Dual-Task Walking in Multiple Sclerosis:

Correlates, Moderators, and Consequences

by

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ABSTRACT

The ability to walk while completing a secondary task, dual-task walking (DTW), poses notable challenges for individuals affected by neurological disorders, such as multiple sclerosis (MS), who experience both cognitive and motor problems secondary to their disease. However, DTW is an everyday activity that has putative importance for optimal function. Although some research in the past decade has begun to examine changes in DTW in MS, there is still limited work to understand the predictors of DTW, the factors that might moderate relationships between baseline cognitive and motor function and DTW ability, and its consequences (e.g., for quality of life [QoL] or fall risk). To contribute to the understanding of these phenomena and their intersections, three secondary data analyses of two relatively large data sets in the area were conducted to address five major aims. The first step was to identify of the most relevant of these inherently involved domains (cognitive [aim 1] and motor [aim 2] abilities). Lasso regression for inference was performed to address this question for both cognitive (South Shore Neurologic Associates, PC data) and motor (University of Kansas Medical Center [KUMC] data) domains. Next, evaluations to explore the moderating role of the psychological impacts that are common in MS (e.g., depression and falls self-efficacy) were undertaken to determine whether the relationships between cognitive and motor function and DTW ability are different for individuals with different levels of these factors using regression with factor scores performed with each data set (aim 3). As a final step, relationships between DTW and distal outcomes like QoL (cross-sectionally using both data sets and factor score regression; aim 4) and falls (cross-sectionally and longitudinally using KUMC data and negative binomial regression; aim 5). These studies contribute to the corpus of knowledge about DTW in MS in needed ways.

DEDICATION

To my wife, Allison, who has been my greatest supporter and comforter despite my limits and vacillations. She has endured the most demanding of roles for spouses—standing by me in both the military and academics. She has loved me even when I do not love myself. She is my great love and my greatest friend.

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CHAPTER 1

Multiple sclerosis (MS) is a debilitating neurological disorder that affects over 2 million people worldwide, and around 1 million of those cases are in the United States (Wallin et al., 2019). The prevalence of MS and the fact that it is usually diagnosed in young adulthood make MS the leading cause of nontraumatic disability in young adults worldwide (Tullman, 2013). MS results from lesions distributed throughout the central nervous system caused by autoimmune attacks on myelin basic protein (Lutton et al., 2004). This leads to myelin sheath loss (Lutton et al., 2004) and, eventually, axonal death (Tallantyre et al., 2010). Not only does severity of damage at the cellular level increase over time but lesion counts also increase over time in most cases (Lutton et al., 2004). Further, symptoms accumulate over time (Kister et al., 2013). Both the damage to the central nervous system (Lucchinetti et al., 2000; Metz et al., 2014) and the resultant symptoms from them are rather heterogeneous (Morales et al., 2006; Weiner, 2009), but factors such as early lesion proliferation levels (Brex et al., 2002) and global gray matter atrophy (Nakamura, 2018) seem to be general indicators of disability. These symptoms include, but may not be limited to, weakness, spasticity, fatigue, and undesirable changes in sensation, cognition, vision, coordination, bladder function, sexual function, and mood and psychological states (Crayton & Rossman, 2006).

MS has a few primary forms: primary progressive, secondary progressive, and relapsing-remitting (RRMS; National Multiple Sclerosis Society [NMSS], 2020a). Progressive-relapsing MS is a rare form of MS that involves disease progression with flare-ups but not remission from the outset (Goldenberg, 2012). Most (≈85%) of MS cases begin as RRMS (NMSS, 2020a). SPMS is only diagnosed when the disease course in RRMS moves from a recurrence of MS “attacks” (relapses) followed by period of partially returned function (remissions) to a state of continual, gradual decline (NMSS, 2020a). As such, all SPMS cases begin with a disease course of relapse and remission (NMSS, 2020a). There is no cure for MS (Goldenberg, 2012; NMSS, 2020b). Although several disease-modifying drugs have been developed, the effects of such drugs are limited, and not all persons with MS can benefit from them (Goldenberg, 2012; NMSS, 2020b). Given this, there is a need to understand the intersections of diverse symptom experiences among those affected by MS not only for the purpose of characterization but also for the purpose of disease management and intervention via rehabilitative efforts (Crayton & Rossman, 2006).

Among the most common and important symptoms of MS is decreased lower limb functioning and trouble walking (Heesen et al., 2008; Zwibel, 2009). In fact, the importance of walking in MS is so patent that the gold standard for measuring MS disability, the Expanded Disability Status Scale (EDSS), includes walking ability as a central determinant of disease status (Kurtzke, 1983). Although this focus of the EDSS, particularly in the 4.0 to 7.0 range of this 0-10 scale, has been criticized by some recently (van Munster & Uitdehaag, 2017), the fact remains that it demonstrates the central role of walking disability in MS evaluation and symptom progression. Not only is walking prioritized clinically, reasonably given that 50-80% of those with MS have gait and balance dysfunction (Cameron & Nilsagård, 2018), but difficulty walking and the loss of independence that results from it are among the chief concerns cited by those affected by MS (Heesen et al., 2008; LaRocca, 2011).

Problems with walking in MS can be mediated by a variety of individual and environmental factors (Cameron & Nilsagård, 2018). For example, disease-related alterations that can result in imbalance, gait dysfunction, and increased fall risk include muscular weakness, motor discoordination, vestibular dysfunction, visual issues, somatosensory impairments, and more (Cameron & Lord, 2010; Cameron & Nilsagård, 2018). Phenomenologically, these mechanistic pathways give rise to the experience of having difficulty with walking and balance, albeit as the result of unique dysfunctions. Given the frequency of these issues, falls are a common experience in MS (Gunn et al., 2014; Nilsagård et al., 2015). Most people with MS will experience a fall (Gunn et al., 2014; Nilsagård et al., 2015), and 37% of those with MS are considered "frequent fallers" (Nilsagård et al., 2015). Falls in MS are also more likely to result in injury (Bazelier et al., 2012; Peterson et al., 2008) and death (Brønnum-Hansen et al., 2006) than falls among matched controls.

Interrelated with the motor difficulties experienced in people with MS are cognitive and psychological changes. These changes, which include changes in falls self-efficacy (FSE; i.e., fear of falling), cognition, and depression, can have important implications for fall risk and quality of life. Recent work has begun to outline the connections between these characteristics and falls. However, their relationships with walking function and falls remain incompletely understood. The following sections outline current literature on FSE and depression on motor and cognitive function in people with MS to establish their possible role in complex walking tasks in everyday contexts and, therefore, possible implications for falls. Then, dual tasking (theories, paradigms, and measures) in people with MS is discussed, as it is a task that sits at the intersection of cognition, walking, and, possibly, fall risk. Finally, a model detailing the hypothesized intersections of these phenomena is presented and methods to address aspects of it are outlined.

Falls Self-Efficacy and Motor and Cognitive Function in MS

Perhaps understandably, fear of falling or low falls self-efficacy (FSE)—which are often considered synonymously in measurement (Tinetti et al., 1990; Hill et al., 1996)—are common among those with MS (Peterson et al., 2007). Fear of falling has been found to occur in those with MS at rates of just over 60% generally (Peterson et al., 2007) to as high as 92% of those who with MS who have fallen specifically (Comber et al., 2017). This often leads to significant activity curtailment, reduced independence, and lowered quality of life (QoL; Peterson et al., 2007). Comber et al. (2017) reported that 79% of participants with MS who have fallen report activity curtailment associated with fear of falling.

It may be that fear of falling or low FSE may simply be a reasonable appraisal of increased risk given symptomatic presentations; however, recent evidence indicates that FSE may lead to unique consequences due to unnecessary activity curtailment and loss of independence. First, a large study in individuals assessed correspondence of perceived fall risk and physiological fall risk (Gunn et al., 2018). Their findings showed that most individuals with MS have a notable disparity between perceived and physiological fall risk and the most common discrepancy is that *the perceived risk is greater than the physiological risk* (Gunn et al., 2018). Second, in older women at risk for falling, FSE was found to independently correlate with total brain and grey matter volume (Davis et al., 2012), and, as noted previously, studies have found that grey matter volume is an important predictor of disability in MS (Nakamura, 2018). Third, a secondary analysis of 12-month longitudinal data from a randomized controlled trial found that improvements in FSE were independently associated with increases in usual gait speed in older women at risk for falling (Liu-Ambrose et al., 2010). Fourth, in neurotypical young adults, global self-efficacy was found to correlate with mean diffusivity in the basal ganglia (putamen and globus pallidus; Nakagawa et al., 2017). In older women at risk for falling, it reasonably possible that overall health status confounds the relationship between neurological health and greater efficacy; however, this seems less compelling as an explanation for the association in a young, neurotypical population. It also would not explain the longitudinal evidence that increases in FSE improve gait speed in older adults at risk for falling. Of course, it is also possible that feedback loops exist wherein FSE is both a consequence and antecedent of neuroplastic and functional changes, and it is acknowledged that there are some patients who may have high FSE despite high physiological fall risk—but this seems to be the minority of cases (Gunn et al., 2018). In sum, although the causes of FSE remain incompletely understood, this evidence suggests that low FSE likely leads to unnecessary curtailment of activities and decrements in independent function as opposed to serving a protective role for the majority of those with MS, as other researchers have also asserted (Peterson et al., 2007).

FSE also has clear predictive utility. FSE is a robust, independent predictor of falls in those with MS when it is considered (Finlayson et al., 2006; Gunn et al., 2018; Quinn et al., 2018; Peterson, 2009; Van Liew et al., 2020). In fact, in a recent meta-analysis of clinical measures for predicting falls in MS, the Activities-specific of Balance Confidence scale (ABC) and Falls Efficacy Scale-International (FES-I)—two highly related, self-report measures of balance confidence and FSE—were two of three (the third being the Berg Balance Scale [BBS]) measures that were indicated as potentially useful, predictive measures of falls in MS (Quinn et al., 2018).

FSE is also highly related to spatiotemporal gait parameters in laboratory settings (Kalron & Achiron, 2014) which could indicate that low FSE leads to alterations in gait. Even in such a case where FSE is an appraisal of one's risk of falling or conscious assessment of sensorimotor feedback indicating one's altered gait, it is still possible that low FSE actually results in unnecessarily overprotective behavior, such as activity curtailment and sacrifices of independence beyond the level necessary to adequately mitigate risk of falling. Reasons that such a potential exists intersect with other common issues in MS, such as changes to one's psychological and cognitive states. For example, objective measures of physical activity have been found to be predicted by self-efficacy (high self-efficacy related to increased physical activity), but anxiety levels significantly moderated this effect such that the effect was attenuated by increasing anxiety (Casey et al., 2018). This highlights how *worry* or *concern* plays into FSE and suggests that other psychological states—not just actual abilities—likely factor into FSE evaluations and their implications for function. Further, avoiding physical activity is likely to lead to reduced physical functioning which provides a putative path via which low FSE could *cause* decreases in walking function via restricted activity. As such, FSE may affect the way that actual abilities are manifested in activity or performance, and this may become more important in the context of more demanding tasks that may heighten stress.

Depression and Motor and Cognitive Function in MS

Adverse psychological experiences—like anxiety and depression—are themselves common issues in MS, too. One meta-analysis found that more than 1 in 3 people with MS had clinically significant symptoms of depression or anxiety in an examination of cross-sectional prevalence estimates (Boeschoten et al., 2017). Approximately 1 in 2 people with MS will have a diagnosis of depression during their lifetime (Siegert & Abernethy, 2005), and just over 1 in 3 people with MS will have a clinical diagnosis of anxiety in their lifetime (Korostil & Feinstein, 2007). Depression negatively affects QoL and daily function (Lobentanz et al., 2004; Gottberg et al., 2007; Zwibel, 2009). Mitchell and colleagues' (2005) analysis of physical and psychological factors that predict QoL in MS found that factors like self-efficacy and mood mattered more than physical factors (e.g., weakness, lesion count), and they noted that cognitive impairment was also an important factor for predicting QoL—even early in the disease.

Further, depression is known to lead to decrements in motor and cognitive function. For example, depressive motor retardation or psychomotor symptoms refer to the phenomenon wherein depression leads to slowed motor function putatively via cognitive and motor sequelae of depression (Caligiuri & Ellwanger, 2000; Sabbe et al., 1996). Evidence indicates that this may occur through the effects of depression on the basal ganglia (Naismith et al., 2002)—a region which is critical not only for its role in motivation but also for its role in the initiation and selection of motor programs (Purves et al., 2018)—and via dopamine deficits (Schrijvers et al., 2008; Walther et al., 2012). In older adults, walking speed has been found to relate to depression, anxiety, and cognition (Biderman et al., 2002; Gage et al., 2003; Kimm et al., 2016; Marino et al., 2019; Van

Kan et al., 2009). Further, factors like anxiety have been found to heighten the attentional demand of walking in older adults in dual-task paradigms (Gage et al., 2003)—again highlighting how psychological and cognitive factors may intersect in important ways to determine walking outcomes especially during complex walking tasks. In terms of cognitive effects, data from the Longitudinal Aging Study Amsterdam that measured over 2,000 adults across 13 years indicated that depression and changes in depression predict longitudinal decline in general cognitive function and information processing speed, but the course of cognitive function was not significantly predictive of the course of depression symptoms (van den Kommer et al., 2013). These findings highlight that mood states may play important moderating roles in the context of ambulation particularly under concurrent cognitive demands.

Relationships between depression and cognitive and motor function have also been examined in those with MS with somewhat mixed results. For example, depression in MS is related to impaired memory, slowed information processing, and executive dysfunction (Arnett et al., 1999; Arnett et al., 2001; Diamond et al., 2008). Julian et al. (2007) showed that depression related to subjective cognitive impairment. However, depression was not related to neuropsychologically assessed impairment, but treating depression resulted in more accurate subjective appraisal of cognitive ability (Julian et al., 2007). This provides some evidence that attending to psychological factors may help to ensure those with MS are evaluating themselves accurately and engaging in activities commensurate with their actual capacity for independent living. Partially contrary to these findings, Ensari and colleagues (2018) reported small but significant associations between motor, but not cognitive, function and depression in a cross-sectional study of

131 people with MS. These lines of evidence, and the general nature of depression, suggest that it is possible that depression affects function and independence directly and via complex interactions with efficacy, cognition, and motor function. In fact, Lynch and colleagues (2001) have averred that the relationship between disability and depression may be characterized by reciprocal causality—not simply as depression being a psychogenic response to disability.

Clearly, there is evidence for the intersections of these diverse symptoms and experiences in MS. All these experiences are not only important to QoL in those with MS, but they are reciprocally and complexly related. As noted, maintaining function in life is paramount, and walking ability is central to physical function in MS (Cameron & Nilsagård, 2018; Heesen et al., 2008). Although many measures of function or disability in MS focus on walking distance, research has indicated that walking speed may be a more reliable and important predictor of these states (Albrecht et al., 2001), and notable decreases in gait speed are present in those with MS—even early in the disease course (Langeskov-Christensen et al., 2017). Researchers have identified that factors like FSE (Kalron, 2014; Kalron & Achiron, 2014), depression (Briggs et al., 2019), and cognition (D'Orio et al., 2012; Kalron, 2014) are related to walking speed in those with MS, and as noted previously, these factors relate to falls rates and risk as well. Such relationships may be even more meaningfully assessed for real-world function by assessing in the context of activities that require the phenomenological intersection of multiple domains at once, such as dual-task walking (DTW), but research examining the relationships among these factors in such paradigms is sparse and incomplete.

Dual Tasking: Intersecting Motor and Cognitive Function

DTW occurs when an individual must walk and engage in another task simultaneously (Mirelman et al., 2018). In general, dual tasking (DT) is only considered to occur if the two tasks have discrete functions or goals (Bayot et al., 2018). The general DT paradigm is commonly employed in neuropsychology to compare individual performance on a particular task (often cognitive) in isolation and under DT (which is often a manual or motor task; Hanny, 1986; Mirelman et al., 2018). The paradigm is based on a theoretically and empirically based tenet that notable performance decrements do not occur when an automatic and an attentional task are performed concurrently, but performance does decrease when two attentional tasks are performed concurrently (Hanny, 1986; Mirelman et al., 2018). In the context of applications to neurological populations, evidence indicates that the increased cognitive load required by dividing attention is the underlying issue, and the effect may manifest irrespective of the complexity or difficulty of the tasks in isolation (Beste et al., 2018; Hamilton et al., 2009). This has been central to the promise and usefulness of evaluating dual-task performance in a variety of contexts. In the context of gait, DTW was initially evaluated to attempt to determine whether walking is an automatic or attentionally demanding task—particularly in populations affected by neurological disease (Mirelman et al., 2018). It is possible that tasks which may be automatic in neurotypical populations require increased effortful attention in neurologically impaired populations. Such differences may be particularly apparent in the context of neurodegenerative disorders where compensation, rather than recovery, is often necessary at the neural level (Kleim, 2012). In fact, there is evidence that the attentional costs of balance and movement are both greater in those with MS than healthy controls (Wajda et al., 2019).

Theories of Dual-Task Inference

Historically, two primary theories have dominated the landscape in terms of explaining the underlying causes of interference that occurs during DT. The first is Attentional Capacity (or Capacity Sharing) Theory (Kahneman, 1973), and the second is the Bottleneck Theory (e.g., see Tombu et al., 2011). However, Bayot et al. (2018), in their review of DT interference in the context of posture and gait, note that there are other theories, such as the Time-Sharing Hypothesis and Cross-Talk Model. Further, there are divisions within these major theoretical perceptions (Bayot et al., 2018). Moreover, researchers have noted that there may be a greater need to recognize the role of higher-order processing in DT to explain the empirical evidence adequately (e.g., see Pashler, 1994 for a general consideration and Yogev-Seligmann et al., 2012; Wajda & Sosnoff, 2015; Wajda et al., 2016 for reviews and applications in DTW specifically).

Attentional capacity theory asserts that humans have limited attentional capacity, and, when these resources are taxed by engaging in activities that require attentional effort (i.e., are nonautomatic), performance on one or both tasks will degrade (either in quality or rapidity) as attentional demands will be exceeded and attention must alternate between tasks (or attention to one task must be sacrificed). Two major version of attentional capacity theory exist: central capacity-sharing and multiple resource models (Bayot et al., 2018). Central capacity sharing models assert that a central attentional regulating process underlies the effects seen in DT, but multiple resource models note that many types of cognitive resources may be involved in the processing (Bayot et al., 2018).

Structural bottleneck theory proposes that neural circuitry limits underlie DT effects. Specific bottleneck theory versions propose that tasks that require pathways that are shared between the neural networks regulating the tasks compete and cause a neural bottleneck (Bayot et al., 2018). Unified (or central) bottleneck theory versions assert that either encoding or response networks in the brain cause general bottleneck for attentional tasks regardless of shared pathways in the networks that usually regulate the individual tasks (Bayot et al., 2018; Tombu et al., 2011). Some bottleneck theory models even assert that multiple neural bottlenecks may exist (e.g., encoding, task-specific neural overlap, and/or response selection).

The cross-talk model is a bit of a third force in DT theory. It accounts for the phenomenological and neural processes that may underlie DT effects, but it provides a view that better accounts for DT *facilitation* (i.e., when one or more of the tasks is improved under DT; Bayot et al., 2018). Essentially, if tasks share related processes or neural networks, the activation of these processes for one task may *facilitate* the activation for the related task. Facilitation has been observed in some studies in healthy controls (Downer et al., 2016) and in some populations with neurological disorders (e.g., Huntington's disease; Delval et al., 2008). Of note, although this approach may help understand motor-motor facilitation (as observed in HD; Delval et al., 2008), it is less adept at explaining cognitive-motor facilitation (e.g., Downer et al., 2016). Also, it does not explain the heterogeneity of responses within individuals when the task-alignments are the same. Within individuals, there are regularly some individuals who show facilitation and some who show interference regardless of task congruence. This heterogeneity was noted by Delval et al. (2016). Similarly, although people with MS on average show cognitive-motor interference, even within MS a minority of persons show cognitive-motor facilitation in DTW (Quinn et al., 2019).

A lesser-known theory of DT is the time-sharing hypothesis (Bayot et al., 2018; Nijboer et al., 2014). This theory attempted to explain why research reports show lesser, equal, and greater neural activation in different DT conditions. This perspective runs contrary to cross-talk model in that it asserts that tasks that share neural networks will be *more likely* to produce interference—not less. The key component is whether time is shared for the neural processing of the tasks. If two tasks use different networks, those networks will be accessed with some degree of alternation meaning they are *less* frequently accessed (decreased activation). Thus, lesser activation of the region involved when the task is performed in isolation is observed. However, if the tasks can be synchronized and "share time," activation can be maintained for both tasks because there is no neural processing interference (equal activation). However, if the tasks share related neural networks, those networks can have *heightened activation that results in interference* (Nijboer et al., 2014). Additionally, Nijboer et al. (2014) proposed these networks may also heighten activation as the result of adding another level of processing that results from the attempt to evaluate errors arising during the DT overlap.

Although there are undoubtedly neural and cognitive processes that are foundational to DT effects, there is no consensus regarding which theory best explains the evidence in DT research and most fail to explain the pantheon of observations fully (Bayot et al., 2018). Recently, there has been a move toward considering that these theories may not adequately explain DT interference in general (Pashler, 1994) and in balance while walking specifically (Yogev-Seligmann et al., 2012). These models note that higher order processing and other person-level factors—which undoubtedly still involve neural and cognitive processes, but in different ways—need to be considered to understand the heterogeneity of responses that can be observed across DT paradigms and within persons within a given DT paradigm. A theory with the potential to be viewed as complementary to many of those in existence, is self-awareness theory (SAT; Wajda & Sosnoff, 2015; Wajda et al., 2019). Yogev-Seligmann et al. (2012) specifically note that assessment of one's abilities in the context of environmental demands may be a critical person-specific factor to consider in understanding heterogeneity in DT. That is, self-efficacy is a putative moderator in understanding how baseline abilities affect the DT processes (Wajda et al., 2019). Thus, this model emphasizes that not just one's *objective* abilities but also one's *subjective evaluations and appraisals* of these abilities are crucial to understanding DT effects, and this may help to explain the great heterogeneity observed in the corpus of literature.

Dual-Task Paradigms

DTW is often explored using a simple paradigm that requires a cognitive task (e.g., serial subtractions, verbal fluency tasks, etc.) to be performed concurrently with walking (Mirelman et al., 2018). Although motor-motor, cognitive-cognitive, and cognitive-motor paradigms all exist, cognitive-motor paradigms are among the most common and may be particularly useful in MS (e.g., Mofateh et al., 2017). However, it is worth noting that these paradigms all have their place and permit exploration of various processes and possible deficits. For example, there have also been calls for the use of cognitive-cognitive DT evaluations in the clinical assessment of MS (Beste & Ziemssen, 2020), as it may reveal cognitive deficits more sensitively than single task (ST) cognitive processes alone (e.g., D'Esposito et al., 1996). Although such paradigms have their clear use given 40-70% of those with MS have some form of cognitive dysfunction (Chiaravolloti & DeLuc, 2008; Rocca et al., 2015) and executive function is a common problem in MS that has been shown to be critical in DT paradigms (Beste et al., 2018), the potential implications of DT producing cognitive-motor interference are particularly notable and consequential (e.g., potential to impair function and increase risk of falling). In fact, the seminal study to explore DTW was based on the premise that it increased fall risk (Lundin-Olsson et al., 1997).

When considering cognitive-motor DT paradigms, there is no consensus regarding the form DT takes, and great heterogeneity in studies leads to the need to answer several outstanding questions (Bayot et al., 2018). It has been explored for a variety of motor tasks—from fine motor tasks (e.g., D'Esposito et al., 1996; Wolkorte et al., 2015; Goverover et al., 2018; Lemmens et al., 2018) and upper limb movement (e.g., Raats et al., 2019) to balance and gait tasks (e.g., see Wajda & Sosnoff, 2015; Learmonth et al., 2017; Postigo-Alonso et al., 2018; Chamard Witkowski et al., 2019 for reviews). Moreover, there is no agreement regarding the type of cognitive task to be used. Serial subtractions (3s or 7s), verbal fluency tasks (i.e., word list generation; e.g., phonemic [e.g., words that start with "D"] or semantic [e.g., animals]), and alternating alphabet tasks are common (Postigo-Alonso et al., 2018). Digit span (Hamilton et al., 2009) and Stroop Color-Word test, both visually (Kalron et al., 2011) and auditorily (Leone et al., 2020), have also been used in MS DT studies. Leone et al. (2020) included *eight* cognitive tasks in the DT study in MS (serial subtraction with 3 and 7, digit span forward and backward, auditory Stroop Color-Word test, clock task, and word list generation phonemic and semantic). There is evidence that a dosing effect may be present in some populations with more demanding cognitive tasks causing greater performance decrements on the concurrent walking task (Kirkland et al., 2015; Mirelman et al., 2018; Leone et al., 2020; *cf*. Hamilton et al., 2009). However, findings vary greatly within specific operationalizations for cognitive tasks, and even studies that have attempted to compare cognitive tasks in DTW in MS have come to different conclusions.

Leone et al. (2020) noted that digit span backwards and phonemic word list generation produced the greatest cognitive-motor interference in MS and auditory Stroop Color-Word test produced the least. The other tasks did not differ from one another. However, Postigo-Alonso et al. (2018) reported in their review that serial subtractions by 7, but not 3, and alternating alphabet produced reliable cognitive-motor interference in MS. They were unable to evaluate digit span given its rare use. The original DTW assessment, the Stops Walking while Talking Test (Lundin-Olsson et al., 1997; see also de Hoon et al., 2003), simply required patients to maintain a conversation while walking from one room to another in their residential facility. The conversation (e.g., questions asked by the experiments) can be more standardized (e.g., de Hoon et al., 2003), and this test has given rise to the Walking while Talking test (Verghese et al., 2002) which includes a 40 ft (≈ 12 m) walk and turn has two different levels of complexity (alphabet recitation and alternating alphabet recitation). It has been used in people with MS (Fritz et al., 2019). Verghese et al. (2002) concluded that the Walking while Talking Test was a reliable and valid indicator for fall risk in older adults. Similarly, the Timed Up and Go-

Cognitive test (TUG-C) can be administered by adding either serial subtractions or verbal fluency tasks (Quinn et al., 2019) to the Timed Up and Go test (TUG) which is a standardized mobility task that includes rising from seated, walking 10 ft (≈ 3 m), turning, and returning to seated (Podsiadlo & Richardson, 1991). This test is a recommended screening test for fall risk, too (Kenny et al., 2011).

Dual-Task Costs as a Measure of Interference

As stated, DT paradigms attempt to probe changes in performance—most frequently and notably deficits—that arise from performing two tasks concurrently. Although, as noted, DT can result in facilitation wherein one or both tasks experience improved performance during DT relative to ST conditions (Bayot et al., 2018), DT costs (DTC) is regularly used in lieu of a more general term like DT effect (Bayot et al., 2018). In fact, Plummer et al. (2013) noted that there are nine possible results from cognitive-motor DT studies: 1) no changes, 2) motor interference, 3) cognitive interference, 4) cognitive and motor interference, 5) cognitive facilitation, 6) motor facilitation, 7) cognitive and motor facilitation, 8) motor interference and cognitive facilitation, and 9) cognitive facilitation and cognitive facilitation. Although DTC may not be the most apropos to describe all these possible outcomes, the phrase DTC is commonly used. The general form of DTC, which can be applied to cognitive, motor, or other performance measures, is computed as the change between ST and DT performance as a ratio of ST performance that is multiplied by 100 to convert to a percent change relative to baseline (Learmonth et al., 2017; Leone et al., 2015; Postigo-Alonso et al., 2018; Wajda & Sosnoff, 2015; see Baddeley et al., 1997 for original proposal of below equation).

$$DTC = \frac{ST - DT}{ST}\ x\ 100$$

This measure, introduced in Baddeley et al. (1997) in neuropsychological assessment, has been used widely without much consideration regarding its performance as a test for DTW in MS (e.g., reliability). It is worth noting that in the seminal study regarding DTW and falls conducted by Lundin-Olsson and colleagues (1997), DTC was not used. Rather, it was simply based on observations made in a clinic that evaluated whether residents stopped walking when conversing. Further, when considering the usefulness of DTC versus other ways of operationalizing DT performance or interference, recent evidence in people with MS suggests that it may not be as useful for repeated testing evaluations as using ST and DT speeds (or other gait characteristics excluding measures of gait variability) in isolation (Chen et al., 2020). It is worth noting that the sample size used for Chen et al.'s (2020) study was quite small, and reliability was assessed based on a weekly reevaluation that occurred at three times only. However, it is possible to examine interference in DT by simply examining the difference in performance between the two conditions or by including condition as a within-persons factor, and DTW performance (e.g., speed, gait variability) alone could serve as useful metrics.

It is worth noting that studies vary in whether they use absolute changes for speed or time or DTC for speed or time. This could produce heterogeneity in results. Consider the following demonstration. Imagine two subjects both experience a slowing of 0.1 m/s under DT. One has a baseline speed of 1.4 m/s (subject 1) and the other a baseline speed of 0.9 m/s (subject 2). This will lead to DTC for speed of 7.1% and 11.1%, respectively. As such, the slower individual (subject 2) will appear to have 1.56 times the DTC than the faster individual (subject 1). If these values were converted to DTC for time, the slower individual would appear to have a DTC 1.63 times greater than subject 1. As such, DTC using speed and time will produce results that differ slightly. This difference alone could produce heterogeneity even when DTC are used.

However, some studies simply consider the absolute change in time. Yet, fixed differences in time will lead to different conclusions. If we evaluated these same people but imagined the difference evaluated was the difference in time (s) not speed (m/s), we would arrive at different conclusions. Imagine they experienced the identical absolute changes in time and took 0.2 s more to complete the DT walk than the ST walk. As such, these people would not appear to differ in the DT outcome for absolute change. However, this would result in a DTC for time of 9.3% for subject 1 and a DTC for time of 6% for subject 2. Thus, the faster individual would appear to have the greater DTC by a factor of 1.56 for time, and this would result in a DTC that is 1.51 times greater for subject 1 relative to subject 2 for speed (see Table 1).

Table 1

Hypothetical Data Comparing Dual-Task Cost Calculation based on Absolute Change Comparisons using Speed and Time

Subj	Distance (m)	ST (m/s)	Δ(m/s)	DTWCS	ST (s)	Δ(s)	DTWCT
1	3	1.4	0.1	0.071	2.143	0.165	0.077
2	3	0.9	0.1	0.111	3.333	0.417	0.125
	Proportional Change (subj1/subj2)			1.556			1.625

Subj	Distance (m)	ST (m/s)	Δ(m/s)	DTWCS	ST (s)	Δ(s)	DTWCT
1	3	1.4	0.120	0.085	2.143	0.2	0.093
2	3	0.9	0.051	0.057	3.333	0.2	0.060
	Proportional Change (subj1/subj2)			0.663			0.643

Note. Subj = Subject. ST = Single task. Delta is the difference between the single-task and dual-task performances. DTWCS = Dual-Task Walking Costs for Speed. DTWCT = Dual-Task Walking Costs for Time.

As such, studies that examine ST and DT as within-persons conditions could have notably different conclusions than those that use DTC, and this reminds that there are reasons to consider treatment of ST and DT performance carefully. Throughout the DT literature in MS, one finds studies that use Baddeley et al.'s (1997) formula, performance in DT (without ST reference), and comparison of performance using within-persons factor treatment. Future literature reviews should account for differences in findings between studies using measures such as DTC versus gait characteristics or time measurements in DT paradigms.

Dual-Task Walking in Multiple Sclerosis

Focusing specifically on DTW, DTW costs (DTWC; that is walking related changes in DT) can and have been calculated for a variety of gait parameters, but the most common and pronounced changes to gait in older adults or those affected by neurological disorders seem to be decreased gait speed and increased stride-to-stride variability (Mirelman et al., 2018). DTW has been assessed among those with MS recently, with the first study occurring in 2009 (Hamilton et al., 2009), after research findings that aging and neurological disease states, such as Alzheimer's disease, stroke, and Parkinson's disease, cause decreases in DTW ability (e.g., Woollacott & Shumway-Cook, 2002; Camicioli et al., 1997). (For later demonstrations of these effects, see also Plummer et al., 2013; Kelly et al., 2012.) In MS, most studies examining DTWC regularly report slowing during DT conditions, and Postigo-Alonso and colleagues' (2018) systematic review reported gait speed to be the most sensitive of the DTWC measures commonly assessed. Wajda and Sosnoff (2015) and Leone et al. (2015) in their reviews focused on gait speed and noted that all studies showed DTWC for speed in those with MS. Coupled with Chen et al.'s (2020) finding that measures of variability (e.g., stride-to-stride variability as noted by Mirelman et al., 2018) were highly unreliable when evaluated for repeated measurements in both people with MS and healthy controls, this provides good indication that the assessment of speed is appropriate for the purpose of evaluating changes in gait during DT. Further, assessing speed is simple and translatable. Clinicians can assess a patient's speed by simply using a stopwatch while patients walk a known distance (e.g., see Montero-Odasso et al., 2020). The rationale for using speed as a primary measure is bolstered further by the aforementioned importance of walking speed in MS generally. Changes in gait speed are widely used and reasonably so.

Although DTC for cognition (DTCC) can be calculated as well, they are rarely included (for relevant reviews, see Chamard Witkowski et al., 2019; Leone et al., 2015; Postigo-Alonso et al., 2018; Wajda & Sosnoff, 2015). The evidence regarding DTCC is mixed. Some studies have reported that DTCC seem useful in MS (Hamilton et al., 2009; Wajda et al., 2016; Wajda et al., 2019; Wajda et al., 2020) and others have indicated otherwise (Leone et al., 2020; Postigo-Alonso et al., 2019). However, there is variability in how DTCC are calculated (e.g., accuracy alone or time-based accuracy) in addition to other variables in the study designs, too. With so few studies reporting DTCC, it is hard to consolidate and interpret them adequately in MS. As stated, there are nine possible profiles for DT effects, but these have not been explored fully or adequately in MS. Interestingly, Quinn et al. (2019) recently assessed 100 participants with MS based on the strategies they employed during DT. They identified six patterns of responders: those who 1) performed well cognitively and motorically, 2) performed worse cognitively but not motorically, 3) performed worse cognitively and motorically, 4) would stop to complete cognitive task and resume, 5) would synchronize their steps and cognitive task responses, and 6) performed worse motorically but not cognitively. They noted that only one pattern was associated with high risk of falling during a 3-month prospective observation: those who exhibited DTWC but not DTCC. This is akin to the "posture-second" strategy that has been discussed in other populations affected by neurological disease (Bloem et al., 2006) and examined more recently in MS as a possible predictor of disability progression (Castelli et al., 2020). Importantly, this was an exploratory analysis and there was small sample size per cell for this 2 x 6 contingency table. Bearing this limitation in mind, although this suggests that understanding both tasks is useful, it provides further indication that altering gait may be what is of particular importance in the context of fall risk, reiterating the importance of DTW effects.

Correlates of Dual-Task Walking in MS

The ability to dual-task may be an important functional process in its own right in MS. Castelli and colleagues (2016) reported that DTWC were related to elements of the 54-item Multiple Sclerosis Quality of Life scale (MSQoL-54), specifically role limitations related to physical problems and social function, in people with MS who had low levels of disability (EDSS $\leq$ 3). Other evidence also suggests that DTW problems may occur early in the disease course (e.g., even in Clinically Isolated Syndrome; e.g., Kalron et al., 2010, 2011). It seems that DTW is a function that is important in MS, and it manifests early in the disease course. It takes only a bit of mental consideration to identify all the daily functional and social activities that require DT—from holding a conversation while walking with a friend, to texting as we navigate through our environments, to recalling our grocery list while strolling through the grocery store, to trying to remember where we parked as we walk through the lot, on and on the list of DTW goes. Thus, it is reasonable to assume that DTW ability would matter to the function and QoL of those affected by MS, particularly if the deficits are perceptible—whether as the result of their novelty (e.g., early in the disease course) or severity (e.g., later in the disease course). Yet, there is a notable paucity of research that explores how important patient reported outcomes (PROs) relate to DTW in those with MS (Leone et al., 2015; Rooney et al., 2020).

In their 2015 review, Leone and colleagues noted that there is a clear neglect of the "invisible symptoms" (p. 128) of MS in the context of DT research. Rooney et al. (2020) found only nine DTW studies (and four DT balance [DTB] studies) that examined correlations with other variables of importance in MS. They reported only two studies that examined depression, two studies that examined FSE (or "balance confidence"), and four studies that examined fatigue. No studies examining QoL were included in their review. Further, in terms of objectively measured correlates, there is a surprising lack of studies examining relationships with disability (e.g., EDSS, $n = 9$), cognition (variable measures, $n = 9$), or balance (BBS, $n = 1$; postural sway, $n = 1$).

Although there are numerous studies evaluating DT in MS, most of them focus on simply characterizing DTW in MS and comparing the performance of those with MS to healthy controls. Although there is strong evidence for DTWC in MS—albeit the evidence is less strong with respect to whether these costs differ from those of healthy controls in magnitude—there is limited examination of the relationships between DTW ability and DTWC and other important constructs in people with MS. (As a reference, 47 studies that included DTW in some form and 17 studies that included DTB in some form were identified during a thorough literature review. Current meta-analyses and reviews [dated 2015 to 2020] in DT in MS included between 13 and 20 studies [see Leone et al., 2015; Wajda & Sosnoff, 2015; Learmonth et al., 2017; Postigo-Alonso et al., 2018; Chamard Witkowski et al., 2019; Rooney et al., 2020].) Thus, it is difficult to ascertain whether and how DTW ability or DTWC relate to other important outcomes in MS. Even the evidence regarding whether cognition relates to DTWC or DTC for balance in MS remains unclear (e.g., Rooney et al. [2020] report 5 of 9 studies reporting correlations between baseline cognition and DTC). One correlate that has been examined most frequently and consistently, disability measured by the EDSS, does not seem to reliably relate to DTWC (Rooney et al., 2020), suggesting that DTWC may capture something distinct from general walking function (which particularly affect EDSS scores, especially in the range of 4.0 to 7.0; van Munster & Uitdehaag, 2017). Clearly, more research is needed to understand the correlates and predictors of DTW ability and DTWC in MS.

Consequences of Dual-Task Walking—Falls

Beyond the possible relevance to patients for DTW ability alone, its importance is further bolstered by possibility that it is related to fall risk and falls. In fact, the seminal study by Lundin-Olsson and colleagues (1997) is considered the first to identify the inability to engage in DTW ability (not DTWC) as a predictor for falls. This study was a small report based on observations in a long-term care facility in Sweden. It found that 12 of 58 residents would stop walking when talking, and 10 of these 12 “stops walking when talking” residents fell in the next 6 months. Lundin-Olsson et al. (1997) also reported that these individuals were assessed to have less safe gait in general and needed more assistance with activities of daily living. Thus, the idea that function and falls are consequents of an inability to perform DTW is at the foundation of this line of research. In fact, Lundin-Olsson and colleagues (1997) found that this simple identification of individuals who stop walking to talk classified fallers with 95% specificity albeit with only 48% sensitivity and had a positive predictive rate of 83%. Comparatively, Bogle Thorbahn and Newton (1996) found that the BBS only had 96% specificity and 53% sensitivity, but it has a much greater burden of administration than merely observing this everyday activity of "walking and talking." Thus, this demonstrated that a simple, everyday ability to walk and talk may be a useful characteristic to evaluate when considering whether someone is at risk for falling among older adults.

In MS, Quinn et al. (2019) found that individuals with MS who provided self-reported indication of difficulty doing two things at once were twice as likely to experience two or more falls during a 3-month prospective study. Finding that such a simple question about an important everyday process was significantly related to prospective fall risk in MS is insightful, as there is a clear need to have measures that adequately predict fall risk and rates in MS. Studies exploring these issues have revealed continued limited ability of available measures to adequately classify fallers and non-fallers (Cattaneo et al., 2006; Nilsagård et al., 2009; Hoang et al., 2016). A recent meta-analysis (Quinn et al., 2018) of predictors of fall risk in MS found that there is limited work in the area permitting a full understanding of the best predictors of fall risk, but the ABC and FES-I—two highly related, self-report measures of FSE (or "balance confidence")—were two of three (the third being the BBS) measures that were found to be useful. However, it was noted that there is not sufficient evidence from prospective studies to adequately identify measures of fall risk in MS. Work has hinted that DTW ability may predict fall risk in MS, as it does in older adults. One study (Wajda et al., 2013) found that DTWC correlated with the Physiological Profile Approach, and objective assessment of various domains that are putatively important for maintaining balance and which performs decently in predicting falls in MS (Gunn et al., 2013; Hoang et al., 2016). However, ST and DT speed alone did not. However, Rooney et al. (2020) noted that only one of the two studies they identified that assessed DTWC and Physiological Profile Approach correlations found such a relationship.

This inconsistency between the two studies examining DTWC and Physiological Profile Approach scores is characteristics of the evidence regarding DTWC and fall risk in MS generally—it is limited and conflicted. For example, one study that included DTWC did not find DTWC to predict future falls (Gunn et al., 2013). Yet, another study (Etemadi, 2017) found that both DTWC and DTCC predicted risk of being a recurrent faller in a 6-month prospective study in 60 people with MS. Nilsagård et al. (2009) found that TUG-C time (not DTWC), which has been reported to have 87% sensitivity and specificity among older adults (Shumway-Cook et al., 2000), was a significant predictor of being a faller albeit it did not perform as well as some of the other measures, such as the BBS. Quinn et al. (2019) evaluated the ability of TUG and TUG-C performance to discriminate both fallers (≥ 1 fall) and multiple fallers (≥ 2 falls) from non-fallers in a 3-month prospective study of 101 people with MS. They found that both assessments performed mediocrely at best (.71 ≤ sensitivity ≤ .82 and .26 ≤ specificity ≤ .34) using ≥ 9s for TUG and ≥11s for TUG-C, and the TUG-C was no better than the TUG alone.

