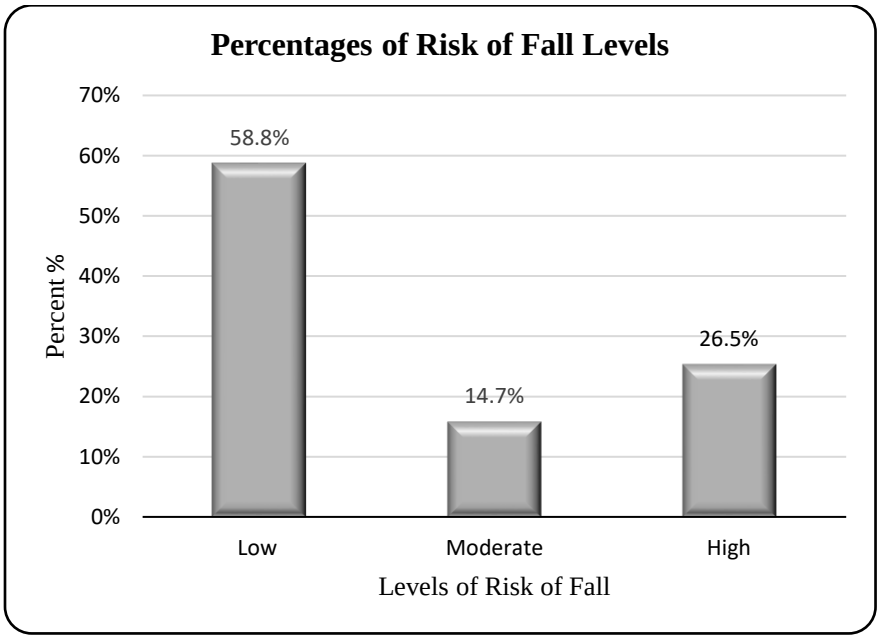


Figure 4-4. Percentages of Risk of Fall among MS Patients

Table 4-3. Paired Sample t-test for variables Examined in both

Parameter	Mean	SD	SEM	t	df	Sig. (p-value)
RT-Handgrip – LT-Handgrip	.778	4.62	.559	1.389	67	.169
RT-Knee Extension- LT-Knee Extension	.588	4.95	.599	.981	67	.330
RT-Sup/Pron - LT-Sup/Pron	-0:00:00.160	00:00:01.37	00:00:00.166	-.967	67	.337
RT-Heel to Knee- LT-Heel to Knee	00:00:01.89	00:00:04.242	00:00:00.518	3.647	67	.001

SD = Standard Deviation, SEM = Standard Error Mean, df = Degree of Freedom.

4.3 Correlation between Cognitive Performance and Motor Function

Pearson correlation coefficient was computed to assess the association between Cognitive and motor variables as listed in **Table 4-4**.

4.3.1 Muscle Strength

No significant correlations were found between MoCA and muscle strength of the handgrip (r= .174, n= 68, p= .157) and knee extension (r= .129, n= 68, p= .296).

4.3.2 Motor Coordination

There was a negative low correlation between MoCA and motor coordination (r= -.377, n= 68, p= .002 for upper extremities, r= -.247, n= 68, p= .044 for lower extremities).

4.3.3 Balance, Gait, and Risk of Fall

Positive moderate correlation was found between MoCA and the total score of POMA (r= .419, n= 68, p= .000). Also, POMA subscales shown positive moderate correlations with MoCA (r= .403, n= 68, p= .000 for balance, r= .416, n= 68, p= .001 for gait).

Table 4-4. Pearson Correlations Between MoCA and Motor Variables

Motor Variables		**MoCA**	
		Pearson Correlation Coefficient	**Sig. (P-value)**
Muscle Strength	Handgrip	.174	.157
	Knee Extension	.129	.296
Coordination	Supination/Pronation	-.377**	.002
	Heel to Knee	-.247	.044
POMA	Balance	.403**	.001
	Gait	.416**	.000
	Risk of Fall	.419**	.000

MoCA= Montreal Cognitive Assessment, POMA= Performance Oriented Mobility Assessment.

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).

4.4 Correlation Between Cognitive Performance and Gait Parameters

Kendall's coefficient of rank correlation tau_b test was used to examine the association between MoCA and GPOMA subdomains **Table4-5**. There were positive low correlations between MoCA and step length (τb = .217, n= 68, p= .036), foot clearance (τb = .276, n= 68, p= .007), step symmetry (τb = .310, n= 68, p= .003), step continuity (τb = .362, n= 68, p= .001), path excursion (τb = .277, n= 68, p= .006), trunk sway (τb = .296, n= 68, p= .003), and base of support (τb = .293, n= 68, p= .005). In contrast, no correlation was found between MoCA and gait initiation (τb = .168, n= 68, p= .106).

Table 4-5. Kendall's tau_b Correlation Coefficient between MoCA and Gait Parameters

Gait Parameters	**MoCA**	
	Kendall's tau_b Correlation Coefficient	**Sig. (P-value)**
Gait Initiation	.168	.106
Step length	.217*	.036
Foot Clearance	.276**	.007
Step Symmetry	.310**	.003
Step Continuity	.362**	.001
Path Excursion	.277**	.006
Trunk Sway	.296**	.003
Base of Support	.293**	.005

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).

4.5 Multiple Linear Regression

Motor variables which revealed significant correlations with MoCA were used in a multiple linear regression to determine the predictor variables (P. D. Allison, 1999; A. J. Miller, 1984). All assumptions of multiple linear regression were tested and met before conducting it (Tranmer & Elliot, 2008). Balance and gait were excluded from the linear regression because they showed high correlation with each other ($r= .890$, $n= 68$, $p \leq .001$), balance with risk of fall ($r= .974$, $n= 68$, $p \leq .001$), and gait with risk of fall ($r= .968$, $n= 68$, $p \leq .001$). Moreover, Muscle strength of handgrip and knee extension were excluded because they showed no significant correlation with MoCA as demonstrated in **Table 4-4.** Thus, risk of fall, upper and lower limbs coordination variables were entered in the regression analysis as independent variables and MoCA was entered as dependent variable. Using (stepwise) method, a significant model emerged ($F(1, 65) = 13.439$, $p < .001$) with an R^2 of .171. Therefore, 17.1 % of the variance in MoCA was predictable from the risk of fall (**Tables 4-6**, **4-7, and 4-8**). The statistical equation that describes the best fit of the regression line is:

$$\hat{Y} = B_0 + B_1X_1$$

Where:

$\hat{Y}$: represents the *outcome variable* (MoCA)

B_0: represents the *intercept* (constant)

B_1: represents the *slope* of the line

X_1: represents the *predictor variable* (Risk of fall)

So,

$\hat{Y} = 18.731 + (.221) * (\text{Risk of fall})$ (**Fig. 4-5**).

Table 4-8. Illustrated with one-unit increase in the total score of POMA, MoCA score increases by .221, which was found to be a significant change $t\ (65) = 3.666$, $p < .001$.

Table 4-6. Multiple Linear regression Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Durbin-Watson
1	.414[a]	.171	.159	3.288	1.683

a. Predictors: (Macniven et al.), Risk of Fall

b. Dependent Variable: MoCA

Table 4-7. Multiple Linear Regression ANOVA.

Model	Sum of Squares	df	Mean Square	F	Sig.
Regression	145.305	1	145.305	13.439	.000[a]
Residual	702.815	65	10.813		
Total	848.119	66			

