5-1-2021

Development of a Novel Cognitive-Motor Dual Task Assessment Battery in Neurodegenerative Disease

Jason Longhurst

DEVELOPMENT OF A NOVEL COGNITIVE-MOTOR DUAL TASK ASSESSMENT BATTERY IN NEURODEGENERATIVE DISEASE

By

Jason Longhurst

Bachelor of Science – Exercise Science
Brigham Young University
2010

Doctor of Physical Therapy
University of Nevada, Las Vegas
2013

A dissertation submitted in partial fulfillment
of the requirements for the

Doctor of Philosophy – Interdisciplinary Health Sciences

The Graduate College

University of Nevada, Las Vegas
May 2021

UNLV | GRADUATE COLLEGE

Dissertation Approval

The Graduate College
The University of Nevada, Las Vegas

March 25, 2021

This dissertation prepared by

Jason Longhurst

entitled

Development of a Novel Cognitive-Motor Dual Task Assessment Battery in Neurodegenerative Disease

is approved in partial fulfillment of the requirements for the degree of

Doctor of Philosophy – Interdisciplinary Health Sciences
Interdisciplinary Health Sciences

Merrill Landers, Ph.D.
Examination Committee Chair

Kathryn Hausbeck Korgan, Ph.D.
Graduate College Dean

Jeffrey Cummings, Ph.D.
Examination Committee Member

Brach Poston, Ph.D.
Examination Committee Member

Samantha John, Ph.D.
Graduate College Faculty Representative

ABSTRACT

Automaticity --- the ability to perform a task with directing attentional resources to its completion --- is a commonly reduced among individuals with neurodegenerative diseases. These automaticity deficits result in impaired functional and daily activities and are sensitive to subtle, subclinical impairments. However, current measurement of automaticity by dual task paradigms is methodologically limited. In order to gain insight into the current state of the literature regarding cognitive-motor interference in symptomatic and prodromal neurodegenerative disease, the author of this dissertation conducted a scoping review (Chapter 1). To address the methodological limitations of current measurement of automaticity, a new measurement tool was proposed and evidence for its reliability and validity provided (Chapter 2). Next, the utility of this novel measure of automaticity was then investigated. In Chapter 3, the relationship between automaticity and cortical thickness was investigated among individuals with AD, revealing a relationship between the dorsal lateral prefrontal and superior parietal cortices. The relationship between amyloidosis and automaticity was then investigated among healthy individuals (Chapter 4), demonstrating the utility of this novel tool to identify individuals with preclinical Alzheimer's disease. Overall the findings of this dissertation provide evidence of the reliability and validity of this novel measure of automaticity, and provide several examples of its utility over previously used measures of automaticity. Future research should investigate similar relationships with real-time functional imaging, such as functional near infrared spectroscopy, during cognitive-motor dual tasks.

ACKNOWLEDGEMENTS

For exceptional mentorship and guidance over many years, I am grateful to my committee chair, Dr. Merrill Landers. He has gone above and beyond in helping me develop my research and career goals. I am honored to consider him a mentor, a colleague, a collaborator, and a friend. I also wish to express my gratitude to the other members of my advisory committee, Dr. Jeffrey Cummings, Dr. Brach Poston, and Dr. Samantha John, for their support, and providing their expertise to these projects and to my development. To the Cleveland Clinic for their support of my goals and providing the opportunity for research and collaboration. Particular thanks goes to my fellow physical therapist at the Cleveland Clinic, Christy Ross, and Trevor Mahoney, who have helped me in refining my theories by lending their clinical expertise and viewpoints. Shaina Meyer and Jennifer Nash who have each served as Cleveland Clinic Lou Ruvo Center for Brain Health manager during my tenure there and have continually encouraged me to excel and reach my career goals. To John Rider for his frequent collaboration and conversations that have helped to refine my theories. I also want to thank the Center for Neurodegneration and Translational Neuroscience, particularly the leadership team of Dr. Jeffrey Cummings, Dr. Aaron Ritter, Dr. Ditmar Cordes, Dr. Brent Bluett, Dr. Jessica Caldwell, Dr. Jefferson Kinney, and Dr. Virendra Mishra. To Karthik Sreenivasan for his collaboration and support on imaging projects. Lastly, great thanks needs to be given to my family who have supported me throughout this process, in every way. Through years of working full time while completing the rigorous demands of PhD training, they have provided me every opportunity to

be successful. I certainly owe my wife Jessica and our three kids (Carter, Christian, and Clara) a vacation and plenty of my attention which has been in short supply. I can't thank them enough.

TABLE OF CONTENTS

LIST OF TABLES

CHAPTER 1

CHAPTER 2

CHAPTER 3

CHAPTER 4

LIST OF FIGURES

CHAPTER 1

CHAPTER 2

CHAPTER 3

CHAPTER 4

CHAPTER 1: INTRODUCTION

COGNITIVE-MOTOR DUAL TASK INTERFERENCE IN ALZHEIMER'S DISEASE, PARKINSON'S DISEASE, AND PRODROMAL NEURODEGENERATION: A SCOPING REVIEW

INTRODUCTION

Cognitive motor interference (CMI) is a phenomenon by which simultaneous completion of cognitive task and motor task results in a decrement in performance in one or both tasks (Abernethy, 1988; Al-Yahya et al., 2011; Yogev-Seligmann et al., 2008). Several models have been proposed to explain the mechanisms of CMI, most prominent are the central capacity sharing model and the central bottle neck model. The central capacity sharing model postulates that processing occurs parallel but it is limited in capacity, resulting functionally in a division of resources among the tasks to be performed (Lehle & Hübner, 2009; Pashler, 1994b; Tombu & Jolicoæur, 2003; Tombu & Jolicœur, 2005). The central bottle neck model proposes that central processing acts on only one task at a time; this results in a bottleneck where tasks are processed serially rather than in parallel (Navon & Miller, 2002; Pashler, 1984, 1994a). In considering the above theories, it is important to understand that both tasks (cognition and motor control) which combine to result in CMI are complex, and that each requires many central nervous system processes, functions, and resources (Al-Yahya et al., 2011; Yogev-Seligmann et al., 2008). They are both reliant on structures throughout the central nervous system, including both cortical and subcortical structures (Yogev-Seligmann et al., 2008). A deficit in any one of the involved structures can result in changes to cognition and motor control, which is manifested as a reduction in automaticity (Wu et al., 2015).

Reduced automaticity, performance of a task requiring more attentional resources be directed to the primary task, is common among individuals with neurodegenerative disease (M. Montero-Odasso et al., 2018; Muir et al., 2012; Wu et al., 2015). It is a key deficit in Parkinson's disease (PD) and is a crucial target of motor retraining and rehabilitation for individuals with PD (Chomiak et al., 2017; Huang et al., 2018; L Rochester et al., 2010). In Alzheimer's disease (AD), decreased motor automaticity has been shown to progress with disease severity (M. M. Montero-Odasso et al., 2017; Muir et al., 2012). Motor automaticity has also been shown to be poorer in individuals with mild cognitive impairment (MCI) relative to healthy individuals (Muir et al., 2012). There is evidence that individuals with MCI who have less motor automaticity progress to dementia more rapidly than those with relatively intact motor automaticity, underscoring the importance of identifying motor automaticity impairment early in cases of cognitive impairment and implementing aggressive management strategies (M. Montero-Odasso et al., 2018; M. M. Montero-Odasso et al., 2017).

Automaticity and CMI are often assessed by dual task (DT) paradigms wherein a motor task and a cognitive task are performed concurrently (Koziol & Budding, 2009; Wu et al., 2004, 2015); however, currently, there is no consensus on the best methods or measures for assessing DT ability, which may lead to inconsistency of results (Cardon-Verbecq et al., 2017; McIsaac et al., 2015; Yang et al., 2017). Yang et al observed that there were many different methods for assessing the effect of DT interference, the relative change in performance as a result of dual tasking, or dual task effect (Yang et al., 2017). Currently, one of the most accepted measures for

assessing DT interference is calculating the motor or cognitive dual task effect (DTE), which relates DT performance to single task (ST) performance (McIsaac et al., 2015; Yang et al., 2017). Increasingly, there have been efforts made to categorize attentional prioritization (the task to which individuals place more attention on during completion of the DT), and to quantify the degree of prioritization using measures such as the attention allocation index (V E Kelly et al., 2010; Plummer et al., 2013; Plummer & Eskes, 2015; Siu & Woollacott, 2007). Despite the utility of these measures, few studies have reported results using these metrics, and even fewer have harnessed all these metrics to give a more complete vision of the entirety of the process that underlies CMI and DT.

There is a need to better understand what occurs when individuals with AD and PD perform cognitive-motor dual tasks. Different disease processes that involve distinct brain regions and networks are likely to exhibit a different CMI profile. For example, individuals with AD would be anticipated to have impairment in the fronto-parietal network, which facilitate attention and processing speed, resulting in greater decrements in cognitive task performance during DT. Whereas, individuals with PD, with greater difficulty in motor planning and motor control stemming from impairment in the subcortical motor pathways, would be anticipated to have great decrements in motor performance during DT. CMI also has the potential to be an identifier of early disease states as it has the ability to draw out subtle, subclinical motor and cognitive deficits. Therefore, the objective of this scoping review was to gain insight into how individuals with AD and PD are impacted by CMI. These insights are likely to include how automaticity is impacted differently by different neurodegenerative disease processes.

Additionally, we aimed to gain a better understanding of the role of CMI and motor automaticity deficits in early and prodromal disease states. Lastly, we have reported how CMI has been measured in individuals with AD and PD.

METHODS

This review was guided by the methodological framework from the Joanna Briggs Institute (JBI) and will follow the Preferred Reporting Items for Systematic reviews and Meta- Analyses extension for Scoping Reviews (PRISMA-ScR) (Tricco et al., 2018). Quality appraisal of studies was not conducted as this review aimed to explore the general scope of research conducted in this field.

Search strategy

The search strategy aimed to find published literature and unpublished studies. A three-step search was utilized in each component of this review. An initial limited search of Medline (PubMed) and CINAHL (EBSCO) was undertaken to identify articles relevant to the topic. This was followed by an analysis of the text words contained in the title and abstract, and of the index terms used to describe relevant articles. A second search using all the identified keywords and index terms was then undertaken across all included databases (see Appendix 1 for an example of a search strategy for one database). All identified keywords and index terms included in the search strategy were adapted to the data sources as needed. Third, the reference list of all included studies was searched for additional studies. Only studies published in English were considered for inclusion in this review. No time limit was imposed on studies for

inclusion in this review. The databases searched included MEDLINE (PubMed), Scopus (Elsevier), APA Psychinfo (EBSCO) and CINAHL (EBSCO). Gray literature was searched through Papers First (OCLC) and ProQuest Dissertations and Theses (ProQuest). All databases were searched on September 29, 2020.

Study selection

The results were reviewed by the research team to ensure validity of the search strategy. Results from each database search were then imported to a single library in the Mendeley 1.19.4 software (Elsevier Inc., 230 Park Avenue, Suite 800, New York, NY, USA). Duplicate studies were identified and removed. Title and abstract screening were guided by the PRISMA framework (Liberati et al., 2009). Application of further eligibility criteria ensured that the content of the included studies was relevant to the aims of this review. This review considered studies that include a measure of cognitive-motor interference during gait or gait-related tasks among adults 18 years of age and older with evidence of AD, PD, or prodromal neurodegeneration. Studies were excluded if: (1) they focused only on case reporting, (2) full-text could not be obtained, (3) they were investigating the effect of a treatment, (4) they did not utilize a salient motor task as part of the DT (i.e. finger taping), and (5) they used a strictly static postural task for the motor task during DT (as the interest of this review was in functional mobility as the primary motor task). Additionally, this review considered experimental, quasi-experimental, and observational study designs. Qualitative studies, as well as text and opinion papers were also considered.

The two reviewers (primary and secondary authors) used the inclusion criteria to determine eligibility of the selected and identified studies for the review and subsequently conducted full-text screening of all eligible articles. Article selection and exclusion required agreement between the two reviewers. Disagreements in study selection (n=2) were managed through discussion of the primary and secondary author until a consensus was reached. The selection process followed the recommendations in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) checklist (Tricco et al., 2018).

Data extraction

Data was extracted from selected studies included in the scoping review by two independent reviewers using a data extraction tool developed by the reviewers based on the standardized tool from JBI System for the Unified Management, Assessment and Review of Information (Peters et al., 2020). Bibliographic details, sample, motor tasks, cognitive tasks, DT outcomes, and key findings relevant to the review objectives were extracted.

RESULTS

A total of 5,534 citations were retrieved by searching databases included in the search criteria for this review, of which 95 articles were considered relevant for this review and were included in the evaluation and synthesis (Figure 1). The articles were grouped into three non-mutually exclusive categories: AD (26 articles), PD (56 articles), and prodromal neurodegeneration (29

articles). Article results relevant to each group and relevant to this review are reported in tables 1-3, respectively.

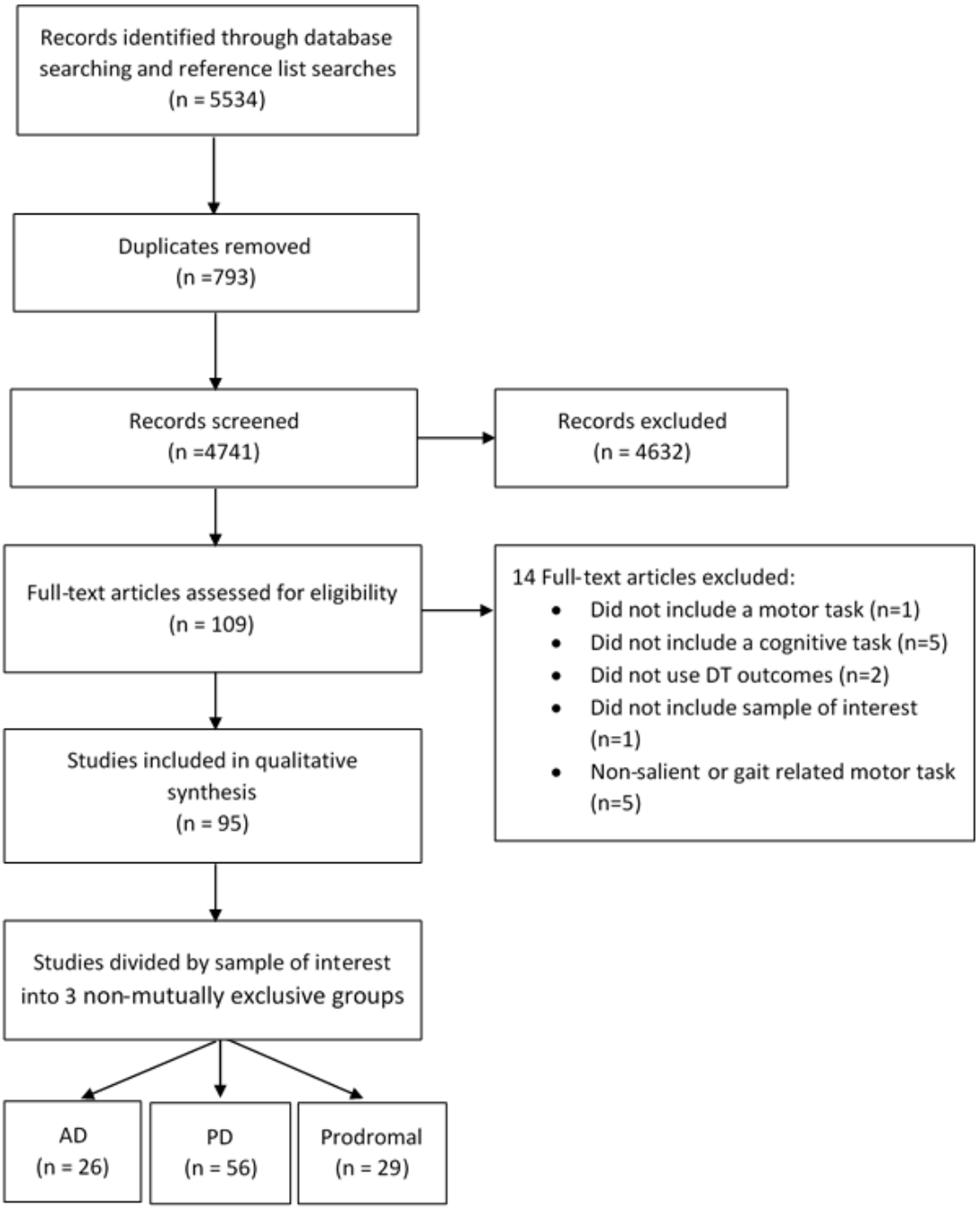


Figure 1. PRISMA flow diagram showing results of search and process of study selection.

Table 1. Articles included in this review with a sample of Alzheimer's disease. This table is organized by primary population/findings of interest into two sections: A) Alzheimer's disease; and B) Neuroimaging and Alzheimer's disease biomarker findings related CMI.

Article	Sample	Motor task	Cognitive task	DT measurement tools	Key findings related to CMI
A. Alzheimer's disease					
(Juliana Hotta Ansai et al., 2018)	38 AD 40 MCI 40 Healthy	TUG	Phone dialing task	(1)mDTE (2)cogDTE (3)Absolute measures of performance	DT performance was associated with visuospatial skills in all groups. Executive function and fluency were the strongest predictors of DT performance in AD.
(Juliana H. Ansai et al., 2017)	38 AD 40 MCI 40 Healthy	TUG	Phone dialing task	(1)mDTE (2)cogDTE (3)Absolute measures of performance	DT performance worse for AD than MCI or healthy. No items distinguished MCI from the healthy group.
(Beauchet et al., 2014)	86 AD	Gait	Serial subtraction by 1	Absolute measures of performance	DT worsens gait variability more in those with AD who don't use Acetylcholinesterase inhibitors.
(Camicioli et al., 1997)	15 AD 20 Healthy	Gait	Controlled oral word association task	Absolute measures of performance	Gait of those with AD slowed more than healthy under DT.
(Camicioli et al., 2006)	42 AD	Gait	Count by 1	Absolute measures of performance	DT decreases cadence. DT increases stride time, swing time, and variability. DT performance does not differ in AD between those with and without Extra-pyramidal signs.
(Cedervall et al., 2014)	21 Mild AD	Gait	Controlled oral word association task	(1)mDTE (2)Absolute measures of performance	DT increases gait disturbance in AD, specifically in increases temporal disturbances, spatial disturbances, and instability in single limb stance. DT performances declines over 2 years in AD.
(Christofoletti et al., 2014)	38 AD 43 PD 45 Healthy	TUG	Counting by 2	Absolute measures of performance	PD and AD both are impacted differently by DT. AD more impacted by a cognitive secondary task, whereas PD more impacted by motor secondary task.
(Cocchini et al., 2004)	15 AD 15 Healthy	Gait	(1)Controlled oral word association task (2)Forward digit span	(1)Average of mDTE and cogDTE (2)Absolute measures of performance	DT results in more impact to gait in AD than healthy older adults. Average of mDTE and cogDTE distinguished groups when the secondary tasks was the controlled oral word association task but not with the digit span.
(Gillain et al., 2009)	6 AD 14 MCI 14 Healthy	Gait	Serial subtraction by 1	Absolute measures of performance	Gait of MCI and AD groups during DT is more impaired than controls. The MCI group demonstrated reduced gait velocity and stride frequency compared to the healthy group. The AD group had reduced gait velocity, stride length, and increased gait variability.

					Gait variability and stride length distinguished between MCI and AD.
(Gonçalves et al., 2018)	38 AD 40 MCI	TUG	Phone dialing task	(1)mDTE (2)Absolute measures of performance	mDTE was associated with more falls in MCI but not AD.
(Hunter et al., 2020)	23 AD	(1)Gait (2)Groningen meander test (3) Figure 8 path	Serial subtraction by 1	(1)mDTE (2)cogDTE (3)Performance operating characteristic plots for task trade-offs (4)Absolute measures of performance	DT worsens gait and cognitive performance in AD, the more complex the motor task the greater the motor prioritization.
(König et al., 2017)	23 AD 24 MCI 22 Healthy	Gait	Serial subtraction by 1	Absolute measures of performance	DT gait differences between AD and MCI, with the AD group having slower gait velocity, decreased cadence, and increased step time variability. There were not differences between MCI and healthy groups.
(Maquet et al., 2010)	6 AD 14 MCI 14 Healthy	Gait	Counting (unspecified)	Absolute measures of performance	Gait velocity during DT varies between all groups, with AD exhibiting the slowest and healthy the fastest gait velocity.
(de Melo Borges et al., 2015)	26 mild AD 42 MCI 36 Healthy	TUG	Controlled oral word association task	Absolute measures of performance	DT-TUG differentiates mild AD, MCI, and healthy, with worse performance in the AD group and the best performance in the healthy group. Receiver-operating characteristic curve analysis showed higher area under the curve for cognitive-motor DT, than for ST TUG, or motor-motor DT. DT worsens functional performance for all groups.
(Muir et al., 2012)	23 AD 29 MCI 22 Healthy	Gait	(1)Serial subtraction by 7 (2)Controlled oral word association task	(1)mDTE (2)Absolute measures of performance	Difference between AD and MCI during DT on gait velocity, stride time, stride time variability and were different from controls. More complex cognitive tasks exert greater interference on gait.
(Oh et al., 2020)	14 AD	Gait	(1)Serial subtraction by 1 (2) Controlled oral word association task	Absolute measures of performance	DT negatively impacted all gait variables and also was associated with poorer cognitive performance.
(Orcioli-Silva et al., 2012)	17 AD	(1)Free gait (2)Adapted gait	Serial subtraction by 1	Absolute measures of performance	DT results in increased double support time and stride duration, with a reduction in stride velocity.
(Pettersson et al., 2007)	6 AD 6 MCI 25 Healthy	Gait with turn	Controlled oral word association task	Differences on absolute measures of performance	Participants with AD had lower walking speed and greater time change between single and dual task compared with healthy controls.

(Rucco et al., 2017)	22 AD 23 FTD 20 Healthy	Gait	Serial Subtraction by 7	Absolute measures of performance	During the cognitive DT, the gait performance of the AD group markedly deteriorated compared to during the motor DT.
(Sheridan et al., 2003)	28 AD	Gait	Forward digit span	Absolute measures of performance	DT reduced gait speed and increased gait variability. Poorer executive function were associated with increased gait variability during DT
(Simieli et al., 2015)	15 AD 15 Healthy	(1)Gait (2)Gait with obstacle crossing	Serial subtraction by 1	Absolute measures of performance	AD used a motor prioritization strategy and showed decreased attention to executive task while walking.
(Sobol et al., 2016)	185 Mild AD	Gait	(1)Serial subtraction by 1 (2)Months in reverse order	(1)mDTE, (2)Absolute measures of performance	All tests of cognition correlated with DT performance. DT performance accounted for 7-15% of variation in cognitive performance, with shorter time to complete DT being associated with better cognitive performance.
(Tarnanas et al., 2015)	86 early AD 65 MCI 76 Healthy	Gait	(1)Serial subtraction by 1 (2) Controlled oral word association task	Intra-individual variability on absolute measures of performance	Motor variables during the DT tasks were a more reliable marker for early diagnosis of MCI than ST.
B) Neuroimaging and Alzheimer's disease biomarker findings related CMI					
(Muurling et al., 2020)	26 AD 58 MCI 58 Healthy	Fast walking with turning	Serial subtraction by 1	Absolute measures of performance	No relationship between DT gait and Aβ42. Total tau was higher in those with more DT gait variability but no relationship was seen with ST gait.
(Nadkarni et al., 2012)	24 AD 20 Healthy	Treadmill gait	(1)1-back (2)2-back	(1)mDTE (2)cogDTE (3)Average of mDTE and cogDTE	AD shows poorer DT performance globally than MCI or healthy. Subcortical hyperintensities were associated with poorer average DTE.
(Nielsen et al., 2018)	26 AD 17 MCI 41 Healthy	TUG	Serial subtraction by 1	(1)mDTE (2)Absolute measures of performance	DT performances (mDTE) distinguishes groups. mDTE more strongly associated with cognitive decline than DT-TUG time and ST-TUG time. mDTE has moderate associations with Mini Mental State Examination and CSF Aβ42, such that worse DT performance is associated with lower score on the Mini Mental State Examination and lower levels of CSF A β42. Similar moderate association between mDTE and CSF T-tau and P-tau were observed; however, it was in the opposite direction. Specifically, poorer DT performance was associated with elevated levels of T-tau and P-tau in the CSF.

DT: dual task, CMI: cognitive-motor interference, AD: Alzheimer's disease, MCI: mild cognitive impairment, TUG: Timed Up and Go, mDTE: motor dual task effect, cogDTE: cognitive dual task effect, PD: Parkinson's disease, DT-TUG: dual task Timed Up and Go, ST: single task, Aβ: Amyloid β, DTE: dual task effect, CSF: cerebral spinal fluid, T-tau: total tau, P-tau: phosphorylated tau, FTD: frontotemporal dementia.

Alzheimer's disease

A total of 26 articles with a sample of participants with AD were included, and combined had a total of 878 participants with AD (see Table 1). Of those articles, 17 included a healthy comparison group, 12 had a MCI comparison group, two had other comparison groups (PD (Christofoletti et al., 2014), and frontotemporal dementia (Rucco et al., 2017)), and eight did not include a comparison group.

Analysis of the motor tasks utilized as a component of the cognitive-motor DT among these studies revealed that 20 utilized a gait task (ranging from self-selected gait to complex gait with turning, obstacles, or adaptation) as the motor task. While six articles utilized the Timed Up and Go (TUG), a measure of functional mobility that includes rising from a chair, gait initiation, gait acceleration, gait deceleration, and turning (Shumway-Cook et al., 2000). The cognitive components of the duals tasks were more varied and often had multiple cognitive tasks utilized. There were 16 studies that utilized arithmetic tasks, eight that utilized controlled oral word association tasks, and seven that utilized other cognitive tasks (phone dialing task (Juliana H. Ansai et al., 2017; Juliana Hotta Ansai et al., 2018; Gonçalves et al., 2018), forward digit span (Cocchini et al., 2004; Sheridan et al., 2003), n-back tasks (Nadkarni et al., 2012), and reciting months in reverse order(Sobol et al., 2016)). Multiple types of measures of DT performance were often utilized; however, the most commonly utilized metrics were absolute measures of performance (utilized in 25 of the articles) and were used in isolation in 16 instances. The remaining 10 articles utilized measures of DTE, which is the decrement in performance during

DT expressed in proportion to ST performance (V E Kelly et al., 2010). The standard equation is found below:

$$DTE(\%) = \frac{DT - ST}{ST} \times 100\%$$

All 10 studies included motor DTE (mDTE), five included cognitive DTE (cogDTE), and two included an average of mDTE and cogDTE (Cocchini et al., 2004; Nadkarni et al., 2012). Hunter et al also included performance-operating characteristic plots to assess attentional prioritization strategies during DT with resultant task trade-offs (Hunter et al., 2020).

Overall, the findings of these studies indicated that DT results in CMI, which has an impact on individuals with AD; however, that impact varied among the studies. The following themes were found consistently among the findings. First, performance of DT negatively impacted gait. Specifically, when performing a DT, individuals with AD exhibited decreased cadence(Cedervall et al., 2014; König et al., 2017; Oh et al., 2020), velocity (Camicioli et al., 1997; de Melo Borges et al., 2015; Gillain et al., 2009; König et al., 2017; Maquet et al., 2010; Muir et al., 2012; Oh et al., 2020; Orcioli-Silva et al., 2012; Pettersson et al., 2007; Sheridan et al., 2003), and stride length (Cedervall et al., 2014; Gillain et al., 2009; Oh et al., 2020), while also exhibiting increased stride time (Cedervall et al., 2014; Muir et al., 2012; Oh et al., 2020; Orcioli-Silva et al., 2012), swing time (Cedervall et al., 2014; Oh et al., 2020), and gait variability (Beauchet et al., 2014; Cedervall et al., 2014; Gillain et al., 2009; König et al., 2017; Muir et al., 2012; Muurling et al., 2020; Oh et al., 2020; Sheridan et al., 2003) compared to ST gait. Next, DT gait was also found to interfere with the cognitive performance during DT, resulting in poorer

cognitive performance during DT (Hunter et al., 2020; Oh et al., 2020; Simieli et al., 2015). Additionally, poorer DT performance was found to be related to lower overall cognition (Nielsen et al., 2018; Sobol et al., 2016) and more impaired visuospatial, executive function, and fluency abilities when not performing a DT (Juliana Hotta Ansai et al., 2018; Sheridan et al., 2003). We also found that cognitive-motor DTs resulted in more DT interference than did motor-motor DTs (e.g. carrying a cup of water) in individuals with AD (Christofoletti et al., 2014; Cocchini et al., 2004; de Melo Borges et al., 2015; Muir et al., 2012; Rucco et al., 2017). Another finding among these studies was that more complex motor tasks resulted in motor (gait) prioritization (Hunter et al., 2020; Simieli et al., 2015), a strategy in which attention is allocated in a greater proportion to the motor task (gait) than to the cognitive task. This results in a greater decline in DT cognitive performance than DT motor performance when compared respectively to ST performance. One of the most consistent findings, and perhaps the most important, was that DT performance was frequently found to discriminate between participants with AD and healthy older adults (Juliana H. Ansai et al., 2017; Camicioli et al., 1997; Christofoletti et al., 2014; de Melo Borges et al., 2015; Gillain et al., 2009; König et al., 2017; Maquet et al., 2010; Muir et al., 2012; Nadkarni et al., 2012; Nielsen et al., 2018; Pettersson et al., 2007; Rucco et al., 2017), as well as those with AD and those with MCI (Juliana H. Ansai et al., 2017; de Melo Borges et al., 2015; König et al., 2017; Maquet et al., 2010; Muir et al., 2012; Nielsen et al., 2018). However, two studies had contradictory results, reporting no difference on DT performance between participants with AD and those with MCI (Gillain et al., 2009; Pettersson et al., 2007). Interestingly both of these studies utilized absolute measures of performance, and not measures of DTE to quantify DT performance. There were additional

findings related to CMI among individuals with AD among the included articles. These findings can be found in Table 1.

Among the 26 articles that included participants with AD, there were three that investigated the relationships between DT performance and neuroimaging or AD biomarkers. These studies included a total of 76 individuals with AD and all included healthy comparison groups, with two articles including MCI comparison groups. Most notable of the findings of these studies was that two studies found moderate relationships between DT performance and cerebral spinal fluid (CSF) tau level, suggesting that poorer DT performance was associated with increased levels of tau (Muurling et al., 2020; Nielsen et al., 2018). In contrast, there were conflicting results regarding the relationship between DT performance and Amyloid β (Aβ). While Nielsen et al showed that poorer DT performance was associated with lower levels of Aβ in the CSF (Nielsen et al., 2018), Muurling et al did not find any relationship between them (Muurling et al., 2020). This discrepancy may be explained by the different DT measures utilized. While Nielsen et al found a relationship between mDTE and CSF Aβ, Muurling et al utilized only absolute measures of performance during DT, which Nielsen et al also found to not be related to CSF Aβ levels (Muurling et al., 2020; Nielsen et al., 2018). Nadkarni et al investigated the relationship between subcortical hyperintensities on MRI and DT performance and found that the presence of global burden of hyperintensities was associated with poorer DT performance (average of mDTE and cogDTE) (Nadkarni et al., 2012).

Table 2. Articles included in this review with a sample of Parkinson's disease. This table is organized by primary population/findings of interest into 3 sections: A) Parkinson's disease; B) Parkinson's disease with freezing of gait; and C) Neuroimaging findings related CMI.

Article	Sample	Motor task	Cognitive task	DT measurement tools	Key findings related to CMI
A. Parkinson's disease					
(Amboni et al., 2012)	19 PD 24 PD-MCI 20 Healthy	Gait	Serial subtraction by 7	Absolute measures of performance	DT results in reduced step length, reduced swing time and increased step length variability in individuals with PD-MCI.
(Amboni et al., 2018)	39 PD	Gait	Serial subtraction by 7	Absolute measures of performance	DT step length reduction precedes and is associated with future executive function / attention deficits by as much as 3 years.
(Baron et al., 2018)	23 PD	Arm swing during gait	(1)N-back test (2)Serial subtraction by 7 (3)Forward digit span (4)Controlled oral word association task (5)Visual Stroop	(1)cogDTE (2)Absolute measures of performance	Arm swing kinematics during gait are more impacted by more challenging cognitive secondary tasks.
(Canning et al., 2006)	16 PD 22 Healthy	Gait	Color classification task	mDTE	No relationship between mDTE and Six Minute Walk Test.
(Chawla et al., 2014)	25 PD	Gait	Serial subtraction by 3	mDTE	DT impacts gait more with a cognitive secondary task than a motor secondary task. These results persist with auditory cueing.
(Christofoletti et al., 2014)	38 AD 43 PD 45 Healthy	TUG	Counting by 2	Absolute measures of performance	PD and AD both are impacted differently by DT. AD more impacted by a cognitive secondary task, whereas PD more impacted by motor secondary task.
(Criminger & Swank, 2020)	31 PD	TUG	Serial subtraction by 3	Absolute measures of performance	DT impacts all mobility elements during the TUG except turn strategy.
(Ehgoetz Martens et al., 2018)	52 PD 18 Healthy	Gait	Digit monitoring task	Absolute measures of performance	DT reduces gait speed, DT reduces the effects of high anxiety on gait.
(Fernandes et al., 2016)	9 PD 10 Healthy	Gait initiation	Stroop test	Absolute measures of performance	DT did not impact gait initiation.
(Fernandes et al., 2017)	9 PD 10 Healthy	Gait initiation	Stroop test	Absolute measures of performance	DT resulted in slower activation times and lower activation values on electromyography among individuals with PD.

(Fino et al., 2018)	95 PD 50 Healthy	Gait	Reciting every other letter of the alphabet	(1)mDTE (2)cogDTE	Differences found between PD and healthy for local dynamic stability during heal strike and weight transfer. This result indicates that declines in DT performance occurs only during times where cortical activity is needed for planning and postural adjustments for individuals with PD.
(Fuller et al., 2013)	154 PD	Gait	Controlled Oral Word Association Test	Absolute measures of performance	DT results in reduced correct response rate. Lower correct response rates were associated with greater disability. PD prioritizes gait performance.
(Galletly & Brauer, 2005)	16 PD 16 Healthy	TUG	(1)Serial subtraction by 3, (2)Controlled Oral Word Association Test	Absolute measures of performance	Cognitive tasks exert greater DT interference on gait than motor secondary tasks.
(Gaßner et al., 2017)	67 PD	Gait	Serial Subtraction by 3	mDTE	DT performance explains 8% of variance in cognition.
(Heinzel et al., 2016)	40 PD	Gait	Serial Subtraction by 7	(1)mDTE (2)cog DTE (3)mDTE + cogDTE	Motor-motor DT may be more related to falls in PD than cognitive-motor DT. The composite of mDTE and cogDTE was more sensitive and predictive of falls.
(Hsiu-Chen et al., 2020)	27 PD	(1)Gait (2)Cycling	(1)Serial subtraction by 3 (2)Spatial memory task (3)Stroop test	(1)mDTE (2)cog DTE	DT worsens performance of cognitive tasks and gait/cycling. Akinesia score most related to walking cogDTE.
(Valerie E. Kelly et al., 2012)	15 PD 15 Healthy	Gait	Auditory Stroop	(1)mDTE (2)cogDTE, (3)mAAI (4)Absolute differences in measures of performance	People with PD can modify their attentional prioritization, but at the trade-off of the other task.
(Valerie E. Kelly & Shumway-Cook, 2014)	11 PD 12 Healthy	(1)Normal velocity gait (2)Fast velocity gait (3)Narrow gait	Auditory Stroop	(1)mDTE (2)cogDTE (3)Absolute measures of performance	In PD the ability to modify walking depends on the complexity of the walking task, with more complex walking tasks requiring more attentional resources in PD compared to healthy older adults.
(Leavy et al., 2016)	13 PD	NA	NA	NA	Participant reported increased difficulty of tasks when a DT was performed.

(Micó-Amigo et al., 2019)	22 Early PD 27 Middle PD 25 Healthy	Fast gait in a circle	Serial subtraction by 7	(1)mDTE (2)cogDTE (3)mDTE + cogDTE	DT did not improve assessment for predicting progression within PD, although there were differences between PD and healthy.
(Nocera et al., 2013)	13 PD 13 Healthy	Gait initiation	2-back task	Absolute measures of performance	Gait initiation not influenced by DT.
(O'Shea et al., 2002)	15 PD 15 Healthy	Gait	Serial Subtraction by 3	Absolute measures of performance	DT worsens temporal spatial gait parameters generally. There was no difference between cognitive and motor secondary tasks.
(Penko et al., 2020)	23 PD	Treadmill gait	(1)1-back, (2)2-back (3)Serial subtraction by 7 (4)Digit recall (5)Controlled Oral Word Association Test (6)Stroop test	Absolute measures of performance	Joint range of motion at the ankle, knee, and hip were reduced during DT gait. DT gait was associated with slower gait speed regardless of cognitive task.
(Penko et al., 2018)	23 PD	Treadmill gait	(1)1-back, (2)2-back (3)Serial subtraction by 7 (4)Digit recall (5)Controlled Oral Word Association Test (6)Stroop test	Absolute measures of performance	Temporal spatial gait parameters worsen with DT, serial subtraction by 7 resulted in the greatest level of gait interference.
(Peterson et al., 2020)	16 PD 14 Healthy	Backward protective step	Auditory Stroop	(1)mDTE (2)cogDTE (3)mAAI, (4)Absolute measures of performance	Reaction time and muscle latency were worse during DT, but not step response. Individuals with PD prioritize protective step over cognitive task.
(Pieruccini-Faria, Ehgoetz Martens, et al., 2014)	18 PD 15 Healthy	Gait over obstacle	Digit monitoring task	Absolute measures of performance	DT performance worse in individuals with PD during obstacle crossing.
(Plotnik et al., 2011)	30 PD	Gait	Serial subtraction by 3 and 7	Absolute measures of performance	DT impacts for gait variability and bilateral coordination more in PD fallers than non-fallers.

(L. Rochester et al., 2014)	121 Early PD 189 Healthy	Gait	(1)Forward Digit span (2)Digit span +1	(1)mDTE (2)cogDTE (3)Absolute measures of performance	DT inference was present for gait (mDTE) but not cognition (cogDTE). DT resulted in reduced step width, and increased gait variability in individuals with PD.
(Lynn Rochester et al., 2004)	20 PD 10 Healthy	Gait	Long-term autobiographical memory task	Absolute measures of performance	DT results in reduced gait velocity and step length.
(Salazar et al., 2017)	19 PD 13 Healthy	Gait	Oral Trail Making Test–Part B	Absolute measures of performance and variability	DT reduces walking speed and stride frequency more in PD than healthy controls.
(Sarbaz & Pourakbari, 2019)	20 PD 18 Healthy	Gait	Counting stride number	Difference in absolute measures of performance	DT results in counting errors and higher variance of stride time interval in PD compared to healthy participants.
(Siragy & Nantel, 2020)	20 PD	Gait with and without arm swing	Word searching task	Absolute measures of performance	DT reduced step time, increased step width variation, and increased mediolateral angular velocity and variability. Mediolateral foot placement is main means of maintaining walking stability during DT.
(Smulders et al., 2012)	263 PD	Gait	Auditory Stroop	(1)mDTE (2)cogDTE	DT decreased gait speed and stride lengths. Recurrent fallers did not exhibit different DT performance compared to non-recurrent fallers.
(Speciali et al., 2014)	14 PD 9 Healthy	Gait	Serial Subtraction by 7	Absolute measures of performance	DT resulted in worse performance on Gait Profile Score and Movement Analysis Profile.
(Stegemöller et al., 2014)	35 PD	Gait	Serial subtraction by 3	(1)mDTE (2)Absolute measures of performance	All gait measures were impacted by the DT. The addition of mDTE to raw gait variables improves the regression models fitting to predict cognitive performance.
(Strouwen, Molenaar, Keus, Münks, Bloem, et al., 2016)	62 PD	Gait	(1)Backwards digit span (2)Auditory Stroop (3)Phone dialing task	(1)mDTE (2)cogDTE (3)Absolute measures of performance	Evidence for reliability of DT measures (ICCs = .86-.95) good to excellent for reaction time of cognitive measures (ICCs=.75-.82) for individuals with PD.
(Strouwen, Molenaar, Keus, Münks, Heremans, et al., 2016)	121 PD	Gait	(1)Backwards digit span (2)Auditory Stroop (3)Phone dialing task	(1)mDTE (2)cogDTE (3)Absolute measures of performance	ST gait velocity, executive function, and disease severity correlate with DT gait performance (mDTE). These variable explain up 73% of variation on DT gait velocity.
(Varalta et al., 2015)	20 PD	TUG	Serial subtraction by 1	Absolute measures of performance	DT TUG correlates with cognitive impairment and ability to switch attention between 2 tasks.

(Wild et al., 2013)	18 PD 18 Healthy	Gait	(1)Text comprehension task (2)Phoneme counting task (3)Serial subtraction by 7	(1)cogDTE (2)Absolute measures of performance	Individuals with PD gave priority to gait while cognitive performance suffered. cogDTE increased with task complexity in PD.
(Xu et al., 2018)	9 PD 9 Healthy	Gait	Serial subtraction by 3	Absolute measures of performance	PD group showed reduced gait velocity, cadence, and increased mediolateral center of mass acceleration when walking on irregular terrain with DT.
(Yogev et al., 2005)	30 PD 28 Healthy	Gait	(1)Text comprehension task (2)Phoneme counting task (3)Serial subtraction by 7	Absolute measures of performance	Gait velocity reduced during DT. Gait variability increased compared to usual walking. DT gait velocity correlates with measures of executive function.
(Yogev-Seligmann et al., 2012)	20 PD 20 Healthy	Gait	Controlled oral word association task	(1)AAI (2)Absolute measures of performance	DT associated reduced gait velocity in the neutral prioritization DT condition. Gait velocity increased when prioritizing walking and maintained when prioritizing the cognitive task. All prioritization conditions increased gait variability. Task prioritization abilities were similar in PD and healthy.
(Zirek et al., 2018)	65 PD 57 Healthy	TUG	(1)Delayed memory task (2)Forward digit span (3)Backwards digit span (4)Serial subtraction by 7	(1)mDTE (2)Absolute measures of performance	DT resulted in increased time to complete TUG when secondary task probed complex attention (serial subtractions test) compared with other DT conditions.
B. Parkinson's disease with freezing of gait					
(Beck et al., 2015)	20 PD 20 PD-FOG	Gait with and without visual cues and visual feedback	Digit monitoring task	Absolute measures of performance	DT increases FOG when visual cues are not present. Visual cues improve gait in FOG regardless of DT. Attention is not exclusively responsible for FOG, FOG may be the result of overload of processing resources and visual cues by decrease processing demand.
(Bertoli et al., 2019)	18 PD 24 PD-FOG	(1)360 degree turn in place,	Serial subtraction by 3	mDTE	Turning worsens under DT similarly between PD and PD with FOG.