It is notable that studies use different timeframes and classification practices (e.g., some use ≥ 1 fall during a given period and some use ≥ 2 falls during a given [and often variable—e.g., 3 months or 6 months] period). They can also vary in the types of task used (in terms of either the walking task [e.g., variable distance, turn inclusion or not, etc.] or cognitive task) and in the operational definition of the DT variable (e.g., DTWC or DTW gait characteristics or time alone). Further, they vary in their model construction approaches. Etemadi (2017) focused on DTC predictors of fall risk whereas Gunn et al. (2013) and Nilsagård et al. (2009) focused on a broader array of predictors of fall risk including a single measure of DTW (with only one using DTWC). Lastly, Nilsagård et al. (2009) and Quinn et al. (2019) both used only the time to complete TUG-C, not DTC specifically, and only Quinn et al. (2019) examined TUG-C performance as a singular test for classifying fallers (not just a predictor in a classification model). A final important note in the context of fall risk and DTW is that recent evidence suggests that DT training may outperform standard physical therapy (balance and gait exercises) based on some small, randomized trials (Elwishy et al., 2020; Molhemi et al., 2017; Sosnoff et al., 2017), including reducing risk of future falls over a 3-month follow-up period (Molhemi et al., 2017). None of these studies explored the mediators or mechanisms—likely due to the small sample sizes and preliminary nature of the work—so it is difficult to ascertain the specific elements being altered by DT training that confer these benefits for more distal outcomes. Clearly, more needs to be understood regarding the relationship between DTW outcomes and fall risk and rates among those with MS (Leone et al., 2015; Wajda & Sosnoff, 2015).

Abilities and Appraisals: A Theory-Based Model

Researchers studying DT in MS have noted the clear need to understand the correlates and consequences of DTW more fully in those with MS (Leone et al., 2015; Rooney et al., 2020; Wajda & Sosnoff, 2015). With few studies—and fewer still exploring the correlates and consequences of DT—heterogeneity in design and results, and frequently, but not exclusively, small sample sizes, there is need to continue to address these questions. If the intention is to affect the lives of those with MS for the better, it is crucial to understand whether there are meaningful effects of DTW on patients' lives (e.g., by examining PRO correlates and predictors and health-related risks). Further, if such relationships do reflect true processes in the population of those affected by MS, there is a need to understand whether these processes work similarly for patients with different clinical profiles.

In the context of a theory of DT that acknowledges the complexity of DT—like the complexity of balance, gait, and falls generally (e.g., see Cameron & Nilsagård, 2018; Robinovitch, 2018)—it is reasonable to propose that person-level moderators—including appraisals of self and one's environmental context (Yogev-Seligmann et al., 2012)—may be important. As noted, SAT (Wajda & Sosnoff, 2015; Wajda et al., 2019; Yogev-Seligmann et al., 2012) proposes that risk evaluation—based on environment and personal ability—operates to affect prioritization processes that occur during DTW (e.g., whether gait and balance or the other task [e.g., cognitive process] is prioritized). There is research that suggests that within people with MS, personal ability or deficits (Lemmens et al., 2018; Saleh et al., 2018), environmental demands (Veldkamp et al., 2019; Wajda et al., 2020), and other factors may affect DT processes. This may indicate that appraisal based on personal ability or environmental hazards are relevant to DTW processes. Further evidence of higher order process involvement comes from evidence that prioritization instructions can affect DTW outcomes in people with MS (Postigo-Alonso et al., 2019). This evidence hints that it is reasonable to hypothesize that higher-order evaluative processes can impact DTW in people with MS and that more basic theories (e.g., bottleneck theory or attentional capacity theory) may not be sufficient to understand DT effects in MS in their entirety (Wajda et al., 2019).

In the context of FSE and depression, which are particularly relevant in MS, as previously noted, and can be reasonably expected to affect motor and cognitive processes, both also affect risk evaluation and personal assessments (Bandura, 1994; Davey et al., 2017). Thus, it is possible that the effects of basic abilities and skills (e.g., motor or cognitive abilities) not only relate to these states, but that their effects on complex functional tasks (e.g., DTW) are moderated by these psychological states. Assessments of abilities would be expected to differ for people with different levels of FSE and depression.

By definition, self-efficacy is an appraisal of one's ability to complete a particular task (Bandura,1994), and the proposition of its relevance to DTW has been made by others (Wajda et al., 2019; Yogev-Seligmann et al., 2012). Importantly, FSE, in true adherence to the meaning of SE, is not an efficacy for falls (i.e., it is not confidence about one's ability to fall), but an efficacy to maintain balance while navigating various environments. As such, two people with similar cognitive or motor skills may not experience similar DTW outcomes as a function of differential appraisals of relevant underlying abilities. A person with low FSE may believe their balance is poor even when it is not (e.g., Gunn et al., 2018) which could produce meaningful differences in how their abilities relate to DTW effects compared to another person with similar motor abilities but different levels of FSE. Further, although it may seem that FSE is only relevant as a moderator of motor ability and DTW ability, research indicates it may be related to DTCC (Wajda et al., 2020). This is reasonable given the two tasks are occurring simultaneously and beliefs about one or both may affect the primacy given to one which would also result in differences in the other. A person with low FSE and high levels of cognition may not experience the same relationship between cognition and DTWC as a person with high FSE and high levels of cognition. Low FSE may make one hypervigilant with respect to walking (e.g., see Kalron & Achiron, 2014); thus, they may be slower than their counterpart with high FSE which may alter the cognitive-motor coupling often seen in those with MS (Benedict et al., 2011; Motl et al., 2013; Yozbatiran et al., 2006). That is, in general, walking speed and cognitive ability appear to be highly correlated in MS, but this correlation may be attenuated by the presence of low FSE due to the perception of less competence and more risk leading to alterations in gait.

Similarly, depression could lead to heightened risk appraisal—in fact, research suggests that depression may lead to more accurate (i.e., less optimistically biased) assessments of risk for future events (Korn et al., 2014) in some interesting research regarding optimism bias and health outcomes (e.g., Garrett & Sharot, 2014; Sharot, 2012). Although no researchers have considered depression as a moderator of the relationships between cognition or motor function and DTW, it has been considered as a moderator of cognitive-motor coupling more generally in MS (Ensari et al., 2018). Ensari et al. (2018) did not find that depression moderated general cognitive-motor coupling in

MS, but further evidence is needed, and it is possible that this role could become more patent in more demanding contexts such as DTW paradigms. Yet, Serra-Blasco et al. (2019) and Potvin et al. (2016) found that depression alters appraisal of one's cognitive ability. Further, Potvin et al. (2016) found that subjective cognitive ability was a better predictor of function in individuals with depression than objective cognitive ability. This highlights the power of subjective appraisal and evaluation in understanding the interplay between cognition and function—albeit in a more general form.

Thus, it is reasonable to hypothesize that either depression or FSE could *moderate* the relationships between cognition and mobility and DT effects. Although simply asking whether depression and FSE are related to DTW ability or DTWC is also important, if the relationships between cognitive ability or motor function and DTW effects are moderated by person-level factors like FSE and depression, this could lead to masked relationships (e.g., if a qualitative moderation exists the marginal effect could wash out). Also, understanding whether these psychological states alter the appraisals made by individuals with MS in a way that produces differential effects of DT may be relevant to understanding the interference that FSE, depression, and DTW pose for those with MS in daily life. It could suggest that different interventions are warranted for DTW problems for individuals with different levels of FSE or depression. Finally, it provides a means to test whether a theory like SAT may be needed—even if just complementarily—to explain DTW effects in people with MS. If FSE or depression moderate the relationships between motor function or cognition and DTW, it would provide some—albeit limited—indication that SAT as an explanation for DTW processes in MS has merit.

However, a necessary starting point given the mixed findings in the literature is identifying which motor and cognitive factors may be related most to DTW and DTWC. As noted, there is still limited understanding regarding which motor and cognitive domains may be particularly relevant (Rooney et al., 2020). Thus, as a first step, identifying the most relevant of these seemingly inherently important domains is warranted. As a final step to explore and understand the implications of DTW in general, it is imperative to understand whether DTW ability or DTWC affect distal outcomes like QoL, disease impact, and falls. Although DTW ability may something that people with MS view as important in and of itself, understanding its full import requires assessing its relationship with distal outcomes that are subjectively important to those affected by MS and objectively affect their health and wellbeing.

Project Aims

To evaluate the phenomena noted above, three thematically-organized, secondary data analyses were completed to address the following aims:

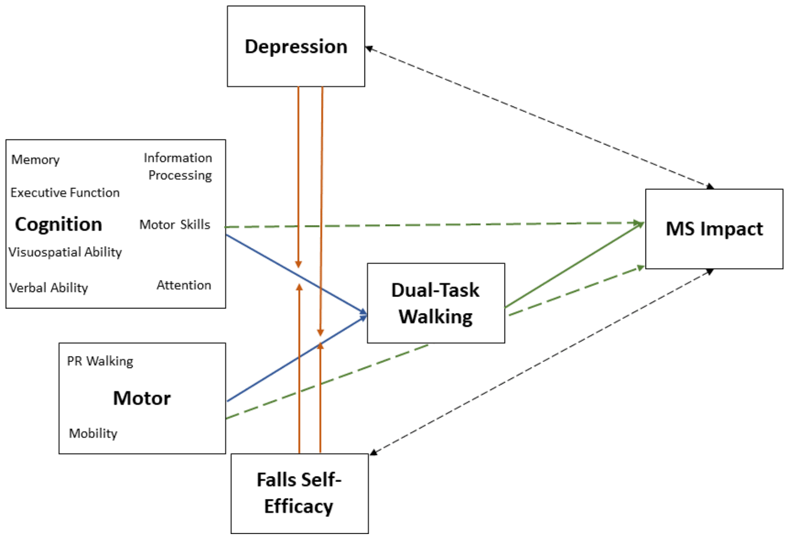
1) Identify cognitive domains that relate to DTW measures in people with MS,
2) Identify motor domains that relate to DTW measures in people with MS,
3) Evaluate FSE and depression as moderators of the relationships between cognitive and motor abilities and DTW measures,
4) Examine whether DTW measures relate to MS Impact and QoL, and
5) Examine whether DTW measures relate to falls both cross-sectionally and longitudinally and whether they explain variance in falls above and beyond baseline walking and cognitive abilities alone.

As part of this process, PROs (e.g., FSE and depression) were evaluated in the context of DTW in MS—something that is generally overlooked by research in the area (Leone et al., 2015). This requires the use of scales that are commonly employed to measure these PROs. Making assumptions that sum scale scores appropriately capture the underlying constructs of interest may notably and detrimentally affect conclusions from statistical models (McNeish & Wolf, 2020). As such, the addition of evaluating these constructs psychometrically is also an important, novel addition to this area of research.

Unfortunately, limitations in available data make it infeasible to assess the entire model in a singular fashion, but its elements can be assessed in discrete components to provide some evidence for the hypothesized model (see Figures 1 and 2). It was hypothesized that 1) cognition (specific domains to be addressed in an exploratory manner) and 2) motor (specific domains to be addressed in an exploratory manner) factors would relate to DTW ability and DTWC, that 3) FSE and depression would moderate relationships between cognitive and motor factors and DTW ability and DTWC, 4) that DTW ability would relate to MS Impact and QoL, and that 5) DTW would relate to falls cross-sectionally and predict falls longitudinally above-and-beyond baseline motor and cognitive abilities.

Figure 1

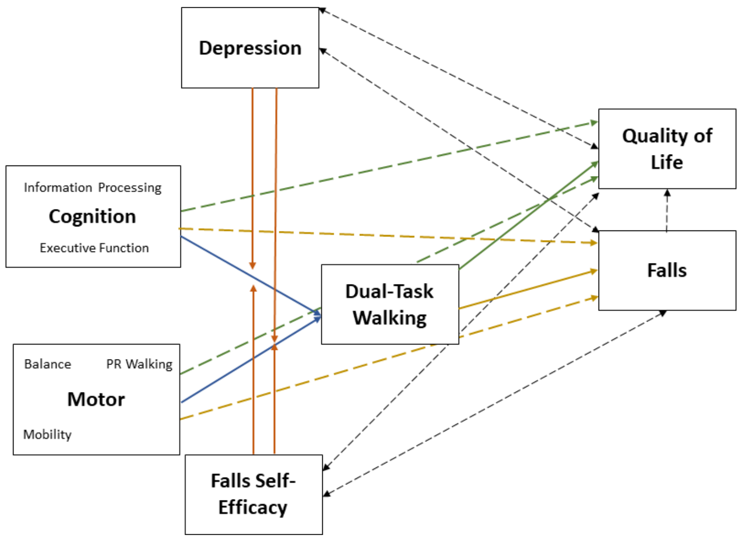
Proposed Model using South Shore Data. PR = Patient-Reported



Note. PR = Patient-Reported. Blue lines correspond to aims 1 and 2. Orange lines correspond to aim 3. Green lines correspond to aim 4. Black lines are expected but not in aims.

Figure 2

Proposed Model using University of Kansas Medical Center Data.



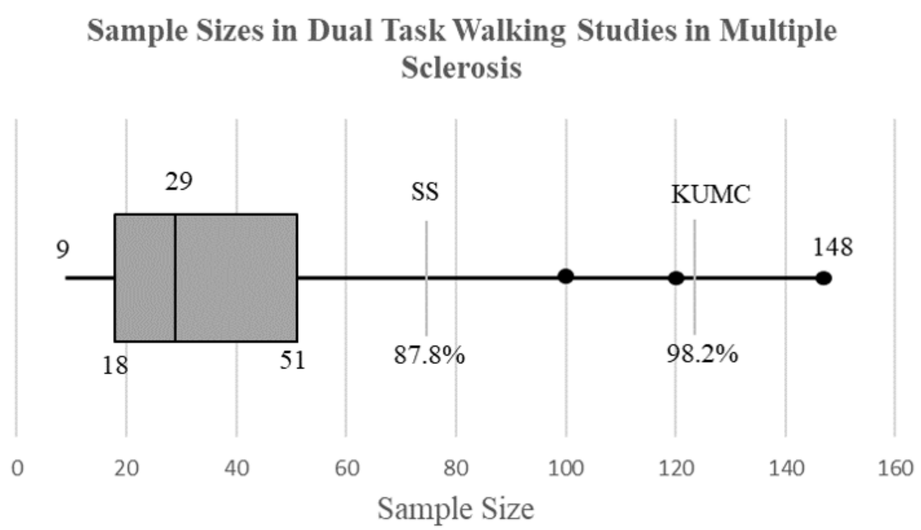
Note. PR = Patient-Reported. Blue lines correspond to aims 1 and 2. Orange lines correspond to aim 3. Green lines correspond to aim 4. Gold lines correspond to aim 5. Black lines are expected but not in aims.

Method

The proposed research performed secondary data analyses on two relatively large data sets that contain the necessary measures to compute DTW ability and DTWC. One set of data comes from South Shore Neurologic Associates, PC (SS) and the other comes from the University of Kansas Medical Center (KUMC). The sample sizes of these data sets are a clear strength. For example, they both fall on the upper end of the sample size distribution compared to existing studies in the area with the SS data being at the 87.8th percentile and the KUMC data being at the 98.2nd percentile—second in size to only one study (see Figure 3). Both available data sets had other, unique strengths that suit them for addressing the proposed research aims (e.g., inclusion of PROs in both, longitudinal data collection for a period greater than any existing studies that include assessments of DTW and falls for KUMC data, etc.).

Figure 3

Boxplot for Sample Size in Dual-Task Walking Studies in Multiple Sclerosis.



Note. Only participants with Multiple Sclerosis are included. SS = South Shore Neurologic Associates. KUMC = University of Kansas Medical Center.

South Shore Neurologic Associates, PC Data

SS is a comprehensive neurological care practice that has multiple facilities in New York (SS & MedNet Technologies, Inc., 2020). It was established in 1980, and it has many specialty groups including a clinical research team involved in multiple research studies and clinical trials. The clinical research team at SS has established a data use agreement with Arizona State University (ASU) to allow for use and analysis of some of its data collected from various neurological populations via clinical samples. The SS data were used to address aims 1, 3, and 4 primarily.

Participants. The current data included 73 people with MS as part of a deidentified data set. This is a convenience sample of clinical patients who agreed to have their data used for research purposes. As such, there are no explicit inclusion or exclusion criteria for the sampling approach. However, the sample is described fully in terms of demographic and clinical features. A trained neurologist completed the EDSS to measure disability levels which are also summarized. Some participants were measured multiple times. Only the first administration of any measure was included to ensure independence of observations between units of analysis and to minimize possible learning effects from re-administration.

Materials.

Expanded Disability Status Scale. The EDSS (Kurtzke, 1983) is considered the gold standard measure for disability due to MS (Bermel et al., 2014) despite some limitations (Amato & Portaccio, 20007; Cohen et al., 2012). For example, the EDSS has been criticized for heavy reliance on ambulation in the middle 4.0 – 7.0 range (van Munster & Uitdehaag, 2017) and having limited reliability and sensitivity to change

(Meyer-Moock et al., 2014; Noseworthy et al., 1990). Nevertheless, it remains an important pillar in disability assessment in MS (Cohen et al., 2012). It assesses multiple functional systems (pyramidal, cerebellar, brain stem, sensory, bowel & bladder, visual, cerebral [mental], and other; Kurtzke, 1983). These systems are all evaluated by neurologists and graded with set scoring systems specific to the domain (higher scores indicating more dysfunction in the system), and the scores on these systems are used to compute the final score of the EDSS—the "disability status scale step" (Kurtzke, 1983). Scores for these steps range from 0 (normal neurological examination) to 10 (death due to MS) and rise by half-point increments (Kurtzke, 1983).

Gait Parameters. Gait parameters (speed) were extracted by the original research team using data from a Zeno™ Walkway gait analysis system measuring 2 ft (width) by 26 ft (length; Protokinetics Inc., Haverton, PA, USA). This mat records footfall data digitally, and this data permits calculation of walking speed. The Zeno™ Walkway has been shown to be a valid (e.g., concurrently) and reliable tool for evaluating gait characteristics (Berg-Poppe et al., 2018; Hynes et al., 2019; Lynall et al., 2017; Vallabhajosula et al., 2019) including for gait speed in clinical care settings (Abizanda et al., 2020), and it has been evaluated for reliability in DTW designs (Montero-Odasso et al., 2020). The walk distance was standardized for all participants to be ≈ 8 m (walkway length). To avoid including acceleration during gait initiation and termination, participants begin walking before reaching the mat and are instructed to continue walking after the mat ends (approximately 1.5 m each). Straight, unobstructed walks without turns, rising from seated, or other elements were performed. Both the ST and DT walks included three trials and the mean of these was used as the outcome variable.

Dual-Task Walking Measures. Given the possible limitations of DTWC in addition to the various approaches for assessing DTW in MS, multiple operationalizations were used for DTW. Specifically, three operationalizations were considered: 1) DTWS, DTWC, and DTWD. The purpose of this was to understand whether these differences in operationalizations can account for disparate outcomes in and of themselves. Further, it permits evaluation of the relative performance of these measures in terms of their correlations with other important outcomes in two large samples of people with MS. For example, two people could have identical DTWC but different DTW ability (e.g., the speed or time in DT alone). Also, two people could have identical DTW ability but very different DTWC. It may be that DTW ability alone relates to outcomes (and perhaps even above-and-beyond ST walking speed [STWS]) but DTWC do not. For example, this could arise from the fact that a relatively high baseline performer with high DTWC may still be rather functional in daily life, but a relatively low baseline performer might experience notable consequences for experiencing the same level of DTWC. (As an additional layer, to be experiencing the same DTWC for these two subjects, the absolute decrements would have to be greater for the higher performer [i.e., faster walker].) As such, it seems reasonable to consider and contrast examinations of DTW ability, DTW absolute differences, and DTWC.

Gait Speed. First, DTW ability was measured simply as gait speed during DTW (i.e., DTWS). DTWD in speed was also used as a measure of raw differences between the two conditions.

$$DTWD = STWS - DTWS$$

For DTWD, positive values indicate faster STWS, and negative values indicate greater DTWS.

DTWC for speed was computed and analyzed based on Baddeley et al.'s (1997) formula.

$$DTWC = \frac{STWS - DTWS}{STWS} \; x\; 100$$

DTWC are calculated in such a way that positive values indicate greater DTWC. That is, more positive values would indicate more proportional slowing in DTWS compared to STWS relative to STWS.

Cognitive Measures. Neurotrax™ *Mindstreams*® is a computerized cognitive test battery with seven domains: 1) verbal and nonverbal memory, 2) executive function, 3) visual spatial processing, 4) verbal function, 5) attention, 6) information processing speed, and 7) motor skills (Doninger, 2007, 2014a, 2014b). The test also produces a measure of global cognition. The test uses computerized adaptive processes to gauge cognitive function effectively for each participant, and it provides precise (ms) measures for tests requiring reaction times (Doninger, 2007). It has been used in MS, including to study relationships with self-reported walking, FSE, and gait speed (Kalron, 2014), but it has not been used in any DTW studies in MS to-date. All measures are standardized automatically by the Neurotrax™ program accounting for age and education (M = 100, SD = 15; Doninger, 2014a). Over 20 studies contributed to the standardization, and the battery has been validated externally (Doninger, 2014a). The normalized scores were used to evaluate the reported cognitive domains.

Motor Measures. Mobility was assessed by the STWS and the Multiple Sclerosis Walking Scale-12 (MSWS-12; Hobart et al., 2003). The MSWS-12 is a self-report measure that assesses walking function and impairment based on a 2-week recall period.

It asks participants to report the degree of limitation they have experienced across 12 domains during this 2-week period on 5-point scales (1 = Not at all; 5 = Extremely). The measure has been found to be highly internally consistent (.94 ≤ Cronbach's α ≤ .97; Hobert et al., 2003; McGuigan & Hutchinson, 2004a) and to have excellent test-retest reliability in short- (e.g., intraclass correlation coefficient [ICC] = .94 for 10 days; Hobart et al., 2003) and long intervals (e.g., ICC = .86 and .87 for 6 and 12 months, respectively; Motl et al., 2011). Item 12 on the MSWS-12 may be particularly relevant in DTW studies, as it asks participants to evaluate the degree to which they had to "concentrate" on their walking in the past 2 weeks. It also has been shown to have criterion validity with established relationships concurrently or prospectively for daily step counts, balance, walking ability, and FSE (Cavanaugh et al., 2011); EDSS, MS Impact, and QoL (Hobart et al., 2003); walking speed (Motl et al., 2010); and fall risk (Nilsagård et al., 2009).

Depression. Depression was measured using the Beck Depression Inventory-II (BDI-II; Beck et al., 1996). Importantly, although the BDI-II aligns well with diagnostic measures for depression, it is a measure of depressive symptoms, not a diagnostic tool for depression (Beck et al., 1996); however, psychometric meta-analytic evidence indicates that it performs comparably with gold standards for diagnosing depression (Wang & Gorenstein, 2013a). The BDI-II contains 21 items that ask about depressive symptoms that have been experienced in the past 2 weeks using a 0 to 3 scale with higher scores indicating higher levels of depressive symptoms (Beck et al., 1996). Suggested cut-offs have been reported as 0-13 (minimal), 14-19 (mild), 20-28 (moderate), and 29-63 (severe; Beck et al., 1996 as cited in Wang & Gorenstein, 2013a). The BDI-II has been used in a variety of samples and has demonstrated excellent internal validity, test-retest reliability, and validity (e.g., construct, criterion) based on a review of 118 studies conducted Wang & Gorenstein (2013b). There is evidence that the 21-item measure has two factors, which the researchers have labeled as cognitive-affective and somatic-vegetative (Wang & Gorenstein, 2013b). There is also evidence that although it performs well in a variety of samples (e.g., general, medical, and psychiatric; Wang & Gorenstein, 2013b), cutoffs appear to vary across populations (e.g., medical versus general; Wang & Gorenstein, 2013a)

Falls Self-Efficacy. FSE was measured using the Modified Falls Efficacy Scale (MFES; Hill et al., 1996) which was developed as an expansion of Tinetti et al.'s (1990) Falls Efficacy Scale (FES). The MFES consists of 14 items, and it expands on the FES by adding 4 items that include more variety in activities (e.g., more challenging contexts including outdoor activities; Hill et al., 1996). The MFES uses an 11-point scale with verbal references provided at 0 (Not confident at all), 5 (Fairly confident), and 10 (Completely confident). The MFES has excellent internal consistency (Cronbach's α = .95) and weekly test-retest reliability (scale ICC = .93; Hill et al., 1996). Significant differences between balance-compromised and healthy older adults were shown as a demonstration of discriminant validity (Hill et al., 1996). Edwards and Lockett (2008) did identify two factors in a sample of 551 community-dwelling older adults: one indicating efficacy for basic activities of daily living (e.g., getting dressed or undressed) and one for efficacy in more complex activities of daily living (e.g., using outdoor steps).

Multiple Sclerosis Impact (Quality of Life Proxy). The Multiple Sclerosis Impact Scale-29 (MSIS-29) was used as a measure of MS disease impact (Hobart et al., 2001) as a proxy for QoL. It contains 29 questions answered using 5-point scales to measure how impacted (1 = Not at all; 5 = Extremely) individuals feel they have been by their MS on a variety of physical and mental health issues of importance in MS over the past 2 weeks (Hobart et al., 2001). It was developed using a large sample of randomly selected individuals from the NMSS membership database (Hobart et al., 2001). Originally 129 questions were evaluated, and these were reduced through factor analytic processes to a final 29-item, 2-factor measure (20 items measuring physical impact and nine items measuring psychological impact; Hobart et al., 2001). It demonstrates excellent internal consistency (Cronbach's αs ≥ .91), test-retest reliability (ICCs ≥ .87), and criterion validity (Hobart et al., 2001). Additional studies have confirmed that it has good internal consistency and criterion and convergent validity (e.g., Costelloe et al., 2007; Hoogervorst et al., 2004; McGuigan & Hutchinson, 2004b; Riazi et al., 2002). Further, Hobart et al. (2005) reported that it was the most responsive measure of physical impact from MS and second most response measure of psychological impact from MS (second to the General Health Questionnaire-12) in a study of 245 people with MS.

Procedures. Participants completed gait analysis using the Zeno™ Walkway, cognitive assessment using *NeuroTrax*™ cognitive battery, and provided PROs during clinic visits at SS. ST and DT gait analyses were performed on the same day in the same order for all participants. The MSWS-12 and MFES were collected on the same day that the gait analysis was performed. The cognitive testing was not completed on the same day as the other assessments for most participants, and the MSIS-29 and BDI-II were collected on the same day as the cognitive testing. Some participants completed cognitive testing before gait analysis, and some participants completed cognitive testing after gait analysis. The distance between measures ranged from the same day to slightly more than 10 months. Within the clinical context, there were 3 different DT paradigms applied—each without any prioritization instructions. Most (n = 49) participants completed serial 3 subtractions starting at the number 50, but 23 completed serial 7 subtractions. Three participants performed other cognitive tasks during DTW and were excluded from analysis. Participants completing different serial subtractions were compared statistically to determine whether it is reasonable to treat them collectively for further analyses. One participant used a rollator during the gait testing. Cognitive performance in ST or DT conditions was not recorded, so it is not possible to calculate DTCC.

University of Kansas Medical Center Data

KUMC is a research and clinical healthcare facility associated with the University of Kansas with facilities located through Kansas (KUMC, 2020). A collaborator (JH) who completed a large, grant-funded study in people with MS has authorized use of data for secondary analyses. A data use agreement between KUMC and ASU was approved by ASU and KUMC. The KUMC data were used primarily to address aims 2, 3, 4, and 5.

Participants. Participants included 122 people with MS recruited through the MS Clinic at KUMC. The study also included 4 time points (baseline, 6 months, 12 months, and 18 months). There was high attrition (> 60%) with only 41, 39, and 34 participants completing the subsequent assessments, respectively. The study was intended to evaluate the use of wearable inertial sensory (Opals, APDM, Portland, OR) for evaluating gait and balance in people with MS, and it included a variety of gait and balance measures (see, e.g., Craig et al., 2017). A trained staff neurologist specializing in

MS evaluated all participants using the EDSS. Inclusion and exclusion criteria as reported in the original research protocols are listed in Table 2.

Table 2

Inclusion and Exclusion Criteria for the KUMC Study

Inclusion	Exclusion
Mini-Mental State Examination ≥ 20	Unable to give informed consent
Not on Fampridine	Expanded Disability Status Scale ≥ 5.5
	Unable to walk without assistive device
	Pregnant, breastfeeding, or within 3 months post-partum
	Non-MS disability that affects mobility or balance
	Non-MS neurological/neurodegenerative disorder
	Part of a vulnerable population
	Primary Investigator-deemed unsuitability

Note. MS = Multiple Sclerosis.

Materials.

Expanded Disability Status Scale. The EDSS was used in this study. A summary of it was provided in the SS study details. It is not reviewed here again for succinctness.

Gait Parameters. Gait parameters in the KUMC study were extracted using MATLAB® (MathWorks, Inc.) from three-dimensional positional data from reflective markers tracked by digital cameras (Raptor-E digital cameras, Motion Analysis, Inc., Santa Rosa, CA). Reflective markers were placed in 35 locations. A marker located on the trunk (sacrum) was used to extract positional data in the X axis and to calculate gait speed. Three-dimensional motion capture provides a valuable, objective means of quantifying gait and balance during common clinical mobility and balance assessments (Abu-Faraj et al., 1999; Rigby & Ray, 2018). They have been shown to produce highly reliable results (Abu-Faraj et al., 1999). Marker-derived motion capture via camera systems have been found to be highly consistent with walkway system gait analytic approaches (Stokic et al., 2009). The data for gait parameters was collected during four walking trials consisting of fast, normal (aka, self-selected), and slow walking speeds. A second self-selected trial was performed using serial subtractions by 3 from a three-digit number; this is the DTW condition. These trials were randomized within subjects to minimize order effects when the sample is analyzed in aggregate. Participants performed five walk trials at baseline for each condition and three walk trials at follow-up visits for each condition. To ensure that gait speed is a realistic measure of performance, visual analysis was performed to identify the acceleration phases associated with gait initiation and termination to truncate the trial data to ensure that participants' gait speed is not based on these phases of the test. The mean for the multiple trials within a given walk condition were used as the outcome for analysis. The protocol included five trials per condition at baseline and three trials per condition at follow-up assessments. In a few rare exceptions, the number of trials was reduced to ease participant burden or for other reasons. All available trials were used to compute a mean for each person at each visit.

Dual-Task Walking Parameters. The calculation of DTW measures mirrored the approach discussed for the SS data. The extraction of DTW measures is not repeated here for succinctness.

Cognitive Measures. As is common in gait studies in MS (e.g., see Leone et al., 2015), a comprehensive neuropsychological assessment was not conducted for the KUMC study. However, two cognitive measures were conducted via computerized testing—a measure of executive function and a measure of information processing. To evaluate executive function a computerized version of the Stroop test, including the Stroop Color-Word test component (Stroop, 1935; see also, Scarpina & Tagini, 2017) was conducted. Participants completed an 8-item practice and proceeded to complete to 30 s trials. The performance on the Stroop Color-Word test (i.e., Stroop interference test) is of particular importance as it measures cognitive inhibitory control as dimension of executive function (Diamond, 2013) which may be relevant in DT contexts. It can detect deficits in inhibitory control that result from aging (West & Allain, 2000) and neurologic disease (Weintraub et al., 2005). Evidence does indicate that individuals with MS, on average, perform worse on the Stroop tests (Denney et al., 2005), suggesting that this measure may be sensitive to changes in MS. However, in MS, it seems that information processing speed may be a more reliable measure of cognitive impact (Denney et al., 2004; Denney & Lynch, 2009). To assess information processing, a computerized reaction time test was administered. Participants are instructed to press the space bar on a computer with their dominant hand when a target stimulus appears on the screen, and performance across 15 trials is used for the final measure of processing speed. This was performed in simple and choice paradigms. Computerized administration of the Stroop tests and reaction time tests of information processing have been shown to be reliable and valid (Gualtieri & Johnson, 2006).

Motor Measures. Given the focus of the original study, there are several measures of mobility, balance, and self-reported walking that are available for inclusion.

Berg Balance Scale. The BBS is a widely used measured of static and dynamic balance. It consists of 14 balance tasks and takes about 15 to 20 minutes to complete (Berg, Wood-Dauphinee, et al., 1992). Trained raters evaluate the participants' performance in each task and rate performance on a 5-point scale from 0 (unable to perform) to 4 (performs independently/normally). The BBS score is the sum of the 14 items with functional balance being indicated by a score of 56 and a score < 45 indicating possible fall risk (Berg, Wood-Dauphinee, et al., 1992). In those affected by MS, the BBS has been found to be reliable across raters (ICC = .96; Cattaneo et al., 2007) and repeated measurements taken three days apart (ICC = .94, Cattaneo et al., 2007) as a measure of balance. Berg, Wood-Dauphinee, et al. (1992) reported that it correlated strongly with functional and motor performance in patients recovering from stroke, and it was predictive of recurrent falls among elderly residents of a long-term care facility. It also demonstrates at least acceptable predictive validity for falling in MS (Cattaneo et al., 2006; Nilsagård et al., 2009; Quinn et al., 2018). However, it may be subject to ceiling effects even within those affected by MS (Ross et al., 2016).

Multiple Sclerosis Walking Scale-12. The MSWS-12 was used in this study. Its psychometric performance was reviewed in detail in the SS study details. It is not reviewed here again for succinctness.

Timed Up and Go. The TUG test includes rising from a seated position with one's back against the chair, walking 3 m, turning 180°, walking 3 m back, and returning to a seated position with one's back against the chair (Berg, Maki, et al., 1992). The TUG has excellent interrater and test-retest reliability for total time in elderly populations (ICCs ≥ .92; Steffen et al., 2002) and has been used in a variety of neurological diseases demonstrating desirable psychometric properties and minimal detectable changes of approximately 3 to 4 seconds (Huang, et al., 2011; Ries et al., 2009). In a previous study, the TUG was not found to be predictive in falls in MS in the presence of other measures of function and efficacy (Van Liew et al., 2020).

Timed 25 Foot Walk Test. The Timed 25 Foot Walk Test (T25FWT) consists of participants being instructed to walk to a 25 ft marker as quickly and safely as possible (Fischer et al., 1999). They begin the task standing statically and walk an unobstructed course. They are instructed to walk past the finish line to exclude gait termination acceleration in the measure. Participants time to complete the task is measured, so total time and gait speed for the trial can be determined. The standardized version includes the task being completed twice with the average time for the two trials being used in the final score (Fischer et al., 1999), but three trials were completed and averaged in this study. The T25FWT has been found to be a valid measure in MS (Motl et al., 2017). It is sensitive to changes in the disease course and treatment effects, and it correlates with QoL measures (Cohen et al., 2014; Coleman et al., 2012; Goldman et al., 2013; Hobart et al., 2013; Kragt et al., 2006; Motl et al., 2017). Changes of approximately 20% in gait speed measured using the T25FWT indicate clinically meaningful differences in MS (Cohen et al., 2014; Motl et al., 2017). However, the T25FWT may be subject to learning effects over repeated administration in MS (Larson et al., 2013).

Falls Self-Efficacy. The ABC was used to evaluate participants' balance confidence (which can rightfully be considered a measure of efficacy within Bandura's theory; Talley et al., 2008). For example, both the ABC and the MFES probe similar constructs—namely they both require participants to report *confidence* in their balance and ability to avoid falling. This may be thought of as conceptually distinct from measures that assess "worry" about falling which may probe anxiety constructs in addition to efficacy (Talley et al., 2008), despite measures of FSE being considered measures of "fear of falling" (e.g., Hill et al., 1996; Tinetti et al., 1990).

The ABC is a 16-item measure that asks an individual to rate his or her confidence that they can perform a variety of tasks without losing their balance or falling using percent confidence from 0% (No confidence) to 100% (Completely confident). The total score is the average confidence on all items. The ABC does require participants to evaluate their confidence in more, and more demanding, contexts than the FES or MFES.

The ABC has been shown to have high test-retest reliability over two-week intervals (r = .92; Powell & Myers, 1995), high internal consistency (Cronbach's $\alpha \geq .95$; Huang & Wang, 2009; Talley et al., 2008), and to have concurrent validity with a variety of psychological, balance, and mobility outcomes that would be expected to be related to it theoretically (Talley et al., 2008). It has also been shown to be a reliable measure in MS (e.g., test-retest reliability ICC = .92; Cattaneo et al., 2006). (The SS data includes the ABC for *some* but not all participants. To maximize the usable data for analyses, the MFES was selected as the measure of FSE in that context.)

The study also included the FES-I (Yardley et al., 2005). The FES-I, despite its name, assesses *concern* about falling. Participants answer 16 questions using a 1 (Not at all concerned) to 4 (Very concerned) scale, so scores range from 16 to 64 with higher scores indicating greater *concern* about falling. Of course, as the name implies, the creators still conceptualize of this measure as a measure of FSE despite it probably being seen more reasonably as a measure of fear of falling. Importantly assessments that have compared fear of falling measures to balance confidence (or FSE) surveys report moderate-to-strong negative correlations (e.g., the Survey of Activities and Fear of Falling and ABC, Talley et al., 2008). (As a reference, the Survey of Activities and Fear of Falling is an 11-item measure that assesses "worry" about falling in a variety of contexts using a 0 [not at all worried] to 3 [very worried] scale.) Yet, when Bower et al. (2015) accepted the conceptualization of FES-I as a measure FSE (not fear of falling, or "concern," as worded in the FES-I), they evaluated the correlation between the Fear of Falling Questionnaire-Revised and the FES-I and only found moderate-to-strong correlations, too. (For reference, the Fear of Falling Questionnaire-Revised contains 15 items on a 1 [strongly disagree] to 4 [strongly agree] scale regarding "fear of falling," and it differs from the other measures in that it focuses on consequences, probability, fear, worry, uncontrollability, etc. related to falling as opposed to context-specific "confidence," "concern," or "worry" as the other measures do.) Thus, many individuals are using these various scales with similar intentions, but there may be differences that exist across all of them (whether due to item-level differences, differences in interpretations of words like "confidence," "concern," and "worry," or other test artifacts or construct differences). The FES-I has been found to be reliable and valid in older adults (Delbaere et al., 2010; Figueiredo & Neves, 2018; Helbostad et al., 2010). Further, in MS, the FES-I does seem to have desirable test properties. It has high internal consistency (Cronbach's $\alpha = .94$; van Vliet et al., 2013), good predictive validity for falls (Van Liew et al., 2020; van Vliet et al., 2013), and evidence for convergent validity with measures of fatigue, balance, fall history, cognition, and muscle strength (van Vliet et al., 2013). For a comparison of items in the MFES, ABC, and FES-I, see Table 3.

Table 3

Comparison of Items in the Modified Falls Efficacy Scale (MFES), Activities-Specific Balance Confidence Scale (ABC), and Falls Efficacy Scale-Intentional (FES-I)

Item	MFES	ABC	FES-I
1	Get dressed and undressed	Walk around the house	Cleaning the house

2	Prepare a simple meal	Walk up or down stairs	Getting dressed or undressed
3	Take a bath or shower	Bend over and pick up a slipper from the front of a closet floor	Preparing simple meals
4	Get in/out of a chair	Reach for a small can off a shelf at eye level	Taking a bath or shower
5	Get in/out of bet	Stand on your tiptoes and reach for something above your head	Going to the shop
6	Answer the door or telephone	Stand on a chair and reach for something	Getting in or out of a chair
7	Walk around the inside of your home	Sweep the floor	Going up or down stairs
8	Reach into cabinets or closets	Walk outside the house to a car parked in the driveway	Walking around in the neighborhood
9	Light house keeping	Get in or out of a car	Reaching for something above your head or on the ground
10	Simple Shopping	Walk across a parking lot to the mall	Going to answer the telephone before it stops ringing
11	Using publish transportation	Walk up or down a ramp	Walking on a slippery surface (e.g., wet or icy)
12	Crossing roads	Walk in a crowded mall where people rapidly walk past you	Visiting a friend or relative
13	Light gardening or hanging out the wash	Bumped into by people as you walk through the mall	Walking in a place with crowds
14	Using front or rear steps at home	Step onto or off an escalator while you are holding onto a railing	Walking on an uneven surface
15		Step onto or off an escalator while holding onto parcels such that you cannot hold onto the railing	Walking up or down a slope
16		Walk outside on icy sidewalks	Going out to a social event

Quality of Life. Short Form-36 item survey (SF-36) was administered as a measure of QoL (Brazier et al., 1992). It measures eight dimensions that are subsumed within the domains of functional status (physical functioning [10 questions], social functioning [2 questions], role limitations from physical problems [4 questions], and role limitations from emotional problems [2 questions]), wellbeing (mental health [5 questions], vitality [3 questions], and pain [2 questions]), and overall health evaluation (general health perception [5 questions] and health change [1 question]; Brazier et al., 1992). The SF-36 has been shown to have high internal reliability—even across disparate populations (Jenkinson et al., 1994). This measure has been used in MS. Although it relates to some disease characteristics (e.g., EDSS, time since last relapse) which provides some evidence of convergent validity with MS-specific measures, it was also found to be related to age and sex because it does not assess QoL specific to MS (Fernández et al., 2017). This means that one must be careful not to interpret SF-36 as a measure of QoL that unilaterally captures disease status elements. Further, although some of its psychometric qualities are strong in MS, there is some evidence for floor and ceiling effects on some of the scales within it (Hobart et al., 2001), and it may not be as responsive as other measures of QoL in MS (Hobart et al., 2005). Lastly, its factor structure in MS may not align with the scale domains or the general population structures (Hobart et al., 2001).

Falls. At baseline, participants reported retrospective falls over the past six months. Falls are defined as a loss of balance (e.g., trip or slip) that causes an individual to come to rest on a lower surface (e.g., floor, ground, furniture, etc.; e.g., see Yoshida, 2007). Importantly, in MS, retrospective falls are correlated with prospective falls, but even in periods as short as three months people with MS have difficulty accurately recalling fall counts and the relationships between these metrics are not as high as one might expect (Nilsagård et al., 2009). However, the evidence suggests that retrospective fall reporting may *underestimate* the true rate of falls (Mackenzie et al., 2006). In previous studies, retrospective reporting (from intervals from 3 to 12 months) indicates that 31-63% of people with MS are fallers (Cattaneo et al., 2002; Einarsson et al., 2003; Finlayson et al., 2006; Matsuda et al., 2011; Nilsagård et al., 2009; Stolze et al., 2004). For the remainder of the study, participants reported the number of falls they experienced during the 6-month period between visits, but this was also done retrospectively.

