Pattern Identification Between Multiple Sclerosis Relapses and Information Processing Speed

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A Clinical Research Project presented to the faculty of the Hawai‘i School of Professional Psychology at Argosy University in partial fulfillment of the requirements for the degree of Doctor of Psychology in Clinical Psychology.

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This Clinical Research Project by (Name of Student), directed and approved by the candidate's Clinical Research Project Committee, was approved by the faculty of the Hawai‘i School of Professional Psychology at Argosy University in partial fulfillment of the requirements of the degree of Doctor of Psychology in Clinical Psychology.

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Hawai‘i School of Professional Psychology at Argosy University - 2018

Dedication

For Jim, who never let his Multiple Sclerosis define him. And for Liz, because beside every great man, is a great woman.

Acknowledgments

Thank you faculty of the Hawai‘i School of Professional Psychology at Argosy University for fostering my goals, as unobtainable as I thought they initially were, your guidance and encouragement has provided me understanding that nothing is left to the impossible.

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CHAPTER I: INTRODUCTION

Multiple Sclerosis (MS) is a debilitating disease that can lead to chronic symptoms (Forn, Belenguer, Parcet-Ibars, & Avila, 2008). Much is known about the physical disabilities of MS, and clinicians continue to work towards finding effective treatments to improve the quality of life. More recently, there has been a shift in focus towards studying cognitive impairment in MS. One cognitive domain that is commonly impaired is information processing speed (IPS) (Bodling, Denney, & Lynch, 2009; Denney, Sworowski, & Lynch, 2005; Drake et al., 2010; Forn et al., 2008). This domain is essential for the function of several other cognitive domains, which is why impairment of IPS can be detrimental (Forn et al., 2008). Indeed, without addressing IPS in cognitive rehabilitation, this can lead to premature life decisions, such as retirement (Aupperle, Beatty, deNAP Shelton & Gontkovsky, 2002).

In an attempt to consider possible factors that explain these phenomena, emergent research has focused on cognitive ability in MS populations (Benedict et al., 2014; Bsteh, 2016; Nickerson et al., 2015;; Scalfari et al., 2010). One factor that has been shown to increase the likelihood of developing cognitive impairment is experiencing one or more MS relapses (Bsteh et al., 2016; Scalfari et al., 2010). Research has begun to conceptualize characteristics of cognitive impairment during and after MS relapses, as well as how the number of relapses can affect cognition long-term. However, there have been mixed results, leaving conclusions controversial (Confavreux, Vukusic, Moreau, & Adeleine, 2000). Additionally, it appears that research on IPS long-term in MS populations, as well as information on the IPS and relapse relationship, is scarce. The combination of mixed research results and few studies has created an absence of a distinct patterns in cognitive impairment, particularly for IPS, in MS populations.

Rationale for Study

Cognitive impairment is a common phenomenon within MS that cannot be ignored (Amato, Ponziani, Siracusa, & Sorbi, 2001). As such, there is a growing consensus that cognitive impairment may be an important symptomology of MS, making it a prominent topic in neurological and psychoneurological research over the last decade (Achiron & Barak, 2003). A cognitive ability that is commonly impaired from MS, if not the most impaired, is IPS (Bodling, Denney, & Lynch, 2009; Drake et al., 2010; Forn et al., 2008; Denney, Sworowski, & Lynch, 2005). Since this cognitive domain appears to underline the performance of many other cognitive abilities, decline in IPS can result in dysfunction in multiple domains, which is quite apparent after experiencing one or more multiple sclerosis relapses (Bsteh et al., 2016; DeLuca et al., 2004; Scalfari et al., 2010).

It is to the best of the researcher's knowledge that this is the first study to examine the relationship between the number of MS relapses and IPS, in attempt to find a distinct pattern of IPS impairment based on the number of relapses individuals may have. Although there are studies that have examined IPS in individuals with MS, particularly during and after a single relapse, it does not seem as though IPS has been specifically measured after experiencing multiple relapses. Further, research has examined cognitive dysfunction over long durations of MS while considering the number of relapses, but it does not appear as though IPS has been examined thoroughly – only cognitive impairment in general. In addition, it does not seem as though that the differences in IPS ability, based on the number of relapses, has been identified in previous literature.

The lack of research on the relationship between the number of MS relapses and IPS has left unanswered questions. There remains an unidentifiable pattern and magnitude of cognitive

impairment in MS, particularly IPS impairment, thus recognizing a distinct clinical course of dysfunction is difficult (Bseth et al., 2016; Zakzanis, 2000). Although it has been suggested that cognitive impairment can result from multiple relapses, thus creating a cumulative-like disability, there has not been well-defined outcomes (Bsteh et al., 2016; Scalfari et al., 2010). This is especially notable for later relapses and progressions of MS (Scalfari et al., 2010). The lack of detailed explanation for what is already known makes it difficult to formulate a pattern or clinical course of IPS impairment, as well as adequately link IPS impairment with the number of MS relapses.

Review of Literature

Multiple Sclerosis

Multiple Sclerosis (MS) is a demyelinating disease of the central nervous system (Benedict, et al., 2014). Demyelination is the process in which the insulating cover of axons are destroyed, damaging the conduction ability of signals within and between neurons, leading to cell death in the brain and spinal cord (Benedict et al., 2014; Bsteh, et al., 2016). MS is also immune-mediated, and the destruction of this system in combination of cell loss from demyelination may result in physical and cognitive problems, as well as death (Benedict et al., 2014). MS is considered the most prevalent cause of irreversible neurological disability in young adults, affecting approximately 120 out of 100,000 (Forn et al., 2008). In Western countries, MS affects 1 in 1,000 individuals (Confavreux, Vukusic, Moreau, & Adeleine, 2000). Further, approximately 400,000 individuals in the United States are currently diagnosed with MS, at a rate of 200 new cases per week.

Types of MS There are four types of MS (Bsteh et al., 2016; Hooper 2011). It is not uncommon for "types" to be interchangeable with "phases" however, not all individuals may experience every phase; therefore, "types" appeared more suited. The first, and most common, is relapsing-remitting multiple sclerosis (RRMS) (Besteh; 2016; Confavreux et al., 2000; Hooper, 2011). This type is typically the most prevalent at onset, and individuals are diagnosed at approximately thirty years of age (Confavruex et al., 2000). RRMS is characterized as episodes of dysfunction, following periods of remission, or clinical stability. These "episodes" are known as relapses, which are either acute inflammation of existing lesions, or the development of new lesions in the central nervous system. As a result, these lesions may create a sudden onset of physical and/or mental disability that is temporary or permanent (Scalfari, et al., 2010). These relapses are diagnosed through a neurological examination and characterized by the Expanded Disability Status Scale (EDSS) (Benedict et al., 2014). The EDSS, specifically designed for MS, quantifies disability by examining several functional systems and rating the disability from "Normal" to "Death due to MS." The severity of relapses and their frequency varies for each person. For individuals with RRMS, the typical course of the disease is followed by a progressive type of the disease, with or without continued relapses or remissions (Confavreux et al., 2000).