a. Predictors: (Macniven et al.), Risk of Fall

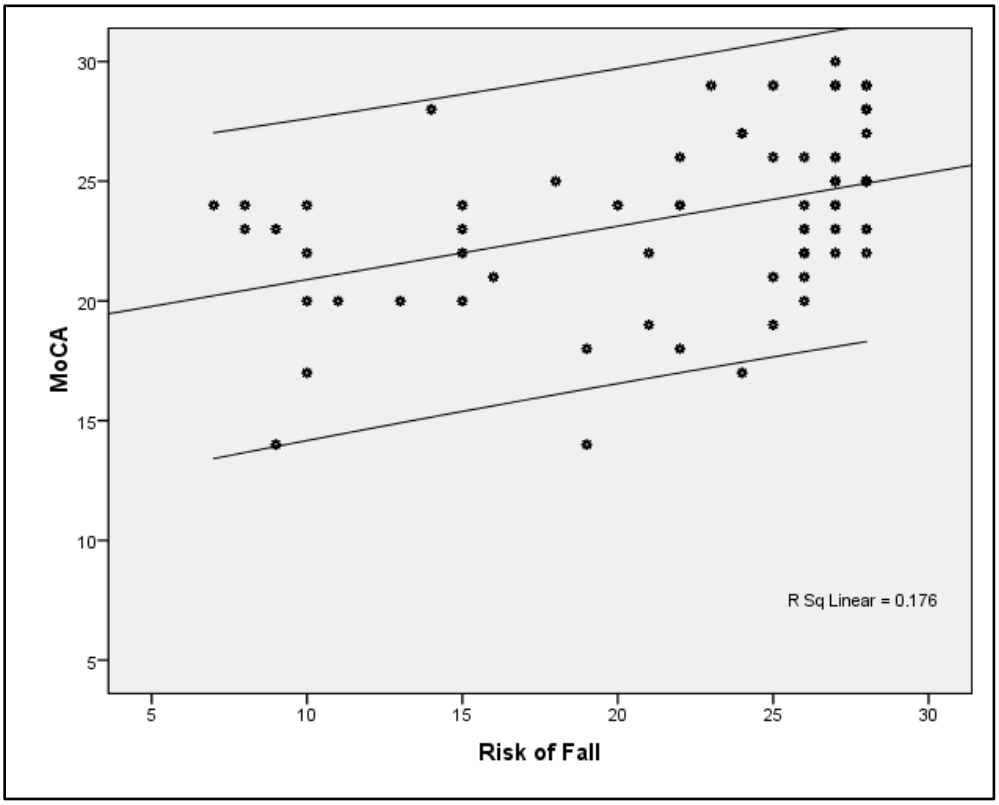
b. Dependent Variable: MoCA

Table 4-8. Stepwise Multiple Linear Regression Coefficients.

Model	B	Std. Error	Beta	t	Sig.
1 (Macniven et al.)	18.731	1.387		13.505	.000
Risk of Fall	.221	.060	.414	3.666	.000

a. Dependent Variable: MoCA

Figure 4-5. Scatter Plot of MoCA on the Risk of Fall with Regression Line and 95% individual Confidence Interval.



5. Discussion

In this study, the association between cognitive impairment and motor dysfunction among patients with multiple sclerosis was determined. The findings of the current study showed that cognitive function is significantly associated with the score of risk of fall, balance, gait, and motor coordination of upper and lower extremities. However, no significant association was found between cognition and muscle strength, as estimated by handgrip and knee extension strength. Moreover, the results demonstrated that reduced the score of coordination of upper and lower extremities and the lower the risk of fall were associated with the higher score of cognitive function. Specifically, POMA test can be a predictor of cognitive impairment in patients with multiple sclerosis.

The current study found that the mean of the total score of MoCA was 23.56 ± 3.57 which indicated mild cognitive impairment and accounted for 66.2% of the patients with cognitive impairment which was consistent with the results of the previous studies (McNicholas et al., 2018; Stephen M Rao et al., 1991). Moreover, several studies confirmed th at the most affected cognitive domains among MS patients were memory, abstract/conceptual reasoning, information processing, attention, and visuospatial skills (Macias Islas & Ciampi, 2019; Rao, 2004). Similarly, we found that memory, visuospatial skills, executive functions, attention, and language were affected domains among patients who had cognitive impairment based on the Montreal Cognitive Assessment.

Numerous studies have shown that cognitive impairment is associated with handgrip strength among healthy older adults (Borges, Canevelli, Cesari, & Aprahamian, 2019; Buchman, Wilson, Boyle, Bienias, & Bennett, 2007). Fritz et al. (2017) found that handgrip strength could be used as a measure for monitoring cognitive decline progression among healthy elderly (Fritz, McCarthy, & Adamo, 2017). Moreover, reduced handgrip could be a predictor of cognitive impairment over a 7 year period among Mexican American older people with normal cognitive function at baseline (Alfaro-Acha et al., 2006). In contrast, Aristotelous et al. 2019, found that cognitive performance was not associated with handgrip strength among patients with multiple sclerosis, which is in the line of our findings (Aristotelous et al., 2019).

On the other hand, this study found no correlation between lower extremity strength and cognitive function. Whilst a recent study found a positive low correlation between cognitive performance and knee extension strength in the MS individuals (Aristotelous et al., 2019). Additionally, knee extension peak torque was associated with cognitive processing speed, but not verbal and visuospatial learning and memory, in 62 persons with multiple sclerosis (Sandroff, Pilutti, Benedict, & Motl, 2015).

The findings of the current study revealed significant low inverse correlations between motor coordination of upper and lower extremities and cognitive performance among people with multiple sclerosis. According to the literature, poor performance on rapid alternating movement and heel to knee is usually the result of cerebellar dysfunction (Sarica, Cerasa, & Quattrone, 2015). Moreover, Valentino et al., (2009), reported that RRMS patients with cerebellar symptoms exhibit poor performance on attention and verbal fluency tests than the RRMS patients without cerebellar

symptoms (Valentino et al., 2009). Furthermore, various studies found that the cerebellum has an important role in both cognitive and motor functions of MS patients (D'Ambrosio et al., 2017; Sarica et al., 2015; Valentino et al., 2009). In fact, different neuroanatomical and neuroimaging studies explained the importance of cerebello-cerebral network which consists of forward cortico-ponto-cerebellar pathway and backward cerebello-thalamo-cortical pathway in cognitive modulation (Baillieux et al., 2010; Schmahmann, 2004; Tedesco et al., 2011). In addition, Baillieux et al., (2010), found that patients with right cerebellar lesions demonstrated left hemispheric dysfunction, which include executive functions, language, and logical reasoning. While patients with left cerebellar lesions experienced right hemispheric symptoms like visuospatial skills, attention, visual working memory, and non-verbal problem solving (Baillieux et al., 2010).

Our findings showed that a balance component of POMA has shown a significant moderate correlation with cognitive performance. In 2017, Perrochon et al., found that working memory, attention, and executive functions were associated with postural control in the upright position with an unstable platform among MS patients (Perrochon et al., 2017). Furthermore, various studies were examined the Postural-Cognitive interference by incorporating the dual-task paradigms among healthy people and those with multiple sclerosis (Beste, Mückschel, Paucke, & Ziemssen, 2018; Chamard Witkowski, Mallet, Bélanger, Marrero, & Handrigan, 2019). A recent review concluded that MS patients showed impaired balance when they simultaneously perform a cognitive and a postural task which increase their risk of fall in most daily activities (Chamard Witkowski et al., 2019).

Furthermore, this study found that gait has a moderate positive correlation with cognition which is consistent with the previous studies that found a significant association between gait variabilities and cognitive decline in PwMS (Hsieh, Sun, & Sosnoff, 2017; A. Kalron, Aloni, et al., 2018). In addition, several studies have illustrated that the relationship between cognitive decline and gait fluctuations among various populations like older adults (Amboni, Barone, & Hausdorff, 2013), people with MCI (Aggarwal et al., 2006; Boyle et al., 2007), subjects with Alzheimer disease (AD) (Verghese, Wang, Lipton, Holtzer, & Xue, 2007), and individuals affected by Parkinson's disease (Amboni et al., 2013). In the present study, apparent significant associations were found between cognitive function and gait parameters like step length, step symmetry, step continuity, foot clearance, path excursion, trunk sway, and base of support. In contrast, no correlation was found between the cognition and gait initiation. Katherine et al. (2017) reported that step length and step time variabilities were associated with cognitive processing speed in MS individuals (Hsieh et al., 2017). Moreover, a previous study demonstrated that alterations in gait spatial and spatiotemporal parameters were predictive of impairment in some cognitive functions like memory, visuospatial skills, executive function, and language among cognitively normal participants (Savica et al., 2017).

The findings of this study show that risk of fall has a significant correlation with a cognitive function and a predictor of cognitive impairment in MS participants which is in the line with previous studies (Amboni et al., 2013). Moreover, the higher score of POMA means decrease the level of risk of fall, which is associated with the higher scores of MoCA. Sosnoff et al. 2013 found that cognitive processing speed was slower in community-dwelling adults with MS who exhibited recurrent falls in comparison with those with a single time fall of the same sample (Sosnoff et al.,

2013). Furthermore, it has been found that fall frequency was significantly correlated with general intelligence, speed of cognitive processing, and executive functioning while, verbal memory was found to be a significant predictor of falls in 81 patients with MS (D'Orio et al., 2012). In addition, it has been reported that MS individuals with history of fall present with cognitive impairment and reduced cerebellar volume in comparison with non-fallers (A. Kalron, Allali, & Achiron, 2018).