Procedures. Participants completed all assessments in one-day visits at each time. Given the number of balance and mobility tasks included, the study protocol allowed for breaks—including completing paper-and-pencil tests between physically demanding tasks—to manage fatigue. The DTW paradigm consisted of serial subtractions by 3 from a 3-digit number for all participants. Seated serial 3 subtractions were performed as a measure of ST cognitive ability with the total number of subtractions performed and the number of errors made being recorded. However, subtraction performance during the DTW task was not recorded to permit a comparison of performance in these conditions or to calculate DTCC. Four conditions for walking trials were completed by participants in randomized order: slow, normal (aka, self-selected), fast, and normal with subtractions.

Analytic Method by Aim

The study required many statistical processes to perform psychometric and inferential tasks. Some analyses took advantage of the relatively large, cross-sectional sample sizes available in both studies, and others tested for longitudinal relationships despite the high levels of attrition. No power analyses were performed because the study utilizes archival data and has fixed sample sizes. However, it is notable that although power in multilevel models (MLM) tends to be high, it has been recommended that sample sizes of at least 100 be used to avoid biased estimation (Maas & Hox, 2005). Although over 100 people are present at baseline, the high level of attrition requires that effects from longitudinal models be interpreted sagaciously. Most outcomes are expected to be able to be treated reasonably as interval-ratio in nature with the expectation of approximately normal distributions based on previous studies with the notable exception of falls. Falls, as a count outcome, are discrete and are expected to be characterized by a Poisson or negative binomial distribution. Based on previous evaluations of this fall data (Van Liew et al., 2020), negative binomial approaches were employed to handle this data. The moments of the data were explored and summarized using descriptive statistics and visual analyses for all data. For a summary of the conceptual variables and their operationalizations, see Table 4.

Table 4

Conceptual and Operational Variables Included in Analyses

Aim(s)	Conceptual Variable	Operationalization	Study
1-5	Dual-Task Walking	Straight Walk, No Prioritization Instructions, Serial 3 or 7 Subtractions from 2-digit Number	SS
1-5	Dual-Task Walking	Straight Walk, No Prioritization Instructions, Serial 3 Subtractions from 3-digit Number	KUMC
1-5	Cognition	Neurotrax™ *Mindstreams©*	SS
	Memory		
	Executive Function		
	Information Processing		
	Motor Skills		
	Visuospatial Ability		
	Verbal Ability		
	Attention		
	Global Cognition		
2-5	Cognition		KUMC
	Executive Function	Stroop Interference Test	
	Information Processing	Reaction Time Tests	
2-5	Motor Abilities		SS
	Self-Reported Walking	MSWS-12	
1-5	Motor Abilities		KUMC
	Self-Reported Walking	MSWS-12	
	Mobility	TUG	
	Walking	T25FWT	
	Balance	BBS	
3	Falls Self-Efficacy	MFES	SS
3	Falls Self-Efficacy	ABC FES-I	KUMC
3	Depression	BDI-II	SS
4	Quality of Life	MSIS-29	SS
4	Quality of Life	SF-36	KUMC
5	Retrospective Falls	Self-Reported Recollection for Previous 6-month Periods	KUMC

Note. SS = South Shore Neurologic Associates, PC; KUMC = University of Kansas Medical Center; MSWS-12 = Multiple Sclerosis Walk Scale-12; TUG = Timed Up and Go; T25FWT = Timed 25 Foot Walk Test; BBS = Berg Balance Scale; MFES = Modified Falls Efficacy Scale; ABC = Activities-specific Balance Confidence scale; FES-I = Falls Efficacy Scale-International; BDI-II = Beck Depression Inventory-II; MSIS-29 = Multiple Sclerosis Impact Scale-29; SF-36 = Short Form-36.

For data coming from the SS study, analyses were performed to compare performance for those who completed serial 3 (n = 49) and those who completed serial 7 (n = 21) subtractions using independent samples t-tests for DTWC and DTWD including a Levene's test to check homogeneity of variance. A two-level MLM with random intercepts and slopes was performed to assess the effect of subtraction type (3 or 7; coded 0 and 1, respectively, for analytic purposes) treating task type as a within-person factor (ST and DT, coded 0 and 1, respectively, for analytic purposes), too. Of interest in this model was the effect of subtraction type on the slope of gait speed (i.e., change from STWS to DTWS). If this effect were significant, it would indicate that the changes experienced between STWS and DTWS in gait speed differ as a function of subtraction type. The results of these analyses informed the decision regarding pooling data from these different DTW paradigms.

MLM here is similar to a mixed, 2 (subtraction type) x 2 (task type) Analysis of Variance (ANOVA). In fact, an ANOVA with a repeated or within-persons factor is a very specific, rigid version of MLM. Using MLM allows for a relaxation of the rigid, often unmet assumptions of ANOVA that includes repeated measures—including the use of various covariance structures (e.g., unstructured, autoregressive, etc.), in addition to other benefits that are less relevant in the current context (e.g., handling missing data, complex time structures, etc.; Gueorguieva & Krystal, 2004; Hoffman & Rovine, 2007). Although the simple structure, complete data, and question form (e.g., difference between only two repeated measures as opposed to growth trajectories) in this case would likely mean a mixed ANOVA would be reasonable, given there are no advantages to mixed

ANOVA over MLM, and, in fact, MLM can be constrained to provide results identical in mixed ANOVA, MLM was used (see equations below).

Level 1: $Y_{ti} = \beta_{0i} + \beta_{1i}X_{1ti} + \epsilon_{ti}$

Level 2: $\beta_{0i} = \gamma_{00} + u_{0i}$

$\beta_{1i} = \gamma_{10} + \gamma_{11}X_{2i} + u_{1i}$

Aims 1 and 2: Identify Cognitive and Motor Domains that Relate to DTW Measures

Aims 1 (SS data) and 2 (KUMC data) were approached using baseline, cross-sectional data only. Stata 16.1 I/C (StataCorp, LLC, College Station, TX) and R 4.0.3 for Windows (The R Foundation) were used to perform the analyses. First, as a note, to abet comparison to other studies in the literature, the scale scores were used for the purpose of estimating relationships bivariate relationships with DTWS, DTWD, and DTWC. The psychometric properties of the scales used to relate to DTW outcomes were assessed using classical test theory methods that are likely to be familiar to a broad readership (e.g., Cronbach's α). However, because Cronbach's α has notable limitations and may underestimate the true internal consistency of a scale (McNeish, 2018; Sijtsma, 2009), additional metrics (e.g., Revelle's ω; McNeish, 2018) were also considered.

Next, throughout the analyses, models were performed separately using these three different operational definitions of DT for speed. Although the inclusion of multiple operationalizations does inflate the number of tests, the purpose is to compare different operationalizations to determine whether a particular metric for DT ability in MS relates most aptly to other important outcomes in MS—not to dredge for significant findings. Although no corrections for Type I error are proposed and a conventional $\alpha = 0.05$ was used for inferential purposes where relevant, all reports clearly state both that multiple operational definitions of the outcome were included and the purpose for doing so.

Further, to assess dimensionality of scales, exploratory factor analyses were performed using iterative principal factoring (IPF). Oblique oblimin rotated solutions were evaluated for comparison for fit with unrotated solutions where appropriate. Loadings, Eigenvalues, and scree plots were evaluated, and a parallel analysis (n = 100) were performed to establish Eigenvalue cutoffs based on the 95th percentile (Hayton et al., 2004) for each measure based on its construction and sample size at each point of measurement.

Next, scatter plots were constructed, and bivariate (zero-order) correlations were computed for all variables. Median splines were fitted to visualize trends in the data. Also, a full multiple regression model was performed to compute partial and semi-partial (aka, part) correlations (Abdi, 2007) for all variables with DTWS, DTWD, and DTWC. (The relationships among these DTW outcomes were also evaluated.) The advantage of including partial and semi-partial correlations is that it permits evaluations of the relationships between a given predictor and the criterion controlling for the presence of all other variables (Judd et al., 2009). The partial correlation partials the shared variance with the covariates out of both the variance in the predictor and the criterion, but the semi-partial only partials the shared variance from the covariates out of the predictor (i.e., the unique variance explained by X_1 out of all the variance of Y controlling for X_2, $X_3 \ldots X_k$). These analyses provide insight into the bivariate relationships that exist among cognitive and motor domains and DTW outcomes, as well as the unique contributions of each of the predictors accounting for the presence of the others.

SS Full Model for Cognitive Domains:

$Y_i = \beta_0 + \beta_1 Memory_i + \beta_2 Executive\ Function_i + \beta_3 VisuosptialAbility_i + \beta_4 VerbalAbility_i + \beta_5 InformationProcessing_i + \beta_6 MotorSkills_i + \beta_7 Attention_i + \epsilon_i$

KUMC Full Model for Motor Domains:

$Y_i = \beta_0 + \beta_1 EDSS_i + \beta_2 MSWS\text{-}12_i + \beta_3 T25FWT_i + \beta_4 BBS_i + \epsilon_i$

However, more importantly, the underlying question is an issue of variable selection; that is, which of the variables most efficiently and effectively explains the variance in the criterion. To address this question, lasso (Tibshirani, 1996) for inference was performed. Lasso is a variable selection approach that is preferable to alternatives like forward and backward stepwise regression given its ability to minimize overfitting (StataCorp LLC, 2019). Lasso uses a shrinkage function, like ridge regression, but unlike ridge regression, lasso can shrink β coefficients to zero (i.e., it performs shrinkage and *selection*). As such, lasso will yield a sparse model that involves only a subset of the original predictors in the final model. Lasso uses an ℓ_1 penalty ($|\beta_j|$) instead of the ℓ_2 penalty (β_j^2) used in ridge regression (see equation), and this allows some coefficients to be shrunk to zero when λ is sufficiently large. Increasing the value of λ reduces the magnitudes of the coefficients. Lasso coefficients, $\hat{\beta}_\lambda^L$, minimize the quantity:

$$\sum_{i=1}^{n}\left(y_i - \beta_0 - \sum_{j=1}^{p}\beta_j x_{ij}\right)^2 + \lambda\sum_{j=1}^{p}|\beta_j| = \mathrm{RSS} + \lambda\sum_{j=1}^{p}|\beta_j|$$

Note. RSS = Residual sum of squares.

(James et al., 2013).

In lasso, it is important to select an optimal value for λ as it directly affects the shrinkage and selection process. To select an ideal value for λ, cross-validation has been recommended (James et al., 2013). The least angle regression (LARS) solution is another expedient algorithmic means of arriving at a solution (Efron et al., 2004). Although historically lasso was used for prediction and not inference as a result of not providing the standard errors necessary for inference (James et al., 2013), techniques have recently been developed to use lasso for inference—not just prediction and model selection (Wang & Michoel, 2017). The “lassopv” function in the lars package in R was used to obtain lasso-based *p* values (Wang & Michoel, 2017) in addition to performing 10-fold cross-validated lasso and LARS models in Stata (StataCorp LLC, 2019).

Aim 3: Psychological Moderators of the Effects of Abilities on DTW Measures

As noted in the above section, for aims 1 and 2, the sum scores were used to enhance interpretability and transferability across researchers in the area. However, factors scores have clear advantages over sum scores (McNeish & Wolf, 2020). For aim 3 (both SS and KUMC data), psychometric scales are central to the hypotheses being tested; therefore, approaches that avoid the assumptions imposed by sum scores were employed. Classical test theory methods and factor analysis were performed on these items for basic evaluation and reporting.

For directly testing the hypotheses, structural equation modeling (SEM) would be a reasonable approach for the purpose of combing measurement and structural models into a single process (Acock, 2013). Although SEM has great utility, it relies on large samples (e.g., several hundred) to provide unbiased estimates (Devlieger & Rosseel, 2017). Devlieger and Rosseel (2017) developed a two-stage method that performs the factoring and regression modeling processes in a stage-wise fashion, factor score path analysis (Devlieger & Rosseel, 2017), or factor score regression (Devlieger et al., 2019).

This approach appears to confer benefits in the context of smaller sample sizes (Devlieger & Rosseel, 2017). For reference in the context of the importance of sample size, their simulation study sample sizes ranged in size from 50 to 2000 (Devlieger & Rosseel, 2017). Devlieger and Rosseel's (2017) method applies Croon's correction to avoid inducing bias in the regression coefficient estimates that can occur from naïve FSR. The R command "fsr" (in lavaan package) developed by Rosseel (2012, 2018) allows for the implementation of Croon's correction as well as the use of Bartlett or regression factor score estimation methods. Regression factor scoring methods are preferable for predictors and moderators (Skrondal & Laake, 2001). Models were specified with observed criteria (DTWS, DTWD, and DTWC, separately). A priori cognitive predictors to test for interactions include response inhibition (executive function; Leone et al., 2015) and information processing (Denney et al., 2004; Denney & Lynch, 2009). These have been selected based on research regarding the impacts of psychological states on cognitive function, the impact of MS on cognitive function, and theorized cognitive domains that are important for DT. They were also treated as observed variables. They are available in both data sets to permit conceptual replication. The predictors from the motor domain included the T25FWT and BBS (KUMC only) and MSWS-12 and STWS (both data sets). Each of these were treated as an observed variable except the MSWS-12 was treated using regression factor estimation (regression method) as mentioned for the moderators (FSE and depression). Moderation was evaluated by interacting (creating a multiplicative term) from the factor score and relevant predictor. The cognitive and motor models were performed separately, and the KUMC and SS data were analyzed separately. As a note, although FSR performs well in terms of convergence (Devlieger & Rosseel, 2017), FSR models can be attempted in SEM or using factor scores as observed variables in regression as alternatives. In cases where FSR limitations (e.g., inability to interact latent variables or achieve convergence), multiple linear regression (aka path analysis) with factor scored predicted from exploratory factor analyses were used.

Aim 4: Examine Relationships between DTW Measures and Quality of Life

To assess the relationship between DTWS, DTWD, and DTWC and QoL, FSR was used. This was addressed in the SS data using the MSIS-29 and in the KUMC data using the SF-36. In this context, the variable that requires factor treatment is the outcome, as such Bartlett's method for factor scoring was considered (Skrondal & Laake, 2001) in addition to regression scoring given that some predictors were also latent variables. No inferential decisions were altered using these different scoring methods. Disability (EDSS step), depression (BDI-II), self-reported walking ability (MSWS-12), and FSE (ABC or FES-I [KUMC] or MFES [SS]) were included as covariates. The EDSS step was treated as an observed variable, but factor scoring methods were applied to the depression, self-reported walking ability, and FSE constructs using the items from the measures listed above.

Aim 5: Examine Relationships between DTW Measures and Falls

Finally, to evaluate whether DTWS, DTWD, or DTWC relate to self-reported falls *at baseline* and *across visits*, negative binomial regression (nbreg Stata command) and a MLM negative binomial regression (Hox, 2010; menbreg Stata command) were performed in Stata 16.1 I/C, respectively. These models used the KUMC data only, as SS did not collect fall data. Analyses to evaluate predictors of attrition were performed using attrition (0 – No, 1 – Yes) at any point in the study as a binary outcome in a logistic regression model given the large level of attrition. ICC for repeated measures were estimated for all predictors in the longitudinal model using one-way random effects models.

Both models included mobility (T25FWT) and executive function (Stroop interference test and information processing [reaction time tests]) as covariates. The MLM negative binomial regression included random effects estimates and person-mean-centered state and trait predictors (all covariates are time variant). Using person-mean-centering permits separation of trait (person-mean) and state (time-based deviations from person-mean) effects for time variant variables in MLM (Curran & Bauer, 2011). This allows a researcher to determine whether the average value on a variable across all times ("between-persons") or the change in that variable over time ("within-persons") is related to the criterion. Incidence rate ratios were calculated from both the retrospective and prospective models to assess the effects of the variables on fall rates. The negative binomial regression MLM is an extension of the Poisson form of MLM where: $Y_{ij}|\lambda_{ij}$ = Poisson (m_{ij}, λ_{ij}) with a log link function for λ, $\eta_{ij} = \log(\lambda_{ij})$. This link function inverse would be $\lambda_{ij} = \mathbf{exp}(\eta_{ij})$, but this equation adds an error term in negative binomial regression MLM: $\lambda_{ij} = \mathbf{exp}(\eta_{ij} + \epsilon_{ij}) = \mathbf{exp}(\eta_{ij})\mathbf{exp}(\epsilon_{ij})$ to allow of inequality of the mean and variance (Hox, 2010). The two-level model then takes the form:

Level 1: $\eta_{ti} = \beta_{0i} + \beta_{1i}\text{Time}_{ti} + \beta_{2i}(X_{2ti} - \bar{X}_{2i}) + \beta_{3i}(X_{3ti} - \bar{X}_{3i}) + \beta_{4i}(X_{4ti} - \bar{X}_{4i})$

$+ \beta_{5i}(X_{5ti} - \bar{X}_{5i})$

Level 2: $\beta_{0i} = \gamma_{00} + \gamma_{01}\bar{X}_{2i} + \gamma_{02}\bar{X}_{3i} + \gamma_{03}\bar{X}_{4i} + \gamma_{04}\bar{X}_{5i} + u_{0i}$

$\beta_{1i} = \gamma_{10} + u_{1i}$

$\beta_{2i} = \gamma_{20}$

$$\beta_{3i} = \gamma_{30}$$

$$\beta_{4i} = \gamma_{40}$$

$$\beta_{5i} = \gamma_{50}$$

CHAPTER 2

Although DTW has been examined in MS, there is still a dearth of information regarding correlates of DTW measures in MS (Leone et al., 2015; Rooney et al., 2020). Although there is some utility in simply knowing whether DTW effects exist, to truly understand the import or usefulness of measuring DTW measures, it is imperative to understand how they relate to the constellation of other symptoms experienced. For example, understanding which physical and cognitive domains predict DTW measures could assist researchers and clinicians in understanding possible targets for optimizing DTW abilities. Similarly, examining correlates can permit a determination of the degree to which DTW measures relate to other outcomes of importance, and could provide a deeper understanding of causes of DTW deficits in people with MS.

In order to address this question, Aims 1 and 2 included analyses to explore the relationships between DTW effects and various cognitive and physical variables. Aim 1 used the data from SS to explore the relationships between cognitive domains measured via a comprehensive, computerized neuropsychological examination (*Neurotrax*^{TM} *Mindstreams*®) and DTW measures. Aim 2 used data from KUMC to assess relationships between DTW measures and computerized cognitive (e.g., Stroop and reaction time tests) and physical (e.g., balance, self-reported physical domains, disability) measures.

Assumption Checks

Before assessing correlates and predictors of DTW effects, tests to check assumptions to ensure reasonable treatment of data were undertaken. All participants in the SS data set who did not complete serial subtractions as part of the DTW paradigm were excluded and only first administrations were included. This left 70 participants in the sample. The tests to compare the use of serial 3 and 7 subtractions in the SS data revealed no significant differences in mean DTWC, $t(68) = -0.012$, $p = 0.991$ between the serial 3 (M = 13.83%, SD = 14.04%) and serial 7 (M = 13.88%, SD = 13.57%). The variances between these conditions did not differ significantly either, $F(48, 20) = 1.07$, $p = 0.900$.

A MLM with speed (m/s) as the outcome walk condition (STW = 0 or DTW = 1) as the within-persons factor and subtraction type (3s = 0 or 7s = 1) as the between-persons factor was also performed to test for differences between these manipulation conditions. Random intercepts and slopes (i.e., change from STW to DTW condition) were included. An unstructured covariance matrix was compared to an independent structure assuming correlations between random effects are zero. Including the correlation between the person and walk condition random effects did not significantly improve the random-effects model, $\Delta\chi^2(1) = 1.71$, $p = 0.192$. An identity matrix with only random intercepts was not significantly worse than the independent inclusion of intercept and slope random effects, $\chi^2(1) = 0.00$, $p = 1.00$. The random-effects portion of the model was significant, $\chi^2(2) = 119.03$, $p < 0.001$. The person-level SD was 0.260, 95% CI[0.218, 0.310].

The fixed effects portion of the model was significant, Wald $\chi^2(3) = 70.66$, $p < 0.001$. There was a significant effect of walk condition, $B = -.123$, 95% CI[-.157, -.090], $z = -7.20$, $p < 0.001$. This indicates that there was a significant slowing observed (by about .12 m/s) in the DTW condition relative to the STW condition in the serial 3 subtraction group (see Table 5 for table of cell and marginal predictions). As such, a DTW effect was present in this study.

Table 5

Marginal Predictions by Walk Condition and Subtraction Type

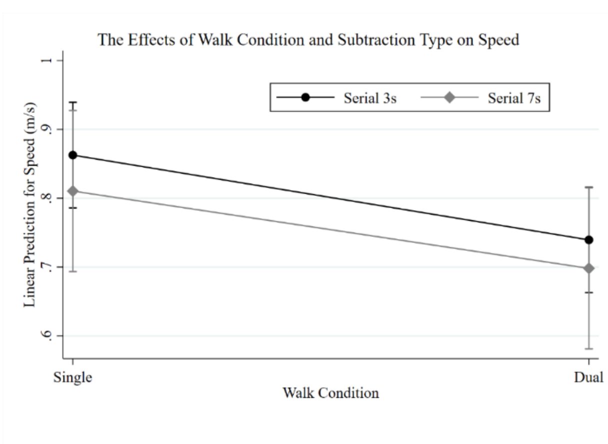
Walk Condition → Subtraction Type ↓	STW	DTW	Marginal
Serial 3s	0.863	0.739	0.801
Serial 7s	0.810	0.698	0.754
Marginal	0.847	0.727	0.787

Note: STW = Single-Task Walk; DTW = Dual-Task Walk. All values in m/s.

The marginal change in speed in the serial 7 condition was 0.112 m/s. There was no effect of subtraction type on STW speed, *B* = -0.052, 95% CI[-0.192, 0.088], *z* = -0.73, *p* = 0.464. Most importantly, the effect of subtraction type on the slope (i.e., change between STW and DTW) was not significant, *B* = 0.011, 95% CI[-0.050, 0.721], *z* = 0.35, *p* = 0.727. Thus, there were not significant differences in the effect of subtraction type on the change in speed that resulted from DTW (see Figure 4), which corresponds to the finding for DTWC. Given these findings, the serial subtraction types were aggregated for further analysis in the SS data.

Figure 4

The Effects of Walk Condition and Subtraction Type on Gait Speed for SS



The KUMC study randomized four walk conditions—slow, fast, normal (ST), and normal with counting (DT; see Figure 5 for comparisons of speeds in these conditions). To determine whether the order of randomization affected the DT effect estimates, a MLM was performed using the baseline data that tested for an interaction of the randomized order difference (calculated as ST order minus DT order such that -3 = ST was first and DT was last and 3 = DT was first and ST was last) as the between-persons factor by walk condition (STW = 0 or DTW = 1) as the within-persons factor on speed (m/s) to test for order effects in the baseline testing. Random intercepts and slopes (i.e., change from STW to DTW condition) were included. An unstructured covariance matrix was compared to an independent structure assuming correlations between random effects are zero. Including the correlation between the person and walk condition random effects did not significantly improve the random-effects model, $\Delta\chi^2(1) = 0.00$, $p = 1.00$, so the independent random-effects model was used. The random-effects portion of the model was significant, $\chi^2(2) = 116.12$, $p < 0.001$. The person-level SD was 0.224, 95% CI[0.194, 0.259], and the order condition SD was 0.129, 95% CI[0.083, 0.202].

The fixed effects portion of the model was significant, Wald $\chi^2(3) = 81.74$, $p < 0.001$. There was a significant effect of walk condition, $B = -0.141$, 95% CI[-0.176, -0.106], $z = -7.90$, $p < 0.001$. This indicates that there was a significant slowing observed (0.141 m/s) in the DTW condition relative to the STW predicted if ST and DT walks were able to be performed simultaneously. (This is based on the value being at the impossible intercept of 0 for difference in walk order. For predictions of change in speed at each observed condition, see Table 6)

Figure 5

Walk Speeds by Condition for KUMC

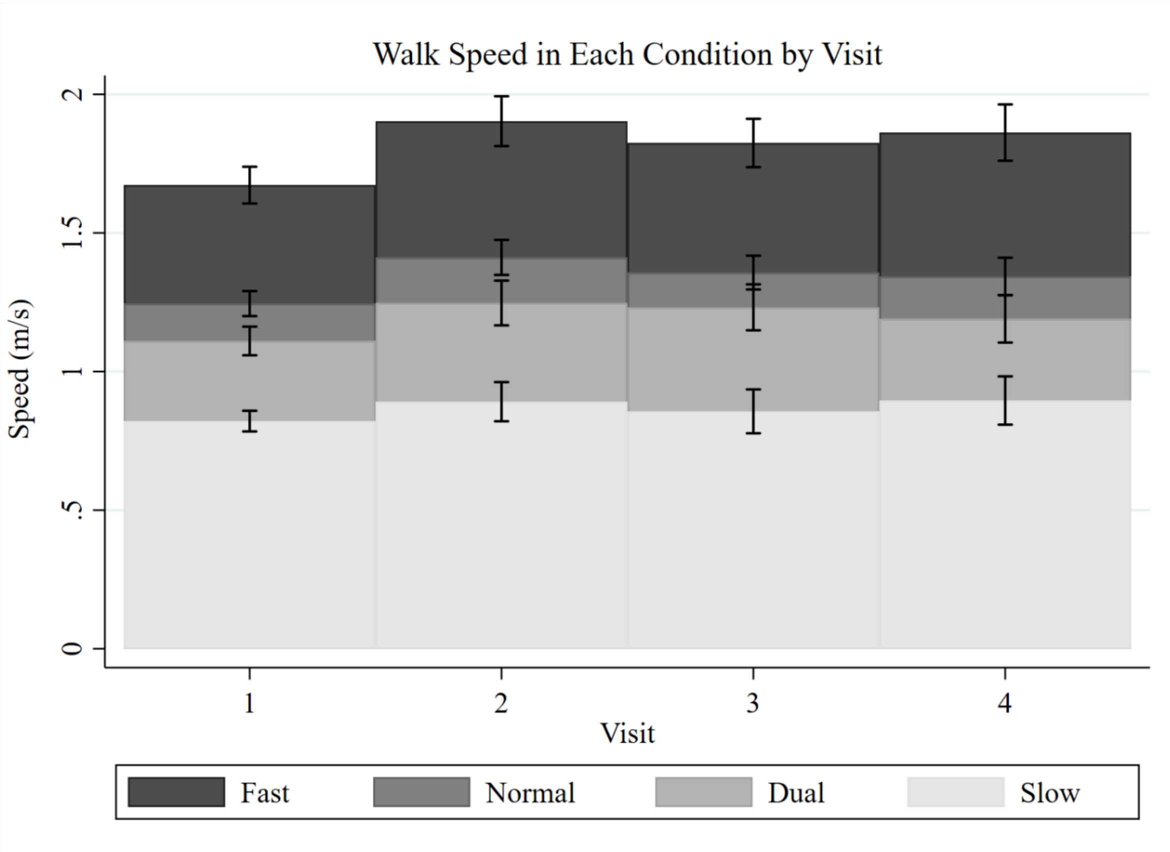


Table 6

Predictions for Dual Task Effect by Order Difference

Walk Condition → Order Difference ↓	DT Effect (ΔSpeed)	*z*	*p*	95% Confidence Interval LB	 UB
ST First, DT Last	-0.142	-6.030	<0.001	-0.188	-0.096
ST 2 Before DT	-0.142	-7.830	<0.001	-0.177	-0.106
ST 1 Before DT	-0.141	-8.950	<0.001	-0.172	-0.110
DT 1 Before ST	-0.141	-7.900	<0.001	-0.176	-0.106
DT 2 Before ST	-0.141	-6.090	<0.001	-0.187	-0.096
DT First, ST Last	-0.141	-4.700	< 0.001	-0.200	-0.082

Note. ST = Single Task; DT = Dual Task; LB = Lower Bound; UB = Upper Bound.

There was no main effect of order operationalized as linear, B = 0.015, 95% CI[-0.008, 0.039], z = 1.29, p = 0.199, or if treated categorically which produced a joint contrast for the effect of $\chi^2(5) = 4.03$, p = 0.545. (No pairwise differences between order differences were significant either, $ps \geq 0.17$. Most importantly, there was no interaction of walk condition and order difference, B = 0.0001, 95% CI[-0.017, 0.017], z = 0.01, p = 0.989 (see Figure 6). This indicates that randomized order did not have a significant effect on differences in speed as a function of walk condition. Using the same modeling approach, the randomization order effect and the interaction of randomization order and condition were not statistically significant in any visit (see Table 7).

Figure 6

The Effects of Walk Condition and Randomization Order on Gait Speed for KUMC at Baseline

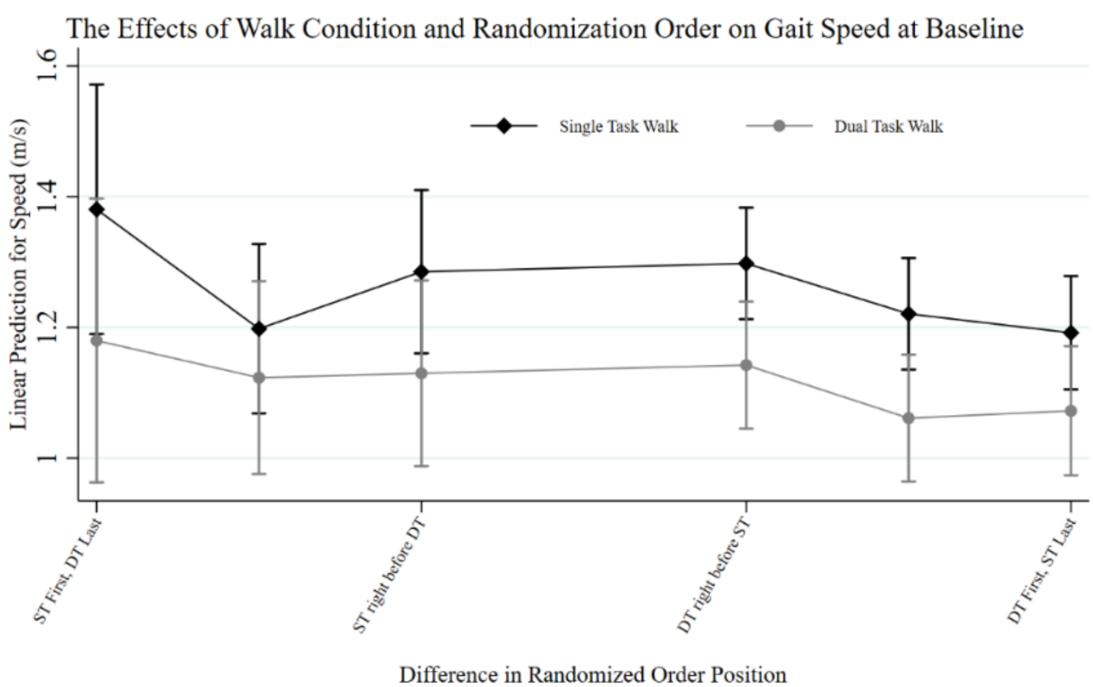


Table 7

Fixed Effects for Multilevel to Check for Randomization of Walk Order Effects across Visits

Visit	*n*	Walk Condition (*B*, *p*)	Randomization (*B*, *p*)	Interaction (*B*, *p*)
Baseline	122	-0.141, < 0.001	0.015, 0.199	.0001, 0.989
Follow-Up 1	42	-0.152, < 0.001	-0.147, 0.343	0.020, 0.237
Follow-Up 2	38	-0.118, < 0.001	0.007, 0.661	0.013, 0.389
Follow-Up 3	37	-0.156, < 0.001	-0.002, 0.917	-0.004, 0.744

Note. Walk condition compares single task (0) to dual task (1). Randomization compares order of randomization for four walks based on distance of single and dual task conditions from one another.

Once determining that the samples would be aggregated across these variables, exploratory data analysis and descriptive statistics were performed. For the SS sample, there were a variety of visits that took place but in no particular order. Gait assessment with the Zeno^{TM} Walkway was accompanied by some self-report outcome assessments, but cognitive examination with *Neurotrax^{TM} Mindstreams®* occurred on a different visit date and was also accompanied by some self-report outcomes assessments (some duplicates of those done during the gait analysis visit). Some participants also had multiple measures for gait assessment or self-reported outcomes (ranging from 1 to 5 assessment points) as these visits were conducted in a clinical setting. To keep measures temporally contiguous to the greatest degree and to minimize learning effects from re-assessment, first measurements for all measures were used for all participants. A check was done to determine whether span of time between gait and cognitive analysis produced a reliable effect, but the bulk of findings indicated that span (in months; M = 2.70, SD = 2.36), which ranged from the same day for one participant to as great as 10 months, was not a reliable moderator of the relationships between cognitive domains and DTW effects (see Table 8).

Table 8

Interaction Effect of Span Between Cognitive and Gait Measures on Dual-Task Walk Effects

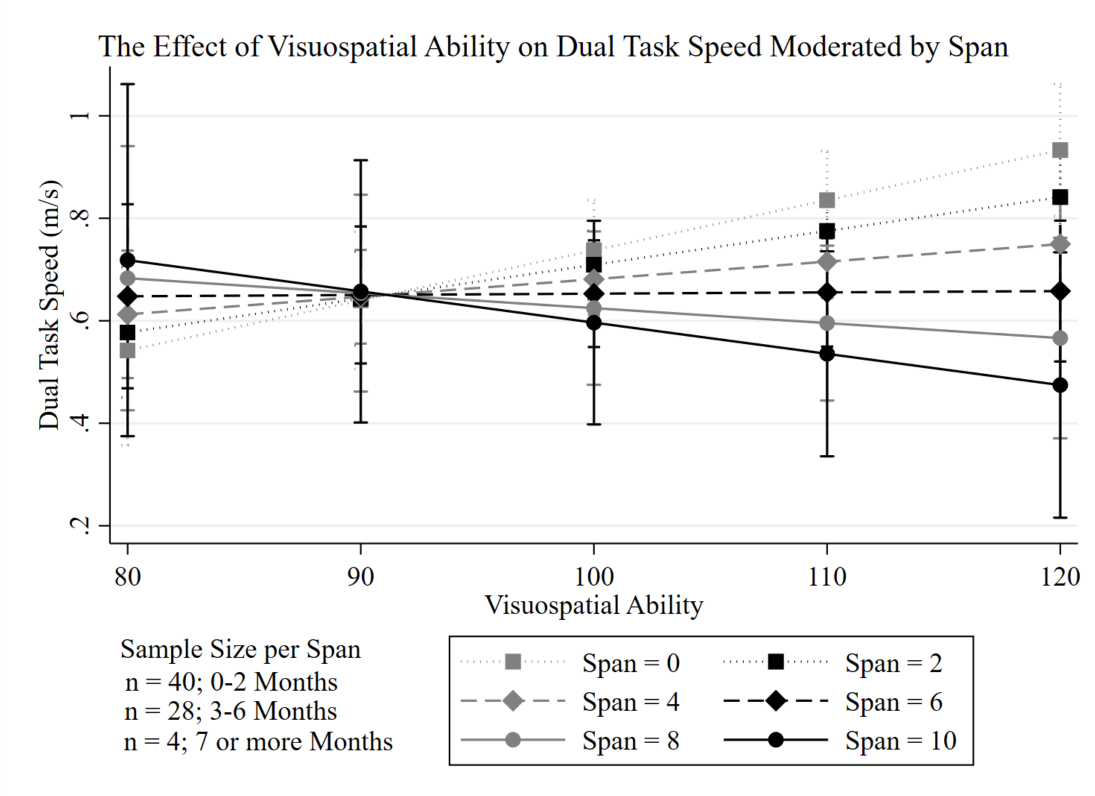
DTW Outcome →	Speed (m/s)	Difference (m/s)	Costs (%)
Cognitive Domain ↓		p (interaction effect)	
Memory	0.252	0.653	0.995
Executive Function	0.908	0.845	0.465
Visuospatial	0.047	0.225	0.162
Verbal	0.205	0.977	0.470
Attention	0.590	0.932	0.726
Information Processing	0.769	0.338	0.308
Motor Skills	0.561	0.937	0.991

Note. DTW = Dual-Task Walking.

Only one interaction was significant at $\alpha = 0.05$ comparison-wise, Visuospatial Ability on DTWS, $p = 0.047$, out of the 21 unplanned comparisons. The interaction would indicate that the relationship between Visuospatial Ability and DTWS decreased as the time between assessments increased (see Figure 7), such the strongest positive relationship observed was between Visuospatial Ability and DTWS when there was less than a month span between cognitive and gait assessments. At the greatest levels of span (>6 months) the relationship between Visuospatial Ability and DTWS become negative. The marginal effect of Visuospatial Ability on DTWS was positive and significant, $B = 0.010$, $t(66) = 3.11$, $p = 0.003$, as 57% ($n = 40$) of participants had 2 months or less between their visits. There were 28 participants who had spans from 3 to 6 months, but only 4 participants had spans of 7 months or more (7-month: $n = 1$; 9-month: $n = 2$; 10-month: $n = 1$). As such, although there may be a diminishing relationship, the evidence that a true qualitative interaction exists is very sparse. Overall, with only one of 21 interactions yielding a significant effect at $p = 0.047$ and the additional evidence found in probing this effect, it was deemed reasonable to aggregate across span in further analyses.

Figure 7

The Effect of Visuospatial Ability on Dual Task Walking Speed Moderated by Span



Aim 1 Results: Cognitive Correlates of Dual-Task Walk Outcomes (SS)

A total of 70 participants remained viable as the full analysis sample for SS. This sample is described in Table 9. Visualizations of cognitive and gait ability are in Figures 8 and 9. Scale internal consistency measures were very high (Cronbach's α ≥ 0.93) for all scales. The sample was mild-to-moderately disabled and middle-aged on average. Most participants were taking some form of disease modifying therapy and most were female.

Table 9

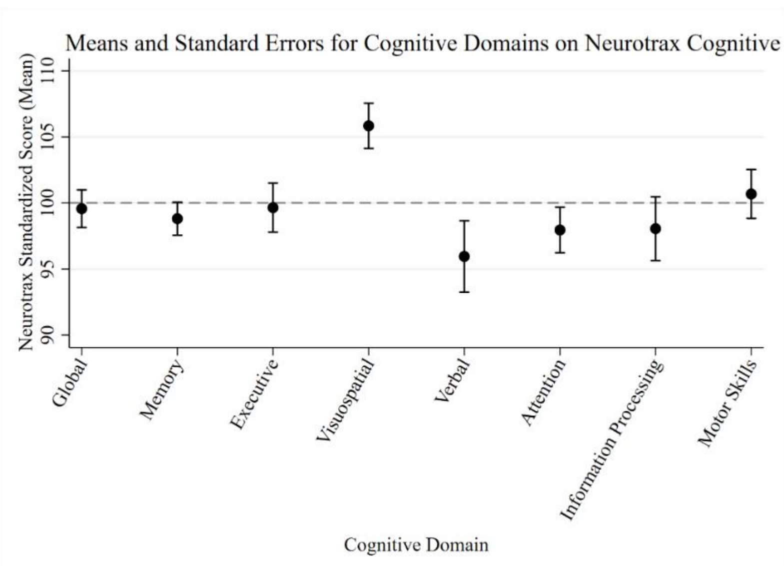
Demographic and Clinical Characteristics for South Shore Sample

Variable (scale)	*n*	Mean	SD	Min	Median	Max	α
Age (Years)	64	53.86	11.96	26	56	79	
EDSS (0 – 10)	70	3.55	1.90	1	3	6.5	
MSWS-12 (1 – 5)	69	3.02	1.21	1	3.25	5	0.97
MFIS (0 – 4)	65	2.03	0.99	0	2.05	3.90	0.97
MSIS-29 (1 – 5)	65	2.48	0.88	1	2.41	4.29	0.96
MFES (0 – 10)	70	7.44	2.56	0	8.07	10	0.97
BDI-II (0 – 63)	59	14.69	10.49	0	13	41	0.93
DMT	***n* (%)**						
Tysabri	30 (43)						
Ocrevus	12 (17)						
Other	18 (26)						
None	10 (14)						
Female	45 (70)						

Note. α = Cronbach's α; EDSS = Expanded Disability Status Scale Step; MSWS-12 = Multiple Sclerosis Walk Scale-12; MFIS = Modified Fatigue Impact Scale; MSIS-29 = Multiple Sclerosis Impact Scale-29; MFES = Modified Falls Efficacy Scale; BDI-II = Beck Depression Inventory-II; DMT = Disease Modifying Therapy. Scale means are used for summary purposes except for the BDI which is a scale sum.

Figure 8

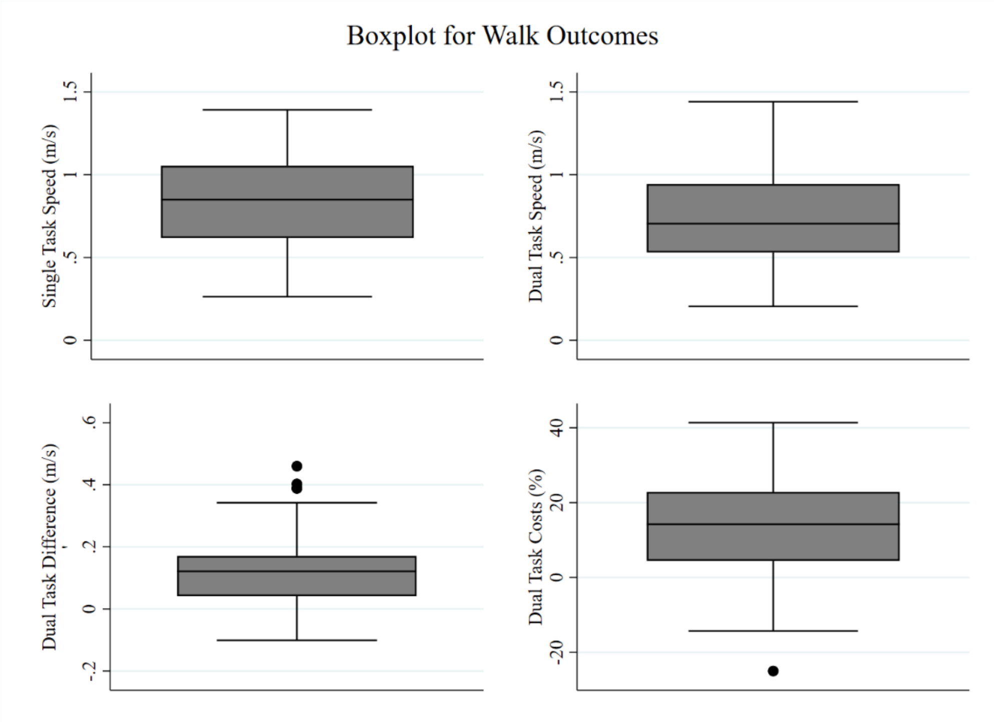
Means and Standard Error Bars for Cognitive Domains on Neurotrax^{TM} Cognitive Battery



Note. Y-axis reference line at standardized mean based on normative data.