The second type of MS is known as secondary-progressive multiple sclerosis (SPMS) (Bsteh et al., 2016; Hooper, 2011). This type is characterized by a gradual progression of symptom severity over time, which may or may not consist of relapses or remissions (Bsteh et al., 2016). SPMS coincides with RRMS most frequently, in that individuals with RRMS typically become diagnosed with SPMS at some point, and creates a greater probability of accumulating permanent disability. The third type, which is less common, is known as primary-

progressive multiple sclerosis (PPMS) (Hooper, 2011). Only occurring in approximately ten percent of those diagnosed with MS, this type is characterized as the progression of symptoms over time beginning at onset, without any relapses or remissions. The last type is known as progressive-relapsing multiple sclerosis (PRMS). Occurring in approximately five percent of individuals diagnosed with MS, this type is characterized as progression of symptom severity at onset, in combination of relapses, but with no remissions.

Each type of MS has its own distinct characterization and course. One type may be diagnosed at onset, but it could manifest into another type – the most common disease course being RRMS to SPMS (Confavreux et al., 2000). Although progressive types could be considered as the most impactful, given the continued worsening of symptoms, relapses should not be overlooked. Specifically, neurologic disability that may result from relapses can lead to permanent loss of physical and/or cognitive function, thus dictating the course and outcome of progressive types in terms of not only symptom severity, but also quality of life. Due to this, RRMS should not be ignored, and may be considered as a significant factor in the medical, social, and economic impact of MS.

Multiple Sclerosis and Cognitive Impairment

The development of cognitive impairments for individuals with MS is not uncommon (Camp et al., 1999; Davis, Williams, Gupta, Finch, & Randolph, 2015). Indeed, cognitive performance of MS individuals, when compared to healthy population norms, has shown to be poorer (Achiron et al., 2013; Demaree, DeLuca, Gaudino, & Diamond, 1999; Forn, Belenguer, Parcet-Ibars, & Avila, 2008; Santos, Pinheiro, & Barros, 2015). However, there has been a relatively wide report in cognitive impairment prevalence rates (Santos, Pinheiro, & Barros, 2015). Research has shown that cognitive impairment has been estimated between 30% to 70%

of cases (Amato, Ponziani, Siracusa, & Sorbi, 2001). There have also been reports of slightly higher rates of 40% to 70% (Achiron et al., 2005). However, according to Achiron et al. (2013), the presence of cognitive impairment in MS individuals has been seen in approximately 20% to 65% of cases, which, according to this literature review, appears to be a well-accepted range in current research. To put this into perspective, considering the previous report of 200 new cases of MS being diagnosed per week in the United States, and only taking the low-end percentage of 20% of cognitive impairment rates, there may still be 40 individuals experiencing cognitive impairment each week, which is approximately 1,900 individuals per year. It is possible that the reason for the wide range of cognitive impairment rates is due to multiple factors, such as the type of MS, its duration, the cognitive assessments used in studies, as well as procedures (Sahraian, & Etesam, 2014; Santos, Pinheiro, & Barros, 2015). Regardless, the rate of cognitive impairment should increase the awareness of clinicians to screen for such impairment (Achiron & Barak, 2003). This is because cognitive impairments may impact daily living significantly (Davis, et al., 2015; Rao et al., 1991; Ross, Halper, & Harris 2012). Further, it could assist in formulating specific treatment plans that tailor to managing activities that are adversely influenced by cognitive impairment, particularly in the early onset of MS to improve the quality of life for the future (Achiron et al., 2013).

Onset of cognitive impairment Cognitive impairment has been seen at onset of MS (Achiron & Barak, 2003; Amato et al., 1995; Santos, Pinheiro, & Barros, 2015). Although research has identified that impairment is more prevalent at a later duration, it has also been detectable earlier, even in the absence of limited physical disability (Deloire et al., 2005). Given this, it may be generally accepted that if cognitive dysfunction occurs, they can present early (Davis et al., 2015; Amato et al, 2001; Amato et al., 1995). According to Achiron and Barak

(2003), cognitive impairment can be present even in probable MS. Probable MS is defined as the first appearance of MS-related symptoms caused by dysfunction of the central nervous system in young adults, even though a diagnosis of MS may not be conclusive. Cognitive impairment has also been prevalent in MS individuals within the first year of diagnosis, and increases in severity with longer duration (Achiron et al., 2013; Achiron et al., 2005; Amato, Zipoli, & Portaccio, 2006). This has been seen in MS individuals who have had a diagnosis between two and six years (Achiron et al., 2005). However, cognitive impairments have been identified at advance progressions (Achiron et al., 2013; Amato, Zipoli, & Portaccio, 2006; Scalfari, 2010; Achiron et al., 2005). Specifically, cognitive impairment has been identified in individuals who had MS for at least ten years (Achiron et al., 2005). Overall, cognitive impairment may develop at any point during the disease, but it typically worsens over time.

Effected Cognitive Domains Research has frequently identified specific cognitive domains that are affected by MS (Achiron et al., 2013; Achiron et al., 2005; Achiron & Barak, 2003; Bodling, Denney, & Lynch, 2009; Patti et al., 2009). Such domains include sustained attention, delayed recall, visuospatial learning, and IPS. However, this is not to say that other domains cannot be impaired, given the possible randomness of brain lesion development during relapses. For example, Achiron et al. (2005) found that attention was commonly impaired in MS individuals, but verbal memory, abstract reasoning, and linguistic domains were also impaired. Executive functioning has also been impaired in MS individuals.

Achiron et al. (2013) examined cognitive patterns of 1,500 MS patients for up to thirty years. The following were cognitive domains that were most impaired, in descending order: IPS, executive function, motor skills, visual spatial perception, memory, attention, and verbal function. Notably, IPS was the domain that was most significantly impaired in MS individuals.