		(2)180 degree turn in gait			
(Jacobs et al., 2014)	10 PD-FOG 10 Healthy	Protective step	Controlled Oral Word Association Test	Absolute measures of performance related to FOG	DT increased fall rate during reactive stepping, did not increase FOG during perturbations.
(Kleiner et al., 2018)	33 PD-FOG 14 Healthy	Gait	Stroop Test	(1)mDTE (2)Absolute measures of performance	DT exerts negative impact on gait in PD-FOG more so than for healthy controls.
(Myers et al., 2020)	31 PD 13 PD-FOG	Gait	Controlled Oral Word Association Test	Absolute measures of performance	DT results in reduced joint angle magnitude and peak angle timing in PD and PDFOG.
(Peterson et al., 2015)	12 PD 13 PD-FOG	Gait	Choice reaction head-turning task	Difference in absolute measures of performance	DT impacts gait more for individuals with FOG. Among those with FOG, DT performance correlates with asymmetry pedunculopontine nucleus structural connectivity, Go-NoGo task, and reaction time.
(Pieruccini-Faria, Jones, et al., 2014)	13 PD 14 PD-FOG 14 Healthy	Gait over obstacle	Digit monitoring task	Difference in absolute measures of performance	DT makes obstacle crossing less consistent in PD-FOG, and is associated with lower cognition, poorer executive function, and poorer spatial planning in PD-FOG.
(Spildooren et al., 2010)	14 PD 14 PD-FOG 14 Healthy	Turning	Color classification task	Absolute measures of performance related to FOG and cognition	DT increases freezing when turning, and number of steps to turn. DT increases cadence during turning in those with PD-FOG whereas in PD it decreases cadence. 360 degree turning in combination with a dual-task is the most important trigger for freezing. Freezers prioritized cognition, whereas PD prioritized turning.
(Vervoort et al., 2016)	60 PD 13 PD-FOG 20 Healthy	(1)Gait (2) 360 degree turns	Auditory Stroop	Absolute measures of performance	DT results in longer stance time, short swing time, and more step length asymmetry in PD compared to healthy. PD-FOG also had increase double limb support compared to PD. PD-FOG had hypoconnectivity between caudate and superior temporal lobe and hyperconnectivity between dorsal putamen and precuneus correlated with DT performance.
C. Neuroimaging findings related to CMI					
(Hirata et al., 2020)	21 PD 12 Healthy	Fast gait	Serial Subtraction by 7	mDTE	mDTE worse in PD than healthy, no relationship reported between DT and DaT scan.

(Maidan et al., 2016)	68 PD 38 Healthy	Gait	Serial Subtraction by 3	(1)mDTE (2)Absolute measures of performance	Frontal activation during DT was not different from ST in PD. Healthy participants had increased frontal activation during DT. PD had higher DT costs.
(Nieuwhof et al., 2017)	19 PD 26 Healthy	Auditory cued ankle movements	Switch-stay task	Absolute measures of performance	DT associated with more performance errors in PD than control. DT activates a region of ventrolateral putamen not activated during ST. Activation of this region was associated with worse DT performance in healthy controls.
(Pelosin et al., 2016)	33 PD 17 Healthy fallers 14 Healthy	Gait	Controlled oral word association task	Absolute measures of performance	DT performance associated with level of cholinergic inhibitory activity in sensory motor cortex and was associated with fall status.

DT: dual task, CMI: cognitive-motor interference, PD: Parkinson's disease, PD-MCI: Parkinson's disease - mild cognitive impairment, cogDTE: cognitive dual task effect, PD-FOG: Parkinson's disease with freezing of gait, FOG: freezing of gait, mDTE: motor dual task effect, TUG: Timed Up and Go, AD: Alzheimer's disease, DT-TUG: dual task Timed Up and Go, DaT: dopamine transporter, mAAI: modified attention allocation index, AAI: attention allocation index.

Parkinson's disease

A total of 56 articles that included a total of 2,235 participants with PD were included in this scoping review (see table 2). Of these articles, 38 utilize a comparison group, with the majority comparing to healthy older adults. Additional comparison groups included PD-MCI (Amboni et al., 2012), healthy fallers (Pelosin et al., 2016), and PD with freezing of gait (PD-FOG) (Beck et al., 2015; Bertoli et al., 2019; Jacobs et al., 2014; Kleiner et al., 2018; Myers et al., 2020; Peterson et al., 2015; Pieruccini-Faria, Jones, et al., 2014; Spildooren et al., 2010; Vervoort et al., 2016). Additionally, four articles investigated the relationship of DT performance to neuroimaging findings in PD (Hirata et al., 2020; Maidan et al., 2016; Nieuwhof et al., 2017; Pelosin et al., 2016), while an additional two articles investigated the same relationship in individuals with PD-FOG (Peterson et al., 2015; Vervoort et al., 2016). One study utilized a qualitative methodology and did not report on collected DT outcomes, but on perceptions of DT performance (Leavy et al., 2016).

Gait was the most frequently used motor task and was utilized in 45 of the articles. Apart from basic gait, several articles investigate specific aspects of gait; three investigated gait initiation (Fernandes et al., 2016, 2017; Nocera et al., 2013), two investigated arm swing during gait (Baron et al., 2018; Siragy & Nantel, 2020), and six utilized complex gait tasks (Hirata et al., 2020; Valerie E. Kelly & Shumway-Cook, 2014; Micó-Amigo et al., 2019; Pieruccini-Faria, Ehgoetz Martens, et al., 2014; Pieruccini-Faria, Jones, et al., 2014). Other motor tasks utilized in PD include the TUG (Christofoletti et al., 2014; Criminger & Swank, 2020; Galletly & Brauer, 2005; Varalta et al., 2015; Zirek et al., 2018), protective stepping reactions (Jacobs et al., 2014;

Peterson et al., 2020), cycling (Hsiu-Chen et al., 2020), turning in place (Bertoli et al., 2019; Vervoort et al., 2016), and auditory cued ankle movements (Nieuwhof et al., 2017). In PD, similar to AD, we found that there was much more variety in the cognitive components of the DT compared to the selection of motor tasks. Arithmetic tasks were the most prevalent in the sample, utilized in 26 of the articles. The next most common were switching tasks, with 18 articles utilizing tasks such as the Stroop test (Baron et al., 2018; Canning et al., 2006; Fernandes et al., 2016, 2017; Hsiu-Chen et al., 2020; Valerie E. Kelly et al., 2012; Valerie E. Kelly & Shumway-Cook, 2014; Kleiner et al., 2018; Nieuwhof et al., 2017; Penko et al., 2018, 2020; Peterson et al., 2020, 2015; Salazar et al., 2017; Smulders et al., 2012; Spildooren et al., 2010; Strouwen, Molenaar, Keus, Münks, Bloem, et al., 2016; Strouwen, Molenaar, Keus, Münks, Heremans, et al., 2016; Vervoort et al., 2016). Other commonly used tasks were controlled oral word association tasks (Baron et al., 2018; Fuller et al., 2013; Galletly & Brauer, 2005; Jacobs et al., 2014; Myers et al., 2020; Pelosin et al., 2016; Penko et al., 2018, 2020; Yogev-Seligmann et al., 2012) and digit span (Baron et al., 2018; Hunt et al., 2013; Penko et al., 2018, 2020; L. Rochester et al., 2014; Strouwen, Molenaar, Keus, Münks, Bloem, et al., 2016; Strouwen, Molenaar, Keus, Münks, Heremans, et al., 2016; Zirek et al., 2018). Additionally, n-back tasks, in which participants were asked to respond when presented with a stimulus that matched one presented *n* stimuli prior, were utilized in four articles (Baron et al., 2018; Nocera et al., 2013; Penko et al., 2018, 2020). Other less commonly utilized cognitive tasks included a digit monitoring task (Beck et al., 2015; Ehgoetz Martens et al., 2018; Pieruccini-Faria, Ehgoetz Martens, et al., 2014; Pieruccini-Faria, Jones, et al., 2014), reciting every other letter of the alphabet (Fino et al., 2018), memory tasks (Penko et al., 2018, 2020; Lynn Rochester et al.,

2004; Zirek et al., 2018), comprehension tasks (Wild et al., 2013; Yogev et al., 2005), other counting tasks (Sarbaz & Pourakbari, 2019; Wild et al., 2013; Yogev et al., 2005), word searching task (Siragy & Nantel, 2020), and phone dialing task (Strouwen, Molenaar, Keus, Münks, Bloem, et al., 2016; Strouwen, Molenaar, Keus, Münks, Heremans, et al., 2016). When considering DT measurement tools, the most utilized in PD were absolute measures of performance, which were utilized in 43 of the articles, of which 34 utilized only these measures of DT performance. Of the 22 articles which utilized a measure of DTE, the majority used mDTE (Canning et al., 2006; Chawla et al., 2014; Fino et al., 2018; Gaßner et al., 2017; Heinzel et al., 2016; Hirata et al., 2020; Hsiu-Chen et al., 2020; Valerie E. Kelly et al., 2012; Valerie E. Kelly & Shumway-Cook, 2014; Kleiner et al., 2018; Maidan et al., 2016; Micó-Amigo et al., 2019; Peterson et al., 2020; L. Rochester et al., 2014; Smulders et al., 2012; Stegemoller et al., 2012; Strouwen, Molenaar, Keus, Münks, Bloem, et al., 2016; Strouwen, Molenaar, Keus, Münks, Heremans, et al., 2016; Zirek et al., 2018), and many also used cogDTE (Baron et al., 2018; Heinzel et al., 2016; Hsiu-Chen et al., 2020; Valerie E. Kelly et al., 2012; Valerie E. Kelly & Shumway-Cook, 2014; Micó-Amigo et al., 2019; Peterson et al., 2020; L. Rochester et al., 2014; Smulders et al., 2012; Strouwen, Molenaar, Keus, Münks, Bloem, et al., 2016; Strouwen, Molenaar, Keus, Münks, Heremans, et al., 2016; Wild et al., 2013). Similar to AD, two articles reported utilizing a type of composite DTE that considers more aspects of CMI, in these instances adding mDTE to cogDTE (Heinzel et al., 2016; Micó-Amigo et al., 2019). A few studies also included the attention allocation index (AAI) (Yogev-Seligmann et al., 2012) or the modified AAI (mAAI) (Valerie E. Kelly et al., 2012; Valerie E. Kelly & Shumway-Cook, 2014; Peterson et al., 2020), a measure that attempts to quantify the degree to which individuals place their attention on a specific task

during competing attentional demands. Positive mAAI values indicate motor prioritization whereas negative values indicate cognitive prioritization. The standard formula for mAAI (V E Kelly et al., 2010; Siu & Woollacott, 2007) has been included below:

$$mAAI = mDTE - cogDTE$$

Overall, the findings of these articles investigating CMI in PD were separated into three categories: findings related to CMI in PD, CMI findings specific to PD-FOG, and DT and neuroimaging in PD (see table 2).

Findings related to CMI in PD: In this, the most general of the three categories, we included 43 studies that had a total of 1,772 PD participants. In our analysis, we found several themes. One of the most prominent themes among the articles was that DT tends to negatively impact gait/motor performance (Criminger & Swank, 2020; Hsiu-Chen et al., 2020; Myers et al., 2020; O'Shea et al., 2002; Penko et al., 2018, 2020; Salazar et al., 2017; Siragy & Nantel, 2020; Smulders et al., 2012; Speciali et al., 2014; Stegemöller et al., 2014; Xu et al., 2018; Yogev et al., 2005; Zirek et al., 2018). Specifically, DT was found to disrupt normal arm swing kinematics (Baron et al., 2018) and was associated with reduced gait velocity (Christofoletti et al., 2014; Ehgoetz Martens et al., 2018; O'Shea et al., 2002; Penko et al., 2020; Smulders et al., 2012; Xu et al., 2018; Yogev-Seligmann et al., 2012; Yogev et al., 2005), local dynamic stability at heel strike (Fino et al., 2018; Siragy & Nantel, 2020; Xu et al., 2018), weight transfer during gait (Fino et al., 2018), step time (Siragy & Nantel, 2020), and stride length (Smulders et al., 2012).

Increased step width (Siragy & Nantel, 2020) and gait variability (Plotnik et al., 2011; Yogev-Seligmann et al., 2012; Yogev et al., 2005) were also associated with DT performance for individuals with PD. Some of these DT-related gait changes were found to be associated with cognitive impairment, particularly reductions in step length and increased gait variability (Amboni et al., 2012, 2018; Varalta et al., 2015). Additionally, these same metrics were found to be predictive of future executive function and attention deficits (Amboni et al., 2012, 2018; Varalta et al., 2015). When investigating predictors of cognitive abilities, DT performance (mDTE) explains 8% of the variance in cognition (Gaßner et al., 2017; Stegemöller et al., 2014). Another consistent finding was that DT performance was different between those with PD and healthy older adults (Hirata et al., 2020; Micó-Amigo et al., 2019; L. Rochester et al., 2014; Salazar et al., 2017; Sarbaz & Pourakbari, 2019). Specifically, people with PD exhibited reduced step width (L. Rochester et al., 2014), gait velocity (Salazar et al., 2017), and stride frequency (Salazar et al., 2017); with increased gait variability (L. Rochester et al., 2014; Sarbaz & Pourakbari, 2019) during DT compared to healthy older adults. Additionally, those with PD had poorer DT performance as measured by DTEs when compared to healthy older adults (Hirata et al., 2020; Maidan et al., 2016). Of note, both mDTE and cogDTE demonstrate excellent reliability in participants with PD, and were more reliable than absolute measures of performance during DT (Strouwen, Molenaar, Keus, Münks, Bloem, et al., 2016). While there were not functional performance changes observed during gait initiation with the addition of a concurrent cognitive task (Fernandes et al., 2016; Nocera et al., 2013), EMG analysis revealed slower activation time and lower activation values than healthy older adults (Fernandes et al., 2017). One article investigated the impact of DT during protective stepping; they found that DT

was associated with increased reaction time (Peterson et al., 2020). However, step response remained similar to ST performance. In addition to gait decrements, DT was also associated with poorer concurrent task performance (e.g. cognitive task) (Fuller et al., 2013; Sarbaz & Pourakbari, 2019). The cognitive decrements during DT were found to be associated with greater levels of disability (Fuller et al., 2013) and more akinesia (Hsiu-Chen et al., 2020).

When considering the makeup of the DT paradigm utilized, we found several studies reported that gait is more impacted by a concurrent cognitive task than a motor task (Chawla et al., 2014; Galletly & Brauer, 2005; Penko et al., 2018, 2020). Christofoletti et al found the opposite (Christofoletti et al., 2014), and O'Shea et al found no difference between the impact of cognitive and motor current tasks during gait (O'Shea et al., 2002). The impact of attentional prioritization may explain the conflicting nature of these findings. Kelly et al found that people with PD can modify their attention prioritization during DT with a trade-off in performance of the other task (Valerie E. Kelly et al., 2012). Several studies provide evidence in support of this notion showing specific attentional resource management in individuals with PD that may be dependent on individual and task factors (Fino et al., 2018; Fuller et al., 2013; Valerie E. Kelly & Shumway-Cook, 2014; Peterson et al., 2020; Wild et al., 2013; Yogev-Seligmann et al., 2012). Finally, poor DT performance was related to falls (Heinzel et al., 2016; Pelosin et al., 2016; Plotnik et al., 2011; Smulders et al., 2012). The measure of CMI that utilized mDTE plus cogDTE was the most sensitive predictor of falls (Heinzel et al., 2016).

CMI findings specific to PD-FOG: There were nine articles included in this section that investigated CMI on a total of 154 participants with FOG. The most notable finding was that DT performance increases FOG frequency and severity (Beck et al., 2015; Kleiner et al., 2018; Peterson et al., 2015; Spildooren et al., 2010; Vervoort et al., 2016). Particularly this occurs during 360 degree turns while performing a concurrent cognitive task (Spildooren et al., 2010). This approach has been recommended by Spildooren et al as a standard method to elicit FOG in individuals with PD. However, Bertoli et al found contradictory results noting that turning worsened similarly between individuals with PD regardless of presence of FOG (Bertoli et al., 2019). Interestingly, Beck et al found that DT-related gait changes in individuals with FOG can be mitigated by the use of visual cues (Beck et al., 2015). When confronted with a DT, participants with FOG were more likely to use a maladaptive cognitive prioritization during turning compared to others with PD (Spildooren et al., 2010). As we consider the findings related to protective stepping, we find that, unlike the findings of Peterson et al in individuals with PD without FOG (Peterson et al., 2020), individuals with FOG were more likely to fall with protective stepping with a concurrent cognitive task (Jacobs et al., 2014). DT performance in participants with PD-FOG was also found to be correlated with executive function (Pieruccini-Faria, Jones, et al., 2014), spatial planning (Pieruccini-Faria, Jones, et al., 2014), inhibition (Peterson et al., 2015), and reaction time (Peterson et al., 2015). Finally, two studies utilized neuroimaging techniques to investigate brain activity in individuals with DT-triggered FOG. In combination, these articles revealed hypoconnectivity between caudate and superior temporal lobe (Vervoort et al., 2016), hyperconnectivity between dorsal putamen and precuneus

(Vervoort et al., 2016), and asymmetric structural connectivity in the pedunculopontine nucleus (Peterson et al., 2015) associated with DT performance.

DT and neuroimaging in PD: There were four articles that used a sample of individuals with PD without FOG that investigated how DT performance related to data obtained through neuroimaging modalities. These studies included a combined 141 participants with PD. Hirata et al found no relationship between DT performance and DaT scan (Hirata et al., 2020). Frontal lobe activation was constant between ST and DT in participants with PD, whereas healthy participants had increased frontal activation during DT (Maidan et al., 2016). In contrast, during DT activities, individuals with PD activated a region of ventrolateral putamen, which in healthy participants was associated with poorer DT performance (Nieuwhof et al., 2017). And finally, Pelosin et al found that poorer DT performance was associated with increased levels of cholinergic inhibitory activity in the sensory motor cortex (Pelosin et al., 2016).

Table 3. Articles included in this review with a sample of prodromal neurodegenerative disease. The table is organized by primary population of interest into four sections: A) mild cognitive impairment; B) subjective cognitive impairment; C) healthy with Alzheimer's disease biomarkers or genetic risk; and D) idiopathic rapid eye movement sleep behavior disorder or early PD.

Article	Sample	Motor task	Cognitive task	DT measurement tools	Key findings related to CMI
A. Mild cognitive impairment					
(Juliana Hotta Ansai et al., 2018)	40 MCI 38 AD 40 Healthy	TUG	Phone dialing task	(1)mDTE (2)cogDTE (3)Absolute measures of performance	DT performance was associated with visuospatial skills in all groups. Executive function and fluency were the strongest predictors of DT performance in AD.
(Juliana H. Ansai et al., 2017)	40 MCI 38 AD 40 Healthy	TUG	Phone dialing task	(1)mDTE (2)cogDTE (3)Absolute measures of performance	DT performance worse for AD than MCI or healthy, with AD group. No items differentiated MCI from the healthy group.
(Gillain et al., 2016)	9 MCI that progressed to AD within 4 years 4 stable MCI	Gait	Serial subtraction by 1	Absolute measures of performance	At baseline, there was a reduction in gait velocity and symmetry during DT gait for those MCI who develop AD compared to those with stable MCI that did not progress.
(Gillain et al., 2009)	14 MCI 6 AD 14 Healthy	Gait	Serial subtraction by 1	Absolute measures of performance	DT gait was more impaired in MCI and AD than controls. With the MCI group having reduced gait velocity and stride frequency compared to healthy. The AD group had reduced gait velocity, stride length, and increased gait variability. Gait variability and stride length distinguished between MCI and AD.
(Gonçalves et al., 2018)	40 MCI 38 AD	TUG	Phone dialing task	(1)mDTE (2)Absolute measures of performance	mDTE was associated with more falls in MCI but not AD.
(König et al., 2017)	24 MCI 23 AD 22 Healthy	Gait	Serial subtraction by 1	Absolute measures of performance	DT gait differences between AD and MCI, with the AD group having slower gait velocity, decreased cadence, and increased step time variability. There were not differences between MCI and healthy.
(Maquet et al., 2010)	14 MCI 6 AD 14 Healthy	Gait	Counting (unspecified)	Absolute measures of performance	Gait velocity during DT varies between all groups, with AD exhibiting the slowest and healthy the fastest gait velocity.
(de Melo Borges et al., 2015)	42 MCI 26 mild AD 36 Healthy	TUG	Controlled oral word association task	Absolute measures of performance	DT-TUG differentiates mild AD, MCI, and healthy, with worse performance in the AD group and the best performance in the healthy

					group. Receiver-operating characteristic curve analysis showed higher area under the curve for cognitive-motor DT, than for ST TUG, or motor-motor DT. DT worsens functional performance for all groups.
(Muir et al., 2012)	29 MCI 23 AD 22 Healthy	Gait	(1)Serial subtraction by 7 (2)Controlled oral word association task	(1)mDTE (2)Absolute measures of performance	Difference between AD and MCI during DT on gait velocity, stride time, stride time variability and were different from controls. More complex cognitive tasks exert greater interference on gait.
(Muurling et al., 2020)	58 MCI 26 AD 58 Healthy	Fast gait with turning	Serial subtraction by 1	Absolute measures of performance	No relationship between DT gait and Aβ42. Total tau was higher in those with more DT gait variability but not with ST gait.
(Nielsen et al., 2018)	17 MCI 26 AD 41 Healthy	TUG	Serial subtraction by 1	(1)mDTE (2)Absolute measures of performance	DT performances (mDTE) distinguishes groups. mDTE more strongly associated with cognitive decline than DT-TUG time or ST TUG time. mDTE has moderate associations with Mini Mental State Examination, CSF Aβ42, T-tau, and P-tau. These findings indicate that poorer DT performance was associated with lower score on the Mini Mental State Examination, lower levels of CSF Aβ42, and higher levels of CSF T-tau, and P-tau.
(Nilsson et al., 2020)	124 MCI 175 Healthy	TUG	Serial subtraction by 3	(1)mDTE (2)Absolute measures of performance	In the whole sample CSF P-tau was associated with DT performance using both mDTE and DT-TUG time, such that a decline in DT performance was associated with higher levels of P-tau. These findings were maintained when analyzed just in the MCI, however they were not found in the healthy group alone.
(Pettersson et al., 2007)	6 MCI 6 AD 25 Healthy	Gait with turn	Controlled oral word association task	Absolute measures of performance	Subjects with AD had lower walking speed and greater time change between single and dual task compared with healthy controls.
(Sakurai et al., 2019)	40 MCI	Gait	(1)Serial subtraction by 1 and 7 (2)Controlled oral word association task	mDTE	Smaller left entorhinal cortex volumes were positively associated with mDTE, such that poorer DT performance was associated with smaller entorhinal cortex volumes.
(Tarnanas et al., 2015)	65 MCI 86 early AD 76 Healthy	Gait	(1)Serial subtraction by 1 (2) Controlled oral word association task	Intra-individual variability on absolute measures of performance	Motor variables during the DT tasks were a more reliable marker for early diagnosis of MCI than ST.

B. Subjective cognitive impairment					
(Hanna B. Åhman et al., 2020)	77 SCI 135 MCI 86 Dementia 166 Healthy	TUG	Controlled oral word association task	(1)mDTE (2)Absolute measures of performance	Correct response rate during DT discriminates between groups. Between groups standardized odds ratios for healthy and SCI was 2.98, for SCI and MCI was 2.15, and for MCI and dementia was 3.29.
(Hanna Bozkurt Åhman et al., 2019)	8 SCI 52 MCI 28 Dementia	TUG	Controlled oral word association task	(1)mDTE (2)Absolute measures of performance	Correct response rate during DT had a moderate positive association with T-tau and P-tau (r=.2-.3). There was no relationship between DT performance and Aβ42.
(Beauchet et al., 2017)	10 SCI (relative) 69 SCI (participant) 32 SCI (both) 15 Healthy	Gait	Serial subtraction by 1	Absolute measures of performance	Increased stride time variability during DT, but not during ST, was associated with SCI reported by a relative.
(Cullen et al., 2019)	46 SCI 77 MCI 71 Dementia	Gait	(1)Serial subtraction by 1 and 7 (2)Controlled oral word association task	(1)mDTE (2)Absolute measures of performance	Proportion of decline in gait velocity during DT (mDTE) is greater in MCI than dementia. Gait velocity slows when combined with a DT for all groups. SCI and MCI groups had statistically comparable DTEs.
(De Cock et al., 2019)	71 CDR 0 122 CDR 0.5 168 CDR 1 51 CDR 2 18 CDR 3 127 progressed to dementia	Gait	(1)Serial subtraction by 2 (2)Controlled oral word association task	(1)mDTE (2)Absolute measures of performance	DT performance (mDTE of step width) in those with CDR of 0 or 0.5 was associated with later (33 -41 months) diagnosis of dementia.
(Kueper et al., 2020)	19 SCI 84 MCI 12 Healthy 8 (of the above) converted to dementia within 36 months	Gait	Serial subtraction by 1	mDTE	Pooled index (ADAS-COG + ST gait velocity + mDTE) discriminates well between healthy, SCI, and MCI. The pooled index improved responsiveness to cognitive decline over time. Adding motor function assessments to the ADAS-Cog may improve responsiveness in pre-dementia populations.
(Lowe et al., 2020)	133 SCI 119 MCI	Gait	Spelling 5 letter words backwards	Absolute measures of performance	MCI had greater impact of DT on gait velocity and on number of correct responses on cognitive task during DT gait. Additionally, those with MCI had poorer performance of measures of executive attention. Executive attention

					explains 25% of the variance in motor performance during DT.
(Rantalainen et al., 2020)	24 SCI 9 mild dementia	Gait	Serial subtraction by 7	Absolute measures of performance	No differences in DT performance noted between SCI and mild dementia with the exception of gait variability, which was higher in dementia group.
C. Cognitively healthy with Alzheimer's disease biomarkers or genetic risk					
(MacAulay et al., 2016)	75 Healthy with APOE ε4 224 Healthy	Gait	Spelling 5 letter words backwards	Absolute measures of performance	APOE ε4 group showed poorer cognitive performance during DT. Decreased stride length during DT and increased stride length variability during DT associated with those that carried at least one APOE ε4 allele.
(Nadkarni et al., 2017)	16 Healthy amyloid+ 11 Healthy amyloid-	Gait	(1)2-back (2)Go No-Go task, (3)Phone dialing task	(1)mDTE (2)cogDTE	Those that were amyloid positive (per PiB PET) had higher mDTEs but not cogDTEs than that were amyloid negative. Specifically mDTE for DT gait with secondary task of working memory (2-back) and phone dialing task were different between groups. Overall, standardized uptake value ratio correlated moderately and inversely with mDTEs, such that as gait performance during DT declined standardized uptake value ratio increased.
(Whitson et al., 2018)	14 Healthy with APOE ε4 allele 15 Healthy	Gait	(1)Word recall task (2)"Stop/Go" task	(1)mDTE (2)cogDTE (3)Performance-operating characteristic plots for task trade-off (4)Absolute measures of performance	Compared to low risk participants, APOE ε4 carriers tended to be more impacted by DT. Both the memory (word recall) and executive function ("stop/go") tasks resulted in DT related decrements on gait, with the executive function task exhibiting larger effect sizes. DT with the executive function task, resulted in larger effect sizes for group difference on mDTE than cogDTE.
D. Idiopathic rapid eye movement sleep behavior disorder and early Parkinson's disease					
(Ehgoetz Martens et al., 2019)	24 iRBD 14 Healthy	Gait	(1)Serial subtraction by 1,4, and 7 (2)Controlled oral word association task	Absolute measures of performance	During DT those with iRBD increased step width variability without increasing step width, while controls increased step width without increase step width variability.

(Micó-Amigo et al., 2019)	22 Early PD 27 Middle PD 25 Healthy	Fast gait in a circle	Serial subtraction by 7	(1)mDTE (2)cogDTE (3)mDTE + cogDTE	DT did not improve assessment for predicting progression within PD although there were differences between PD and healthy.
(L. Rochester et al., 2014)	121 Early PD 189 Healthy	Gait	(1)Forward Digit span (2)Digit span +1	(1)mDTE (2)cogDTE (3)Absolute measures of performance	DT inference was present for gait (mDTE) but not cognition (cogDTE). DT resulted in reduced step width, and increased gait variability in individuals with early PD compared to healthy older adults.

DT: dual task, CMI: cognitive-motor interference, MCI: mild cognitive impairment, AD: Alzheimer's disease, TUG: Timed Up and Go, mDTE: motor dual task effect, cogDTE: cognitive dual task effect, DT-TUG: dual task Timed Up and Go, ST: single task, Aβ: Amyloid β, CSF: cerebral spinal fluid, T-tau: total tau, P-tau: phosphorylated tau, SCI: subjective cognitive impairment, CDR: clinical dementia rating scale, ADAS-COG: Alzheimer's Disease Assessment Scale-Cognitive Subscale, APOE: Apolipoprotein E, amyloid+: amyloid positive, amyloid-: amyloid negative, PiB: Pittsburgh compound B, PET: position emission tomography, iRBD: idiopathic rapid eye movement sleep behavior disorder, PD: Parkinson's disease.

Prodromal neurodegeneration

A total of 29 articles investigating CMI in prodromal neurodegeneration 26 of which investigated prodromal AD, were included in this review. With one exception (Sakurai et al., 2019), all studies utilized comparison groups. In regard to prodromal population of interest, 15 articles included participants with MCI, eight articles included participants with subjective cognitive impairment (SCI), three articles included cognitively healthy older adults with AD biomarkers or genetic risk of AD, and three articles included participants with early PD or idiopathic rapid eye movement sleep behavior disorder (iRBD), a condition that precedes many neurodegenerative diseases, most notably PD. (See table 3)

Among all articles with samples of prodromal neurodegeneration, gait was the most common motor task, utilized in 20 of the articles. The remaining eight articles utilized the TUG for the motor component of the DT (Hanna B. Åhman et al., 2020; Hanna Bozkurt Åhman et al., 2019; Juliana H. Ansai et al., 2017; Juliana Hotta Ansai et al., 2018; de Melo Borges et al., 2015; Gonçalves et al., 2018; Nielsen et al., 2018; Nilsson et al., 2020). The cognitive tasks used during the DT paradigms varied much more greatly than the motor task selection. Arithmetic tasks were the most commonly used, being utilized in 18 articles, with controlled oral word association tasks next most frequent at 10 articles. Other cognitive tasks utilized in the DT paradigms included a phone dialing task (Juliana H. Ansai et al., 2017; Juliana Hotta Ansai et al., 2018; Gonçalves et al., 2018; Nadkarni et al., 2012), spelling backwards task (Lowe et al., 2020; MacAulay et al., 2016), inhibition tasks (Nadkarni et al., 2017; Whitson et al., 2018), digit span (L. Rochester et al., 2014), recall tasks (Whitson et al., 2018), and n-back tasks (Nadkarni et al.,

2017). Measurement of DT performance was most often done using absolute measures of performance, although 16 of the studies did utilize one or more measures of DTE. Among the 16 articles that utilized DTE measures, all 16 utilized mDTE (Hanna B. Åhman et al., 2020; Hanna Bozkurt Åhman et al., 2019; Juliana H. Ansai et al., 2017; Juliana Hotta Ansai et al., 2018; Cullen et al., 2019; De Cock et al., 2019; Gonçalves et al., 2018; Kueper et al., 2020; Micó-Amigo et al., 2019; Muir et al., 2012; Nadkarni et al., 2017; Nielsen et al., 2018; Nilsson et al., 2020; L. Rochester et al., 2014; Sakurai et al., 2019; Whitson et al., 2018), six utilized cogDTE (Juliana H. Ansai et al., 2017; Juliana Hotta Ansai et al., 2018; Micó-Amigo et al., 2019; Nadkarni et al., 2017; L. Rochester et al., 2014; Whitson et al., 2018), one utilized a composite DTE adding mDTE to cogDTE (Micó-Amigo et al., 2019), and one utilized performance-operating characteristics plots for assessing task trade-off (Whitson et al., 2018). Overall, the findings of these articles investigating CMI in prodromal conditions were separated by populations of interest as described and are reported.

CMI findings in MCI: There were 15 articles included with a sample of individuals with MCI, including a total of 566 participants. We observed that participants with MCI exhibited differences in DT performance compared to participants with AD (Juliana H. Ansai et al., 2017; Gillain et al., 2009; König et al., 2017; Maquet et al., 2010; Muir et al., 2012; Tarnanas et al., 2015). Specifically, gait variability was greater (Gillain et al., 2009; König et al., 2017; Muir et al., 2012; Nielsen et al., 2018), while stride length (Gillain et al., 2009), gait velocity (König et al., 2017; Maquet et al., 2010; Muir et al., 2012), and cadence (König et al., 2017) were reduced in AD participants. Additionally, time to complete TUG was greater in those with AD (de Melo

Borges et al., 2015). In contrast to these findings, one study showed no differences between those with MCI and those with AD, though this study was limited by a small sample size, and may have been underpowered (Pettersson et al., 2007). Among the articles, there was not a consensus regarding DT-related differences between those with MCI and healthy older adults. While six studies found DT performance differences to exist between MCI and healthy older adults (de Melo Borges et al., 2015; Gillain et al., 2009; Maquet et al., 2010; Muir et al., 2012; Nielsen et al., 2018; Tarnanas et al., 2015), two studies found no differences between these groups (Juliana H. Ansai et al., 2017; König et al., 2017). Among the studies that did find DT related differences between MCI and healthy older adults, they specifically noted that those with MCI had reduced gait velocity (Gillain et al., 2009; Maquet et al., 2010), stride frequency (Gillain et al., 2009), and increased time to complete functional mobility (de Melo Borges et al., 2015).

Three articles investigated the utility of DT measures to distinguish between different healthy older adults, those with MCI, and those with AD. De Melo Borges et al found that cognitive-motor DT performance had higher area under the curve than either ST performance, or motor-motor DT performance during analysis of receiver-operating characteristic curves (de Melo Borges et al., 2015). Tarnanas et al found that motor during DT were more reliable marker for early diagnosis of MCI (Tarnanas et al., 2015), when compared to ST. Nielsen et al found similar results with mDTE (Nielsen et al., 2018). Additionally, DT performance was also shown to be different in those with MCI who later developed AD (Gillain et al., 2016).

Overall, DTs worsen performance on both cognitive and motor tasks (de Melo Borges et al., 2015) with more complex cognitive tasks resulting in greater impact on gait for individuals with MCI (Muir et al., 2012). DT performance, as measured by mDTE, was found to be associated with falls and visuospatial skill in those with MCI (Juliana Hotta Ansai et al., 2018; Gonçalves et al., 2018). Additionally, mDTE was found to be related to entorhinal cortex volumes in participants with MCI, such that poorer DT performance was related to smaller volumes (Sakurai et al., 2019).

Three articles reported the results from findings investigating the relationship between DT performance and AD biomarkers. Conflicting results were found with CSF Aβ42 with one study noting no relationship with DT performance (Muurling et al., 2020), while another study found that participants with greater decline in motor performance with DT (mDTE) had lower levels of Aβ42 (Nielsen et al., 2018). The relationship between DT performance and tau was more consistent, with three studies identifying moderately strong associations between them, such that decrements in DT performance was associated with greater levels of CSF total tau (T-tau) and phosphorylated tau (P-tau) (Muurling et al., 2020; Nielsen et al., 2018; Nilsson et al., 2020).

CMI findings in SCI: Eight articles were included with samples that fit the population of interests, combining for a total of 508 participants with SCI. Similar to the findings of those with MCI, four articles reported DT performance differences between cognitively healthy

participants and those with SCI, with those with SCI having poorer performance during DT conditions (Hanna B. Åhman et al., 2020; Beauchet et al., 2017; De Cock et al., 2019; Kueper et al., 2020). However, Cullen et al and Lowe et al found conflicting results and reported that participants with SCI and those with MCI had statistically comparable DT performance (Cullen et al., 2019; Lowe et al., 2020). Additionally, poorer DT performance among individuals with clinical dementia rating (CDR) of 0 or 0.5 was found to precede a diagnosis of dementia by more than 36 months (De Cock et al., 2019). Discrimination between individuals that are cognitively healthy, those with SCI, and those with MCI improved when DT performance decrements were added to the AD Assessment Scale – Cognitive Subscale (ADAS-cog), a measure frequently used for early detection of subtle impairments related to AD (Kueper et al., 2020). Åhman et al found that cognitive performance during DT was more responsive to group difference than was changes in motor performance, reporting a standardized odds ratio between cognitively healthy participants and those with SCI of 2.98 (Hanna B. Åhman et al., 2020). They also found that cognitive performance during DT was associated with CSF T-tau and P-tau levels; however, they found no relationship with Aβ42 (Hanna Bozkurt Åhman et al., 2019). Two articles reported differences between participants with SCI and those with MCI on DT performance (Lowe et al., 2020; Rantalainen et al., 2020). Similar to the results of Åhman et al (B Åhman et al., 2020), Lowe et al found that measures of cognitive performance during DT were more effective at discriminating between participants with SCI and those with MCI (Lowe et al., 2020). In contrast, Rantalainen et al found that gait variability during DT was lower in those with SCI compared to those with mild dementia (Rantalainen et al., 2020).

Cognitively healthy with AD biomarkers or genetic risk of AD: Three articles included in this review investigated CMI in cognitively healthy individuals that demonstrated an increased risk for AD development. Combined between these studies there were 89 participants that were apolipoprotein E (APOE) ε4 allele carriers, and 16 participants with amyloid positive positron emission tomography (PET) scan. MacAulay et al and Whitson investigate the impact of cognitive-motor DTs in participants that carried at least one APOE ε4 allele. They both found that DT performance was different between participants that did and those that did not carry an APOE ε4 allele (MacAulay et al., 2016; Whitson et al., 2018). Specifically, MacAulay et al found that APOE ε4 carriers had decreased stride length and increased stride length variability during DT conditions, compared to those who did not carry an APOE ε4 allele (MacAulay et al., 2016). Similar to findings in other populations, MacAulay et al also found that cognitive performance decreased during DT (MacAulay et al., 2016) among ε4 carriers, while Whitson et al found that more challenging cognitive tasks (i.e., executive function task) impacted gait more than cognition (Whitson et al., 2018). Nadkarni et al compared DT performance of 16 cognitively healthy older adults with positive amyloid PET scans to 11 healthy older adults with negative amyloid PET scans. They found that those that were amyloid positive had higher mDTEs but not cogDTEs (Nadkarni et al., 2017). Additionally, DT performance was moderately and inversely associated to standardized uptake value ratio (SUVR), such that worse DT performance was correlated with elevated SUVR (Nadkarni et al., 2017).

CMI in iRBD and early PD: Three articles were included in this category, which is analogous to prodromal PD. Among the three studies included, there were a total of 143 participants with

early PD and 24 with iRBD. Two found mDTE was different between those with early PD and healthy older adults, but found no difference on cogDTE (Micó-Amigo et al., 2019; L. Rochester et al., 2014). Additionally, Rochester et al found that DT was associated with reduced step width and gait variability only in individuals with early PD and not healthy older adults (L. Rochester et al., 2014). Ehgoetz Martens et al made similar comparisons between 29 participants with iRBD and 14 healthy adults. They found that participants with iRBD exhibited increased step width variability in response to DT, but no change in step width. Whereas, healthy adults increased step width in response to DT, without increasing step width variability (Ehgoetz Martens et al., 2019).

DISCUSSION

The primary aim of this scoping review was to gain insights into how individuals with AD and PD are impacted by CMI. The findings of this review can be used to better characterize the impact of CMI in AD and PD. Our findings confirm that individuals with AD and PD are impacted by CMI more than their healthy counterparts and that individuals with AD respond differently to CMI than do those with PD. Specifically, AD was found to be impacted most consistently in gait variability and gait velocity, though measures of DTE appear to be more robust and sensitive in this population than are absolute measures of performance, such as specific gait parameters. This may be because absolute measures of performance are inherently biased by the lack of control for ST performance. Individuals with AD also appear to be more impacted by a cognitive-motor DT than a motor-motor DT. On the other hand, mediolateral stability and gait velocity appear to be most impacted during DT in PD, though this profile was shown to be

prone to change based on allocation of attentional resources during DT (Valerie E. Kelly et al., 2012). However, it is important to note that though AD and PD were consistently found to have different responses to CMI, no specific CMI profile was clearly demonstrated for either AD or PD. This finding is likely due to the diverse combination of motor and cognitive tasks utilized in the DT paradigms and their varying degrees of novelty and complexity. Previous research has shown that there is an optimal combination of novelty and complexity in order to create the optimal level of effort while maximizing CMI (McIsaac et al., 2015). While this combination is likely related to individual factors, it is also impacted by factors related to disease status and severity and could be approximated with more homogenous populations. The development of distinct and well-characterized CMI profiles for specific neurodegenerative disease states and severities would allow for better comparison across diseases and among differing stages of degenerative disease.

DT performance had consistent weak to moderate correlations with motor abilities (gait, mobility functions, etc.) as well as cognitive abilities (executive function, attention, etc.), regardless of population. One possible explanation for these associations is that DT performance is simply an expression of similar deficits in one of the domains being probed with DT paradigm. If this were the case, DT paradigms would offer little benefit over simply observing the outcome of interest in ST conditions. However, an alternative explanation is that only a portion of the variance of DT performance is obtained through contributions from the underlying single task domains. This notion is supported by the lack of strong correlations observed. This explanation is supported by neuroimaging studies which identify additional brain

regions active during DT that are not activated during either of the component tasks when performed individually (Nieuwhof et al., 2017), as well as studies showing that ST performance explains only a small portion of the variance in DT performance (Strouwen, Molenaar, Keus, Münks, Heremans, et al., 2016).