This study has several limitations. First, the sample size is small and further studies are required with a larger sample size for better regression results. Second, most of the participants have RRMS while few participants have PPMS and SPMS. Therefore, future studies could involve all MS subtypes and compare between them. Third, Gait assessment that used is based on the examiner's observations and less sensitive to detect gait abnormalities. So, future studies are needed to use advanced gait analysis systems for better detection of temporal and visuospatial parameters.

6. Conclusion

Overall, this study concludes that cognitive impairment is significantly associated with motor coordination, balance, gait, and risk of fall. The risk of fall emerged as the best predictor of cognitive impairment among MS population. Incorporating coordination and balance training in the rehabilitation program may enhance cognitive functions in individuals with multiple sclerosis, but this remains to be investigated.

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Conflicts of interest

The author declares no conflicts of interest.

VII. Bibliography

Aggarwal, N. T., Wilson, R. S., Beck, T. L., Bienias, J. L., & Bennett, D. A. (2006). Motor dysfunction in mild cognitive impairment and the risk of incident Alzheimer disease. *Arch Neurol, 63*(12), 1763-1769. doi:10.1001/archneur.63.12.1763

Agre, J. C., Magness, J. L., Hull, S. Z., Wright, K. C., Baxter, T. L., Patterson, R., & Stradel, L. (1987). Strength testing with a portable dynamometer: reliability for upper and lower extremities. *Arch Phys Med Rehabil, 68*(7), 454-458.

Al Wutayd, O., Mohamed, A. G., Saeedi, J., Al Otaibi, H., & Al Jumah, M. (2018). Environmental exposures and the risk of multiple sclerosis in Saudi Arabia. *BMC neurology, 18*(1), 86-86. doi:10.1186/s12883-018-1090-8

Alfaro-Acha, A., Snih, S. A., Raji, M. A., Kuo, Y.-F., Markides, K. S., & Ottenbacher, K. J. (2006). Handgrip Strength and Cognitive Decline in Older Mexican Americans. *The Journals of Gerontology: Series A, 61*(8), 859-865. doi:10.1093/gerona/61.8.859

AlJumah, M., Bunyan, R., Al Otaibi, H., Al Towaijri, G., Karim, A., Al Malik, Y., . . . Algahtani, H. (2020). Rising prevalence of multiple sclerosis in Saudi Arabia, a descriptive study. *BMC neurology, 20*(1), 49.

Allison, P. D. (1999). *Multiple regression: A primer*: Pine Forge Press.

Allison, S. C., Abraham, L. D., & Petersen, C. L. (1996). Reliability of the Modified Ashworth Scale in the assessment of plantarflexor muscle spasticity in patients with traumatic brain injury. *Int J Rehabil Res, 19*(1), 67-78. doi:10.1097/00004356-199603000-00007

Alusi, S. H., Worthington, J., Glickman, S., & Bain, P. G. (2001). A study of tremor in multiple sclerosis. *Brain, 124*(Pt 4), 720-730. doi:10.1093/brain/124.4.720

Alusi, S. H., Worthington, J., Glickman, S., Findley, L. J., & Bain, P. G. (2000). Evaluation of three different ways of assessing tremor in multiple sclerosis. *J Neurol Neurosurg Psychiatry, 68*(6), 756-760. doi:10.1136/jnnp.68.6.756

Amato, M. P., Prestipino, E., & Bellinvia, A. (2019). Identifying risk factors for cognitive issues in multiple sclerosis. *Expert Review of Neurotherapeutics, 19*(4), 333-347. doi:10.1080/14737175.2019.1590199

Amboni, M., Barone, P., & Hausdorff, J. M. (2013). Cognitive contributions to gait and falls: evidence and implications. *Mov Disord, 28*(11), 1520-1533. doi:10.1002/mds.25674

Andrews, A. W., Folger, S. E., Norbet, S. E., & Swift, L. C. (2008). Tests and measures used by specialist physical therapists when examining patients with stroke. *J Neurol Phys Ther, 32*(3), 122-128. doi:10.1097/NPT.0b013e3181847a2f

Ansari, N. N., Naghdi, S., Arab, T. K., & Jalaie, S. (2008). The interrater and intrarater reliability of the Modified Ashworth Scale in the assessment of muscle spasticity: limb and muscle group effect. *NeuroRehabilitation, 23*(3), 231-237.

Aristotelous, P., Stefanakis, M., Pantzaris, M., Pattichis, C., Hadjigeorgiou, G. M., & Giannaki, C. D. (2019). Associations between functional capacity, isokinetic leg strength, sleep quality and cognitive function in multiple sclerosis patients: a cross-sectional study. *Postgrad Med, 131*(7), 453-460. doi:10.1080/00325481.2019.1662271

Bagert, B., Camplair, P., & Bourdette, D. (2002). Cognitive Dysfunction in Multiple Sclerosis. *CNS Drugs, 16*(7), 445-455. doi:10.2165/00023210-200216070-00002

Baillieux, H., De Smet, H. J., Dobbeleir, A., Paquier, P. F., De Deyn, P. P., & Mariën, P. (2010). Cognitive and affective disturbances following focal cerebellar damage in adults: a neuropsychological and SPECT study. *Cortex, 46*(7), 869-879. doi:10.1016/j.cortex.2009.09.002

Balci, B. P. (2018). Spasticity Measurement. *Noro Psikiyatr Ars, 55*(Suppl 1), S49-S53. doi:10.29399/npa.23339

Benedict, R. H., Holtzer, R., Motl, R. W., Foley, F. W., Kaur, S., Hojnacki, D., & Weinstock-Guttman, B. (2011). Upper and lower extremity motor function and cognitive impairment in multiple sclerosis. *J Int Neuropsychol Soc, 17*(4), 643-653. doi:10.1017/S1355617711000403

Bergman, R. A., & Afifi, A. K. (2005). *Functional neuroanatomy: Text and atlas*: Lange Medical Books/McGraw-Hill.

Besios, T., Nikolaos, A., Vassilios, G., & Giorgos, M. (2019). COMPARATIVE RELIABILITY OF TINETTI MOBILITY TEST AND TUG TESTS IN PEOPLE WITH NEUROLOGICAL DISORDERS. *International journal of physiotherapy, 6*.

Beste, C., Mückschel, M., Paucke, M., & Ziemssen, T. (2018). Dual-Tasking in Multiple Sclerosis - Implications for a Cognitive Screening Instrument. *Frontiers in human neuroscience, 12*, 24-24. doi:10.3389/fnhum.2018.00024

Bishop, M., & Rumrill, P. D. (2015). Multiple sclerosis: Etiology, symptoms, incidence and prevalence, and implications for community living and employment. *Work, 52*(4), 725-734. doi:10.3233/WOR-152200

Bohannon, R. W. (1986). Test-retest reliability of hand-held dynamometry during a single session of strength assessment. *Phys Ther, 66*(2), 206-209. doi:10.1093/ptj/66.2.206

Bohannon, R. W., & Smith, M. B. (1987). Interrater Reliability of a Modified Ashworth Scale of Muscle Spasticity. *Physical Therapy, 67*(2), 206-207. doi:10.1093/ptj/67.2.206

Borges, M. K., Canevelli, M., Cesari, M., & Aprahamian, I. (2019). Frailty as a Predictor of Cognitive Disorders: A Systematic Review and Meta-Analysis. *Frontiers in Medicine, 6*(26). doi:10.3389/fmed.2019.00026

Boyle, P. A., Wilson, R. S., Buchman, A. S., Aggarwal, N. T., Tang, Y., Arvanitakis, Z., . . . Bennett, D. A. (2007). Lower extremity motor function and disability in mild cognitive impairment. *Exp Aging Res, 33*(3), 355-371. doi:10.1080/03610730701319210

Buchman, A. S., Wilson, R. S., Boyle, P. A., Bienias, J. L., & Bennett, D. A. (2007). Grip strength and the risk of incident Alzheimer's disease. *Neuroepidemiology, 29*(1-2), 66-73. doi:10.1159/000109498

Byl, N. N. (2002). Multisensory Control of Upper Extremity Function. *Journal of Neurologic Physical Therapy, 26*(1), 32-43. Retrieved from https://journals.lww.com/jnpt/Fulltext/2002/26010/Multisensory_Control_of_Upper_Extremity_Function.8.aspx

Celis-Morales, C. A., Lyall, D. M., Anderson, J., Iliodromiti, S., Fan, Y., Ntuk, U. E., . . . Gill, J. M. (2017). The association between physical activity and risk of mortality is modulated by grip strength and cardiorespiratory fitness: evidence from 498 135 UK-Biobank participants. *Eur Heart J, 38*(2), 116-122. doi:10.1093/eurheartj/ehw249