Figure 9

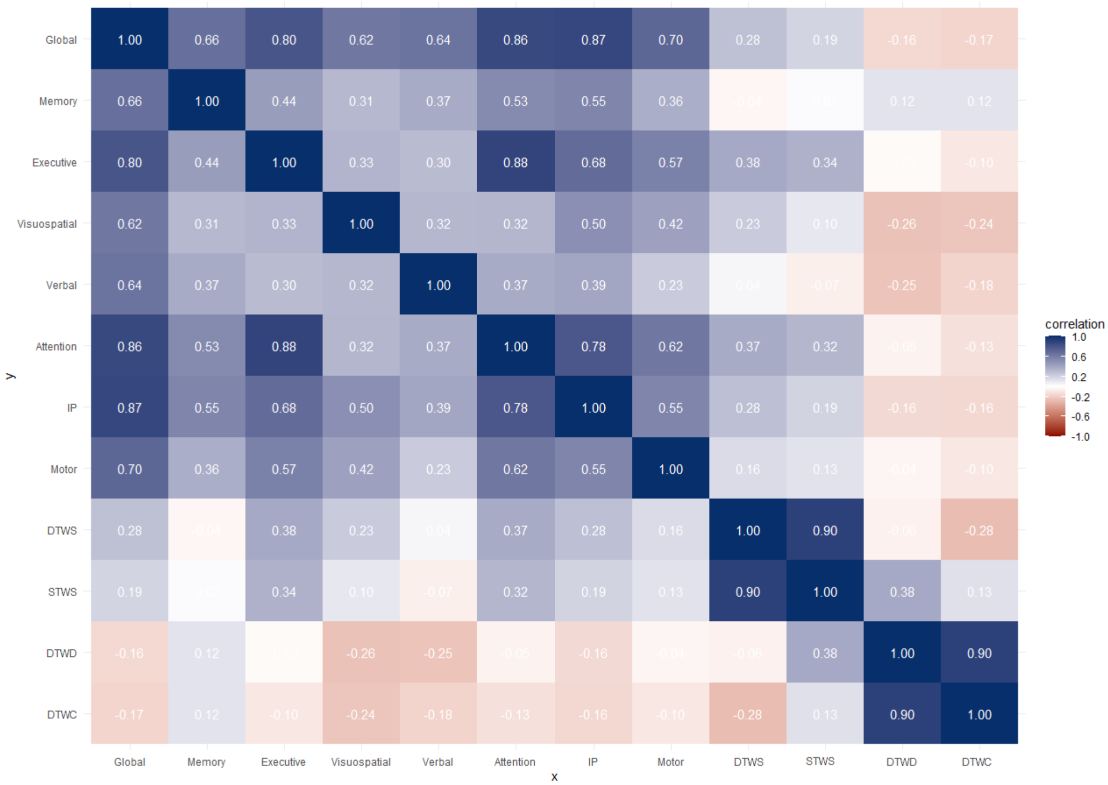
Boxplots for Walk Outcomes for SS



To address Aim 1, lasso regression was performed. Before doing so, visualizations were evaluated, and correlations (zero order, partial, and semi-partial) were estimated. The bivariate correlations for the cognitive and walk outcomes can be seen in Figure 10. Of note, some participants were missing Information Processing outcomes which reduced the sample size to 66 participants whenever this variable was included in the model.

Figure 10

Zero-Order Correlation Heatmap for SS



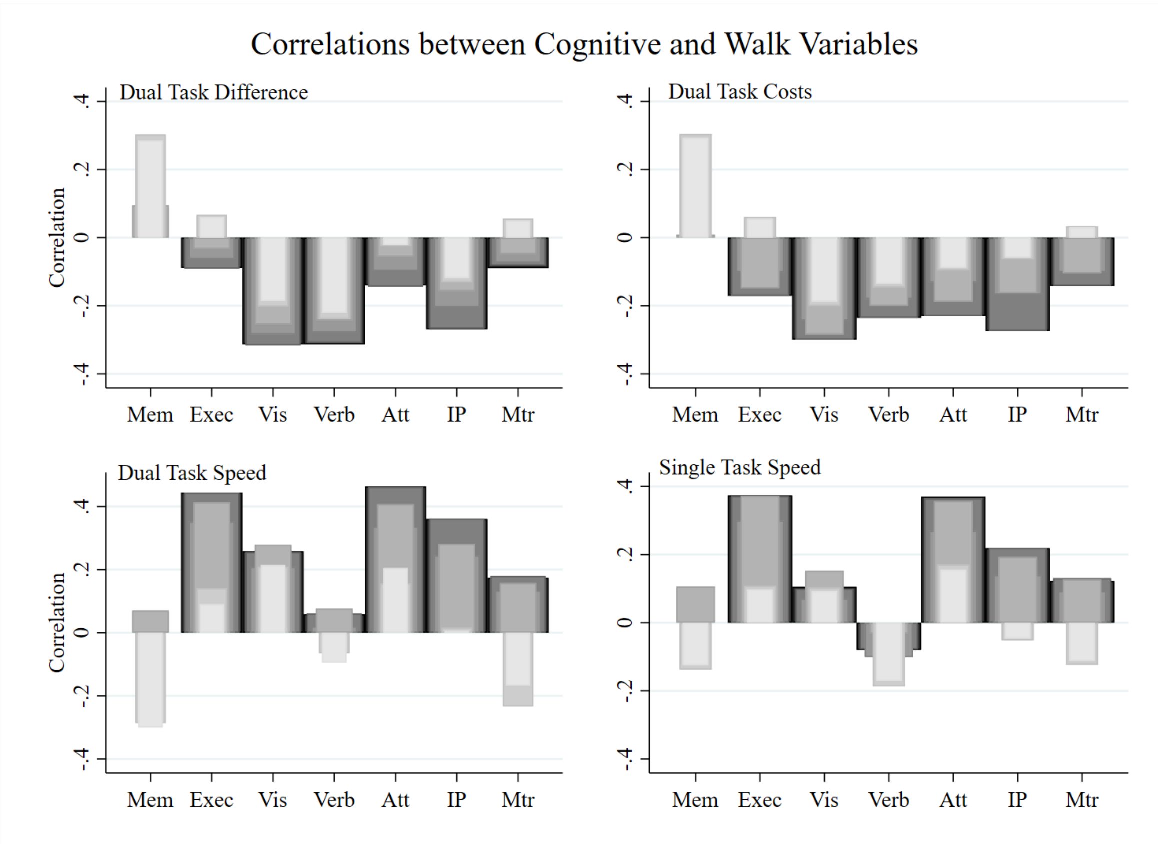
Note. IP = Information Processing; DTWS = Dual Task Walking Speed; STWS = Single Task Walking Speed; DTWD = Dual Task Walking Difference; DTWC = Dual Task Walking Costs. All cognitive domains are from Neurotrax™ Mindstreams© computerized cognitive assessment. Walk outcomes from Zeno™ Walkway.

Significant bivariate correlations included DTWC and Visuospatial Ability, p = 0.017, DTWD and Visuopatial Ability, p = 0.033, and Verbal Function, p = 0.042. STWS was significantly correlated with Global Cognition, p = 0.049, Executive Function, p = 0.002, and Attention, p = 0.002. DTWS was also correlated with each of these three cognitive domains, ps = 0.006, 0.004, 0.001, respectively, as well as being correlated with Visuospatial Ability, p = 0.020, and Information Processing, p = 0.022. As such, these bivariate relationships indicate that DTWS captures both the variables related to STWS and DTWC.

In addition to estimating bivariate correlations, partial correlations were estimated for all walk outcomes with modeling including all cognitive variables to assess the relative contributions of each cognitive domain in the presence of all others. The partial correlations revealed interesting patterns that provide insight into the dynamic relationships between cognitive domains and walk outcomes in MS (see Figure 11). For example, when partial correlations were performed, the only cognitive predictor that was statistically significant was Memory, and this was true for DTWS, $p = 0.020$, DTWD, $p = 0.019$, and DTWC, $p = 0.018$. No cognitive predictors remained significant when controlling for all others for STWS. These patterns of relationship for the DTW measures indicated that Memory was acting as a suppressor variable—that is, Memory is contributing significantly to the full model despite not having a significant bivariate correlation with the DTW measures. This generally arises because the suppressor variable accounts for residual variance in the other predictors, and it can indicate that the suppressor is inconsistently mediated by the variables it suppresses. For example, the relationships were in opposite directions of what might be expected. For example, better Memory predicted slower DTWS, $r_{\text{DTWS(Memory.All)}} = -0.2684$, controlling for all other variables, and better Memory predicted greater DTWD, $r_{\text{DTWS(Memory.All)}} = 0.285$, and DTWC, $r_{\text{DTWS(Memory.All)}} = 0.293$. This pattern, coupled with the previously significant bivariate correlations with these outcomes becoming not statistically significant, indicated the possibility that Memory was part of an inconsistently mediated model with other cognitive domains. Correlations between walk outcomes and all cognitive domains other than Memory were computed after residualizing 1) the cognitive domains by Memory, 2) the walk outcomes by Memory, and 3) both the cognitive domains and walk outcomes by Memory (see Figure 10).

Figure 11

Zero-Order, Partial, and Semi-Partial Correlations between Cognitive and Walk Variables



Note. Mem = Memory; Exec = Executive Function; Vis = Visuospatial Ability; Verb = Verbal Ability; Att = Attention; IP = Information Processing; Mtr = Motor Skills. Gradient from lightest to darkest for bars: 1) Semi-partial all cognitive variables, 2) Partial all cognitive variables, 3) Zero-order, 4) Walk outcome residualized by Memory, 5) Cognitive predictor residualized by Memory, 6) Walk outcome and cognitive predictor residualized by Memory. Results indicate the Memory operates as a suppressor variable for other cognitive domains. All graphs based on n = 66 sample to ensure equality across full partials and other correlations.

To identify models that may optimize prediction of DTW measures, selection models using lasso with a 10-fold cross-validation approach to select the value of λ

(James et al., 2013) and LARS (Efron et al., 2004) were used (see Table 10). For the 10-fold lasso model, out-of-sample prediction performance is used for model selection. For the LARS solution, minimization of Mallows's C_p was used (Mallows, 1973) as the metric to balance model prediction and parsimony. Finally, to obtain inferential values for the lasso predictors, lassopv in the R package lars was used to obtain *p* values based on the lasso model (Wang & Michoel, 2017). For DTWS, Executive Function, Attention, Visuospatial Ability, and Memory were selected. For DTWD, Visuospatial Ability, Verbal Function, Memory, and Information Processing were selected. For DTWC, the lasso and LARS solutions diverged. Based on all three metrics, it is difficult to say there are any reliable cognitive predictors of DTWC found, but the LARS solution selected Visuospatial Ability, Memory, Verbal Function, Information Processing, and Attention. On the whole, there is evidence that there are cognitive predictors of DTW, but the operationalization of the outcome may lead to differences in which are identified. Visuospatial Ability and Memory were among the most robust predictors across all operationalizations of DTW. Of note, it seems that DTWS likely captures cognitive processes that relate to both STWS and DTWD or DTWC.

Table 10

Lasso Models for SS Data

			***k*-fold CV Lasso**			**LARS**		
Outcome	**Predictor**	**Step**	**MPE**	***B***	**C_p**	**R^2**	***B***	***p***
DTWS								
	Executive	1	0.0716	0.003	13.23	0.06	0.003	0.002
	Attention	2	0.0700	0.004	9.66	0.13	0.005	0.012
	VS	3	0.0674	0.002	11.62	0.13	0.002	0.195
	Memory	4	0.0673*	-0.005	5.48*	0.23	-0.006	0.199
	Motor	5	0.0633		7.03	0.24		0.600
	Verbal	6	0.0634		6.08	0.27		0.628
	IP	7			8.00	0.27		0.935
DTWD								
	VS	1	0.0157	-0.002	9.39	0.01	-0.002	0.038
	Verbal	2	0.0157	-0.001	8.02	0.05	-0.001	0.051
	Memory	3	0.0155	0.003	4.18	0.14	0.003	0.175
	IP	4	0.0146*	-0.0003	3.38*	0.17	-0.0005	0.435
	Executive	5	0.0144		5.19	0.18		0.724
	Motor	6	0.0144		6.06	0.19		0.746
	Attention	7			8.00	0.19		0.961
DTWC								
	VS	1	194.763		4.42	0.04	-0.192	0.051
	Memory	2			6.38	0.04	0.427	0.227
	Verbal	3			5.73	0.08	-0.090	0.229
	IP	4			5.50	0.11	-0.072	0.346
	Attention	5			4.37*	0.15	-0.085	0.470
	Executive	6			6.37	0.15		0.905
	Motor	7			8.00	0.16		0.906

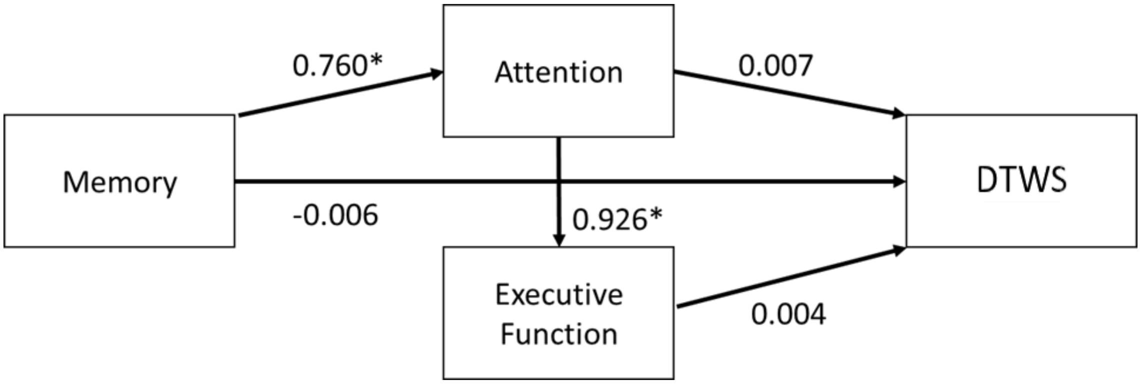
Note. DTWS = Dual-Task Walking Speed; DTWD = Dual-Task Walking Difference; DTWC = Dual-Task Walking Costs; VS = Visuospatial; IP = Information Processing; MPE = Cross-validated mean prediction error for 10-fold cross-validated λ selection process. Selected λ from 10-fold cross-validated models = 0.019, 0.007, and 3.28, respectively and producing out-of-sample R^2 of 0.09, 0.05, and -0.05, respectively. Mallow's C_p and R^2 values are in-sample values from least angle regression (LARS) algorithmic solution. *P* values obtained using lassopv function in lars package in R. *Indicates model selected based on criterion.

Next, based on the observed complexity of relationships among cognitive predictors and walk outcomes, post hoc checks for inconsistent mediation were tested in variables showing suppressor type relationships with memory and motor skills specifically for DTWS. Path analysis with bootstrapped (200 replications), bias-corrected confidence intervals (BC CI) were used for inferential purposes given the bias incurred by using normal theory estimates for mediated effects (MacKinnon, 2012). Using BC CI has also shown superior statistical power for detecting mediation (Fritz & MacKinnon, 2007).

A multiple mediation model was found for Memory via Attention and Executive Function on DTWS (see Figure 12). The effect of Memory on Executive Function is significantly mediated by Attention, $B = 0.704$, 95% BC CI[0.489, 0.9029]. The effect of Memory on DTWS is significantly mediated via Attention and Attention via Executive Function, $B = 0.008$, 95% BC CI[0.004, 0.012]. The total effects Memory on Executive Function, $B = 0.704$, 95% BC CI[0.489, 0.902], and Attention on DTWS, $B = 0.010$, 95% BC CI[0.005, 0.014] were statistically significant. The total effect of Memory on DTWS was not statistically significant, $B = 0.002$, 95% BC CI[-0.005, 0.007], as the direct effect of Memory on DTWS is antagonistic to the mediated effect (i.e., inconsistent mediation) albeit not statistically significant in its own right, $B = -0.006$, 95% BC CI[-0.0125, 0.0003]. Importantly, these relationships are all cross-sectional, so an inference about a causal sequence cannot be inferred. Nevertheless, consistent with the suppressor patterns noted previously, these findings demonstrate that understanding the relationships between cognitive abilities and DTW outcomes may be more complex and nuanced than can be revealed by bivariate relationships alone.

Figure 12

Multiple Mediation Model for Memory, Attention, Executive Function, and Dual-Task Speed

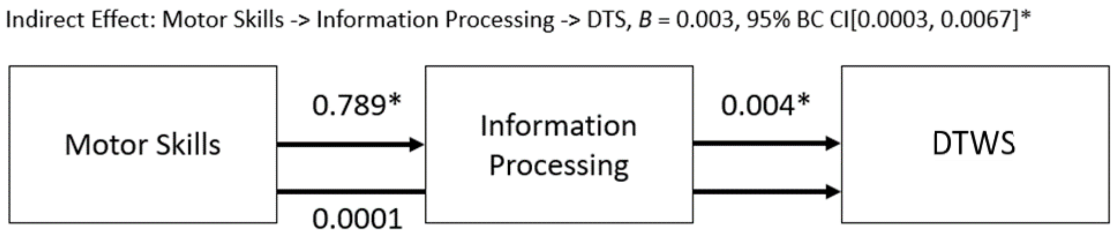


Note. Direct effects are depicted. *95% bias-corrected confidence interval from 200 bootstrap replications does not contain 0. DTWS = Dual Task Walking Speed.

A mediation model was also tested for Motor Skills via Information Processing on DTWS (see Figure 13). Importantly, the Motor Skills assessment requires rapid finger tapping on the left mouse button. The Information Processing assessment requires tapping one's finger on the left mouse as quickly as possible in response to a particular stimulus. As such, it is reasonable that basic reaction time assessed by Motor Skills would predict complex reaction times assessed by Information Processing. In fact, this was observed. The direct effect of Information Processing on DTWS was statistically significant, $B = 0.004$, 95% BC CI[0.0001, 0.0081]. The direct effect of Motor on Information Processing was statistically significant, $B = 0.789$, 95% BC CI[0.571, 1.083]. Neither the direct effect of Motor on DTWS, $B = 0.0001$, 95% BC CI[-0.006, 0.006], nor the total effect of Motor of DTWS, $B = 0.003$, 95% BC CI [-0.001, 0.009], was statistically significant, but the indirect (i.e., mediated) effect was, $B = 0.003$, 95% BC CI [0.0003, 0.0067].

Figure 13

Mediation Model for Motor Skills, Information Processing, and Dual-Task Speed



Note. Direct effects are depicted. *95% bias-corrected confidence interval from 200 bootstrap replications does not contain 0. DTWS = Dual Task Walking Speed.

Aim 2 Results: Physical, Cognitive, and Self-Report Correlates of Dual-Task Walk Outcomes (KUMC)

The KUMC study recruited 122 people with MS to evaluate whether wearable sensors could detect changes in gait and balance sensitively. The participants were relatively functional in terms of disease status and measured balance and gait. Yet, over one-third of participants still reported having fallen in the past 6 months at baseline. For a description of the sample at baseline, see Table 11.

Table 11

Demographic and Clinical Characteristics for KUMC Sample across Visits

Variable	*n*	Mean	SD	Min	Median	Max
Age (Years)	122	45.53	9.02	21.67	47.5	60.92
EDSS (0-10)	121	2.23	1.14	0	2	5.5
YSD (Years)	121	10.98	7.66	0	10	38
ABC (0-100)	122	80.25	17.46	27.5	85.94	100
Falls	119	2.14	8.21	0	0	72
	***n* (%)**					
Female	96 (79)					
Faller	41 (34)					

Note. EDSS = Expanded Disability Status Scale Step; YSD = Years since Diagnosis; ABC = Activities-specific Balance Confidence.

In addition to concurrent measurements and a large sample size, the study included many measures across a variety of domains that provides a unique opportunity to further the exploration of predictors of DTW measures. Importantly, the samples do differ in terms of functional outcomes. For example, comparing the two samples at baseline for walk outcomes revealed significant differences in the speed outcomes but not the differences and costs associated with DTW. Both samples exhibited significant DTWD and DTWC (see Table 12).

Table 12

Comparison of KUMC and SS Walk Outcomes

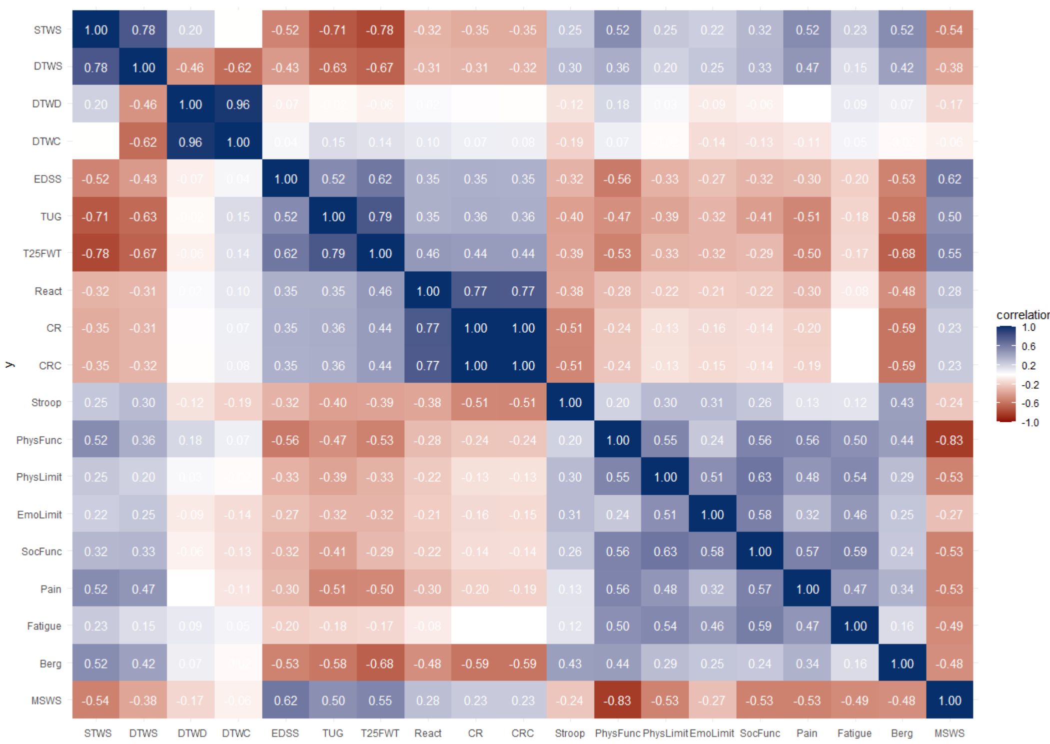
Variable	***n***	**Mean**	**SD**	***t***	***p***
STWS				10.20	< 0.001
KUMC	122	1.246	0.245		
SS	70	0.847	0.286		
DTWS				9.24	< 0.001
KUMC	122	1.104	0.275		
SS	70	0.727	0.270		
DTWDS				0.91	0.362
KUMC	122	0.141*	0.016		
SS	70	0.120*	0.014		
DTWC				-1.20	0.231
KUMC	122	11.411*	13.377		
SS	70	13.847*	13.803		

Note. STWS = Single Task Walking Speed; DTWS = Dual-Task Walking Speed; DTWD = Dual-Task Walking Difference in Speed; DTWC = Dual-Task Walking Costs; KUMC = University of Kansas Medical Center sample; SS = South Shore Neurologic Associated, PC sample. All *t* tests are independent samples tests with 190 degrees of freedom. *Value is different ($p < 0.001$) from 0 using one-sample *t*-test indicating presence of DTW effect.

As such, extending to the KUMC sample allows for a sort of conceptual replication with extension, but the sample does represent a different, less-affected subset of the MS population. As was done for SS, the first step was the perform exploratory data analysis including computing bivariate correlations across outcomes. A heatmap of the relationships in the KUMC sample can be found in Figure 14. Of note is the general lack of relationships that exist between the DTWD and DTWC outcomes with all others in the data set. Other clusters demonstrate expected moderate-to-strong correlations across various domains. For example, subscales of the SF-36 clearly cluster together, so do walk, disability, and cognitive measures. Further these two clusters tend to have negative relationships with the variables from the other cluster.

Figure 14

Zero-Order Correlation Heatmaps for KUMC



Note. STWS = Single Task Walking Speed; DTWS = Dual-Task Walking Speed; DTWD = Dual-Task Walking Difference; DTWC = Dual-Task Walking Costs; EDSS = Expanded Disability Status Scale Disease Step; TUG = Timed Up and Go; T25FWT = Timed 25-Foot Walk Test; React = Reaction Time; CR = Choice Reaction Time; CRC = Choice Reaction Time for Correct Responses; Stroop = Stroop Interference Test; PhysFunc = Short Form-36 Physical Function subscale; PhysLimit = Short Form-36 Physical Limitations subscale; EmoLimit = Short Form-36 Emotional Limitations subscale; SocFunc = Short Form-36 Social Function subscale; Pain = Short Form-36 Pain subscale; Fatigue = Short Form-36 Fatigue/Energy subscale; Berg = Berg Balance Scale; MSWS = Multiple Sclerosis Walk Scale-12.

Model selection was undertaken in the same fashion as was done in the SS analyses. The TUG and T25FWT were intentionally omitted from models because the desire to determine how other domains relate to DTW measures and the strong correlations between "walk speed" in all the different ways it was measured could mask other relationships. Similar to what was observed in the SS sample, DTWS seems to relate to more and more strongly to various other outcomes. Five predictors were selected by both approaches including, SF-36 Pain, EDSS, BBS, Stroop Interference, and Choice Reaction Time for Correct Responses. Of note, Stroop Interference and a Go-NoGo Task are central to measuring Executive Function and Attention in the *Neurotrax*^{TM} *Mindstreams*® battery, so the selection of the Stroop task and Choice Reaction Time for Correct Responses here are conceptual replications of these findings. Similarly, the basic Reaction Time task that was not selected for DTWS mirrors the non-selection of the Motor Skills variable in SS. Beyond these conceptual replications, self-reported Pain on the SF-36, disability on the EDSS, and objectively assessed balance on the BBS were selected as DTWS predictors. No predictors were selected for DTWD, and only the Stroop task as a measure of executive function was selected as a predictor of DTWC (see Table 13). These findings corroborate the importance of executive function and attention for predicting DTWS, and they add three unique physical constructs of importance. Of note, the MSWS-12 was not selected even for DTWS.

Table 13

Selection Decisions from Lasso Models for KUMC Data

Outcome	Predictor	Step	MPE	*B*	C_p	R^2	*B*	*p*
DTWS								
	Pain	1	0.0720	0.003	45.00	0.06	0.003	< 0.001
	EDSS	2	0.0697	-0.040	41.80	0.09	-0.043	< 0.001
	Berg	3	0.0669	0.006	15.21	0.26	0.006	< 0.001
	Stroop	4	0.0057	0.004	7.96	0.32	0.005	0.011
	CRC	5	0.0534*	-0.023	6.39*	0.34	-0.042	0.127
	PhysLimits	6	0.0533		7.14	0.35		0.414
	Fatigue	7			9.13	0.35		0.492
	EmoLimits	8			9.78	0.36		0.492
	SocFunc	9			8.50	0.38		0.562
	PhysFunc	10			10.11	0.38		0.829
	MSWS	11			11.90	0.38		0.899
	CR	12			13.79	0.38		0.985
	React	13			14.00	0.39		0.985
DTWD								
	PhysFunc	1	0.031		1.62	0.01		0.063
	MSWS	2			3.30	0.01		0.136
	Stroop	3			3.10	0.03		0.166
	EmoLimits	4			5.06	0.03		0.289
	SocFunc	5			2.75	0.07		0.291
	Fatigue	6			3.95	0.08		0.543
	Pain	7			5.40	0.08		0.606
	Berg	8			5.95	0.10		0.646
	CR	9			7.60	0.10		0.767
	React	10			9.20	0.10		0.804
	PhysLimits	11			10.60	0.11		0.838
	EDSS	12			12.15	0.11		0.898
	CRC	13			14.00	0.12		0.996
DTWC								
	Stroop	1	176.685*	-0.158	2.69*	0.02	-0.183	0.042
	EmoLimits	2			3.70	0.03		0.189
	SocFunc	3			5.66	0.03		0.296
	PhysFunc	4			6.84	0.04		0.302
	Pain	5			7.79	0.05		0.338
	MSWS	6			9.37	0.05		0.379
	Fatigue	7			5.57	0.10		0.395
	PhysLimits	8			7.42	0.10		0.686
	React	9			8.96	0.11		0.697
	Berg	10			10.74	0.11		0.733
	EDSS	11			11.61	0.12		0.750
	CR	12			12.40	0.13		0.835
	CRC	13			14.00	0.13		0.993

Note. STS = Single Task Walking Speed; DTS = Dual-Task Walking Speed; DTD = Dual-Task Walking Difference; DTC = Dual-Task Walking Costs; EDSS = Expanded Disability Status Scale Disease Step; React = Reaction Time; CR = Choice Reaction Time; CRC = Choice Reaction Time for Correct Selections; Stroop = Stroop Interference Test; PhysFunc = Short Form-36 Physical Function subscale; PhysLimit = Short Form-36 Physical Limitations subscale; EmoLimit = Short Form-36 Emotional Limitations subscale; SocFunc = Short Form-36 Social Function subscale; Pain = Short Form-36 Pain subscale; Fatigue = Short Form-36 Fatigue/Energy subscale; Berg = Berg Balance Scale; MSWS = Multiple Sclerosis Walk Scale-12; CV MPE = Cross-validated mean prediction error for 10-fold cross-validated λ selection process. Selected λ from 10-fold cross-validated models = 0.024, 0.030, and 1.745, respectively and producing out-of-sample R^2 of 0.27, -0.02, and -0.01, respectively. Mallow's C_p and R^2 values are in-sample values from least angle regression (LARS) algorithmic solution. *P* values obtained using lassopv function in lars package in R. *Indicates model selected based on criterion.

Discussion

The current analyses were performed in some of the largest samples used to-date to evaluate relationships between other putatively relevant domains and DTW measures. The findings are informative and provide novel insights into correlates of DTW. First, among these is that DTWD and DTWC may not relate to other outcomes as reliably as DTWS. Although Baddeley et al.'s (1997) formula has been applied commonly in the study of DTW in MS (Learmonth et al., 2017; Leone et al., 2015; Postigo-Alonso et al., 2018; Wajda & Sosnoff, 2015), it is worth giving careful consideration to the information it actually provides. Although normalizing the change in speed between ST and DT conditions by the STWS makes sense simply as a means to quantify *whether* DTW produces substantive alterations to gait under DT, it may not be the most useful measure in the context of understanding how DTW is related to other facets in the corpus of MS symptoms.

Walking speed has been found to be related to a variety of important outcomes in MS (Albrecht et al., 2001; Briggs et al., 2019; D'Orio et al., 2012; Kalron, 2014; Kalron & Achiron, 2014), so removing the information about speed may be undesirable if researchers are interested in understanding how DTW fits into the constellation of MS symptoms. Further, the normalizing equation may obfuscate many relationships of importance in DT research when used in isolation because its calculation means that two people with very different walking abilities who experience different absolute amounts of change can have the same DTWC. Removing the information about the base rates—that is, understanding that these two people with the same DTWC are very different in raw performance of the DTW or general walking ability—may gloss over important relationships between DTWC and other outcomes. Researchers should consider whether DTWC have similar relationships to other outcomes across the spectrum of DTWS. That is, it may be that a person with slow DTWS and high DTWC experiences different outcomes than a person with high DTWS and high DTWC. As such, DTWC seems to be a good way to operationalize simply *whether* there is an effect of DTW, but DTWS may be a better single variable to use for examining how DTW fits into the constellation of MS symptoms. When predictors of DTWD and DTWC emerged, DTWS tended to capture these relationships, too. DTWS also related to more domains that STWS alone. This indicates that DTWS may be a worthwhile construct to consider in understanding symptom overlap in MS.

In terms of cognition, executive function and attention seem to be particularly relevant predictors of DTW, as these domains emerged in both studies as variables selected early in the models. Further, the SS study suggests that visuospatial ability, information processing, and memory may also relate that DTW outcomes. In particularly, memory was found to play a unique, suppressing role—being the only cognitive domains that related to DTW outcomes in full models—and to be inconsistently mediated by the attention and executive function domains that were so reliably selected in the SS study. Unfortunately, no measures of memory, objective or subjective, were available to determine whether it performed a similar suppressor role in the KUMC data.

Horst and colleagues (1941) originally defined suppressor variables as predictors that have zero correlation with the outcome while improving the predictive ability of the overall model. Suppression relationships are great reminders that bivariate relationships can often be entirely inadequate to understand the processes that give rise to the true model dynamics (Lancaster, 1999). Originally, it was believed that suppression was a rare occurrence, but decades after Horst introduced the concept, researchers began to realize it occurred more often than initially thought (Lancaster, 1999; Thompson & Levine, 1997). The same can be said for inconsistent mediation (MacKinnon, 2012). There is a relevant classic example in the literature of suppression regarding using cognitive test batteries to predict performance on a cognitively and physically demanding task provided by Horst (1966) regarding fighter pilot performance during WWII. Verbal ability had a near-zero correlation with pilot performance but was highly correlated with other predictors considered—mechanical, numerical, and spatial ability. When verbal ability was included in the model for predicting pilot success the overall model improved significantly. This example has been noted to be an example of introduction of measurement artifact variance—that is, verbal ability was required to perform well on the other tasks because pilots had to read instructions on the paper-pencil tests (Lancaster, 1999).

Similarly, the dynamics seen in the SS data could reasonably be measurement artifacts of test construction, as several domains have overlapping measures that are included in the computation of the standardized scores for domains. For example, the Stroop is used for both Attention and Executive Function, as is a Go-NoGo task. Similarly, the ‘Catch’ Game (a pong-like task) is used in computing both Executive Function and Motor Skills. Further, rapid response of finger tapping is inherently involved in many of these tasks—as many are timed and all require responding via a mouse on a computer—but rapid finger tapping on a mouse is the primary measure for Motor Skills (Doninger, 2007, 2014b). Moreover, being able to *remember* instructions is obviously key to successful completion of computerized cognitive tests and *how quickly one can click the mouse button* is similarly relevant to performance across assessments. As such, the patterns observed for Memory and Motor Skills in the full model for predicting DTW measures may simply reveal that these domains are essential to task completion across domains—even when they are not intended to be measured explicitly. As such, the suppressor dynamics could be related to measurement variance artifacts.

Lastly, the KUMC analyses not only confirmed the importance of executive function and attention via conceptual replication, but also indicated that DTWS was predicted by other important physical domains such as EDSS step, BBS (balance), and self-reported pain on the SF-36. However, consistent with previous studies looking at EDSS and BBS predicting DTWC (Rooney et al., 2020), these constructs were unrelated to DTWC. The only variable that related to either DTWD or DTWC in the KUMC study was the Stroop interference task for DTWC, but this measure was also related to the DTWS. Further, the out-of-sample performance for the DTWC model was poor which limits confidence in this conclusion. Again, the findings confirm that DTWS may be a better way to capture how DTW relates to the constellation of MS symptoms in that it is predicted by both the predictors of STWS and DTWC. It seems that little if anything is lost in understanding how DTW fits into the constellation of MS symptoms by using DTWS and much is gained. In terms of implications in clinical contexts, this evidence indicates that ways to improve DTW ability may include enhancing executive function, attention, and balance, as well as reducing pain—which research in other populations indicates may cause interference in both the cognition (Berryman et al., 2013; Low, 2013; Moriarty & Finn, 2014) and walking (Bendall, 1989). Further research is needed to determine the importance of memory to evaluate the possibility that measurement artifact variance alone accounts for its unique relationships with DTWS in the SS study. It is possible that memory may be a key component to ensure executive function and attention can be improved through training, or it may just be that memory needs to be accounted for in models given its role in *measuring* other cognitive performance (i.e., one must remember the instructions). Either way, researchers attempting to intervene in the cognitive domains to improve DTW performance may want to include memory as part of the predictive model to explain DTW outcomes.

CHAPTER 3

Dual tasking is a phenomenon that occurs in many forms. Originally, a great deal of the research regarding dual tasking was performed in neuropsychology (e.g., Baddeley et al., 1997). It involves performing two tasks with distinct functions concurrently (Bayot et al., 2018). Dual tasking was initially intended to help understand the degree to which a task required effortful attention (*cf*. a task that can be performed “automatically”; Bayot et al., 2018; Hanny, 1986; Mirelman et al., 2018). Dual task research quickly began in a variety of contexts. In the realm of neurological disease and geriatric research, dual task researchers began to examine cognitive-motor coupling in dual task research to determine whether there was interference that may pose additional risk of injury to those affected by neurological disease when performing motor tasks assumed to be automatic (e.g., walking) while engaging in a cognitive task simultaneously (e.g., holding a conversation). For example, a classic dual task study was conducted by Lundin-Olsson and colleagues (1997) that indicated that older adults in a residential facility who stopped walking to talk were at a greater risk of falling that those who did not. They also found that arresting one’s gait to hold a conversation correlated with objectively poorer gait qualities, and this simple metric performed nearly as well from a classification standpoint as the clinical measures used at the time for assessing fall risk (e.g., the BBS). The notion that DTWC exist are rather well established (e.g., Mirelman et al., 2018). However, there is no resolution regarding which of several theories might be explain the presence of DTWC (Bayot et al., 2018).

Theories such as the Attentional Capacity (or Capacity Sharing) Theory (Kahneman, 1973) and Bottleneck Theory (e.g., see Tombu et al., 2011) are two major theories of DT intereference. However, Bayot et al. (2018), note that there are other theories, such as the Time-Sharing Hypothesis and Cross-Talk Model. Further, there are divisions within these major theoretical perceptions (Bayot et al., 2018). However, most of these theories discuss how either cognitive limits or neural activity patterns explain DTC. Yet, researchers have noted that there may be a greater need to recognize the role of higher-order processing in DT to explain the empirical evidence adequately (e.g., see Pashler, 1994 for a general consideration and Yogev-Seligmann et al., 2012; Wajda & Sosnoff, 2015; Wajda et al., 2016 for reviews and applications in DTW specifically).

Although there are undoubtedly neural and cognitive processes that may apply generally in DT, there is no consensus regarding which theory best explains the evidence in DT research and most fail to explain the pantheon of observations fully (Bayot et al., 2018). Recently, there has been a move toward considering that these theories may not adequately explain DT interference in general (Pashler, 1994) and in balance while walking specifically (Yogev-Seligmann et al., 2012). These models note that higher-order processing and other person-level factors—which undoubtedly still involve neural and cognitive processes, but in different ways—need to be considered to understand the heterogeneity of responses that can be observed across DT paradigms and within persons within a given DT paradigm. A theory with the potential to be viewed as complementary to many of those in existence is SAT (Wajda & Sosnoff, 2015; Wajda et al., 2019). Yogev-Seligmann et al. (2012) note that a central tenet of SAT is that assessment of one's abilities in the context of environmental demands may be a critical person-specific factor to consider in understanding heterogeneity in DT. That is, self-evaluative processes (e.g., self-efficacy) are putative moderators of the effects of basic abilities on DTW outcomes (Wajda et al., 2019). Thus, this model emphasizes that not just one's *objective* abilities but also one's *subjective evaluations and appraisals* of these abilities are crucial to understanding DTW outcomes, and this may help to explain the great heterogeneity observed in the corpus of literature. Lupien et al. (2007) in their review summarized evidence that demonstrates how stressors and *reactivity* to environmental stressors affects neuroendocrinological processes that relate to task performance in cognitive domains which reminds of the possible mechanisms by which appraisals of self and environment may cause alterations in the lower-level neurophysiological processes.

Aim 3 examines whether FSE and depression (and emotional role limitations as a surrogate in KUMC data) act as moderators of the relationships between measures of objective ability (i.e., cognitive and physical abilities) and performance under the more trying DTW conditions. In such cases where task complexity increases, the effects of efficacy beliefs and emotional appraisals are likely to be more important, as efficacy can act as a moderator of the relationship between task complexity and task performance (e.g., Beattie et al., 2014). For example, the Yerkes Dodson (1908) law stipulates that more challenging tasks exhibit inverse-parabolic relationships between arousal and performance for difficult tasks but an s-shaped relationship for simple tasks. Efficacy beliefs could be expected to shift the inverse-parabolic curve along the "Arousal" axis or could even cause a discrete shift such that a task that is "difficult" to one person is "simple" to another based on their *appraisals* of their abilities and the task. As such, performance outcomes could reasonably be expected to be a function not only of ability but appraisals of ability and emotional dispositions that affect these appraisals.

Depression and FSE are not only theoretically-reasonable moderators in this context, but they are also common issues in MS—which makes understanding their role in the dynamics of ability and performance in DTW even more important. One meta-analysis found that more than 1 in 3 people with MS had clinically significant symptoms of depression or anxiety in an examination of cross-sectional prevalence estimates (Boeschoten et al., 2017). Approximately 1 in 2 people with MS will have a diagnosis of depression during their lifetime (Siegert & Abernethy, 2005). Even more, fear of falling has been found to occur in those with MS at rates of just over 60% of individuals with MS (Peterson et al., 2007) to as high as 92% of those who with MS who have fallen (Comber et al., 2017). This often leads to significant activity curtailment, reduced independence, and lowered QoL (Peterson et al., 2007). Comber et al. (2017) reported that 79% of participants with MS who have fallen report activity curtailment associated with fear of falling. It may be that fear of falling or low FSE may simply be a reasonable appraisal of increased risk given symptomatic presentations; however, recent evidence indicates that FSE may lead to unique consequences due to unnecessary activity curtailment and loss of independence. A large study in individuals assessed correspondence of perceived fall risk and physiological fall risk (Gunn et al., 2018). Their findings showed that most individuals with MS have a notable disparity between perceived and physiological fall risk and the most common discrepancy is that *the perceived risk is greater than the physiological risk* (Gunn et al., 2018). This evidence highlights the potential use of understanding whether the effect of physical ability of performance is moderated by FSE because the two measures do not necessarily align and different beliefs about one's abilities or risks may affect the way that their actual abilities manifest—particularly in challenging contexts.