Investigating the impact of CMI in prodromal and early neurodegenerative disease states resulted in more evidence for the impact of CMI in prodromal AD, than prodromal or early PD. CMI was found generally to exert a greater impact as the disease states become more severe. It was consistently found to elicit even subtle deficits in individuals that would later develop AD and those that were at elevated risk for AD development and were otherwise healthy. This ability to compare generally across the severity of AD is facilitated by the multistate model (among others) that describes the development and progression of AD in distinct stages, which includes as many as six prodromal stages and has been implemented extensively in the literature (Brookmeyer et al., 2018). Conversely, in PD the CMI pattern across disease severity is more difficult to observe as the prodromal states of PD are less frequently investigated, and the distinction between early/mild disease, moderate disease, and severe disease states are not well reported in the literature. Despite this, it is important to note that subtle deficits were elicited by CMI even in the earliest prodromal state (Ehgoetz Martens et al., 2019). These subtle changes in the prodromal state were different and more pronounced in the clinically defined disease state. Overall, two gaps in the existing literature would be the most impactful in better understanding the influence of the CMI in prodromal neurodegeneration. The first is clearly defined prodromal and early disease states in PD that are utilized with high frequency in the

literature. The next gap is the lack of consistency of DT paradigms and DT measures utilized, which impacts all CMI research.

In recent years, attempts have been made to better characterize CMI through the use of more robust measures and observing measures across multiple task domains (McIsaac et al., 2018; Plummer & Eskes, 2015; Yang et al., 2017). Particularly key in the understanding of CMI in these populations is having insight into the attentional strategies utilized during the DT paradigm (Valerie E. Kelly et al., 2012; Valerie E. Kelly & Shumway-Cook, 2014). The utilization of attentional strategies can be categorized into four primary strategies as described by Plummer et al (Plummer et al., 2013; Plummer & Eskes, 2015). 1) mutual facilitation in which the performance of DT results in improved performance of both the motor and cognitive tasks. 2) Motor-priority trade-off where attention is allocated in a greater degree to the motor task resulting in minimal to no decline in motor performance with DT, but at the cost of cognitive performance. 3) Cognitive-priority trade-off in which cognitive performance has minimal decrements with DT but motor performance worsens. This is accomplished by the allocation of attentional resources to a greater degree to cognitive tasks during the DT paradigm. 4) Mutual facilitation wherein both cognitive and motor task performance deteriorate during DT. Beyond these classifications, the degree of attention allocation can be quantified using the attention allocation index (V E Kelly et al., 2010; Siu & Woollacott, 2007). Reporting of dominant attentional strategies and the degree to which specific tasks are prioritized can greatly influence how results of DT paradigms are interpreted. For example, if mDTE is the only measure obtained and no differences are observed, the conclusion is often that there was no or

sufficiently minimal impact from CMI; however, this same finding could result from allocating attentional resources to the motor task, and attending minimally to the cognitive task. Comparison of the interference observed in both the cognitive and motor tasks then provides more insight into DT performance as well as attentional strategy selection and resource management.

Several themes emerged in our investigation of DT outcome measures across the groups. First, the most frequently utilized outcomes were absolute measures of performance, which, as noted above, have many inherent drawbacks. Among DTEs, the most frequently utilized was mDTE; however, nearly 60% of articles used it without capturing other DTE outcomes. As noted above, this creates a gap and provides an incomplete picture, which increase the potential bias in the interpretation of these results. Next most frequently employed was cogDTE, followed by measures of attention allocation, which were utilized sparingly. Few studies utilized measures of composite interference which appear to be the more sensitive and robust than either mDTE or cogDTE in isolation (Cocchini et al., 2004; Heinzel et al., 2016; Micó-Amigo et al., 2019; Nadkarni et al., 2012; L. Rochester et al., 2014). These composite measures also have the potential to be the most sensitive to the subtle deficits of early and prodromal disease states. In these populations of relevance to this review, the two methods utilized for creating a composite interference value were averaging or summing mDTE and cogDTE. Two additional methods for creating a composite value have been proposed. One method utilizes an approach that quantifies the change in “area under the curve” between ST and DT performance taking into account two task domains (J.K. Longhurst et al., 2020; Jason K Longhurst & Landers, 2019).

Utilizing a similar theoretical method, the other method proposes utilizing the Euclidean distance. Both methods are attempts to quantify the "total" interference (Wahn & Sinnett, 2019). The benefit to these approaches, as well as the summing approach, is that regardless of attention allocation, theoretically, the overall magnitude of interference would remain constant. Further research is needed regarding their psychometric properties and utility in neurodegeneration.

While this scoping review provides insights into CMI in individuals with neurodegeneration, it has several limitations. The primary limitation of this review is that only articles that utilized gait-related motor tasks were considered, with the most pertinent omission from the literature being studies that utilized postural stability motor tasks. This review was primarily interested in tasks that involved complex processes that have good evidence of overlap with the disease process of both AD and PD. While PD impacts postural stability and gait, the literature identifies the primary motor changes associated with AD being gait-related changes. Future reviews should consider the difference in CMI related to motor task selection for inclusion in the DT paradigms. Additionally, as this review was primarily interested in the impact of CMI, it did not include studies that included interventions that could potentially mitigate the effects of CMI, by either improving automaticity or modifying attentional strategies.

CONCLUSIONS

The authors of this scoping review investigated the current state of the literature to provide better insights into the impact of CMI on individuals with AD and PD. The findings discussed in this review demonstrate that AD and PD are both impacted by CMI, though the impact is likely different for each disease. Additionally, we found a robust body of evidence regarding the utility of CMI in the detection of subtle deficits in prodromal AD, and some evidence of utility in prodromal AD. Several key methodological challenges related to the use of DT paradigms for the measurement of CMI in neurodegeneration were identified and discussed. Overall, DT paradigms show good potential as a clinical method to probe specific brain regions and networks; however, task selection and effect measurement must be carefully considered in order to capture a more complete picture of DT performance.

DIRECTIONS FOR DISSERTATION

Many themes for future directions were identified in this scoping review. As all of these themes cannot be fully addressed in this dissertation, the following three themes will be addressed: 1) lack of reliable measures of DT automaticity in neurodegenerative disease, 2) limited understanding of the neurological mechanisms that contribute to impaired automaticity in AD, and 3) the potential utility of automaticity in the identification of preclinical AD.

The first theme we will address is the lack of reliable measures of DT automaticity (Chapter 2). This was a flaw seen throughout the literature across all the diagnostic groups. Without a

reliable standard in measurement, researchers have used a myriad of different metrics to assess DT performance. Among these measures, few assess the construct of automaticity, leading to poorly informed inferences regarding automaticity in neurodegenerative disease. To address this, we will propose a battery of measures of DT performance across three domains of DT performance (task specific interference, task prioritization, and automaticity), which will include a recently formulated measure of automaticity. We will aim to establish the psychometric properties of the measures in this battery, and in particular the measure of automaticity. We will assess each measure's test-retest reliability, calculate minimal detectable change, and investigate convergent, divergent, and known-groups validity in individuals with PD, AD, and healthy adults.

Next, we will carry out a study aimed at investigating the neurological mechanisms that contribute to impaired automaticity in AD (Chapter 3). In conducting this scoping review, we found only one study that investigated the relationship between DT performance and brain imaging in individuals with AD (Nadkarni et al., 2012). This study found that DT performance was inversely related to subcortical hyperintensities. AD is characterized by tau-mediated neurodegeneration, which results in cortical gray matter atrophy and cognitive impairment (Ballatore et al., 2007; Bejanin et al., 2017). DT performance is related to tau levels in individuals with AD (Nielsen et al., 2018). There is limited evidence to infer specific disease process or brain regions that contribute to declines in automaticity that occur in AD. As AD is characterized by cortical atrophy we will conduct a hypothesis-guided regions-of-interest study

to investigate if cortical thinning characteristic of AD contributes to changes in DT performance, with particular interest given to automaticity.

The last observed theme that we will address is the potential utility of automaticity in identifying preclinical AD (Chapter 4). DT performance declines early in AD can differentiate healthy individuals, those with MCI, and those with AD. This has led to DT performance being proposed as a possible clinical biomarker of AD. Several studies utilizing measures of task-specific interference (mDTE and cogDTE) investigated this further by examining the relationship between DT performance and other AD biomarkers. The findings of these studies revealed signals of relationships between DT performance and tau and APOE, and conflicting results regarding the relationship between DT performance and amyloidosis. We will conduct a study investigating the value of automaticity in identifying healthy individuals with amyloidosis consistent with preclinical AD.

REFERENCES

Abernethy, B. (1988). Dual-task methodology and motor skills research: Some applications and methodological constraints. *Journal of Human Movement Studies*.

Åhman, Hanna B., Cedervall, Y., Kilander, L., Giedraitis, V., Berglund, L., McKee, K. J., Rosendahl, E., Ingelsson, M., & Åberg, A. C. (2020). Dual-task tests discriminate between dementia, mild cognitive impairment, subjective cognitive impairment, and healthy controls - A cross-sectional cohort study. *BMC Geriatrics*, *20*(1), 258. https://doi.org/10.1186/s12877-020-01645-1

Åhman, Hanna Bozkurt, Giedraitis, V., Cedervall, Y., Lennhed, B., Berglund, L., McKee, K., Kilander, L., Rosendahl, E., Ingelsson, M., Åberg, A. C., Ahman, H. B., Giedraitis, V., Cedervall, Y., Lennhed, B., Berglund, L., McKee, K., Kilander, L., Rosendahl, E., Ingelsson, M., & Aberg, A. C. (2019). Dual-Task Performance and Neurodegeneration: Correlations Between Timed Up-and-Go Dual-Task Test Outcomes and Alzheimer's Disease Cerebrospinal Fluid Biomarkers. *J Alzheimers Dis*, *71*(s1), S75–S83. https://doi.org/10.3233/JAD-181265

Al-Yahya, E., Dawes, H., Smith, L., Dennis, A., Howells, K., & Cockburn, J. (2011). Cognitive motor interference while walking: A systematic review and meta-analysis. In *Neuroscience and Biobehavioral Reviews*. https://doi.org/10.1016/j.neubiorev.2010.08.008

Amboni, M., Barone, P., Iuppariello, L., Lista, I., Tranfaglia, R., Fasano, A., Picillo, M., Vitale, C., Santangelo, G., Agosti, V., Iavarone, A., & Sorrentino, G. (2012). Gait patterns in parkinsonian patients with or without mild cognitive impairment. *Movement Disorders*, *27*(12), 1536–1543. https://doi.org/10.1002/mds.25165

Amboni, M., Iuppariello, L., Iavarone, A., Fasano, A., Palladino, R., Rucco, R., Picillo, M., Lista, I., Varriale, P., Vitale, C., Cesarelli, M., Sorrentino, G., & Barone, P. (2018). Step length predicts executive dysfunction in Parkinson's disease: a 3-year prospective study. *Journal of Neurology*, *265*(10),

2211–2220. https://doi.org/10.1007/s00415-018-8973-x

Ansai, Juliana H., Andrade, L. P., Rossi, P. G., Takahashi, A. C. M. M., Vale, F. A. C. C., & Rebelatto, J. R. (2017). Gait, dual task and history of falls in elderly with preserved cognition, mild cognitive impairment, and mild Alzheimer's disease. *Braz J Phys Ther*, *21*(2), 144–151. https://doi.org/10.1016/j.bjpt.2017.03.010

Ansai, Juliana Hotta, Andrade, L. P. de, Rossi, P. G., Almeida, M. L., Carvalho Vale, F. A., & Rebelatto, J. R. (2018). Association Between Gait and Dual Task With Cognitive Domains in Older People With Cognitive Impairment. *Journal of Motor Behavior*, *50*(4), 409–415. https://doi.org/10.1080/00222895.2017.1363702

B Åhman, H., Berglund, L., Cedervall, Y., Kilander, L., Giedraitis, V., McKee, K. J., Ingelsson, M., Rosendahl, E., & Åberg, A. C. (2020). Dual-Task Tests Predict Conversion to Dementia—A Prospective Memory-Clinic-Based Cohort Study. *International Journal of Environmental Research and Public Health*, *17*(21), 8129. https://doi.org/10.3390/ijerph17218129

Ballatore, C., Lee, V. M. Y., & Trojanowski, J. Q. (2007). Tau-mediated neurodegeneration in Alzheimer's disease and related disorders. In *Nature Reviews Neuroscience* (Vol. 8, Issue 9, pp. 663–672). Nature Publishing Group. https://doi.org/10.1038/nrn2194

Baron, E. I., Miller Koop, M., Streicher, M. C., Rosenfeldt, A. B., & Alberts, J. L. (2018). Altered kinematics of arm swing in Parkinson's disease patients indicates declines in gait under dual-task conditions. *Parkinsonism and Related Disorders*, *48*, 61–67. https://doi.org/10.1016/j.parkreldis.2017.12.017

Beauchet, O., Launay, C. P., Allali, G., Herrmann, F. R., & Annweiler, C. (2014). Gait changes with anti-dementia drugs: A prospective, open-label study combining single and dual task assessments in patients with Alzheimer's disease. *Drugs and Aging*, *31*(5), 363–372.

https://doi.org/10.1007/s40266-014-0175-3

Beauchet, O., Launay, C. P., Chabot, J., Levinoff, E. J., & Allali, G. (2017). Subjective memory impairment and gait variability in cognitively healthy individuals: Results from a cross-sectional pilot study. *Journal of Alzheimer's Disease*, *55*(3), 965–971. https://doi.org/10.3233/JAD-160604

Beck, E. N., Ehgoetz Martens, K. A., & Almeida, Q. J. (2015). Freezing of Gait in Parkinson's Disease: An Overload Problem? *PLOS ONE*, *10*(12), e0144986. https://doi.org/10.1371/journal.pone.0144986

Bejanin, A., Schonhaut, D. R., La Joie, R., Kramer, J. H., Baker, S. L., Sosa, N., Ayakta, N., Cantwell, A., Janabi, M., Lauriola, M., O'Neil, J. P., Gorno-Tempini, M. L., Miller, Z. A., Rosen, H. J., Miller, B. L., Jagust, W. J., & Rabinovici, G. D. (2017). Tau pathology and neurodegeneration contribute to cognitive impairment in Alzheimer's disease. *Brain*, *140*(12), 3286–3300. https://doi.org/10.1093/brain/awx243

Bertoli, M., Croce, U. Della, Cereatti, A., & Mancini, M. (2019). Objective measures to investigate turning impairments and freezing of gait in people with Parkinson's disease. *Gait & Posture*, *74*, 187–193. https://doi.org/10.1016/j.gaitpost.2019.09.001

Brookmeyer, R., Abdalla, N., Kawas, C. H., & Corrada, M. M. (2018). Forecasting the prevalence of preclinical and clinical Alzheimer's disease in the United States. *Alzheimers Dement*, *14*(2), 121–129. https://doi.org/10.1016/j.jalz.2017.10.009

Camicioli, R., Bouchard, T., & Licis, L. (2006). Dual-tasks and walking fast: Relationship to extra-pyramidal signs in advanced Alzheimer disease. *Journal of the Neurological Sciences*, *248*(1–2), 205–209. https://doi.org/10.1016/j.jns.2006.05.013

Camicioli, R., Howieson, D., Lehman, S., & Kaye, J. (1997). Talking while walking: The effect of a dual task in aging and Alzheimer's disease. *Neurology*, *48*(4), 955–958.

https://doi.org/10.1212/WNL.48.4.955

Canning, C. G., Ada, L., Johnson, J. J., & McWhirter, S. (2006). Walking capacity in mild to moderate Parkinson's disease. *Archives of Physical Medicine and Rehabilitation*, *87*(3), 371–375. https://doi.org/10.1016/j.apmr.2005.11.021

Cardon-Verbecq, C., Loustau, M., Guitard, E., Bonduelle, M., Delahaye, E., Koskas, P., & Raynaud-Simon, A. (2017). Predicting falls with the cognitive timed up-and-go dual task in frail older patients. *Ann Phys Rehabil Med*, *60*(2), 83–86. https://doi.org/10.1016/j.rehab.2016.07.003

Cedervall, Y., Halvorsen, K., Åberg, A. C., & Aberg, A. C. (2014). A longitudinal study of gait function and characteristics of gait disturbance in individuals with Alzheimer's disease. *Gait & Posture*, *39*(4), 1022–1027. https://doi.org/10.1016/j.gaitpost.2013.12.026

Chawla, H., Walia, S., Behari, M., & Noohu, M. M. (2014). Effect of type of secondary task on cued gait on people with idiopathic Parkinson's disease. *Journal of Neurosciences in Rural Practice*, *5*(1), 18–23. https://doi.org/10.4103/0976-3147.127865

Chomiak, T., Watts, A., Meyer, N., Pereira, F. V, & Hu, B. (2017). A training approach to improve stepping automaticity while dual-tasking in Parkinson's disease: A prospective pilot study. *Medicine (Baltimore)*, *96*(5), e5934. https://doi.org/10.1097/MD.0000000000005934

Christofoletti, G., Andrade, L. P. de, Beinotti, F., Borges, G., de Andrade, L. P., Beinotti, F., & Borges, G. (2014). Cognition and dual-task performance in older adults with Parkinson's and Alzheimer's disease. *International Journal of General Medicine*, *7*, 383–388. https://doi.org/10.2147/IJGM.S65803

Cocchini, G., Della Sala, S., Logie, R., Pagani, R., Sacco, L., & Spinnler, H. (2004). No Dual task effects of walking when talking in Alzheimer's disease. *Rev Neurol (Paris)*, *160*(1), 74–80.

Criminger, C., & Swank, C. (2020). Impact of dual-tasking on mobility tasks in Parkinson's disease as described through 2D kinematic analysis. *Aging Clinical and Experimental Research*, *32*(5), 835–840. https://doi.org/10.1007/s40520-019-01256-w

Cullen, S., Borrie, M., Carroll, S., Sarquis-Adamson, Y., Pieruccini-Faria, F., Mckay, S., & Montero-Odasso, M. (2019). Are Cognitive Subtypes Associated with Dual-Task Gait Performance in a Clinical Setting? *Journal of Alzheimer's Disease : JAD*, *71*(s1), S57–S64. https://doi.org/10.3233/JAD-181196

De Cock, A.-M. M., Fransen, E., Perkisas, S., Verhoeven, V., Beauchet, O., Vandewoude, M., & Remmen, R. (2019). Comprehensive Quantitative Spatiotemporal Gait Analysis Identifies Gait Characteristics for Early Dementia Subtyping in Community Dwelling Older Adults. *Frontiers in Neurology*, *10*(APR), 313. https://doi.org/10.3389/fneur.2019.00313

de Melo Borges, S., Radanovic, M., & Forlenza, O. V. (2015). Functional Mobility in a Divided Attention Task in Older Adults With Cognitive Impairment. *Journal of Motor Behavior*, *47*(5), 378–385. https://doi.org/10.1080/00222895.2014.998331

Ehgoetz Martens, K. A., Matar, E., Hall, J. M., Phillips, J., Szeto, J. Y. Y., Gouelle, A., Grunstein, R. R., Halliday, G. M., & Lewis, S. J. G. (2019). Subtle gait and balance impairments occur in idiopathic rapid eye movement sleep behavior disorder. *Movement Disorders*, *34*(9), 1374–1380. https://doi.org/10.1002/mds.27780

Ehgoetz Martens, K. A., Silveira, C. R. A., Intzandt, B. N., & Almeida, Q. J. (2018). Overload from anxiety: A non-motor cause for gait impairments in Parkinson's disease. *Journal of Neuropsychiatry and Clinical Neurosciences*, *30*(1), 77–80. https://doi.org/10.1176/appi.neuropsych.16110298

Fernandes, Â., Sousa, A. S. P., Rocha, N., & Tavares, J. M. R. S. (2016). Parkinson's Disease and Cognitive-Motor Dual-Task: Is Motor Prioritization Possible in the Early Stages of the Disease? *Journal of*

Motor Behavior, *48*(4), 377–383. https://doi.org/10.1080/00222895.2015.1105194

Fernandes, Â., Sousa, A. S. P., Rocha, N., & Tavares, J. M. R. S. (2017). The influence of a cognitive task on the postural phase of gait initiation in Parkinson's disease: An electromyographic-based analysis. *Motor Control*, *21*(3), 249–264. https://doi.org/10.1123/mc.2015-0032

Fino, P. C., Mancini, M., Curtze, C., Nutt, J. G., & Horak, F. B. (2018). Gait stability has phase-dependent dual-task costs in Parkinson's disease. *Frontiers in Neurology*, *9*(MAY). https://doi.org/10.3389/fneur.2018.00373

Fuller, R. L., Van Winkle, E. P., Anderson, K. E., Gruber-Baldini, A. L., Hill, T., Zampieri, C., Weiner, W. J., & Shulman, L. M. (2013). Dual task performance in Parkinson's disease: a sensitive predictor of impairment and disability. *Parkinsonism Relat Disord*, *19*(3), 325–328. https://doi.org/10.1016/j.parkreldis.2012.11.011

Galletly, R., & Brauer, S. G. (2005). Does the type of concurrent task affect preferred and cued gait in people with Parkinson's disease? *Australian Journal of Physiotherapy*, *51*(3), 175–180. https://doi.org/10.1016/S0004-9514(05)70024-6

Gaßner, H., Marxreiter, F., Steib, S., Kohl, Z., Schlachetzki, J. C. M., Adler, W., Eskofier, B. M., Pfeifer, K., Winkler, J., & Klucken, J. (2017). Gait and cognition in parkinson's disease: Cognitive impairment is inadequately reflected by gait performance during dual task. *Frontiers in Neurology*, *8*(OCT). https://doi.org/10.3389/fneur.2017.00550

Gillain, S., Dramé, M., Lekeu, F., Wojtasik, V., Ricour, C., Croisier, J. L., Salmon, E., & Petermans, J. (2016). Gait speed or gait variability, which one to use as a marker of risk to develop Alzheimer disease? A pilot study. *Aging Clinical and Experimental Research*, *28*(2), 249–255. https://doi.org/10.1007/s40520-015-0392-6

Gillain, S., Warzee, E., Lekeu, F., Wojtasik, V., Maquet, D., Croisier, J. L., Salmon, E., & Petermans, J. (2009). The value of instrumental gait analysis in elderly healthy, MCI or Alzheimer's disease subjects and a comparison with other clinical tests used in single and dual-task conditions. *Annals of Physical and Rehabilitation Medicine*, *52*(6), 453–474. https://doi.org/10.1016/j.rehab.2008.10.004

Gonçalves, J., Ansai, J. H., Masse, F. A. A., Vale, F. A. C., Takahashi, A. C. de M., & Andrade, L. P. de. (2018). Dual-task as a predictor of falls in older people with mild cognitive impairment and mild Alzheimer's disease: a prospective cohort study. *Brazilian Journal of Physical Therapy*, *22*(5), 417–423. https://doi.org/10.1016/j.bjpt.2018.03.011

Heinzel, S., Maechtel, M., Hasmann, S. E., Hobert, M. A., Heger, T., Berg, D., & Maetzler, W. (2016). Motor dual-tasking deficits predict falls in Parkinson's disease: A prospective study. *Parkinsonism and Related Disorders*, *26*, 73–77. https://doi.org/10.1016/j.parkreldis.2016.03.007

Hirata, K., Hattori, T., Kina, S., Chen, Q., Ohara, M., & Yokota, T. (2020). Striatal Dopamine Denervation Impairs Gait Automaticity in Drug-Naïve Parkinson's Disease Patients. *Movement Disorders : Official Journal of the Movement Disorder Society*, *35*(6), 1037–1045. https://doi.org/10.1002/mds.28024

Hsiu-Chen, C., Chiung-Chu, C., Jiunn-Woei, L., Wei-Da, C., Yi-Hsin, W., Ya-Ju, C., & Chin-Song, L. (2020). The effects of dual-task in patients with Parkinson's disease performing cognitive-motor paradigms. *Journal of Clinical Neuroscience*, *72*, 72–78. https://doi.org/10.1016/j.jocn.2020.01.024

Huang, C. Y., Chen, Y. A., Hwang, I. S., & Wu, R. M. (2018). Improving Dual-Task Control With a Posture-Second Strategy in Early-Stage Parkinson Disease. *Arch Phys Med Rehabil*, *99*(8), 1540-1546 e2. https://doi.org/10.1016/j.apmr.2018.02.013

Hunt, S., Cimino, J. J., & Koziol, D. E. (2013). A comparison of clinicians' access to online knowledge resources using two types of information retrieval applications in an academic hospital setting. *Journal of the Medical Library Association*, *101*(1), 26–31.

Hunter, S. W., Omana, H., Madou, E., Wittich, W., Hill, K. D., Johnson, A. M., Divine, A., & Holmes, J. D. (2020). Effect of dual-tasking on walking and cognitive demands in adults with Alzheimer's dementia experienced in using a 4-wheeled walker. *Gait Posture*, *77*, 164–170. https://doi.org/10.1016/j.gaitpost.2020.01.024

Jacobs, J. V., Nutt, J. G., Carlson-Kuhta, P., Allen, R., & Horak, F. B. (2014). Dual tasking during postural stepping responses increases falls but not freezing in people with Parkinson's disease. *Parkinsonism and Related Disorders*, *20*(7), 779–781. https://doi.org/10.1016/j.parkreldis.2014.04.001

Kelly, V E, Janke, A. A., & Shumway-Cook, A. (2010). Effects of instructed focus and task difficulty on concurrent walking and cognitive task performance in healthy young adults. *Exp Brain Res*, *207*(1–2), 65–73. https://doi.org/10.1007/s00221-010-2429-6

Kelly, Valerie E., Eusterbrock, A. J., & Shumway-Cook, A. (2012). The effects of instructions on dual-task walking and cognitive task performance in people with parkinson's disease. *Parkinson's Disease*, *2012*. https://doi.org/10.1155/2012/671261

Kelly, Valerie E., & Shumway-Cook, A. (2014). The ability of people with Parkinson's disease to modify dual-task performance in response to instructions during simple and complex walking tasks. *Experimental Brain Research*, *232*(1), 263–271. https://doi.org/10.1007/s00221-013-3737-4

Kleiner, A. F. R., Pagnussat, A. S., Prisco, G. di, Vagnini, A., Stocchi, F., De Pandis, M. F., & Galli, M. (2018). Analyzing gait variability and dual-task interference in patients with Parkinson's disease and

freezing by means of the word-color Stroop test. *Aging Clinical and Experimental Research*, *30*(9), 1137–1142. https://doi.org/10.1007/s40520-017-0862-0

König, A., Klaming, L., Pijl, M., Demeurraux, A., David, R., & Robert, P. (2017). Objective measurement of gait parameters in healthy and cognitively impaired elderly using the dual-task paradigm. *Aging Clinical and Experimental Research*, *29*(6), 1181–1189. https://doi.org/10.1007/s40520-016-0703-6

Koziol, L. F., & Budding, D. E. (2009). Subcortical structures and cognition: Implications for neuropsychological assessment. In *Subcortical Structures and Cognition: Implications for Neuropsychological Assessment*. https://doi.org/10.1007/978-0-387-84868-6

Kueper, J. K., Lizotte, D. J., Montero-Odasso, M., & Speechley, M. (2020). Cognition and motor function: The gait and cognition pooled index. *PLoS ONE*, *15*(9), e0238690. https://doi.org/10.1371/journal.pone.0238690

Leavy, B., Roaldsen, K. S., Nylund, K., Hagstromer, M., & Franzen, E. (2016). "Pushing the Limits": Rethinking Motor and Cognitive Resources After a Highly Challenging Balance Training Program for Parkinson Disease. *Physical Therapy*, *97*(1), 81–89. https://doi.org/10.2522/ptj.20160090

Lehle, C., & Hübner, R. (2009). Strategic capacity sharing between two tasks: Evidence from tasks with the same and with different task sets. *Psychological Research*. https://doi.org/10.1007/s00426-008-0162-6

Liberati, A., Altman, D. G., Tetzlaff, J., Mulrow, C., Gøtzsche, P. C., Ioannidis, J. P. A., Clarke, M., Devereaux, P. J., Kleijnen, J., & Moher, D. (2009). The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ (Clinical Research Ed.)*. https://doi.org/10.1136/bmj.b2700

Longhurst, J.K., Wise, M. A., Krist, D. J., Moreland, C. A., Basterrechea, J. A., & Landers, M. R. (2020).

Brain volumes and dual-task performance correlates among individuals with cognitive impairment: a retrospective analysis. *Journal of Neural Transmission*, *127*(7). https://doi.org/10.1007/s00702-020-02199-7

Longhurst, Jason K, & Landers, M. R. (2019). A new way of measuring dual task cost: the construct validity of the comprehensive dual task cost equation in individuals with Parkinson's disease. *American Physical Therapy Association, Combined Sections Meeting*.

Lowe, D. A., MacAulay, R. K., Szeles, D. M., Milano, N. J., & Wagner, M. T. (2020). Dual-Task Gait Assessment in a Clinical Sample: Implications for Improved Detection of Mild Cognitive Impairment. *The Journals of Gerontology. Series B, Psychological Sciences and Social Sciences*, *75*(7), 1372–1381. https://doi.org/10.1093/geronb/gbz119

MacAulay, R. K., Allaire, T., Brouillette, R., Foil, H., Bruce-Keller, A. J., & Keller, J. N. (2016). Apolipoprotein E Genotype Linked to Spatial Gait Characteristics: Predictors of Cognitive Dual Task Gait Change. *PLoS One*, *11*(8), e0156732. https://doi.org/10.1371/journal.pone.0156732

Maidan, I., Nieuwhof, F., Bernad-Elazari, H., Reelick, M. F., Bloem, B. R., Giladi, N., Deutsch, J. E., Hausdorff, J. M., Claassen, J. A. H., & Mirelman, A. (2016). The Role of the Frontal Lobe in Complex Walking among Patients with Parkinson's Disease and Healthy Older Adults: An fNIRS Study. *Neurorehabilitation and Neural Repair*, *30*(10), 963–971. https://doi.org/10.1177/1545968316650426

Maquet, D., Lekeu, F., Warzee, E., Gillain, S., Wojtasik, V., Salmon, E., Petermans, J., & Croisier, J. L. (2010). Gait analysis in elderly adult patients with mild cognitive impairment and patients with mild Alzheimer's disease: Simple versus dual task: A preliminary report. *Clinical Physiology and Functional Imaging*, *30*(1), 51–56. https://doi.org/10.1111/j.1475-097X.2009.00903.x

McIsaac, T. L., Fritz, N. E., Quinn, L., & Muratori, L. M. (2018). Cognitive-motor interference in neurodegenerative disease: A narrative review and implications for clinical management. In *Frontiers in Psychology* (Vol. 9, Issue OCT). Frontiers Media S.A. https://doi.org/10.3389/fpsyg.2018.02061

McIsaac, T. L., Lamberg, E. M., & Muratori, L. M. (2015). Building a framework for a dual task taxonomy. *BioMed Research International*, *2015*, 591475. https://doi.org/10.1155/2015/591475

Micó-Amigo, M. E., Kingma, I., Heinzel, S., Nussbaum, S., Heger, T., Lummel, R. C. va., Berg, D., Maetzler, W., & Dieën, J. H. va. (2019). Dual vs. Single Tasking During Circular Walking: What Better Reflects Progression in Parkinson's Disease? *Frontiers in Neurology*, *10*. https://doi.org/10.3389/fneur.2019.00372

Montero-Odasso, M., Almeida, Q. J., Bherer, L., Burhan, A. M., Camicioli, R., Doyon, J., Fraser, S., Muir-Hunter, S., Li, K. Z. H., Liu-Ambrose, T., McIlroy, W., Middleton, L., Morais, J. A., Sakurai, R., Speechley, M., Vasudev, A., Beauchet, O., Hausdorff, J. M., Rosano, C., … Cognition, N. (2018). Consensus on Shared Measures of Mobility and Cognition: From the Canadian Consortium on Neurodegeneration in Aging (CCNA). *J Gerontol A Biol Sci Med Sci*. https://doi.org/10.1093/gerona/gly148

Montero-Odasso, M. M., Sarquis-Adamson, Y., Speechley, M., Borrie, M. J., Hachinski, V. C., Wells, J., Riccio, P. M., Schapira, M., Sejdic, E., Camicioli, R. M., Bartha, R., McIlroy, W. E., & Muir-Hunter, S. (2017). Association of Dual-Task Gait With Incident Dementia in Mild Cognitive Impairment: Results From the Gait and Brain Study. *JAMA Neurol*, *74*(7), 857–865. https://doi.org/10.1001/jamaneurol.2017.0643

Muir, S. W., Speechley, M., Wells, J., Borrie, M., Gopaul, K., & Montero-Odasso, M. (2012). Gait assessment in mild cognitive impairment and Alzheimer's disease: the effect of dual-task

challenges across the cognitive spectrum. *Gait Posture*, *35*(1), 96–100. https://doi.org/10.1016/j.gaitpost.2011.08.014

Muurling, M., Rhodius-Meester, H. F. M., Pärkkä, J., Van Gils, M., Frederiksen, K. S., Bruun, M., Hasselbalch, S. G., Soininen, H., Herukka, S. K., Hallikainen, M., Teunissen, C. E., Visser, P. J., Scheltens, P., Van Der Flier, W. M., Mattila, J., Lötjönen, J., & De Boer, C. (2020). Gait Disturbances are Associated with Increased Cognitive Impairment and Cerebrospinal Fluid Tau Levels in a Memory Clinic Cohort. *Journal of Alzheimer's Disease*, *76*(3), 1061–1070. https://doi.org/10.3233/JAD-200225

Myers, P. S., Rawson, K. S., Harrison, E. C., Horin, A. P., Sutter, E. N., McNeely, M. E., & Earhart, G. M. (2020). Cross-sectional analysis of backward, forward, and dual task gait kinematics in people with Parkinson disease with and without freezing of gait. *Journal of Applied Biomechanics*, *36*(2), 85–95. https://doi.org/10.1123/JAB.2019-0253

Nadkarni, N. K., Levine, B., McIlroy, W. E., & Black, S. E. (2012). Impact of subcortical hyperintensities on dual-tasking in Alzheimer disease and aging. *Alzheimer Disease and Associated Disorders*, *26*(1), 28–35. https://doi.org/10.1097/WAD.0b013e3182172c58

Nadkarni, N. K., Lopez, O. L., Perera, S., Studenski, S. A., Snitz, B. E., Erickson, K. I., Mathis, C. A., Nebes, R. D., Redfern, M., & Klunk, W. E. (2017). Cerebral amyloid deposition and dual-tasking in cognitively normal, mobility unimpaired older adults. *Journals of Gerontology - Series A Biological Sciences and Medical Sciences*, *72*(3), 431–437. https://doi.org/10.1093/gerona/glw211

Navon, D., & Miller, J. (2002). Queuing or sharing? A critical evaluation of the single-bottleneck notion. *Cognitive Psychology*. https://doi.org/10.1006/cogp.2001.0767

Nielsen, M. S., Simonsen, A. H., Siersma, V., Hasselbalch, S. G., & Hoegh, P. (2018). The Diagnostic and

Prognostic Value of a Dual-Tasking Paradigm in a Memory Clinic. *Journal of Alzheimer's Disease*, *61*(3), 1189–1199. https://doi.org/10.3233/JAD-161310

Nieuwhof, F., Bloem, B. R., Reelick, M. F., Aarts, E., Maidan, I., Mirelman, A., Hausdorff, J. M., Toni, I., & Helmich, R. C. (2017). Impaired dual tasking in Parkinson's disease is associated with reduced focusing of cortico-striatal activity. *Brain*, *140*(5), 1384–1398. https://doi.org/10.1093/brain/awx042

Nilsson, M. H., Tangen, G. G., Palmqvist, S., van Westen, D., Mattsson-Carlgren, N., Stomrud, E., & Hansson, O. (2020). The effects of tau, amyloid and white matter lesions on mobility, dual tasking and balance in older people. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*. https://doi.org/10.1093/gerona/glaa143

Nocera, J. R., Roemmich, R., Elrod, J., Altmann, L. J. P., & Hass, C. J. (2013). Effects of cognitive task on gait initiation in Parkinson disease: Evidence of motor prioritization? *Journal of Rehabilitation Research and Development*, *50*(5), 699–708. https://doi.org/10.1682/JRRD.2012.06.0114

O'Shea, S., Morris, M. E., & Iansek, R. (2002). Dual task interference during gait in people with Parkinson disease: effects of motor versus cognitive secondary tasks. *Phys Ther*, *82*(9), 888–897. https://doi.org/10.1093/ptj/82.9.888

Oh, C., Morris, R. J., LaPointe, L. L., & Stierwalt, J. A. G. (2020). Spatial-Temporal Parameters of Gait Associated With Alzheimer Disease: A Longitudinal Analysis. *Journal of Geriatric Psychiatry and Neurology*, 089198872090177. https://doi.org/10.1177/0891988720901779

Orcioli-Silva, D., Simieli, L., Barbieri, F. A., Stella, F., & Gobbi, L. T. B. (2012). Adaptive walking in alzheimer's disease. *International Journal of Alzheimer's Disease*, *2012*. https://doi.org/10.1155/2012/674589

Pashler, H. (1984). Processing stages in overlapping tasks: Evidence for a central bottleneck. *Journal of Experimental Psychology: Human Perception and Performance*. https://doi.org/10.1037/0096-1523.10.3.358

Pashler, H. (1994a). Dual-Task Interference in Simple Tasks: Data and Theory. In *Psychological Bulletin*. https://doi.org/10.1037//0033-2909.116.2.220

Pashler, H. (1994b). Graded Capacity-Sharing in Dual-Task Interference? *Journal of Experimental Psychology: Human Perception and Performance*. https://doi.org/10.1037/0096-1523.20.2.330

Pelosin, E., Ogliastro, C., Lagravinese, G., Bonassi, G., Mirelman, A., Hausdorff, J. M., Abbruzzese, G., & Avanzino, L. (2016). Attentional control of gait and falls: Is cholinergic dysfunction a common substrate in the elderly and Parkinson's disease? *Frontiers in Aging Neuroscience*, *8*(MAY). https://doi.org/10.3389/fnagi.2016.00104

Penko, A. L., Streicher, M. C., Dey, T., Rosenfeldt, A. B., & Alberts, J. L. (2020). Parkinson's gait kinematics deteriorates across multiple cognitive domains under dual-task paradigms. *Clinical Neurology and Neurosurgery*, *197*. https://doi.org/10.1016/j.clineuro.2020.106083

Penko, A. L., Streicher, M. C., Koop, M. M., Dey, T., Rosenfeldt, A. B., Bazyk, A. S., & Alberts, J. L. (2018). Dual-task Interference Disrupts Parkinson's Gait Across Multiple Cognitive Domains. *Neuroscience*, *379*, 375–382. https://doi.org/10.1016/j.neuroscience.2018.03.021

Peters, M. D. J., Godfrey, C. M., McInerney, P., Munn, Z., Tricco, A. C., & Khalil, H. (2020). Chapter 11: Scoping reviews (2020 version). In *Joanna Briggs Institute Reviewer's Manual*.

Peterson, D. S., Barajas, J. S., Denney, L., & Mehta, S. H. (2020). Backward Protective Stepping During Dual-Task Scenarios in People With Parkinson's Disease: A Pilot Study. *Neurorehabilitation and Neural Repair*, *34*(8), 702–710. https://doi.org/10.1177/1545968320935814

Peterson, D. S., Fling, B. W., Mancini, M., Cohen, R. G., Nutt, J. G., & Horak, F. B. (2015). Dual-task interference and brain structural connectivity in people with Parkinson's disease who freeze. *J Neurol Neurosurg Psychiatry*, *86*(7), 786–792. https://doi.org/10.1136/jnnp-2014-308840

Pettersson, A. F., Olsson, E., & Wahlund, L. O. (2007). Effect of divided attention on gait in subjects with and without cognitive impairment. *Journal of Geriatric Psychiatry and Neurology*, *20*(1), 58–62. https://doi.org/10.1177/0891988706293528

Pieruccini-Faria, F., Ehgoetz Martens, K. A., Silveira, C. R. A., Jones, J. A., & Almeida, Q. J. (2014). Interactions between cognitive and sensory load while planning and controlling complex gait adaptations in Parkinson's disease. *BMC Neurology*, *14*(1). https://doi.org/10.1186/s12883-014-0250-8

Pieruccini-Faria, F., Jones, J. A., & Almeida, Q. J. (2014). Motor planning in Parkinson's disease patients experiencing freezing of gait: The influence of cognitive load when approaching obstacles. *Brain and Cognition*, *87*(1), 76–85. https://doi.org/10.1016/j.bandc.2014.03.005

Plotnik, M., Giladi, N., Dagan, Y., & Hausdorff, J. M. (2011). Postural instability and fall risk in Parkinson's disease: Impaired dual tasking, pacing, and bilateral coordination of gait during the "oN" medication state. *Experimental Brain Research*, *210*(3–4), 529–538. https://doi.org/10.1007/s00221-011-2551-0

Plummer, P., & Eskes, G. (2015). Measuring treatment effects on dual-task performance: a framework for research and clinical practice. *Front Hum Neurosci*, *9*, 225. https://doi.org/10.3389/fnhum.2015.00225

Plummer, P., Eskes, G., Wallace, S., Giuffrida, C., Fraas, M., Campbell, G., Clifton, K., Skidmore, E. R., & American Congress of Rehabilitation Medicine Stroke Networking Group Cognition Task, F. (2013).