Research has repeatedly shown IPS as the most common impaired domain (Achiron et al., 2013; Achiron et al., 2005; Bodling, Denney, & Lynch, 2009; Petsanis et al., 2011). This is particularly evident in those who have had the disease for longer duration, but can still be seen at onset (Achiron et al., 2003; Nickerson et al., 2015; Sclafari et al., 2010).

Information Processing Speed

Definition Information processing speed (IPS) is a cognitive domain that is described as the speed or time in which it takes an individual to perform a mental task (Batista et al., 2012). In other words, IPS is the speed at which individuals can react to incoming various forms of stimuli, and then provide a response. Depending on the task, it may take individuals more time to complete tasks than others, which is typically based on the complexity of the task (Demaree, DeLuca, Gaudino, & Diamond, 1999). Notably, IPS is not related to intelligence, therefore having lower intelligence does not indicate that IPS would be slow. However, the higher, or quicker the processing speed, the greater efficiency in the ability to learn and automatically process previously learned information, as well as the better function of other cognitive domains.

Neuroanatomy Research suggests that IPS is associated with several different brain regions (Batista et al., 2012; Filippi et al., 2010; Filippi et al., 2000). Given this, it appears difficult to identify a central region responsible in the production of IPS. Research has used MS individuals to better understand the neuroanatomy of IPS because of the possible, significant deterioration of this domain in these individuals. According to DeLuca et al. (2004) IPS appears to be executed through the fronto-parietal region, similar to working memory. Additional functional magnetic resonance imaging (fMRI) emphasized the diffuse localization of IPS and therefore concluded that this domain is a multi-sourced process of various brain regions. Other

studies have had congruent findings. Batista et al. (2012), who examined the brain regions associated with IPS by studying MS patients, concluded that the basal ganglia, thalamus, and neocortex were key contributors in IPS production. However, they also concluded that MS patients had lower reduction in the caudate, putamen, globus allidus, and nucleus accumbens during IPS-related tasks. Although multiple brain regions were identified, results suggested that both thalamus and putamen atrophy appeared most significant in IPS slowing.

IPS appears to be associated with several brain regions. Because MS is a disease the can result in widespread deterioration, particularly at later durations, the probability of affecting a region that is associated with IPS may be high, which could explain why this domain is so commonly affected.

Assessments of information processing speed There are multiple assessments used to measure IPS, typical ones being the Digit Span subtest from the Wechsler Adult Intelligence Scale (WAIS), Trail Making Test (TMT), Stroop Color and Word Test, Sternberg Memory Scanning Test, and the Symbol Digit Modalities Test (SDMT) (Demaree et al., 1999). Another common, but effective assessment in measuring IPS, is the Paced Auditory Serial Addition Test (PASAT) (Aupperle et al., 2002; Bodling, Denney, & Lynch, 2009; DeLuca, Chelune, Tulsky, Lengenfelder, & Chiaravalloti, 2004; Demaree et al., 1999; Denney, Sworowski, & Lynch, 2005; Drake et al., 2010; Forn, et al., 2008; Solari, Radice, Manneschi, Motti, & Montanari, 2005). Originally developed by Dr. Dorothy Gronwall in 1977, the PASAT has individuals listen to numbers at a fixed rate of three-second intervals, adding a number to the one that immediately precedes it as quickly as possible (Drake et al., 2010). It can also be administered in two-second intervals for more thorough IPS results.

Not only does the PASAT demand the utilization of the IPS domain, but multiple domains, including attention and memory (DeLuca et al., 2004; Demaree et al., 1999; Forn et al., 2008). Due to this, there was a concern as to whether the results of the PASAT could solely describe one's IPS (Denney, Sworowski, & Lynch, 2005; Forn et al., 2008). In other words, it has been questionable as to whether the PASAT could be used as test of solely IPS, or should other domains be considered in the results (DeLuca et al., 2004). Forn et al. (2008) acknowledged that the PASAT entailed the utilization of multiple domains. Using MS patients as subjects, they developed two questions for their research: What domains were specific to the PASAT, and which domains were involved in PASAT performance and reduced accuracy? In answer to the first question, researchers concluded that the PASAT utilized primarily working memory (divided attention) and IPS. In answer to the second question, it was concluded that reduced IPS in their MS patients was the reason for PASAT performance and lower scores. This is congruent with the "relative consequence model" as suggested by Deluca et al. (2004), which states that impairment in working memory ability is the result of deficiency of IPS. These findings are also consistent with the Demaree et al. (1999) study, who modified the PASAT so that results were performance-based and not processing speed-based. The results showed that that low PASAT scores are the result of declined processing speed rather than performance. Therefore, it appears that the PASAT may be used as a main measure for IPS.

Although the PASAT seems empirically sound, there have been suggested drawbacks. For example, professionals have found it difficult to administer to patients, given the time and repetitiveness of the protocol (Drake et al., 2010). As a result, it is possible that administration of the PASAT may cause stress and agitation, and they discontinue. However, it has been suggested that clinicians could administer PASAT-3 (three-second intervals) without the

PASAT-2 (two-second intervals) and would yield the same results, or still obtain an accurate reading of their IPS (Aupperle, et al., 2002). Additionally, repeating testing of the PASAT is not needed all at one time – individuals could be re-assessed throughout their lifetime.

Another concern may be that the PASAT is associated with large practice effects because of the repeated testing. To overcome this, research suggests that clinicians perform three pre-baseline scores prior to a patient's actual baseline (Solari et al., 2005). This has been particularly effective and a common procedure in the Multiple Sclerosis Functional Composite (MSFC) which includes the PASAT as an MS-specific outcome measure.

The PASAT continues to be a leading assessment for measuring IPS due to its validity, reliability, and sensitivity (when accounted for by protocol), and appears to clearly indicate changes in neurological and neuropsychological statuses (Bodling, Denney, & Lynch, 2009; Denney, Sworowski, & Lynch, 2005; Drake et al., 2010). As a result, it has been recommended that if clinicians use other assessments to measure IPS, they should use the PASAT to confirm results (Bodling, Denney, & Lynch, 2009). Although the PASAT may be time-consuming and practice effects may arise, there have been suggested ways to address these concerns. If clinicians can overcome these challenges, the PASAT can not only be used to measure IPS, but because it includes other domains, scores can summarize overall degree of cognitive impairment, particularly with MS patients (DeLuca et al., 2004). This most likely explains why the PASAT is the primary cognitive measurement in the MSFC. Notably, in MS individuals, the reason for low scores on the PASAT appears to be associated with IPS, therefore using the PASAT as main measure for IPS in this population is appropriate (Aupperle, et al., 2002; Drake et al., 2010; Solari et al., 2005).