This is one example of that fact that FSE and depression affect risk evaluation and personal assessments (Bandura, 1994; Davey et al., 2017). It is possible that the effects of basic abilities and skills (e.g., motor or cognitive abilities) not only relate to these states, but that their effects on complex functional tasks (e.g., DTW) are moderated by these psychological states. Assessments of abilities would be expected to differ for people with different levels of FSE and depression. For example, a person with low FSE may believe their balance is poor even when it is not (e.g., Gunn et al., 2018) which could produce meaningful differences in how their abilities relate to DTW outcomes compared to another person with similar motor abilities but different levels of FSE.

Similarly, depression could lead to heightened risk appraisal—in fact, research suggests that depression may lead to more accurate (i.e., less optimistically biased) assessments of risk for future events (Korn et al., 2014) in some interesting research regarding optimism bias and health outcomes (e.g., Garrett & Sharot, 2014; Sharot, 2012). In the context of the already elevated perceived risk that has been shown to be present for people with MS regarding falling (Comber et al., 2017; Peterson et al., 2007), depression could plausibly result in a further inaccurate elevation of fall risk in this population, leading to additional activity curtailment. Although no researchers have considered depression as a moderator of the relationships between cognition or motor function and DTW, it has been considered as a moderator of cognitive-motor coupling more generally in MS (Ensari et al., 2018). Ensari et al. (2018) did not find that depression moderated general cognitive-motor coupling in MS, but further evidence is needed, and it is possible that this role could become more patent in more demanding contexts such as DTW paradigms. Yet, Serra-Blasco et al. (2019) and Potvin et al. (2016) found that depression alters appraisal of one's cognitive ability. Further, Potvin et al. (2016) found that subjective cognitive ability was a better predictor of function in individuals with depression than objective cognitive ability. This highlights the power of subjective appraisal and evaluation in understanding the interplay between cognition and function—albeit in a more general form.

Thus, it is reasonable to hypothesize that either depression or FSE could *moderate* the relationships between cognition and mobility and DTW measures. It seems most likely that depression may moderate cognitive effects and FSE may moderate physical effects, but both are possible given the entanglement of processes in DTW. Although simply asking whether physical states, cognitive abilities, depression, and FSE are related to DTWS or DTWC is also important, if the relationships between cognitive or physical ability and DTW measures are moderated by person-level factors like FSE and depression, this could lead to masked or incompletely understood relationships (e.g., if a qualitative moderation exists the marginal effect could wash out). This could also have repercussions for clinical considerations regarding which type of approaches or interventions may help most to promote function or performance of complex everyday tasks—for which DTW acts as a measure. If the limitations lie in physical abilities alone, then solely assessing and addressing them is sufficient, but if there is a complex interplay between these abilities and individuals' personal appraisals—their efficacy or emotional states—then it may indicate that interventions will be more successful to consider these domains as intervention targets in tandem with the physical or cognitive abilities they affect.

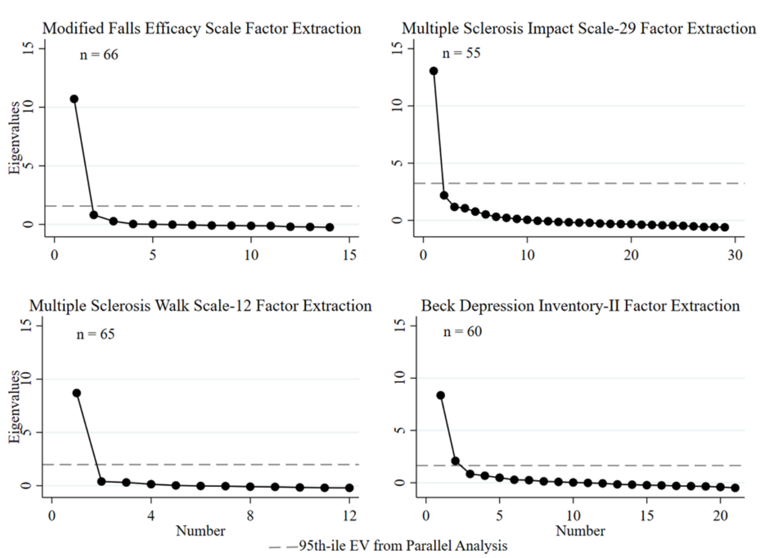
Aim 3: Psychological Moderators of the Effects of Ability and Dual-Task Outcomes

South Shore Neurologic Associates, PC Analyses

The first study in Aim 3 uses the data from SS. A key first step to evaluating these moderation questions was to perform psychometric evaluations on the scales used for the constructs of FSE and depression. To do this, exploratory factor analysis was performed using IPF. To determine the number of factors measured, parallel analyses were performed by constructing 100 random samples of size *n* and using the Eigenvalue at the 95th percentile from these analyses as the threshold for a factor being present (Hayton et al., 2004). This was coupled with visual analysis using scree plots (see Figure 15). The results of the exploratory factor analysis revealed strong, one-factor solutions for all the PROs except depression measured by the BDI-II.

Figure 15

Scree Plots for Factor Extraction for Patient-Reported Outcomes in SS



Consistent with previous research (Wang & Gorenstein, 2013b), the BDI-II had two factors with the first factor capturing affective states and the second capturing somatic states (Wang & Gorenstein, 2013b). Factor scores were predicted from analyses to be used as the moderating variables in analyses predicting DTWS and DTWC. A single factor was extracted for the MFES and MSWS-12, and two factors were extracted for the BDI-II (Factor 1: *Affective* and Factor 2: *Somatic-Vegetative* are reasonable monikers for these consistent with Wang & Gorenstein, 2013b). There were several multivocal items; however, all but "Agitation" had a clear dominating factor onto which they loaded. For the loadings of items onto factors for the BDI-II following oblique oblimin rotation to allow for correlated factors, $r = 0.403$, see Table 14.

Table 14

Factor Loadings for the Beck Depression Inventory-II

Item	Factor 1 Loading	Factor 2 Loading
1. Sadness	0.669	
2. Pessimism	0.513	
3. Past Failures	0.772	
4. Loss of Pleasure	0.395	0.493*
5. Guilt	0.690	
6. Punishment	0.885	
7. Self-Dislike	0.780	
8. Self-Criticalness	0.636	
9. Suicide	0.670	
10. Crying	0.340	0.458*
11. Agitation	0.357*	0.356
12. Loss of Interest	0.374	0.565*
13. Indecisiveness	0.371	0.518*
14. Worthlessness	0.606*	0.307
15. Loss of Energy		0.814
16. Changes in Sleep		0.649
17. Irritability		0.749
18. Changes in Appetite	0.352	0.458*

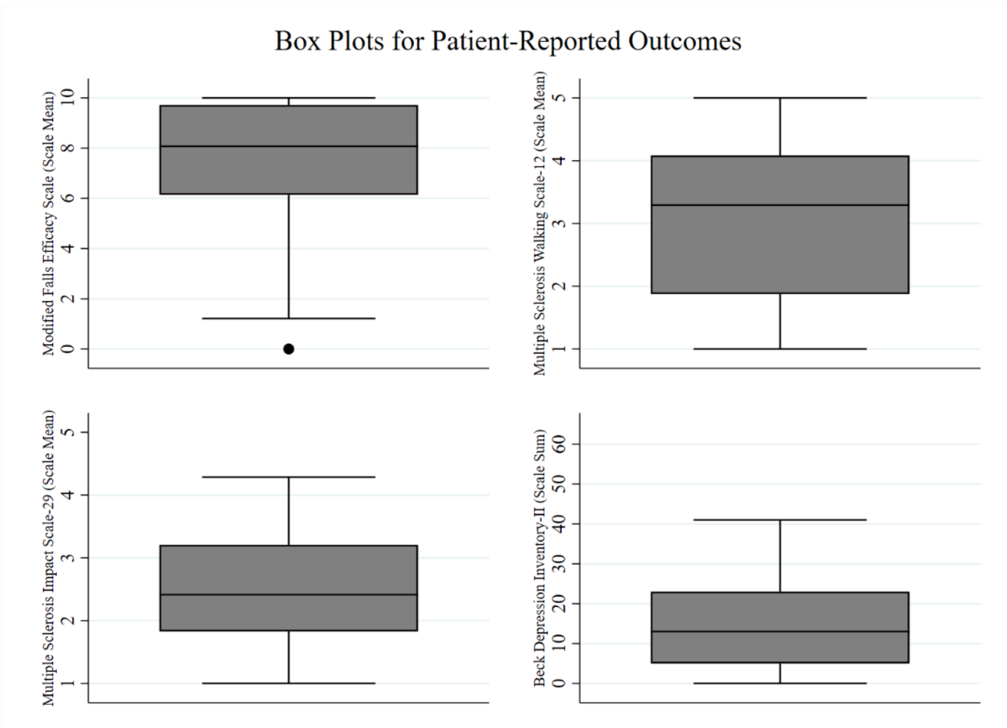
19. Concentration	0.633
20. Tiredness	0.814
21. Loss of Interest in Sex	0.467

Note. Factor loadings are from oblimin oblique rotated iterative principal axis factoring. Only loadings ≥ 0.30 are shown. *Stronger loading for multivocal item.

The sample has been summarized previously. Table 9 contains the demographic and clinical information for the sample. Additionally, given the use of self-report outcomes here, Figure 16 depicts these outcomes in box plots. These show that there was a fair amount of variability in the distribution of these outcomes, so ceiling and floor effects were not significant concerns. However, it is worth nothing that FSE, measured by the MFES, was relatively high albeit still with appreciable variability.

Figure 16

Box Plots for Patient Reported Outcomes from SS



Based on a priori hypotheses, Executive Function and Information Processing were tested for moderation by depression and FSE. Also, STWS was used a measure of basic physical ability and it was also tested for moderation by depression and FSE for its relationship with DTW outcomes. Lastly, MSWS-12 was used as a measure of physical ability. Importantly, this is a *subjective* appraisal—like the moderators in the analysis—not an objective assessment. However, the psychometric distinction between efficacy and the MSWS-12 is important. The MSWS-12 asks participants to report how much their *abilities have been limited in the past two weeks* not *how confident* they are in particular abilities or *how concerned* they are about particular outcomes given their abilities. So, although it is a subjective, recollective measure of walking ability, it is still conceptually a measure of walking ability—not efficacy.

DTWS was the primary outcome of interest as it is a measure of *performance* in the context of a complex task. However, given its regular use in the literature DTWC (Learmonth et al., 2017; Leone et al., 2015; Postigo-Alonso et al., 2018; Wajda & Sosnoff, 2015), including the few considerations of SAT that have been made (Wajda & Sosnoff, 2015; Wajda et al., 2019), it was also included as an outcome. However, it is worth noting that DTWC is a measure of the change in speed between ST and DT conditions as a percentage of STWS. As such, it actually captures a cognitive effect. That is, it removes the "speed" metric and becomes a "percent change" where change is caused by the presence of a concurrent cognitive task. Thus, it is not an ideal operationalization for testing SAT to determine whether self-appraisals alter *physical performance* in a complex task, as it is not a measure of physical performance under DT but a measure of change that *removes* the physical measure of performance (which is speed in this case). For example, it would not be expected the STWS predicts DTWC in the same way that it would be expected that STWS would predict DTWS. As such, moderation of basic, objective abilities on *physical* performance is best modeled using DTWS, not DTWC.

Similarly, it is more reasonable to expect that DTWC actually captures a *cognitive* construct by “removing” the physical performance metric and becoming a “percent change” that cognitive demand causes. This is exemplified by the fact that two people who perform very differently in terms of DTWS as a measure of physical performance (e.g., 0.5 m/s and 1.3 m/s) could have identical DTWC (e.g., 20%). Similarly, two people who perform identically on the physical task (e.g., 1.2 m/s) could have very different DTWC (e.g., 0% and 30%). As such, DTWC tells us little about *physical performance* under DT conditions; instead, it tells us about the change that occurs in the presence of cognitive load—clearly a cognitive construct. In fact, Chapter 2 revealed that physical performance metrics do not relate to DTWC, which is generally consistent with past research (Leone et al., 2015; Rooney et al., 2020). However, executive function was related to DTWC. Again, for a full description, both outcomes are considered. Table 15 contains a summary of the multiple regression models tested using factor scores using regression scoring methods to evaluate whether FSE or depression moderate the effect of physical and cognitive ability on DTWS and DTWC.

Table 15

Regression Models Evaluating Falls Self-Efficacy and Depression as Moderators of the Effects of Walking Speed and Cognition on Dual Task Walking Outcomes

Outcome Predictor	***n***	**Effect 1** *B, p*	**Effect 2** *B, p*	**Interaction** *B, p*	**Covariate** *B, p*
DTWS					
STWS, MFES	64	**0.81, < 0.001**	-0.03, 0.454	**0.09, 0.032**	-
STWS, BDI-II[1]	58	**0.85, < 0.001**	0.06, 0.197	-0.09, 0.083	-0.04, 0.014
STWS, BDI-II[2]	58	**0.83, < 0.001**	-0.001, 0.974	-0.04, 0.472	-0.02, 0.301
MSWS-12, MFES	59	**-0.14, < 0.001**	**0.07, 0.032**	0.03, 0.207	-
MSWS-12, BDI-II[1]	42	**-0.17, < 0.001**	-0.07, 0.145	-0.03, 0.354	0.06, 0.234
MSWS-12, BDI-II[2]	42	**-0.19, < 0.001**	0.07, 0.188	-0.06, 0.291	-0.05, 0.242
EF, MFES	64	**0.01, 0.002**	0.08, 0.663	0.0003, 0.852	-
EF, BDI-II[1]	58	**0.01, 0.001**	0.01, 0.964	0.0004, 0.890	-0.06, 0.160
EF, BDI-II[2]	58	**0.01, 0.001**	0.37, 0.146	-0.004, 0.092	0.06, 0.147
IP, MFES	61	0.002, 0.221	0.11, 0.556	0.0003, 0.880	-
IP, BDI-II[1]	54	**0.004, 0.043**	-0.07, 0.774	0.002, 0.654	-0.07, 0.146
IP, BDI-II[2]	54	0.004, 0.052	-0.10, 0.668	0.0003, 0.889	0.04, 0.385
DTWC					
STWS, MFES	64	6.72, 0.301	3.21, 0.505	-8.40, 0.505	-
STWS, BDI-II[1]	58	3.92, 0.521	-2.21, 0.709	4.26, 0.502	**5.24, 0.016**
STWS, BDI-II[2]	58	4.09, 0.519	4.42, 0.499	0.71, 0.923	1.55, 0.460
MSWS-12, MFES	59	-2.74, 0.175	**-6.42, 0.007**	-1.86, 0.298	-
MSWS-12, BDI-II[1]	42	-0.77, 0.699	2.40, 0.314	1.51, 0.369	4.99, 0.055
MSWS-12, BDI-II[2]	42	0.71, 0.745	3.78, 0.165	4.00, 0.141	1.43, 0.498
EF, MFES	64	-0.09, 0.467	6.38, 0.572	-0.09, 0.405	-
EF, BDI-II[1]	58	-0.04, 0.717	-8.00, 0.605	0.10, 0.536	**4.76, 0.027**
EF, BDI-II[2]	58	-0.06, 0.634	-4.15, 0.762	0.09, 0.506	1.40, 0.507
IP, MFES	61	-0.03, 0.747	-0.93, 0.935	-0.03, 0.825	-

IP, BDI-II[1]	54	-0.09, 0.350	**24.47, 0.026**	**-0.23, 0.034**	**5.36, 0.015**
IP, BDI-II[2]	54	-0.10, 0.313	21.27, 0.060	-0.20, 0.153	1.98, 0.337

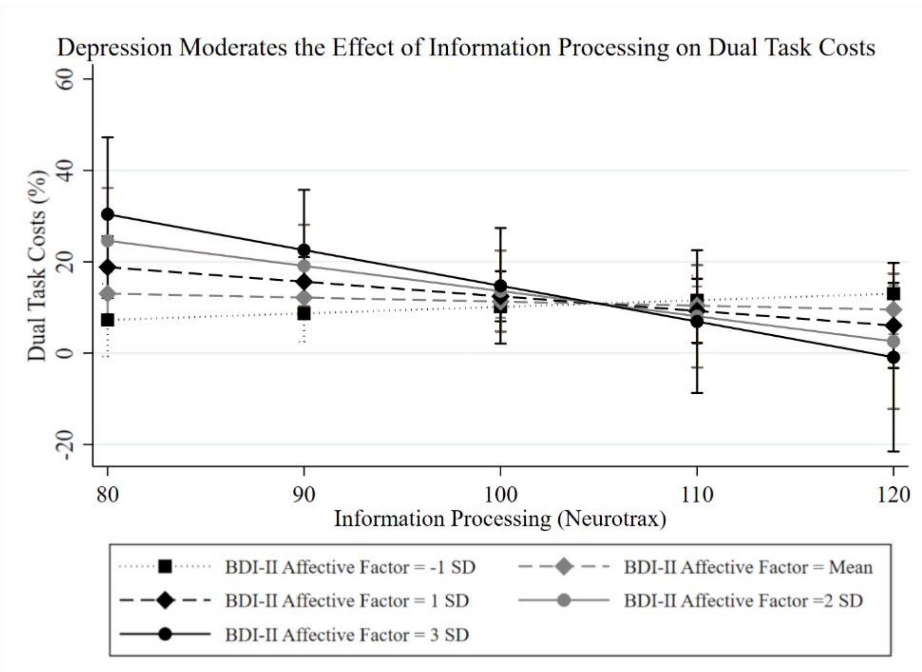
Note. DTWS = Dual Task Walking Speed; DTWC = Dual Task Walking Costs; STWS = Single Task Walking Speed; MFES = Modified Falls Efficacy Scale (Factor Score); BDI-II = Beck-Depression Inventory-II (Factor Scores); MSWS-12 = Multiple Sclerosis Walking Scale-12; EF= Executive Function; IP = Information Processing. [1]Factor 1, Affective, is tested as a moderator. [2]Factor 2, Somatic, is tested as a moderator. Cognitive domains are from *Neurotrax*™ cognitive battery. Covariates are included for the models using the BDI-II to control for the correlated BDI-II factors. Effects 1 and 2 are in the order listed in the predictor statement in column 1. **Bold font** indicates $p \leq 0.05$.

A few patterns emerge from these analyses worth noting. As reported in Chapter 2, DTWS relates more robustly to both physical (e.g., STWS and MSWS-12) and cognitive (e.g., Executive Function and Information Processing) predictors than DTWC. For DTWC, the most reliable predictor was the main effect of BDI-II Somatic factor. This factor includes items like lack of energy, problems with concentration, sleep problems, tiredness, etc. It emerged as a significant covariate in the models that examined STWS, executive function, and information processing as primary predictors—despite these primary predictors themselves not relating significantly to DTWC.

More interestingly and in support of SAT, when modeling information processing as a primary predictor, the effects of *both* BDI-II factors *and the interaction between the Affective factor and information processing* were statistically significant predictors of DTWC within the model specified as such (see Figure 17). These findings are particularly intriguing considering the mixed evidence regarding depression (which hitherto has been treated simply as a total scale score in the literature) and its relationships with DTW measures (Butchard et al., 2018; Hamilton et al., 2009; Motl et al., 2014; Postigo-Alonso et al., 2018), as well as the lack of established correlates of DTWC themselves (Leone et al., 2015; Rooney et al., 2020). The findings indicate that increases in depression (on both factors) predict increases in DTWC. However, the effect of the *Affective* factor is moderated qualitatively by information processing ability such that the effect of the *Affective* factor on DTWC inverts around 105 on the Information Processing domain. As such, those with lower information processing abilities experience greater DTWC at higher levels of negative affect, but those with greater information processing abilities experience greater DTWC at lower levels of negative affect. Thus, those experiencing the greatest DTWC have high negative affect and low information processing according to this model, but those experiencing the least DTWC are those who have high negative affect and high information processing. Those around the mean of negative affect have similar DTWC regardless of information processing ability which can explain the lack of relationship when the moderator is ignored.

Figure 17

Affective Factor from Beck Depression Inventory-II Moderates the Effect of Information Processing on Dual Task Walking Costs



Note. The BDI-II = Beck Depression Inventory-II. Dual Task Costs are calculated as the difference between Single Task and Dual Task Walk Speeds divided by Single Task Walk Speed and multiplied by 100. Higher values indicate greater "costs" associated with dual tasking.

Examining the findings regarding DTWS, there are three notable findings beyond the domination of walking ability (STWS and MSWS-12) and executive function as main effect predictors of DTWS. The first finding of note is that information processing becomes a significant predictor of DTWS when both BDI-II factors and the interaction between information processing and BDI-II *Affective* factor are included. Controlling for both depression factors, higher information processing abilities predict faster DTWS in this model. Connecting with both the DTWC interaction model and the findings in Chapter 2, this again highlights the importance of considering the intersections—by modeling covariates, mediators, and moderators—of the multiple symptomatic presentation that occur in MS. Once the effect of depression, and the interaction identified in the DTWC model, are controlled in this sample, information processing does become a significant predictor of DTWS despite not being identified as such at a bivariate level. This is important as depression (Boeschoten et al., 2017; Siegert & Abernethy, 2005) and information processing (Arnett et al., 1999; Arnett et al., 2001; Diamond et al., 2008) have both been highlighted as important constructs in MS symptomatology.

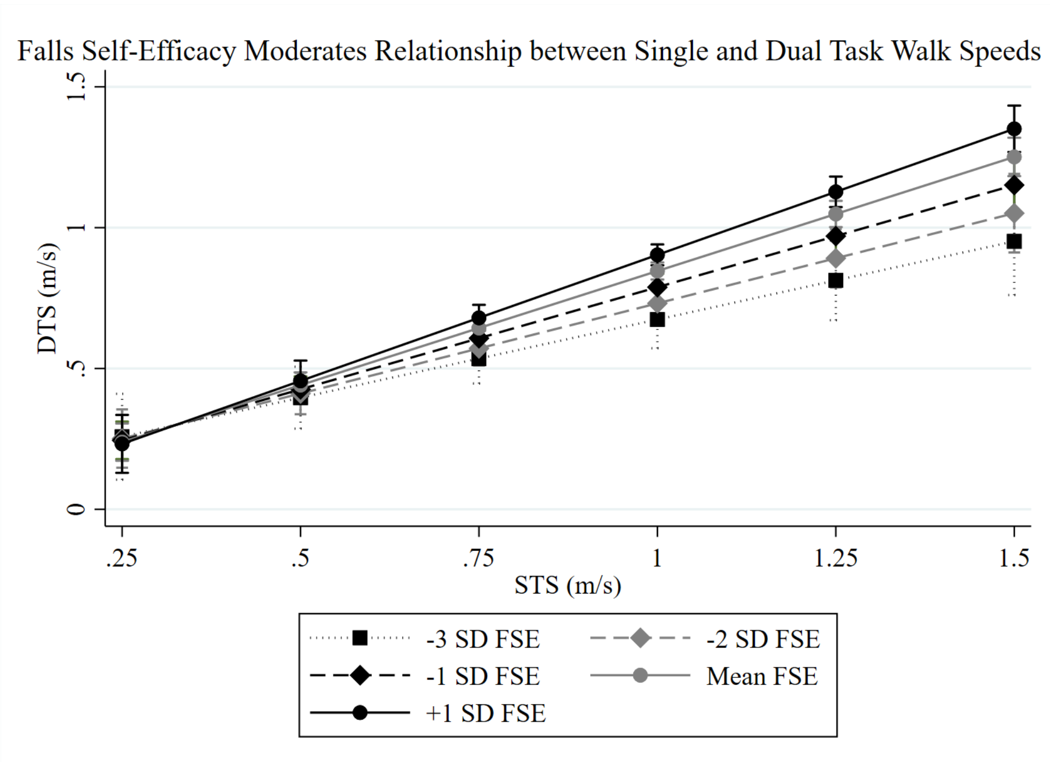
It is also worth note that the MFES and MSWS-12, which were intended as measures of distinct constructs, both uniquely predicted DTWS when modeled together—despite there being no interaction. Less limited walking ability (MSWS-12) and greater balance confidence (MFES) predicted greater DTWS when modeled simultaneously. Although both were correlated at the bivariate level, rs = -0.60 and -0.49, ps < 0.001, respectively, it is interesting to note that they accounted for unique variance in DTWS.

More interestingly and supporting the SAT, the objective measure of baseline physical ability—STWS—was significantly moderated by FSE measured by the MFES factor. Unsurprisingly, there is a strong, positive relationship between STWS and DTWS.

However, that effect is quantitatively moderated by FSE such that the strength of the relationship is attenuated as FSE decreases (see Figure 18). That is, having higher balance confidence makes it such that participants are more likely to maintain more similar walking speed under DT as ST consistent with the SAT and general self-efficacy theory.

Figure 18

Falls Self-Efficacy Moderates the Relationship between Single and Dual Task Walk Speeds



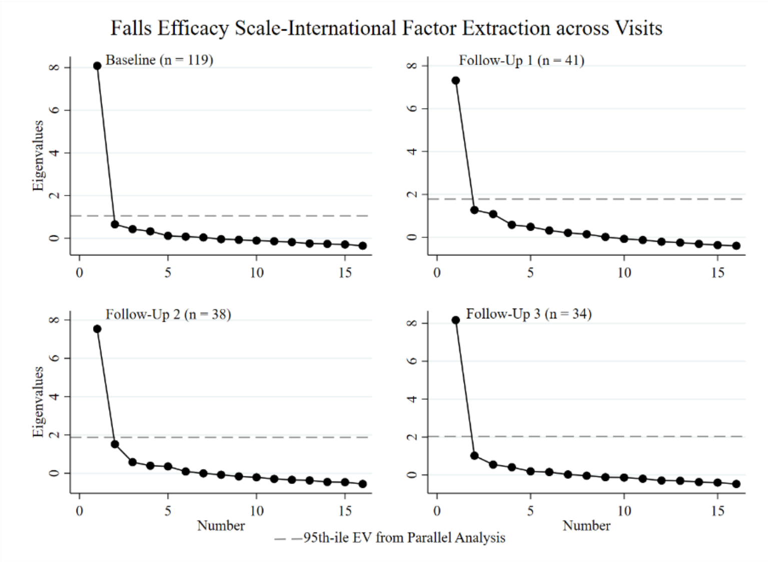
Note. FSE = Falls Self-Efficacy measured by the factor score from the Modified Falls Efficacy Scale; DTS = Dual-Task Speed; STS = Single Task Speed.

University of Kansas Medical Center Analyses

The second study in Aim 3 uses the data from KUMC. Psychometric evaluations on the scales were performed. As was the case in the SS study, the MSWS-12 was available as a subjective evaluation of walking ability. Two measures that are related to FSE were administered: the FES-I and the ABC. Importantly, the FES-I asks about *concern* regarding falling and the ABC asks about *confidence* in one's ability to maintain balance. Unfortunately, in this case, a measure of depression was not available. As a surrogate, it was decided in advance to use the SF-36 which was available. Exploratory factor analysis was performed using IPF. To determine the number of factors measured, parallel analyses were performed by constructing 100 random samples of size *n* based on the *n* at each visit in this 4-visit longitudinal study and using the Eigenvalue at the 95th percentile from these analyses as the threshold for a factor being present (Hayton et al., 2004). This was coupled with visual analysis using scree plots (see Figures 19-22).

Figure 19

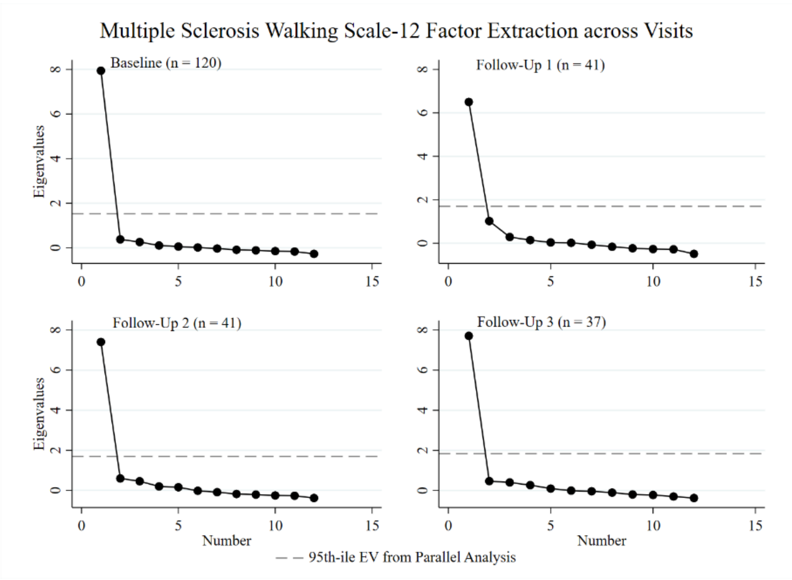
Scree Plots for Factor Extraction for Falls Efficacy Scale-International across Visits



Note. EV = Eigenvalue. Parallel analyses performed with 100 samples of size *n* for each visit. All item loadings ≥ 0.38 across all visits. A one-factor solution fits the data across visits.

Figure 20

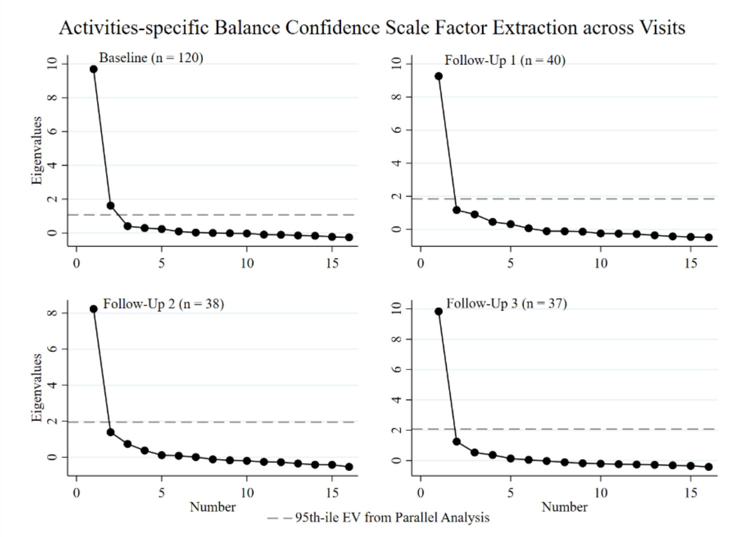
Scree Plots for Factor Extraction for Multiple Sclerosis Walk Scale-12 across Visits



Note. EV = Eigenvalue. Parallel analyses performed with 100 samples of size *n* for each visit. All item loadings ≥ 0.52 across all visits. A one-factor solution fits the data across visits.

Figure 21

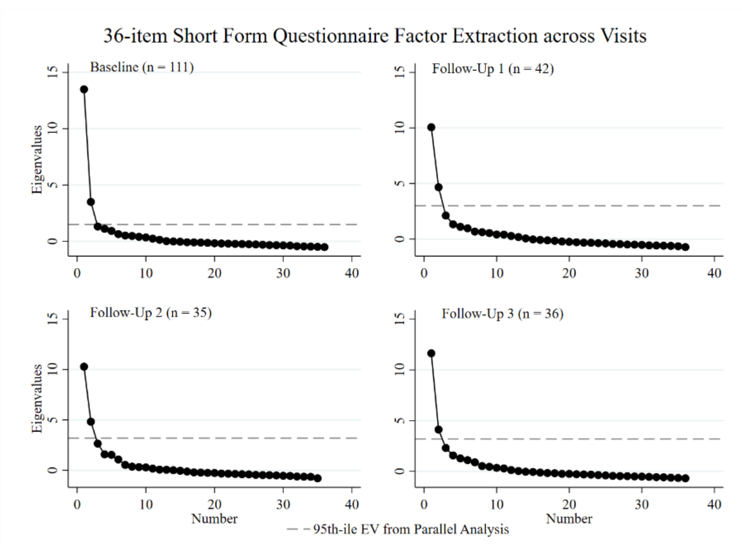
Scree Plots for Factor Extraction for Activities-specific Balance Confidence scale across Visits



Note. EV = Eigenvalue. Parallel analyses performed with 100 samples of size *n* for each visit. All item loadings ≥ 0.41 for first factor across all visits. A one-factor solution fits the data across visits, but a two-factor solution was selected for the baseline assessment.

Figure 22

Scree Plots for Factor Extraction for 36-item Short Form Questionnaire across Visits



Note. EV = Eigenvalue. Parallel analyses performed with 100 samples of size *n* for each visit. A two-factor solution emerged with correlation between the factors using oblique oblimin rotation of 0.413, 0.231, 0.240, and 0.305 at visits baseline through final follow-up, respectively.

The results of the exploratory factor analysis revealed strong, one-factor solutions for the MSWS-12 and FES-I at all time points. The ABC had two factors at baseline, but only one factor following. The two factors were: ABC-Hard and ABC-Easy (see Table 16) which were moderately-to-strongly correlated, $r = 0.57$. The SF-36 had a two-factor solution at all times. Although the loading patterns were not identical across all visits, the pattern was generally consistent that factor 1 was an *Emotion* factor and factor 2 was a *Physical* factor (see Table 17). At baseline, the factors were correlated, $r = 0.41$, and the *Emotion* factor was correlated with the Emotional Wellbeing scale from the standardized scoring for the SF-36, $r = 0.86$.

Table 16

Factor Loadings for the Activities-specific Balance Confidence Scale at Baseline

Item	Factor 1 Loading	Factor 2 Loading
1. Walk around the house	0.353	0.399*
2. Walk up or down stairs	0.669	
3. Bend over and pick up a slipper from the front of a closet floor	0.438	0.466*
4. Reach for a small can off a shelf at eye level		0.559
5. Stand on your tiptoes and reach for something above your head	0.937	
6. Stand on a chair and reach for something	0.866	
7. Sweep the floor		0.706
8. Walk outside the house to a car parked in the driveway		0.974
9. Get in or out of a car		1.021
10. Walk across a parking lot to the mall		0.822
11. Walk up or down a ramp		0.727
12. Walk in a crowded mall where people rapidly walk past you	0.411	0.491*
13. Bumped into by people as you walk through the mall	0.616*	0.343
14. Step onto or off an escalator while you are holding onto a railing	0.677	
15. Step onto or off an escalator while holding onto parcels such that you cannot hold onto the railing	0.818	
16. Walk outside on icy sidewalks	0.912	

Note. Factor loadings are from oblimin oblique rotated iterative principal axis factoring. Only loadings ≥ 0.30 are shown. *Stronger loading for multivocal item. Factor 1 is "Hard" tasks. Factor 2 is "Easy" tasks.

Table 17

Factor Loadings for the Short Form-36 at Baseline

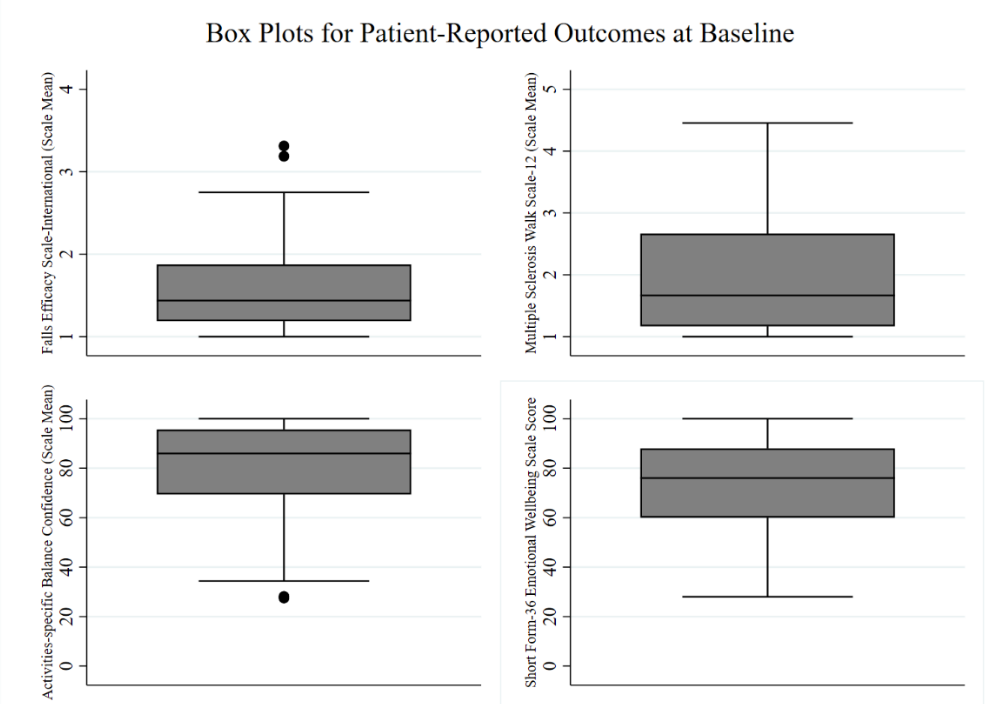
Item	Factor 1 Loading	Factor 2 Loading
1. Your general health is (higher = poorer)	-0.503	
2. Get sick a little easier (higher = falser)	0.466	
3. Am as healthy as anybody (higher = falser)	-0.506	
4. Expect health to get worse (higher = falser)		
5. Health is excellent (higher = falser)	-0.560	
6. Compared to a year ago health is... (higher = worse)		
7. Vigorous activity limited (higher = less)		0.605
8. Moderate activity limited (higher = less)		0.775
9. Lifting/carrying groceries limited (higher = less)		0.716
10. Climbing flights of stairs limited (higher = less)		0.670
11. Climbing a flight of stairs limited (higher = less)		0.695
12. Bending, kneeling, or stooping limited (higher = less)		0.643
13. Walking more than a mile limited (higher = less)		0.873
14. Walking several blocks limited (higher = less)		0.921
15. Walking one block limited (higher = less)		0.801
16. Bathing and dressing limited (higher = less)		0.495
17. Cut down on time doing work/activities (higher = no)	0.359*	0.339
18. Accomplished less than would like (higher = no)	0.436*	0.308
19. Limited in kind of work or activities (higher = no)		0.442
20. Difficulty performing work or activities (higher = no)	0.402	0.404*
21. Bodily pain (higher = more severe)	-0.362	-0.375*
22. Pain interferes with normal work (higher = more)	-0.345	-0.417*
23. Cut down on time doing work/activities (emo; higher = no)	0.704	
24. Accomplished less than would like (emo; higher = no)	0.765	
25. Did work/activities less carefully (emo; higher = no)	0.678	
26. Extent interfered with social activity (phys/emo; higher = more)	-0.571*	-0.349
27. Full of pep (higher = less often)	-0.617	
28. Been very nervous (higher = less often)	0.632	
29. Felt so down nothing could cheer (higher = less often)	0.802	
30. Felt calm and peaceful (higher = less often)	-0.813	
31. Have a lot of energy (higher = less often)	-0.670	
32. Felt down hearted and blue (higher = less often)	0.724	
33. Felt worn out (higher = less often)	0.504	
34. Been a happy person (higher = less often)	-0.707	
35. Felt tired (higher = less often)	0.613	
36. How much of the time interfered with social activity (phys/emo; higher = less often)	0.544*	0.358

Note. Phys = Physical; Emo = Emotional. Factor loadings are from oblimin oblique rotated iterative principal axis factoring. Loadings ≥ 0.30 shown. *Stronger loading for multivocal item.

The sample at baseline has been summarized previously. Table 11 contains the demographic and clinical information for the sample at baseline. Additionally, given the use of self-report outcomes here, Figure 23 depicts these outcomes in box plots. These show that there was some variability in the measures at baseline, but participants were generally high in FSE and low in walking limitations.

Figure 23

Box Plots for Patient-Reported Outcomes at Baseline



Note. The scale means are used for descriptive purposes for the Falls Efficacy Scale-International (1-4), Multiple Sclerosis Walk Scale-12 (1-5), and Activities-specific Balance Confidence scale (0-100). The Emotional Wellbeing subscale from the Short Form-36 is used as a summary for emotional state. It includes items 24-26, 28, and 30 from Table 17 rescaled (0 - 100). Higher scores reflect greater concern about falling, greater limitations in walking ability, greater balance confidence, and greater emotional wellbeing, respectively.

Based on a priori hypotheses, executive function (measured by the Stroop interference task) and information processing (measured by choice reaction time tasks) were tested for moderation by emotional wellbeing and FSE. Also, T25FWT and STWS were used as measures of basic physical ability to be tested for moderation by depression and FSE for its relationship with DTW outcomes. MSWS-12 was used as a measure of physical ability—albeit subjectively evaluated. Lastly, given the identification of EDSS step and BBS as physical predictors of DTWS in Chapter 2, they were tested as well per the process detailed before analyses began. As was true in the SS study, DTWS was the primary outcome of interest as it is a measure of *physical performance* in the context of a complex task, and DTWC was included given its prevalence in the literature (Learmonth et al., 2017; Leone et al., 2015; Postigo-Alonso et al., 2018; Wajda & Sosnoff, 2015) and as a performance measure that captures a more cognitive construct. For a summary of the effects for DTWS and DTWC, see Tables 18 and 19, respectively.