Cognitive-motor interference during functional mobility after stroke: state of the science and implications for future research. *Arch Phys Med Rehabil*, *94*(12), 2565-2574 e6. https://doi.org/10.1016/j.apmr.2013.08.002

Rantalainen, T., Teo, W. P., Ridgers, N. D., Nuzum, N. D., Valente, L., & Macpherson, H. (2020). Laboratory-Based Gait Variability and Habitual Gait Entropy Do Not Differentiate Community-Dwelling Older Adults from Those with Subjective Memory Complaints. *Gait and Posture*, *80*, 20–25. https://doi.org/10.1016/j.gaitpost.2020.05.024

Rochester, L., Galna, B., Lord, S., & Burn, D. (2014). The nature of dual-task interference during gait in incident Parkinson's disease. *Neuroscience*, *265*, 83–94. https://doi.org/10.1016/j.neuroscience.2014.01.041

Rochester, L, Baker, K., Hetherington, V., Jones, D., Willems, A. M., Kwakkel, G., Van Wegen, E., Lim, I., & Nieuwboer, A. (2010). Evidence for motor learning in Parkinson's disease: acquisition, automaticity and retention of cued gait performance after training with external rhythmical cues. *Brain Res*, *1319*, 103–111. https://doi.org/10.1016/j.brainres.2010.01.001

Rochester, Lynn, Hetherington, V., Jones, D., Nieuwboer, A., Willems, A. M., Kwakkel, G., & Van Wegen, E. (2004). Attending to the task: Interference effects of functional tasks on walking in Parkinson's disease and the roles of cognition, depression, fatigue, and balance. *Archives of Physical Medicine and Rehabilitation*, *85*(10), 1578–1585. https://doi.org/10.1016/j.apmr.2004.01.025

Rucco, R., Agosti, V., Jacini, F., Sorrentino, P., Varriale, P., De Stefano, M., Milan, G., Montella, P., & Sorrentino, G. (2017). Spatio-temporal and kinematic gait analysis in patients with Frontotemporal dementia and Alzheimer's disease through 3D motion capture. *Gait and Posture*, *52*, 312–317. https://doi.org/10.1016/j.gaitpost.2016.12.021

Sakurai, R., Bartha, R., & Montero-Odasso, M. (2019). Entorhinal Cortex Volume Is Associated With Dual-Task Gait Cost Among Older Adults With MCI: Results From the Gait and Brain Study. *J Gerontol A Biol Sci Med Sci*, *74*(5), 698–704. https://doi.org/10.1093/gerona/gly084

Salazar, R. D., Ren, X., Ellis, T. D., Toraif, N., Barthelemy, O. J., Neargarder, S., & Cronin-Golomb, A. (2017). Dual tasking in Parkinson's disease: Cognitive consequences while walking. *Neuropsychology*, *31*(6), 613–623. https://doi.org/10.1037/neu0000331

Sarbaz, Y., & Pourakbari, H. (2019). The effects of counting the stride numbers on the Parkinsonian gait: Suggesting a possible reason for dual task interference. *Basic and Clinical Neuroscience*, *10*(3), 269–279. https://doi.org/10.32598/bcn.9.10.245

Sheridan, P. L., Solomont, J., Kowall, N., & Hausdorff, J. M. (2003). Influence of Executive Function on Locomotor Function: Divided Attention Increases Gait Variability in Alzheimer's Disease. *Journal of the American Geriatrics Society*, *51*(11), 1633–1637. https://doi.org/10.1046/j.1532-5415.2003.51516.x

Shumway-Cook, A., Brauer, S., & Woollacott, M. (2000). Predicting the probability for falls in community-dwelling older adults using the Timed Up & Go Test. *Phys Ther*, *80*(9), 896–903. https://doi.org/10.1093/ptj/80.9.896

Simieli, L., Barbieri, F. A., Orcioli-Silva, D., Lirani-Silva, E., Stella, F., & Gobbi, L. T. B. (2015). Obstacle crossing with dual tasking is a danger for individuals with Alzheimer's disease and for healthy older people. *Journal of Alzheimer's Disease*, *43*(2), 435–441. https://doi.org/10.3233/JAD-140807

Siragy, T., & Nantel, J. (2020). Absent Arm Swing and Dual Tasking Decreases Trunk Postural Control and Dynamic Balance in People With Parkinson's Disease. *Frontiers in Neurology*, *11*. https://doi.org/10.3389/fneur.2020.00213

Siu, K. C., & Woollacott, M. H. (2007). Attentional demands of postural control: the ability to selectively allocate information-processing resources. *Gait Posture*, *25*(1), 121–126. https://doi.org/10.1016/j.gaitpost.2006.02.002

Smulders, K., Esselink, R. A. J., Weiss, A., Kessels, R. P. C., Geurts, A. C. H., & Bloem, B. R. (2012). Assessment of dual tasking has no clinical value for fall prediction in Parkinson's disease. *Journal of Neurology*, *259*(9), 1840–1847. https://doi.org/10.1007/s00415-012-6419-4

Sobol, N. A., Hoffmann, K., Vogel, A., Lolk, A., Gottrup, H., Høgh, P., Hasselbalch, S. G., & Beyer, N. (2016). Associations between physical function, dual-task performance and cognition in patients with mild Alzheimer's disease. *Aging & Mental Health*, *20*(11), 1139–1146. https://doi.org/10.1080/13607863.2015.1063108

Speciali, D. S., Oliveira, E. M., Cardoso, J. R., Correa, J. C. F., Baker, R., & Lucareli, P. R. G. (2014). Gait profile score and movement analysis profile in patients with Parkinson's disease during concurrent cognitive load. *Brazilian Journal of Physical Therapy*, *18*(4), 315–322. https://doi.org/10.1590/bjpt-rbf.2014.0049

Spildooren, J., Vercruysse, S., Desloovere, K., Vandenberghe, W., Kerckhofs, E., & Nieuwboer, A. (2010). Freezing of gait in Parkinson's disease: The impact of dual-tasking and turning. *Movement Disorders*, *25*(15), 2563–2570. https://doi.org/10.1002/mds.23327

Stegemoller, E. L., Buckley, T. A., Pitsikoulis, C., Barthelemy, E., Roemmich, R., & Hass, C. J. (2012). Postural instability and gait impairment during obstacle crossing in Parkinson's disease. *Arch Phys Med Rehabil*, *93*(4), 703–709. https://doi.org/10.1016/j.apmr.2011.11.004

Stegemöller, E. L., Wilson, J. P., Hazamy, A., Shelley, M. C., Okun, M. S., Altmann, L. J. P., & Hass, C. J. (2014). Associations between cognitive and gait performance during single- and dual-task walking

in people with Parkinson disease. *Physical Therapy*, *94*(6), 757–766. https://doi.org/10.2522/ptj.20130251

Strouwen, C., Molenaar, E. A. L. M., Keus, S. H. J., Münks, L., Bloem, B. R., & Nieuwboer, A. (2016). Test-retest reliability of dual-task outcome measures in people with Parkinson disease. *Physical Therapy*, *96*(8), 1276–1286. https://doi.org/10.2522/ptj.20150244

Strouwen, C., Molenaar, E. A. L. M., Keus, S. H. J., Münks, L., Heremans, E., Vandenberghe, W., Bloem, B. R., & Nieuwboer, A. (2016). Are factors related to dual-task performance in people with Parkinson's disease dependent on the type of dual task? *Parkinsonism and Related Disorders*, *23*, 23–30. https://doi.org/10.1016/j.parkreldis.2015.11.020

Tarnanas, I., Papagiannopoulos, S., Kazis, D., Wiederhold, M., Widerhold, B., Vuillermot, S., & Tsolaki, M. (2015). Reliability of a novel serious game using dual-task gait profiles to early characterize aMCI. *Frontiers in Aging Neuroscience*, *7*(MAR). https://doi.org/10.3389/fnagi.2015.00050

Tombu, M., & Jolicoæur, P. (2003). A Central Capacity Sharing Model of Dual-Task Performance. *Journal of Experimental Psychology: Human Perception and Performance*. https://doi.org/10.1037/0096-1523.29.1.3

Tombu, M., & Jolicœur, P. (2005). Testing the predictions of the central capacity sharing model. *Journal of Experimental Psychology: Human Perception and Performance*. https://doi.org/10.1037/0096-1523.31.4.790

Tricco, A. C., Lillie, E., Zarin, W., O'Brien, K. K., Colquhoun, H., Levac, D., Moher, D., Peters, M. D. J., Horsley, T., Weeks, L., Hempel, S., Akl, E. A., Chang, C., McGowan, J., Stewart, L., Hartling, L., Aldcroft, A., Wilson, M. G., Garritty, C., … Straus, S. E. (2018). PRISMA extension for scoping reviews (PRISMA-ScR): Checklist and explanation. In *Annals of Internal Medicine*.

https://doi.org/10.7326/M18-0850

Varalta, V., Picelli, A., Fonte, C., Amato, S., Melotti, C., Zatezalo, V., Saltuari, L., & Smania, N. (2015). Relationship between cognitive performance and motor dysfunction in patients with Parkinson's disease: A pilot cross-sectional study. *BioMed Research International*, *2015*. https://doi.org/10.1155/2015/365959

Vervoort, G., Heremans, E., Bengevoord, A., Strouwen, C., Nackaerts, E., Vandenberghe, W., & Nieuwboer, A. (2016). Dual-task-related neural connectivity changes in patients with Parkinson' disease. *Neuroscience*, *317*, 36–46. https://doi.org/10.1016/j.neuroscience.2015.12.056

Wahn, B., & Sinnett, S. (2019). Shared or Distinct Attentional Resources? Confounds in Dual Task Designs, Countermeasures, and Guidelines. *Multisens Res*, *32*(2), 145–163. https://doi.org/10.1163/22134808-20181328

Whitson, H. E., Potter, G. G., Feld, J. A., Plassman, B. L., Reynolds, K., Sloane, R., & Welsh-Bohmer, K. A. (2018). Dual-Task Gait and Alzheimer's Disease Genetic Risk in Cognitively Normal Adults: A Pilot Study. *J Alzheimers Dis*, *64*(4), 1137–1148. https://doi.org/10.3233/JAD-180016

Wild, L. B., De Lima, D. B., Balardin, J. B., Rizzi, L., Giacobbo, B. L., Oliveira, H. B., De Lima Argimon, I. I., Peyré-Tartaruga, L. A., Rieder, C. R. M., Bromberg, E., de Lima II, A., Peyre-Tartaruga, L. A., Rieder, C. R. M., & Bromberg, E. (2013). Characterization of cognitive and motor performance during dual-tasking in healthy older adults and patients with Parkinson's disease. *J Neurol*, *260*(2), 580–589. https://doi.org/10.1007/s00415-012-6683-3

Wu, T., Hallett, M., & Chan, P. (2015). Motor automaticity in Parkinson's disease. *Neurobiol Dis*, *82*, 226–234. https://doi.org/10.1016/j.nbd.2015.06.014

Wu, T., Kansaku, K., & Hallett, M. (2004). How self-initiated memorized movements become automatic:

a functional MRI study. *J Neurophysiol*, *91*(4), 1690–1698. https://doi.org/10.1152/jn.01052.2003

Xu, H., Merryweather, A., Foreman, K. B., Zhao, J., & Hunt, M. E. (2018). Dual-task interference during gait on irregular terrain in people with Parkinson's disease. *Gait and Posture*, *63*, 17–22. https://doi.org/10.1016/j.gaitpost.2018.04.027

Yang, L., Lam, F. M. H., Liao, L. R., Huang, M. Z., He, C. Q., & Pang, M. Y. C. (2017). Psychometric properties of dual-task balance and walking assessments for individuals with neurological conditions: A systematic review. *Gait Posture*, *52*, 110–123. https://doi.org/10.1016/j.gaitpost.2016.11.007

Yogev-Seligmann, G., Hausdorff, J. M., & Giladi, N. (2008). The role of executive function and attention in gait. In *Movement Disorders*. https://doi.org/10.1002/mds.21720

Yogev-Seligmann, G., Rotem-Galili, Y., Dickstein, R., Giladi, N., & Hausdorff, J. M. (2012). Effects of explicit prioritization on dual task walking in patients with Parkinson's disease. *Gait and Posture*, *35*(4), 641–646. https://doi.org/10.1016/j.gaitpost.2011.12.016

Yogev, G., Giladi, N., Peretz, C., Springer, S., Simon, E. S., & Hausdorff, J. M. (2005). Dual tasking, gait rhythmicity, and Parkinson's disease: which aspects of gait are attention demanding? *Eur J Neurosci*, *22*(5), 1248–1256. https://doi.org/10.1111/j.1460-9568.2005.04298.x

Zirek, E., Ersoz Huseyinsinoglu, B., Tufekcioglu, Z., Bilgic, B., & Hanagasi, H. (2018). Which cognitive dual-task walking causes most interference on the Timed Up and Go test in Parkinson's disease: a controlled study. *Neurol Sci*, *39*(12), 2151–2157. https://doi.org/10.1007/s10072-018-3564-2

CHAPTER 2: PROJECT 1

A NOVEL WAY OF MEASURING DUAL TASK INTERFERENCE: THE RELIABILITY AND CONSTRUCT VALIDITY OF THE DUAL TASK EFFECT BATTERY IN HEALTHY ADULTS AND INDIVIDUALS WITH NEURODEGENERATIVE DISEASE

ABSTRACT

Decreased motor automaticity is common among individuals with neurodegenerative disease. Movement automaticity is often assessed using dual task (DT) paradigms; however, there is a lack of consensus regarding the best methods for assessing impact on performance related to dual task demands. The purpose of this study was to investigate the reliability and validity among healthy adults and those with neurodegenerative disease of a novel battery of DT measures (Dual Task Effect – Battery (DTE-B)) that encompass three domains: task-specific interference, task prioritization, and automaticity. Data for this cross-sectional study was derived from the medical records of 125 patients with Parkinson disease (PD), 127 patients with Alzheimer disease (AD), and 84 healthy older adults [BLINDED – CNTN study] at [BLINDED - CCLRCBH]. Reliability analyses were conducted using a subset of each population (PD = 37, AD = 34, healthy adults = 34). Measurements in the DTE-B were calculated from single task and DT impact on the Timed Up and Go test, and a serial subtraction task. Additionally, measures of PD symptoms (PD group only), cognition and mood, balance and falls, and gait were collected. Construct validity was evaluated by investigating the associations within the DTE-B and between specific metrics and measures that theoretically support the construct they purport to represent. Lastly, known-groups validity analyses were conducted comparing the performance

on DTE-B between the PD, AD, and healthy groups. Good to excellent reliability was found for DTE-B measures of task interference (motor and cognitive DT effects) (ICCs≥.658) and automaticity (combined DT effect (cDTE)) (ICCs≥.938). Evidence for convergent validity was found with moderate to strong relationships among measurements within the DTE-B. Convergent and divergent validity assessment revealed weak to moderate relationships with other measures. Known-groups validity analyses revealed differences in the DTE-B among the healthy group and PD and AD groups (*p*s≤.001), excepting task prioritization (*p*s≥.061). There were no differences between the PD and AD groups (*p*s≥.245). This study provides evidence to support the use of the DTE-B as a reliable measure of multiple constructs pertinent to DT performance. The cDTE demonstrated adequate evidence to support its validity as a measure of automaticity. Further investigation of the utility of the DTE-B in both PD and AD, as well as other populations, is warranted.

Introduction

A decrease in motor automaticity --- performance of a motor activity without attention directed to the motor task --- is common among individuals with neurodegenerative disease (Christofoletti et al., 2014; Wu et al., 2015). It is a key deficit in Parkinson disease (PD) and is a crucial target of motor retraining and rehabilitation for individuals with PD (Chomiak et al., 2017; C. Y. Huang et al., 2018; Rochester et al., 2010). In PD, motor automaticity is more impaired among those with freezing of gait and cognitive impairment (Amboni et al., 2012, 2018; Peterson et al., 2015; Spildooren et al., 2010; Vervoort et al., 2016). In Alzheimer disease (AD), deficits in motor automaticity progress with disease severity (Ansai et al., 2017; König et

al., 2017; Muir et al., 2012). Motor automaticity is compromised in individuals with mild cognitive impairment (MCI) relative to healthy individuals (de Melo Borges et al., 2015; Maquet et al., 2010; Muir et al., 2012) and individuals with MCI with impaired motor automaticity progress to dementia more rapidly than those with comparatively intact motor automaticity (Gillain et al., 2009; Montero-Odasso et al., 2017).

Motor automaticity is often assessed by dual task (DT) paradigms wherein a motor task and a secondary task (frequently a cognitive task) are done concurrently (Wu et al., 2015); however, there is no consensus on the best methods or measures for assessing DT ability (Cardon-Verbecq et al., 2017; McIsaac et al., 2015; Yang et al., 2017). Yang et al observed that there were many different methods for assessing the dual task effect (DTE) or the relative change in performance resulting from conducting a DT (Yang et al., 2017). DT assessment is performed by quantifying the change in primary motor task performance or the change in secondary task performance, frequently a cognitive task, while completing the combined task (Fritz et al., 2015; Kelly et al., 2010; P Plummer & Eskes, 2015; Yang et al., 2017). One of the most accepted measures for assessing DT interference is calculating the motor or cognitive DTE, which relates DT performance to single task performance (Yang et al., 2017). While this method is valuable in assessing individual task components as they relate to automaticity, a measure of assessing DT interference which quantifies the combined interference of the motor and the cognitive task components may be a more sensitive measure to DTE and may provide a more complete picture of automaticity (Longhurst et al., 2020; Wahn & Sinnett, 2019). Task prioritization (i.e., which task domain (motor or cognitive) is prioritized during DT) in DT paradigms is most often

determined by the manner of instruction for performing the DT. Recently, there have been efforts made to classify task prioritization categorically, and to quantify it using the attention allocation index (AAI) (Kelly et al., 2010; P Plummer & Eskes, 2015; Siu & Woollacott, 2007).

While PD, which has more motor impairment than cognitive, and AD, which has more cognitive impairment than motor, are informative populations in which to study the impact of DT on performance, few studies investigating DT performance in these populations have included measures that individually assess change in performance of both the primary and secondary tasks that comprise the DT (motor and/or cognitive DTEs). Fewer still have utilized a measure of task prioritization. To our knowledge, only one study has previously utilized a robust measure of combined interference (Longhurst et al., 2020). The inclusion of measures of motor, cognitive, and combined effects of DT interference, as well as task prioritization, may help to elucidate subtle motor and cognitive deficits, particularly in individuals with neurodegenerative disease (Belghali et al., 2017). In addition, they could prove useful for assessing disability, disease progression, and response to treatment (McIsaac et al., 2018).

The purpose of this study was to investigate the reliability and validity of a novel combination of DT assessments, labeled the DTE battery (DTE-B). The DTE-B includes several DT measures falling into three domains: 1) Task specific interference or effects (motor dual task effect (mDTE) and cognitive dual task effect (cogDTE)); 2) Task prioritization (task prioritization category and modified AAI (mAAI)); and 3) Automaticity (combined dual task effect (cDTE) - a

novel measure of combined DT interference). The first aim of this study was to investigate the test-retest reliability of the DTE-B in individuals with PD, AD, and healthy older adults. The second aim was to investigate the construct validity (encompassing convergent validity, divergent validity, and known-groups validity) of the DTE-B in individuals with PD, AD, and healthy older adults. We hypothesized that evidence for the validity of the cDTE will be demonstrated through moderate to strong associations with measures of other DT metrics and more automatic tasks, as well as weak to no relationship with tasks with relatively high attentional demands (e.g., high task complexity involving many sensory, motor, and cognitive functions). We anticipated that analysis of known-groups validity will provide further evidence for the validity of the DTE-B as a measure of compromised function. We hypothesized that automaticity (cDTE) would be least impacted in the healthy older adult group, while both the PD and AD groups would be more impacted, though not different between groups. However, since PD has more motor impairment than cognitive impairment, and AD is characterized by greater cognitive impairment than motor impairment, we predicted that mDTE and cogDTE would be different between these two groups with the AD group showing a greater cogDTE and less mDTE than the PD group. We hypothesized that mAAI would differ between groups, with the PD group prioritizing cognitive performance at the expense of motor performance and the AD group prioritizing motor performance at the expense of cognitive performance. We anticipated that the healthy older adult group would demonstrate no clear prioritization strategy.

Methods

Design

A cross-sectional analysis of data collected from Cleveland Clinic Lou Ruvo Center for Brain Health (CCLRCBH) patient and research data sets was conducted (Ritter et al., 2018). Demographic data, DT performance, disease status/symptoms, cognition and mood, balance and falls, and gait in individuals with PD and AD were captured. Patients that completed repeat DT measurement at least 7 days but no more than 28 days apart were included in the reliability analyses. For Aim 1, we investigated the test-retest reliability of the DTE-B in a subset of 105 participants made up of individuals from the PD (n=37), AD (n=34), and healthy (n=34) groups. For Aim 2, we explored the construct validity of the DTE-B by comparing its components to measures of other constructs (PD symptoms (PD group only), cognition and mood, balance and falls, and gait). Convergent validity was assessed by comparing the DTE-B with measures of the same or similar constructs and divergent validity was evaluated by comparing the DTE-B to un-related constructs such as depression (Patient Health Questionnaire-9; PHQ-9) and non-motor symptoms of PD (Movement Disorder Society-Unified Parkinson's Disease Rating Scale; MDS-UPDRS part I).

Participants

Parkinson's disease and Alzheimer's disease cohorts. All patients with an initial physical therapy evaluation at CCLRCBH from July 2017 to June 2019 were identified from medical records. Clinical diagnosis of PD or AD was completed by a neurologist using contemporary diagnostic criteria (Albert et al., 2011; Hughes et al., 1992; Jack et al., 2011). Inclusion criterion

for this study was a referral to physical therapy for primary treatment of PD or AD and completion of the dual task assessment (described below). All patients included in the analyses had a standardized physical therapy assessment consisting of assessments of balance, gait, and DT performance. Assessments were conducted by four licensed physical therapist at one facility.

The AD cohort included individuals ranging in symptomatic presentation from MCI to moderate dementia. Patients were excluded if they were referred to physical therapy for primary treatment of any condition that was not a result of PD or AD, including: vestibular dysfunction, significant osteoarthritis, acute lower extremity surgery, lower extremity injury (fractures, strains, sprains), or any orthopedic comorbid diagnoses. Data from 252 medical records were extracted --- 125 individuals with PD, and 127 individuals with AD (Figure 1). All PD assessments were conducted in the "ON" PD medication state. All patients with PD and AD were community-dwelling.

Healthy older adult cohort. This cohort consisted of individuals ages 55-85 who were neurologically healthy and community-dwelling. Individuals were excluded from this group if they had significant orthopedic conditions that affected their gait or if they had any evidence of cognitive impairment (Montreal Cognitive Assessment (MoCA) <26). Participants for the reliability analysis were a convenience sample recruited consecutively from the community. All assessments were completed by a single tester (JL) between July 2017 and February 2021.

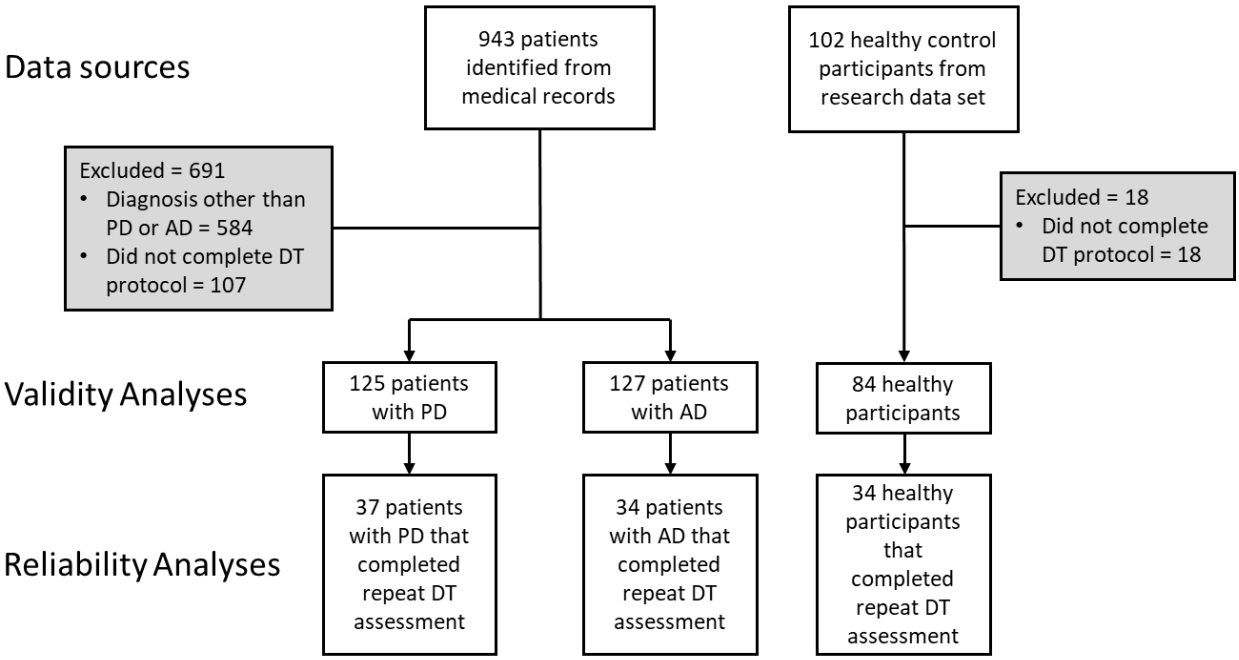


Figure 1. Study data sources flow diagram.

There were group differences observed in demographic characteristics (Table 1). Specifically, the healthy group was younger and the PD group more predominantly male compared to other groups. Additionally, the racial composition of the groups differed.

Table 1. Demographics for the PD, AD, and healthy groups. Analyses adjusted for multiple comparison using Benjamini Hochberg correction, with significant results marked in red.

	PD (n=125)	**AD** (n=127)	**Healthy** (n=84)	**p value**
Age	74.3 (±8.6)	75.3 (±9.3)	70.3 (±5.8)	<.001
Sex (F %)	37 (29.6%)	59 (46.5%)	46 (54.8%)	.001
Race	White: 113	White: 102	White: 75	
	Black: 1	Black: 12	Black: 4	
	Multiracial: 4	Multiracial: 4	Multiracial: 0	.036
	Asian: 7	Asian: 3	Asian: 5	
	Pacific Islander: 0	Pacific Islander: 1	Pacific Islander: 0	
Ethnicity	Hispanic: 2	Hispanic: 2	Hispanic: 4	.261
	Non-Hispanic: 123	Non-Hispanic: 125	Non-Hispanic: 80	
Years since onset	5.9 (±4.9)	4.8 (±3.6)	NA	.217

Measures

DTE-B. The DTE-B includes measures of task specific interference (mDTE and cogDTE), task prioritization (task prioritization category and mAAI) and automaticity (cDTE) which can be derived from performance of a single DT assessment (Figure 3). Times for the following measures were included: Timed UP and Go (TUG) and Timed Up and Go Cognitive (TUGcog) as described by Shumway-Cook et al (Shumway-Cook et al., 2000). The TUG exhibits good test-retest (ICCs>0.80) reliability in individuals with PD and AD (S. L. Huang et al., 2011; Ries et al., 2009). The TUGcog has excellent test-retest reliability (ICC = 0.85) and interrater reliability (ICC = 0.99) for individuals with PD (Morris et al., 2001; Steffen & Seney, 2008). The TUGcog has excellent test-retest reliability (ICC = 0.98), intrarater reliability (ICC = 0.94), and interrater reliability (ICC = 0.99) for community-dwelling older adults (Hofheinz & Schusterschitz, 2010; Shumway-Cook et al., 2000). Single task (ST) cognitive performance during serial subtraction by three was captured by recording the number of correct responses during a specified time frame (20 seconds) and then calculating the correct response rate. DT cognitive performance was obtained during the TUGcog using the same method beginning from a different number between 80 and 100. These variables were then used to calculate mDTE and cogDTE using the equation (Kelly et al., 2010):

$$DTE(\%) = \frac{DT - ST}{ST} \times 100\%$$

The cDTE equation was designed based on the DTE equation and expanded to assess the combined interference of both mDTE and cDTE (Figure 2). The cDTE was calculated using the following equation:

$$cDTE\ (\%) = \frac{(motor\ DT \times Cognitive\ DT) - (motor\ ST \times cognitive\ ST)}{(motor\ ST \times cognitive\ ST)} \times 100\%$$

For both the DTE equations for variables in which higher values indicate poorer performance a negative sign was inserted into the formula (Kelly et al., 2010; P Plummer & Eskes, 2015):

$$DTE(\%) = \frac{-DT - ST}{ST} \times 100\%$$

$$cDTE\ (\%) = \frac{-(motor\ DT \times Cognitive\ DT) - (motor\ ST \times cognitive\ ST)}{(motor\ ST \times cognitive\ ST)} \times 100\%$$

This approach creates the convention that all negative DTE values are indicative of performance that deteriorated under DT conditions compared to single task conditions (DT cost). A positive DTE value is indicative of a relative improvement on performance under DT conditions (DT facilitation) (Kelly et al., 2010; P Plummer & Eskes, 2015). While mDTE and cogDTE are measures of task specific interference, it is proposed that cDTE is a measure of automaticity as it is a measure of relative change in a combination of both motor and cognitive performance and quantifies the overall loss of automaticity while performing a DT.

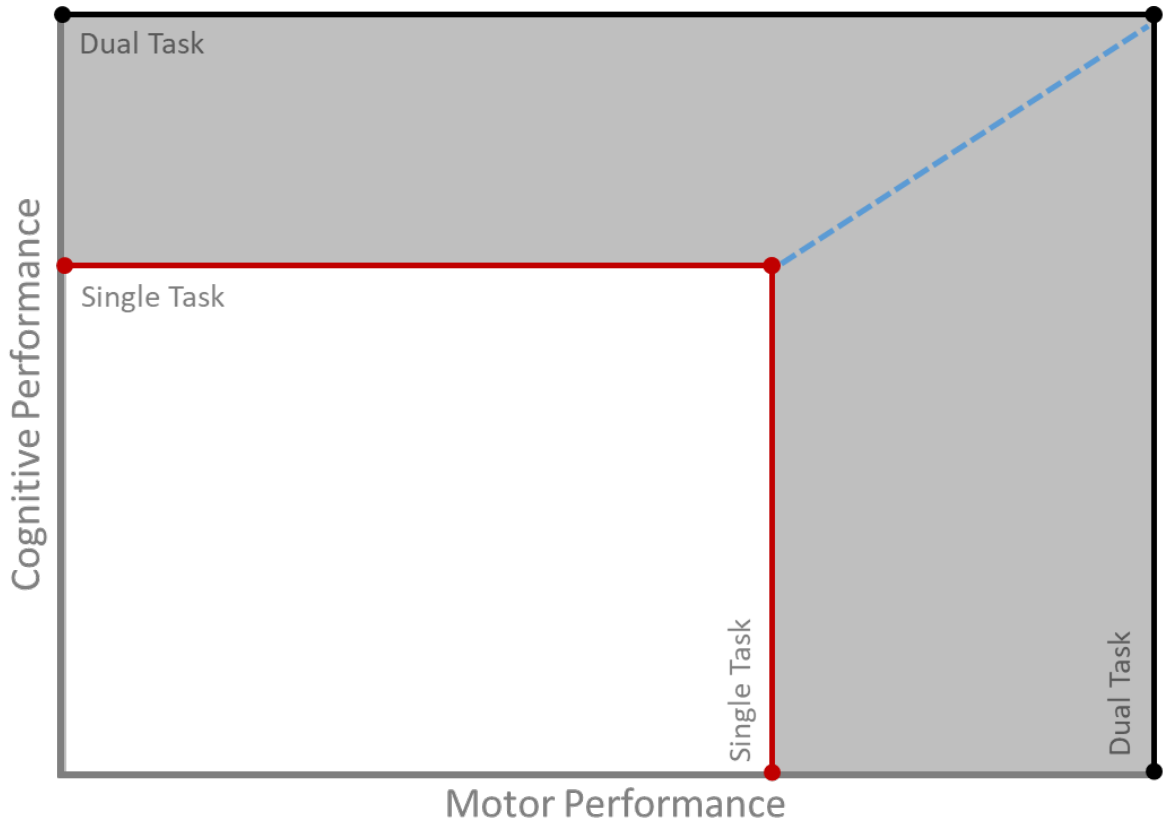


Figure 2. Example of compound interference measures. Red lines represent single task performance, while black lines indicate dual task performance. The compound measure proposed by Longhurst et al is represent with the area in grey, while the Euclidean distance method proposed by Wahn & Sinnett (Wahn & Sinnett, 2019) is represented by the dashed blue line. Both methods represent the difference between single and dual task performance.

In addition to the measures of DTE, task prioritization category (based on the criteria established by Plummer et al) (P Plummer et al., 2013; P Plummer & Eskes, 2015) and mAAI were utilized to assess task prioritization during DT performance. Task prioritization category was categorized by plotting the mDTE against the cogDTE with each quadrant representative of one of the following categories: mutual interference (decline in motor performance accompanied by decline in cognitive performance under DT conditions), cognitive priority

trade-off (improved or unchanged cognitive performance accompanied by decline in motor performance under DT conditions), motor priority trade-off (improved or unchanged motor performance accompanied by decline in cognitive performance under DT conditions), and mutual facilitation (improved motor performance accompanied by improved cognitive performance under DT conditions) (P Plummer & Eskes, 2015). mAAI was calculated utilizing mDTE and cogDTE values to assess for trade-offs within the task.(Kelly et al., 2010) The following formula was utilized to calculate mAAI (Kelly et al., 2010; Siu & Woollacott, 2007):

$$mAAI = mDTE - cogDTE$$

Positive values are indicative of greater mDTE compared to cogDTE and represent a shift in attention toward the motor task, whereas a negative value is indicative of a shift in attention toward the cognitive task. Figure 3 provides an overview of the DTE-B.

Task specific interference

Motor Dual Task Effect	$\frac{motorDT - motorST}{motorST} \times 100\%$	(+) Facilitation (-) Interference
Cognitive Dual Task Effect	$\frac{cognitiveDT - cognitiveST}{cognitiveST} \times 100$	(+) Facilitation (-) Interference

Task prioritization

Task Prioritization Category	Motor priority trade off: (+) motorDTE (-) CognitiveDTE	Cognitive priority trade off: (-) motorDTE (+) CognitiveDTE	Mutual Interference: (-) motorDTE (-) CognitiveDTE	Mutual Facilitation: (+) motorDTE (+) CognitiveDTE
Modified Attention Allocation Index	$Motor\ DTE - Cognitive\ DTE$			(+) Motor priority (0) No Priority (-) Cognitive priority

Automaticity

Combined Dual task Effect	$\frac{(motorDT \times Cognitive\ DT) - (motorST \times cognitiveST)}{(motorST \times cognitiveST)} \times 100\%$	(+) Facilitation (-) Interference

Figure 3. Dual task effect battery.

PD symptoms. The MDS-UPDRDS parts I-III were used for PD symptoms and this was assessed

only for patients with PD (Goetz et al., 2008).

Cognition and Depression. Global cognition was measured using the MoCA (Nasreddine et al., 2005). The MoCA has excellent test-retest reliability (correlation coefficient = 0.92) (Nasreddine et al., 2005) and has evidence for its validity in early PD (Kletzel et al., 2017). The PHQ-9 was used to measure depression in the PD and AD groups. Kroenke et al offer evidence for the reliability and validity of the PHQ-9 with a reported sensitivity of 95% and specificity of 84% for identifying major depressive disorder at a cut off score of >9 (Kroenke et al., 2001).

Balance and falls. Scores from the Mini Balance Evaluation Systems Test (MiniBESTest) and the Five Times Sit-to-Stand Test were included to describe patient balance performance. The MiniBESTest measures anticipatory postural control, reactive balance, sensory orientation, and dynamic gait. The MiniBESTest has excellent inter-rater reliability (ICC = 0.98) (Godi et al., 2013). Although it is typically used to measure functional lower limb strength, the Five Times Sit-to-Stand Test is considered a measure of dynamic balance in older adults and was collected in the AD and PD cohorts (Goldberg et al., 2012). The Five Times Sit-to-Stand Test has excellent test-retest and inter-rater reliability among individuals with PD with ICC values of 0.91 and 0.99, respectively, and excellent test-retest reliability for community-dwelling elderly (ICC = 0.957) (R W Bohannon et al., 2010; Duncan et al., 2011; Paul et al., 2012). Falls in the last 30 days, falls in the last year, and fall-related injuries in the last year were extracted from the patient records. A fall was defined as any unintentional lowering to the ground.

Gait. Scores from the following gait measures were included: 10 meter walk test, 10 meter walk test – Fast, and Six Minute Walk Test (6MWT) (Richard W. Bohannon, 1997; Crapo et al., 2002).

Both the 10 meter walk test and 10 meter walk test – fast have high test-retest reliability in individuals with PD (ICC = 0.96 and 0.97, respectively) and among older adults with dementia for the 10 meter walk test (ICC = 0.91) (Chan & Pin, 2019; Steffen & Seney, 2008). The 6MWT has excellent test-retest reliability (ICC = 0.95-0.96) for individuals with PD (Steffen & Seney, 2008). It has excellent test-retest reliability (ICC = 0.982-0.987), interrater reliability (ICC = 0.97-0.99), and intrarater reliability (ICC = 0.76-0.9) for individuals with AD (Ries et al., 2009; Tappen et al., 1997).

Sample size estimation

Sample size was estimated using effect size and standard deviation for cDTE obtained from pilot data using PASS 20.0.3 (NCSS, LLC. Kaysville, Utah, USA, www.ncss.com/software/pass) for both aims. For the reliability analysis (aim 1), confidence intervals for interclass correction module was utilized. The estimate revealed that a sample of 34 participants, who were each measured twice, would produce a two-sided 95% confidence interval with a width of .200 when the estimated interclass correlation is .850 utilizing a two-way random-effects ANOVA model (Intraclass correlation coefficient (ICC) 3,2). For construct validity (aim 2), a sample of 84 achieves 80% power to detect a difference of .3 between the null hypothesis correlation and the alternative hypothesis correlation using a two-sided hypothesis test with a significance level set at α=.05.

Data Analysis

All analyses were conducted using SPSS 24.0 (IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp) with $\alpha = 0.05$. Descriptive statistics and between group comparisons were conducted using chi square for nominal data and nonparametric (Quade's) ANCOVA, due to lack of homogeneity of variance between groups and to include age as a covariate. Statistical corrections for multiple comparisons were completed using Benjamini-Hochberg corrections.

For Aim 1 (test-retest reliability and minimal detectable change (MDC)), a subset of participants from each group (PD (n=37), AD (n=34), healthy (n=34)) completed DT assessment twice, approximately 1 week apart (8.9±3.7 days). These data were analyzed using the ICC model 3 for continuous data and Cohen's kappa for categorical data (task prioritization category). ICC conventions were defined as poor (<.4), fair (.4 to .59), good (.6 to .74), and excellent (.75 to 1.00) (Cicchetti, 1994). Kappa values were interpreted as level of agreement according to the following criteria: poor (<.00), slight (.00 to .20), fair (.21 to .40), moderate (.41 to .60), substantial (.61 to .80), and almost perfect (.81 to 1.00) (Landis & Koch, 1977). To determine the MDC, standard error of measurement (SEM) was calculated using the ICC test-retest reliability statistic, where SD=standard deviation and rxx= ICC test-retest reliability statistic:

$$SEM = SD\sqrt{1 - r_{xx}}$$

Once the SEM was determined, the minimal detectable change at a 95% confidence level (MDC_{95}) for cDTE was calculated by multiplying the SEM by 1.96 (representing 95% of the area

under the curve of a normal distribution) and 1.41 (the square root of 2 to control for possible error associated with calculating the coefficient from 2 time points [i.e., test and retest])

$$MDC = SEM \times Z \times \sqrt{2}$$

For Aim 2 (construct validity), convergent validity, divergent validity, and known-groups analysis were assessed for the DTE-B. In this study, we compared the DTE-B to four domains of outcomes (PD symptoms, cognition and depression, balance and falls, and gait) using correlational statistics (Pearson product moment correlations or Spearman's rho). We anticipated evidence for convergent relationship between cDTE and measures in the DTE-B, and more automatic tasks such as gait (10 meter walk test and 6MWT), and balance reactions (MiniBESTest reactive balance and sensory organization subscales). We anticipated that mDTE or cogDTE would correlate more strongly with tasks requiring attentional resources such as anticipatory balance control and dynamic balance during gait (Five Times Sit-to-Stand Test and MiniBESTest anticipatory and dynamic gait subscales) as well as cognition as measured by the MoCA. Tasks requiring higher levels of decision making and attentional resource allocation (falls, modified Fear of Falling Avoidance Behavior Questionnaire (mFFABQ), and MDS-UPDRS part II) we anticipated to be more closely related to mAAI. Conversely, we expected divergent validity, for cDTE specifically, to be demonstrated by minimal to no relationship between cDTE and the MDS-UPDRS part I and PHQ-9, and relationships with outcomes that require attentional resources (Five Times Sit-to-Stand Test, MiniBESTest anticipatory and dynamic gait sub-scales) that are weaker than their counterparts in the task interference domain (mDTE and/or cogDTE).

In this study, the groups for the known-groups validity analysis were created based on neurologic diagnosis into the following groups: PD group (more motor impairment than cognitive impairment), AD group (more cognitive impairment than motor impairment), and a healthy older adult group (no impairment). Due to the age differences between groups non-parametric (Quade's) ANCOVA was conducted comparing performance on DTE-B measures (mDTE, cogDTE, mAAI, and cDTE) across groups entering age as a covariate.

RESULTS

There were several between group differences on the outcomes of interest. These are presented in Table 2.

Table 2. Descriptive statistics and p-values for between group differences (Quade's ANCOVA, or Chi square test as appropriate) for the PD, AD, and healthy groups. Benjamini-Hochberg correction applied to control for family wise error. Significant p-values after correction are marked in red.

	PD (n=125)	AD (n=127)	Healthy (n=84)	p-value
DUAL TASK PERFORMANCE				
ST TUG	12.8 ± 10.9	12.8 ± 6.4	7.1 ± 1.8	<.001
ST correct response rate	3.0 ± 1.9	4.4 ± 3.0	2.1 ± .8	<.001
DT TUG (TUGcog)	18.7 ± 20.8	19.4 ± 12.1	8.7 ± 2.7	<.001
DT correct response rate	6.5 ± 9.9	9.1 ± 9.2	2.9 ± 2.5	<.001
mDTE	-42.0 ± 45.3	-52.1 ± 51.8	-24.6 ± 27.3	<.001
cogDTE	-103.6 ± 252.7	-112.6 ± 156.5	-35.6 ± 71.6	<.001
Task prioritization category	MPT – 4 CPT – 21 MI – 100 MF – 0	MPT – 10 CPT – 18 MI – 97 MF – 2	MPT – 8 CPT – 16 MI – 56 MF – 4	.061
mAAI	61.5 ± 247.1	60.6 ± 150.8	11.0 ± 69.3	.413
cDTE	-213.3 ± 421.9	-245.5 ± 320.1	-74.2 ± 131.3	<.001
PD SYMPTOMS				
MDS-UPDRS Part I	8.2 ± 5.0			
MDS-UPDRS Part II	13.6 ± 6.2			
MDS-UPDRS Part III	27.4 ± 13.2			
COGNITION & DEPRESSION				
MoCA	26.74± 5.0	18.3 ± 5.4	27.4 ± 2.0	<.001
PHQ-9	6.8 ± 5.6	7.5 ± 6.1		.341
BALANCE & FALLS				
MiniBESTest				
Anticipatory	4.2 ± 1.0	3.9 ± .8	5.5 ± .7	<.001
Reactive	4.0 ± 1.8	3.7 ± 1.4	5.7 ± .7	<.001
Sensory Organization	5.1 ± 1.2	5.1 ± 1.0	5.8 ± .5	.001
Dynamic Gait	6.7 ± 2.3	6.1 ± 1.9	9.0 ± .9	<.001
MiniBESTest total score	20.1 ± 5.4	18.8 ± 4.0	25.9 ± 1.9	<.001
5 times sit to stand	16.1 ± 11.1	17.0 ± 9.3		.042
Falls in last 30 Days	.88 ± 3.2	.59 ± 1.4	.00 ± .00	<.001
Falls in last Year	9.6 ± 35.0	2.5 ± 7.7	.3 ± .6	<.001
Injurious Falls	.39 ± .83	.37 ± .68	.06 ± .238	.003
mFFABQ	16.6 ± 12.1	18.4 ± 14.2	.3 ± 1.2	<.001
GAIT				
10 meter walk test	.95 ± .33	.92 ± .40	1.28 ± .20	<.001
10 meter walk fast	1.39 ± .49	1.35 ± .70	1.71 ± .33	<.001
6 minute walk test	341.1 ± 140.3	312.1 ± 124.1	508.5 ± 70.9	<.001

ST – Single Task, TUG – Timed Up and Go, DT – Dual task, TUGCog – Timed Up and Go Cognitive, mDTE – motor dual task effect, cogDTE – cognitive dual task effect, MPT – motor priority trade-off, CPT – cognitive priority trade-off, MI – mutual interference, MF- mutual facilitation, mAAI – modified attention allocation index, cDTE – combined dual task effect, MDS-UPDRS – Movement Disorder Society – Unified Parkinson Disease Rating Scale, MoCA – Montreal Cognitive Assessment, PHQ-9 – Patient Health Questionnaire, mFFABQ- modified Fear of Falling Avoidance Behavior Questionnaire.