Celis-Morales, C. A., Welsh, P., Lyall, D. M., Steell, L., Petermann, F., Anderson, J., . . . Gray, S. R. (2018). Associations of grip strength with cardiovascular, respiratory, and cancer outcomes and

all cause mortality: prospective cohort study of half a million UK Biobank participants. *Bmj, 361*, k1651. doi:10.1136/bmj.k1651

Chamard Witkowski, L., Mallet, M., Bélanger, M., Marrero, A., & Handrigan, G. (2019). Cognitive-Postural Interference in Multiple Sclerosis. *Frontiers in Neurology, 10*, 913. Retrieved from https://www.frontiersin.org/article/10.3389/fneur.2019.00913

Charvet, L., Taub, E., Cersosimo, B., Rosicki, C., Melville, P., & Krupp, L. (2015). The Montreal Cognitive Assessment (MoCA) in Multiple Sclerosis: Relation to Clinical Features. *Journal of Multiple Sclerosis, 2*. doi:10.4172/2376-0389.1000135

Chen, C. C., Kasven, N., Karpatkin, H. I., & Sylvester, A. (2007). Hand strength and perceived manual ability among patients with multiple sclerosis. *Arch Phys Med Rehabil, 88*(6), 794-797. doi:10.1016/j.apmr.2007.03.010

Chiaravalloti, N. D., & DeLuca, J. (2008). Cognitive impairment in multiple sclerosis. *Lancet Neurol, 7*(12), 1139-1151. doi:10.1016/s1474-4422(08)70259-x

Chung, L. (2015). *Muscle weakness in persons with multiple sclerosis.*

Clark, T. K., Newman, M. C., Karmali, F., Oman, C. M., & Merfeld, D. M. (2019). Chapter 5 - Mathematical models for dynamic, multisensory spatial orientation perception. In S. Ramat & A. G. Shaikh (Eds.), *Progress in Brain Research* (Vol. 248, pp. 65-90): Elsevier.

Csukly, G., Sirály, E., Fodor, Z., Horváth, A., Salacz, P., Hidasi, Z., . . . Szabó, Á. (2016). The Differentiation of Amnestic Type MCI from the Non-Amnestic Types by Structural MRI. *Frontiers in aging neuroscience, 8*, 52-52. doi:10.3389/fnagi.2016.00052

D'Ambrosio, A., Pagani, E., Riccitelli, G. C., Colombo, B., Rodegher, M., Falini, A., . . . Rocca, M. A. (2017). Cerebellar contribution to motor and cognitive performance in multiple sclerosis: An MRI sub-regional volumetric analysis. *Mult Scler, 23*(9), 1194-1203. doi:10.1177/1352458516674567

D'Orio, V. L., Foley, F. W., Armentano, F., Picone, M. A., Kim, S., & Holtzer, R. (2012). Cognitive and motor functioning in patients with multiple sclerosis: neuropsychological predictors of walking speed and falls. *J Neurol Sci, 316*(1-2), 42-46. doi:10.1016/j.jns.2012.02.003

Dagenais, E., Rouleau, I., Demers, M., Jobin, C., Roger, E., Chamelian, L., & Duquette, P. (2013). Value of the MoCA test as a screening instrument in multiple sclerosis. *Can J Neurol Sci, 40*(3), 410-415. doi:10.1017/s0317167100014384

Datta, S., & Roy, D. (2015). Abstract reasoning and Spatial Visualization in Formal. *International Journal of Scientific and Research Publications, 5*(10), 1-6.

Desrosiers, J., Rochette, A., & Corriveau, H. (2005). Validation of a new lower-extremity motor coordination test. *Arch Phys Med Rehabil, 86*(5), 993-998. doi:10.1016/j.apmr.2004.11.007

Dobson, R., & Giovannoni, G. (2019). Multiple sclerosis - a review. *Eur J Neurol, 26*(1), 27-40. doi:10.1111/ene.13819

Doshi, A., & Chataway, J. (2016). Multiple sclerosis, a treatable disease. *Clinical medicine (London, England), 16*(Suppl 6), s53-s59. doi:10.7861/clinmedicine.16-6-s53

Files, D. K., Jausurawong, T., Katrajian, R., & Danoff, R. (2015). Multiple sclerosis. *Prim Care, 42*(2), 159-175. doi:10.1016/j.pop.2015.01.007

Finlayson, M., Guglielmello, L., & Liefer, K. (2001). Describing and predicting the possession of assistive devices among persons with multiple sclerosis. *Am J Occup Ther, 55*(5), 545-551. doi:10.5014/ajot.55.5.545

Finlayson, M. L., Peterson, E. W., & Cho, C. C. (2006). Risk factors for falling among people aged 45 to 90 years with multiple sclerosis. *Arch Phys Med Rehabil, 87*(9), 1274-1279; quiz 1287. doi:10.1016/j.apmr.2006.06.002

Franssen, E. H., Souren, L. E., Torossian, C. L., & Reisberg, B. (1999). Equilibrium and limb coordination in mild cognitive impairment and mild Alzheimer's disease. *J Am Geriatr Soc, 47*(4), 463-469. doi:10.1111/j.1532-5415.1999.tb07240.x

Freitas, S., Batista, S., Afonso, A. C., Simoes, M. R., de Sousa, L., Cunha, L., & Santana, I. (2018). The Montreal Cognitive Assessment (MoCA) as a screening test for cognitive dysfunction in multiple sclerosis. *Appl Neuropsychol Adult, 25*(1), 57-70. doi:10.1080/23279095.2016.1243108

Freitas, S., Batista, S., Afonso, A. C., Simões, M. R., de Sousa, L., Cunha, L., & Santana, I. (2018). The Montreal Cognitive Assessment (MoCA) as a screening test for cognitive dysfunction in multiple sclerosis. *Applied Neuropsychology: Adult, 25*(1), 57-70. doi:10.1080/23279095.2016.1243108

Fritz, N. E., McCarthy, C. J., & Adamo, D. E. (2017). Handgrip strength as a means of monitoring progression of cognitive decline - A scoping review. *Ageing Res Rev, 35*, 112-123. doi:10.1016/j.arr.2017.01.004

Frohman, E. M., Racke, M. K., & Raine, C. S. (2006). Multiple sclerosis--the plaque and its pathogenesis. *N Engl J Med, 354*(9), 942-955. doi:10.1056/NEJMra052130

Gale, C. R., & Martyn, C. N. (1995). Migrant studies in multiple sclerosis. *Prog Neurobiol, 47*(4-5), 425-448.

Gelfand, J. M. (2014). Multiple sclerosis: diagnosis, differential diagnosis, and clinical presentation. *Handb Clin Neurol, 122*, 269-290. doi:10.1016/B978-0-444-52001-2.00011-X

Gonzalez-Chica, D. A., Bastos, J. L., Duquia, R. P., Bonamigo, R. R., & Martínez-Mesa, J. (2015). Test of association: which one is the most appropriate for my study? *Anais Brasileiros de Dermatologia, 90*, 523-528.

Gor-García-Fogeda, M. D., Cano-de-la-Cuerda, R., Daly, J. J., & Molina-Rueda, F. (2021). Construct Validity of the Gait Assessment and Intervention Tool (GAIT) in People With Multiple Sclerosis. *Pm r, 13*(3), 307-313. doi:10.1002/pmrj.12423

Green, S. B. (1991). How Many Subjects Does It Take To Do A Regression Analysis. *Multivariate Behav Res, 26*(3), 499-510. doi:10.1207/s15327906mbr2603_7

Grothe, M., Lotze, M., Langner, S., & Dressel, A. (2017). Impairments in Walking Ability, Dexterity, and Cognitive Function in Multiple Sclerosis Are Associated with Different Regional Cerebellar Gray Matter Loss. *Cerebellum, 16*(5-6), 945-950. doi:10.1007/s12311-017-0871-8

Grundman, M., Petersen, R. C., Ferris, S. H., Thomas, R. G., Aisen, P. S., Bennett, D. A., . . . Thal, L. J. (2004). Mild cognitive impairment can be distinguished from Alzheimer disease and normal aging for clinical trials. *Arch Neurol, 61*(1), 59-66. doi:10.1001/archneur.61.1.59

Guimarães, J., & Sá, M. J. (2012). Cognitive Dysfunction in Multiple Sclerosis. *Frontiers in Neurology, 3*(74). doi:10.3389/fneur.2012.00074