Table 18

Regression Models Evaluating Falls Self-Efficacy and Depression as Moderators of the Effects of Physical and Cognition Ability on Dual Task Walking Speed at Baseline

Predictor Moderator	***n***	**Effect 1** *B, p*	**Effect 2** *B, p*	**Interaction** *B, p*
STWS (m/s)				
FES-I	119	**0.89, < 0.001**	-0.03, 0.790	0.03, 0.740
ABC (Hard)	119	**0.87, < 0.001**	0.07, 0.406	-0.06, 0.421
SF-36 Emotional	111	**0.84, < 0.001**	0.02, 0.789	0.003, 0.967
T25FWT (s)				
FES-I	119	**-0.11, < 0.001**	-0.09, 0.252	0.01, 0.236
ABC (Hard)	119	**-0.11, < 0.001**	0.05, 0.503	-0.01, 0.607
SF-36 Emotional	111	**-0.12, < 0.001**	**0.19, 0.011**	**-0.03, 0.031**
MSWS-12				
FES-I	117	**-0.10, 0.012**	-0.04, 0.423	0.02, 0.373
ABC (Hard)	118	**-0.07, 0.045**	**0.07, 0.043**	-0.02, 0.386
SF-36 Emotional	109	**-0.09, < 0.001**	0.04, 0.070	-0.01, 0.662
BBS (0-56)				
FES-I	109	**0.04, < 0.001**	**0.92, 0.002**	**-0.02, 0.001**
ABC (Hard)	112	**0.03, < 0.001**	-0.73, 0.071	**0.01, 0.047**
SF-36 Emotional	101	**0.03, 0.001**	-0.68, 0.083	0.01, 0.059
EDSS Step (0-10)				
FES-I	117	**-0.09, < 0.001**	-0.09, 0.217	0.02, 0.465
ABC (Hard)	117	**-0.08, 0.003**	0.02, 0.736	0.02, 0.487
SF-36 Emotional	109	**-0.08, 0.001**	0.04, 0.466	0.01, 0.728
Stroop Interference (30 s)				
FES-I	117	**0.01, 0.01**	-0.12, 0.310	0.002, 0.733
ABC (Hard)	117	**0.27, 0.020**	**0.01, 0.013**	-0.01, 0.114
SF-36 Emotional	109	**0.01, 0.016**	0.03, 0.804	0.002, 0.729
CRC Time (s)				
FES-I	116	**-0.69, 0.001**	**-0.21, 0.016**	0.30, 0.095
ABC (Hard)	116	**-0.49, 0.012**	0.07, 0.486	0.04, 0.827
SF-36 Emotional	108	**-0.59, 0.002**	0.18, 0.056	-0.26, 0.203

Note. STWS = Single Task Walking Speed; FES-I = Fall-Efficacy Scale-International; ABC = Activities-specific Balance Confidence; SF-36 = Short Form-36; T25FWT = Timed 25-Foot Walk Test; MSWS-12 = Multiple Sclerosis Walk Scale-12. BBS = Berg Balance Scale; EDSS = Expanded Disability Status Scale; CRC = Choice Reaction for Correct responses. Factor scores were used for FES-I, ABC (using the "hard" factor to increase variability in scores), and the SF-36 Emotional variables, as well as MSWS-12. Effects 1 is for predictor. Effect 2 is for moderator. **Bold font** indicates $p \leq 0.05$.

Table 19

Regression Models Evaluating Falls Self-Efficacy and Depression as Moderators of the Effects of Physical and Cognition Ability on Dual Task Walking Costs at Baseline

Predictors / Moderator	*n*	Effect 1 *B, p*	Effect 2 *B, p*	Interaction *B, p*
STWS (m/s)				
FES-I	119	-2.52, 0.661	-0.20, 0.979	-0.56, 0.932
ABC (Hard)	119	-1.52, 0.798	-4.73, 0.476	3.85, 0.485
SF-36 Emotional	111	2.68, 0.638	-2.72, 0.683	0.52, 0.921
T25FWT (s)				
FES-I	119	**1.83, 0.030**	3.15, 0.538	-0.86, 0.287
ABC (Hard)	119	**1.88, 0.049**	-1.33, 0.784	0.45, 0.594
SF-36 Emotional	111	0.47, 0.620	-3.32, 0.498	0.31, 0.739
MSWS-12				
FES-I	117	-0.52, 0.804	1.63, 0.498	-1.89, 0.190
ABC (Hard)	118	-0.54, 0.772	-1.69, 0.353	2.44, 0.103
SF-36 Emotional	109	-1.27, 0.366	-2.50, 0.062	1.13, 0.387
BBS (0-56)				
FES-I	109	-0.744, 0.086	-29.61, 0.066	0.54, 0.073
ABC (Hard)	112	-0.433, 0.384	16.66, 0.457	-0.30, 0.464
SF-36 Emotional	101	-0.2, 0.662	13.77, 0.519	-0.29, 0.461
EDSS Step (0-10)				
FES-I	117	1.26, 0.319	5.25, 0.167	-2.46, 0.059
ABC (Hard)	117	1.36, 0.328	-2.29, 0.503	1.16, 0.382
SF-36 Emotional	109	-0.74, 0.550	-3.09, 0.316	0.53, 0.700
Stroop Interference (30 s)				
FES-I	117	**-0.59, 0.029**	-4.81, 0.422	0.16, 0.537
ABC (Hard)	117	**-0.59, 0.025**	-0.36, 0.954	0.03, 0.918
SF-36 Emotional	109	-0.27, 0.320	-0.17, 0.978	-0.06, 0.796
CRC Time (s)				
FES-I	116	12.70, 0.251	2.06, 0.661	-6.61, 0.485
ABC (Hard)	116	6.29, 0.546	3.09, 0.559	-6.28, 0.563
SF-36 Emotional	108	7.52, 0.452	-2.42, 0.631	2.13, 0.843

Note. STWS = Single Task Walking Speed; FES-I = Fall-Efficacy Scale-International; ABC = Activities-specific Balance Confidence; SF-36 = Short Form-36; T25FWT = Timed 25-Foot Walk Test; MSWS-12 = Multiple Sclerosis Walk Scale-12. BBS = Berg Balance Scale; EDSS = Expanded Disability Status Scale; CRC = Choice Reaction for Correct responses. Factor scores were used for FES-I, ABC (using the “hard” factor to increase variability in scores), and the SF-36 Emotional variables, as well as MSWS-12. Effects 1 is for predictor. Effect 2 is for moderator. **Bold font** indicates $p \leq 0.05$.

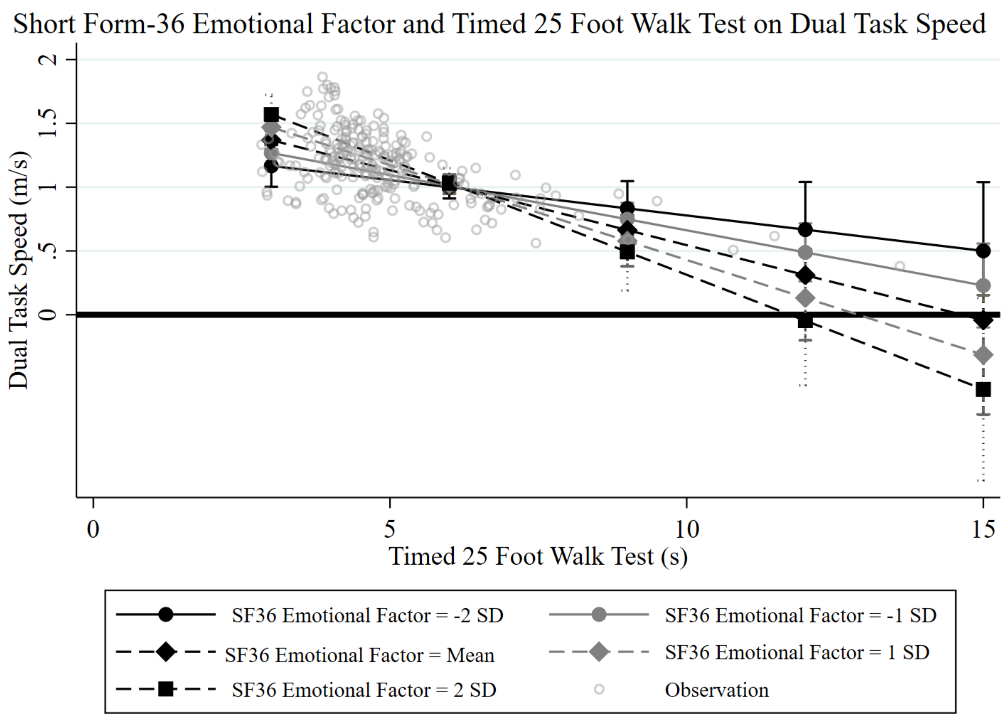
These results provide some interesting corroboration and conceptual replication of the SS findings. As reported in Chapter 2 and the first study in Chapter 3, DTWS relates more robustly to both physical and cognitive predictors than DTWC. In fact, *all* the physical and cognitive predictors were significant in *all* the models when controlling for FSE or emotional wellbeing. For DTWC, the only significant effects at baseline were the T25FWT and executive function measured by Stroop interference *controlling for FSE*. Emotional wellbeing did not emerge as a significant predictor of DTWC in the KUMC study as depression did in the SS study; however, these are conceptually distinct constructs.

There were several models in which FSE or emotional wellbeing were significant predictors of DTWS. These included ABC-Hard controlling for MSWS-12, FES-I controlling for BBS, ABC-Hard controlling for Stroop interference (a measure of executive function), FES-I controlling for choice reaction time for correct answers response time (a measure of information processing), and emotional wellbeing controlling for T25FWT. It is worth noting that the SS study also found that FSE (measured by the MFES) was a significant predictor of DTWS controlling for MSWS-12 and that it contributed to the model with STWS as a predictor as a significant moderator. Both these analyses concur that including a basic measure of physical performance and a measure of self-appraised ability (e.g., FSE) is likely to improve prediction of DTWS. They also hint that including both forms of predictors may improve prediction of DTWC. In the SS findings, MFES was a significant predictor of DTWC controlling for MSWS-12, and in the KUMC findings, the T25FWT was only a significant predictor when controlling for FSE in the form of the ABC-Hard or FES-I. Although these differ in terms of whether the subjective appraisal or basic physical measure emerges as significant, they both indicate that the covariation of these two types of measure may be worthwhile to consider when attempting to model DTW outcomes. It is possible that the differences in functional ability between the two samples may explain this slight disparity (see Table 12 for direct comparisons of STWS and DTWS and see Tables 9 and 11 for clinical and demographic summaries for comparison).

Finally, conceptually corroborating the SS findings in support of SAT, self-appraisals were significant moderators in several predictive models for DTWS. First, not only were T25FWT and *Emotion* both significant as main effect terms, but the interaction between them was also statistically significant. Faster T25FWT time predicted faster DTWS (relationship sign is negative given T25FWT is measured in s and DTWS is in m/s), and more positive *Emotion* predicted faster DTWS; however, a qualitative interaction emerged around the time of 6 s on the T25FWT, such that less positive *Emotion* predicted faster DTWS than more positive *Emotion* (see Figure 24). However, it is worth noting that most observations occurred in the span of the interaction being quantitative—that is, that the relationship between positive *Emotion* and DTWS was attenuated as T25FWT times increased (i.e., for those who were less physically able). This may indicate that being characterized by things like “being full of pep” and “having a lot of energy” and *not* “feeling down” or being “blue” have the potential to *invigorate* one to an extent that allows them to maintain high levels of performance under more complex conditions (e.g., DT), given they have generally high levels of basic physical ability. However, the potential for this to occur wanes as basic physical ability decreases because there may not be the same capacity for maintaining performance under complex tasks for such persons.

Figure 24

Emotional State Moderates the Effect of Timed 25-Foot Walk Test on Dual-Task Walking Speed

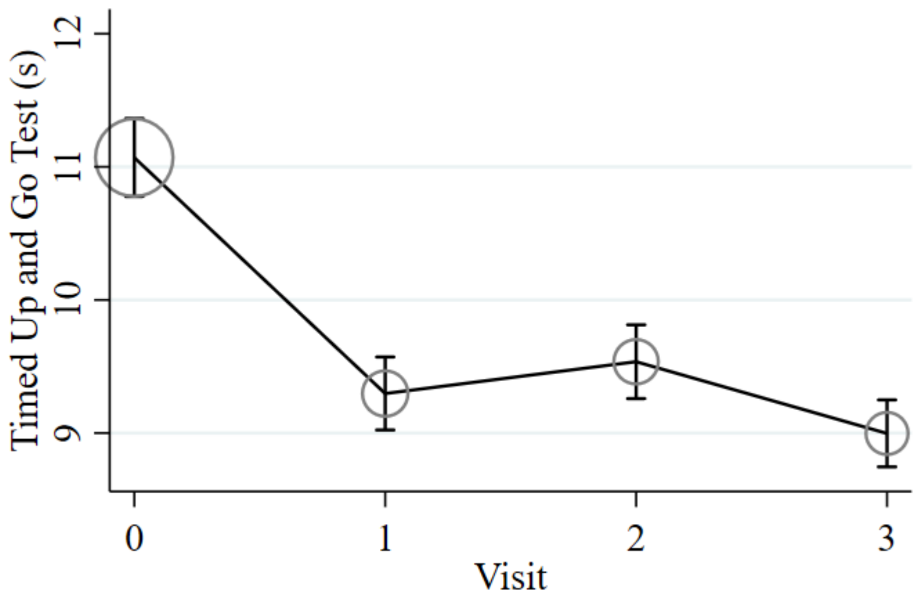


Note. Thick black line indicates lower limit for Dual Task Walking Speed. As observation marks indicate, no actual observations were made below this threshold, but the predict model was created to extend to capture observations across Timed 25-Foot Walk times which takes the model predictions into unobserved and *unobservable* territory.

However, it is worth noting that this effect did not quite persist when modeled as a between-persons effect (interaction of person means) in MLMs with random intercepts and slopes across visits despite the patterns of effects remaining. The between-persons effect of T25FWT remained, $B = -0.12$, $p < 0.001$, but the between-persons effect of *Emotion*, $B = .16$, $p = 0.058$, and the interaction, $B = -0.03$, $p = 0.086$, were not quite statistically significant. This may be a result of the fact that those who dropped out of the study were both less physically able in terms of T25FWT times, OR = 4.00, $p < 0.001$ (see Figure 25) and had less positive *Emotion*, OR = 0.72, $p = 0.122$, albeit not significantly for the latter. DTWS was also a significant predictor of attrition from the study, OR = 0.06, $p = 0.001$. As such, the weighting of the effect becomes more affected by those who are more able when modeled longitudinally which may explain the difference.

Figure 25

Timed 25-Foot Walk Test Performance across Visits



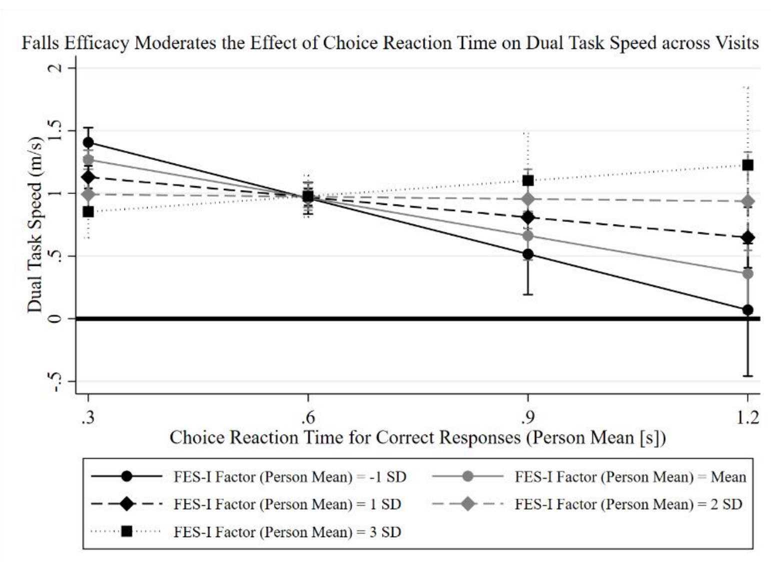
Note. Markers are weighted by sample size. Standard error of the mean represented by error bars.

Inversely, although the effect of information processing (choice reaction time [s] for correct responses) was not quite significantly moderated by FES-I scores in the baseline only model despite both main effects being significant, the effect was significant when modeled as a between-persons difference in a longitudinal model using MLM (see

Figure 26). The main effect of choice reaction time was such that slower average response rates for correct responses predicted slower DTWS, *B* = -1.01, *p* < 0.001. The main effect of FSE (measured by FES-I) was such that greater *concern about falling* predicted slower DTWS, *B* = -0.28, *p* = 0.001. The interaction was qualitative with the effect of high concern about falling predicting slower speed when information processing was rapid but greater DTWS when information processing was slow, *B* = 0.47, *p* = 0.008. This suggests that the more quickly the information can be processed the more slowing occurs as a result of low FSE which suggests a processing of risk is occurring and that the faster that can occur the more likely it is to affect DTWS. This further corroborates how self-appraisals, cognition, and physical performance on complex tasks like DTW intersect in a manner that is consistent with SAT.

Figure 26

Falls Self-Efficacy Moderates the Effect of Choice Reaction Time for Correct Responses on Dual Task Speed as a Between-Persons Effect in Longitudinal Model

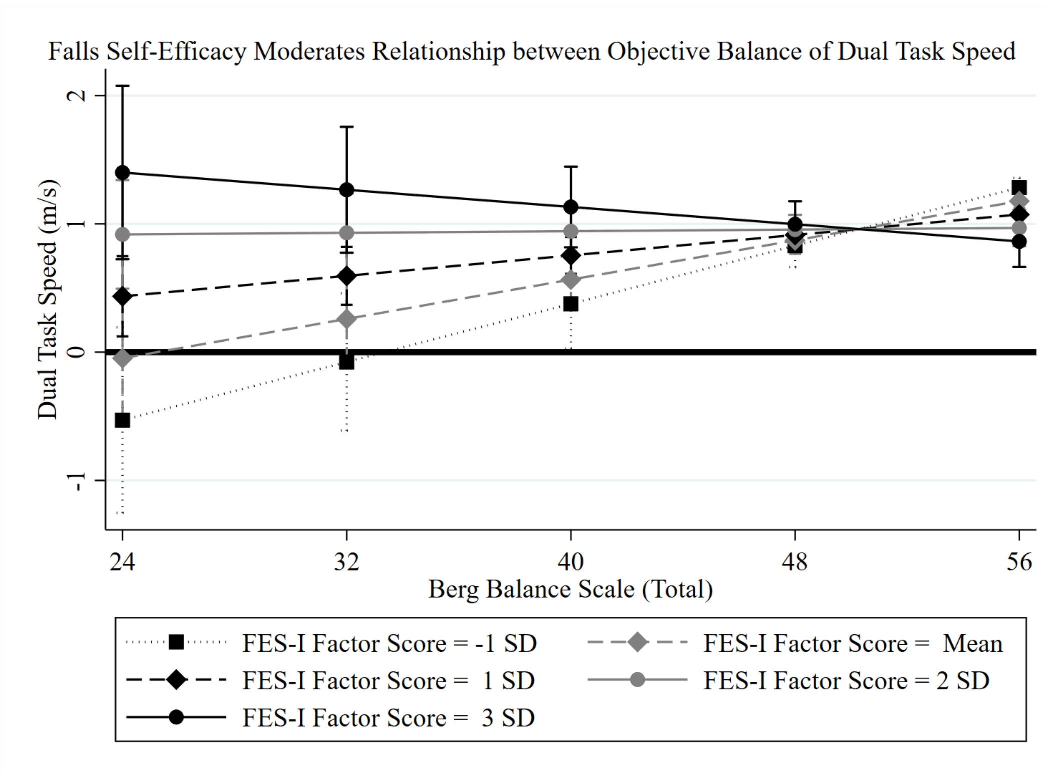


Note. Thick black line indicates lower limit for Dual Task Walking Speed.

Further, both FES-I and ABC-Hard were found to significantly moderate the effect of *objective balance* (measured by the BBS) on DTWS. So, although the interaction in the SS study of STWS and FSE did not directly replicate, the hypothesis that self-appraisals of physical abilities moderate the effect of objective ability on physical performance in a complex, DT task did replicate. Controlling for FES-I, better balance on the BBS predicted faster DTWS. Controlling for BBS, greater concern about falling predicted faster DTWS. However, the interaction was such that around BBS = 49 a qualitative shift occurred (see Figure 27). For those with BBS scores above this point, higher concern about falling predicted slower DTWS, but for those with balance worse than this, higher concern about falling predicted faster DTWS. It is also interesting to note, especially given past research regarding the lack of relationship between the BBS and DTW outcomes (Rooney et al., 2020), that at the mean FES-I factor score there was no relationship between BBS and DTWS. That is, if one has average levels of concern about falling their objective balance is not predictive of their DTWS. Objective balance measured by the BBS *only* emerges as related to DTWS when you move away from the mean of concern about falling. It is worth noting that although BBS scores ranged from 25 to 56, the mean was 53.4 and the median was 55 at baseline. The 10th percentile was a BBS of 48. As such, most participants were in the realm of the interaction being quantitative in nature; that is, as concern about falling increased, the relationship between objective balance and DTWS waned.

Figure 27

Falls Self-Efficacy Moderates the Relationship between Objective Balance and Dual Task Speed

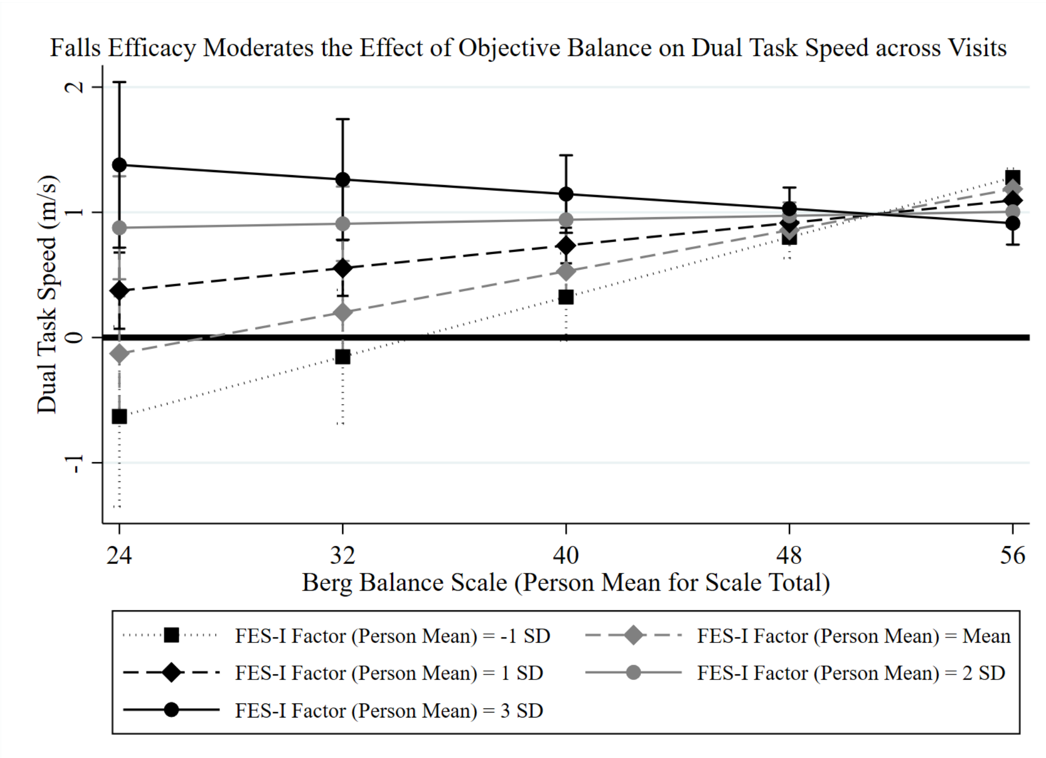


Note. FES-I = Falls Efficacy Scale-International. Thick black line indicates lower limit for Dual Task Walking Speed.

This effect was replicated as a between-persons effect modeled longitudinally using MLM. The effects were in the same directions. Controlling for FES-I factor scores, higher BBS predicted faster DTWS, $B = 0.04$, $p < 0.001$. Controlling for BBS scores, concern about falling predicted faster DTWS, $B = 0.95$, $p = 0.001$. The interaction was identical in form and statistically significant, $B = -0.19$, $p < 0.001$ (see Figure 28).

Figure 28

Falls Self-Efficacy Moderates the Relationship between Objective Balance and Dual Task Speed as a Between-Persons Effect in Longitudinal Model

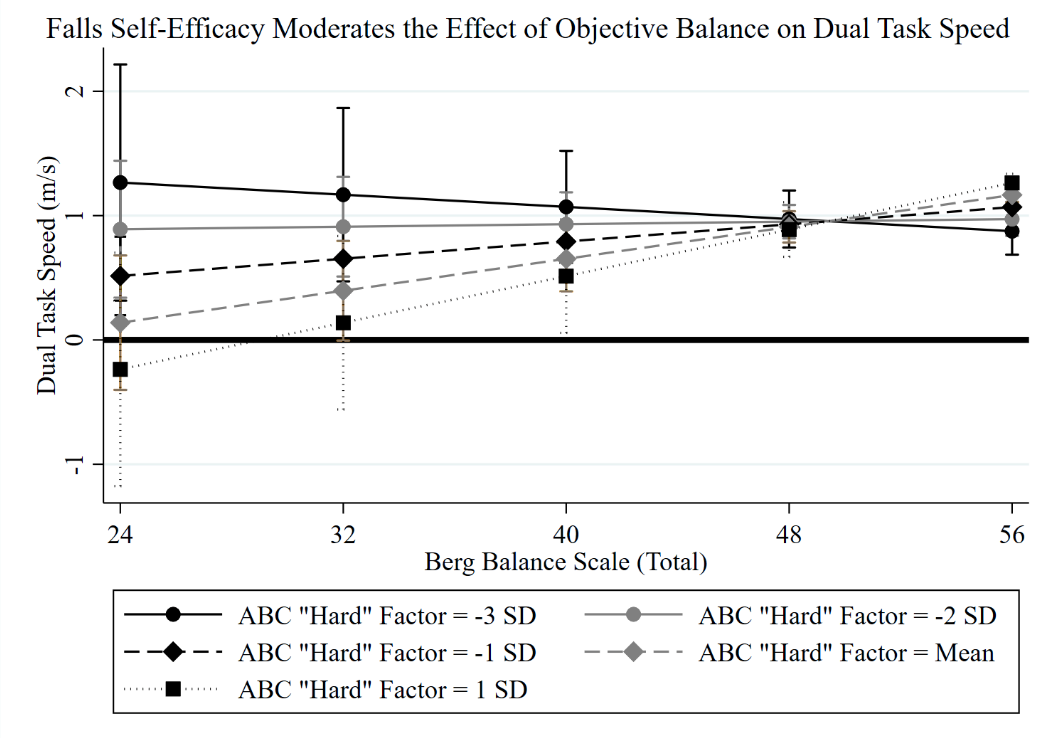


Note. FES-I = Falls Efficacy Scale-International. Thick black line indicates lower limit for Dual Task Walking Speed.

These same patterns were found when the ABC-Hard was included as the moderator. Interestingly, the main effect of ABC-Hard was not quite significant—unlike the main effect of FES-I—which suggests that "concern" or "fear" of falling may be slightly yet importantly nuanced constructs compared to "confidence" in one's balance and that "concern" may be capturing something unique and important in this interactive dynamic. Controlling for ABC-Hard, higher BBS predicted faster DTWS. Controlling for BBS, higher ABC-Hard scores (greater confidence) predicted *slower* DTWS albeit not quite significantly as a main effect. However, the interaction was significant (see Figure 29). Again, around a BBS score of 49, a qualitative interaction occurs. Higher confidence predicted faster DTWS for those above BBS = 49, but it predicted slower DTWS for those below BBS = 49. Again, however, most participants had BBS above this inflection point, so the quantitative interaction characterizes that pattern observed in most the data. That is, the effect of objective balance on DTWS wanes as balance confidence decreases. These findings are entirely consistent with SAT.

Figure 29

Falls Self-Efficacy Moderates the Effect of Objective Balance on Dual Task Speed

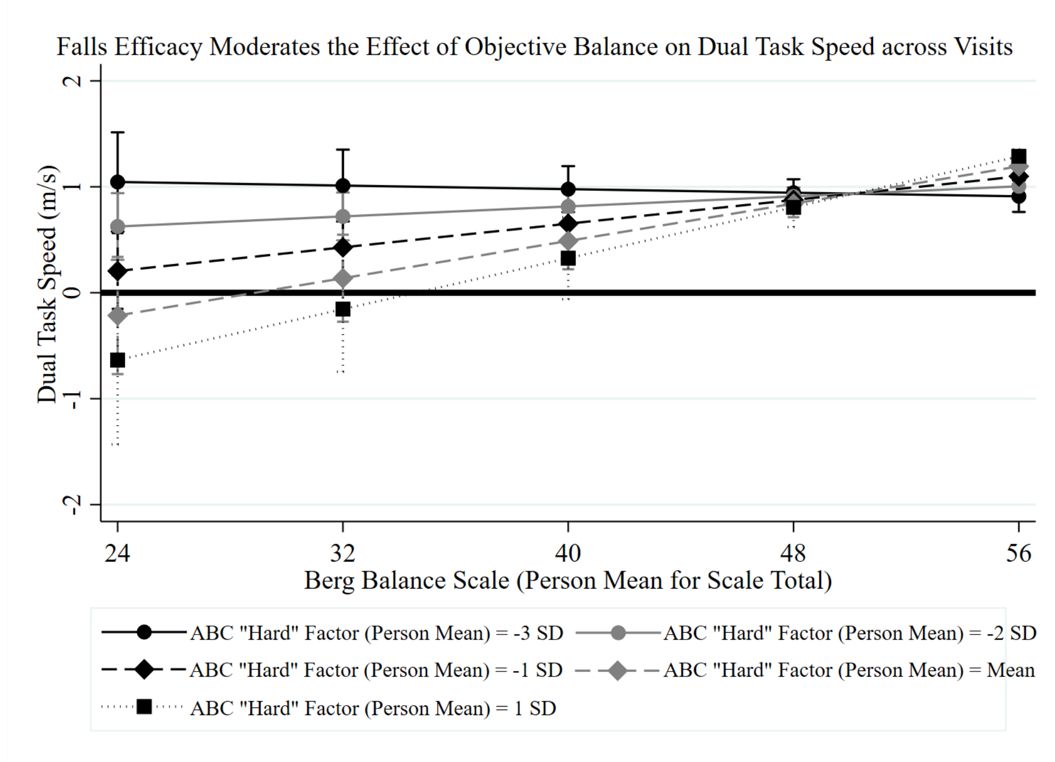


Note. ABC = Activities-specific Balance Confidence scale. The “Hard” factor was used from the two-factor solution found at baseline. Thick black line indicates lower limit for Dual Task Walking Speed.

This effect also replicated as a between-persons effect in a longitudinal MLM. In fact, in this model, the “not quite significant” main effect of ABC-Hard is statistically significant controlling for BBS, $B = -0.81$, $p = 0.001$. The main effect of BBS controlling for ABC-Hard remains significant, *B* = 0.04, $p < 0.001$. The interaction is also significant and takes the same form, *B* = 0.02, $p = 0.001$ (see Figure 30).

Figure 30

Falls Self-Efficacy Moderates the Relationship between Objective Balance and Dual Task Speed as a Between-Persons Effect in Longitudinal Model



Note. ABC = Activities-specific Balance Confidence scale. The "Hard" factor was used from the two-factor solution found at baseline. Thick black line indicates lower limit for Dual Task Walking Speed.

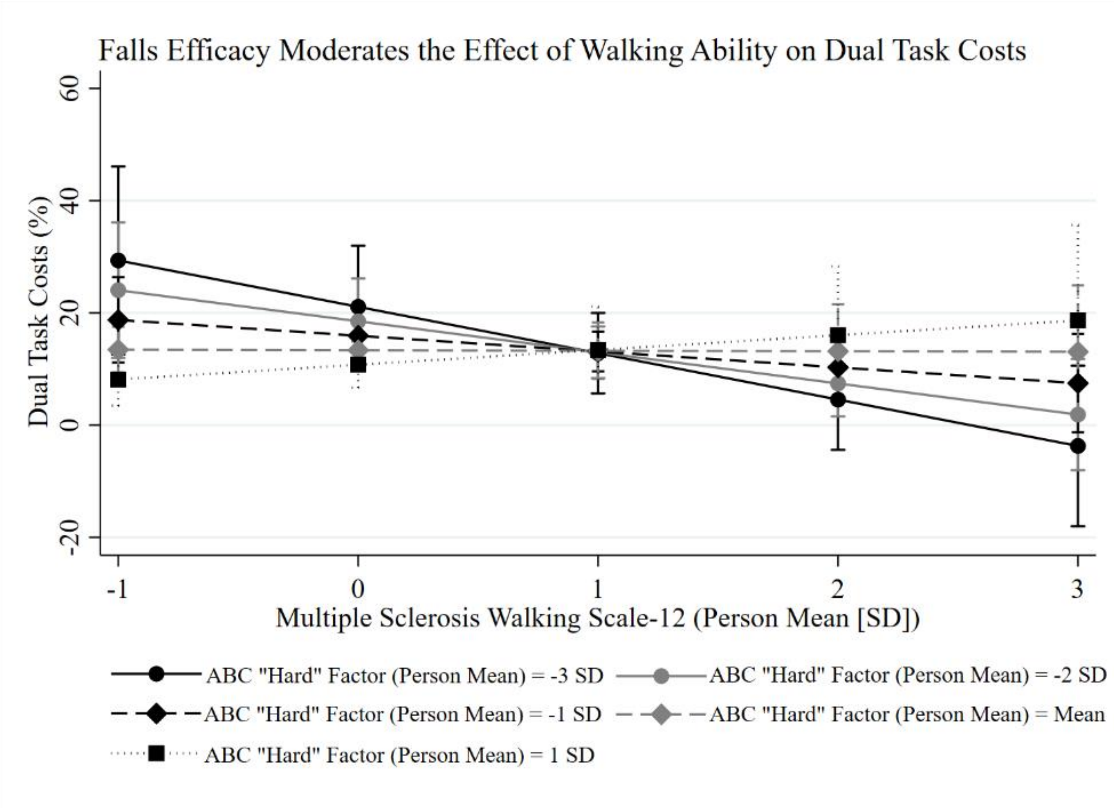
Consistent with findings reported thus far, there was very little found that predicted DTWC—unlike DTWS. The two predictors that emerged as significant main effects were already noted—T25FWT controlling for FSE and Stroop inteference controlling for FSE (in both cases using either operationalization). There were three models with FSE that had patterns that warranted further exploration using all available data in longitudinal models. These were the interactions of self-reported walking ability

(MSWS-12) by FSE (ABC-Hard), objective balance (BBS) by FSE (FES-I), and neurologist-rated disability (EDSS Step) by FSE (FES-I).

The model including BBS and FES-I had effects that remained only on the cusp of statistical significance. The main effects of BBS, $B = -0.76$, $p = 0.074$, FES-I, $B = -30.22$, $p = 0.056$, and the interaction, $B = 0.54$, $p = 0.064$ were not quite statistically significant. However, the patterns are in the expected directions based on the DTWS model. Both the interaction of ABC-Hard and MSWS-12 and EDSS Step and FES-I were statistically significant modeled as between-persons effects in MLM. For walking ability and balance confidence, neither main effect was significant in the presence of the other and the interaction, MSWS-12: $B = -0.09$, $p = 0.960$; ABC-Hard: $B = -2.58$, $p = 0.137$. However, the interaction was significant, $B = 2.72$, $p = 0.023$ (see Figure 31). The interaction was such that greater balance confidence predicted greater DTWC for those with higher self-reported walking limitations; however, greater balance confidence predicted lesser DTWC for those with lower self-reported walking limitations. Not only does this suggest that self-reported walking limitations and measures of FSE are capturing distinct constructs in the context of DTW outcomes—as also evidenced in the SS analyses—but it suggests that those with lower subjective walking limitations experience the greatest DTWC as a function of having low balance confidence (FSE). Again, this highlights the importance of understanding one’s subjective appraisal to identifying the type of sacrifices they make or priorities they have during complex DTW tasks. For those at the mean ABC-Hard, subjective walking-ability was not related to DTWC; the relationship only emerges as a person’s score moves away from the mean.

Figure 31

Falls Efficacy Moderates the Effect of Subjective Walking Ability on Dual Task Costs

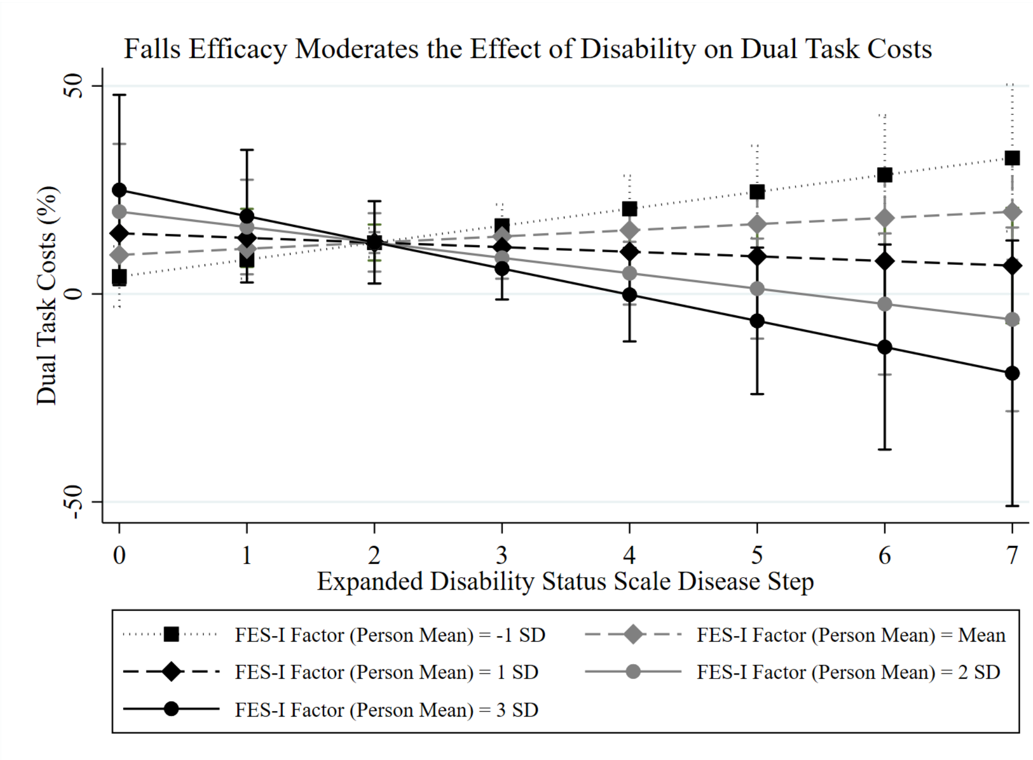


Note. ABC = Activities-specific Balance Confidence scale. The "Hard" factor was used from the two-factor solution found at baseline.

Lastly, FSE measured by the FES-I as "concern" about falling acted as a moderator of disability (time invariant) as a between-persons effect in the MLM. Neither the main effect of EDSS step, $B = 1.48$, $p = 0.207$, nor the main effect of FES-I, $B = 5.20$, $p = 0.136$, was significant in the presence of the other factors. However, the interaction was, $B = -2.59$, $p = 0.035$ (see Figure 32).

Figure 32

Falls Efficacy Moderates the Effect of Disability on Dual Task Walking Costs



Note. FES-I = Falls Efficacy Scale-International.

The interaction is such that for those with higher levels of "concern" about falling, greater DTWC are predicted for those with lesser disability, but higher "concern" about falling predicts lesser DTWC for those with greater disability. Of note, the inflection point is at the median level of disability (EDSS Step = 2) in this sample. So, for those above median disability, higher costs occurred as a result of lesser "concern" about falling; however, for those below the median disability, higher costs occur as a result of greater "concern" about falling. This sort of moderated effect may also help to understand the lack of relationship often reported between the EDSS and DTWC (Rooney et al., 2020).

Discussion

The findings from these analyses rather robustly support the SAT of DTW (Yogev-Seligmann et al., 2012). Specifically, the interactions observed are consistent with the a priori hypotheses based in SAT that individual appraisals of abilities and risks within a given context are important for understanding outcomes in complex contexts like DTW. These findings are supported in the literature given the great deal of evidence that subjective appraisals and emotional states act as important moderators of the relationship between basic abilities (e.g., objective measures of balance, disability, and cognition and self-reported walking ability) and performance under more complex, DT conditions.

In the SS analyses, those who are experiencing affective symptoms of depression experienced lesser DTWC *if they had high information processing ability*. Presented with a cognitive challenge—like DTW—it is not surprising that those with the highest levels of information processing ability would work hard to demonstrate their competence at the task and preserve what is likely an important part of their self-concept, but feelings of "worthlessness" and "self-criticalness" captured in the *Affective* construct of the BDI-II may spur them on to prove their abilities even more. As some research has indicated, depression may not directly impair one's cognitive abilities (Julian et al., 2007) despite predicting one's subjective evaluations about cognitive abilities (Potvin et al., 2016; Serra-Blasco et al., 2019). The incongruence between actual ability and subjective appraisal of ability may lead to greater motivation for ego protection under challenging circumstances.

It is important to note that in our study, using conventional cutoffs for the BDI-II, 31, 10, 14, and 4 participants had "minimal," "mild," "moderate," and "severe" levels of depression, respectively. Further, both the main effects of the BDI-II factors were significant and positive—indicating that controlling for information processing and each other, both *Affective* and *Somatic-Vegetative* factors of the BDI-II predicted greater DTWC. The interaction only existed for the *Affective* component controlling for the *Somatic-Vegetative*. The notion that any level of depressive symptoms would inherently result in "less effort" may not be reasonable—especially in the context of a two-factor solution with the latter being the *Somatic-Vegetative* factor that would capture the minimization of effort while the *Affective* factor captures negativity about self (Wang & Gorenstein, 2013b). For example, two meta-analyses—one examining longitudinal relationships between perfectionism and depression controlling for neuroticism (Smith et al., 2016) and one examining perfectionism as a predictor of various forms of psychopathology—noted that perfectionism is *positively* related to depression. The studies reported in their meta-analysis showed that perfectionism and depressiveness are, in fact, positively correlated above-and-beyond the relationship between depression and neuroticism (Limburg et al., 2016). Similarly, recent research has shown that narcissism (Twenge et al., 2014), perfectionism (Curran & Hill, 2017), and depression (Twenge, 2014; Twenge, 2015; Twenge et al., 2018) are all concurrently increasing in U.S. society. Thus, it is clearly unreasonable to assume that higher levels of *Affective* symptoms of depression would not result in greater effort to demonstrate one's ability and protect one's ego. Those not experiencing such high levels of negative affect may be less compelled to work to demonstrate their abilities. However, for those with lower levels of information processing ability, negative affect predicts worst performance, which may reflect a basic cognitive inability to overcome the task complexity to maintain high performance during the DTW paradigm.