Reliability analysis (aim 1). The results of the test-retest reliability analysis for mDTE, cogDTE, task prioritization category, mAAI, and cDTE are summarized in Table 3. Briefly, mDTE, cogDTE, and cDTE all exhibited good-to-excellent reliability in all three groups. Among these DT metrics, cDTE was the most reliable. Task prioritization category was found to have poor reliability in the PD and AD groups as kappa values were not found to be significantly different from zero. However, task prioritization category was found to have moderate reliability in the healthy group. As task prioritization category was found to have poor reliability it will not be further discussed. Lastly, mAAI had excellent reliability in the PD group, good reliability in the AD group, and poor reliability in the healthy group.

Table 3. Test-retest reliability (ICC(3,2) with 95% confidence interval) and minimal detectable change (MDC_{95}) for the motor dual task effect, cognitive dual task effect, modified attention allocation index, and combined dual task effect for each groups (PD, AD, and healthy). Test-retest reliability (Cohen's κ with 95% confidence interval) for task prioritization category for each group.

	PD (n=37)	**AD** (n=34)	**Healthy** (n=34)
mDTE	ICC=.825 (.687 to .906)** MDC= 21.0	ICC=.841 (.705 to .917)** MDC= 18.9	ICC=.815 (.710 to .885)* MDC= 8.9
CogDTE	ICC=.887 (.792 to .940)** MDC= 42.5	ICC=.827 (.681 to .910)** MDC= 40.9	ICC=.658 (.416 to .813)** MDC= 10.9
Task prioritization category	κ=.236 (-.089 to.561)	κ=.171 (-.201 to.543)	κ=.457 (.126 to.788)**
mAAI	ICC=.776 (.607 to .878)** MDC= 42.1	ICC=.690 (.462 to .832)** MDC= 40.8	ICC=.353 (.022 to .641)* MDC= 13.1
cDTE	ICC=.968 (.940 to .984)** MDC= 92.4	ICC=.938 (.880 to .969)** MDC= 80.5	ICC=.945 (.892 to .972)** MDC= 18.2

*=p value <.05, **=p value<.001, PD – Parkinson's disease, AD – Alzheimer's disease, mDTE – motor dual task effect, cogDTE – cognitive dual task effect, mAAI – modified attention allocation index, cDTE – combined dual task effect

Convergent validity analysis (aim 2). Many relationships between DTE-B and measured variables were observed and are reported in Table 4. Briefly, correlational analyses revealed strong associations between mDTE and cDTE, cogDTE and cDTE, cogDTE and mAAI, and mAAI and cDTE for each of the three groups, with moderate relationships observed between mDTE and cogDTE. Additionally, mDTE demonstrated minimal relationship with outcomes across all groups. The cogDTE, mAAI, and cDTE all exhibited distinct patterns of associations within each group. cogDTE was found to be moderately related to MDS-UPDRS part III (PD), MoCA (PD, AD), MiniBESTest (PD), Five Times Sit-to-Stand Test (PD), gait (all groups), and inversely with prior falls (healthy controls), and mFFABQ (PD). mAAI had moderate relationships with MDS-UPDRS part II (PD), MoCA (PD), MiniBESTest (PD, AD) and gait (all groups). Lastly, cDTE demonstrated moderate strength of relationships with MoCA (AD), MiniBESTest (PD, healthy), Five Times Sit-to-Stand Test (PD), prior falls (healthy), and gait (all groups). Among the DTE-B variables, cDTE was found to be most strongly associated with gait and the MiniBESTest reactive balance subscale in the PD group.

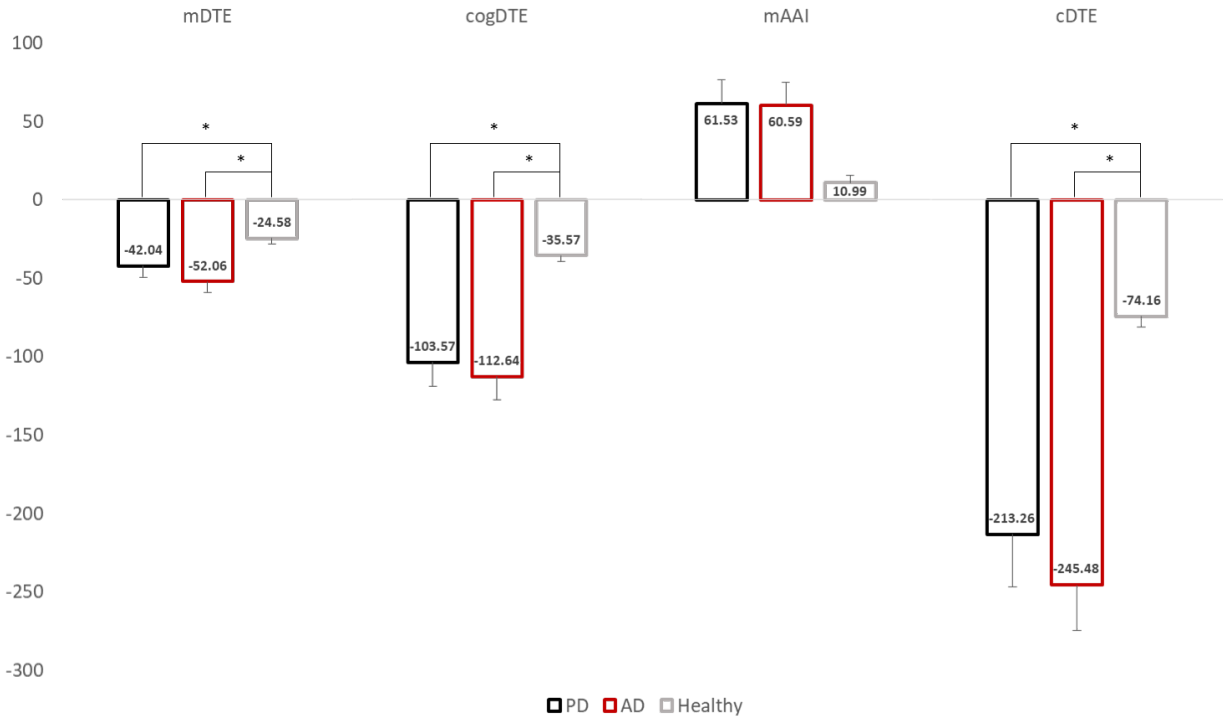
Divergent validity analysis (aim 2). The details of the results of the correlational analysis can be found in Table 4. No DTE-B measures were associated with MDS-UPDRS part I or with PHQ-9. In observing relative strengths of relationships between DTE-B and other outcomes, cogDTE is more strongly associated with MiniBESTest anticipatory balance subscale, and Five Times Sit-to-Stand Test, than cDTE. cDTE is more strongly related to MiniBESTest dynamic gait in the PD group than mDTE or cogDTE.

Table 4. Pearson product moment correlation coefficient or Spearman's rho for mDTE, cogDTE, mAAI, and cDTE on PD symptom, cognition and mental health, balance and falls, and gait domains among the PD, AD, and healthy groups. Benjamini-Hochberg corrections were applied to control for family wise error. Significant p-values after correction are marked in red.

	PD				AD				HEALTHY			
VARIABLE (STATISTIC)	***mDTE***	***cogDTE***	***mAAI***	***cDTE***	***mDTE***	***cogDTE***	***mAAI***	***cDTE***	***mDTE***	***cogDTE***	***mAAI***	***cDTE***
DTE-B												
Motor DTE (r)	X	.212*	-.034	.498**	X	.275*	.058	.604**	X	.272*	.113	.498**
Cognitive DTE (r)	.212*	X	-.984**	.929**	.275*	X	-.944**	.882**	.272*	X	-.925**	.951**
mAAI (r)	-.034	-.984**	X	-.859**	.058	-.944**	X	-.708**	.113	-.925**	x	-.785**
cDTE (r)	.498**	.929**	-.859**	X	.604**	.882**	-.708**	X	.498**	.951**	-.785**	X
PD SYMPTOMS												
MDS-UPDRS Part I (ρ)	.117	-.045	.174	.002								
MDS-UPDRS Part II (ρ)	-.047	-.337	.384*	-.275								
MDS-UPDRS Part III (ρ)	-.014	-.189*	.260*	-.149								
COGNITION & DEPRSRESSION												
MoCA (ρ)	.298	.419*	-.426*	.430*	.102	.251*	-.215*	.276*	.003	-.038	.071	-.021
PHQ-9 (ρ)	-.151	-.175	.146	-.166	.125	-.028	.123	.039				
BALANCE & FALLS												
MiniBESTest												
Anticipatory (ρ)	.053	.273*	-.281*	.239*	.013	.008	-.097	.033	-.005	.269*	-.229	.230
Reactive (ρ)	.249*	.298**	-.207*	.327**	.169	.099	-.184	.010	.139	.034	-.114	.076
Sensory Organization (ρ)	.140	.186*	-.190*	.190*	.236*	.032	-.225*	.073	.168	.024	-.122	.068
Dynamic Gait (ρ)	.250*	.372**	-.276*	.379**	.048	.274*	-.312**	.201*	.369*	.213	-.069	.356*
MiniBESTest Total Score (ρ)	.237*	.347**	-.276*	.357**	.108	.197*	-.291*	.105	.228	.063	.145	.077
5 times sit to stand (r)	-.123	-.422**	.409**	-.411**	-.136	-.200*	-161	-.196*				
Falls in last 30 Days (r)	.061	.033	-.023	.055	.028	-.105	.188	-.044	.000	.000	.000	.000
Falls in last Year (r)	.094	.060	-.044	.072	-.044	-.038	-.024	-.037	-.259*	-.349**	.259*	-.399**
Injurious Falls (r)	.022	-.021	.025	-.048	-.081	-.117	.095	-.153	.066	.064	-.043	.069
mFFABQ (ρ)	-.139	-.287*	.303*	-.269*	-.048	-.120	.168	-.053	.331	.229	-.025	.306
GAIT												
10 meter walk test (r)	.099	.249*	-.237*	.261*	.082	.215*	-.195*	.188	-.059	.179	-.208	.150
10 meter walk fast (r)	.114	.314**	-.299**	.331**	.023	.189	-.188	.152	-.045	.085	-.103	.073
6 minute walk test (r)	.189	.281*	-.244*	.298*	.124	.352**	-.313*	.347**	.057	.294*	-.282*	.282*

*=p value <.05, **=p value<.001, DTE-B – dual task effect battery, DTE – dual task effect, mAAI – modified attention allocation index, cDTE – combined dual task effect, MDS-UPDRS – movement disorder society – Unified Parkinson Disease Rating Scale, MoCA – Montreal Cognitive Assessment, PHQ-9 – Patient Health Questionnaire, mFFABQ-modified Fear of Falling Avoidance Behavior Questionnaire.

Known-groups validity analysis (aim 2). The known-groups validity analyses revealed significant between group differences on Quade's ANCOVA for mDTE, cogDTE, and cDTE (*p*s<.001), while showing no difference on mAAI (*p*=.245) (Figure 4). Schefe post hoc tests revealed that both the PD and AD groups differed from the healthy group, but not from each other on mDTE (*p*s≤.033), cogDTE (*p*s≤.017), and cDTE (*p*s≤.004).



*indicates groups that are statistically different from each other

Figure 4. Means and standard errors of the mDTE, cogDTE, mAAI, and cDTE among PD, AD, and healthy groups.

DISCUSSION

This study demonstrated that task specific DT interference and DT related automaticity are highly reliable. Measures of task specific interference (mDTE and cogDTE) and automaticity

(cDTE) demonstrated excellent reliability. Of these measures, the cDTE exhibited the highest level of reliability in each group. This is consistent with the observation that cDTE is a measure of a more stable construct, such as automaticity, compared to the other measures of DT performance, which can be highly influenced by allocation of attention or task prioritization. As task prioritization is greatly influenced by volitional attention allocation, it was unsurprising that task prioritization category and mAAI were found to be the least reliable of the DTE-B. This was particularly true of mAAI in the healthy group and is likely a result of this group having no distinct deficit in either cognition or motor control for which they need to actively compensate with their attention. This allows their task prioritization strategy to be more fluid than individuals with cognitive or motor deficits. MDCs found in this study were substantially smaller than those reported by Venema et al (Venema et al., 2019). These differences are primarily attributable to smaller ICC values found by Venema et al., which may be due to insufficient power with an inadequate sample size and/or inclusion of a more heterogeneous sample with several diagnoses represented in the population.

We investigated the construct validity of the DTE-B and particularly of the novel measure of automaticity, cDTE. In accordance with our hypothesis, there were moderate to strong relationships with mDTE, cogDTE, and mAAI in all groups, indicating the highly related nature of task specific interference, task prioritization, and automaticity, as they relate to DT performance. Among individuals with PD, there were moderate relationships identified between cDTE and measures of gait, and reactive balance. These outcomes were among those anticipated to have a higher component of automaticity involved in their execution, and thus

provide evidence of the validity of the cDTE as a measure of automaticity. Among the other variables in the DTE-B, cDTE was most strongly associated with mDTE, cogDTE, and mAAI. There were no relationships identified among the sensory organization test variables and the cDTE, though in the PD group there was a significant relationship prior to Benjamini-Hochberg correction. Additionally, the pattern observed in the PD group was partially recapitulated in the AD and healthy groups, with both groups showing moderate associations between cDTE and the 6MWT, indicating that individuals with greater impairments in automaticity ambulated less distance during six minutes. Overall, there is substantial evidence for cDTE as a measure of automaticity in the PD group, while in the AD and healthy groups this is less conclusive and requires further investigation.

We anticipated that mDTE, and cogDTE would be more related to tasks requiring attentional resources as well as cognition, than would cDTE. Across all groups, the findings generally support this hypothesis, with one notable exception; the MoCA, related strongly to cDTE in both the PD and AD groups. This may indicate that the MoCA is related to automatic task execution, as previously reported (Lv et al., 2020). This study provides evidence supporting the divergent validity of the DTE-B with a lack of association seen between unrelated constructs (i.e., DTE-B and MDS UDPRS I and PHQ 9). The pattern of findings in the AD group are similar to findings previously reported among individuals with cognitive impairment (Longhurst et al., 2020), indicating that cognitive specific interference (cogDTE) plays a leading role in driving DT-related performance in those with AD. We found mDTE was not strongly related to gait, balance and falls, or cognition, highlighting the importance of considering multiple outcomes when

evaluating DT performance. In summary, the findings of this study support the DTE-B as a measure of the multiple DT dimensions.

In the known-groups validity analyses, in accordance with our hypothesis, we found that DT performance was uniformly better in the healthy group compared to the PD and AD groups. In contrast to our hypothesis, we found no difference in the presentation of DT performance among the PD and AD groups. This is primarily driven by task prioritization during DT, which in both groups was motor prioritized, which may be a strategy that prioritizes safety over cognition during a functional task (G Yogev-Seligmann et al., 2012). These results are supported by the literature showing that both individuals with PD and AD tend to self-prioritize motor activities over cognitive activities during DT (Simieli et al., 2015; Galit Yogev-Seligmann et al., 2012). One possible explanation for our results is that task prioritization may be more a function of the task involved (Canning, 2005; Rapp et al., 2006; Verghese et al., 2007; G Yogev-Seligmann et al., 2012). Alternatively, this lack of difference may be due to the instructional language used, which encouraged neutral prioritization (Prudence Plummer et al., 2020). DT performance is different between healthy and neurodegenerative populations; however, the patterns of DT performance may not be related to disease pathology.

In contrast to previous findings, this study found little association between DT performance and falls. Among all groups, only the healthy older adult group was found to have an association between falls and cogDTE as well as cDTE. This finding is consistent with previous research

indicating the relationship between DT performance and falls in the healthy older adult population (Menant et al., 2014). In the PD and AD group, no relationship between DT performance and falls was identified. However, in the PD group there was a relationship between DT performance and mFFABQ, indicating that when DT performance was poorer individuals had more avoidance behavior related to fear of falling. This may support the hypothesis that poor DT performance is related to falls; however, a sufficiently large portion of patients in the PD group may have recognized this risk and adapted by avoiding more risky behaviors, thereby reducing their falls. This would most likely occur in the PD group given the higher fall history and greater need to avoid risky behaviors relative to the other groups (Landers et al., 2017; Nilsson et al., 2010). We postulate that individuals with AD are less likely to adapt to these impairments by avoiding risky behaviors and activities as this adaptation necessitates a certain level of memory and learned behavior, both of which are compromised in AD.

Limitations of this study should be considered with interpreting the results. This study utilized data collected during routine physical therapy practice for the PD and AD, and as such, it is possible that these samples represent unique subpopulations with uncertain generalizability. Additionally, while this study did utilize consistent instructional language encouraging neutral task prioritization, it is possible that the instructional language influenced task performance resulting in changes in attentional resource allocation from usual performance.

CONCLUSION

The DTE-B is a reliable, novel tool that may improve the consistency of measurement and reporting of DT-related performance and abilities. The DTE-B may improve the characterization of multiple domains within DT performance, specifically attention allocation and automaticity, which are underutilized both clinically and in research. The novel measure of combined interference, cDTE, demonstrated adequate evidence to support its validity as a measure of automaticity, as shown in analyses of convergent, divergent, and known-groups validity. Further investigation of the utility of the DTE-B in both PD and AD is warranted.

REFERENCES

Albert, M. S., DeKosky, S. T., Dickson, D., Dubois, B., Feldman, H. H., Fox, N. C., Gamst, A., Holtzman, D. M., Jagust, W. J., Petersen, R. C., Snyder, P. J., Carrillo, M. C., Thies, B., & Phelps, C. H. (2011). The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia*, *7*(3), 270–279. https://doi.org/10.1016/j.jalz.2011.03.008

Amboni, M., Barone, P., Iuppariello, L., Lista, I., Tranfaglia, R., Fasano, A., Picillo, M., Vitale, C., Santangelo, G., Agosti, V., Iavarone, A., & Sorrentino, G. (2012). Gait patterns in parkinsonian patients with or without mild cognitive impairment. *Movement Disorders*, *27*(12), 1536–1543. https://doi.org/10.1002/mds.25165

Amboni, M., Iuppariello, L., Iavarone, A., Fasano, A., Palladino, R., Rucco, R., Picillo, M., Lista, I., Varriale, P., Vitale, C., Cesarelli, M., Sorrentino, G., & Barone, P. (2018). Step length predicts executive dysfunction in Parkinson's disease: a 3-year prospective study. *Journal of Neurology*, *265*(10), 2211–2220. https://doi.org/10.1007/s00415-018-8973-x

Ansai, J. H., Andrade, L. P., Rossi, P. G., Takahashi, A. C. M. M., Vale, F. A. C. C., & Rebelatto, J. R. (2017). Gait, dual task and history of falls in elderly with preserved cognition, mild cognitive impairment, and mild Alzheimer's disease. *Braz J Phys Ther*, *21*(2), 144–151. https://doi.org/10.1016/j.bjpt.2017.03.010

Belghali, M., Chastan, N., Cignetti, F., Davenne, D., & Decker, L. M. (2017). Loss of gait control assessed by cognitive-motor dual-tasks: pros and cons in detecting people at risk of

developing Alzheimer's and Parkinson's diseases. *Geroscience*, *39*(3), 305–329. https://doi.org/10.1007/s11357-017-9977-7

Bohannon, R W, Bubela, D. J., Magasi, S. R., Wang, Y. C., & Gershon, R. C. (2010). Sit-to-stand test: Performance and determinants across the age-span. *Isokinet Exerc Sci*, *18*(4), 235–240. https://doi.org/10.3233/IES-2010-0389

Bohannon, Richard W. (1997). Comfortable and maximum walking speed of adults aged 20-79 years: Reference values and determinants. *Age and Ageing*. https://doi.org/10.1093/ageing/26.1.15

Canning, C. G. (2005). The effect of directing attention during walking under dual-task conditions in Parkinson's disease. *Parkinsonism and Related Disorders*, *11*(2), 95–99. https://doi.org/10.1016/j.parkreldis.2004.09.006

Cardon-Verbecq, C., Loustau, M., Guitard, E., Bonduelle, M., Delahaye, E., Koskas, P., & Raynaud-Simon, A. (2017). Predicting falls with the cognitive timed up-and-go dual task in frail older patients. *Ann Phys Rehabil Med*, *60*(2), 83–86. https://doi.org/10.1016/j.rehab.2016.07.003

Chan, W. L. S., & Pin, T. W. (2019). Reliability, validity and minimal detectable change of 2-minute walk test, 6-minute walk test and 10-meter walk test in frail older adults with dementia. *Exp Gerontol*, *115*, 9–18. https://doi.org/10.1016/j.exger.2018.11.001

Chomiak, T., Watts, A., Meyer, N., Pereira, F. V, & Hu, B. (2017). A training approach to improve stepping automaticity while dual-tasking in Parkinson's disease: A prospective pilot study.

Medicine (Baltimore), *96*(5), e5934. https://doi.org/10.1097/MD.0000000000005934

Christofoletti, G., Andrade, L. P. de, Beinotti, F., Borges, G., de Andrade, L. P., Beinotti, F., & Borges, G. (2014). Cognition and dual-task performance in older adults with Parkinson's and Alzheimer's disease. *International Journal of General Medicine*, *7*, 383–388. https://doi.org/10.2147/IJGM.S65803

Cicchetti, D. V. (1994). Guidelines, Criteria, and Rules of Thumb for Evaluating Normed and Standardized Assessment Instruments in Psychology. *Psychological Assessment*. https://doi.org/10.1037/1040-3590.6.4.284

Crapo, R. O., Casaburi, R., Coates, A. L., Enright, P. L., MacIntyre, N. R., McKay, R. T., Johnson, D., Wanger, J. S., Zeballos, R. J., Bittner, V., & Mottram, C. (2002). ATS statement: Guidelines for the six-minute walk test. In *American Journal of Respiratory and Critical Care Medicine*. https://doi.org/10.1164/ajrccm.166.1.at1102

de Melo Borges, S., Radanovic, M., & Forlenza, O. V. (2015). Functional Mobility in a Divided Attention Task in Older Adults With Cognitive Impairment. *Journal of Motor Behavior*, *47*(5), 378–385. https://doi.org/10.1080/00222895.2014.998331

Duncan, R. P., Leddy, A. L., & Earhart, G. M. (2011). Five times sit-to-stand test performance in Parkinson's disease. *Arch Phys Med Rehabil*, *92*(9), 1431–1436. https://doi.org/10.1016/j.apmr.2011.04.008

Fritz, N. E., Cheek, F. M., & Nichols-Larsen, D. S. (2015). Motor-Cognitive Dual-Task Training in Persons With Neurologic Disorders: A Systematic Review. *J Neurol Phys Ther*, *39*(3), 142–

153. https://doi.org/10.1097/NPT.0000000000000090

Gillain, S., Warzee, E., Lekeu, F., Wojtasik, V., Maquet, D., Croisier, J. L., Salmon, E., & Petermans, J. (2009). The value of instrumental gait analysis in elderly healthy, MCI or Alzheimer's disease subjects and a comparison with other clinical tests used in single and dual-task conditions. *Annals of Physical and Rehabilitation Medicine*, *52*(6), 453–474. https://doi.org/10.1016/j.rehab.2008.10.004

Godi, M., Franchignoni, F., Caligari, M., Giordano, A., Turcato, A. M., & Nardone, A. (2013). Comparison of reliability, validity, and responsiveness of the mini-BESTest and Berg Balance Scale in patients with balance disorders. *Phys Ther*, *93*(2), 158–167. https://doi.org/10.2522/ptj.20120171

Goetz, C. G., Tilley, B. C., Shaftman, S. R., Stebbins, G. T., Fahn, S., Martinez-Martin, P., Poewe, W., Sampaio, C., Stern, M. B., Dodel, R., Dubois, B., Holloway, R., Jankovic, J., Kulisevsky, J., Lang, A. E., Lees, A., Leurgans, S., LeWitt, P. A., Nyenhuis, D., … Movement Disorder Society, U. R. T. F. (2008). Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. *Mov Disord*, *23*(15), 2129–2170. https://doi.org/10.1002/mds.22340

Goldberg, A., Chavis, M., Watkins, J., & Wilson, T. (2012). The five-times-sit-to-stand test: Validity, reliability and detectable change in older females. *Aging - Clinical and Experimental Research*. https://doi.org/10.1007/BF03325265

Hofheinz, M., & Schusterschitz, C. (2010). Dual task interference in estimating the risk of falls and measuring change: a comparative, psychometric study of four measurements. *Clin*

Rehabil, *24*(9), 831–842. https://doi.org/10.1177/0269215510367993

Huang, C. Y., Chen, Y. A., Hwang, I. S., & Wu, R. M. (2018). Improving Dual-Task Control With a Posture-Second Strategy in Early-Stage Parkinson Disease. *Arch Phys Med Rehabil*, *99*(8), 1540-1546 e2. https://doi.org/10.1016/j.apmr.2018.02.013

Huang, S. L., Hsieh, C. L., Wu, R. M., Tai, C. H., Lin, C. H., & Lu, W. S. (2011). Minimal detectable change of the timed "up & go" test and the dynamic gait index in people with Parkinson disease. *Phys Ther*, *91*(1), 114–121. https://doi.org/10.2522/ptj.20090126

Hughes, A. J., Daniel, S. E., Kilford, L., & Lees, A. J. (1992). Accuracy of clinical diagnosis of idiopathic Parkinson's disease: A clinico-pathological study of 100 cases. *Journal of Neurology Neurosurgery and Psychiatry*, *55*(3), 181–184. https://doi.org/10.1136/jnnp.55.3.181

Jack, C. R., Albert, M. S., Knopman, D. S., McKhann, G. M., Sperling, R. A., Carrillo, M. C., Thies, B., & Phelps, C. H. (2011). Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia*, *7*(3), 257–262. https://doi.org/10.1016/j.jalz.2011.03.004

Kelly, V. E., Janke, A. A., & Shumway-Cook, A. (2010). Effects of instructed focus and task difficulty on concurrent walking and cognitive task performance in healthy young adults. *Exp Brain Res*, *207*(1–2), 65–73. https://doi.org/10.1007/s00221-010-2429-6

Kletzel, S. L., Hernandez, J. M., Miskiel, E. F., Mallinson, T., & Pape, T. L. (2017). Evaluating the

performance of the Montreal Cognitive Assessment in early stage Parkinson's disease. *Parkinsonism Relat Disord*, *37*, 58–64. https://doi.org/10.1016/j.parkreldis.2017.01.012

König, A., Klaming, L., Pijl, M., Demeurraux, A., David, R., & Robert, P. (2017). Objective measurement of gait parameters in healthy and cognitively impaired elderly using the dual-task paradigm. *Aging Clinical and Experimental Research*, *29*(6), 1181–1189. https://doi.org/10.1007/s40520-016-0703-6

Kroenke, K., Spitzer, R. L., & Williams, J. B. (2001). The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*, *16*(9), 606–613. https://www.ncbi.nlm.nih.gov/pubmed/11556941

Landers, M. R., Lopker, M., Newman, M., Gourlie, R., Sorensen, S., & Vong, R. (2017). A Cross-sectional Analysis of the Characteristics of Individuals With Parkinson Disease Who Avoid Activities and Participation Due to Fear of Falling. *J Neurol Phys Ther*, *41*(1), 31–42. https://doi.org/10.1097/NPT.0000000000000162

Landis, J. R., & Koch, G. G. (1977). The Measurement of Observer Agreement for Categorical Data. *Biometrics*, *33*(1), 159. https://doi.org/10.2307/2529310

Longhurst, J. K., Wise, M. A., Krist, D. J., Moreland, C. A., Basterrechea, J. A., & Landers, M. R. (2020). Brain volumes and dual-task performance correlates among individuals with cognitive impairment: a retrospective analysis. *Journal of Neural Transmission*, *127*(7). https://doi.org/10.1007/s00702-020-02199-7

Lv, R., Nie, S., Liu, Z., Guo, Y., Zhang, Y., Xu, S., Hou, X., Chen, J., Ma, Y., Fan, Z., & Liu, X. (2020).

Dysfunction in automatic processing of emotional facial expressions in patients with obstructive sleep apnea syndrome: An event-related potential study. *Nature and Science of Sleep*, *12*, 637–647. https://doi.org/10.2147/NSS.S267775

Maquet, D., Lekeu, F., Warzee, E., Gillain, S., Wojtasik, V., Salmon, E., Petermans, J., & Croisier, J. L. (2010). Gait analysis in elderly adult patients with mild cognitive impairment and patients with mild Alzheimer's disease: Simple versus dual task: A preliminary report. *Clinical Physiology and Functional Imaging*, *30*(1), 51–56. https://doi.org/10.1111/j.1475-097X.2009.00903.x

McIsaac, T. L., Fritz, N. E., Quinn, L., & Muratori, L. M. (2018). Cognitive-motor interference in neurodegenerative disease: A narrative review and implications for clinical management. In *Frontiers in Psychology* (Vol. 9, Issue OCT). Frontiers Media S.A. https://doi.org/10.3389/fpsyg.2018.02061

McIsaac, T. L., Lamberg, E. M., & Muratori, L. M. (2015). Building a framework for a dual task taxonomy. *BioMed Research International*, *2015*, 591475. https://doi.org/10.1155/2015/591475

Menant, J. C., Schoene, D., Sarofim, M., & Lord, S. R. (2014). Single and dual task tests of gait speed are equivalent in the prediction of falls in older people: A systematic review and meta-analysis. In *Ageing Research Reviews* (Vol. 16, Issue 1, pp. 83–104). Elsevier Ireland Ltd. https://doi.org/10.1016/j.arr.2014.06.001

Montero-Odasso, M. M., Sarquis-Adamson, Y., Speechley, M., Borrie, M. J., Hachinski, V. C., Wells, J., Riccio, P. M., Schapira, M., Sejdic, E., Camicioli, R. M., Bartha, R., McIlroy, W. E., &

Muir-Hunter, S. (2017). Association of Dual-Task Gait With Incident Dementia in Mild Cognitive Impairment: Results From the Gait and Brain Study. *JAMA Neurol*, *74*(7), 857–865. https://doi.org/10.1001/jamaneurol.2017.0643

Morris, S., Morris, M. E., & Iansek, R. (2001). Reliability of measurements obtained with the Timed "Up & Go" test in people with Parkinson disease. *Phys Ther*, *81*(2), 810–818. https://www.ncbi.nlm.nih.gov/pubmed/11175678

Muir, S. W., Speechley, M., Wells, J., Borrie, M., Gopaul, K., & Montero-Odasso, M. (2012). Gait assessment in mild cognitive impairment and Alzheimer's disease: the effect of dual-task challenges across the cognitive spectrum. *Gait Posture*, *35*(1), 96–100. https://doi.org/10.1016/j.gaitpost.2011.08.014

Nasreddine, Z. S., Phillips, N. A., Bedirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J. L., & Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*, *53*(4), 695–699. https://doi.org/10.1111/j.1532-5415.2005.53221.x

Nilsson, M. H., Drake, A. M., & Hagell, P. (2010). Assessment of fall-related self-efficacy and activity avoidance in people with Parkinson's disease. *BMC Geriatr*, *10*, 78. https://doi.org/10.1186/1471-2318-10-78

Paul, S. S., Canning, C. G., Sherrington, C., & Fung, V. S. (2012). Reproducibility of measures of leg muscle power, leg muscle strength, postural sway and mobility in people with Parkinson's disease. *Gait Posture*, *36*(3), 639–642. https://doi.org/10.1016/j.gaitpost.2012.04.013

Peterson, D. S., Fling, B. W., Mancini, M., Cohen, R. G., Nutt, J. G., & Horak, F. B. (2015). Dual-task interference and brain structural connectivity in people with Parkinson's disease who freeze. *J Neurol Neurosurg Psychiatry*, *86*(7), 786–792. https://doi.org/10.1136/jnnp-2014-308840

Plummer, P, & Eskes, G. (2015). Measuring treatment effects on dual-task performance: a framework for research and clinical practice. *Front Hum Neurosci*, *9*, 225. https://doi.org/10.3389/fnhum.2015.00225

Plummer, P, Eskes, G., Wallace, S., Giuffrida, C., Fraas, M., Campbell, G., Clifton, K., Skidmore, E. R., & American Congress of Rehabilitation Medicine Stroke Networking Group Cognition Task, F. (2013). Cognitive-motor interference during functional mobility after stroke: state of the science and implications for future research. *Arch Phys Med Rehabil*, *94*(12), 2565-2574 e6. https://doi.org/10.1016/j.apmr.2013.08.002

Plummer, Prudence, Altmann, L., Feld, J., Zukowski, L., Najafi, B., & Giuliani, C. (2020). Attentional prioritization in dual-task walking: Effects of stroke, environment, and instructed focus. *Gait and Posture*, *79*, 3–9. https://doi.org/10.1016/j.gaitpost.2020.03.013

Rapp, M. A., Krampe, R. T., & Baltes, P. B. (2006). Adaptive task prioritization in aging: selective resource allocation to postural control is preserved in Alzheimer disease. *Am J Geriatr Psychiatry*, *14*(1), 52–61. https://doi.org/10.1097/01.JGP.0000192490.43179.e7

Ries, J. D., Echternach, J. L., Nof, L., & Gagnon Blodgett, M. (2009). Test-retest reliability and minimal detectable change scores for the timed "up & go" test, the six-minute walk test, and gait speed in people with Alzheimer disease. *Phys Ther*, *89*(6), 569–579.

https://doi.org/10.2522/ptj.20080258

Ritter, A., Cummings, J., Nance, C., & Miller, J. B. (2018). Neuroscience learning from longitudinal cohort studies of Alzheimer's disease: Lessons for disease-modifying drug programs and an introduction to the Center for Neurodegeneration and Translational Neuroscience. *Alzheimer's & Dementia: Translational Research & Clinical Interventions*, *4*(1), 350–356. https://doi.org/10.1016/J.TRCI.2018.06.006

Rochester, L., Baker, K., Hetherington, V., Jones, D., Willems, A. M., Kwakkel, G., Van Wegen, E., Lim, I., & Nieuwboer, A. (2010). Evidence for motor learning in Parkinson's disease: acquisition, automaticity and retention of cued gait performance after training with external rhythmical cues. *Brain Res*, *1319*, 103–111. https://doi.org/10.1016/j.brainres.2010.01.001

Shumway-Cook, A., Brauer, S., & Woollacott, M. (2000). Predicting the probability for falls in community-dwelling older adults using the Timed Up & Go Test. *Phys Ther*, *80*(9), 896–903. https://doi.org/10.1093/ptj/80.9.896

Simieli, L., Barbieri, F. A., Orcioli-Silva, D., Lirani-Silva, E., Stella, F., & Gobbi, L. T. B. (2015). Obstacle crossing with dual tasking is a danger for individuals with Alzheimer's disease and for healthy older people. *Journal of Alzheimer's Disease*, *43*(2), 435–441. https://doi.org/10.3233/JAD-140807

Siu, K. C., & Woollacott, M. H. (2007). Attentional demands of postural control: the ability to selectively allocate information-processing resources. *Gait Posture*, *25*(1), 121–126. https://doi.org/10.1016/j.gaitpost.2006.02.002

Spildooren, J., Vercruysse, S., Desloovere, K., Vandenberghe, W., Kerckhofs, E., & Nieuwboer, A. (2010). Freezing of gait in Parkinson's disease: The impact of dual-tasking and turning. *Movement Disorders*, *25*(15), 2563–2570. https://doi.org/10.1002/mds.23327

Steffen, T., & Seney, M. (2008). Test-retest reliability and minimal detectable change on balance and ambulation tests, the 36-item short-form health survey, and the unified Parkinson disease rating scale in people with parkinsonism. *Phys Ther*, *88*(6), 733–746. https://doi.org/10.2522/ptj.20070214

Tappen, R. M., Roach, K. E., Buchner, D., Barry, C., & Edelstein, J. (1997). Reliability of physical performance measures in nursing home residents with Alzheimer's disease. *J Gerontol A Biol Sci Med Sci*, *52*(1), M52-5. https://www.ncbi.nlm.nih.gov/pubmed/9008669

Venema, D. M., Hansen, H., High, R., Goetsch, T., & Siu, K.-C. C. (2019). Minimal Detectable Change in Dual-Task Cost for Older Adults With and Without Cognitive Impairment. *J Geriatr Phys Ther*, *42*(4), E32–E38. https://doi.org/10.1519/JPT.0000000000000194

Verghese, J., Kuslansky, G., Holtzer, R., Katz, M., Xue, X., Buschke, H., & Pahor, M. (2007). Walking While Talking: Effect of Task Prioritization in the Elderly. *Archives of Physical Medicine and Rehabilitation*, *88*(1), 50–53. https://doi.org/10.1016/j.apmr.2006.10.007

Vervoort, G., Heremans, E., Bengevoord, A., Strouwen, C., Nackaerts, E., Vandenberghe, W., & Nieuwboer, A. (2016). Dual-task-related neural connectivity changes in patients with Parkinson' disease. *Neuroscience*, *317*, 36–46. https://doi.org/10.1016/j.neuroscience.2015.12.056

Wahn, B., & Sinnett, S. (2019). Shared or Distinct Attentional Resources? Confounds in Dual Task Designs, Countermeasures, and Guidelines. *Multisens Res*, *32*(2), 145–163. https://doi.org/10.1163/22134808-20181328

Wu, T., Hallett, M., & Chan, P. (2015). Motor automaticity in Parkinson's disease. *Neurobiol Dis*, *82*, 226–234. https://doi.org/10.1016/j.nbd.2015.06.014

Yang, L., Lam, F. M. H., Liao, L. R., Huang, M. Z., He, C. Q., & Pang, M. Y. C. (2017). Psychometric properties of dual-task balance and walking assessments for individuals with neurological conditions: A systematic review. *Gait Posture*, *52*, 110–123. https://doi.org/10.1016/j.gaitpost.2016.11.007

Yogev-Seligmann, G, Hausdorff, J. M., & Giladi, N. (2012). Do we always prioritize balance when walking? Towards an integrated model of task prioritization. *Mov Disord*, *27*(6), 765–770. https://doi.org/10.1002/mds.24963

Yogev-Seligmann, Galit, Rotem-Galili, Y., Dickstein, R., Giladi, N., & Hausdorff, J. M. (2012). Effects of explicit prioritization on dual task walking in patients with Parkinson's disease. *Gait and Posture*, *35*(4), 641–646. https://doi.org/10.1016/j.gaitpost.2011.12.016

CHAPTER 3: PROJECT 2

CORTICAL THICKNESS IS RELATED TO COGNITIVE-MOTOR AUTOMATICITY IN INDIVIDUALS WITH ALZHEIMER'S DISEASE: A REGIONS OF INTEREST STUDY.

ABSTRACT

Background: Alzheimer's disease (AD) is characterized by a distinct pattern of cortical thinning and resultant changes in cognition and function. These result in prominent deficits in cognitive-motor automaticity. The relationship between AD-related cortical thinning and decreased automaticity is not well understood. We aimed to investigate the relationship between cortical thickness regions-of-interest and automaticity in AD using both hypothesis driven and exploratory approaches. We performed a regions-of-interest (ROI) analysis of 46 patients with AD. Data regarding MRI images, demographic characteristics, cognitive-motor dual task performance, and cognition were extracted from medical records. Cortical thickness was calculated from MRI images using FreeSurfer software. Data from dual task assessment was used to calculate combined dual task effect, a measure of cognitive-motor automaticity. Two hierarchical multiple linear regression models were conducted on 1) hypothesis generated ROIs and 2) exploratory ROIs. The hypothesis driven and data driven models each consisted of four ROIs, and differed from each other by only one brain region. Overall hypothesis driven and data driven ROIs explained 21.5% (p=.010) and 24.8% (p=.003) variability in automaticity, respectively. The dorsal lateral prefrontal cortex and superior parietal cortex were significant predictors of automaticity (ps≤.011). Cortical thinning in AD was related to cognitive-motor automaticity, particularly in the dorsal lateral prefrontal and superior parietal cortices. This

suggests that these regions may play a primary role in automaticity. Further research is warranted.

INTRODUCTION

Alzheimer's disease (AD) is the leading cause of dementia and it is characterized by memory loss and associated, decreased processing speed, and difficulty in performing previously familiar tasks (Du et al., 2007; Jahn, 2013). AD is the most prevalent neurodegenerative disease, impacting more than 26 million people worldwide, and that number is projected to quadruple by 2050, indicating that 1 in every 85 persons worldwide will be living with the AD (Brookmeyer et al., 2007). These staggering statistics and projections highlight the need to better understand this disease and develop targeted interventions.

Traditionally, AD is thought to result in primarily cognitive deficits; however, these prominent cognitive symptoms are accompanied by motor deficits which are more subtle. Particularly, these motor deficits in AD are seen at the intersection of cognitive and motor function as an impairment of automaticity, the ability to perform a task without requiring attention be directed to its completion, such as during the execution of a dual task (DT) (M. Montero-Odasso et al., 2018; M. M. Montero-Odasso et al., 2017; Schwenk et al., 2010). In AD, automaticity related to cognitive-motor DT performance is impaired and worsens with disease severity (Ansai et al., 2017; König et al., 2017; Jason K. Longhurst et al., n.d.; Muir et al., 2012; Rucco et al., 2017).