Multiple Sclerosis and information processing speed As mentioned, there is vast research that supports the association of MS and impaired IPS, and that this is the main factor for lowered scores on cognitive tests, such as the PASAT (Bodling, Denney, & Lynch, 2009; Denney, Sworowski, & Lynch, 2005; Drake et al., 2010; Forn et al., 2008). Indeed, IPS impairment is a primary domain and its prevalence could be as common as physical disabilities (Batista et al., 2009; Bodling, Denney, & Lynch, 2009). Specifically, Denney, Sworowski, and Lynch (2005) found that cognitive impairment in MS individuals was equally as prevalent as bradykinesia, or motor impairment, a common physical disability of MS. The common prevalence of cognitive impairment most likely explains why poor performance on the PASAT has been consistently present for MS individuals (Bodling, Denney, & Lynch, 2009; Forn et al., 2008). Further, significant impairment on the PASAT for MS individuals suggests that it could be the most sensitive domain of decline over time, and may occur near or at onset of MS well before the first year of diagnosis (Bodling, Denney, & Lynch, 2009).

Neurology and biological mechanisms Impaired cognitive function may reflect the presence of damage to specific brain regions (Patti, 2009). Studies have consistently shown the relationship between cognitive impairment and diffused damage of brain tissue (Deloire et al., 2005; Filippi et al., 2010; Patti, 2009; Filippi et al., 2000). This is especially prevalent if multiple brain regions within the same neural network of a cognitive domain are damaged (Deloire et al., 2005). However, even focal lesions of the neural networks can create significant impairment. In MS specifically, lesions are typically formed when there is either inflammation, demyelination, or both, and the number of lesions can increase the longer MS is present (Confavreux, et al., 2000). Axonal loss as the result of myelin destruction has also shown to be a biological mechanism in cognitive impairment for MS individuals. Regardless of damage

etiology, cognitive impairment has been correlated with the total amount of lesion load. Deloire et al. (2005) supported this when they found that lesion load was significantly correlated with low scores on the PASAT, concluding that IPS in particular was correlated with lesion load. This has been supported by other studies using the PASAT-2 and PASAT-3 (Audoin et al., 2005; Bellmann-Strobl et al., 2009; Deloire et al., 2005; Forn et al., 2008). Also, duration appears to be a variable in the extent of both damage and cognitive impairment (Deloire et al., 2005). Specifically, damage and impairment have been seen at the earliest stages of MS. Amato et al. (2001) not only supported this, but their longitudinal study indicated that this association can also be seen at later stages. Additionally, lesions that are not detectable, or "silent lesions" may result in cognitive impairments at any time during the MS course. It should also be mentioned that not all lesions may be responsible for cognitive impairments – even lesions at first onset.

From a biological lens, cognitive impairment in MS individuals appears to develop in many different ways. Due to this, it is debatable as to whether a single pattern of mechanisms can accurately describe all MS individuals who develop cognitive impairment. However, IPS impairment does appear to be associated with lesion load, and because there are multiple brain regions responsible for IPS, this domain may be most susceptible to being impaired.

Other Possible Covariates in Multiple Sclerosis and Information Processing Speed Relationship

Depression It has been suggested that depression is a main contributor of cognitive decline (DeLuca, Johnson, Beldowicz, & Natelson, 1995; Denney, Sworowski, & Lynch, 2005). Depression, as the result of having MS, creates cognitive slowing in individuals, which could be due to low motivation and psychomotor slowing (Denney, Sworowski, & Lynch, 2005). These symptoms mimic cognitive impairment, such as IPS decline. Research has shown that MS

patients who also met criteria for depression showed poorer performance on executive functioning and IPS tasks (DeLuca, et al., 1995). However, other researchers refute this concept. Denney, Sworowski, and Lynch (2005) suggest that researchers may have a difficult time distinguishing fatigue from depression or from MS. Further, much research explains that, although depression may have an impact on cognitive impairment for MS individuals, it mostly pertains to executive functioning, and not a factor for IPS. Overall, unless depression appears to be severe, there is a general consensus that it does not have a significant effect on IPS in MS individuals.

Age Although there appears to be a strong correlation between MS and impaired IPS, there is another variable to consider. Congruent with research, IPS slows as age increases, regardless of having MS (Bsteh et al., 2016; Bodling, Denney, & Lynch, 2009; Forn et al., 2008). However, the probability of IPS becoming significantly impaired increases at later ages of MS. (Amato et al., 2001; Bodling, Denney, & Lynch, 2009). This is true for not only IPS, for older individuals have a higher probability to develop cognitive deterioration in general (Bsteh et al., 2016). Given this, question may arise as to whether IPS in MS individuals either becomes impaired due to the disease, or because their age increases. Bodling, Denney, and Lynch (2009) examined the relationships between age, IPS, and MS. Their results concluded that older patients showed more decline in IPS than younger patients. Given this, it may be recommended to consider age as a covariate when analyzing IPS, particularly for individuals over age twenty. This has been congruent in additional research, with the general conclusion being that both age and MS can have impact on IPS, therefore both should be considered when examining these relationships (Amato et al., 2001; Bodling, Denney, & Lynch, 2009; Bsteh et al., 2016). Notably, age does not result in a significantly fast rate of cognitive decline (Murman, 2015).

Specifically, IPS begins to decline within the third decade of life, and then decreases on an average of 0.02 standard deviation per year. It then remains consistent per year until death (Eckert, Keren, Roberts, Calhoun, & Harris, 2010). Therefore, it appears that only longitudinal studies may need to consider age. Regardless of age, the impact of MS on IPS cannot be ignored, and both MS and age may be examined when researching impaired IPS, depending on the length of study (Bsteh et al, 2016).