Hamilton, F., Rochester, L., Paul, L., Rafferty, D., O'Leary, C. P., & Evans, J. J. (2009). Walking and talking: an investigation of cognitive-motor dual tasking in multiple sclerosis. *Mult Scler, 15*(10), 1215-1227. doi:10.1177/1352458509106712

Hayes, K. W., & Johnson, M. E. (2003). Measures of adult general performance tests: The Berg Balance Scale, Dynamic Gait Index (DGI), Gait Velocity, Physical Performance Test (PPT), Timed Chair

Stand Test, Timed Up and Go, and Tinetti Performance-Oriented Mobility Assessment (POMA). *Arthritis Care & Research, 49*(S5), S28-S42. doi:10.1002/art.11411

Heremans, E., D'Hooge A, M., De Bondt, S., Helsen, W., & Feys, P. (2012). The relation between cognitive and motor dysfunction and motor imagery ability in patients with multiple sclerosis. *Mult Scler, 18*(9), 1303-1309. doi:10.1177/1352458512437812

Hoang, P. D., Gandevia, S. C., & Herbert, R. D. (2014). Prevalence of joint contractures and muscle weakness in people with multiple sclerosis. *Disability and Rehabilitation, 36*(19), 1588-1593. doi:10.3109/09638288.2013.854841

Hsieh, K. L., Sun, R., & Sosnoff, J. J. (2017). Cognition is associated with gait variability in individuals with multiple sclerosis. *J Neural Transm (Vienna), 124*(12), 1503-1508. doi:10.1007/s00702-017-1801-0

Huang, W. J., Chen, W. W., & Zhang, X. (2017). Multiple sclerosis: Pathology, diagnosis and treatments. *Exp Ther Med, 13*(6), 3163-3166. doi:10.3892/etm.2017.4410

Johansson, S., Ytterberg, C., Claesson, I. M., Lindberg, J., Hillert, J., Andersson, M., . . . von Koch, L. (2007). High concurrent presence of disability in multiple sclerosis. Associations with perceived health. *J Neurol, 254*(6), 767-773. doi:10.1007/s00415-006-0431-5

Kalron, A., Achiron, A., & Dvir, Z. (2011). Muscular and Gait Abnormalities in Persons With Early Onset Multiple Sclerosis. *Journal of Neurologic Physical Therapy, 35*(4). Retrieved from https://journals.lww.com/jnpt/Fulltext/2011/12000/Muscular_and_Gait_Abnormalities_in_Persons_With.3.aspx

Kalron, A., Allali, G., & Achiron, A. (2018). Cerebellum and cognition in multiple sclerosis: the fall status matters. *J Neurol, 265*(4), 809-816. doi:10.1007/s00415-018-8774-2

Kalron, A., Aloni, R., Dolev, M., Frid, L., Givon, U., & Menascu, S. (2018). The relationship between gait variability and cognitive functions differs between fallers and non-fallers in MS. *J Neural Transm (Vienna), 125*(6), 945-952. doi:10.1007/s00702-018-1843-y

Karussis, D. (2014). The diagnosis of multiple sclerosis and the various related demyelinating syndromes: a critical review. *J Autoimmun, 48-49*, 134-142. doi:10.1016/j.jaut.2014.01.022

Kent-Braun, J. A., Ng, A. V., Castro, M., Weiner, M. W., Gelinas, D., Dudley, G. A., & Miller, R. G. (1997). Strength, skeletal muscle composition, and enzyme activity in multiple sclerosis. *Journal of Applied Physiology, 83*(6), 1998-2004. doi:10.1152/jappl.1997.83.6.1998

Kerr, A., Syddall, H. E., Cooper, C., Turner, G. F., Briggs, R. S., & Sayer, A. A. (2006). Does admission grip strength predict length of stay in hospitalised older patients? *Age Ageing, 35*(1), 82-84. doi:10.1093/ageing/afj010

Koch-Henriksen, N., & Sorensen, P. S. (2010). The changing demographic pattern of multiple sclerosis epidemiology. *Lancet Neurol, 9*(5), 520-532. doi:10.1016/s1474-4422(10)70064-8

Krishnan, V., Kanekar, N., & Aruin, A. S. (2012). Feedforward postural control in individuals with multiple sclerosis during load release. *Gait Posture, 36*(2), 225-230. doi:https://doi.org/10.1016/j.gaitpost.2012.02.022

Kurtzke, J. F. (1983). Rating neurologic impairment in multiple sclerosis. *Neurology, 33*(11), 1444. doi:10.1212/WNL.33.11.1444

Lam, B., Middleton, L. E., Masellis, M., Stuss, D. T., Harry, R. D., Kiss, A., & Black, S. E. (2013). Criterion and convergent validity of the Montreal cognitive assessment with screening and

standardized neuropsychological testing. *J Am Geriatr Soc, 61*(12), 2181-2185. doi:10.1111/jgs.12541

Lamers, I., Kelchtermans, S., Baert, I., & Feys, P. (2014). Upper limb assessment in multiple sclerosis: a systematic review of outcome measures and their psychometric properties. *Arch Phys Med Rehabil, 95*(6), 1184-1200. doi:10.1016/j.apmr.2014.02.023

Lanzino, D. J., Conner, M. N., Goodman, K. A., Kremer, K. H., Petkus, M. T., & Hollman, J. H. (2012). Values for timed limb coordination tests in a sample of healthy older adults. *Age Ageing, 41*(6), 803-807. doi:10.1093/ageing/afs070

Lanzino, D. J., Rabinstein, A., Kinlaw, D., Hepburn, S. B., Ness, B. M., Olson, K. J., . . . Hollman, J. H. (2012). Coordination tests in persons with acute central nervous system pathology: assessment of interrater reliability and known-group validity. *J Neurol Phys Ther, 36*(3), 122-130. doi:10.1097/NPT.0b013e3182641d36

Larocca, N. (2011). Impact of Walking Impairment in Multiple Sclerosis Perspectives of Patients and Care Partners. *Patient, 4*, 189-201. doi:10.2165/11591150-000000000-00000

Larocca, N. G. (2011). Impact of walking impairment in multiple sclerosis: perspectives of patients and care partners. *Patient, 4*(3), 189-201. doi:10.2165/11591150-000000000-00000

Lassmann, H. (2011). Pathophysiology of inflammation and tissue injury in multiple sclerosis: what are the targets for therapy. *J Neurol Sci, 306*(1-2), 167-169. doi:10.1016/j.jns.2010.07.023

Lohman, D. F. (1979). *Spatial Ability: A Review and Reanalysis of the Correlational Literature*. Retrieved from

Lublin, F. D. (2005). Clinical features and diagnosis of multiple sclerosis. *Neurol Clin, 23*(1), 1-15, v. doi:10.1016/j.ncl.2004.09.003

Lublin, F. D., & Reingold, S. C. (1996). Defining the clinical course of multiple sclerosis. *Neurology, 46*(4), 907. doi:10.1212/WNL.46.4.907

Macias Islas, M. A., & Ciampi, E. (2019). Assessment and Impact of Cognitive Impairment in Multiple Sclerosis: An Overview. *Biomedicines, 7*(1). doi:10.3390/biomedicines7010022

Macniven, J. A., Davis, C., Ho, M. Y., Bradshaw, C. M., Szabadi, E., & Constantinescu, C. S. (2008). Stroop performance in multiple sclerosis: information processing, selective attention, or executive functioning? *J Int Neuropsychol Soc, 14*(5), 805-814. doi:10.1017/s1355617708080946

Mañago, M. M., Hebert, J. R., & Schenkman, M. (2017). Psychometric Properties of a Clinical Strength Assessment Protocol in People with Multiple Sclerosis. *International Journal of MS Care, 19*(5), 253-262. doi:10.7224/1537-2073.2016-078

Mapstone, M. (2005). Neuropsychological Assessment, 4th Edition. *Neurology, 64*, 1103-1103. doi:10.1212/01.WNL.0000156290.58489.54

Matsuda, P. N., Shumway-Cook, A., Bamer, A. M., Johnson, S. L., Amtmann, D., & Kraft, G. H. (2011). Falls in multiple sclerosis. *Pm r, 3*(7), 624-632; quiz 632. doi:10.1016/j.pmrj.2011.04.015

McNicholas, N., O'Connell, K., Yap, S. M., Killeen, R. P., Hutchinson, M., & McGuigan, C. (2018). Cognitive dysfunction in early multiple sclerosis: a review. *Qjm, 111*(6), 359-364. doi:10.1093/qjmed/hcx070

Middleton, F. A., & Strick, P. L. (1994). Anatomical evidence for cerebellar and basal ganglia involvement in higher cognitive function. *Science, 266*(5184), 458-461. doi:10.1126/science.7939688

Miller, A. J. (1984). Sélection of subsets of regression variables. *Journal of the Royal Statistical Society, 147*, 389-425.