Similarly, the notion that FSE moderates the relationship between STWS and DTWS is entirely consistent with SAT (Yogev-Seligmann et al., 2012) and with previous studies that began to consider how FSE may factor into DTW research in MS (Wajda et al., 2016; Wajda et al., 2020). Yet, no research has examined FSE as a moderator of the dynamics between basic abilities and DTW outcomes—which is precisely what SAT would predict should occur. In the SS study, for those who have high efficacy for balance, the added challenge is perceived as less threatening—even "less difficult". As such, performance decrements do not occur in the same way that they do for those with low levels of FSE. Although DTWS was predicted to be slowed for lower STWS for all, the extent of slowing was predicted by FSE as SAT would predict.

The findings from the SS study were greatly, at least in conceptual form, replicated in the KUMC analyses which indicated the presence of moderating effects of *Emotion* (an emotional wellbeing factor from the SF-36) and FSE (measured by both the ABC-Hard and FES-I factors). These effects were also reliably in forms that SAT would predict demonstrated that individuals with equal basic abilities are predicted to have different outcomes under complex DTW conditions as a function of their differing levels of self-appraisal. The fact that multiple analyses demonstrated that at mean levels of FSE no or minimal relationships are observed between predictors like disability (EDSS Step) and objective balance (BBS) is consistent with the mixed or null findings commonly reported between these measures and DTW outcomes (Leone et al., 2015; Postigo-Alonso et al., 2018; Rooney et al., 2020). Perhaps ironically, mixed and null findings are precisely what would be expected when a moderated relationship exists but is neglected. Of course, it is also noteworthy that the use of DTWS and DTWC—not surprisingly—is critical. Basic metrics of physical ability, like the BBS score and MSWS-12 were moderated by measures of FSE when predicting DTWS with the most robust effect being the interactions between the measures of FSE and objective balance which is also, arguably, the most consistent and truest model in terms of aligning objective ability and subjective appraisal of *that* ability.

Consistent with Chapter 2, it seems that DTWS is a much more reliable contributor to the nexus of symptoms and factors in MS, and it has the potential to capture important aspects related to both walking and increased challenges resultant from cognitive demand. There were a couple effects that were intriguing for DTWC when modeling as between-persons factors in MLMs, including FES-I moderating the effect of disability (EDSS Step) and ABC-Hard moderating the effect of self-reported walking limitations (MSWS-12) on DTWC. As noted, DTWC, as it removes the physical performance metric via standardization by STWS, becomes an outcome that is best conceptualized as cognitive. It is the percent change caused by concurrent cognitive task performance—it measures a "cognitive effect" or an "effect of concurrent cognition" without any actual reference in physical performance. This means that DTWS (as a measure of physical performance under DT) and DTWC need not be related. In fact, because the nature of the calculation, walking speeds are reliably unrelated to DTWC in these studies.

Unfortunately, we did not have a direct measure of *cognitive performance* during DT. We also did not have a self-appraisal of cognitive ability (e.g., a cognitive self-efficacy measure). It would be very informative to take a similar approach in examining how *performance* on the cognitive task under DT fits into the nexus of symptoms in MS and whether efficacy for cognition may act as a moderator. It may be that "costs" are not as useful as the regular reliance on them suggests. Even in the classic study (Lundin-Olsson et al., 1997), which established the importance of DTW in the context of fall risk and brought it into purview of mobility researchers in geriatric and neurological populations, simply looked at changes in performance. They even did it in a very coarse way by asking whether people *stopped walking* to hold a conversation. It may be that adding more refined measures of gait (speed and stride-to-stride variability have been found to be reliably affected by DT; Mirelman et al., 2018) will add even greater insight into the role DTW plays in predicting adverse outcomes—and what predicts the manifestation of DTW problems—in these populations. Yet, it may be that "costs" calculations add less to this understanding. However, it may also be that DTWC as a more "cognitive" outcome would be understood better by considering whether efficacy for cognition plays a moderating role in predicting DTWC that has been masked by glossing over such a factor in the extant literature. It also may be that carefully measuring *performance* in walking and *performance* in cognition and retaining the original units of measure (e.g., speed in the case of DTWS) is simply more useful for understanding how DT abilities factor into and are predicted by the experiences and symptoms of those with MS. For example, it is well-established that walking speed is a very important factor in MS (Albrecht et al., 2001; Briggs et al., 2019; D'Orio et al., 2012; Kalron, 2014; Kalron & Achrion, 2014; Langeskov-Christensen et al., 2017), so it is awkward that walking speed would be intentionally removed in much of the DTW research. There is reason neither to presume that DTWS cannot tell us more than STWS alone nor to neglect DTWS as a primary outcome in such studies. In fact, in studies where "condition" (ST or DT) is used as a within-subjects factor, the speed metric is retained which may explain some of the discrepant findings in the literature.

Admittedly, although a limited number of constructs are included (i.e., physical ability, cognitive ability, FSE, and depressive symptoms), there are multiple measurements of these constructs. As such, there are many tests performed. Although the decision was made to report all results using $\alpha = 0.05$ per comparison, the findings should be considered given the multiple comparisons. However, the unique opportunity to evaluate models in two, independent, relatively large samples and findings corroboration of basic conceptual models across them provides additional confidence in the support provided for SAT by these analyses.

These findings greatly indicate that it is important to understand how the myriad symptoms and constructs that are relevant in MS interact to understand how and for whom certain outcomes manifest in more challenging DTW conditions. This understanding may help to design interventions that are tailored to meet the needs of given individuals to maximize their function—including under complex conditions—at a level commensurate to their basic, physical abilities. For some, it seems that improving their FSE would be the most effective route to improve daily function. For others, it seems that working directly on their balance or gait would be most useful. As SAT purports, we must understand an individual's appraisals of their abilities and risks to understand what they prioritize in complex walking situations (Yogev-Seligmann et al., 2012). The potential to amplify the effects of interventions that seek to improve DTW as a basic, everyday ability by tailoring them based on understanding both patients' basic levels of cognitive and physical ability and psychological states like FSE, *Affective* symptoms of depression, and emotional wellbeing.

CHAPTER 4

Understanding factors that predict DTW may be useful for identifying targets to improve this ability or identifying individuals who may be at-risk for complications when performing this everyday task. The ability to DTW may be an important functional process in its own right in MS. However, the importance of understanding the dynamics that may give rise to DTW would be bolstered more by determining whether DTW ability predicts other outcomes of importance to those affected by MS.

It takes only a bit of mental consideration to identify all the daily functional and social activities that require DT—from holding a conversation while walking with a friend, to texting as we navigate through our environments, to recalling our grocery list while strolling through the grocery store, to trying to remember where we parked as we walk through the lot, on and on the list of DTW goes. Thus, it is reasonable to assume that DTW ability would matter to the function and QoL of those affected by MS, particularly if the deficits are perceptible—whether as the result of their novelty (e.g., early in the disease course) or severity (e.g., later in the disease course). Yet, there is a notable paucity of research that explores how DTW predicts—or even relates to—important PROs in those with MS (Leone et al., 2015; Rooney et al., 2020).

In their 2015 review, Leone and colleagues noted that there is a clear neglect of the “invisible symptoms” (p. 128) of MS in the context of DT research. Rooney et al. (2020) found only nine DTW studies (and four DT balance [DTB] studies) that examined correlations with other variables of importance in MS. No studies examining QoL were identified in their review. One study that was identified was completed by Castelli and colleagues (2016). They reported that DTWC were related to elements of the MSQoL-54, specifically role limitations related to physical problems and social function, in people with MS who had low levels of disability (EDSS ≤ 3). Although there are numerous studies evaluating DT in MS, most of them focus on simply characterizing DTW in MS and comparing the performance of those with MS to healthy controls. Although there is strong evidence for DTWC in MS—albeit the evidence is less strong with respect to whether these costs differ from those of healthy controls in magnitude—there is limited examination of the relationships between DTW and other important constructs in people with MS.

Beyond the possible relevance to patients' appraisals of their function and QoL, the importance of DTW in MS is further bolstered by the possibility that it is related to fall risk and falls. In fact, the seminal study by Lundin-Olsson and colleagues (1997) is considered the first to identify the inability to engage in DTW ability (not DTWC) as a predictor for falls. This study was a small report based on observations in a long-term care facility in Sweden. It found that 12 of 58 residents would stop walking when talking, and 10 of these 12 "stops walking when talking" residents fell in the next 6 months. Lundin-Olsson et al. (1997) also reported that these individuals were assessed to have less safe gait in general and needed more assistance with activities of daily living. Thus, the idea that function and falls are consequents of an inability to perform DTW is at the foundation of this line of research. In fact, Lundin-Olsson and colleagues (1997) found that this simple identification of individuals who stop walking to talk classified fallers with 95% specificity albeit with only 48% sensitivity and had a positive predictive rate of 83%. Comparatively, Bogle Thorbahn and Newton (1996) found that the BBS only had 96% specificity and 53% sensitivity, but it has a much greater burden of administration than merely observing this everyday activity of “walking and talking.” Thus, this demonstrated that a simple, everyday ability to walk and talk may be a useful characteristic to evaluate when considering whether someone is at risk for falling among older adults.

In MS, Quinn et al. (2019) found that individuals with MS who provided self-reported indication of difficulty doing two things at once were twice as likely to experience two or more falls during a 3-month prospective study. Finding that such a simple question about an important everyday process was significantly related to prospective fall risk in MS is insightful, as there is a clear need to have measures that adequately predict fall risk and rates in MS. Studies exploring these issues have revealed continued limited ability of available measures to adequately classify fallers and non-fallers (Cattaneo et al., 2006; Nilsagård et al., 2009; Hoang et al., 2016). A recent meta-analysis (Quinn et al., 2018) of predictors of fall risk in MS found that there is limited work in the area permitting a full understanding of the best predictors of fall risk, but the ABC and FES-I—two highly related, self-report measures of FSE (or “balance confidence”)—were two of three (the third being the BBS) measures that were found to be useful. However, it was noted that there is not sufficient evidence from prospective studies to adequately identify measures of fall risk in MS.

Work has hinted that DTW outcomes may predict fall risk in MS, but the evidence is mixed. One study (Wajda et al., 2013) found that DTWC correlated with the Physiological Profile Approach, and objective assessment of various domains that are putatively important for maintaining balance and which performs decently in predicting falls in MS (Gunn et al., 2013; Hoang et al., 2016). However, STWS and DTWS alone did not. However, Rooney et al. (2020) noted that only one of the two studies they identified that assessed DTWC and Physiological Profile Approach correlations found such a relationship.

The limited evidence regarding DTWC and fall risk in MS is conflicted. One study examining DTWC did not find DTWC to predict future falls (Gunn et al., 2013). Yet, another study (Etemadi, 2017) found that both DTWC and DTCC predicted risk of being a recurrent faller in a 6-month prospective study in 60 people with MS. Quinn et al. (2019) evaluated the ability of TUG and TUG-C performance to discriminate both fallers ($\geq$ 1 fall) and multiple fallers ($\geq$ 2 falls) from non-fallers in a 3-month prospective study of 101 people with MS. The TUG-C, which uses a DTW paradigm, has been reported to have 87% sensitivity and specificity among older adults (Shumway-Cook et al., 2000). They found that both assessments performed mediocrely at best (.71 $\leq$ sensitivity $\leq$ .82 and .26 $\leq$ specificity $\leq$ .34) using $\geq$ 9s for TUG and $\geq$11s for TUG-C, and the TUG-C was no better than the TUG alone. Nilsagård et al. (2009) also found that TUG-C time (not DTWC) was a significant predictor of being a faller albeit it did not perform as well as some of the other measures such as the BBS.

It is notable that studies use different timeframes and classification practices (e.g., some use $\geq$ 1 fall during a given period and some use $\geq$ 2 falls during a given [and often variable—e.g., 3 months or 6 months] period). They can also vary in the types of task used (in terms of either the walking task [e.g., variable distance, turn inclusion or not, etc.] or cognitive task) and in the operational definition of the DT variable (e.g., DTWC or DTW gait characteristics or time alone). Further, they vary in their model construction approaches. Etemadi (2017) focused on DTC predictors of fall risk whereas Gunn et al.

(2013) and Nilsagård et al. (2009) focused on a broader array of predictors of fall risk including a single measure of DTW (with only one using DTWC). Lastly, Nilsagård et al. (2009) and Quinn et al. (2019) both used only the time to complete TUG-C, not DTWC specifically, and only Quinn et al. (2019) examined TUG-C performance as a singular test for classifying fallers (not just a predictor in a classification model). A final important note in the context of fall risk and DTW is that recent evidence suggests that DT training may outperform standard physical therapy (balance and gait exercises) based on some small, randomized trials (Elwishy et al., 2020; Molhemi et al., 2017; Sosnoff et al., 2017), including reducing risk of future falls over a 3-month follow-up period (Molhemi et al., 2017).

Of note, none of these studies consider the interaction of DTWC and DTWS in predicting falls. Including both DTWS and DTWC in a single model with an interaction term allows for a fuller picture of participants' performance under DT. The reason is that DTWS alone provides information about walking performance under DT and DTWC provides information about relative effect of cognitive load on walking performance. As noted previously, two people with very different walking abilities (or performance) can have identical DTWC because the costs are not a measure of walking ability but of the change that occurs under cognitive load. It is entirely reasonable to posit that DTWC have different consequences for individuals who have different levels of walking ability under DT. That is, for someone who is a capable walker with a fast pace, it is possible that relative changes in speed under cognitive load matter differently than for someone who is a less capable walker. The need for relative slowing of gait speed under cognitive demand may very well depend on one's basic walking ability under DT. As such, modeling the interaction of DTWS and DTWC allows for a more complete picture of DTW measures as a predictor of falls rates.

Clearly, more needs to be understood regarding the relationship between DTWC and fall risk and rates among those with MS (Leone et al., 2015; Wajda & Sosnoff, 2015). The analyses performed to address Aim 4 explores how DTW outcomes relate to QoL. The analyses for Aim 5 assesses whether DTW outcomes—including the interaction of DTWC and DTWS—predict falls in people with MS using cross-sectional and longitudinal analyses.

Aim 4: Dual-Talk Walking as a Predictor of Quality of Life

South Shore Neurologic Associates, PC Analyses

In the SS data, the analysis examining how DTW outcomes relate to QoL in MS was completed using the MSIS-29—a measure of disease impact used as a proxy for QoL. The MSIS-29 contains 29 questions answered using 5-point scales to measure how impacted (1 = Not at all; 5 = Extremely) individuals feel they have been by their MS on a variety of physical and mental health issues of importance in MS over the past 2 weeks (Hobart et al., 2001). First, the scale, and other scales intended as covariates in models, were assessed psychometrically (see Chapter 3 for details and Figure 15 for scree plots). The MSIS-29 was found to have one factor using Eigenvalue cutoffs based on 100 sample parallel analysis. See Table 20 for the item loadings for the one-factor solution.

Table 20

Multiple Sclerosis Impact Scale-29 Item Loadings for One-Factor Solution

Item	Loading
In past 2 weeks, how much has MS limited your abilities…	
1. Do physically demanding tasks	0.617
2. Grip things tightly	0.679
3. Carry things	0.761
In past 2 weeks, how much have you been bothered by…	
4. Problems with your balance	0.751
5. Difficulties moving about indoors	0.715
6. Being clumsy	0.743
7. Stiffness	0.614
8. Heavy arms and/or legs	0.696
9. Tremor of your arms or legs	0.467
10. Spasms in your limbs	0.624
11. Your body not doing what you want it to do	0.810
12. Having to depend on others to do things for you	0.691
13. Limitations in your social and leisure activities at home	0.804
14. Being stuck at home more than you would like to be	0.770
15. Difficulties using your hands in everyday tasks	0.597
16. Having to cut down amount of time you spent on work or other daily activities	0.754
17. Problems using transport	0.470
18. Taking longer to do things	0.805
19. Difficulty doing things spontaneously	0.693
20. Needing to do to the toilet urgently	0.548
21. Feeling unwell	0.730
22. Problems sleeping	0.686
23. Feeling mentally fatigued	0.708
24. Worries related to your MS	0.614
25. Feeling anxious or tense	0.534
26. Feeling irritable, impatient, or short tempered	0.545
27. Problems concentrating	0.626
28. Lack of confidence	0.712
29. Feeling depressed	0.475

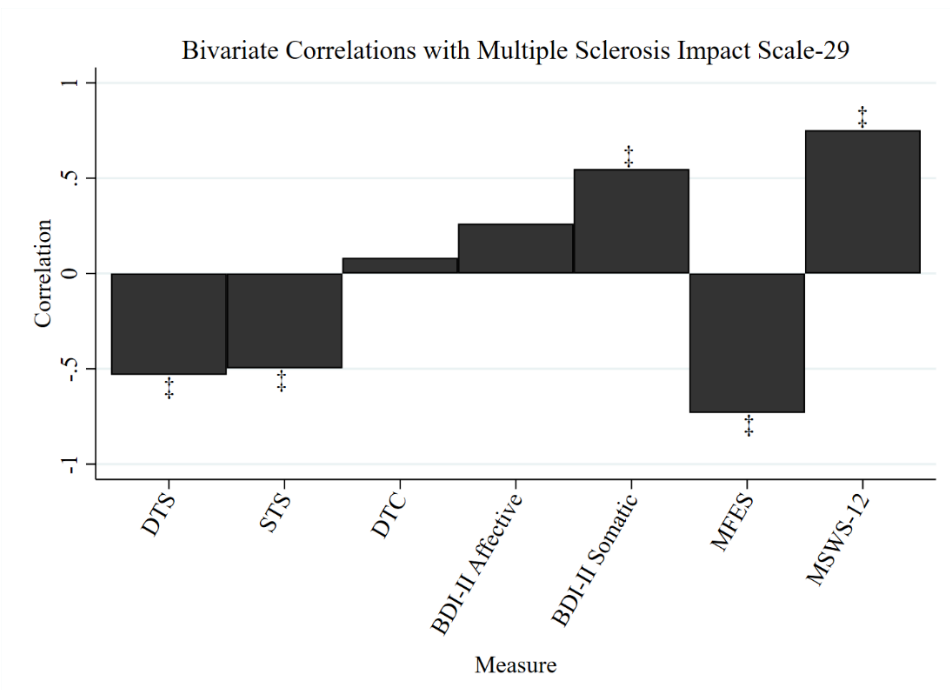
The factor scores for the MSIS-29 were used as the measure of QoL. Examining bivariate correlations, it was found that DTWS, r = -0.53, p < 0.001, but not DTWC, r = 0.08, p = 0.555, was significantly related to QoL. As a reference, the correlation between

STWS and QoL was also significant, $r = -0.50$, $p < 0.001$. Testing DTWS and STWS simultaneously in a regression model to test whether their relationships with QoL differ revealed no significant difference between the coefficients, $F(1, 51) = 0.55$, $p = 0.462$, with the total variance explained in QoL being 28%.

The correlations between the MSWS-12, $r = 0.75$, and MFES, $r = -0.73$, and QoL were very large. The correlation with the *Affective* aspect of depression was smaller, $r = 0.26$, but the *Somatic-Vegetative* factor of the BDI-II had a strong correlation with QoL, $r = 0.55$. See Figure 33 for bivariate correlations between other PROs and walk outcomes with QoL.

Figure 33

Bivariate Correlations of Walk and Patient Reported Outcomes with Multiple Sclerosis Impact Scale-29

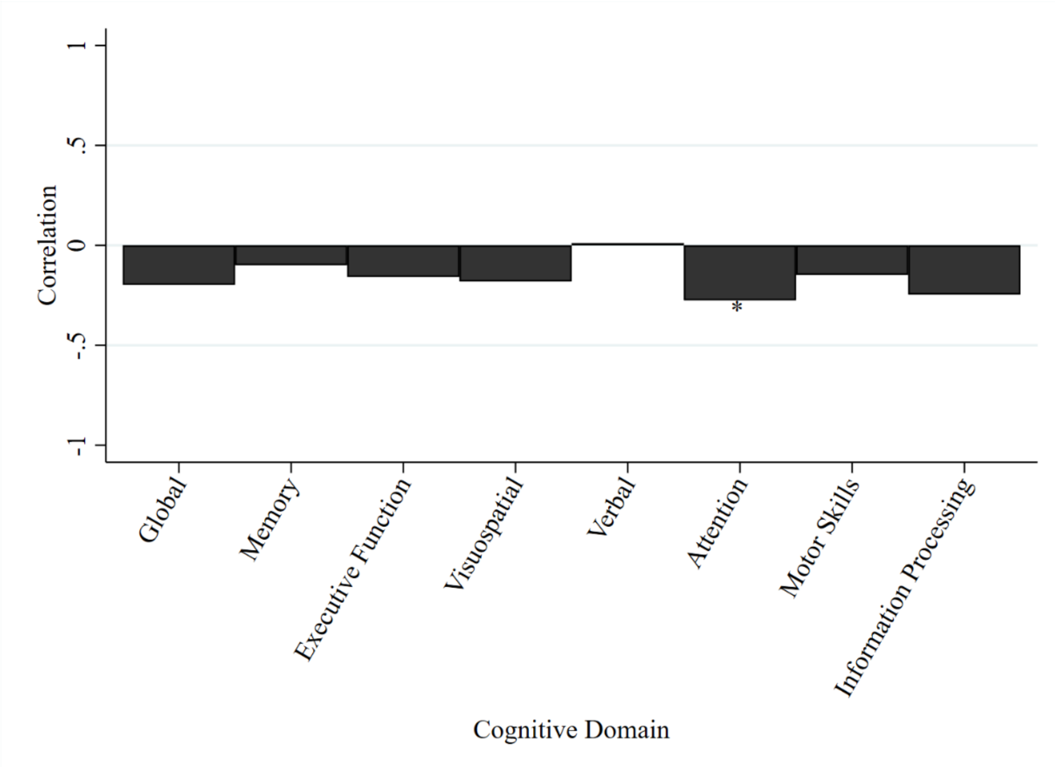


Note. DTS = Dual Task Speed; STS = Single Task Speed; DTC = Dual Task Costs; BDI-II = Beck Depression Inventory-II; MFES = Modified Falls Efficacy Scale; MSWS-12 = Multiple Sclerosis Walk Scale-12. Factor scores used for all patient-reported outcomes. ‡$p \leq 0.001$.

Of the cognitive domains measured, only Attention was significantly related with QoL, $r = -0.31$, $p = 0.023$. See Figure 34 for all correlations between cognitive measures and QoL.

Figure 34

Bivariate Correlations of Cognitive Measures with Multiple Sclerosis Impact Scale-29



Note. All cognitive domains are measures from *Neurotrax*™ cognitive battery. $^*p \leq 0.05$.

To determine whether DTW measures, particularly DTWS, predicted QoL beyond other self-report measures, factor score regressions were performed (Devlieger & Rosseel, 2017; Devlieger et al., 2019). The MFES, MSWS-12, BDI-II *Somatic-Vegetative* factor, and EDSS step were included as covariates. The EDSS step and DTW measure (DTWC in one model and DTWS in the other) were observed variables, and all others were latent variables that were estimated in the two-step process of FSR (Devlieger et al., 2019). Croon's correction and Bartlett scoring methods were implemented. Based on the alignment of all measures using only complete data, 42 observations were included in the full models. Tables 21 and 22 contain the estimates from the DTWS and DTWC models, respectively.

Table 21

Factor Score Regression Estimates for Predicting Quality of Life: Dual Task Walking Speed

Outcome **Predictor**	**Estimate**	**SE**	***z***	***p***
MSIS-29				
BDI-II Somatic	0.496	0.193	2.563	0.010
MFES	-0.109	0.052	-2.112	0.035
MSWS-12	0.550	0.189	2.903	0.004
EDSS	0.056	0.061	0.917	0.359
DTWS	-0.276	0.394	-0.707	0.480
Covariances				
BDI-II Somatic				
MFES	-0.524	0.220	-2.388	0.017
MSWS-12	0.041	0.056	0.739	0.460
MFES				
MSWS-12	-0.611	0.245	-2.493	0.013
EDSS	-0.810	0.439	-1.844	0.065
MSWS-12				
EDSS	0.842	0.259	3.247	0.001
DTWS	-0.094	0.033	-2.822	0.005
EDSS				
DTWS	-0.260	0.078	-3.330	0.001

Note. MSIS = Multiple Sclerosis Impact Scale-29; BDI-II Somatic = Beck Depression Inventory-II *Somatic-Vegetative* factor; MFES = Modified Falls Efficacy Scale; EDSS = Expanded Disability Status Scale Step; DTWS = Dual Task Walking Speed. Model fit: $\chi^2(3) = 18.239$, $p < 0.001$.

Table 22

Factor Score Regression Estimates for Predicting Quality of Life: Dual Task Walking Costs

Outcome **Predictor**	**Estimate**	**SE**	***z***	***p***
MSIS-29				
BDI-II Somatic	0.471	0.194	2.431	0.015
MFES	-0.117	0.060	-1.950	0.051
MSWS-12	0.574	0.190	3.017	0.003
EDSS	0.070	0.058	1.200	0.230
DTWC	0.099	0.580	0.170	0.865
Covariances				
BDI-II Somatic				
MFES	-0.494	0.199	-2.482	0.013
MSWS-12	0.047	0.058	0.798	0.425
MFES				
MSWS-12	-1.020	0.332	-3.074	0.002
EDSS	-1.929	0.637	-3.027	0.002
MSWS-12				
EDSS	1.120	0.334	3.349	0.001
DTWC	-0.016	0.014	-1.132	0.257
EDSS				
DTWC	-0.037	0.034	-1.098	0.272

Note. MSIS = Multiple Sclerosis Impact Scale-29; BDI-II Somatic = Beck Depression Inventory-II *Somatic-Vegetative* factor; MFES = Modified Falls Efficacy Scale; EDSS = Expanded Disability Status Scale Step; DTWC = Dual Task Walking Costs. Model fit: $\chi^2(3) = 5.544$, $p = 0.136$.

In general, these models both indicate that FSE, walking limitations, and somatic symptoms of depression are related to QoL in MS in expected ways, and each of these contributes uniquely to predicting QoL in MS. The findings indicate that higher QoL (lower MS disease impact) is predicted by lower somatic depression levels, greater FSE, and lower walking limitations controlling for the presence of the other factors. Neither EDSS step nor DTW outcomes (speed or costs) predicted QoL above these factors. Although DTWS does relate to MFES, MSWS-12, and EDSS in these models, DTWC does not.

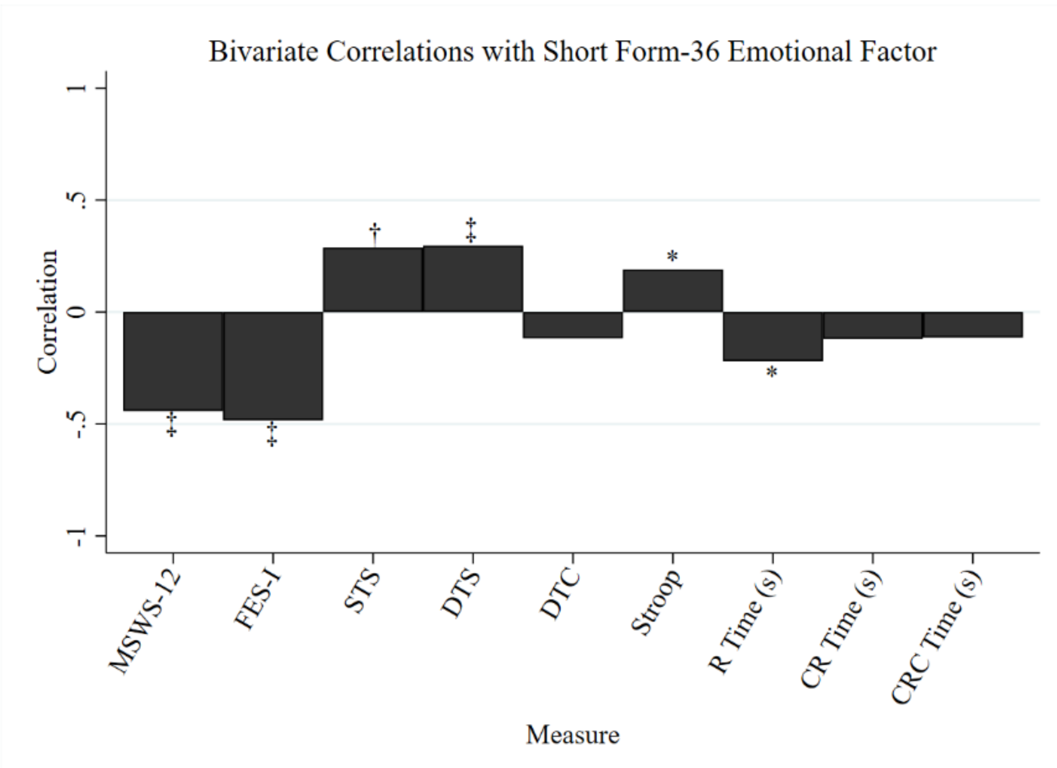
University of Kansas Medical Center Analyses

In the KUMC data, the analysis examining how DTW outcomes relate to QoL in MS was completed using the SF-36—a measure for QoL used in various populations (Brazier et al., 1992; Jenkinson et al., 1994). The SF-36 contains 36 questions that are considered to fall into eight domains (Brazier et al., 1992). Although some of its psychometric qualities are strong in MS—which was corroborated by analyses here—it may not be as responsive as other measures of QoL in MS (Hobart et al., 2005), and its factor structure in MS may not align with the scale domains or the general population structures (Hobart et al., 2001). In fact, the SF-36 was found to contain two, related factors—an emotional and physical factor (see Chapter 3, especially Figure 22 and Table 17)—using parallel analysis with 100 samples to determine minimum Eigenvalues for factor extraction. These factors were used as measures of emotional and physical QoL.

First, bivariate correlations were assessed for relationships between self-report, walk, and cognitive measures and the QoL factors. Figure 35 depicts the correlations with the *Emotional* QoL factor and Figure 36 depicts the correlations with the *Physical* QoL factor. In general, the MSWS-12 and FES-I were the strongest predictors of QoL followed by walking speeds. DTWC correlated with neither *Emotional* nor *Physical* QoL. The cognitive predictors had generally small, but sometimes significant, relationships with QoL—particularly the *Physical* factor. The relationships between STWS and DTWS and the *Emotional* QoL factor did not differ significantly when the slopes were tested in a regression model, $F(1, 108) = 0.16$, $p = 0.686$. However, the relationship between STWS and the *Physical* QoL factor was significantly stronger than the relationship between DTWS and the *Physical* QoL factor, $F(1, 108) = 11.93$, $p = 0.001$. Both walking speeds accounted for only 10% of the variance in *Emotional* QoL, but they accounted for 32% of the variance in *Physical* QoL. This could be considered a suggestion that the *Physical* QoL factor is more consistent with the MSIS-29 used in the SS study. A consideration of the item loadings (see Table 17) also suggests this could be the case, as the MSIS-29 focuses more on physical interference (22 items) than emotional interference (7 items).

Figure 35

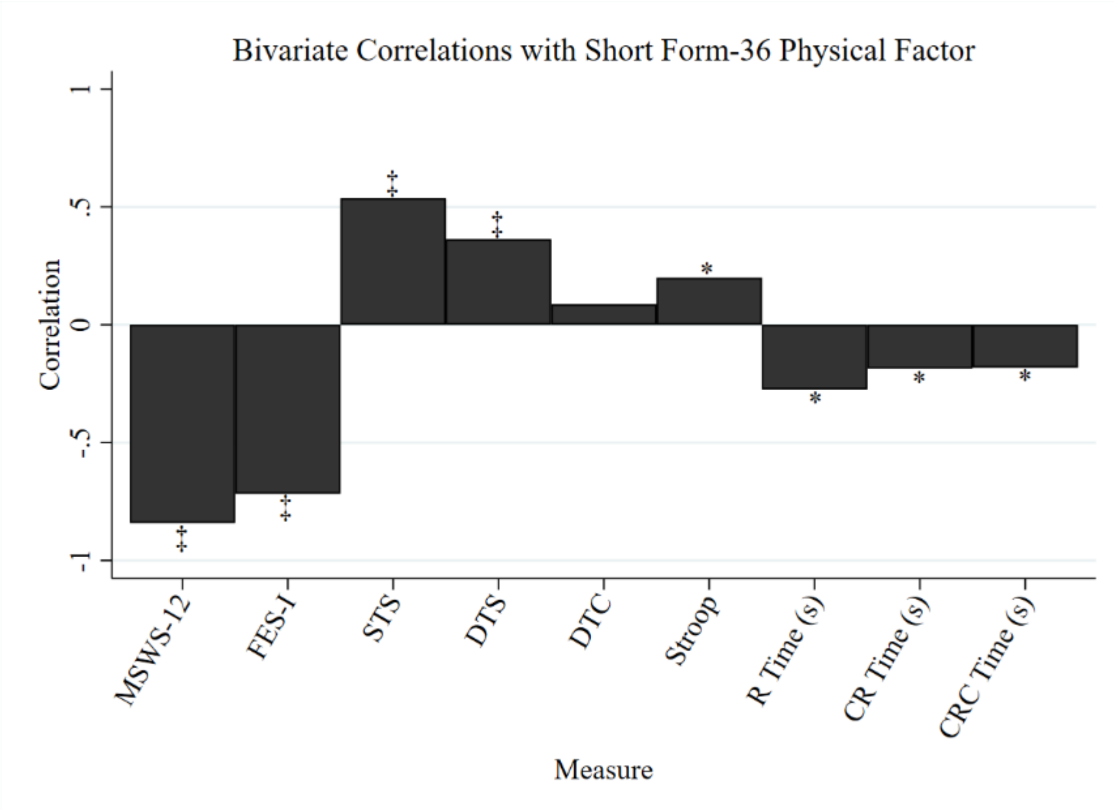
Bivariate Correlations with Short Form-36 Emotional Factor



Note. MSWS-12 = Multiple Sclerosis Walk Scale-12; FES-I = Falls Efficacy Scale-International; STS = Single Task Speed; DTS = Dual Task Speed; DTC = Dual Task Costs; Stroop = Stroop Interference task; R Time = Reaction Time; CR Time = Choice Reaction Time; CRC Time = Choice Reaction for Correct responses Time. *$0.01 < p \leq 0.05$. †$0.001 < p \leq 0.01$. ‡$p \leq 0.001$.

Figure 36

Bivariate Correlations with Short Form-36 Physical Factor



Note. MSWS-12 = Multiple Sclerosis Walk Scale-12; FES-I = Falls Efficacy Scale-International; STS = Single Task Speed; DTS = Dual Task Speed; DTC = Dual Task Costs; Stroop = Stroop Interference task; R Time = Reaction Time; CR Time = Choice Reaction Time; CRC Time = Choice Reaction for Correct responses Time. *$0.01 < p \leq 0.05$. †$0.001 < p \leq 0.01$. ‡$p \leq 0.001$.

To determine whether DTW measures, particularly DTWS, predicted QoL beyond other self-report measures, factor score regressions were performed (Devlieger & Rosseel, 2017; Devlieger et al., 2019). The FES-I, MSWS-12, and EDSS step were included as covariates. A measure of depression was not available in the study and the *Emotional* factor of the SF-36 was one of the QoL outcomes, so items from it could not be included as predictors. Items with negative loadings for the SF-36 factors in the EFA solutions were reversed scored to abet fitting. The EDSS step and DTW measure were observed variables, and all others were latent variables that were estimated in the two-step process of FSR (Devlieger et al., 2019). Croon's correction and Bartlett scoring methods were implemented. A total of 99 observations were included in the full models. Tables 23 and 24 contain the estimates from the DTWS and DTWC models, respectively.

Table 23

Factor Score Regression Estimates for Predicting Quality of Life: Dual Task Walking Speed

Outcome **Predictor**	***B***	**SE**	***z***	***p***
SF-36 *Emotional*				
FES-I	-0.825	0.332	-2.489	0.013
MSWS-12	-0.19	0.161	-1.179	0.238
EDSS	0.045	0.067	0.672	0.502
DTS	0.214	0.21	1.016	0.310
SF-36 *Physical*				
FES-I	-0.552	0.197	-2.806	0.005
MSWS-12	-0.394	0.105	-3.733	< 0.001
EDSS	0.028	0.039	0.708	0.479
DTS	0.047	0.122	0.386	0.699
Covariances				
FES-I				
MSWS-12	0.218	0.045	4.806	< 0.001
EDSS	0.205	0.048	4.296	< 0.001
DTS	-0.035	0.011	-3.293	0.010
MSWS-12				
EDSS	0.501	0.099	5.067	< 0.001
DTS	-0.076	0.022	-3.499	< 0.001
EDSS				
DTS	-0.079	0.028	-2.87	0.004
Residual Covariances				
e.SF36 *Emotional*				
e.SF36 *Physical*	0.076	0.020	3.882	< 0.001

Note. SE = Standard Error; SF36 = Short Form-36; FES-I = Falls Efficacy Scale-International; EDSS = Expanded Disability Status Scale Step; DTS = Dual Task Speed. Model just identified. No fit statistics are provided.

Table 24

Factor Score Regression Estimates for Predicting Quality of Life: Dual Task Walking Costs

Outcome **Predictor**	**Estimate**	**SE**	***z***	***p***
SF-36 *Emotional*				
FES-I	-0.842	0.331	-2.539	0.011
MSWS-12	-0.214	0.162	-1.322	0.186
EDSS	0.042	0.067	0.62	0.535
DTC	-0.004	0.004	-1.044	0.296
SF-36 *Physical*				
FES-I	-0.561	0.197	-2.852	0.004
MSWS-12	-0.395	0.105	-3.75	< 0.001
EDSS	0.027	0.039	0.692	0.489
DTC	0.001	0.002	0.326	0.745
Covariances				
FES-I				
MSWS-12	0.218	0.045	4.806	< 0.001
EDSS	0.205	0.048	4.296	< 0.001
DTC	-0.06	0.476	-0.126	0.900
MSWS-12				
EDSS	0.501	0.099	5.067	< 0.001
DTC	-0.437	0.983	-0.444	0.657
EDSS				
DTC	-0.453	1.332	-0.34	0.734
Residual Covariances				
e.SF36 *Emotional*				
e.SF36 *Physical*	0.077	0.020	3.904	< 0.001

Note. SE = Standard Error; SF36 = Short Form-36; FES-I = Falls Efficacy Scale-International; EDSS = Expanded Disability Status Scale Step; DTC = Dual Task Costs. Model just identified. No fit statistics are provided.

In general, these models both confirm the importance of FSE and walking limitations for QoL in MS in expected ways. However, only the FES-I, not the MSWS-12, related to both *Emotional* and *Physical* QoL factors. The findings indicate that higher QoL is predicted by less concern about falling (i.e., greater FSE) and less walking limitations controlling for the presence of the other factors. Neither EDSS step nor DTW outcomes (speed or costs) predicted QoL above these factors. Although DTWS does relate to FES-I, MSWS-12, and EDSS in these models, DTWC does not.

Aim 5: Dual-Task Walking as a Predictor of Falls Reported Longitudinally (KUMC)

Although self-reported QoL is clearly an important outcome, it is not the only outcome of consequence in the context of MS generally or DTW research specifically. Another very important distal outcome is falling. Falls are common experience in MS (Gunn et al., 2014; Nilsagård et al., 2015). Most people with MS will experience a fall (Gunn et al., 2014; Nilsagård et al., 2015), and 37% of those with MS are considered “frequent fallers” (Nilsagård et al., 2015). Falls in MS are also more likely to result in injury (Bazelier et al., 2012; Peterson et al., 2008) and death (Brønnum-Hansen et al., 2006) than falls among matched controls. In our study, although the sample was highly functional in general (e.g., STWS: M = 1.25, SD = 0.25), over one-third of participants had experienced a fall in the past six months when the study began (see Table 11 for more). Given the focality of fall risk in the nexus of DTW issues in its historical conceptualization (e.g., Lundin-Olsson, 1997), it seems worthwhile to examine whether falling is predicted by DTW measures. Although there is a handful of studies that have explored this relationship, the findings remain mixed. Using the data collected over 6-month intervals for an 18-month period at KUMC, longitudinal, negative binomial regression models were performed to assess whether DTW outcomes predict fall rates above-and-beyond basic physical ability (e.g., T25FWT time). This is a key consideration because DTW paradigms can be administered almost as easily and readily as STW paradigms, so if DTW outcomes can predict fall rates better than basic walking ability measured in ST conditions, their use may be warranted more regularly in MS evaluation.

Assumption Checks

Given these models were assessed longitudinally and there was a great deal of attrition across visits, predictors of attrition were evaluated. Given nearly all the attrition occurred after the baseline visit, attrition was binarized (0 = Completed All Visits; 1 = Did Not Complete All Visits). Logistic regression models were performed to test whether a variety of factors of importance predicted attrition. DTWC was not a predictor of attrition throughout the study, OR = 1.006, $\chi^2(1, n = 122) = 0.19$, $p = 0.667$. However, DTWS, OR = 0.06, $\chi^2(1, n = 122) = 11.90$, $p < 0.001$, McFadden's $R^2 = 0.09$, and STWS, OR = 0.01, $\chi^2(1, n = 122) = 20.38$, $p < 0.001$, McFadden's $R^2 = 0.14$, were both significant predictors of attrition. The odds ratios show that the likelihood of dropping out of the study decreased for those who had faster walk speeds in DT and ST conditions. Similarly, other measures of function indicate that more functional participants were more likely to complete all visits, see Table 25. Of note, falls reported at baseline was not a significant predictor of attrition. For visualizations of DTWS, EDSS, and other functional measures across visits, see Figures 37-39, respectively.

Table 25

Predictors of Attrition in KUMC Study

Predictor	*n*	OR	SE	*z*	*p*
DTWC	122	1.01	0.015	0.43	0.667
DTWS	122	0.06	0.049	-3.39	0.001
STWS	122	0.01	0.014	-3.92	< 0.001
T25FWT	122	4.00	1.317	4.22	< 0.001
BBS	112	0.77	0.084	-2.40	0.016
Stroop	120	0.89	0.040	-2.61	0.009
React	121	40.90	89.443	1.70	0.090
FES-I	119	2.48	0.739	3.05	0.002
MSWS-12	120	2.75	0.817	3.41	0.001
ABC-Hard	119	0.422	0.113	-3.22	0.001
EDSS	120	1.57	0.312	2.26	0.024
Falls	119	1.28	0.186	1.70	0.090

Note. OR = Odds Ratio; SE = Standard Error; DTWC = Dual Task Walking Costs (%); DTWS = Dual Task Walking Speed (m/s); STWS = Single Task Walking Speed (m/s); T25FWT = Timed 25 Foot Walk Test (s); BBS = Berg Balance Scale; Stroop = Stroop Interference task; React = Reaction Time (s); FES-I = Falls Efficacy Scale-International; MSWS-12; Multiple Sclerosis Walk Scale-12; ABC = Activities-specific Balance Confidence scale; EDSS = Expanded Disability Status Scale Step. Factor scores used for scales.