Multiple sclerosis disease types Vast research has indicated that there are significant differences between MS types in terms of cognitive impairment, especially when comparing progressive and relapse-remitting types (Amato, Zipoli, & Portaccio, 2006; Bodling, Denney, & Lynch, 2009; Bsteh et al., 2016; Santos, Pinheiro, & Barros, 2015; Winkelmann, Engel, Apel, & Zettl, 2007; Zakzanis, 2000). Cognitive impairment appears most prevalent in progressive types, to the extent of irreversible disability in most cases (Bsteh et al., 2016; Winkelmann et al., 2007). As the disease progresses, the cognitive impairments tend to extend beyond typical domains affected by MS and may extend to initial intact domains (Denney, & Lynch, 2009; Amato et al., 2001). Therefore, it is suggested that as MS progresses, both neurological and cognitive impairments will eventually converge (Amato et al., 2001). This appears true for both MS types that start as progressive at onset or first begin as relapse-remitting then transition to a progressive type. However, MS individuals with secondary-progressive types appear to have the most significant cases of cognitive impairment, increasing the chance of developing cognitive impairment 500-fold within a ten-year period (Bodling, Denney, & Lynch, 2009). This is particularly true for individuals having relapses prior to secondary-progressive development (Amato et al., 2001; Santos, Pinheiro, & Barros, 2015). Although it appears that progressive types of MS have more severe cognitive impairment that relapse-remitting type, the research has

been mixed. Progressive types tend to become more prevalent in older individuals; therefore research may be controversial regarding whether either age or the actual type of MS is more strongly associated with cognitive impairment (Bodling, Denney, & Lynch, 2009).

Although it is possible that progressive types of MS may have more severe cognitive impairment, the prevalence rates may differ (Amato et al., 2001). Camp et al. (1999) found that there are significant differences in cognitive impairments between progressive types and relapse-remitting type. Notably, cognitive impairment was only found in 7% of patients with progressive types, and 53% of patients with relapse-remitting types had prevalence of cognitive impairments. Also, having relapses may be the reason as to why secondary-progressive type has the most cases of cognitive impairments. It is also considered the most significant predictor of long term outcome regarding cognitive impairment (Bodling, Denney, & Lynch, 2009; Bsteh et al., 2016).

Regardless of the MS type, it appears that IPS impairment has been found across all (Amato et al., 2001; Denney & Lynch, 2009; Denney, Sworowski, & Lynch, 2005). Further, relapses appear to be a main factor in all MS types that result in cognitive impairment. This appears particularly true for both the severity and prevalence of cognitive impairment (Achiron et al., 2005).

Duration The research regarding whether the duration of MS disease is a significant factor in IPS impairment has been controversial (Achiron et al., 2013; Achiron et al., 2005; Denney, Sworowski, & Lynch, 2005). Although length of time of having MS has shown to not be strongly correlated with cognitive impairment, especially in early phases of MS, some research have found contradictory results (Achiron et al., 2013). Amato, Ponziani, Siracusa, and Sorbi (2001) acknowledge the controversial results on this topic, however, their findings suggest

that as MS does progress with time, the number of patients with cognitive impairment increased. This has been congruent with other research, which indicate a higher frequency of cognitive impairment with longer disease duration (Achiron et al., 2013; Amato et al., 2001). This appears to be prevalent in all cognitive domains (Achiron et al, 2013). However, this is particularly true for sustained attention, working memory, and IPS (Denney, Sworowski, & Lynch, 2005). Achiron et al. (2005) found that cognitive decline increased in severity after they measured abilities over seven years. Notably, they also found that IPS was generally impaired around the seven-year mark. However, other research suggests that IPS can be impaired even at the earliest onset and become progressive in nature as the disease duration increases (Achrion et al., 2013). The issue, however, as that there are several covariates to consider when examining the relationship between cognitive impairment and MS duration, which may be why most research does not consider duration as a strong covariate.

MS relapses Over the years, the relationship between MS relapses and cognitive impairment has increasingly become a popular topic in research (Benedict et al., 2014; Bsteh, 2016; Nickerson et al., 2015; Scalfari, 2010). This is because clinicians have realized the importance of understanding cognitive impairments in MS individuals and how relapses may dictate such dysfunction (Bsteh et al., 2016; Scalfari, 2010). Benedict et al. (2014) examined the effect of relapses has on cognition by examining cognitive abilities before, during, and after relapses. They concluded that during and after a relapse, MS patients had significant decline in cognitive domains, with IPS as a primary deficit. They measured IPS using the PASAT, and also noticed that scores not only significantly decreased, but scores began to improve over time during remission, thus suggesting that this ability may be regained, but to the extent of recovery varies. This has also been seen in attentional tasks. However, the report of improved scores has

been interpreted differently in other research (Achron et al., 2005). Specifically, it is generally accepted that if cognitive impairment becomes prevalent, it may improve to some extent, but there is an overall gradual decline in impairment that does not cease (Achron et al., 2005; Benedict et al., 2014). Further, while some cognitive domains may remain stable over a period of time, they usually will begin to decline at some point (Confavreux et al., 2000). The reason for this overall gradual decline in cognitive impairment appears to result from a relapse, which can be especially true if cognitive impairments show no improvement three months post-relapse.

Current literature on number of Multiple Sclerosis relapses and information processing speed Most research acknowledges that relapses are a prominent covariable in cognitive impairment (Benedict et al., 2014; Confavreux et al., 2000; Foong et al., 1998; Migliore et al., 2017; Nickerson et al., 2015; Patti et al., 2009; Scalafri et al., 2010). Regarding the number of relapses and how this may contribute to cognitive impairment, correlational significance has appeared controversial (Bsteh et al., 2016; Confavreux et al., 2000). For example, literature appears to have mixed opinions as to whether the number of relapses in the duration of MS has the most impact on cognition (Confavreux et al., 2000). It has been suggested that the earlier frequent relapses occur, the more severe the cognitive impairment (Bsteh et al., 2016; Scalfari, 2010). Specifically, the number of relapses in earlier durations of the disease can dictate the presence and severity of cognitive impairment (Scalfari, 2010). In other words, cognitive impairment appears worse and with poorer prognosis for MS individuals who had more relapses within the first two to five years. This seems especially true for relapses within the first two years (Bsteh et al., 2016). Additionally, the number of relapses may dictate the long-term outcome of cognitive impairment in later years (Benedict et al., 2014; Bsteh et al., 2016; Migliore et al., 2017).

There is also research which proposes that the number of relapses over the course of the disease may influence the development and severity of cognitive impairment, and not just within the first five years of the disease (Bsteh et al., 2016; Scalfari, 2010). Bsteh et al. (2016) found that the total number of MS relapses over a ten-year span had a significant correlation with cognitive disability; however, relapses were only a "minor" factor. They also found that earlier relapses before the five-year mark of having MS had a stronger correlation with cognitive impairment than later relapses (five to ten years). A limitation of this study that should be mentioned was that only 4.8% of their sample of 753 patients presented cognitive disabilities. Regardless, it is possible that the reason why relapses may only significantly affect cognition up to a certain point is because progressive types may develop, therefore cognitive decline becomes consistent regardless of relapses (Confavreux et al., 2000; Scalfari, 2010). When comparing MS patients with either RRMS or SPMS types, the SPMS has typically shown more cognitive decline. However, Confavreux, et al. (2000) suggest that MS individuals who experience relapses at onset of the disease (RRMS type) and progress to SPMS type had quicker progression of disability, even in the presence of superimposed relapses. However, at a significantly later point of progression, relapses may become irrelevant.