There is much we do not know about how the pathologic features of AD impact DT performance and automaticity. AD results in widespread cortical thinning and atrophy (Du et al., 2007); however, the cognitive and executive deficits in AD are associated with atrophy in specific brain areas (Bruen et al., 2008; Laakso et al., 1995). Previous studies identified brain regions correlated with DT performance. These include the dorsal lateral pre frontal cortex, medial orbital frontal cortex, entorhinal cortex, and association areas among both healthy individuals and those with MCI (Doi et al., 2017; Tripathi et al., 2019). There is evidence that among individuals with cognitive impairment that automaticity is most related to brain volumes in the frontal and temporal regions (J.K. Longhurst et al., 2020). However, it remains to be seen if AD-related neurodegeneration and cortical thinning have a distinct neuroanatomical contribution to automaticity deficits, arising from its distinct pattern of cortical atrophy compared to other causes of cognitive impairment (Du et al., 2007; Jack et al., 2012).

Automaticity may be impacted by the pathologic development of AD, particularly regional cortical thinning associated with neurodegeneration. The aim of this study was to investigate the relationship between cortical thickness of hypothesized regions-of-interest (ROIs) and automaticity related to cognitive-motor DT performance. Based on a review of the literature and our previous work, specific, hypothesis driven ROIs were selected and specified (Allali et al., 2019; Blumen et al., 2019; J.K. Longhurst et al., 2020; Pelosin et al., 2016; Poldrack et al., 2005; Sakurai et al., 2019; Tripathi et al., 2019; Zheng et al., 2014). Specifically, we hypothesized that

poorer automaticity during DT will be predicted by thinning of the entorhinal cortex, dorsal lateral prefrontal cortex (dlPFC), superior parietal cortex, and medial orbitofrontal cortex, beyond the influence of age, sex, and cognition. We also aimed to explore which cortical regions contributed most to poorer automaticity by conducting an exploratory analysis of 34 cortical regions.

METHODS

Design

A ROI analysis of data extracted from records for patients diagnosed with AD who underwent dual-task assessment at the Cleveland Clinic Lou Ruvo Center for Brain Health (CCLRCBH) from January of 2017 to December 2020 was conducted. Items that were extracted from the patient medical records included the following: demographic information (e.g., age, sex, race, ethnicity), cognition, dual task performance, and T1 MRI scans. All data were collected under institutional review board approval.

Sample

All patients that underwent DT assessment were identified from the medical records and records were screened for inclusion in the study. Neurologists completed clinical diagnosis of probable dementia or mild cognitive impairment due AD using National Institute on Aging-Alzheimer's Association workgroups diagnostic guidelines (Albert et al., 2011; McKhann et al.,

2011). Patients that did not complete DT assessment or without MRI imaging from within 6 months of DT assessment were excluded (Figure 1).

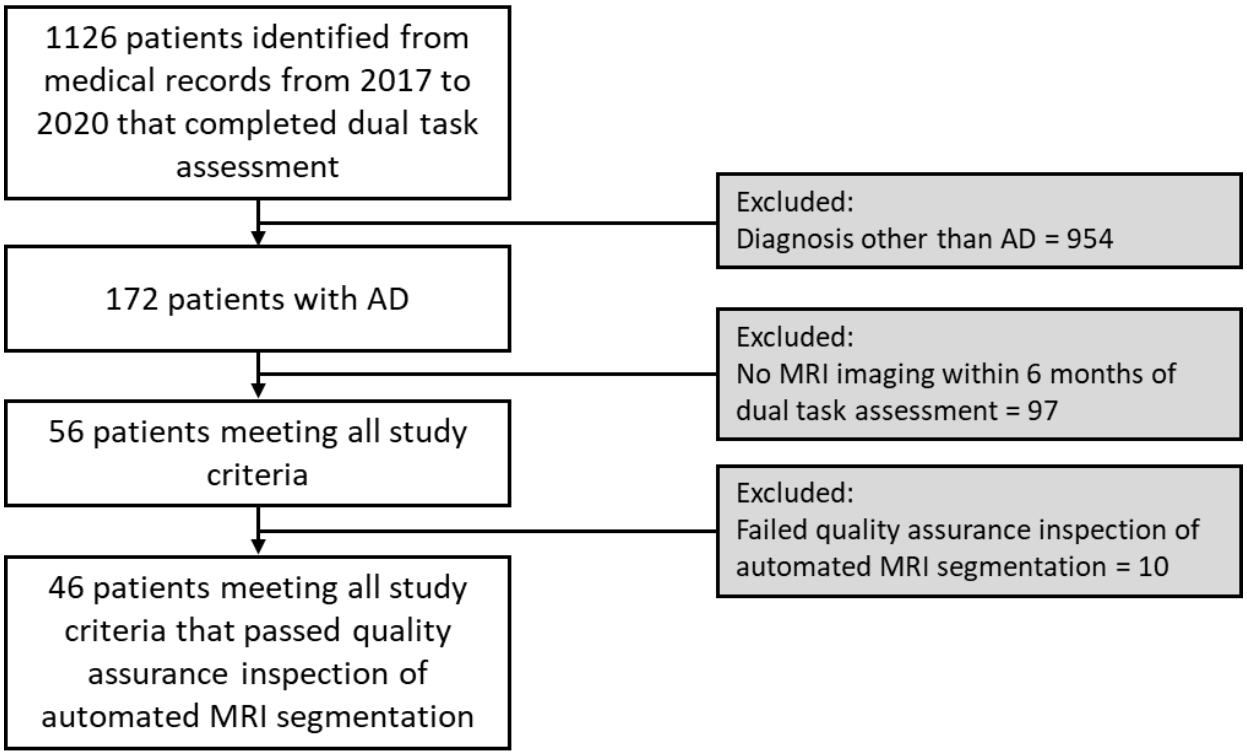


Figure 1. Data extraction flow diagram.

Instrumentation

MRI imaging and data processing. All patients were scanned on a Siemens Skyra 3T scanner (Siemens Medical Solutions USA Inc., Malvern, PA, USA). T1-weighted images were obtained from which cortical reconstruction and volumetric segmentation was performed with the FreeSurfer image analysis suite, version 6.0 (http://surfer.nmr.mgh.harvard.edu/). The technical details of these procedures have been described previously (Dale et al., 1999; Fischl et al., 2004;

Fischl & Dale, 2000). A brief description of the procedures is provided in Supplemental File 1. Following reconstruction and segmentation, scans were visually inspected for accurate segmentation. Cortical thickness measurements were then extracted from FreeSurfer and the values from the left and right hemispheres were averaged to obtain the mean cortical thickness for each ROI.

DT Assessment. DT metrics were based on performance of a motor and cognitive task as described below. Patients completed both the motor and cognitive tasks simultaneously. Instructions encouraging neutral prioritization were utilized; patients were asked to complete both tasks as quickly and accurately as possible.

Motor task. Patients completed the Timed Up and Go Test (TUG) to assess single task (ST) motor performance and DT-TUG in which patients completed the TUG while simultaneously completing a cognitive task to assess DT motor performance. These methods have been described previously (J.K. Longhurst et al., 2020; Jason K. Longhurst et al., n.d.). Motor performance was measured in seconds to complete the TUG.

Cognitive task. Beginning seated, each patient completed serial subtraction by three from an arbitrary number between 80 and 100 for 20 seconds to assess their ST cognitive performance. Next, the same method was used to assess cognitive performance during DT-TUG but, to minimize learning effects, they began at a different number between 80 and 100. The number of correct responses was recorded from which was calculated correct response rate (the

average number of seconds per correct response), a measure which was adapted from previous studies (Kelly et al., 2010; Jason K. Longhurst et al., n.d.; Yang et al., 2016).

Automaticity. Combined dual task effect (cDTE), a measure of automaticity that includes both cognitive and motor aspects of dual task performance, was calculated using the following equation (J.K. Longhurst et al., 2020; Jason K. Longhurst et al., n.d.):

$$cDTE\ (\%) = \frac{-(motorDT \times Cognitive\ DT) - (motorST \times cognitiveST)}{(motorST \times cognitiveST)} \times 100\%$$

A negative score indicates poorer DT performance (poorer automaticity) relative to single task performance, whereas a positive DTE reflects improved performance (better automaticity) under DT conditions relative to single task performance.

Cognition. Scores from the Montreal Cognitive Assessment (MoCA) were used to measure cognition. The MoCA has excellent test-retest reliability (correlation coefficient = 0:92) and excellent positive and negative predictive values for AD (89% and 100%, respectively) (Nasreddine et al., 2005).

Sample Size Estimation

The sample size was estimated using PASS 20.0.3 (NCSS, LLC. Kaysville, Utah, USA, www.ncss.com/software/pass) and effect sizes were based on prior findings.(J.K. Longhurst et al., 2020) The multiple regression model using conditional power calculation method resulted in a requisite sample size of n=42 with 80% power to detect an R^2 of .200 attributed to 4 predictor

variables with a significance level of α=.05. The variables tested are adjusted for 3 covariates which have a combined R^2 of .250 by themselves. It was anticipated that 20% of MRI scans would not pass quality assurance review, resulting in a sample estimate of n=51.

Data Analysis

All analyses were conducted using SPSS 24.0 (IBM SPSS Statistics for Windows, Armonk, New York, USA: IBM Corp) with α = 0.05. A hypothesis driven hierarchical multiple linear regression analysis was conducted to account for the influence of covariates (age, sex, MoCA). cDTE or automaticity was regressed on the covariates in block 1, followed by the hypothesized ROIs (entorhinal cortex, dlPFC, superior parietal cortex, and medial orbitofrontal cortex) in block 2. Exploratory automatic linear modeling with a forward stepwise selection method was then conducted, regressing cDTE on 34 cortical thickness variables, to identify the four cortical thickness variables that generate the largest adjusted R^2. A data-driven hierarchal regression model was then conducted regressing cDTE on covariates in block 1 and the four cortical regions identified in the exploratory analysis (fusiform gyrus, dlPFC, superior parietal cortex, and medial orbitofrontal cortex) in block 2.

RESULTS

Data from 46 patients with AD were analyzed (mean age = 77.5 ± 6.7 years; females =24; white = 35). The mean days between DT assessment and MRI imaging was 84.1 ± 32.4 days. (Table 1)

Table 1. Means, proportions and standard deviations for demographics, dual task performance, and cognition.

	n	*Mean or Proportion*
DEMOGRAPHICS		
Age (years)	46	77.5 ± 6.7
Sex		
Male	22	47.8%
Female	24	52.2%
Race		
White	35	76.1%
Black	5	10.9%
Asian	5	10.9%
Multiracial	1	2.2%
Ethnicity		
Non-Hispanic	44	95.7%
Hispanic	2	4.3%
DUAL TASK PEFORMANCE		
Motor Dual Task Effect	46	-49.0 ± 44.2
Cognitive Dual Task Effect	46	-111.6 ± 142.4
Modified Attention Allocation Index	46	62.6 ± 147.3
Combined Dual Task Effect	46	-217.8 ± 251.5
COGNITION		
Montreal Cognitive Assessment (scale points)	46	17.4 ± 5.7

Hypothesis driven model. Statistically significant regression equations were found in block 1 ($F_{(3,42)}$=4.923, p=.005) and block 2 ($F_{(7,38)}$=5.601, p<.001). Block 1 explained 26.0% of variance in cDTE, while the whole model explained 47.5%. Additionally, block 2 had an R^2 change of .215 (p=.010) (Table 2).

Data driven model. Automatic linear modeling identified the fusiform gyrus (ΔR^2=.128), dlPFC (ΔR^2=.033), the superior parietal cortex (ΔR^2=.039), and the medial orbitofrontal cortex (ΔR^2=.032) as the four most impactful predictors on cDTE. The data driven hierarchal regression

(with identified predictors entered in block 2) found statistically significant regression equations in block 1 ($F_{(3,42)}$=4.923, *p*=.005) and block 2 ($F_{(7,38)}$=4.916, *p*=.001). Again, 26.0% of variance in cDTE was explained by block 1, while the whole model explained 50.8%. The R^2 change with the addition of block 2 was .248 (*p*=.003) (Table 2).

Table 2. Statistics from multiple linear hierarchical regression analyses for covariates (age, sex, and MoCA) and cortical thickness of regions-of-interest predicting automaticity (cDTE). Models include hypothesis driven ROIs in model 1, and data driven ROIs in model 2.

Variable	*b*	SE	β	p value	R^2	ΔR^2
Hypothesis Driven Model						
Block 1				.005*	.260*	.260*
Age	-7.92	5.27	-.210	.140		
Sex	-76.26	76.25	-.153	.324		
MoCA	17.72	6.48	.402	.009*		
Block 2				.001*	.475*	.210*
Age	-5.63	5.27	-.150	.292		
Sex	-73.88	68.68	-.148	.289		
MoCA	17.58	6.37	.399	.009*		
Entorhinal cortex	80.21	84.88	.143	.351		
Dorsal lateral prefrontal cortex	-550.01	205.05	-.441	.011*		
Superior parietal cortex	747.73	206.18	.527	.001*		
Medial orbitofrontal cortex	208.96	159.06	.169	.197		
Data Driven Model						
Block 1				.005*	.260*	.260*
Age	-7.92	5.27	-.210	.140		
Sex	-76.26	76.25	-.153	.324		
MoCA	17.72	6.48	.402	.009*		
Block 2				<.001*	.508*	.248*
Age	-8.00	4.68	-.212	.095		
Sex	-56.54	66.98	-.114	.404		
MoCA	14.94	6.38	.339	.025*		
Fusiform gyrus	421.58	226.44	.358	.070		
Dorsal lateral prefrontal cortex	-717.61	224.73	-.575	.003*		
Superior parietal cortex	655.14	206.29	.462	.003*		
Medial orbitofrontal cortex	198.60	151.67	.161	.198		

*indicates statistically significant result

DISCUSSION

Cortical thickness of theoretically hypothesized ROIs explained 21.0% of the variance in automaticity after controlling for age, sex, and MoCA. The ROIs in the data driven model explained 24.8% of variance in automaticity after controlling for age, sex, and MoCA. There was substantial overlap of the predictors between the two models, with both models including dlPFC, superior parietal cortex, and medial orbitofrontal cortex. The lone difference between the hypothesis driven model and the data driven model was the inclusion of the fusiform gyrus in the data driven model in place of the entorhinal cortex in the hypothesis driven model. Superior parietal cortex and dlPFC were the only significant predictor ROIs in both models suggesting their importance in automaticity. Below, we discuss the roles of each of these brain regions in automaticity.

Superior parietal cortex. The superior parietal cortex plays a critical in visuospatial attention as well as shifts of attention (Shomstein, 2012; Y. Wu et al., 2016). Allocation of attention plays a key role DT performance and automaticity is likely influenced by learned patterns of attention allocation (Plummer & Eskes, 2015). In this study, we found that cortical thinning of the superior parietal cortex was associated with poorer automaticity. The DT paradigm we utilized in this study requires use of visuospatial attention to interpret the relevant cues in the environment for proper completion of the TUG. Additionally, a decrease in ability to selectively shift attention would likely result in an increase reliance on executive control during DT in order to accurately task completion so as to avoid frequent shifts in attention that would rely on this cortical area. The superior parietal cortex thins very early in AD and can even be detected in

preclinical AD (Dickerson et al., 2009), temporally correlating well with the onset of automaticity deficits (De Cock et al., 2019).

Dorsal lateral prefrontal cortex. As a key center of executive control and working memory, the dlPFC contributes to task planning as well as execution of both cognitive and motor tasks (Clark, 2015). Our data shows that lower levels of automaticity were associated with relative preservation of cortical thickness in dlPFC. One possible explanation of our results is that cortical thinning of the PFC encourages a relative reliance on subcortical automaticity circuitry that is less impacted by AD. This is supported by the literature showing that the dlPFC is more active in executive task control and is also less active during automatic task execution (Tripathi et al., 2019).

Other cortical regions. Our results showed that the entorhinal cortex, the fusiform gyrus, and the medial orbitofrontal cortices contributed to their respective models, but were not found to statistically significant predictors of automaticity. The entorhinal cotex is a hub for learning and memory and also plays a key role in spatial navigation (Schultz et al., 2015). Sakurai et al found that entorhinal cortex volumes were associated with DT performance in individuals with MCI (Sakurai et al., 2019). In AD, the entorhinal region is one of the earliest sites to be impacted by neurodegeneration, with significant early disease neurofibrillary pathology and atrophy (Braak et al., 2011; Rucco et al., 2017). As the sample in our study had progressed beyond MCI (MoCA=17.4), it is possible that the majority of atrophy in the entorhinal cortex occurred earlier

in the disease process. While the fusiform gyrus' dominant function is one of visual processing and association, it has a more applicable function to automaticity, that of multisensory integration (Renier et al., 2009; Zhang et al., 2016). During DT performance, multisensory integration and processing leads to better task completion, and less need for executive control during the DT. Lastly, the medial orbitofrontal cortex is involved in goal directed problem solving by responding to reward (Elliott, 2000). This region is also associated with automatic performance of gait and balance tasks (Gilat et al., 2017; Wilson et al., 2017).

Taken together, the results of this study reveal that cortical thinning of regions that moderate attention are associate with poorer automaticity in AD, with our findings showing a relationship between automaticity and the superior parietal cortex and the dlPFC. This is consistent with the central bottleneck theory, in which task are processed serially, often in an alternating fashion, giving the appearance of simultaneous completion and automaticity, while relying heavily on attentional resources (Pashler, 1984). In AD, attentional capacity is compromised leading to impaired DT performance and observed automaticity (Simieli et al., 2015).

A key limitation of this study is that we did not consider subcortical brain regions and structures that are involved in automaticity in our analyses. There is strong evidence that the cerebellum, brain stem, mesencephalic locomotor region, subthalamic locomotor region, and sensorimotor striatum all have key roles in gait automaticity (Clark, 2015; T. Wu et al., 2015), and their inclusion in the models would likely have improved model fit. Lastly, this study design is not

strong for inferring causality and temporality; thus, we cannot confirm that the cortical thinning caused worse DT performance.

CONCLUSION

The results of this study provide insights regarding the role of AD-related cortical thinning in automaticity. Specifically, these results provide evidence that the superior parietal cortex and the dlPFC figure prominently in cognitive-motor automaticity in AD. Future studies should target these cortical regions with functional imaging during cognitive-motor DT in individuals with AD, as cortical thinning is these regions not only contributes to abnormal DT performance, but also is characteristic of early AD. Additionally, the entorhinal cortex, the fusiform gyrus, and medial orbital frontal cortex may be involved in DT-related automaticity.

REFERENCES

Albert, M. S., DeKosky, S. T., Dickson, D., Dubois, B., Feldman, H. H., Fox, N. C., Gamst, A., Holtzman, D. M., Jagust, W. J., Petersen, R. C., Snyder, P. J., Carrillo, M. C., Thies, B., & Phelps, C. H. (2011). The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia*, *7*(3), 270–279. https://doi.org/10.1016/j.jalz.2011.03.008

Allali, G., Montembeault, M., Brambati, S. M., Bherer, L., Blumen, H. M., Launay, C. P., Liu-Ambrose, T., Helbostad, J. L., Verghese, J., & Beauchet, O. (2019). Brain Structure Covariance Associated With Gait Control in Aging. *J Gerontol A Biol Sci Med Sci*, *74*(5), 705–713. https://doi.org/10.1093/gerona/gly123

Ansai, J. H., Andrade, L. P., Rossi, P. G., Takahashi, A. C. M. M., Vale, F. A. C. C., & Rebelatto, J. R. (2017). Gait, dual task and history of falls in elderly with preserved cognition, mild cognitive impairment, and mild Alzheimer's disease. *Braz J Phys Ther*, *21*(2), 144–151. https://doi.org/10.1016/j.bjpt.2017.03.010

Blumen, H. M., Brown, L. L., Habeck, C., Allali, G., Ayers, E., Beauchet, O., Callisaya, M., Lipton, R. B., Mathuranath, P. S., Phan, T. G., Pradeep Kumar, V. G., Srikanth, V., & Verghese, J. (2019). Gray matter volume covariance patterns associated with gait speed in older adults: a multi-cohort MRI study. *Brain Imaging Behav*, *13*(2), 446–460. https://doi.org/10.1007/s11682-018-9871-7

Braak, H., Thal, D. R., Ghebremedhin, E., & Del Tredici, K. (2011). Stages of the pathologic

process in alzheimer disease: Age categories from 1 to 100 years. *Journal of Neuropathology and Experimental Neurology*, *70*(11), 960–969. https://doi.org/10.1097/NEN.0b013e318232a379

Brookmeyer, R., Johnson, E., Ziegler-Graham, K., & Arrighi, H. M. (2007). Forecasting the global burden of Alzheimer's disease. *Alzheimers Dement*, *3*(3), 186–191. https://doi.org/10.1016/j.jalz.2007.04.381

Bruen, P. D., McGeown, W. J., Shanks, M. F., & Venneri, A. (2008). Neuroanatomical correlates of neuropsychiatric symptoms in Alzheimer's disease. *Brain*, *131*(Pt 9), 2455–2463. https://doi.org/10.1093/brain/awn151

Clark, D. J. (2015). Automaticity of walking: Functional significance, mechanisms, measurement and rehabilitation strategies. In *Frontiers in Human Neuroscience* (Vol. 9, Issue MAY). Frontiers Media S. A. https://doi.org/10.3389/fnhum.2015.00246

Dale, A. M., Fischl, B., & Sereno, M. I. (1999). Cortical surface-based analysis. I. Segmentation and surface reconstruction. *Neuroimage*, *9*(2), 179–194. https://doi.org/10.1006/nimg.1998.0395

De Cock, A.-M. M., Fransen, E., Perkisas, S., Verhoeven, V., Beauchet, O., Vandewoude, M., & Remmen, R. (2019). Comprehensive Quantitative Spatiotemporal Gait Analysis Identifies Gait Characteristics for Early Dementia Subtyping in Community Dwelling Older Adults. *Frontiers in Neurology*, *10*(APR), 313. https://doi.org/10.3389/fneur.2019.00313

Dickerson, B. C., Bakkour, A., Salat, D. H., Feczko, E., Pacheco, J., Greve, D. N., Grodstein, F.,

Wright, C. I., Blacker, D., Rosas, H. D., Sperling, R. A., Atri, A., Growdon, J. H., Hyman, B. T., Morris, J. C., Fischl, B., & Buckner, R. L. (2009). The Cortical Signature of Alzheimer's Disease: Regionally Specific Cortical Thinning Relates to Symptom Severity in Very Mild to Mild AD Dementia and is Detectable in Asymptomatic Amyloid-Positive Individuals. *Cerebral Cortex*, *19*(3), 497–510. https://doi.org/10.1093/cercor/bhn113

Doi, T., Blumen, H. M., Verghese, J., Shimada, H., Makizako, H., Tsutsumimoto, K., Hotta, R., Nakakubo, S., & Suzuki, T. (2017). Gray matter volume and dual-task gait performance in mild cognitive impairment. *Brain Imaging and Behavior*, *11*(3), 887–898. https://doi.org/10.1007/s11682-016-9562-1

Du, A. T., Schuff, N., Kramer, J. H., Rosen, H. J., Gorno-Tempini, M. L., Rankin, K., Miller, B. L., & Weiner, M. W. (2007). Different regional patterns of cortical thinning in Alzheimer's disease and frontotemporal dementia. *Brain*, *130*(4), 1159–1166. https://doi.org/10.1093/brain/awm016

Elliott, R. (2000). Dissociable Functions in the Medial and Lateral Orbitofrontal Cortex: Evidence from Human Neuroimaging Studies. *Cerebral Cortex*, *10*(3), 308–317. https://doi.org/10.1093/cercor/10.3.308

Fischl, B., & Dale, A. M. (2000). Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proc Natl Acad Sci U S A*, *97*(20), 11050–11055. https://doi.org/10.1073/pnas.200033797

Fischl, B., van der Kouwe, A., Destrieux, C., Halgren, E., Segonne, F., Salat, D. H., Busa, E., Seidman, L. J., Goldstein, J., Kennedy, D., Caviness, V., Makris, N., Rosen, B., & Dale, A. M.

(2004). Automatically parcellating the human cerebral cortex. *Cereb Cortex*, *14*(1), 11–22. https://doi.org/10.1093/cercor/bhg087

Gilat, M., Bell, P. T., Ehgoetz Martens, K. A., Georgiades, M. J., Hall, J. M., Walton, C. C., Lewis, S. J. G., & Shine, J. M. (2017). Dopamine depletion impairs gait automaticity by altering cortico-striatal and cerebellar processing in Parkinson's disease. *NeuroImage*, *152*, 207–220. https://doi.org/10.1016/j.neuroimage.2017.02.073

Jack, C. R., Knopman, D. S., Weigand, S. D., Wiste, H. J., Vemuri, P., Lowe, V., Kantarci, K., Gunter, J. L., Senjem, M. L., Ivnik, R. J., Roberts, R. O., Rocca, W. A., Boeve, B. F., & Petersen, R. C. (2012). An operational approach to National Institute on Aging-Alzheimer's Association criteria for preclinical Alzheimer disease. *Annals of Neurology*, *71*(6), 765–775. https://doi.org/10.1002/ana.22628

Jahn, H. (2013). Memory loss in alzheimer's disease. *Dialogues in Clinical Neuroscience*, *15*(4), 445–454. https://doi.org/10.31887/dcns.2013.15.4/hjahn

Kelly, V. E., Janke, A. A., & Shumway-Cook, A. (2010). Effects of instructed focus and task difficulty on concurrent walking and cognitive task performance in healthy young adults. *Exp Brain Res*, *207*(1–2), 65–73. https://doi.org/10.1007/s00221-010-2429-6

König, A., Klaming, L., Pijl, M., Demeurraux, A., David, R., & Robert, P. (2017). Objective measurement of gait parameters in healthy and cognitively impaired elderly using the dual-task paradigm. *Aging Clinical and Experimental Research*, *29*(6), 1181–1189. https://doi.org/10.1007/s40520-016-0703-6

Laakso, M. P., Soininen, H., Partanen, K., Helkala, E. L., Hartikainen, P., Vainio, P., Hallikainen, M., Hanninen, T., & Riekkinen Sr., P. J. (1995). Volumes of hippocampus, amygdala and frontal lobes in the MRI-based diagnosis of early Alzheimer's disease: correlation with memory functions. *J Neural Transm Park Dis Dement Sect*, *9*(1), 73–86. https://www.ncbi.nlm.nih.gov/pubmed/7605591

Longhurst, J.K., Wise, M. A., Krist, D. J., Moreland, C. A., Basterrechea, J. A., & Landers, M. R. (2020). Brain volumes and dual-task performance correlates among individuals with cognitive impairment: a retrospective analysis. *Journal of Neural Transmission*, *127*(7). https://doi.org/10.1007/s00702-020-02199-7

Longhurst, Jason K., Rider, J. V, Cummings, J., John, S., Poston, B., & Landers, M. R. (n.d.). A novel way of measuring dual task interference: the reliability and construct validity of the dual task effect battery in healthy adults and individuals with neurodegenerative disease. *Under Review*.

McKhann, G. M., Knopman, D. S., Chertkow, H., Hyman, B. T., Jack, C. R., Kawas, C. H., Klunk, W. E., Koroshetz, W. J., Manly, J. J., Mayeux, R., Mohs, R. C., Morris, J. C., Rossor, M. N., Scheltens, P., Carrillo, M. C., Thies, B., Weintraub, S., & Phelps, C. H. (2011). The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's and Dementia*, *7*(3), 263–269. https://doi.org/10.1016/j.jalz.2011.03.005

Montero-Odasso, M. M., Sarquis-Adamson, Y., Speechley, M., Borrie, M. J., Hachinski, V. C.,

Wells, J., Riccio, P. M., Schapira, M., Sejdic, E., Camicioli, R. M., Bartha, R., McIlroy, W. E., & Muir-Hunter, S. (2017). Association of Dual-Task Gait With Incident Dementia in Mild Cognitive Impairment: Results From the Gait and Brain Study. *JAMA Neurol*, *74*(7), 857–865. https://doi.org/10.1001/jamaneurol.2017.0643

Montero-Odasso, M., Speechley, M., Muir-Hunter, S. W., Sarquis-Adamson, Y., Sposato, L. A., Hachinski, V., Borrie, M., Wells, J., Black, A., Sejdic, E., Bherer, L., Chertkow, H., Canadian, G., & Cognition, N. (2018). Motor and Cognitive Trajectories Before Dementia: Results from Gait and Brain Study. *J Am Geriatr Soc*, *66*(9), 1676–1683. https://doi.org/10.1111/jgs.15341

Muir, S. W., Speechley, M., Wells, J., Borrie, M., Gopaul, K., & Montero-Odasso, M. (2012). Gait assessment in mild cognitive impairment and Alzheimer's disease: the effect of dual-task challenges across the cognitive spectrum. *Gait Posture*, *35*(1), 96–100. https://doi.org/10.1016/j.gaitpost.2011.08.014

Nasreddine, Z. S., Phillips, N. A., Bedirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J. L., & Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*, *53*(4), 695–699. https://doi.org/10.1111/j.1532-5415.2005.53221.x

Pashler, H. (1984). Processing stages in overlapping tasks: Evidence for a central bottleneck. *Journal of Experimental Psychology: Human Perception and Performance*. https://doi.org/10.1037/0096-1523.10.3.358

Pelosin, E., Ogliastro, C., Lagravinese, G., Bonassi, G., Mirelman, A., Hausdorff, J. M.,

Abbruzzese, G., & Avanzino, L. (2016). Attentional control of gait and falls: Is cholinergic dysfunction a common substrate in the elderly and Parkinson's disease? *Frontiers in Aging Neuroscience*, *8*(MAY). https://doi.org/10.3389/fnagi.2016.00104

Plummer, P., & Eskes, G. (2015). Measuring treatment effects on dual-task performance: a framework for research and clinical practice. *Front Hum Neurosci*, *9*, 225. https://doi.org/10.3389/fnhum.2015.00225

Poldrack, R. A., Sabb, F. W., Foerde, K., Tom, S. M., Asarnow, R. F., Bookheimer, S. Y., & Knowlton, B. J. (2005). The neural correlates of motor skill automaticity. *J Neurosci*, *25*(22), 5356–5364. https://doi.org/10.1523/JNEUROSCI.3880-04.2005

Renier, L. A., Anurova, I., De Volder, A. G., Carlson, S., VanMeter, J., & Rauschecker, J. P. (2009). Multisensory integration of sounds and vibrotactile stimuli in processing streams for "what" and "where." *Journal of Neuroscience*, *29*(35), 10950–10960. https://doi.org/10.1523/JNEUROSCI.0910-09.2009

Rucco, R., Agosti, V., Jacini, F., Sorrentino, P., Varriale, P., De Stefano, M., Milan, G., Montella, P., & Sorrentino, G. (2017). Spatio-temporal and kinematic gait analysis in patients with Frontotemporal dementia and Alzheimer's disease through 3D motion capture. *Gait and Posture*, *52*, 312–317. https://doi.org/10.1016/j.gaitpost.2016.12.021

Sakurai, R., Bartha, R., & Montero-Odasso, M. (2019). Entorhinal Cortex Volume Is Associated With Dual-Task Gait Cost Among Older Adults With MCI: Results From the Gait and Brain Study. *J Gerontol A Biol Sci Med Sci*, *74*(5), 698–704. https://doi.org/10.1093/gerona/gly084

Schultz, H., Sommer, T., & Peters, J. (2015). The role of the human entorhinal cortex in a representational account of memory. In *Frontiers in Human Neuroscience* (Vol. 9, Issue NOVEMBER). Frontiers Media S. A. https://doi.org/10.3389/fnhum.2015.00628

Schwenk, M., Zieschang, T., Oster, P., & Hauer, K. (2010). Dual-task performances can be improved in patients with dementia: a randomized controlled trial. *Neurology*, *74*(24), 1961–1968. https://doi.org/10.1212/WNL.0b013e3181e39696

Shomstein, S. (2012). Cognitive functions of the posterior parietal cortex: top-down and bottom-up attentional control. *Frontiers in Integrative Neuroscience*, *6*(JULY 2012), 38. https://doi.org/10.3389/fnint.2012.00038

Simieli, L., Barbieri, F. A., Orcioli-Silva, D., Lirani-Silva, E., Stella, F., & Gobbi, L. T. B. (2015). Obstacle crossing with dual tasking is a danger for individuals with Alzheimer's disease and for healthy older people. *Journal of Alzheimer's Disease*, *43*(2), 435–441. https://doi.org/10.3233/JAD-140807

Tripathi, S., Verghese, J., & Blumen, H. M. (2019). Gray matter volume covariance networks associated with dual-task cost during walking-while-talking. *Human Brain Mapping*, *40*(7), 2229–2240. https://doi.org/10.1002/hbm.24520

Wilson, P. H., Smits-Engelsman, B., Caeyenberghs, K., Steenbergen, B., Sugden, D., Clark, J., Mumford, N., & Blank, R. (2017). Cognitive and neuroimaging findings in developmental coordination disorder: new insights from a systematic review of recent research. In *Developmental Medicine and Child Neurology* (Vol. 59, Issue 11, pp. 1117–1129). Blackwell Publishing Ltd. https://doi.org/10.1111/dmcn.13530

Wu, T., Hallett, M., & Chan, P. (2015). Motor automaticity in Parkinson's disease. *Neurobiol Dis*, *82*, 226–234. https://doi.org/10.1016/j.nbd.2015.06.014

Wu, Y., Wang, J., Zhang, Y., Zheng, D., Zhang, J., Rong, M., Wu, H., Wang, Y., Zhou, K., & Jiang, T. (2016). The Neuroanatomical Basis for Posterior Superior Parietal Lobule Control Lateralization of Visuospatial Attention. *Frontiers in Neuroanatomy*, *10*(MAR), 32. https://doi.org/10.3389/fnana.2016.00032

Yang, L., He, C., & Pang, M. Y. (2016). Reliability and Validity of Dual-Task Mobility Assessments in People with Chronic Stroke. *PLoS One*, *11*(1), e0147833. https://doi.org/10.1371/journal.pone.0147833

Zhang, W., Wang, J., Fan, L., Zhang, Y., Fox, P. T., Eickhoff, S. B., Yu, C., & Jiang, T. (2016). Functional organization of the fusiform gyrus revealed with connectivity profiles. *Human Brain Mapping*, *37*(8), 3003–3016. https://doi.org/10.1002/hbm.23222

Zheng, D., Sun, H., Dong, X., Liu, B., Xu, Y., Chen, S., Song, L., Zhang, H., & Wang, X. (2014). Executive dysfunction and gray matter atrophy in amnestic mild cognitive impairment. *Neurobiol Aging*, *35*(3), 548–555. https://doi.org/10.1016/j.neurobiolaging.2013.09.007

CHAPTER 4: PROJECT 3

DUAL TASK PERFORMANCE IS ASSOCIATED WITH AMYLOIDOSIS IN COGNITIVELY HEALTHY ADULTS.

ABSTRACT

Preclinical Alzheimer's disease (AD) provides an opportunity for the study and implementation of interventions and strategies aimed at delaying, mitigating, and preventing AD. While this preclinical state is an ideal target, it is difficult to efficiently and cost-effectively identify. Recent findings have suggested that cognitive-motor dual task (DT) paradigms may provide additional inference. This study aimed to investigate the relationship between DT performance and amyloidosis, suggestive of preclinical AD, and whether DT performance provides additional information beyond a commonly used cognitive composite, the Preclinical Alzheimer's Cognitive Composite (PACC) to help in the identification of amyloidosis. Data from 52 cognitively healthy adults were obtained for this cross-sectional study. The data included demographics, amyloid standardized uptake value ratio (SUVR) obtained via florbetapir-PET, neuropsychological testing, apolipoprotien E (APOE) genotype, and DT performance measures. Data were analyzed via hierarchal multiple linear regression or logistic regression, controlling for age, education, and APOE genotype. ROC curves were plotted, and sensitivity and specificity calculated via 2x2 contingency tables. There was a moderate relationship (rs>.30) between motor and cognitive DT effects (DTE) and amyloid SUVR (ps<.042). A strong relationship (r=.58) was found between combined DTE (cDTE), a measure of automaticity derived from DT performance, and amyloid SUVR (p<.001). Additionally, cDTE showed promise in its unique

contributions to amyloid SUVR, accounting for 7.8% of amyloid SUVR variance beyond PACC scores (*p*=.018). Additionally, when incorporated into PACC, cDTE resulted in improved diagnostic accuracy for determining elevated amyloid SUVR, and increased the sensitivity and specificity of the PACC. DT performance using the cDTE, a measure of automaticity, was a moderate predictor of cerebral amyloidosis, which suggests that it has utility in the screening and diagnosis of individuals for preclinical AD. Additionally, when combined with the PACC, the cDTE improves diagnostic accuracy. Further research is warranted.

INTRODUCTION

Early identification of preclinical Alzheimer's disease (AD) is key in implementing disease modifying strategies against AD. It is estimated that by 2050, one in every 85 people will be living with AD and that a modest one year delay in onset would result in 9.2 million fewer cases over the next 30 years (Brookmeyer et al., 2007). Additionally, this preclinical phase of AD can begin decades before the onset of clinical symptoms (Jack et al., 2013; Sutphen et al., 2015) and nearly eightfold as many people have preclinical AD as have symptomatic AD (Brookmeyer et al., 2018). This makes the preclinical state of AD a promising target for clinical trials and preventive interventions. Earlier identification may allow for changes to modifiable risk factors and delay onset or mitigate progressive decline in cognition and function (Aisen et al., 2013; J. Cummings et al., 2018; J. L. Cummings et al., 2014).

Current diagnostic methods for preclinical AD, defined by the National Institute on Aging and the Alzheimer's Association (NIA-AA) workgroup, require imaging biomarkers, such as abnormal amyloid or fluorodeoxyglucose (FDG) positron emission tomography (PET), hippocampal volumes on magnetic resonance imaging (MRI), and cerebrospinal fluid (CSF) biomarkers (Jack et al., 2012; Rice & Bisdas, 2017; Sperling et al., 2011). These methods for identifying preclinical AD, while very useful, are expensive, time consuming, invasive, and are not often clinically available during the preclinical state (Hanna B. Åhman, Berglund, et al., 2020). Behavioral markers are needed to improve the identification of individuals who are likely to have preclinical AD and to respond to this need, several cognitive batteries have been developed (Bransby et al., 2019; Donohue et al., 2014; Gross et al., 2017). These cognitive batteries, while useful, have modest utility for predicting amyloidosis (Bransby et al., 2019), which is the earliest marker to emerge during the preclinical period (Jack et al., 2012, 2013).

Cognitive-motor dual task (DT) performance has been suggested as a sensitive indicator of risk for cognitive decline (Hanna B. Åhman, Berglund, et al., 2020; Montero-Odasso et al., 2017). Preclinical AD-related changes in brain processes may reduce cognitive resources or limit recruitment efficiency and resource coordination with impaired capacity for performance in novel and challenging conditions, such as DT performance (Whitson et al., 2018). In support of this, Nadkarni and colleagues found a moderate relationship between cerebral amyloid deposition and DT performance (Nadkarni et al., 2017). Conversely, Åhman and colleagues found no relationship between CSF amyloid beta protein (Aβ)-42 and DT performance (Hanna Bozkurt Åhman et al., 2019). To our knowledge, those two studies are the only ones to

investigate the relationship between DT performance and amyloidosis, showing conflicting results, and both are limited by small samples. Additionally, the studies utilized only measures of single task (ST) performance during DT (i.e., they evaluated change in either motor or cognitive performance during DT). Neither study included measures of DT automaticity, defined as the ability to perform a task without directing attention to it (Wu et al., 2015). Previous work has shown that measures probing automaticity are strongly associated with levels of cognition, motor performance, brain volumes, and disease severity (J.K. Longhurst et al., 2020; Jason K. Longhurst et al., n.d.).

The purpose of this study was to investigate the role of cognitive-motor automaticity in predicting levels of cerebral amyloid deposition in cognitively normal older adults. Overall, we hypothesized that cerebral amyloid deposition reduces automaticity and we predicted that individuals with preclinical AD will perform worse than their healthy counterparts. As such, the first aim of this study was to examine the relationship between DT automaticity and cerebral amyloid levels and whether this relationship extends beyond the influence of a commonly used cognitive composite used for predicting preclinical AD (Preclinical Alzheimer's Cognitive Composite (PACC)). We hypothesized that automaticity would predict a significant amount of variation in cerebral amyloid levels, after controlling for age, years of education, and presence of the apolipoprotien E (APOE) ε-4 genotype. Additionally, automaticity would explain a unique amount of variance over and above the PACC. Lastly, we aimed to determine the diagnostic accuracy of DT automaticity in identifying amyloidosis and whether the addition of DT automaticity improved the diagnostic accuracy of the PACC.

METHODS

Design

A cross-sectional analysis of data was performed on data from the Center for Neurodegeneration and Translational Neuroscience (Ritter et al., 2018), a longitudinal cohort study of older adults. Detailed methods have been described elsewhere (Ritter et al., 2018). Consent and data were collected under Cleveland Clinic Institutional Review Board approval.

Participants

Baseline measurements of the cognitively healthy control cohort included demographic characteristics, neuropsychological measures, functional measures, and imaging and genetic biomarkers. The inclusion criteria for this cohort included: age 55 to 90, possess adequate visual and auditory acuity for neuropsychological testing, and speak fluent English. Exclusion criteria included: significant neurologic disorders, unstable medical conditions, and evidence of cognitive impairment (operationally defined as greater than 1 standard deviation from age-matched normative values for more than one neuropsychological test). Additionally, participants were excluded from this study if they did not complete amyloid PET or DT assessments at baseline. Demographic data were collected at baseline and included age, sex, race, ethnicity, years of education, and the Montreal Cognitive Assessment (MoCA).

Instrumentation

Dual Task Assessment. DT metrics were calculated from performance on a motor and cognitive task as described below. Participants were instructed to perform both the motor and cognitive tasks simultaneously as quickly and accurately as possible. These instructions were intended to encourage neutral prioritization between motor and cognitive tasks.

Motor task. Participants completed the Timed Up and Go Test (TUG) (motor single task (ST)) and DT-TUG, in which participants completed the TUG while simultaneously completing a serial subtraction task. These methods have been described previously (J.K. Longhurst et al., 2020). Motor performance was measured in seconds to complete the TUG.

Cognitive task. Participants completed serial subtraction by three from an arbitrary number between 80 and 100 in a seated position for 20 seconds to assess their ST cognitive performance. Following this, cognitive performance during DT-TUG was completed using the same method but beginning at a different number between 80 and 100 to minimize learning effects. The number of correct responses was recorded from which was calculated correct response rate (the average number of seconds per correct response), a measure adapted from previous studies (Kelly et al., 2010; Yang et al., 2016).