Figure 37

Boxplots for Expanded Disability Status Scale Step by Visit for KUMC

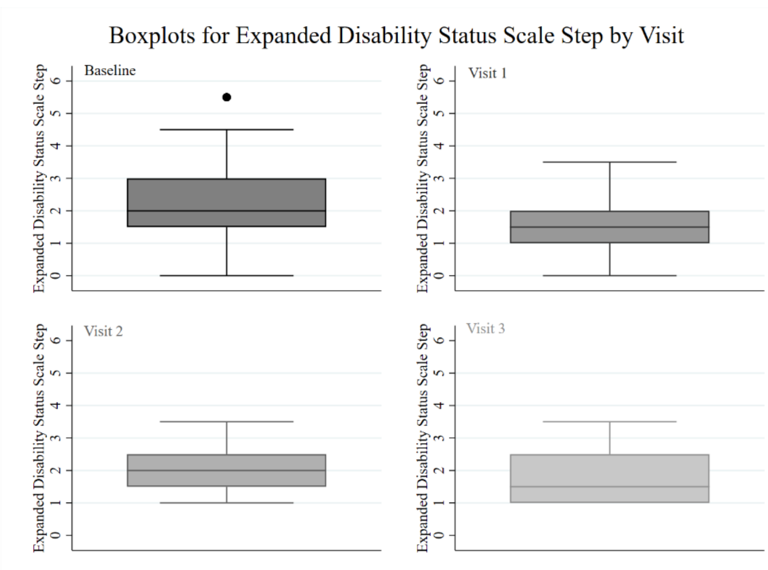


Figure 38

Boxplots for Dual Task Walking Speed by Visit for KUMC

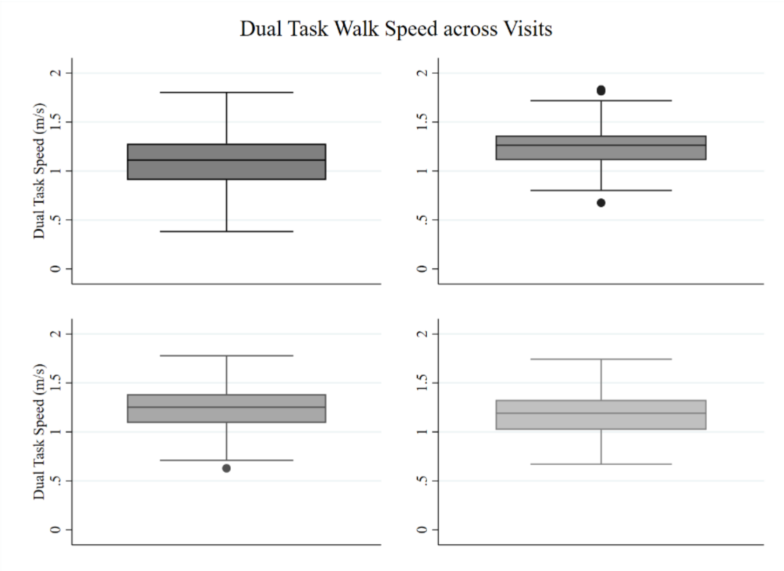
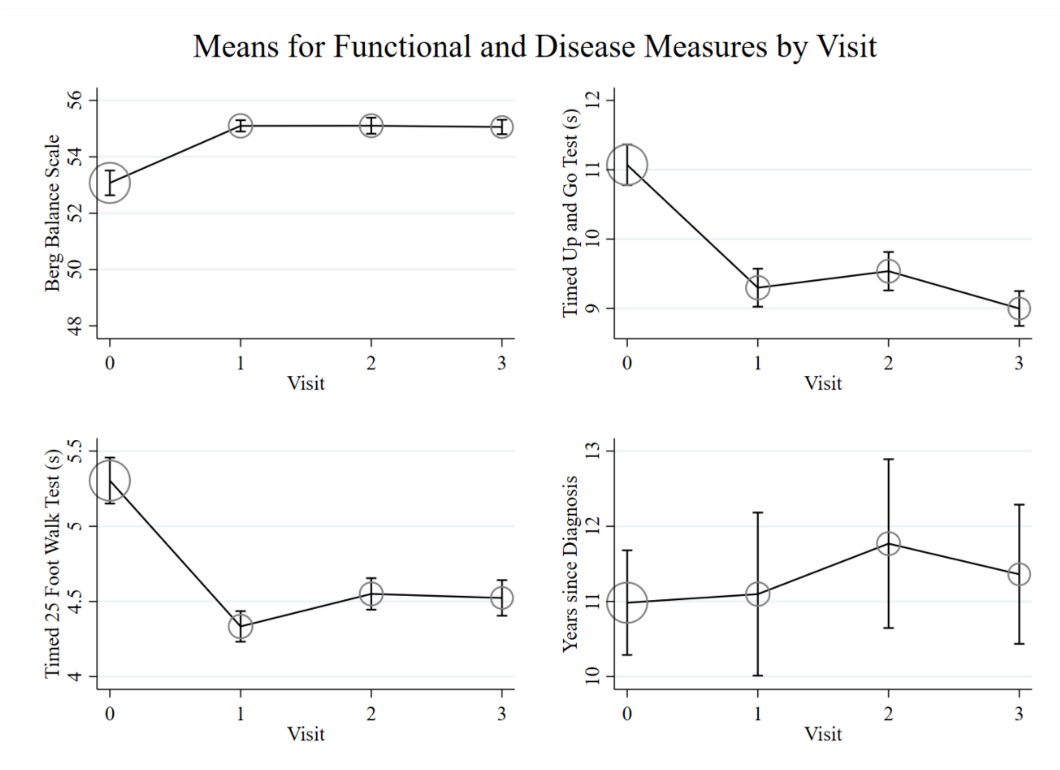


Figure 39

Measures of Function across Visits in KUMC Study



Note. Markers are weighted by sample size.

Further, estimates of repeated administration reliability were computed using ICC with random intercepts in the full information maximum likelihood model. Both STWS, ICC = 0.841, 95% CI[0.778, 0.888], and DTWS, ICC = 0.776, 95% CI[0.694, 0.842], were rather reliable across visits. As comparisons given the presence of four walk conditions in the testing, *fast* walk speed was the most reliable across visits, ICC = 0.875, 95% CI[0.825, 0.913], and *slow* walk speed was the least—but still reasonably—reliable across visits, ICC = 0.605, 95% CI[0.493, 0.717]. These patterns of reliability are reasonable with the order of ICC magnitudes being fast, single, dual, and slow indicating that participants had the most consistent walk speeds for fast and regular walking, but reliability decreased some with DT and even more when trying to walk as slow as possible.

Results

To test whether DTW measures predicted falls cross-sectionally, negative binomial regression models were performed with the count of falls reported at baseline serving as the outcome. Basic abilities—physical and cognitive—were considered as covariates to determine whether DTW measures predicted falls above-and-beyond such measures. These measures were selected *a priori* and included the T25FWT, Reaction Time, and performance on the Stroop interference task. DTWS and DTWC were considered separately *and* interactively.

The results indicate that the overdispersion model was significantly better than assuming Poisson distributional characteristics (i.e., $\alpha = 0$) for all models: DTWS Only, $\chi^2(1) = 603.12$, $p < 0.001$; DTWC Only, $\chi^2(1) = 728.24$, $p < 0.001$; Interaction Model, $\chi^2(1) = 361.74$, $p < 0.001$. At baseline only, DTWS was the only significant predictor of falls rates in the full model when included. If DTWC alone was included with the covariates, only T25FWT time significantly predicted falls rates. However, when both DTWS and DTWC were included, the effect of DTWS, DTWC, and the interaction between them were statistically significant predictors above-and-beyond the covariates (which were not significant in the presence of DTW measures; see Table 26). These models were followed-up with mixed effects negative binomial regression models to determine whether these relationships persisted when modeled across visits with person as a random factor. These models used person-centered means and deviations (Curran & Bauer, 2011) and included the interaction the person-means for DTWS and DTWC. Models again confirmed the appropriateness of overdispersion, DTWS Only, $\chi^2(1) = 22.88$, $p < 0.001$; DTWC Only, $\chi^2(1) = 24.43$, $p < 0.001$; Interaction Model, $\chi^2(1) = 21.31$, $p < 0.001$. The substantive findings also corroborate those of the baseline only, cross-sectional models (see Table 27). The only notable difference was the between-persons effect of DTWS was not quite statistically significant in the longitudinal model in the DTWS only model.

Table 26

Negative Binomial Regressions to Predict Falls Rates at Baseline Only

Predictor	IRR	SE	*z*	*p*
Model with DTWS Only				
T25FWT (s)	1.14	0.322	0.47	0.635
Reaction Time (s)	0.56	1.440	-0.22	0.822
Stroop Interference	0.98	0.055	-0.33	0.741
DTWS	0.02	0.027	-3.10	0.002*
Model with DTWC Only				
T25FWT (s)	2.13	0.618	2.61	0.009*
Reaction Time (s)	0.16	0.458	-0.65	0.518
Stroop Interference	0.94	0.055	-1.01	0.312
DTWC	1.00	0.025	-0.18	0.859

Model with Interaction				
T25FWT (s)	0.93	0.226	-0.30	0.762
Reaction Time (s)	0.498	1.177	-0.29	0.768
Stroop Interference	0.98	0.047	-0.33	0.741
DTWS	0.001	0.001	-4.39	< 0.001*
DTWC	0.77	0.068	-2.99	0.003*
DTWS*DTWC	1.20	0.097	2.30	0.021*

Note. IRR = Incidence Rate Ratio; SE = Standard Error; T25FWT = Timed 25 Foot Walk Test (s); DTWS = Dual Task Walking Speed (m/s); DTWC = Dual Task Walking Costs (%). DTWS Model: $\chi^2(4, n = 117) = 20.89$, $p < 0.001$, McFadden's $R^2 = 0.06$, Cragg & Uhler's $R^2 = 0.172$. DTWC Model: $\chi^2(4, n = 117) = 11.86$, $p = 0.018$, McFadden's $R^2 = 0.03$, Cragg & Uhler's $R^2 = 0.101$. Interaction Model: $\chi^2(6, n = 117) = 31.46$, $p < 0.001$, McFadden's $R^2 = 0.09$, Cragg & Uhler's $R^2 = 0.248$. $*p \leq 0.05$.

Table 27

Mixed Effects Negative Binomial Regressions to Predict Falls Rates across Visits

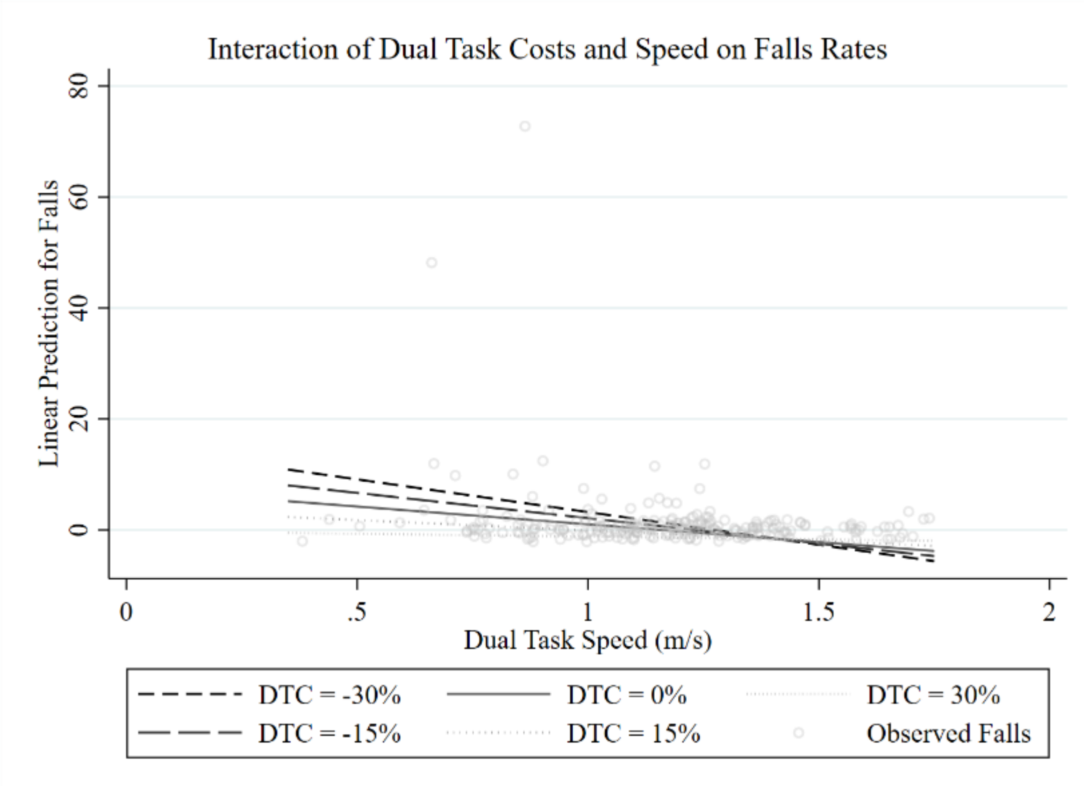
Predictor	IRR	SE	*z*	*p*
Model with DTWS Only				
Visit	0.882	0.166	-0.670	0.504
T25FWT (s) – PM	1.302	0.268	1.280	0.199
T25FWT (s) – PD	0.730	0.456	-0.500	0.614
Reaction Time (s) – PM	0.736	1.680	-0.130	0.893
Reaction Time (s) – PD	0.083	0.434	-0.480	0.633
Stroop Interference – PM	0.906	0.052	-1.710	0.088
Stroop Interference – PD	1.056	0.083	0.690	0.489
DTWS – PM	0.107	0.133	-1.800	0.071
DTWS – PD	0.583	1.014	-0.310	0.756
Model with DTWC Only				
Visit	0.895	0.164	-0.610	0.542
T25FWT (s) – PM	1.623	0.280	2.810	0.005*
T25FWT (s) – PD	0.753	0.482	-0.440	0.658
Reaction Time (s) – PM	0.814	1.889	-0.090	0.929
Reaction Time (s) – PD	0.100	0.517	-0.450	0.656
Stroop Interference – PM	0.884	0.053	-2.050	0.040*
Stroop Interference – PD	1.049	0.084	0.590	0.553
DTWC – PM	0.989	0.021	-0.530	0.594
DTWC – PD	0.995	0.026	-0.200	0.841
Model with Interaction				
Visit	0.894	0.161	-0.620	0.534
T25FWT (s) – PM	1.132	0.256	0.550	0.581
T25FWT (s) – PD	0.772	0.469	-0.430	0.670
Reaction Time (s) – PM	0.230	0.501	-0.670	0.500
Reaction Time (s) – PD	0.071	0.353	-0.530	0.596
Stroop Interference – PM	0.912	0.049	-1.740	0.083
Stroop Interference – PD	1.044	0.077	0.580	0.559
DTWS – PM	0.001	0.002	-3.860	< 0.001*
DTWS – PD	0.168	0.432	-0.690	0.488
DTWC – PM	0.735	0.068	-3.330	0.001*
DTWC – PD	0.977	0.037	-0.610	0.540
DTWS*DTWC – PM	1.264	0.109	2.710	0.007*

Note. IRR = Incidence Rate Ratio; SE = Standard Error; PM = Person Mean; PD = Person Deviation; T25FWT = Timed 25 Foot Walk Test (s); DTWS = Dual Task Walking Speed (m/s); DTWC = Dual Task Walking Costs (%). DTWS Model: $\chi^2(9, n_j = 120, n_i = 227) = 28.41$, $p < 0.001$, AIC = 489.60. DTWC Model: $\chi^2(9, n_j = 120, n_i = 227) = 25.37$, $p = 0.003$, AIC = 492.62. Interaction Model: $\chi^2(12, n_j = 120, n_i = 227) = 42.81$, $p < 0.001$, AIC = 480.34. *$p \leq 0.05$.

Examining the substantive nature of the interaction reveals that controlling for all other factors, faster DTWS predicts fewer falls between persons, higher DTWC predicts fewer falls between persons, but the effect of DTWC is moderated by DTWS such that as DTWS increases lesser DTWC predicts fewer falls (see Figure 40). Basically, for those who are capable walkers under DT conditions (i.e., can maintain a fast speed), it appears to be desirable to have minimal DTWC (or even experience cognitive-motor facilitation). However, for those who are not capable walkers under DT conditions (i.e., cannot maintain a fast speed), the model prediction is such that greater DTWC are protective against falls. Essentially, those who are most affected in terms of their DTWS (i.e., slower) are benefitted by a greater relative slowing under DT compared to ST (i.e., higher DTWC). This suggests that the added demands of a cognitive task while walking should be approached cautiously by those who are less capable walkers but do not merit a particular alteration in walking speed for those who are more capable walkers. Of note, the inflection point for the interaction comes around a DTWS of 1.4 m/s – a fast pace under DT.

Figure 40

Interaction of Dual-Task Costs and Dual-Task Speed on Fall Rates



Note. DTC = Dual Task Costs.

Discussion

These findings help to fill the gap in understanding how DTW measures fit into the nexus of constructs that are important in MS (Leone et al., 2015; Rooney et al., 2020). Although both the SS and KUMC analyses found that DTW measures are not significantly related to QoL above-and-beyond other PROs, bivariate relationships between DTWS, but not DTWC, and QoL measures did exist in both analyses. These findings are both useful as the most recent meta-analysis of correlates of DTW measures conducted by Rooney et al. (2020) did not report any estimates of the relationship between DTW measures and QoL. Castelli et al. (2016) did report that some items on the

MSQoL-54 correlated with DTWC, but only specific items and in a sample with low levels of disability (EDSS ≤ 3).

The finding that DTWS, but not DTWC, relates to other variables of important in MS is consistent with findings in Chapters 3 and 4. DTWS, but not DTWC, is regularly the measure that relates to other important domains in MS. Yet, DTWS did not relate to QoL more strongly than STWS when the coefficients were tested against one another, so it does not seem that DTWS adds more to the prediction of QoL than STWS alone. In fact, for the *Physical* QoL factor from the SF-36 in the KUMC analyses, STWS was a significantly better predictor than DTWS. The analyses indicate that predicting QoL in MS was done best by using other self-reported outcomes, such as measures of FSE or walking limitations. This is consistent with past research in MS (Mitchell et al., 2005). This may be a function of the true dependence of the constructs evaluated by these measures, but it also may be a partial artifact of the measurement of these constructs. That is, it is possible that these self-reported outcomes simply correlated based on participants' tendencies to respond in particular ways when completing the assessments (e.g., optimistic or pessimistic assessments). DTW outcomes were variably and modestly related to QoL outcomes, with *walking speed* under ST and DT conditions being a predictor of QoL but not DTWC. The relationship between walking speed and QoL—especially physical aspects of it—has been shown in other populations affected by neurological disorders (Khanittanuphong & Tipchatyotin, 2017; Paker et al., 2015) and MS previously (Kohn et al., 2014). For example, T25FWT have been found to be correlated with QoL measures in various MS studies (Cohen et al., 2014; Coleman et al., 2012; Goldman et al., 2013; Hobart et al., 2013; Kragt et al., 2006; Motl et al., 2017). In fact, it has been called the “6th vital sign” because of its robust relationships with measures of health and wellbeing (Middleton et al., 2014).

Perhaps more importantly, the analyses of falls in the KUMC study suggests that DTW measures do add to the prediction of falls rates above-and-beyond basic physical and cognitive measures. As was true in all past analyses, DTWS is the single DTW measure that seems to be useful in predicting falls when DTWS and DTWC are treated separately. However, it was found that DTWC *does add significantly* to a falls prediction model when it is considered *within the context of DTWS*. Moreover, it was found that these two measures interacted in predicting falls rates. Consistent with the repeated assertion about the limitations of DTWC treated as an isolated measure in DTW paradigms, these results indicate that DTWC alone is not particularly useful *because it must be understood in the context of the individuals’ actual abilities*. The fact that DTWC is standardized by STWS actually removes valuable information regarding a participants’ actual walking abilities. Considering it in the context of DTW abilities as measured by DTWS allows for a greater understanding of the possible importance of DTWC. In fact, when considered in the context of DTWS, DTWC becomes a useful measure for predicting falls. The fact that it is moderated by DTWS also can explain the mixed findings regarding the relationship between DTWC and falls in the extant literature (e.g., Cattaneo et al., 2006; Gunn et al., 2013; Hoang et al., 2016; Nilsagård et al., 2009; Quinn et al., 2018, 2019; Wajda et al., 2013). This analysis reveals that high DTWC may be advantageous for the least capable DT walkers but disadvantageous for the most capable DT walkers. This suggests that one must know about a participant’s abilities when engaging in DTW to understand the effect of DTWC. Future analyses should consider whether similar interactive relationships exist between DTWS and DTWC for other putative outcomes.

There are several important limitations for these analyses. First, the sample sizes are rather small for the analyses performed. Although factor score regression has been studied in small samples (e.g., n = 50; Devlieger et al., 2019), with only 42 and 99 participants in the SS and KUMC studies, respectively, this limitation should still be noted. Further, negative binomial regression—and particularly mixed effects forms—are best for large samples. The KUMC sample, albeit relatively large for research in this area, is small in the context of such models, and there was also a high level of attrition which poses an additional, noteworthy limitation for the longitudinal models. Also, the falls reports were collected every six months, but they were retrospective at each visit. As such, the limits of recollection for reporting falls should be acknowledged even though retrospective and prospective falls do tend to correlate (Nilsagård et al., 2009) with underestimation indicated for retrospective reports of falls (Mackenzie et al., 2006).

Nevertheless, these findings provide novel insights into the role of DTW measures for predicting critical outcomes in MS. These findings indicate that improving DTW may not directly affect self-reported QoL above-and-beyond other, more predictive measures of QoL. However, the findings indicate that unique strategies may be most beneficial in helping those with MS to avoid falling when engaging in the everyday phenomenon on DTW. It may be advantageous for those who have more limited walking abilities to *slow down more* in the face of DT—which is not a particularly surprising finding. However, those with MS who are still not very limited in their walking abilities should be encouraged to tackle these complex DTW conditions when they manifest in life by just trying to maintain a normal walking speed. Additional caution in the face of DTW demands may not be desirable for all persons with MS.

CHAPTER 5

Multiple sclerosis is a disease with manifold symptoms that affects approximately 1 million people in the United States (Wallin et al., 2019). It usually onsets in young adulthood and can result in many years of disability (Tullman et al., 2013) with symptoms that often increase over time (Kister et al., 2013), including weakness, spasticity, fatigue, and undesirable changes in sensation, cognition, vision, coordination, bladder function, sexual function, and mood and psychological states (Crayton & Rossman, 2006). Mood (Siegert & Abernethy, 2005; Siegert & Abernethy, 2005), cognitive (Chiaravolloti & DeLuc, 2008; Rocca et al., 2015), and walking and balance (Cameron & Nilsagård, 2018) problems are common, and decreased function and independence resultant from trouble walking is a central concern to those affected by MS (Heesen et al., 2008; LaRocca, 2011; Zwibel, 2009). Those with MS also have high rates of fear of falling given the issues with balance and walking that occur (Comber et al., 2017; Peterson et al., 2007), and this can result in even greater losses of independence, activity curtailment, and decreases in QoL (Peterson et al., 2007). These alterations may even extend beyond what is necessary—as falling is certainly a greater risk for this with MS (Gunn et al., 2014; Nilsagård et al., 2015)—given that FSE may be low despite relatively intact physical ability (Gunn et al., 2018). This is just one of several examples regarding how these multifarious symptoms intersect to affect important distal outcomes like independence, falls, and QoL.

Not only may these diverse symptoms interact in MS, but many activities in daily life are affected by the intersection of psychological, cognitive, and physical functions. DTW is a paradigm that allows some exploration of these intersections as they may occur in real-world contexts where one engages in a social or cognitive task concurrently with walking (Bayot et al., 2018; Mirelman et al., 2018). Not only is DTW ubiquitous in daily life, but the fact that it impacts walking generally (Mirelman et al., 2018) and in MS specifically (Leone et al., 2015; Postigo-Alonso et al., 2018) is well-established. DTW is reasonably believed to be associated with falls, and although evidence is mixed, classic work (Lundin-Olsson et al., 1997) and more recent work in MS (Etemadi, 2017; Quinn et al., 2019) does suggest that it may relate to fall risk. Of course, DTW also occurs at the intersection of multiple functional abilities that may be affected by MS which makes considering how other psychological and cognitive states may factor into a full understanding of DTW in MS. Despite the importance of DTW performance and its presumed interaction with other affective and cognitive participant characteristics, these relationships have not been well described in the literature. The aims of these analyses were to explore the intersections of psychological, cognitive, and physical variables in the context of DTW in those affected by MS in order to understand: 1) correlates of DTW outcomes across various domains, 2) moderating effects of psychological states in predicting DTW outcomes as a function of cognitive and physical abilities, and 3) understanding how DTW outcomes relate to and predict distal outcomes like QoL and falls in those affected by MS.

These aims attempted to address gaps in the current corpus of scientific knowledge regarding understanding the correlates and consequences of DTW ability (Leone et al., 2015; Rooney et al., 2020)—particularly how the "invisible symptoms" (Leone et al., 2015, p. 128) that are important in MS fit into our understanding of DTW. Current DTW analyses include a variety of means of operationalization DT effects. As such, the current research included a few operationalizations of DTW to evaluate which may be most robustly related to other outcomes of importance in MS. This included examining DTWS alone—as walking speed is a valuable measure in MS (Albrecht et al., 2001; Briggs et al., 2019; D'Orio et al., 2012; Kalron, 2014; Kalron & Achrion, 2014; Langeskov-Christensen et al., 2017) and given that change in speed is one of, if not the, most robust and reliable gait parameters affected by DTW (Chen et al., 2020; Leone et al., 2015; Mirelman et al., 2018; Postigo-Alonso et al., 2018; Wajda & Sosnoff, 2015). It also included use of both a commonly calculated DTW outcome, DTWC, based on Baddeley et al.'s (1997) formula, and the use of other metrics that are often used, too—such as raw differences in DTWS (as is done when condition [ST or DT] is treated as a within-subjects factor) and DTWS itself, because these metrics contain different information and likely have unique limitations.

Further, the SAT (Self-Awareness Theory; Wajda & Sosnoff, 2015; Wajda et al., 2019; Yogev-Seligmann et al., 2012) was tested as an explanatory model that may enhance our understanding of DTW outcomes. This theory purports that appraisals of one's abilities and environmental hazards affect the prioritizations and performances of individuals in DTW contexts (Yogev-Seligmann et al., 2012). This could be conceptualized as a specific extension of reciprocal determinism which posits that a person's beliefs about their abilities—self-efficacy—is one important person-level factor that affects the dynamic interplay of environment-behavior relationships (Bandura, 1978, 1994). As such, person-level psychological states—like FSE and depression—were evaluated as moderators of the relationships between basic physical and cognitive abilities and performance under more complex environmental demands in DTW.

The findings of the present analyses, therefore, add to the understanding of DTW in MS in numerous ways. The ability to add to the corpus of literature on the topic was furthered by the availability of two, relatively large, independent samples of people with MS completing DTW—a research sample from KUMC and a clinical sample from SS. This permitted both unique evaluations and conceptual replications.

First, across all analyses, the evidence indicates that measuring DTWS—perhaps unsurprisingly—is a more reliable contributor to understanding relationships among DTW ability and other variables of importance in MS than measuring DTWC. Walking speed is known to be an important variable in MS (Albrecht et al., 2001; Briggs et al., 2019; D'Orio et al., 2012; Kalron, 2014; Kalron & Achiron, 2014). It may even be a better measure of disease progression than the ability to walk certain distances (Albrecht et al., 2001), which is focal in the most common means of assessing disability in MS, the EDSS (van Munster & Uitdehaag, 2017). Although DTWC, in the form of DTC proposed by Baddeley et al. (1997), is a reasonable means of assessing the impact of DT, it may not be the best means by which DTW can be understood in the nexus of MS symptomatology. DTWC, because it standardizes the difference in speed by STWS, actually removes information about walking performance. As such, two individuals with very different walking abilities can have identical DTWC—whether they be large or small. DTWC actually captures a cognitive construct; that is, it measures the percentage change caused by concurrent cognitive demand. It is reasonable that DTC captures a cognitive construct given their historical roots in neuropsychology (Baddeley et al., 1997; Hanny, 1986) and the intention to determine the degree to which an action is automatic or effortful. This, again, is a cognitive—or at least computational—question, not a physical one. This is also why the dominant theories involved in DT literature (Bayot et al., 2018) have been, first, cognitive (e.g., attentional capacity), and then neural (e.g., bottleneck theory). Although often unmeasured (for relevant reviews, see Chamard Witkowski et al., 2019; Leone et al., 2015; Postigo-Alonso et al., 2018; Wajda & Sosnoff, 2015), DTCC may be a better "motor" measure (e.g., to measure the attentional demand of walking in MS) as it quantifies the impact of concurrent *ambulation* on cognition.

Although it is worthwhile to ask, as most have done (for reviews, see Leone et al., 2015; Postigo-Alonso et al., 2018), whether DTWC exist in MS and whether the effects differ from those in neurotypical populations, it also seems worthwhile to understand how DTW ability fits into the tapestry of MS symptoms and risks (e.g., Leone et al., 2015; Rooney et al., 2020; Wajda & Sosnoff, 2015). The research clearly shows that DTWC exist in MS (Leone et al., 2015; Postigo-Alonso et al., 2018), but the findings are mixed regarding whether these costs are greater than in neurotypical populations. Consistent with past research, these analyses confirmed the presence of DTWC in both samples—and in degrees that would be expected. They also found that DTWC do not tend to be a particularly strong correlate of other variables often measured in MS. However, DTWS was found to be related to many variables—including cognitive domains like executive function and attention and physical domains like self-reported pain, balance, and disability. DTWS also seems to relate to variables that are found to relate to both STWS and DTWC (when the latter did exhibit any relationships). As such, it seems that DTWS may provide more information that STWS alone—not just related to more variables than DTWC.

These analyses also help to reveal how DTW outcomes relate to various cognitive measures—something that has been notably absent from the DTW literature in MS (Leone et al., 2015; Rooney et al., 2020). The analyses suggest that DTWS is rather more reliably and robustly predicted by cognitive abilities and physical factors (with pain, balance, and disability emerging as particularly relevant) than DTWC. Not only were various cognitive domains related to DTWS, most notably executive function and attention, but these analyses were the first to consider multiple cognitive predictors of DTW outcomes in singular models. These models revealed unique patterns of relationships that highlight the need to consider the intersections and interactions of different cognitive abilities when attempting to understand their relationships with DTW outcomes. They also emphasize a need to consider the possible overlap in measurement that may lead to measurement variance artifacts (e.g., see Lancaster, 1999). However, although DTWS, but not DTWC, did relate to QoL at a bivariate level—consistent with past research indicating that walking speed relates to QoL in MS (Kohn et al., 2014), DTW outcomes did not predict QoL above-and-beyond self-report measures of walking interference, FSE, or depression—although these covariates did predict QoL as in past research (Mitchell et al., 2005).

The primacy of DTWS—as conceptualized a priori and manifested throughout the analyses—makes it worth noting that there is no reason to assume that walking speed should always be measured in ST contexts. There are innumerable cases in which "walking *and*" occurs in daily life, so performance in such contexts is reasonable to assess. Similarly, there is no inherent reason that DTW ability must be measured by referencing STWS. DTWS, both theoretically and based on these empirical findings, is a construct that seems valuable to measure in MS. This was not only evidenced by the models that examined predictors of DTWS and DTWC, but it is also clear when daily experiences are considered that performance measures (e.g., actual gait parameters) will be critical to understanding the consequences of DTW, too. That is, whether one slows substantially or not relative to one's "normal" walking speed may not be as important as the actual speed at which one is walking under DT conditions. And it is entirely possible, and indicated throughout these analyses, that DTWS may be more informative than STWS in many ways. Although it is possible that relative slowing, or even relative slowing standardized by STWS, would matter on its own, the evidence in the literature (Leone et al., 2015; Rooney et al., 2020; Wajda & Sosnoff, 2015) and from these studies indicates that DTWC is not a strong or reliable correlate of other variables in MS when considered in isolation. However, the current analyses indicated that it may add to our ability to understand consequences of DTW such as fall rates. Although the findings regarding DTW and fall risk in MS have been mixed (Etemadi, 2017; Gunn et al., 2013; Nilsagård et al., 2009; Quinn et al., 2019; Wajda et al., 2013), and, notably, have used different operationalizations of DTW (e.g., DTWC versus DTWS), the present analyses may help shed light on these mixed findings.

First, if considered in isolation, DTWS emerged as a better predictor of fall rates than STWS (measured by the T25FWT). Second, although DTWC was not a significant predictor of fall rates when considered in isolation, both DTWS and DTWC, as well as the interaction, all emerged as significant—with basic cognitive and walking measures not contributing significantly to the model. The findings indicate that DTWC would not always be expected to relate to fall rates, and the way in which it relates is dependent on the basic DTW ability (i.e., DTWS) of the individual. Those with fast DTWS benefit from no DTWC, or even cognitive-motor facilitation, in terms of fall rate predictions, but those with slow DTWS benefit from greater DTWC. These findings indicate both that DTWS may be more information as an isolated measure than STWS *and* that DTWC may strengthen prediction of fall rates further. It is worth noting that in the longitudinal analyses performed over 4 measurements across 18 months, only the between-person (i.e., “trait”) effects were significant—*changes within person did not emerge as significant for any predictors considered*. This may be in part due to the fact that the sample was relatively functional to begin and that those who were most functional were those who continued in the study. It is possible that if disease progression were occurring more reliably or rapidly, or if sample retention or size were greater throughout, that within-persons effects could be detected. However, these findings indicate that it is the differences that exist *between* persons (e.g., a “fast” or “slow” walker or someone with “high” or “low” DTWC), not the differences *within* persons (i.e., having speed slow over time or DTWC increase), that mattered.

Considering these findings in the context of past research regarding DTW and falls in MS, a few notes are important. First, this model was longitudinal—not just prospective (i.e., all measures were taken repeatedly over time, it was not only a single baseline measure of ability to predict future fall reports). It also employed full-information maximum likelihood which allows for all available data to be used in the model—that is, even if someone withdrew at some point in the study, the measures they had completed could still be used in the model. Second, it used fall *rates*—a count measure—not classification (i.e., “faller” or “multiple faller”). Although classification approaches have their use, dichotomization sacrifices information and reduces statistical sensitivity (Fedorov et al., 2009; MacCallum et al., 2002). Lastly, it controlled for cognitive ability (executive function [Stroop test]) and walking ability (T2FWT time), and it is the first evaluation to consider *both* DTWS and DTWC—as well as their interaction.

Lastly, beyond the clear additions made by these analyses with respect to the correlates and consequences of DTW ability in MS, several important findings emerged across both samples to indicate that SAT (Yogev-Seligmann et al., 2012), as an instantiation of Bandura’s (1978, 1994) reciprocal determinism theory and the role of self-efficacy as a person-level factor in the model, may enhance our understanding and prediction of DTW outcomes in MS. This theory leads avers that subjective appraisals of one’s abilities—as well as how these factor into the context of the current environment and its hazards—will improve prediction of performance in DTW. As such, it was predicted that psychological states that could be expected to affect appraisals of self and environmental risk, such as FSE and depression, would moderate the relationships between basic (i.e., cognitive and walking ability in ST contexts) abilities and performance in the context of greater demands (i.e., under DT). In support of this general hypothesis, several of the tested moderation effects determined by a priori considerations were found to be significant.

Two patterns of effect seem most notable. First, although DTWC were notably less related to basic cognitive and physical abilities, depressive symptoms and FSE did seem to improve these models. In the SS analyses, only depression and FSE (measured by MFES) emerged as significant predictors of DTWC in any of the analyses. Depressive symptoms were the most robust predictor with *Somatic* depressive symptoms being a significant predictor in models that controlled for *Affective* depressive symptoms and STWS, executive function, and information processing abilities. This hints at a form of appraisal processing and self-monitoring in which people's psychological states and self-appraisals are important to the degree to which they alter their speed under more complex DTW contexts. Further, *Affective* aspects of depression moderated the effect of information processing on DTWC in the SS study controlling for the significant effect of *Somatic* depressive symptoms. (It is also possible that a shared, lower-level effect or cause of depression affects both depressive symptoms and DTWC in conjunction with or in lieu of depressive symptoms leading to alterations in appraisals that affect DTWC.) Unfortunately, a specific measure of depression was not available for consideration in the KUMC analyses. A measure of emotional wellbeing—factored from the SF-36—was considered in the stead of depressive symptoms, but the same relationships did not emerge with this distinct, but related, construct. (Of note, the measure of information processing was similar but distinct in both studies, too.) Future research should explore how depression, as a common (Boeschoten et al., 2017; Siegert & Abernethy, 2005) "invisible symptom" (Leone et al., p. 128) in MS, relates to DTW outcomes at a variety of levels of analysis.

Next, both the SS and KUMC analyses revealed that FSE moderated the relationship between basic physical abilities and DTWS—which is the most apropos measure of *performance* under increased demand (i.e., "speed" is the measure of performance and ST and DT are the contexts in which it manifests). In the SS study, STWS was moderated by FSE (measured by the MFES) such that as FSE decreased the relationship between STWS and DTWS was attenuated. The same type of pattern was observed in the KUMC study with the BBS being moderated by both the ABC-Hard factor and the FES-I. For those with greater FSE, objective balance related more strongly to DTWS. Although a qualitative interaction was technically observed, most observations were in the area of the quantitative interaction. These findings indicate that there may be more involved in how DT contexts affect performance than fundamental, universal attentional capacities or neural limits—even though these may be important to understanding the fact that DTC *exist* at all. Otherwise, they indicate that these psychological states, or the mechanistic processes that underlie them, are able to modify these lower-level processes (i.e., attention capacity or neural processes). To understand DTW, the evidence indicates that considering the whole person—physically, cognitively, and psychologically—in the context will enhance prediction of DTW abilities which is consistent with Bandura's reciprocal determinism (1978) and SAT (Wajda et al., 2016; Yogev-Seligmann et al., 2012), as well as some previous DT literature in MS in other areas of motor control (e.g., Lemmens et al., 2018). It is worth noting that other moderating effects of psychological states and physical or cognitive abilities were observed, including the interaction of emotional wellbeing and T25FWT time and the interaction of FES-I and information processing (Choice Reaction Time for Correct Responses) for DTWS, as well as the interaction of ABC-Hard and MSWS-12 and the interaction of FES-I and EDSS step for DTWC in the KUMC analyses. On the whole, the evidence indicates that, at minimum, further consideration of how SAT enhances our understanding of DTW in MS—which has been riddled by notably heterogeneous results consistent with the presence of moderating effects (Leone et al., 2015; Rooney et al., 2020).

Although these analyses provide many valuable insights, they are not without their limitations. First, although these analyses do allow for some conceptual replications and come from two, independent samples, there are still only two samples that have been used throughout all analyses, and the analyses are retrospective, secondary data analyses. Further extension and replication are necessary. Only serial subtractions were used as the cognitive dual task, and there were no measures of cognitive performance under DT.

Also, although the samples are rather large within the context of DTW research in MS, the samples are not particularly large in the context of analyses performed and missing data and attrition further limit some the sample sizes for the various models. Yet, even for the longitudinal models using count data and affected by attrition, it seems worth employing these methods that provide additional insights. For example, there is evidence that even with sample sizes as small as 25 in count MLM, the trustworthiness of estimates is reasonable (McNeish, 2019). Not all conceptual variables had strong operationalizations in both studies (e.g., depression in SS analyses versus emotional wellbeing in KUMC). Also, the use of a more disabled, clinical sample and a less disabled, research sample enhances the degree of confidence in findings that replicated across studies, but some analyses (e.g., falls models) were performed only in one sample and should be examined in more diverse samples—perhaps particularly in terms of disease state. It is also possible that demand characteristics of the experimental procedures are involved in the effects observed. Examining DTW in more mundane environments may provide further insights regarding how these relationships manifest in real-world contexts and abet greater understanding of the consequences of DTW ability in MS. Also, falls were reported over time but recalled retrospectively. Understanding the real-world importance of DTW for falls would benefit from longitudinal modeling of prospectively reported falls in the future.

Several analyses were performed. Although they were specified a priori, as was the decision to use comparison-wise α control, this should be considered when interpreting the findings and considering the need for replication to arrive at confident conclusions about these relationships and dynamics. Further, attempts to more singularly and directly test full conceptual models presented with large samples would be desirable to get a better picture of the dynamic interplay of variables involved in producing DTW outcomes and in determining the consequences of DTW abilities. As these analyses indicated, the dynamics that may need to be considered to fully understand the models that give rise to these outcomes may be more complex than often, or herein, considered.

Nevertheless, these analyses provide many novel insights. They fill gaps in the literature regarding the understanding of how DTW outcomes fit into the nexus of symptoms in MS (Leone et al., 2015, Rooney et al., 2020; Wajda & Sosnoff, 2015). They emphasize the importance of considering DTWS as a measure when the desire is to understand how DTW fits into the broader context of MS—not just whether DTWC exist. They also provide evidence that may help to understand the mixed findings that have often emerged—including around the relationship between DTW abilities and falls in MS (Etemadi, 2017; Gunn et al., 2013; Nilsagård et al., 2009; Quinn et al., 2019; Wajda et al., 2013). They also provide evidence in support of SAT and indicate that considering physical, cognitive, and psychological processes together may enhance our understanding of DTW outcomes—and help to explain some of the heterogeneity that has been observed previously. The analyses remind that approaches to improving DTW abilities, or decreasing possible risks associated with DTW which often occurs in daily life, may require tailored approaches based on more holistic assessments of the individual.

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