As mentioned earlier, another variable to consider when examining the relationship between MS and IPS impairment was age. This should also be considered as a covariate when examining MS relapses frequency and cognitive impairment. Specifically, research has shown that age may dictate the frequency of MS relapses (Gorman, Healy, Polgar-Turcsanvi, & Chitnis, 2009; Tremlett, Zhao, Joseph, & Devonshire, 2008). However, results have been mixed regarding what ages experience the most relapses. Some research suggests that MS individuals who experience relapses in their thirties and forties will most likely experience a higher

frequency than other ages (Tremlett et al., 2008). However, other research suggests a higher frequency in earlier age ranges, such as pediatrics (Gorman et al., 2009).

After reviewing this research, it appears evident that there is a correlation between MS relapses and cognitive impairments (Benedict et al., 2014; Confavreux et al., 2000; Deloire et al., 2005; Migliore et al., 2017; Nickerson et al., 2015; Patti et al., 2009; Scalfari, 2010). Cognition becomes impaired during and after MS relapses (Scalfari, 2010). Although it has been suggested that cognition could improve after relapses, it is widely accepted that cognitive impairment declines as the disease progresses overall (Foong et al., 1998; Nickerson et al., 2015). The correlation between the number of MS relapses and cognitive impairment remains controversial (Confravreux et al., 2000). Research appears to evidence that the number of relapses within the first five years significantly dictates the presence and severity of cognitive impairment (Scalfari, 2010). There is also evidence to suggest that this is true in later years, but the correlation is not as strong (Bsteh et al., 2016; Migliore et al., 2017). A reason why is because the disease may become progressive at a certain point, thus declining cognition anyway, therefore the presence of relapses becomes irrelevant (Benedict et al., 2014; Confavreux et al., 2000; Scalfari, 2010). A notable covariate that has been shown to influence both cognitive impairment (particularly IPS dysfunction) and the frequency of multiple sclerosis relapses, is age (Bodling, Denney, & Lynch, 2009; Bsteh et al., 2016; Forn et al., 2008; Gorman, Healy, Polgar-Turcsanvi, & Chitnis, 2009; Tremlett, Zhao, Joseph, & Devonshire, 2008). Given this, much research has considered this variable when examining the relationship between MS and cognitive impairment.

Purpose of the Study

The purpose of this study is to examine the possible pattern of IPS impairment in MS by examining the relationship between the number of MS relapses and IPS ability. At this stage in

the research, *multiple sclerosis relapses (MS relapses)* will be provisionally defined as acute increase in physical and/or mental disability, as measured and identified by the Expanded Disability Status Scale (EDSS). *Information processing speed (IPS)* will be provisionally defined as the cognitive domain that dictates the speed or time in which it takes individuals to perform a mental task, as measured by the PASAT.

Research Questions

Quantitative studies are often driven by questions that can be concretely measured and assist in delimiting the study. The research question for this study is as follows:

(1) Is there a significant difference in IPS ability by the number of MS relapses?"

The null hypothesis is as stated, "There is no significant difference in IPS ability by the number of MS relapses." The alternative hypothesis is as stated, "There is a significant difference in IPS ability by the number of MS relapses."

Significance of the Study

Cognitive decline, including IPS impairment, can be seen throughout the course of MS. Research has shown the significant impact of relapses can have on cognition, to the extent that it can dictate the course of cognitive impairment throughout an individual's lifetime (Achiron et al., 2005). IPS impairment can result in premature retirement increasing the probability of needing daily living assistance (Aupperle et al., 2002). It is possible that this study may contribute in identifying a distinct pattern of IPS impairment in MS. Specifically, if this study, as well as future research, can conclude that there is a pattern of IPS impairment using the number of relapses as concrete markers, there are ways in which this knowledge may contribute

many aspects of MS. For example, it could help predict the course of cognitive impairment in other non-relapsing types of MS (Achiron et al., 2005). It could also assist in identifying effective treatments for cognitive impairments and relapses. Specifically, it may alter the course of cognitive rehabilitation, as it may emphasize the need for earlier and frequent intervention, focus on IPS, and tailor treatment based on an individual's relapse rates. Further, it may explain why some forms of pharmacological treatments may not be effective because cognitive decline has been seen in individuals with MS regardless, even after administering drug intervention (Achiron et al., 2005; Bsteh et al., 2016). This has been identified in pharmacological treatments that are even specific to reducing the number of MS, and perhaps understanding the relationship of IPS impairment and relapse rates may assist in modifying such drugs (Bsteh et al., 2016).

This pattern of impairment, if identified, could also contribute to the growing notion that cognitive assessment should be emphasized for individuals with MS, and be integrated into primary care more frequently (Amato et al., 2001; Zakanis, 2000). Implying that a medical phenomenon (relapses) has a relationship with a neuropsychological phenomenon (IPS impairment) could suggest the need for neuropsychological assessments and the results be a main factor in decision-making in treatment that is implemented by primary care (Amato et al., 2001). A distinct pattern could also aid clinicians in distinguishing MS from other neurological disorders, leading to accurate diagnoses (Zakanis, 2000).

CHAPTER II: APPROACH

Rationale for Use of Quantitative Methodology

This study focuses on understanding the relationship between the number of MS relapses and IPS ability. In doing so, I will attempt to identify a recognizable pattern between these two variables so that it may contribute to the understanding of IPS impairment in MS individuals. I

will do this by using PASAT scores as a measure of IPS and grouping participants based on the number of the MS relapses they have experienced. I will then compare the groups based on their scores and determine if a significant difference is present, then conceptualizing these differences into a pattern, if possible.

Sample and Selection Criteria

Archival data will be used from the Multiple Sclerosis Outcome Assessments Consortium (MSOAC) Placebo Database. This database has over 2,400 sanitized, individual patient records and consists of information that includes, but not limited to, demographics, medical history, performance outcome measures on specific assessments, relapse information, and multiple sclerosis diagnoses. This information is inputted by clinicians who have previously conducted research. Approval was granted by the Critical Path Institute: Data Collaboration Center to access this data for the current study.