Dual task effects. Calculation of motor (mDTE) and cognitive (cDTE) dual task effects were completed using the following equation (McIsaac et al., 2015; Yang et al., 2017):

$$DTE(\%) = \frac{-DT - ST}{ST} \times 100\%$$

Calculation of combined dual task effect (cDTE), a measure of automaticity that includes both cognitive and motor aspects of dual task performance, was completed using the following equation (J.K. Longhurst et al., 2020; Jason K. Longhurst et al., n.d.):

$$cDTE\ (\%) = \frac{-(motorDT \times Cognitive\ DT) - (motorST \times cognitiveST)}{(motorST \times cognitiveST)} \times 100\%$$

A negative DTE score indicates poorer DT performance relative to single task performance, whereas a positive DTE reflects improved performance under DT conditions relative to single task performance.

Amyloid PET data acquisition and processing. All participants underwent florbetapir-PET scans, which were acquired on a Siemens Biograph mCT PET/CT scanner 50 minutes after injection of 370 MBq of florbetapir. The procedure for processing of PET imaging has been previously described (Decourt et al., 2020). Standard up-take value ratios (SUVRs) were calculated and summarized SUVRs were utilized in the analyses. The summarized SUVR comprised frontal cortex, temporal cortex, parietal cortex, anterior cingulate gyrus, posterior cingulate gyrus, and the precuneus region, using the cerebellum as the reference region. Participant amyloid status (amyloid +/-) was determined using a cut-off of 1.1 for summarized SUVR (Camus et al., 2012).

APOE Genotype. Plasma samples were collected at the baseline visit. Following DNA isolation, APOE genotyping was conducted (procedures detailed in Supplemental File 1). For statistical analysis, APOE haplotypes were categorized into a two-level variable based on the presence or

absence of ε4 alleles for analyses. Categorization into three groups (no ε4 alleles, one ε4 allele, and two ε4 alleles) was not possible due to the very small number of participants carrying two ε4 alleles (n=2).

Preclinical Alzheimer's Cognitive Composite. PACC scores were calculated following methods described by Donohue and colleagues (Donohue et al., 2014). Cognitive measures were collected during the baseline neuropsychological assessment. PACC scores were computed from measures of episodic memory (delayed recall from the Alzheimer's Disease Assessment Scale and the delayed recall score on the Logical Memory IIa subtest from the Wechsler Memory Scale), attention (the digit symbol substitution test score), and the total MMSE score (Bransby et al., 2019; Lim et al., 2016). These measures were standardized as z-scores using the mean and standardized deviation derived from the sample. The standardized scores were summed to create a composite score that was subsequently utilized in the analyses. An additional composite variable, consisting of standardized PACC and cDTE values, was created.

Sample Size Estimation

Sample size was estimated using PASS 20.0.3 (NCSS, LLC. Kaysville, Utah, USA, www.ncss.com/software/pass) using the multiple regression module and the conditional power calculation method and was powered based on aim 1. Based on the estimate, a sample size of 38 total participants would be required to achieve 80% power to detect an R^2 of .20

attributable to two independent variables using an F-Test with an α of .05. The variables tested were adjusted for an additional three covariates with a combined R^2 of .1 by themselves.

Analysis

All analyses were conducted using SPSS 24.0 (IBM SPSS Statistics for Windows, Armonk, New York, USA: IBM Corp) with α=.05. For aim 1, hierarchal multiple linear regression (summary SUVR) and hierarchal logistic regression (Amyloid +/-) were conducted to account for potential covariates. Amyloid SUVR (linear regression) or amyloid status (logistic regression) was regressed on age, years of education, and APOE genotype in block 1, and then on DT performance (mDTE, cogDTE, or cDTE) in block 2. The same analyses were repeated with the addition of PACC to block 1. For all analyses, dummy coding was used for the coding of APOE genotype. Additionally, two hierarchal multiple linear regression models were analyzed for PACC and PACC+cDTE with the intent of examining the impact of adding the cDTE to the PACC. Following these analyses, receiver operating characteristic (ROC) curves were plotted and area under the curve (AUC) analyzed for cDTE, PACC, and PACC+cDTE to determine accuracy of identifying individuals with elevated cerebral amyloid deposition (SUVR cut point of 1.11). The degree of the accuracy was classified based on AUC value using the following criteria: no discrimination (0.5), poor (.5-.7), acceptable (.7-.8), excellent (.8-.9), outstanding (>0.9), and perfect test (AUC = 1) (Hosmer et al., 2013). Optimal cut points were determined as the closest point to the upper left corner of the ROC plot, confirmed using the Youden index (Perkins & Schisterman, 2006), and sensitivity, specificity, and positive likelihood ratios (+LR) were

calculated for each measure. Changes in probability were also calculated in accordance with Bayes' Theorem.

RESULTS

A total of 52 cognitively normal participants (age = 70.4±6.8 years; males = 53.8%; white = 88.4%) were analyzed. The median level of education was four years of college. The average MoCA was 26.7±2.4, and there were 12 (23.1%) APOE ε4 carriers, with two of those being homozygotes. Additional descriptive characteristics can be found in Table 1.

Table 1. Means, medians, proportions and standard deviations for demographics, covariates, dual task performance, and components of the Preclinical Alzheimer's Cognitive Composite.

	n	*Mean, Median, or Proportion*
DEMOGRAPHICS		
Age (years)	52	70.4 ± 6.8
Sex		
Male	28	53.8%
Female	24	46.2%
Race		
White	46	88.4%
Black	2	3.8%
Asian	4	7.7%
Ethnicity		
Non-Hispanic	48	92.3%
Hispanic	4	7.7%
Years of education	52	College 4 years
Montreal Cognitive Assessment (scale points)	52	26.7 ± 2.4
APOE Genotype		
No ε4 alleles	40	76.9%
One ε4 allele	10	19.2%
Two ε4 alleles	2	3.8%
DUAL TASK PEFORMANCE		
Motor Dual Task Effect	52	-28.1 ± 31.0
Cognitive Dual Task Effect	52	-42.9 ± 63.3
Combined Dual Task Effect	52	-85.7 ± 98.0
PRECLINICAL ALZHEIMER'S COGNITIVE COMPOSITE		
Total recall score	52	24.7 ± 5.2
Delayed recall score	52	11.8 ± 3.2
Symbol Digit Modalities Test	52	45.5 ± 7.8
Mini Mental State Exam (scale points)	52	28.9 ± 1.2

DT performance as a predictor of cerebral amyloid deposition. No statistically significant regression equations were found in block 1 of any of the hierarchical multiple regression analyses (*p*s=.985) for the prediction of amyloid SUVR. Statistically significant regression equations were found in the second block for the cogDTE ($F_{(4,48)}$=3.483, *p*=.014), and cDTE ($F_{(4,48)}$=5.891, *p*=.001) models, such that the models accounted for 22.9% and 33.4% of the variability in amyloid SUVR, respectively (Table 2).

Table 2. Statistics from hierarchical regression analyses for covariates and dual task performance variables predicting amyloid SUVR.

Variable	*b*	SE	β	p value	R^2	ΔR^2
Block 1 (same for all models)				.985	.003	.003
Age	-.001	.005	-.027	.854		
Education	.004	.014	.040	.781		
APOE	-.014	.082	-.025	.864		
mDTE model				.354		
Block 2				.042	.088	.085
Age	-.001	.005	-.017	.850		
Education	.006	.013	.069	.629		
APOE	-.010	.079	-.017	.903		
mDTE	-.002	.001	-.292	.042		
cogDTE model				.014		
Block 2				<.001	.229	.226
Age	-.001	.005	-.026	.844		
Education	.007	.012	.079	.544		
APOE	.011	.073	.019	.884		
cogDTE	-.002	<.001	-.478	<.001		
cDTE model				<.001		
Block 2				<.001	.334	.331
Age	-.001	.004	-.016	.893		
Education	.010	.011	.104	.392		
APOE	.010	.068	.017	.886		
cDTE	-.001	<.001	-.580	<.001		

No statistically significant logistic regression equations were found in block 1 of any of the analyses (*p*s=.956) for the prediction of amyloid status (+/-). Statistically significant regression equations were found in the second block for the cogDTE ($\chi^2_{(1)}$= 6.614, *p*=.010), and cDTE ($\chi^2_{(1)}$=10.597, *p*=.001) models (Table 3).

Table 3. Statistics from logistic regression analyses for covariates and dual task performance variables predicting amyloid status (+/-).

Variable	*b*	SE	Wald's χ^2	p value	Odds ratio
Block 1 (same for all models)			.319	.956	
Age	-.018	.045	.156	.693	.982
Education	.043	.120	.129	.720	1.044
APOE	.007	.712	<.001	.992	1.007
mDTE model			3.646	.456	
Block 2			3.326	.068	
Age	-.018	.046	.151	.698	.982
Education	.069	.126	.298	.585	1.071
APOE	.045	.726	.004	.951	1.046
mDTE	-.018	.011	2.801	.094	1.018
cogDTE model			6.933	.139	
Block 2			6.614	.010	
Age	-.019	.048	.152	.697	.981
Education	.075	.131	.331	.565	1.078
APOE	.223	.749	.089	.765	1.250
cogDTE	-.013	.005	5.388	.020	1.013
cDTE model			10.917	.028	
Block 2			10.597	.001	
Age	-.017	.051	.109	.742	.983
Education	.110	.140	.614	.433	1.116
APOE	.244	.779	.098	.754	1.276
cDTE	-.001	<.001	7.962	.005	1.011

DT performance as a predictor of cerebral amyloid deposition above and beyond PACC.

Statistically significant regression equations were found in block 1 of all analyses ($F_{(5,47)}$=6.857, *p*<.001) for the prediction of amyloid SUVR. Statistically significant regression equations were found after block 2 for all analyses (*p*s<.001). However, a statistically significant change in R^2 was only identified in the cDTE analysis ($F_{(5,47)}$=7.286, *p*<.001) with an R^2 change of .074 and a p value of .018 (Table 4).

Table 4. Statistics from hierarchical regression analyses for covariates and PACC (block 1) and dual task performance variables (block 2) predicting amyloid SUVR.

Variable	*b*	SE	β	p value	R^2	ΔR^2
Block 1 (same for all models)				<.001	.374	.374
Age	-.007	.004	-.193	.122		
Education	.015	.012	.155	.201		
APOE	-.078	.067	-.140	.249		
PACC	-.061	.012	-.652	<.001		
mDTE model				<.001		
Block 2				.362	.385	.012
Age	-.006	.004	-.180	.153		
Education	.015	.012	.155	.200		
APOE	-.073	.068	-.131	.283		
PACC	-.057	.012	-.613	<.001		
mDTE	-.002	.001	-.292	.362		
cogDTE model				<.001		
Block 2				.088	.413	.040
Age	-.006	.004	-.162	.189		
Education	.015	.011	.152	.199		
APOE	-.054	.067	-.097	.422		
PACC	-.061	.012	-.652	<.001		
cogDTE	-.001	<.001	-.231	.088		
cDTE model				<.001		
Block 2				.018	.447	.074
Age	-.005	.004	-.129	.283		
Education	.014	.011	.150	.193		
APOE	-.045	.065	-.080	.499		
PACC	-.041	.014	-.442	.004		
cDTE	-.001	<.001	-.337	.018		

A statistically significant regression equation was found in block 1 for all analyses ($\chi^2_{(4)}$=21.126, *p*<.001) for the prediction of amyloid status (+/-). However, no statistically significant improvements to model fit were found with the addition of any of the DT variables to the model (*ps*<.320) (Table 5).

Table 5. Statistics from hierarchical logistic regression analyses for covariates and dual task performance variables predicting amyloid status (+/-).

Variable	*b*	SE	Wald's χ^2	p value	Odds ratio
Block 1 (same for all models)			21.126	<.001	
Age	-.105	.067	2.421	.120	.901
Education	.168	.157	1.145	.285	1.183
APOE	-1.052	1.020	1.064	.302	.349
PACC	-.781	.235	11.053	.001	.458
mDTE model			21.632	.001	
Block 2			.506	.477	
Age	-.100	.068	2.161	.142	.905
Education	.159	.158	1.020	.313	1.173
APOE	-.987	1.030	.918	.338	.373
PACC	-.766	.242	10.002	.002	.465
mDTE	-.008	.012	.539	.463	1.009
cogDTE model			21.405	.001	
Block 2			.279	.597	
Age	-.101	.068	2.201	.138	.904
Education	.177	.160	1.231	.267	1.194
APOE	-.945	1.036	.833	.361	.389
PACC	-.744	.245	9.260	.002	.475
cogDTE	-.003	.006	.274	.600	1.003
cDTE model			22.113	<.001	
Block 2			.987	.320	
Age	-.093	.069	1.806	.179	.911
Education	.181	.162	1.241	.265	1.198
APOE	-.832	1.041	.639	.424	.435
PACC	-.700	.251	7.795	.005	.497
cDTE	-.005	.005	.945	.331	1.005

Statistically significant regression equations were found for both models (*p*s<.001) for the prediction of amyloid SUVR. The PACC model explained 37.4% of the variability in amyloid SUVR, while the PACC+cDTE model explained 43.7% of the variability in SUVR (Table 6).

Table 6. Statistics from hierarchical regression analyses for covariates and dual task performance variables predicting amyloid SUVR.

Variable	*b*	SE	β	p value	R^2	ΔR^2
Block 1 (same for all models)				.985	.003	.003
Age	-.001	.005	-.027	.854		
Education	.004	.014	.040	.781		
APOE	-.014	.082	-.025	.864		
PACC model				<.001		
Block 2				<.001	.374	.371
Age	-.007	.004	-.193	.122		
Education	.015	.012	.155	.201		
APOE	-.078	.067	-.140	.249		
PACC	-.061	.012	-.652	<.001		
PACC+cDTE model				<.001		
Block 2				<.001	.437	.434
Age	-.006	.004	-.160	.168		
Education	.015	.011	.157	.171		
APOE	-.060	.063	-.107	.349		
PACC+cDTE	-.051	.009	-.689	<.001		

Diagnostic accuracy. ROC curves were plotted for cDTE, PACC, and PACC+cDTE (Figure 1). AUCs were significant for all variables (*ps*<.007) with AUC values of .734, .796, and .817 for cDTE, PACC, and PACC+cDTE, respectively. Using a cut point of 76.5, cDTE had a sensitivity of 70.6% and a specificity of 73.5%. At a cut point of -1.0 for PACC, sensitivity and specificity were 58.8% and 73.5%, respectively. For PACC+cDTE sensitivity was 64.7% and specificity was 85.3%, utilizing a -1.0 cut point. Based on the above sensitivity and specificity values, +LR for cDTE was 2.66, PACC was 2.21, and PACC+cDTE was 4.40. Pre-test probability was 32.7%. Post-test probability for cDTE was 56.4%, resulting in a shift in probability of 23.7%. For PACC the post-test probability was 51.8%, for a shift in probability of 19.1%. Lastly, post-test probability for PACC+cDTE was 68.1%, for a resultant shift in probability of 35.4% (Figure 2).

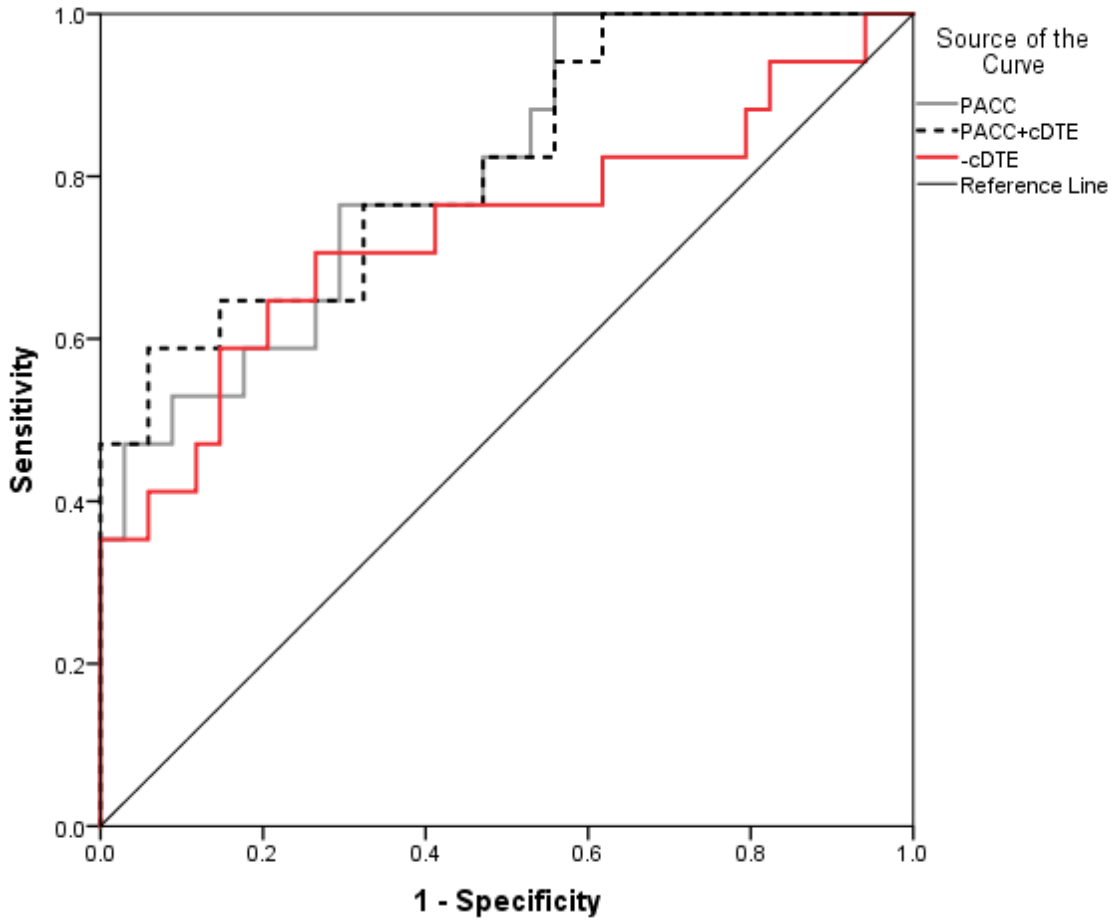


Figure 1. Receiver operating characteristic curve plot for combined dual task effect, Preclinical Alzheimer's Cognitive Composite, and Preclinical Alzheimer's Cognitive Composite with combined dual task effect.

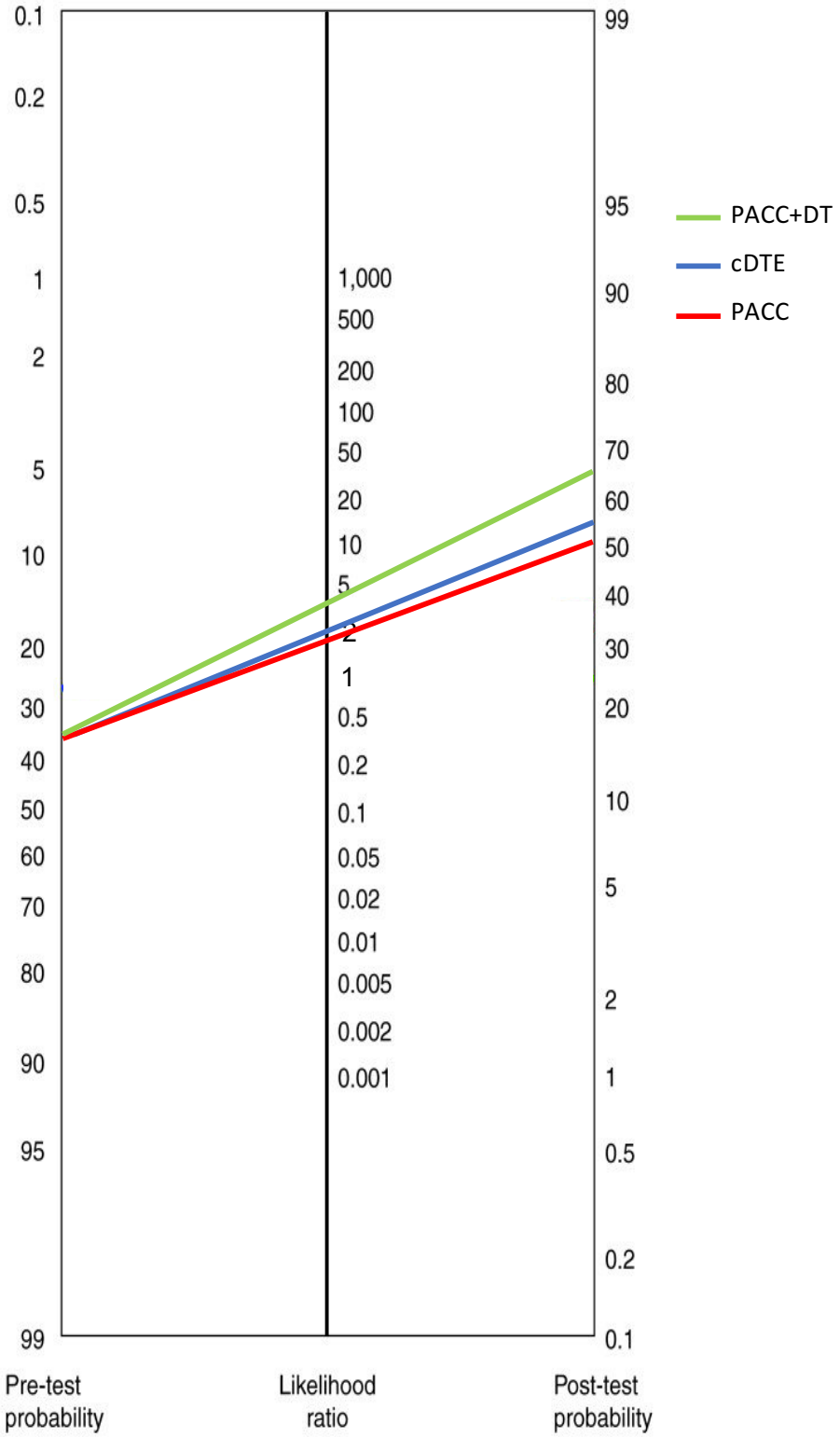


Figure 2. Nomogram plotting pre-test probability, positive likelihood ratios, and post-test probabilities for combined dual task effect, Preclinical Alzheimer's Cognitive Composite, and Preclinical Alzheimer's Cognitive Composite with combined dual task effect.

DISCUSSION

These findings are consistent with our original hypothesis that DT performance, and specifically automaticity, would explain a significant amount of variability in amyloid SUVR. The results of this study indicate that DT performance is moderately and inversely related to cerebral amyloid deposition, consistent with the findings of Nadkarni and colleagues (Nadkarni et al., 2017). Additionally, cDTE, as a measure of automaticity, was more strongly related to amyloid SUVR (ΔR^2=.331) than was either mDTE (ΔR^2=.085) or cogDTE (ΔR^2=.226). These findings extend our previous work showing that, among individuals with cognitive impairment, cDTE was more strongly related to brain volumes, particularly for the anterior cingulate and the entorhinal and medial orbital frontal cortices, than other measures of DT performance (J.K. Longhurst et al., 2020). Interpreting those findings with this study of individuals with preclinical AD, provides insight into a potential mechanism for volume loss in later disease, that of amyloidosis. These findings stand somewhat in contrast to those of Åhman and colleagues who found no relationship between CSF Aβ-42 and DT performance (Hanna Bozkurt Åhman et al., 2019). A potential explanation for these seemingly inconsistent findings is that the samples from the two studies differed greatly. While this study included 52 individuals that were cognitively normal, the Åhman study had 88 participants, of which 80 had symptomatic AD. It has been shown that while CSF tau levels continue to progress well into the symptomatic phase of the disease, CSF Aβ and cerebral amyloid deposition begin earliest in the disease process and peak at the onset of symptomatic disease, remaining relatively stable after that point (Bateman et al., 2012; Jack et al., 2013). Unsurprisingly, the degree of amyloidosis may not be related to the magnitude of symptoms among those with symptomatic disease (Aizenstein et al., 2008; Bennett et al.,

2006), while the relationship between amyloid and subtle manifestations of disease pathology is strong among those with preclinical AD (Bransby et al., 2019).

This study found that DT performance has potential as an indicator of risk for future cognitive decline, which is consistent with the literature. DT performance worsens with disease severity, even in the earliest disease states (Hanna B. Åhman, Cedervall, et al., 2020; Beauchet et al., 2017; Cullen et al., 2019; De Cock et al., 2019; Kueper et al., 2020; Lowe et al., 2020; R K MacAulay et al., 2017). In cognitively normal adults, DT performance has been shown to be worse among carriers of at least 1 APOE ε4 allele (Rebecca K. MacAulay et al., 2016; Whitson et al., 2018). Additionally, DT performance has been shown to be a significant indicator of the progression of cognitive impairment (De Cock et al., 2019; Montero-Odasso et al., 2017).

While there was much common variability between the PACC and measures of DT performance, we found that cDTE contributed uniquely to the variability in cerebral amyloid SUVR beyond the covariates and the PACC. This suggests that DT performance or automaticity relies on regions, networks, and/or processes that are different than those probed by the PACC. DT paradigms tap into multiple cognitive and motor regions and networks, which are dependent on the nature of the component tasks involved (Tripathi et al., 2019). Unsurprisingly, both motor control and cognitive regions have been implicated in DT performance. Specifically, the motor cortex, dorsal basal ganglia, brain stem, and cerebellum are related to motor automaticity, whereas the prefrontal cortex, cingulate, and paracingulate regions are related to executive

function and attention (Tripathi et al., 2019; Yogev-Seligmann et al., 2008). The confluence of these networks has been proposed as a control pathway of locomotion, which is active when activity shifts from motor to the control path, which occurs during complex tasks, such as DT (Leisman et al., 2016). Another possible explanation is that DT performance is mediated by a widespread gray matter network, and, thus, is associated with generalized neuronal loss (Allali et al., 2019; Blumen et al., 2014; Leisman et al., 2016; Tripathi et al., 2019). In either case, DT performance, may be sensitive to functional or structural neural changes associated with AD that are not well tested by traditional cognitive batteries. Of the measures of DT performance, cDTE alone was found to be a significant predictor of amyloid deposition, which points to the utility of this novel measure and its sensitivity to subtle changes early in the disease process (J.K. Longhurst et al., 2020; Jason K. Longhurst et al., n.d.). It also supports the notion that cDTE taps into neural resources involved in automaticity (J.K. Longhurst et al., 2020), a construct not probed by the PACC or fully elucidated by the other DT measures.

Both cDTE and PACC had acceptable discrimination of amyloid positive and negative states which was improved by the inclusion of cDTE as a component of PACC (PACC+cDTE). Sensitivity and specificity analyses revealed that cDTE was more sensitive than PACC to elevated amyloid SUVR (70.6% to 58.8%), while performing similarly in specificity (both at 73.5%). The addition of cDTE to the composite scoring of the PACC resulted in improved sensitivity compared to the PACC alone and improved specificity compared to cDTE and the PACC. Overall, our results point to a strong relationship between dual task performance and cerebral amyloid deposition in cognitively healthy adults. Taken together, these results indicate that cDTE is the best measure,

of those in this study, for ruling out high levels of cerebral amyloid. The cDTE and PACC were comparable in identifying elevated levels of cerebral amyloid; however; in combination (PACC+cDTE), they were more effective than either measure individually. Additionally, AUCs indicate that PACC+cDTE had the greatest diagnostic accuracy. Similarly, PACC+cDTE had the largest +LR indicating that a positive test increases the odds of having elevated levels of cerebral amyloid by 4.4, resulting in the largest shift in probability (35.4%) of the three measures analyzed. As noted above, this is supported by the findings of Nadkarni and colleagues (Nadkarni et al., 2017). These results implicate cDTE as a potentially useful tool in helping to identify individuals with preclinical AD. Importantly, our findings suggest that the utilization of DT in the identification of those with preclinical AD is most effective when done with a traditional cognitive composite, such as the PACC.

While the findings of this study are notable, there are limitations that should be acknowledged. The primary limitation was that this preliminary study was cross-sectional in nature, and, therefore cannot make claims about temporality, and, as such, is not a robust design for causality. In light of these limitations, these promising findings should be interpreted cautiously. In particular, longitudinal investigation of the relationship between automaticity and amyloidosis in the development of preclinical and symptomatic AD is warranted.

CONCLUSION

DT performance was found to be a moderate to strong predictor of cerebral amyloid deposition. Additionally, cDTE, a recently developed measure of automaticity derived from DT performance, contributed uniquely to variation in amyloid SUVR beyond the influence of the PACC. DT performance appears to be sensitive to functional or structural neural changes associated with AD that are not well probed by cognitive batteries. The inclusion of cDTE improved the diagnostic accuracy of the PACC, as well as its sensitivity and specificity.

REFERENCES

Åhman, Hanna B., Berglund, L., Cedervall, Y., Kilander, L., Giedraitis, V., McKee, K. J., Ingelsson, M., Rosendahl, E., & Åberg, A. C. (2020). Dual-task tests predict conversion to dementia—a prospective memory-clinic-based cohort study. *International Journal of Environmental Research and Public Health*, *17*(21), 1–14. https://doi.org/10.3390/ijerph17218129

Åhman, Hanna B., Cedervall, Y., Kilander, L., Giedraitis, V., Berglund, L., McKee, K. J., Rosendahl, E., Ingelsson, M., & Åberg, A. C. (2020). Dual-task tests discriminate between dementia, mild cognitive impairment, subjective cognitive impairment, and healthy controls - A cross-sectional cohort study. *BMC Geriatrics*, *20*(1), 258. https://doi.org/10.1186/s12877-020-01645-1

Åhman, Hanna Bozkurt, Giedraitis, V., Cedervall, Y., Lennhed, B., Berglund, L., McKee, K., Kilander, L., Rosendahl, E., Ingelsson, M., Åberg, A. C., Ahman, H. B., Giedraitis, V., Cedervall, Y., Lennhed, B., Berglund, L., McKee, K., Kilander, L., Rosendahl, E., Ingelsson, M., & Aberg, A. C. (2019). Dual-Task Performance and Neurodegeneration: Correlations Between Timed Up-and-Go Dual-Task Test Outcomes and Alzheimer's Disease Cerebrospinal Fluid Biomarkers. *J Alzheimers Dis*, *71*(s1), S75–S83. https://doi.org/10.3233/JAD-181265

Aisen, P. S., Vellas, B., & Hampel, H. (2013). Moving towards early clinical trials for amyloid-targeted therapy in Alzheimer's disease. In *Nature Reviews Drug Discovery* (Vol. 12, Issue 4, p. 324). https://doi.org/10.1038/nrd3842-c1

Aizenstein, H. J., Nebes, R. D., Saxton, J. A., Price, J. C., Mathis, C. A., Tsopelas, N. D., Ziolko, S. K., James, J. A., Snitz, B. E., Houck, P. R., Bi, W., Cohen, A. D., Lopresti, B. J., DeKosky, S. T.,

Halligan, E. M., & Klunk, W. E. (2008). Frequent amyloid deposition without significant cognitive impairment among the elderly. *Archives of Neurology*, *65*(11), 1509–1517. https://doi.org/10.1001/archneur.65.11.1509

Allali, G., Montembeault, M., Brambati, S. M., Bherer, L., Blumen, H. M., Launay, C. P., Liu-Ambrose, T., Helbostad, J. L., Verghese, J., & Beauchet, O. (2019). Brain Structure Covariance Associated With Gait Control in Aging. *J Gerontol A Biol Sci Med Sci*, *74*(5), 705–713. https://doi.org/10.1093/gerona/gly123

Bateman, R. J., Xiong, C., Benzinger, T. L. S., Fagan, A. M., Goate, A., Fox, N. C., Marcus, D. S., Cairns, N. J., Xie, X., Blazey, T. M., Holtzman, D. M., Santacruz, A., Buckles, V., Oliver, A., Moulder, K., Aisen, P. S., Ghetti, B., Klunk, W. E., McDade, E., … Morris, J. C. (2012). Clinical and Biomarker Changes in Dominantly Inherited Alzheimer's Disease. *New England Journal of Medicine*, *367*(9), 795–804. https://doi.org/10.1056/nejmoa1202753

Beauchet, O., Launay, C. P., Chabot, J., Levinoff, E. J., & Allali, G. (2017). Subjective memory impairment and gait variability in cognitively healthy individuals: Results from a cross-sectional pilot study. *Journal of Alzheimer's Disease*, *55*(3), 965–971. https://doi.org/10.3233/JAD-160604

Bennett, D. A., Schneider, J. A., Arvanitakis, Z., Kelly, J. F., Aggarwal, N. T., Shah, R. C., & Wilson, R. S. (2006). Neuropathology of older persons without cognitive impairment from two community-based studies. *Neurology*, *66*(12), 1837–1844. https://doi.org/10.1212/01.wnl.0000219668.47116.e6

Blumen, H. M., Holtzer, R., Brown, L. L., Gazes, Y., & Verghese, J. (2014). Behavioral and neural correlates of imagined walking and walking-while-talking in the elderly. *Human Brain*

Mapping, *35*(8), 4090–4104. https://doi.org/10.1002/hbm.22461

Bransby, L., Lim, Y. Y., Ames, D., Fowler, C., Roberston, J., Harrington, K., Snyder, P. J., Villemagne, V. L., Salvado, O., Masters, C. L., & Maruff, P. for the A. R. G. (2019). Sensitivity of a Preclinical Alzheimer's Cognitive Composite (PACC) to amyloid beta load in preclinical Alzheimer's disease. *J Clin Exp Neuropsychol*, *41*(6), 591–600. https://doi.org/10.1080/13803395.2019.1593949

Brookmeyer, R., Abdalla, N., Kawas, C. H., & Corrada, M. M. (2018). Forecasting the prevalence of preclinical and clinical Alzheimer's disease in the United States. *Alzheimers Dement*, *14*(2), 121–129. https://doi.org/10.1016/j.jalz.2017.10.009

Brookmeyer, R., Johnson, E., Ziegler-Graham, K., & Arrighi, H. M. (2007). Forecasting the global burden of Alzheimer's disease. *Alzheimers Dement*, *3*(3), 186–191. https://doi.org/10.1016/j.jalz.2007.04.381

Camus, V., Payoux, P., Barré, L., Desgranges, B., Voisin, T., Tauber, C., La Joie, R., Tafani, M., Hommet, C., Chételat, G., Mondon, K., De La Sayette, V., Cottier, J. P., Beaufils, E., Ribeiro, M. J., Gissot, V., Vierron, E., Vercouillie, J., Vellas, B., … Guilloteau, D. (2012). Using PET with 18F-AV-45 (florbetapir) to quantify brain amyloid load in a clinical environment. *European Journal of Nuclear Medicine and Molecular Imaging*, *39*(4), 621–631. https://doi.org/10.1007/s00259-011-2021-8

Cullen, S., Borrie, M., Carroll, S., Sarquis-Adamson, Y., Pieruccini-Faria, F., Mckay, S., & Montero-Odasso, M. (2019). Are Cognitive Subtypes Associated with Dual-Task Gait Performance in a Clinical Setting? *Journal of Alzheimer's Disease : JAD*, *71*(s1), S57–S64. https://doi.org/10.3233/JAD-181196

Cummings, J. L., Morstorf, T., & Zhong, K. (2014). Alzheimer's disease drug-development pipeline: few candidates, frequent failures. *Alzheimers Res Ther*, *6*(4), 37. https://doi.org/10.1186/alzrt269

Cummings, J., Lee, G., Ritter, A., & Zhong, K. (2018). Alzheimer's disease drug development pipeline: 2018. *Alzheimers Dement (N Y)*, *4*, 195–214. https://doi.org/10.1016/j.trci.2018.03.009

De Cock, A.-M. M., Fransen, E., Perkisas, S., Verhoeven, V., Beauchet, O., Vandewoude, M., & Remmen, R. (2019). Comprehensive Quantitative Spatiotemporal Gait Analysis Identifies Gait Characteristics for Early Dementia Subtyping in Community Dwelling Older Adults. *Frontiers in Neurology*, *10*(APR), 313. https://doi.org/10.3389/fneur.2019.00313

Decourt, B., Wilson, J., Ritter, A., Dardis, C., Difilippo, F. P., Zhuang, X., Cordes, D., Lee, G., Fulkerson, N. D., Rose, T. S., Hartley, K., & Sabbagh, M. N. (2020). MCLENA-1: A phase ii clinical trial for the assessment of safety, tolerability, and efficacy of lenalidomide in patients with mild cognitive impairment due to alzheimer's disease. *Open Access Journal of Clinical Trials*, *12*, 1–13. https://doi.org/10.2147/OAJCT.S221914

Donohue, M. C., Sperling, R. A., Salmon, D. P., Rentz, D. M., Raman, R., Thomas, R. G., Weiner, M., & Aisen, P. S. (2014). The preclinical Alzheimer cognitive composite: Measuring amyloid-related decline. *JAMA Neurology*, *71*(8), 961–970. https://doi.org/10.1001/jamaneurol.2014.803

Gross, A. L., Hassenstab, J. J., Johnson, S. C., Clark, L. R., Resnick, S. M., Kitner-Triolo, M., Masters, C. L., Maruff, P., Morris, J. C., Soldan, A., Pettigrew, C., & Albert, M. S. (2017). A classification algorithm for predicting progression from normal cognition to mild cognitive

impairment across five cohorts: The preclinical AD consortium. *Alzheimers Dement (Amst)*, *8*, 147–155. https://doi.org/10.1016/j.dadm.2017.05.003

Hosmer, D. W., Lemeshow, S., Sturdivant, R. X., & Hosmer, D. W. J. (2013). *Applied Logistic Regression*. John Wiley & Sons, Incorporated. https://ebookcentral.proquest.com/lib/unlv/detail.action?docID=1138225

Jack, C. R., Knopman, D. S., Jagust, W. J., Petersen, R. C., Weiner, M. W., Aisen, P. S., Shaw, L. M., Vemuri, P., Wiste, H. J., Weigand, S. D., Lesnick, T. G., Pankratz, V. S., Donohue, M. C., & Trojanowski, J. Q. (2013). Tracking pathophysiological processes in Alzheimer's disease: An updated hypothetical model of dynamic biomarkers. In *The Lancet Neurology* (Vol. 12, Issue 2, pp. 207–216). Elsevier. https://doi.org/10.1016/S1474-4422(12)70291-0

Jack, C. R., Knopman, D. S., Weigand, S. D., Wiste, H. J., Vemuri, P., Lowe, V., Kantarci, K., Gunter, J. L., Senjem, M. L., Ivnik, R. J., Roberts, R. O., Rocca, W. A., Boeve, B. F., & Petersen, R. C. (2012). An operational approach to National Institute on Aging-Alzheimer's Association criteria for preclinical Alzheimer disease. *Annals of Neurology*, *71*(6), 765–775. https://doi.org/10.1002/ana.22628

Kelly, V. E., Janke, A. A., & Shumway-Cook, A. (2010). Effects of instructed focus and task difficulty on concurrent walking and cognitive task performance in healthy young adults. *Exp Brain Res*, *207*(1–2), 65–73. https://doi.org/10.1007/s00221-010-2429-6

Kueper, J. K., Lizotte, D. J., Montero-Odasso, M., & Speechley, M. (2020). Cognition and motor function: The gait and cognition pooled index. *PLoS ONE*, *15*(9), e0238690. https://doi.org/10.1371/journal.pone.0238690

Leisman, G., Moustafa, A., & Shafir, T. (2016). Thinking, Walking, Talking: Integratory Motor and

Cognitive Brain Function. *Frontiers in Public Health*, *4*, 1. https://doi.org/10.3389/fpubh.2016.00094

Lim, Y. Y., Snyder, P. J., Pietrzak, R. H., Ukiqi, A., Villemagne, V. L., Ames, D., Salvado, O., Bourgeat, P., Martins, R. N., Masters, C. L., Rowe, C. C., & Maruff, P. (2016). Sensitivity of composite scores to amyloid burden in preclinical Alzheimer's disease: Introducing the Z-scores of Attention, Verbal fluency, and Episodic memory for Nondemented older adults composite score. *Alzheimers Dement (Amst)*, *2*, 19–26. https://doi.org/10.1016/j.dadm.2015.11.003

Longhurst, J.K., Wise, M. A., Krist, D. J., Moreland, C. A., Basterrechea, J. A., & Landers, M. R. (2020). Brain volumes and dual-task performance correlates among individuals with cognitive impairment: a retrospective analysis. *Journal of Neural Transmission*, *127*(7). https://doi.org/10.1007/s00702-020-02199-7

Longhurst, Jason K., Rider, J. V, Cummings, J., John, S., Poston, B., & Landers, M. R. (n.d.). A novel way of measuring dual task interference: the reliability and construct validity of the dual task effect battery in healthy adults and individuals with neurodegenerative disease. *Under Review*.