Miller, D. H., Barkhof, F., Frank, J. A., Parker, G. J., & Thompson, A. J. (2002). Measurement of atrophy in multiple sclerosis: pathological basis, methodological aspects and clinical relevance. *Brain, 125*(Pt 8), 1676-1695. doi:10.1093/brain/awf177

Mills, R. J., Yap, L., & Young, C. A. (2007). Treatment for ataxia in multiple sclerosis. *Cochrane Database Syst Rev*(1), Cd005029. doi:10.1002/14651858.CD005029.pub2

Mirsky, A. F., Fantie, B. D., & Tatman, J. E. (1995). Assessment of attention across the lifespan. In *Clinical Neuropsychological Assessment* (pp. 17-48): Springer.

Miyake, A., & Friedman, N. P. (2012). The Nature and Organization of Individual Differences in Executive Functions: Four General Conclusions. *Current directions in psychological science, 21*(1), 8-14. doi:10.1177/0963721411429458

Morey, M. C., Pieper, C. F., & Cornoni-Huntley, J. (1998). Physical fitness and functional limitations in community-dwelling older adults. *Med Sci Sports Exerc, 30*(5), 715-723. doi:10.1097/00005768-199805000-00012

Myhr, K. M., Riise, T., Vedeler, C., Nortvedt, M. W., Gronning, R., Midgard, R., & Nyland, H. I. (2001). Disability and prognosis in multiple sclerosis: demographic and clinical variables important for the ability to walk and awarding of disability pension. *Mult Scler, 7*(1), 59-65. doi:10.1177/135245850100700110

Nilsagard, Y., Denison, E., Gunnarsson, L. G., & Bostrom, K. (2009). Factors perceived as being related to accidental falls by persons with multiple sclerosis. *Disabil Rehabil, 31*(16), 1301-1310. doi:10.1080/09638280802532639

Nilsagard, Y., Lundholm, C., Denison, E., & Gunnarsson, L. G. (2009). Predicting accidental falls in people with multiple sclerosis -- a longitudinal study. *Clin Rehabil, 23*(3), 259-269. doi:10.1177/0269215508095087

Paltamaa, J., West, H., Sarasoja, T., Wikström, J., & Mälkiä, E. (2005). Reliability of physical functioning measures in ambulatory subjects with MS. *Physiother Res Int, 10*(2), 93-109. doi:10.1002/pri.30

Parish, L., & Guilford, J. P. (1957). Fundamental Statistics in Psychology and Education. *British Journal of Educational Studies, 5*, 191.

Perrochon, A., Holtzer, R., Laidet, M., Armand, S., Assal, F., Lalive, P. H., & Allali, G. (2017). Postural control is associated with cognition and fear of falling in patients with multiple sclerosis. *J Neural Transm (Vienna), 124*(4), 495-500. doi:10.1007/s00702-016-1668-5

Peterson, E. W., Cho, C. C., von Koch, L., & Finlayson, M. L. (2008). Injurious falls among middle aged and older adults with multiple sclerosis. *Arch Phys Med Rehabil, 89*(6), 1031-1037. doi:10.1016/j.apmr.2007.10.043

Pinheiro, M. d. B., Menezes, K. K. P. d., & Teixeira-Salmela, L. F. (2014). Review of the psychometric properties of lower limb motor coordination tests. *Fisioterapia em Movimento, 27*, 541-553. Retrieved from http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0103-51502014000400541&nrm=iso

Piras, M. R., Magnano, I., Canu, E. D. G., Paulus, K. S., Satta, W. M., Soddu, A., . . . Aiello, I. (2003). Longitudinal study of cognitive dysfunction in multiple sclerosis: neuropsychological,

neuroradiological, and neurophysiological findings. *Journal of Neurology, Neurosurgery & Psychiatry, 74*(7), 878-885.

Popescu, B. F., Pirko, I., & Lucchinetti, C. F. (2013). Pathology of multiple sclerosis: where do we stand? *Continuum (Minneap Minn), 19*(4 Multiple Sclerosis), 901-921. doi:10.1212/01.Con.0000433291.23091.65

Posner, M. I. (1994). Attention: the mechanisms of consciousness. *Proceedings of the National Academy of Sciences, 91*(16), 7398. doi:10.1073/pnas.91.16.7398

Rahman, T. T., & El Gaafary, M. M. (2009). Montreal Cognitive Assessment Arabic version: reliability and validity prevalence of mild cognitive impairment among elderly attending geriatric clubs in Cairo. *Geriatr Gerontol Int, 9*(1), 54-61. doi:10.1111/j.1447-0594.2008.00509.x

Raiche, M., Hebert, R., Prince, F., & Corriveau, H. (2000). Screening older adults at risk of falling with the Tinetti balance scale. *Lancet, 356*(9234), 1001-1002. doi:10.1016/s0140-6736(00)02695-7

Ramagopalan, S. V., & Sadovnick, A. D. (2011). Epidemiology of Multiple Sclerosis. *Neurologic Clinics, 29*(2), 207-217. doi:https://doi.org/10.1016/j.ncl.2010.12.010

Rao, S. M. (2004). Cognitive Function in Patients with Multiple Sclerosis: Impairment and Treatment. *International Journal of MS Care, 6*(1), 9-22. doi:10.7224/1537-2073-6.1.9

Rao, S. M., Leo, G. J., Bernardin, L., & Unverzagt, F. (1991). Cognitive dysfunction in multiple sclerosis. I. Frequency, patterns, and prediction. *Neurology, 41*(5), 685-691. doi:10.1212/wnl.41.5.685

Rao, S. M., Leo, G. J., Bernardin, L., & Unverzagt, F. (1991). Cognitive dysfunction in multiple sclerosis.: I. Frequency, patterns, and prediction. *Neurology, 41*(5), 685-691.

Rasova, K., Martinkova, P., Vyskotova, J., & Sedova, M. (2012). Assessment set for evaluation of clinical outcomes in multiple sclerosis: psychometric properties. *Patient Relat Outcome Meas, 3*, 59-70. doi:10.2147/PROM.S32241

Reich, D. S., Zackowski, K. M., Gordon-Lipkin, E. M., Smith, S. A., Chodkowski, B. A., Cutter, G. R., & Calabresi, P. A. (2008). Corticospinal Tract Abnormalities Are Associated with Weakness in Multiple Sclerosis. *American Journal of Neuroradiology, 29*(2), 333. doi:10.3174/ajnr.A0788

Roberts, H. C., Syddall, H. E., Cooper, C., & Aihie Sayer, A. (2012). Is grip strength associated with length of stay in hospitalised older patients admitted for rehabilitation? Findings from the Southampton grip strength study. *Age Ageing, 41*(5), 641-646. doi:10.1093/ageing/afs089

Rogers, A. W. (1988). Mosby's Guide to Physical Examination. *Journal of Anatomy, 157*, 235-235. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1261959/

Ruet, A., Hamel, D., Deloire, M. S., Charre-Morin, J., Saubusse, A., & Brochet, B. (2014). Information processing speed impairment and cerebellar dysfunction in relapsing-remitting multiple sclerosis. *J Neurol Sci, 347*(1-2), 246-250. doi:10.1016/j.jns.2014.10.008

Rycroft, S. S., Quach, L. T., Ward, R. E., Pedersen, M. M., Grande, L., & Bean, J. F. (2019). The Relationship Between Cognitive Impairment and Upper Extremity Function in Older Primary Care Patients. *J Gerontol A Biol Sci Med Sci, 74*(4), 568-574. doi:10.1093/gerona/gly246

Sandroff, B. M., Pilutti, L. A., Benedict, R. H., & Motl, R. W. (2015). Association between physical fitness and cognitive function in multiple sclerosis: does disability status matter? *Neurorehabil Neural Repair, 29*(3), 214-223. doi:10.1177/1545968314541331

Sarica, A., Cerasa, A., & Quattrone, A. (2015). The neurocognitive profile of the cerebellum in multiple sclerosis. *Int J Mol Sci, 16*(6), 12185-12198. doi:10.3390/ijms160612185

Savica, R., Wennberg, A. M., Hagen, C., Edwards, K., Roberts, R. O., Hollman, J. H., . . . Mielke, M. M. (2017). Comparison of Gait Parameters for Predicting Cognitive Decline: The Mayo Clinic Study of Aging. *J Alzheimers Dis, 55*(2), 559-567. doi:10.3233/jad-160697