Individuals will be selected based on the following criteria, which is first determined by either the presence or absence of specific data: number of MS relapses and PASAT scores. Individuals must have both present in their records. An additional consideration will be the age of participants. The data does not provide the age at which individuals were administered the PASAT – only the age at which they first began data collection. To control for the variable of age, participants must be under thirty-five (the data does not have any individuals under age eighteen). This age was selected because, after reviewing the literature, IPS does not appear to begin to reduce significantly until after the third decade of life. Therefore, IPS would most likely be optimal at age thirty-five in healthy populations, so this may control for age.

An additional criteria is the chronological order of MS relapses and PASAT scores. Specifically, a PASAT score must be present following the individual's last MS relapse. If a MS

relapse was recorded, but a PASAT score was not recorded, then that MS relapse will not be used in the current study.

The final criteria is that subjects must have been diagnosed with only RRMS, which may control for impairment due to progressive types and therefore imply that impairment was due to solely relapses.

Instruments

Given that archival data will be collected from the MSOAC database, no additional instruments will be used. The Paced Auditory Serial Addition Test (PASAT) results will be collected as a measurement for IPS, which appears justified as a reasonable measure of IPS (Aupperle, et al., 2002; Demaree, et al., 1999, Drake, et al., 2010; Solari, et al., 2005). Further, the PASAT has shown to have adequate validity, reliability, and sensitivity (Bodling, Denney, & Lynch, 2009; Drake et al., 2010; Denney, Sworowski, & Lynch, 2005). One concern may be the influence of practice effects because it was administered multiple times. However, congruent with research, the data shows that the PASAT was given two to three times prior to taking a baseline score, which has shown to overcome practice effects (Solari et al., 2005).

Clinicians from the archival data used the EDSS to confirm relapses. This measure is a well-known tool in identifying relapses and confirming accurate diagnoses (Denney, Sworowski, & Lynch, 2005). Therefore, confirmed relapses by the EDSS is a strong indicator of actual relapses (Bsteh et al., 2016, Deloire et al., 2005; Denney, Sworowski, & Lynch, 2005; Migliore et al., 2017).

Research Design

This study is a between-subjects design. The independent variable (x) is the number of MS relapses. This variable is measured on four different levels: (1) individuals that have had one MS relapse (2) individuals that have had two MS relapses (3) individuals that have had three MS relapses (4) individuals who have had four or more relapses. The dependent variable (y) is PASAT scores. This design appears to be the most appropriate given the nature of the independent variable. The number of MS relapses may be difficult to use as a continuous variable, because it is assumed that there will be a small range of relapses – no more than five or six, and higher number of relapses is most likely rare. This due to data availability. Specifically, data was used from previous studies, and according to the literature review, studies are typically less than ten years. With an average of one relapse per year (without treatment), it would be challenging to make the number of relapses a continuous variable and therefore make it difficult to use a regression or correlational design (Chang, Tourtellotte, Rudick, & Trapp, 2002).

Data Collection and Analysis

Participants will be selected from the MSOAC database based on the criteria explained previously, and sorted into groups (independent variable levels). A one-way analysis of variance (ANOVA) will be used to analyze the data. This will determine whether there is an overall significance between groups, or in this case, if the mean PASAT scores were significantly different between groups. A post hoc analysis will also be used to determine which groups significantly differed from each other. This will be determined after the one-way ANOVA identifies whether there is homogeneity of the variance (Levene's test). If present, Tukey's

honestly significant difference post hoc test will be used, but if not, Games Howell post hoc test will be used.

CHAPTER III: RESULTS

A total of 299 individuals met the previously discussed criteria and were used as participants. In Group 1, or individuals with one recorded relapse, there were a total of 161 participants, with an average PASAT score of 44.360 (*SD* = 13.373). Group 2, or individuals with two relapses, there were a total of 75 participants, with an average PASAT score of 43.867 (*SD* = 13.915). In Group 3, or individuals with three recorded relapses, there were a total of 30 participants, with an average PASAT score of 44.300 (*SD* = 13.747). In Group 4, or individuals with four or more recorded relapses, there were a total of 33 participants, with an average PASAT score of 45.727 (*SD* = 14.583). The average PASAT score across all groups was 44.381 (*SD* = 13.623) (See Table 1).

Table 1. **Descriptive Analysis**

					95% Confidence Interval for Mean			
Group	N	Mean PASAT Score	Std. Deviation	Std. Error	Lower Bound	Upper Bound	Minimum	Maximum
1	161	44.360	13.373	1.054	42.279	46.442	13.00	60.00
2	75	43.867	13.915	1.607	40.665	47.068	5.00	60.00
3	30	44.300	13.747	2.510	39.167	49.433	14.00	60.00
4	33	45.727	14.583	2.538	40.557	50.898	11.00	60.00
Total	299	44.381	13.623	.788	42.831	45.932	5.00	60.00

*Descriptive analysis for each group of participants. There was a total mean PASAT score (*M* = 44.3813) and total standard deviation of *SD* = 13.62323.

A one-way ANOVA was used to examine possible effects of multiple sclerosis relapses on PASAT scores in one relapse, two relapses, three relapses, or four or more relapse conditions. There was not a significant effect of multiple sclerosis relapses on PASAT scores at the $p < 0.5$ level in all conditions [F (3, 295) = .142, p = .935].