Lowe, D. A., MacAulay, R. K., Szeles, D. M., Milano, N. J., & Wagner, M. T. (2020). Dual-Task Gait Assessment in a Clinical Sample: Implications for Improved Detection of Mild Cognitive Impairment. *The Journals of Gerontology. Series B, Psychological Sciences and Social Sciences*, *75*(7), 1372–1381. https://doi.org/10.1093/geronb/gbz119

MacAulay, R K, Wagner, M. T., Szeles, D., & Milano, N. J. (2017). Improving Sensitivity to Detect Mild Cognitive Impairment: Cognitive Load Dual-Task Gait Speed Assessment. *J Int*

Neuropsychol Soc, *23*(6), 493–501. https://doi.org/10.1017/S1355617717000261

MacAulay, Rebecca K., Allaire, T., Brouillette, R., Foil, H., Bruce-Keller, A. J., & Keller, J. N. (2016). Apolipoprotein E Genotype Linked to Spatial Gait Characteristics: Predictors of Cognitive Dual Task Gait Change. *PLoS One*, *11*(8), e0156732. https://doi.org/10.1371/journal.pone.0156732

McIsaac, T. L., Lamberg, E. M., & Muratori, L. M. (2015). Building a framework for a dual task taxonomy. *BioMed Research International*, *2015*, 591475. https://doi.org/10.1155/2015/591475

Montero-Odasso, M. M., Sarquis-Adamson, Y., Speechley, M., Borrie, M. J., Hachinski, V. C., Wells, J., Riccio, P. M., Schapira, M., Sejdic, E., Camicioli, R. M., Bartha, R., McIlroy, W. E., & Muir-Hunter, S. (2017). Association of Dual-Task Gait With Incident Dementia in Mild Cognitive Impairment: Results From the Gait and Brain Study. *JAMA Neurol*, *74*(7), 857–865. https://doi.org/10.1001/jamaneurol.2017.0643

Nadkarni, N. K., Lopez, O. L., Perera, S., Studenski, S. A., Snitz, B. E., Erickson, K. I., Mathis, C. A., Nebes, R. D., Redfern, M., & Klunk, W. E. (2017). Cerebral amyloid deposition and dual-tasking in cognitively normal, mobility unimpaired older adults. *Journals of Gerontology - Series A Biological Sciences and Medical Sciences*, *72*(3), 431–437. https://doi.org/10.1093/gerona/glw211

Perkins, N. J., & Schisterman, E. F. (2006). The inconsistency of “optimal” cutpoints obtained using two criteria based on the receiver operating characteristic curve. *American Journal of Epidemiology*, *163*(7), 670–675. https://doi.org/10.1093/aje/kwj063

Rice, L., & Bisdas, S. (2017). The diagnostic value of FDG and amyloid PET in Alzheimer’s

disease-A systematic review. *Eur J Radiol*, *94*, 16–24. https://doi.org/10.1016/j.ejrad.2017.07.014

Ritter, A., Cummings, J., Nance, C., & Miller, J. B. (2018). Neuroscience learning from longitudinal cohort studies of Alzheimer's disease: Lessons for disease-modifying drug programs and an introduction to the Center for Neurodegeneration and Translational Neuroscience. *Alzheimer's & Dementia: Translational Research & Clinical Interventions*, *4*(1), 350–356. https://doi.org/10.1016/J.TRCI.2018.06.006

Sperling, R. A., Aisen, P. S., Beckett, L. A., Bennett, D. A., Craft, S., Fagan, A. M., Iwatsubo, T., Jack, C. R., Kaye, J., Montine, T. J., Park, D. C., Reiman, E. M., Rowe, C. C., Siemers, E., Stern, Y., Yaffe, K., Carrillo, M. C., Thies, B., Morrison-Bogorad, M., … Phelps, C. H. (2011). Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's and Dementia*, *7*(3), 280–292. https://doi.org/10.1016/j.jalz.2011.03.003

Sutphen, C. L., Jasielec, M. S., Shah, A. R., Macy, E. M., Xiong, C., Vlassenko, A. G., Benzinger, T. L. S., Stoops, E. E. J., Vanderstichele, H. M. J., Brix, B., Darby, H. D., Vandijck, M. L. J., Ladenson, J. H., Morris, J. C., Holtzman, D. M., & Fagan, A. M. (2015). Longitudinal cerebrospinal fluid biomarker changes in preclinical Alzheimer disease during middle age. *JAMA Neurology*, *72*(9), 1029–1042. https://doi.org/10.1001/jamaneurol.2015.1285

Tripathi, S., Verghese, J., & Blumen, H. M. (2019). Gray matter volume covariance networks associated with dual-task cost during walking-while-talking. *Human Brain Mapping*, *40*(7), 2229–2240. https://doi.org/10.1002/hbm.24520

Whitson, H. E., Potter, G. G., Feld, J. A., Plassman, B. L., Reynolds, K., Sloane, R., & Welsh-Bohmer, K. A. (2018). Dual-Task Gait and Alzheimer's Disease Genetic Risk in Cognitively Normal Adults: A Pilot Study. *J Alzheimers Dis*, *64*(4), 1137–1148. https://doi.org/10.3233/JAD-180016

Wu, T., Hallett, M., & Chan, P. (2015). Motor automaticity in Parkinson's disease. *Neurobiol Dis*, *82*, 226–234. https://doi.org/10.1016/j.nbd.2015.06.014

Yang, L., He, C., & Pang, M. Y. (2016). Reliability and Validity of Dual-Task Mobility Assessments in People with Chronic Stroke. *PLoS One*, *11*(1), e0147833. https://doi.org/10.1371/journal.pone.0147833

Yang, L., Lam, F. M. H., Liao, L. R., Huang, M. Z., He, C. Q., & Pang, M. Y. C. (2017). Psychometric properties of dual-task balance and walking assessments for individuals with neurological conditions: A systematic review. *Gait Posture*, *52*, 110–123. https://doi.org/10.1016/j.gaitpost.2016.11.007

Yogev-Seligmann, G., Hausdorff, J. M., & Giladi, N. (2008). The role of executive function and attention in gait. In *Movement Disorders*. https://doi.org/10.1002/mds.21720

CHAPTER 5

SUMMARY, SIGNIFICANCE, AND FUTURE STUDIES

Deficits in executive attention and automatic control are common in neurodegenerative diseases, such as Alzheimer's disease (AD) and Parkinson's disease (PD) (Muir et al., 2012; Wu et al., 2015). Deficits in these domains are among the earliest that develop during the disease course of both AD and PD, and are likely present during preclinical disease states, the period of time prior to sufficient symptom onset to detect disease-related symptoms (Belghali, Chastan, Cignetti, et al., 2017). These often subtle, early deficits can be elicited and assessed using cognitive-motor dual task (DT) paradigms, in which a cognitive and motor task are concurrently performed. The performance of DT paradigms not only allows for observation of subtle deficits in executive attention and automaticity but they are also highly related to daily function. This has resulted in great interest in the utility of DT paradigms to investigate cognitive and motor function and neurological mechanisms related to neurodegenerative disease.

While the potential utility of DT assessments is high, there have been methodological limitations in the implementation of DT paradigms and their measurement that have limited their impact (Belghali, Chastan, Davenne, et al., 2017; Yang et al., 2017). One of the key limitations is the lack of consensus regarding the best measures to obtain and report when implementing DT paradigms. This has led to the use of many different metrics to quantify the impact of DT. Quantifying and interpreting the impact of a DT can be challenging as there are

three separate domains of performance that can be considered: 1) task specific interference (or effects) – which relates directly to changes in performance of a single component task, 2) task prioritization – degree to which attention is allocated to one task (e.g., favoring cognitive performance) versus the other (e.g., favoring motor performance), and 3) automaticity – the ability to complete a task without requiring attention resources be directed to its completion. Automaticity is related to a central capacity and is not influenced by allocation of attention (Clark, 2015). Due to this, automaticity has the potential to be a better prognostic and diagnostic marker than the other two domains of DT performance. Additionally, there is poor understanding of the neurological mechanisms of automaticity and the impact of neurodegenerative disease. Lastly, while DT paradigms have been shown to have potential to elicit subtle deficits in neurodegenerative disease (Christofoletti et al., 2014), their utility in the preclinical disease state has not been well established.

The overarching premise of this dissertation was that DT automaticity is impacted by the development and progression of neurodegenerative disease. Within neurodegenerative disease, there is evidence that as disease advances, DT performance worsens (Amboni et al., 2012, 2018; Tarnanas et al., 2015). This dissertation aimed to investigate the diagnostic utility of measures of automaticity. As a necessary first step, the lack of reliable metrics of automaticity was addressed with the proposal of a battery of dual task measures across the three domains of DT performance (task specific interference, task prioritization, and automaticity) (Chapter 2). This battery incorporates a newly proposed measure of automaticity developed by the author that is designed to improve assessment of automaticity. The

relationship between automaticity and cerebral cortical thickness in individuals with AD was next addressed (Chapter 3). Lastly, automaticity was utilized to predict amyloidosis in healthy adults, indicating that automaticity is impacted in the preclinical stage of AD (Chapter 4). Additionally, Chapters 3 and 4 were both designed to provide additional evidence of the validity of this novel measure of automaticity, and demonstrate its utility over previous measures.

In Chapter 2, the dual task effect battery (DTE-B) was proposed as a measure of each of the domains of DT performance and proposed the use of a newly formulated measure of automaticity, combined DT effect (cDTE) (Longhurst et al., 2020). Strong evidence was found for the reliability of cDTE in PD, AD, and healthy adults. While the remaining measures had mostly good evidence of reliability, they were less reliable than this newer measure of automaticity. As a measure of automaticity, it would be anticipated that cDTE would be more reliable because it is a measure of a central capacity. This was the first piece of evidence to support cDTE as a measure of automaticity. Next, convergent and divergent validity of cDTE as a measure of automaticity was investigated by evaluating its relationship with measures of cognition, balance, and gait. Lastly, known-groups validity analyses revealed no difference between PD and AD on automaticity; however, both groups had poorer automaticity than the healthy adult group. Taken together, the pattern of association and known-groups validity analyses were supportive of the DTE-B measures within the domains proposed, including cDTE representing automaticity.

To further explore the construct validity of the DTE-B, two different studies were designed to examine the predictive abilities of the different elements of the battery. In Chapter 3, the relationship between automaticity and cortical thickness was investigated among individuals with AD. The results showed that automaticity was related to two cortical regions, the dorsal lateral prefrontal cortex and the superior parietal cortex, while other cortical regions were not found to have a significant contribution to automaticity in an exploratory analysis. While we did not investigate subcortical regions, it is likely that structures such as the striatum, brain stem, and mesencephalic locomotor region play a primary role in cognitive-motor automaticity. Lastly, in Chapter 4, the relationship between cerebral amyloid deposition and automaticity was investigated. Automaticity was found to be a significant predictor of amyloidosis beyond the influence of a cognitive composite score that approximates a commonly accepted measure used to predict preclinical AD. When added to the cognitive composite, automaticity, as measured by cDTE, improved diagnostic accuracy.

An overarching theme of the results presented in this dissertation is the potential value of assessing automaticity through the administration of cognitive-motor DT paradigms in neurodegenerative disease, particularly AD. Automaticity was found to relate to physical and cognitive abilities, as well as neurological markers of disease. Beyond this, automaticity was affected at all stages of disease in AD, from the preclinical state, to the symptomatic manifestation of dementia. Clearly, neurodegeneration has a detrimental impact on automaticity, likely leading to worsening of functional abilities and perhaps contributing to disease progression. This provides a target to which future interventions could be applied.

Despite these promising findings, an additional theme in the findings is that automaticity is not a complete answer to the questions asked in any of the studies presented here. In Chapter 2, while we found good evidence for the reliability and validity of the cDTE, we found that the overall pattern of dual tasking did not lend itself to drawing conclusions about the influence of task prioritization on automaticity. Conceptually, automaticity would be unaffected by task prioritization. Had the PD and AD groups had differences in task prioritization, as hypothesized, it would have provided the opportunity to investigate this relationship, and it could have lent additional credence to cDTE as a measure of automaticity. In Chapter 3, automaticity was related to the superior parietal and dorsolateral prefrontal cortices within patients with AD. However, statistically significant relationships between other cortical regions and automaticity were not discovered. While it was anticipated that the entorhinal cortex would be associated with automaticity, the results did not bear out this relationship. However, it is important to note that the entorhinal cortex did contribute to the overall fit of model. The implication of entorhinal cortex involvement would have been significant as it is one the earliest areas affected during the development of AD. It is possible that entorhinal cortex thinning could be more related to memory and learning during the dementia stages of AD than to automaticity. Subsequently, there is potential that the entorhinal cortex could be more related to automaticity in the earlier stages of the disease, which is consistent with the literature (Sakurai et al., 2019). Lastly, Chapter 4 demonstrates the predictive and diagnostic value of automaticity for individuals with preclinical AD. While the results of this study may be impactful and meaningful, there remain many unaccounted for and unexplained factors that contribute to

preclinical AD and these results should be interpreted in the context of those other putative factors.

In discussing the value of these results, one must also consider the practical utility of the tools being proposed. While this dissertation used one paradigm (DT – Timed Up and Go with a secondary serial subtraction task), this could be adapted to many differing situations and patient/participant ability levels. From a clinical perspective, the ability to adapt a measure to the needs, goals, and abilities of a patient is very appealing. In the rehabilitation fields the majority of performance measures allow for little to no flexibility to adapt the tool to individual and situation demands. This is a great strength of DT paradigms. In fact, it has been hypothesized that the information gathered from the most salient and individualized paradigms may provide the greatest insights, though this requires further investigation. From a research perspective, this ability to tailor paradigms means that the tools discussed in this dissertation could find application in fields and populations far beyond those discussed here.

This dissertation has a key limitation that is consistent across all three studies, each utilized a cross-sectional design. This design does not provide strong evidence for causality, and limits observations and conclusions regarding temporality. The data discussed in this dissertation would have been augmented by longitudinally observed data, especially regarding the development and onset of neurodegenerative disease and deficits in automaticity. Additional limitations include lack of comparison group in Chapter 3, as well as potential confounders and

biases that enter the data as a consequence of using retrospective clinical practice data in Chapters 2 and 3.

This dissertation informs future studies in the realms of neurodegenerative disease and automaticity. The use of functional imaging that can be utilized during completion of these task, such as portable functional near infrared spectroscopy, would provide additional insights in the neurological mechanisms of impairments in automaticity. Another direct step from these findings is to expand upon them using longitudinal observations. This would provide greater evidence for casual relationships especially if conducted in individuals with preclinical or early disease. Additionally, these results provide starting points and target for development of interventions that specifically address automaticity and its impact in neurodegenerative disease. Lastly, the application of these findings to related populations may provide new insights.

In summary, this dissertation provides evidence of a strong link between automaticity and neurodegenerative disease along the continuum of disease progression. The three studies that make up Chapters 2, 3, and 4 each provide insights into automaticity in different aspects of neurodegenerative disease. There remains the need to further understand the neurological mechanisms involved in automaticity in neurodegenerative disease and develop intervention and prevention strategies that can directly impact these neurological mechanisms as well as related functions.

REFERENCES

Amboni, M., Barone, P., Iuppariello, L., Lista, I., Tranfaglia, R., Fasano, A., Picillo, M., Vitale, C., Santangelo, G., Agosti, V., Iavarone, A., & Sorrentino, G. (2012). Gait patterns in parkinsonian patients with or without mild cognitive impairment. *Movement Disorders*, *27*(12), 1536–1543. https://doi.org/10.1002/mds.25165

Amboni, M., Iuppariello, L., Iavarone, A., Fasano, A., Palladino, R., Rucco, R., Picillo, M., Lista, I., Varriale, P., Vitale, C., Cesarelli, M., Sorrentino, G., & Barone, P. (2018). Step length predicts executive dysfunction in Parkinson's disease: a 3-year prospective study. *Journal of Neurology*, *265*(10), 2211–2220. https://doi.org/10.1007/s00415-018-8973-x

Belghali, M., Chastan, N., Cignetti, F., Davenne, D., & Decker, L. M. (2017). Loss of gait control assessed by cognitive-motor dual-tasks: pros and cons in detecting people at risk of developing Alzheimer's and Parkinson's diseases. *Geroscience*, *39*(3), 305–329. https://doi.org/10.1007/s11357-017-9977-7

Belghali, M., Chastan, N., Davenne, D., & Decker, L. M. (2017). Improving Dual-Task Walking Paradigms to Detect Prodromal Parkinson's and Alzheimer's Diseases. *Front Neurol*, *8*, 207. https://doi.org/10.3389/fneur.2017.00207

Christofoletti, G., Andrade, L. P. de, Beinotti, F., Borges, G., de Andrade, L. P., Beinotti, F., & Borges, G. (2014). Cognition and dual-task performance in older adults with Parkinson's and Alzheimer's disease. *International Journal of General Medicine*, *7*, 383–388. https://doi.org/10.2147/IJGM.S65803

Clark, D. J. (2015). Automaticity of walking: Functional significance, mechanisms, measurement and rehabilitation strategies. In *Frontiers in Human Neuroscience* (Vol. 9, Issue MAY). Frontiers Media S. A. https://doi.org/10.3389/fnhum.2015.00246

Longhurst, J. K., Wise, M. A., Krist, D. J., Moreland, C. A., Basterrechea, J. A., & Landers, M. R. (2020). Brain volumes and dual-task performance correlates among individuals with cognitive impairment: a retrospective analysis. *Journal of Neural Transmission*, *127*(7). https://doi.org/10.1007/s00702-020-02199-7

Muir, S. W., Speechley, M., Wells, J., Borrie, M., Gopaul, K., & Montero-Odasso, M. (2012). Gait assessment in mild cognitive impairment and Alzheimer's disease: the effect of dual-task challenges across the cognitive spectrum. *Gait Posture*, *35*(1), 96–100. https://doi.org/10.1016/j.gaitpost.2011.08.014

Sakurai, R., Bartha, R., & Montero-Odasso, M. (2019). Entorhinal Cortex Volume Is Associated With Dual-Task Gait Cost Among Older Adults With MCI: Results From the Gait and Brain Study. *J Gerontol A Biol Sci Med Sci*, *74*(5), 698–704. https://doi.org/10.1093/gerona/gly084

Tarnanas, I., Papagiannopoulos, S., Kazis, D., Wiederhold, M., Widerhold, B., Vuillermot, S., & Tsolaki, M. (2015). Reliability of a novel serious game using dual-task gait profiles to early characterize aMCI. *Frontiers in Aging Neuroscience*, *7*(MAR). https://doi.org/10.3389/fnagi.2015.00050

Wu, T., Hallett, M., & Chan, P. (2015). Motor automaticity in Parkinson's disease. *Neurobiol Dis*, *82*, 226–234. https://doi.org/10.1016/j.nbd.2015.06.014

Yang, L., Lam, F. M. H., Liao, L. R., Huang, M. Z., He, C. Q., & Pang, M. Y. C. (2017). Psychometric properties of dual-task balance and walking assessments for individuals with neurological conditions: A systematic review. *Gait Posture*, *52*, 110–123. https://doi.org/10.1016/j.gaitpost.2016.11.007

APPENDIX 1

SEARCH STRATEGY

Search conducted in PubMed on September 29, 2020.

(("alzheimer disease"[MeSH Major Topic] OR "alzheimer s"[Title/Abstract] OR "parkinson disease"[MeSH Major Topic] OR "parkinson s"[Title/Abstract]) AND ("multitasking behavior"[MeSH Major Topic] OR "multitasking behavior/physiology"[MeSH Major Topic] OR "multitasking behavior/drug effects"[MeSH Major Topic]) AND "cognitive-motor"[Text Word] AND "dual task"[Text Word]) OR "dual-task"[Text Word]) – 4655 hits returned

CURRICULUM VITAE

JASON K. LONGHURST

jasonklonghurst@gmail.com

EDUCATION

University of Nevada – Las Vegas Las Vegas, Nevada May 2021
PhD(c) in Interdisciplinary Health Sciences (Rehabilitation Sciences track)
Dissertation title: Development of a cognitive motor dual-task assessment battery in neurodegenerative disease

University of Nevada – Las Vegas Las Vegas, Nevada May 2013
Doctor of Physical Therapy

Brigham Young University Provo, Utah April 2010
Bachelors in Exercise Science

LICENSURE

Nevada State Board of Physical Therapy Examiners, License #2873

CERTIFICATIONS

Clinical Specialist in Neurologic Physical Therapy (NCS) #47824 2016
American Board Physical Therapy Specialties

Multiple Sclerosis Certified Specialist (MSCS) 2016
Consortium of Multiple Sclerosis Centers

Certified Dementia Practitioner (CDP) 2017
National Council of Certified Dementia Practitioners

Vestibular Competency Certified Therapist 2015
American Physical Therapy Association

PWR! Certified Therapist 2015
Parkinson's Wellness Recovery

TEACHING EXPERIENCE

Part Time Instructor May 2017 – December 2020
Department of Physical Therapy
School of Allied Health Sciences, Division of Health Sciences, University of Nevada, Las Vegas
Courses: Movement Science, Neuroanatomy Lab

CLINCAL EXPERIENCE

Outpatient Physical Therapist and Clinical Researcher September 2014 – Present
Cleveland Clinic Lou Ruvo Center for Brain Health, Las Vegas, Nevada

Outpatient Physical Therapist May 2013 – August 2014
HealthSouth Rehabilitation Hospital of Henderson, Nevada

PEER REVIEWED PUBLICATIONS (*DPT student authors)

1. Bluett B, Bayram E, **Longhurst JK**. Discrepancy in assessment and classification of freezing of gait assessment in Parkinson's disease. *Under review.*
2. Sreenivasan K, Bayram E, Zhuang X, **Longhurst J**, Yang Z, Cordes D, Ritter A, Caldwell J, Mari Z, Litvan I, Bluett B, Mishra V. Resting-state functional connectivity in "ON" state freezing of gait in Parkinson's disease: A pilot fMRI study. *Under review.*
3. Campbell J*, **Longhurst JK**. High-intensity task-specific physical therapy in non-remitting spinal myoclonus: a case report. *Under review.*
4. Landers MR, Jacobson KM*, Matsunami NE*, McCarl HE*, Regis MT*, **Longhurst JK**. A vicious cycle of fear of falling avoidance behavior in Parkinson disease: a path analysis. *Clinical Parkinsonism & Related Disorders.* 2021, doi:10.1016/j.prdoa.2021.100089. *In press.*
5. Rider JR, **Longhurst JK**. Fear of falling avoidance behavior in Parkinson's disease: a scoping review protocol. *JBI Evidence Synthesis*. 2021; Online First. doi: 10.11124/JBIES-20-00396
6. **Longhurst JK**, Phan J*, Chen E*, Jackson S*, Landers MR. Physical therapy for gait, balance, and cognition in individuals with cognitive impairment: a retrospective analysis. *Rehabilitation Research and Practice*. 2020;2020. doi:10.1155/2020/8861004
7. **Longhurst JK**, Wise MA*, Krist DJ*, Moreland CA*, Basterrechea JA*, Landers MR. Brain volumes and dual-task performance correlates among individuals with cognitive impairment: a retrospective analysis. *Journal of Neural Transmission*. 2020;127(7). doi:10.1007/s00702-020-02199-7
8. Landers MR, Addis KA*, **Longhurst JK***, Vom Steeg B-L*, Puentedura EJ, Daubs MD. Anterior cervical decompression and fusion on neck range of motion, pain, and function: a prospective analysis. *Spine Journal*. 2013;13(11). doi:10.1016/j.spinee.2013.06.020

PEER REVIEWED PLATFORM PRESENTATIONS – NATIONAL AND REGIONAL

1. **Longhurst J**, Caldwell J, Ritter A, Mishra V, Bluett B, Landers M. The cognitive profiles differ among freezing of gait subtypes in Parkinson's disease. UNLV 22nd Annual Graduate & Professional Student Research Forum, Las Vegas, Nevada, February 29, 2020.
    a. Awarded "Best Integrated Health Sciences" presentation.
2. **Longhurst J**, Landers M. A new way of measuring dual task cost: the construct validity of the comprehensive dual task cost equation in individuals with Parkinson's disease. 2019 APTA Combined Sections Meeting, Washington D.C., January 23-26, 2019.
3. Bluett B, Bayram E, **Longhurst J**, Banks S, Litvan I. Discrepancy in freezing of gait measurements: self-report, clinical, and physical therapy assessments. NIH, NIGMS seventh biennial National IDeA symposium of Biomedical Research Excellence, Washington, D.C., June 24-26, 2018.

PEER REVIEWED PLATFORM PRESENTATIONS – INTERNATIONAL

1. **Longhurst J**, Ritter A, Rider J, Landers M. Physical therapy is associated with improvements in gait and balance in individuals with Lewy Body Dementia: A retrospective analysis. International Lewy Body Dementia Conference 2019, Las Vegas, Nevada, June 24-26, 2019.

PEER REVIEWED POSTER PRESENTATIONS – NATIONAL AND REGIONAL

1. Landers MR, Jacobson K, Matsunami N, McCarl H, Regis M, **Longhurst JK.** A Vicious Cycle of Fear of Falling Avoidance Behavior in Parkinson's Disease: A Path Analysis. 2021 APTA Combined Sections Meeting, February 12-15, 2020.
2. Rider J, **Longhurst J**. The impact of freezing of gait on activities of daily living among individuals with Parkinson's disease and mild cognitive impairment. Archives of Physical Medicine and Rehabilitation Annual Conference, October 19-24, 2020.
3. **Longhurst J**, Caldwell J, Ritter A, Mishra V, Bluett B, Landers M. The cognitive profiles differ among freezing of gait subtypes in Parkinson's disease. UNLV 22nd Annual Graduate & Professional Student Research Forum, Las Vegas, Nevada, February 29, 2020.
4. **Longhurst JK**, Wise MA, Krist DJ, Moreland CA, Basterrechea JA, Landers MR. Associations of Brain Volumetry and Dual Task Interference Among Older Adults with Cognitive Impairment. 2020 APTA Combined Sections Meeting, Denver, Colorado, February 12-15, 2020.
5. **Longhurst J**, Bayram E, Mahoney T, Ross C, Bluett B, Landers M. The relationship between freezing of gait, levodopa, dual task cost, and task complexity in Parkinson's disease. 2019 Tri-State Physical Therapy Conference, Las Vegas, Nevada, October 11-13, 2019.
6. **Longhurst J**, Bayram E, Mahoney T, Ross C, Bluett B, Landers M. The relationship between freezing of gait, levodopa, dual task cost, and task complexity in Parkinson's disease. 2019 Friends of Parkinson's Disease Health Symposium, Las Vegas, Nevada, August 18, 2019.
7. **Longhurst J**, Bayram E, Mahoney T, Ross C, Bluett B, Landers M. The relationship between freezing of gait, levodopa, dual task cost, and task complexity in Parkinson's disease. 2019 APTA Combined Sections Meeting, Washington D.C., January 23-26, 2019.
8. Bayram E, Banks S, **Longhurst J**, Bluett B. The relationship between inhibitory control and freezing of gait in Parkinson's disease. NIH, NIGMS seventh biennial National IDeA symposium of Biomedical Research Excellence, Washington, D.C., June 24-26, 2018.
9. Bayram E, **Longhurst J**, Banks S, Mari Z, Bluett B. The effect of levodopa on dual-tasking in Parkinson's disease freezing of gait. NIH, NIGMS seventh biennial National IDeA symposium of Biomedical Research Excellence, Washington, D.C., June 24-26, 2018.
10. Landers MR, Contreras D, Heim J, Nelson KJ, Nash JM, **Longhurst JK**. Gait and balance in Alzheimer's disease: a retrospective data analysis of function across varying levels of cognitive impairment. APTA Combined Sections Meeting, San Antonio, Texas, February 15-18, 2017.
11. Landers MR, Poston B, Nash J, **Longhurst J.** Freezing of gait is associated with more fear of falling avoidance behavior and less participation in daily physical activity. 9th Annual Interdisciplinary Research Scholarship Day. UNLV, Las Vegas, Nevada, April 1, 2016.
12. Landers MR, Addis K, **Longhurst J**, vom Steeg B, Puentedura E, Daubs M. Anterior cervical decompression and fusion improves neck range of motion: a prospective analysis. 7th Annual Interdisciplinary Research & Scholarship Day, UNLV, Las Vegas, Nevada, April 21, 2014.
13. Landers MR, Addis K, **Longhurst J**, vom Steeg B, Puentedura E, Daubs M. Anterior cervical decompression and fusion improves neck range of motion: a prospective analysis. 2014 APTA Combined Sections Meeting, Las Vegas, Nevada, February 3-6, 2014.

PEER REVIEWED POSTER PRESENTATIONS – INTERNATIONAL

1. **Longhurst J**, Rider J, Bluett B, Landers M. The effect of levodopa and cognitive-motor dual interference on gait parameters for individuals with Parkinson's disease freezing of gait. 24th International Congress of Parkinson's Disease and Movement Disorders, September 12-16, 2020.
2. Rider J, **Longhurst J**, Landers M. Cognitive and functional predictors of ADL performance in persons with Parkinson's disease. 24th International Congress of Parkinson's Disease and Movement Disorders, September 12-16, 2020.
3. **Longhurst J**, Caldwell J, Ritter A, Mishra V, Bluett B, Landers M. The cognitive profiles differ among freezing of gait subtypes in Parkinson's disease. 23rd International Congress of Parkinson's Disease and Movement Disorders, Nice, France, September 22-25, 2019.
4. Mishra V, Sreenivasan K, Bayram D, Banks SJ, **Longhurst J**, Yang Z, Zhuang X, Cordes D, Cummings J, Litvan I, Ritter A, Caldwell J, Bluett B. Graph-Theoretical Findings in Structural Connectivity of Parkinson's Disease Patients, With and Without, Memory Impairment. 2019 Organization for Human Brain Mapping Annual Meeting. Rome, Italy, June 9-13, 2019.
5. Sreenivasan K, Bayram D, Banks SJ, **Longhurst J**, Yang Z, Zhuang X, Cordes D, Ritter A, Caldwell J, Cummings J, Litvan I, Bluett B, Mishra V. Functional Network Topology in Parkinson's Disease Patients with Mild Cognitive Impairment. 2019 Organization for Human Brain Mapping Annual Meeting. Rome, Italy, June 9-13, 2019.
6. Sreenivasan K, Bayram D, Banks SJ, **Longhurst J**, Yang Z, Zhuang X, Cordes D, Ritter A, Caldwell J, Cummings J, Litvan I, Bluett B, Mishra V. Aberrant Functional Connectivity of the Claustrum in Parkinson's disease Patients with Mild Cognitive Impairment. 2019 Organization for Human Brain Mapping Annual Meeting. Rome, Italy, June 9-13, 2019.
7. Mishra V, Sreenivasan K, Bayram E, Banks S, **Longhurst J**, Yang Z, Zhuang X, Cordes D, Ritter A, Caldwell J, Cummings J, Litvan I, Bluett B. Towards identification of diagnostic imaging biomarker in Parkinson's Disease Patients, with and Without, Memory Impairment. International Society for Magnetic Resonance in Medicine 27th annual meeting, Montreal, Canada, May 11-16, 2019.
8. Mishra V, Sreenivasan K, Bayram E, Banks S, **Longhurst J**, Yang Z, Zhuang X, Cordes D, Ritter A, Caldwell J, Cummings J, Litvan I, Bluett B. Towards identification of diagnostic imaging biomarker in Parkinson's Disease Patients, with and Without, Memory Impairment. International Society for Magnetic Resonance in Medicine 27th annual meeting, Montreal, Canada, May 11-16, 2019.
9. Bayram E, Sreenivasan K, Banks S, **Longhurst J**, Yang Z, Zhuang X, Cordes D, Ritter A, Caldwell J, Cummings J, Litvan I, Bluett B, Mishra V. Associations Between Dual-Tasking Cost and Striatal Functional Connectivity in Parkinson's Disease with Mild Cognitive Impairment. International Society for Magnetic Resonance in Medicine 27th annual meeting, Montreal, Canada, May 11-16, 2019.
10. Sreenivasan K, Bayram E, Banks S, **Longhurst J**, Yang Z, Zhuang X, Cordes D, Ritter A, Caldwell J, Cummings J, Litvan I, Bluett B, Mishra V. Altered Claustral Functional Connectivity in Parkinson's Disease Patients with Mild Cognitive Impairment. International Society for Magnetic Resonance in Medicine 27th annual meeting, Montreal, Canada, May 11-16, 2019.
11. Sreenivasan K, Bayram E, Banks S, **Longhurst J**, Yang Z, Zhuang X, Cordes D, Ritter A, Caldwell J, Cummings J, Litvan I, Bluett B, Mishra V. Aberrant Functional Connectivity and Network Topology in Parkinson's Disease Patients with Mild Cognitive Impairment. International Society for Magnetic Resonance in Medicine 27th annual meeting, Montreal, Canada, May 11-16, 2019.
12. **Longhurst J**, Phan J, Chen E, Jackson S, Landers M. Physiotherapy improves gait and balance in individuals with cognitive impairment: a retrospective analysis. World Confederation for Physical Therapy Congress 2019, Geneva, Switzerland, May 10-13, 2019.
13. Bluett B, Bayram E, **Longhurst J**, Banks S, Litvan I. Discrepancy in freezing of gait measurements: self-report, clinical, and physical therapy assessments. 22nd International Congress of Parkinson's Disease and Movement Disorders, Hong Kong, October 5-9, 2018.

14. Bayram E, Banks S, **Longhurst J**, Bluett B. The relationship between inhibitory control and freezing of gait in Parkinson's disease. 22nd International Congress of Parkinson's Disease and Movement Disorders, Hong Kong, October 5-9, 2018.
15. Bayram E, **Longhurst J**, Banks S, Mari Z, Bluett B. The effect of levodopa on dual-tasking in Parkinson's disease freezing of gait. 22nd International Congress of Parkinson's Disease and Movement Disorders, Hong Kong, October 5-9, 2018.
16. Landers MR, Poston B, Nash J, **Longhurst J**. Freezing of gait is associated with more fear of falling avoidance behavior and less participation in daily physical activity. 4th World Parkinson Congress, Portland, Oregon, USA, September 20-23, 2016.

ABSTRACTS

1. Rider J, **Longhurst J**. The impact of freezing of gait on activities of daily living among individuals with Parkinson's disease and mild cognitive impairment. *Archives of Physical Medicine and Rehabilitation.* 2020; 101(12), e152 Available at: https://doi.org/10.1016/j.apmr.2020.10.082
2. Sreenivasan K, Zhuang X, **Longhurst J**, Yang Z, Cordes D, Ritter A, Caldwell J, Mari Z, Litvan I, Bluett B, Mishra V. Resting state functional connectivity in levodopa non responsive Parkinson's disease patients with freezing of gait. *Parkinsonism and Related Disorders*. 2020 79(S1), e8. https://doi.org/10.1016/j.parkreldis.2020.06.057
3. **Longhurst J**, Rider J, Bluett B, Landers M. The effect of levodopa and cognitive-motor dual interference on gait parameters for individuals with Parkinson's disease freezing of gait. *Movement Disorders*. 2020; 35(S1): Poster 1208. Available at: https://doi.org/10.1002/mds.28268
4. Rider J, **Longhurst J**, Landers M. Cognitive and functional predictors of ADL performance in persons with Parkinson's disease. *Movement Disorders*. 2020; 35(S1): Poster 15. Available at: https://doi.org/10.1002/mds.28268
5. Rider J, Lee H, **Longhurst J**, Landers M. The Feasibility of Wearable Activity Monitors as an Outcome Measurement in Mild Cognitive Impairment: A Pilot Study. *American Journal of Occupational Therapy*. 2020; 74(4_Supplement_1). Available at: https://doi.org/10.5014/ajot.2020.74S1-PO2726
6. **Longhurst JK**, Wise MA, Krist DJ, Moreland CA, Basterrechea JA, Landers MR. Associations of Brain Volumetry and Dual Task Interference Among Older Adults with Cognitive Impairment. *Journal of Neurologic Physical Therapy*. 2020: poster: 25517. Available at: https://journals.lww.com/jnpt/Documents/ANPT%20Poster%20Abstracts_CSM%202020.pdf
7. **Longhurst J**, Caldwell J, Ritter A, Mishra V, Bluett B, Landers M. The cognitive profiles differ among freezing of gait subtypes in Parkinson's disease. *Movement Disorders*. 2019; 34(S2). Available at: https://www.mdsabstracts.org/abstract/the-cognitive-profiles-differ-among-freezing-of-gait-subtypes-in-parkinsons-disease/.
8. **Longhurst J**, Bayram E, Mahoney T, Ross C, Bluett B, Landers M. The relationship between freezing of gait, levodopa, dual task cost, and task complexity in Parkinson's disease. *Journal of Neurologic Physical Therapy*. 2019: poster: 3041618. Available at: https://journals.lww.com/jnpt/Documents/CSM%202019%20PosterAbstracts_and_cover%20page.pdf
9. **Longhurst J**, Landers M. A new way of measuring dual task cost: the construct validity of the comprehensive dual task cost equation in individuals with Parkinson's disease. *Journal of Neurologic Physical Therapy*. 2019. Available at: https://journals.lww.com/jnpt/Documents/CSM%202019%20PlatformAbstracts_and_cover%20page.pdf

10. Bayram E, **Longhurst J**, Banks S, Mari Z, Bluett B. The effect of levodopa on dual-tasking in Parkinson's disease freezing of gait. *Movement Disorders*. 2018; 33(S2). Available at: https://www.mdsabstracts.org/abstract/levodopa-effect-on-dual-tasking-in-freezing-of-gait-in-parkinsons-disease/
11. Bluett B, Bayram E, **Longhurst J**, Banks S, Litvan I. Discrepancy in freezing of gait measurements: self-report, clinical, and physical therapy assessments. *Movement Disorders*. 2018; 33(S2). Available at: https://www.mdsabstracts.org/abstract/discrepancies-in-assessments-of-freezing-of-gait-self-report-clinical-and-physical-therapy-assessments/
12. Bayram E, Banks S, **Longhurst J**, Bluett B. The relationship between inhibitory control and freezing of gait in Parkinson's disease. *Movement Disorders*. 2018; 33(S2). Available at: https://www.mdsabstracts.org/abstract/the-association-between-inhibitory-control-and-freezing-of-gait-severity-in-parkinsons-disease/
13. Landers MR, Contreras D, Heim J, Nelson KJ, Nash JM, **Longhurst JK**. Gait and balance in Alzheimer's disease: a retrospective data analysis of function across varying levels of cognitive impairment. *Journal of Neurologic Physical Therapy*. 2017: Poster:199. Available at: https://journals.lww.com/jnpt/Documents/Poster%20Abstracts%20CSM%202017.pdf
14. Landers MR, Poston B, Nash J, **Longhurst J**. Freezing of gait is associated with more fear of falling avoidance behavior and less participation in daily physical activity. *Movement Disorders*. 2016; 31(S2). Available at: https://www.mdsabstracts.org/abstract/freezing-of-gait-is-associated-with-more-fear-of-falling-avoidance-behavior-and-less-participation-in-daily-physical-activity/
15. Landers MR, Addis K, **Longhurst J**, vom Steeg B, Puentedura E, Daubs M. Anterior cervical decompression and fusion improves neck range of motion: a prospective analysis. *Journal of Orthopaedic & Sports Physical Therapy*. 2014;44:A123. Available at: http://www.jospt.org/doi/pdf/10.2519/jospt.2014.44.1.A75

FUNDED GRANT ACTIVITY

1. **Longhurst J**. The cognitive profiles differ among freezing of gait subtypes in Parkinson's disease. Travel and Research Sponsorship, Graduate and Professional Student Association, University of Nevada, Las Vegas. 2019. $1250.
2. Contreras D, Heim J, Nelson J, Nash J, **Longhurst J**, Landers MR. Physical therapy for individuals with mild cognitive impairment. UNLVPT Student Opportunity Award. 2015-2017. $3,000.

NON-PEER REVIEWED PRESENTATIONS

1. "How exercise modifies cerebral circuitry" 2019 – Advancing Neurologic Therapeutics - The Cleveland Clinic, Las Vegas, Nevada, May 26, 2019.
2. "Anxiety and cognition in gait disorders." Advancing therapeutics for Parkinson's disease – The Cleveland Clinic, Las Vegas, Nevada, November 3, 2018.
3. "Physical therapy for individuals with Parkinson's disease." Cleveland Clinic Parkinson's education series – The Cleveland Clinic, Las Vegas, Nevada, May 15, 2018.
4. "Neurological and physical rehabilitation for the patient with Multiple Sclerosis" Advancing Therapeutics for Multiple Sclerosis– The Cleveland Clinic, Las Vegas, Nevada, December 9, 2017.
5. "Freezing of gait in Parkinson's disease" Nevada Physical Therapy Association, Southern District Meeting, Las Vegas, Nevada, November 14, 2017.
6. "Neurologic physical therapy" Lambda Kappa Delta Pre-Physical Therapy Honor Society meeting, Las Vegas, Nevada, September 28, 2017.

7. "Freezing of gait in Parkinson's disease," Friends of Parkinson's Interprofessional Health Symposium on the Latest Treatment Options for Parkinson's Disease, Las Vegas, Nevada, August 19, 2017.
8. "Advances in physical therapy for the neurological patient" Advancing Neuro-Therapeutics – The Cleveland Clinic, Las Vegas, Nevada, November 5, 2016.
9. "The innovations and advances of physical therapy for the neurodegenerative population" Cleveland Clinic Lou Ruvo Center for Brain Health Lunch and Learn Series, August 31, 2016.
10. "Therapeutic recommendations for Parkinson's disease" Neuro-Therapeutics for the Rehab Professional – The Cleveland Clinic, Las Vegas, Nevada, November 6, 2015.
11. "No fooling...successful aging requires hard work" Cleveland Clinic Lou Ruvo Center for Brain Health Lunch and Learn Series, Las Vegas, Nevada, April 1, 2015.
12. "Maximizing your mobility: fall prevention" – Victory Summit of the Davis Phinney Foundation, Las Vegas, Nevada, February 7, 2015.

MEMBERSHIP IN SCIENTIFIC/PROFESSIONAL ORGANIZATIONS

American Physical Therapy Association	2010 – Present
Neurology Section	2010 – Present
Research Section	2010 – Present
Nevada Physical Therapy Association	2010 – Present
Treasurer	2015 – 2017
International Parkinson and Movement Disorder Society	2018 – Present

PROFESSIONAL SERVICE

Clinical Instructor *University of Southern California*	2017 – Present
Clinical Instructor *University of Nevada, Las Vegas*	2015 – Present
Clinical Instructor *Touro University Nevada*	2016
NPTE Item Writer *Federation of State Boards of Physical Therapy*	2018
Manuscript Peer Reviewer	
Parkinsonism and Related Disorders (4)	2018 – 2020
Brain Impairment (1)	2020
Clinical Rehabilitation (2)	2020
Journal of Neurologic Physical Therapy (1)	2020
BMC Geriatrics (1)	2020

CONTINUING EDUCATION ATTENDED

American Physical Therapy Association Combined Section Meeting

- Virtual CSM, February 1-28. 2021
- Denver, CO, February 12-15, 2020
- Washington DC, January 23-26, 2019
- San Antonio, Texas, February 15-18, 2017
- Anaheim, California, February 17-20, 2016
- Las Vegas, Nevada, February 4-6, 2014

A Comprehensive Review of Movement Disorders for the Clinical Practitioner Virtual Aspen Course – International Parkinson and Movement Disorder Society, July 20 – August 15, 2020.

24th International Congress of Parkinson's Disease and Movement Disorders - International Parkinson and Movement Disorder Society, held virtually, September 12-16, 2020.

23rd International Congress of Parkinson's Disease and Movement Disorders - International Parkinson and Movement Disorder Society, Nice, France, September 22-25, 2019.

International Lewy Body Dementia Conference – Lewy Body Dementia Association, Las Vegas, Nevada, June 24-26, 2019.

Certified Dementia Practitioners Course – Las Vegas, NV, October 22, 2016.

A Comprehensive Approach to Evidence-Based Rehabilitation of Patients with Parkinson Diseases across the Continuum of Disability – APTA Pre-Conference course, Anaheim, CA, February 2016.

Neurologic Physical Therapy Professional Education Consortium – University of Southern California – 2015. (26 hours)

Vestibular Rehabilitation: a Competency Based Course – Los Angeles, California, July 6-11, 2015. (40 hours)

Parkinson's Wellness Recovery training course – Phoenix, AZ, 2014.