Schapiro, R. T. (1994). Symptom management in multiple sclerosis. *Ann Neurol, 36 Suppl*, S123-129. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/8017873

Schiavolin, S., Leonardi, M., Giovannetti, A. M., Antozzi, C., Brambilla, L., Confalonieri, P., . . . Raggi, A. (2013). Factors related to difficulties with employment in patients with multiple sclerosis: a review of 2002-2011 literature. *Int J Rehabil Res, 36*(2), 105-111. doi:10.1097/MRR.0b013e32835c79ea

Schmahmann, J. D. (2004). Disorders of the cerebellum: ataxia, dysmetria of thought, and the cerebellar cognitive affective syndrome. *J Neuropsychiatry Clin Neurosci, 16*(3), 367-378. doi:10.1176/jnp.16.3.367

Schwartz, S., Cohen, M. E., Herbison, G. J., & Shah, A. (1992). Relationship between two measures of upper extremity strength: Manual muscle test compared to hand-held myometry. *Arch Phys Med Rehabil, 73*(11), 1063-1068. doi:10.5555/uri:pii:000399939290172S

Shyam Kumar, A. J., Beresford-Cleary, N., Kumar, P., Barai, A., Vasukutty, N., Yasin, S., & Sinha, A. (2013). Preoperative grip strength measurement and duration of hospital stay in patients undergoing total hip and knee arthroplasty. *Eur J Orthop Surg Traumatol, 23*(5), 553-556. doi:10.1007/s00590-012-1029-5

Sosnoff, J. J., Balantrapu, S., Pilutti, L. A., Sandroff, B. M., Morrison, S., & Motl, R. W. (2013). Cognitive processing speed is related to fall frequency in older adults with multiple sclerosis. *Arch Phys Med Rehabil, 94*(8), 1567-1572. doi:10.1016/j.apmr.2013.02.009

Sosnoff, J. J., Socie, M. J., Boes, M. K., Sandroff, B. M., Pula, J. H., Suh, Y., . . . Motl, R. W. (2011). Mobility, balance and falls in persons with multiple sclerosis. *PLoS One, 6*(11), e28021. doi:10.1371/journal.pone.0028021

Speers, R. A., Kuo, A. D., & Horak, F. B. (2002). Contributions of altered sensation and feedback responses to changes in coordination of postural control due to aging. *Gait Posture, 16*(1), 20-30. doi:10.1016/s0966-6362(02)00003-6

Stevens, V., Goodman, K., Rough, K., & Kraft, G. H. (2013). Gait impairment and optimizing mobility in multiple sclerosis. *Phys Med Rehabil Clin N Am, 24*(4), 573-592. doi:10.1016/j.pmr.2013.07.002

Swingler, R. J., & Compston, D. A. (1992). The morbidity of multiple sclerosis. *Q J Med, 83*(300), 325-337.

Tedesco, A. M., Chiricozzi, F. R., Clausi, S., Lupo, M., Molinari, M., & Leggio, M. G. (2011). The cerebellar cognitive profile. *Brain, 134*(Pt 12), 3672-3686. doi:10.1093/brain/awr266

Tinetti, M. E. (1986). Performance-oriented assessment of mobility problems in elderly patients. *J Am Geriatr Soc, 34*(2), 119-126. doi:10.1111/j.1532-5415.1986.tb05480.x

Tranmer, M., & Elliot, M. (2008). Multiple linear regression. *The Cathie Marsh Centre for Census and Survey Research (CCSR), 5*(5), 1-5.

Trosclair, D., Bellar, D., Judge, L. W., Smith, J., Mazerat, N., & Brignac, A. (2011). Hand-Grip Strength as a Predictor of Muscular Strength and Endurance. *The Journal of Strength & Conditioning Research, 25*, S99. doi:10.1097/01.JSC.0000395736.42557.bc

Valentino, P., Cerasa, A., Chiriaco, C., Nisticò, R., Pirritano, D., Gioia, M., . . . Quattrone, A. (2009). Cognitive deficits in multiple sclerosis patients with cerebellar symptoms. *Mult Scler, 15*, 854-859. doi:10.1177/1352458509104589

Vander Linden, D. W. (1996). Shumway-Cook A, Wollacott MH. Motor Control: Theory and Practical Applications. Baltimore, Md:: Williams and Wilkins Inc; 1995. Hardcover, 475 pp, $43. *Journal of Neurologic Physical Therapy, 20*(1), 64-65.

Verghese, J., Wang, C., Lipton, R. B., Holtzer, R., & Xue, X. (2007). Quantitative gait dysfunction and risk of cognitive decline and dementia. *Journal of Neurology, Neurosurgery & Psychiatry, 78*(9), 929. doi:10.1136/jnnp.2006.106914

Walton, C., King, R., Rechtman, L., Kaye, W., Leray, E., Marrie, R. A., . . . Baneke, P. (2020). Rising prevalence of multiple sclerosis worldwide: Insights from the Atlas of MS, third edition. *Multiple Sclerosis Journal, 26*(14), 1816-1821. doi:10.1177/1352458520970841

Wang, M., Leger, A. B., & Dumas, G. A. (2005). Prediction of back strength using anthropometric and strength measurements in healthy females. *Clin Biomech (Bristol, Avon), 20*(7), 685-692. doi:10.1016/j.clinbiomech.2005.03.003

Weinshenker, B. G., Bass, B., Rice, G. P., Noseworthy, J., Carriere, W., Baskerville, J., & Ebers, G. C. (1989). The natural history of multiple sclerosis: a geographically based study. I. Clinical course and disability. *Brain, 112 (Pt 1)*, 133-146. doi:10.1093/brain/112.1.133

WHO/International Classification of Functioning: Walking. *[Online] http://apps.who.int/classifications/icfbrowser/*. Retrieved from http://apps.who.int/classifications/icfbrowser/

Wilkins, A. (2017). Cerebellar Dysfunction in Multiple Sclerosis. *Front Neurol, 8*, 312. doi:10.3389/fneur.2017.00312

Wind, A. E., Takken, T., Helders, P. J., & Engelbert, R. H. (2010). Is grip strength a predictor for total muscle strength in healthy children, adolescents, and young adults? *Eur J Pediatr, 169*(3), 281-287. doi:10.1007/s00431-009-1010-4

Woollacott, M. (2009). Anticipatory Postural Responses. In M. D. Binder, N. Hirokawa, & U. Windhorst (Eds.), *Encyclopedia of Neuroscience* (pp. 134-135). Berlin, Heidelberg: Springer Berlin Heidelberg.

Zwibel, H. L. (2009). Contribution of impaired mobility and general symptoms to the burden of multiple sclerosis. *Adv Ther, 26*(12), 1043-1057. doi:10.1007/s12325-009-0082-x

VIII. Appendices

Appendix A. Tinetti Performance Oriented Mobility Assessment (POMA)

Tinetti Performance Oriented Mobility Assessment (POMA)	Date	Date	Date	Date
Balance Tests: Subject is seated on hard, armless chair				
SITTING BALANCE Leans or slides in chair =0, Steady, safe =1				
ARISES Unable without help =0; Able, uses arms =1, Able without using arms = 2				
ATTEMPTS TO RISE: Unable w/o help=0; Able, requires > 1 attempt =1; Able in 1 attempt =2				
IMMEDIATE STANDING BALANCE (first 5 seconds) Unsteady (sway/stagger/feet move)=0; Steady, w/ support =1;Steady w/o support =2				
STANDING BALANCE Unsteady =0; Steady, stance > 4 inch BOS & requires support =1; Narrow stance, w/o support =2				
STERNAL NUDGE (feet close together) Begins to fall =0; Staggers, grabs, catches self =1; Steady =2				
EYES CLOSED (feet close together) Unsteady =0; Steady =1				
TURNING 360 DEGREES Discontinuous steps =0; Continuous steps =1				
TURNING 360 DEGREES Unsteady (staggers, grabs) =0;Steady =1				
SITTING DOWN Unsafe (misjudges distance, falls) =0;Uses arms, or not a smooth motion =1; Safe, smooth motion =2				
BALANCE SCORE TOTAL	/16	/16	/16	/16
GAIT INITATION (immediate after told "go) Any hesitancy, multiple attempts to start =0; No hesitancy =1				
STEP LENGTH R swing foot passes L stance leg =1; L swing foot passes R =1				
FOOT CLEARANCE R foot completely clears floor =1; L foot completely clears floor =1				
STEP SYMMETRY R and L step length unequal =0; R and L step length equal=1				
STEP CONTINUITY Stop/discontinuity between steps =0; Steps appear continuous =1				
PATH (excursion) Marked deviation =0; Mild/moderate deviation or use of aid =1; Straight without device=2				
TRUNK Marked sway or uses device =0; No sway but knee or trunk flexion or spread arms while walking =1; None of the above deviations=2				
BASE OF SUPPORT Heels apart =0; Heels close while walking =1				
GAIT SCORE TOTAL	/12	/12	/12	/12
ASSISTIVE DEVICE				
TOTAL SCORE (BALANCE + GAIT) **FALL RISK** **(minimal >23, Mod. 19-23, High < 19)**	/28	/28	/28	/28
Therapist initials				