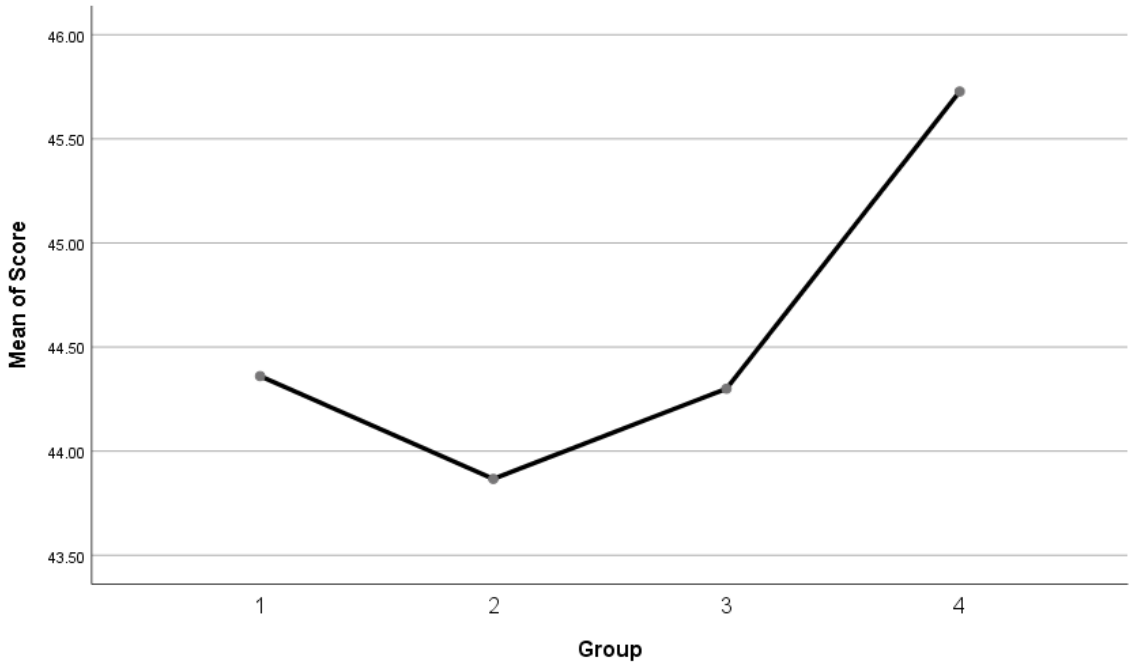
Table 2. **ANOVA Analysis**

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	79.917	3	26.639	.142	.935
Within Groups	55226.618	295	187.209		
Total	55306.535	298			

*One-way ANOVA analysis between groups from Table 1. There was no significant differences in PASAT scores between groups ($p = .935$) at the $p < .05$ level.

Since there were no significant group differences in PASAT scores based on the number of multiple sclerosis relapses (see Table 2), a mentionable pattern between these two variables was un-identifiable. This is further evidenced in Graph 1.

Graph 1. **Relationship Between Multiple Sclerosis Relapses Numbers and PASAT Scores**



*The average score in Group 1 was 44.360. The average score in Group 2 was 43.867. The average score in Group 3 was 44.300. The average score in Group 4 was 45.727. There was no distinct pattern in scores when comparing Groups.

CHAPTER IV: DISCUSSION

Findings

Based on the results, the study found no significance in PASAT scores based on the number of relapses. Therefore, it did not appear to be a significant difference in IPS ability by the number of MS relapses. As a result, a recognizable pattern between these two variables could not be identified. Overall, the null hypothesis, "There is no significant difference in IPS ability by the number of MS relapses" could not be rejected.

Reviewing the mean scores of each group, they fall just under the average scores of the normal population of the PASAT-3, which is approximately between 46.7 and 50.4. Additionally, the overall mean scores between groups were relatively close, approximately -2/+2 in difference. The decline in scores can be considered minimal, and could be explained by Bsteh et al. (2016), who suggested that relapses may only be a "minor" factor in cognitive disability, which may also explain why there was no significance between groups. Reviewing the literature, I conclude that a main reason why relapses may be only a "minor" factor is because brain damage varies from relapse to relapse, and therefore may not affect all individuals (Deloire et al., 2005).

There was no identifiable pattern between the two variables. Specifically, it was originally thought that, as the number of relapses increased, the PASAT scores would lower, thus a negative regression might have been seen in the Graph 1. However, not only was this not recognizable, the highest scoring individuals on the PASAT was in Group 4. This appears to contradict previous studies which suggested that cognitive impairment has an overall gradual decline, and would not cease (Achron et al., 2005; Benedict et al., 2014). Rather, this finding may support studies that suggest IPS abilities can be recovered with time (Benedict et al., 2014). It is possible that IPS may be more immune from relapses than other cognitive domains.

Clinical Implications

As mentioned previously, it was to the best of the researcher's knowledge that this is the first study to examine the relationship between the number of MS relapses and IPS, in attempt to find a distinct pattern of IPS impairment based on the number of relapses individuals may have. In addition, it does not appear as though the differences in IPS ability, based on the number of relapses, has been specifically examined in previous literature. It is possible that the reason why such a study has not been performed previously (or has primarily focused on these two variables in a single study) is because other variables, such as the covariates discussed, are more significant in influencing cognitive decline, particularly with IPS. Therefore, MS relapses are most likely not good predictors of IPS decline in these individuals. This is probably due to previous research that emphasizes the difficulty in recognizing a distinct clinical course of IPS dysfunction in MS individuals (Bseth et al., 2016; Zakzanis, 2000). This further demonstrates the difficulty in formulating a clinical course of IPS impairment for MS individuals. Additionally, IPS ability may not only be unaffected after a relapse, but it can be recovered with time, so IPS could be a domain that is not a primary concern after a relapse. Overall, IPS may not contribute to a long-term assessment of an individual's cognitive decline.

Limitations

There were several limitations in this study. However, it should be noted that this was a "general" study to determine whether a more in-depth study on these variables alone would be worth-while. First, only 299 individuals met criteria for the study. Although this is not an extraordinary low number, it would have been interesting to see the results based on a much larger sample. Second, there were multiple variables that were not accounted for, particularly the ones discussed in the literature review. Notable variables would include, depression, age, and duration. Since these were not accounted for, the conceptualization of the results lacked,

particularly when determining why relapses did not have a significant effect on PASAT scores. Third, there was information about the participants that may have been beneficial when considering the results, such as treatment, or specifically, treatment for IPS impairment, as this could have influenced PASAT scores. Lastly, there were no controls to compare the groups to, and this could have provide additional support that relapses had a significant impact on IPS, should the research find significance between groups.

Recommendations for Future Study

Future research should consider running a similar study between these two variables, but with a larger population and finding solutions to control for other covariates. Furthermore, researchers should consider examining brain damage as the result of MS relapses to confirm whether brain areas responsible for IPS were damaged. It may also be beneficial to perform a study that examines an individual's PASAT scores after one or more relapses, and compare these scores to determine if there is a pattern throughout their MS course. If there are notable findings, perhaps it would only then be beneficial to compare the number of relapses of several individuals, or between groups.

Conclusion

Although MS relapses did not appear to be a significant predictor in IPS ability, it is hoped that this study emphasizes the difficulty in developing a concrete understanding of the relationship between IPS and MS relapses. Research should continue to study IPS and how it

could be affected by not just relapses, but MS in general, so that there is an identified clinical course of IPS in these individuals. IPS ability can be a significant factor throughout the course of various types of MS treatment. This is vitally important in overall outcome and improving the quality of life for these individuals.

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