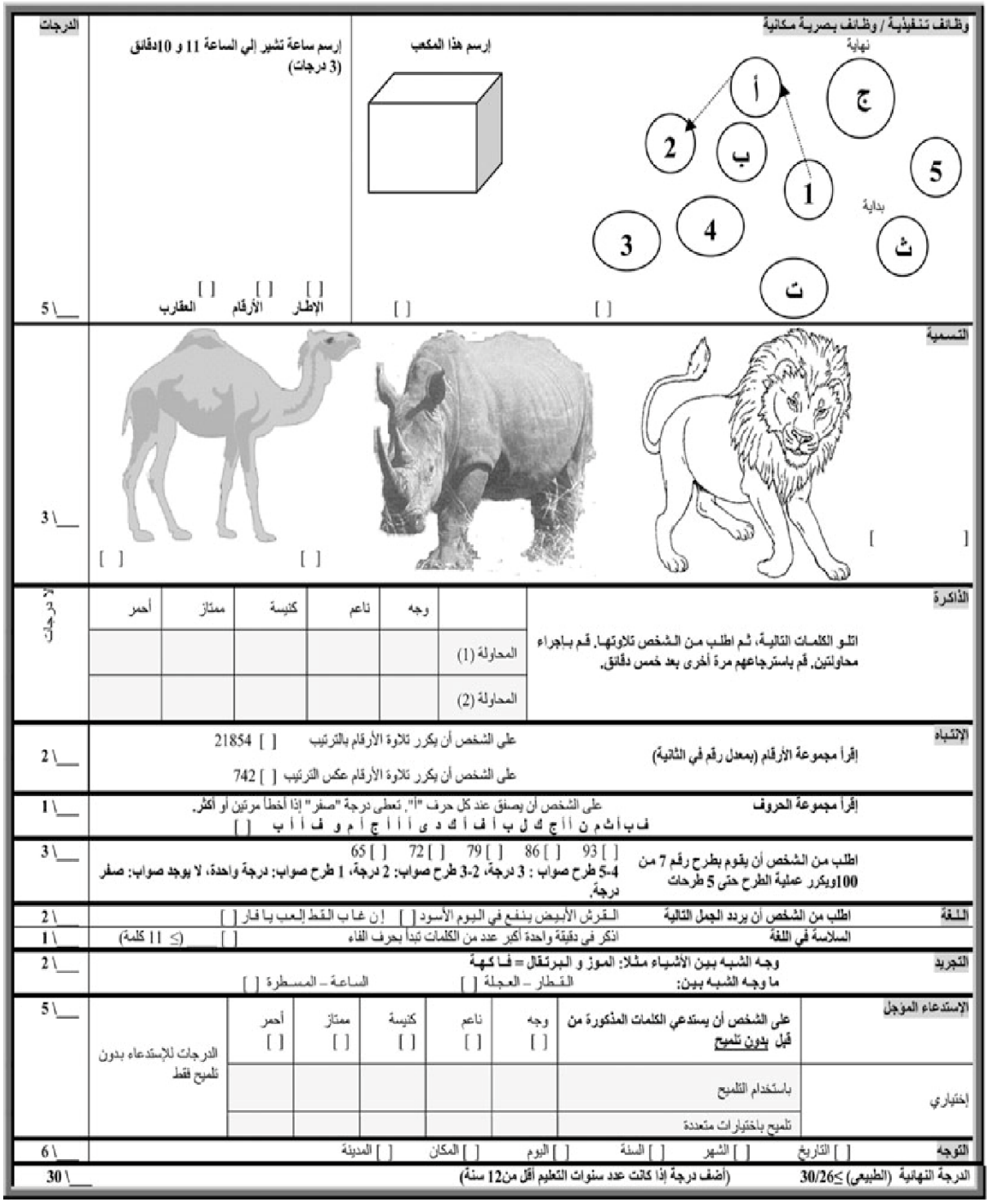
Appendix B. Modified Ashworth Scale (MAS)

Grade	Description
0	No increase in muscle tone
1	Slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of the range of motion when the affected part/s is/are moved in flexion or extension.
1+	Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the ROM.
2	More marked increase in muscle tone through most of the ROM, but affected part(s) easily moved.
3	Considerable increase in muscle tone, passive movement difficult.
4	Affected part(s) rigid in flexion or extension.

ROM, range of motion.

Appendix C. Montreal Cognitive Assessment Scale (MoCA)

النسخة العربية المعدلة من تقييم مونتريال المعرفي الإسم: تاريخ الميلاد: التاريخ: التعليم: الجنس (النوع):



Appendix D. Patient's Consent Form

جامعة الملك سعود
King Saud University

نموذج الموافقة على المشاركة في دراسة بحثية

اسم الباحث الأساسي: هنادي مطر الحارثي

اسم و عنوان الجامعة: جامعة الملك سعود بالرياض

رقم الاتصال: 0557272503

عنوان مشروع البحث:

العلاقة بين الضعف الإدراكي والإختلال الحركي لدى مرضى التصلب العصبي المتعدد الإنتكاسي.

أهمية البحث:

دراسة العلاقة بين ضعف الإدراك والإختلال الحركي لدى مرضى التصلب العصبي الإنتكاسي تساعد أخصائي العلاج الطبيعي لمعرفة حالة المريض بشكل أوضح، وكذلك تمكنه من تصميم واختيار العلاج المناسب له بما يتوافق مع قدراته الحركية والإدراكية، وبما يضمن تعاون المريض معه للحصول على نتيجة أفضل في كلا الجانبين الحركي والإدراكي معاً.

طريقة البحث:

سيقوم أخصائي العلاج الطبيعي بجمع بيانات متعلقة بعدة مقاييس تخص كلا الجانبين الإدراكي والحركي لدى مرضى التصلب العصبي المتعدد لغرض دراسة العلاقة بينهما. المقاييس تشمل: مقياس مونتريال لتقييم القدرة الإدراكية، مقياس تينتي لتقييم التوازن والمشي وخطر السقوط، واختبار التناسق الحركي للأطراف العلوية والسفلية.

المشاركة في هذه الدراسة البحثية ستكون تطوعية، ويحق للمتطوع رفض المشاركة بدون فرض عقوبات ولا يؤثر على خطة العلاج.

جميع المعلومات في هذا البحث سيتم التعامل معها بسرية تامة.

هل ترغب في المشاركة في هذه الدراسة البحثية؟

نعم أوافق أنا ..... على المشاركة في هذه الدراسة البحثية
التوقيع.....

Appendix E. Certificate of Completion Training and Certification Program to Administer and Score Montreal Cognitive Assessment MoCA©

MoCA
MONTREAL
COGNITIVE ASSESSMENT

CERTIFICATE OF COMPLETION

This certificate acknowledges that

Hanadi Alharthi

has successfully completed a one hour training and certification to administer and score the Montreal Cognitive Assessment, MoCA. Only health professionals with expertise in cognition can interpret test results.

Completion date: 2020/02/25

Expiration date: 2022/02/25

Dr Nasreddine, Ziad

Appendix F. Demographic Data Screening Sheet

King Saud University

College of Applied Medical Sciences

Department of Medical Rehabilitation Sciences

Physical Therapy Department

Screening Sheet Participant's Demographic Data		
Code:	Date:	
Participant Name:	Medical File No.	
Date of Birth:	Contact No.	
Nationality: ○ Saudi ○ Non-Saudi		
Dominant Hand: ○ Right ○ Left		
Gender: ○ Male ○ Female		
Educational Level: ○ Primary ○ Intermediate ○ Secondary ○ Bachelor ○ Other:		
Weight: Kg	Height: cm	BMI:
MS subtype		
Age at onset of symptoms		
Disease duration		
Ability to walk	○ Yes ○ No	Assistive device: _____
This from completed by ○ Patient ○ Other, Specify: _____Signature: _____		
Examiner Name: _____ Signature: _____ Date _____		