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**ASSOCIATIONS BETWEEN PHYSICAL AND COGNITIVE FUNCTION IN HEALTHY
OLDER ADULTS**

A Dissertation in
Human Development and Family Studies

by

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ABSTRACT

There is a positive relationship between objective physical and cognitive function in older adults. The magnitude of the subjective relationship across older adulthood is unknown, and understanding relationship (in)stability across adulthood has implications for statistical modeling and clinical practice. Another gap in the literature is the long-term effect of cognitive interventions on physical function. Emerging literature identifies cognitive interventions as promising for ameliorating late-life physical function degradations, but most studies are underpowered and include immediate posttest only. This dissertation addresses these limitations in a large sample of older adults. Study 1 examined the cross-sectional relationship between subjective physical and memory function, as well as whether subjective or objective physical function was a better predictor of subjective or objective memory, using a flexible extension of regression, *time-varying effect modeling*. Study 2 explored the 10-year effects of three cognitive training programs (speed of processing, memory, or reasoning) on multiple measures of objective physical function (grip strength, Digit Symbol Copy, and Turn 360). A secondary aim was to examine whether the training benefits were equivalent across various baseline psychosocial factors and baseline subjective bodily pain. Both studies utilized a ($N = 2,802$) sample of healthy older adults from the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) trial. This dissertation demonstrated that subjective physical and memory function were related and the relationship was stable across older adulthood. Subjective physical function better predicted subjective memory function, and objective physical function better predicted objective memory function (Study 1). Study 2 found that cognitive training did not attenuate age-related decline in physical function across 10 years in intention-to-treat (ITT) analyses (Study 2), and baseline factors did not moderate this relationship.

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Chapter 1: Introduction

Maintaining physical and cognitive function in older adulthood is vital for healthy aging (Rowe & Kahn, 1997), and degradations in either domain are associated with poor health outcomes such as hospitalization (Cesari et al., 2004; Mathews, Arnold, & Epperson, 2014), disability (Buchman et al., 2016; Dodge et al., 2005), and increased mortality risk (Al Snih, Markides, Ray, Ostir, & Goodwin, 2002; Cesari et al., 2004; Nofuji et al., 2016; Sabia et al., 2014; Sachs et al., 2011). Both physical and cognitive impairments are costly (Mackin, Delucchi, Bennett, & Areán, 2011), and programs designed to prevent, delay, or slow impairment are expected to positively affect healthcare costs (Barnes & Yaffe, 2011). For example, a one-year delay in Alzheimer's disease diagnoses are projected to save \$70 billion in formal and \$43 billion in informal caregiving costs by 2030 (Zissimopoulos, Crimmins, & St. Clair, 2014). Furthermore, examining the interplay between physical and cognitive function is critical for understanding health and disease trajectories (Bäckman, Jones, Small, Agüero-Torres, & Fratiglioni, 2003; Nguyen, Evans, & Zonderman, 2007; Stenholm et al., 2015; Vu, Finch, & Day, 2011) and has implications for intervention delivery (Smith et al., 2013), and mortality risk (Chikuda et al., 2013). Ultimately, the goal of understanding the relationship between physical and cognitive function in older adulthood is to exploit multiple avenues of health promotion, e.g., providing more personalized interventions for mobility-limited individuals, for the increasing older adult population.

Objective Physical and Cognitive Function: Observational Findings

There are directionally consistent, significant observational cross-sectional relationships between objective physical and cognitive function such that higher physical function is associated with higher cognitive function. However, the magnitude of these associations is inconsistent across measures. Simple physical function (e.g., grip strength) consistently covaries with memory (Blankevoort et al., 2013) and dementia status (Atkinson et al., 2010; Auyeung et al., 2008; Blankevoort et al., 2013; Clouston et al., 2013; Cooper et al., 2011; Fritz, McCarthy, & Adamo, 2017; Jang & Kim, 2015;

Narazaki et al., 2014; Stessman, Rottenberg, Fischer, Hammerman-Rozenberg, & Jacobs, 2017; Vaz-Patto, Bueno, Ribeiro, Teixeira, & Afonso, 2017). It is also consistently correlated with reasoning (Blankevoort et al., 2013) but is infrequently evaluated. Grip strength inconsistently predicts speed of processing (H. Christensen, Mackinnon, Korten, & Jorm, 2001; Ritchie, Tucker-Drob, Starr, & Deary, 2016). Complex physical function (e.g., balance, walking, gait) generally covaries with speed of processing (Demnitz et al., 2016; Desjardins-Crépeau et al., 2014; Donoghue et al., 2012; MacDonald et al., 2017; Rosano et al., 2005), while memory (Berkman et al., 1993; Blankevoort et al., 2013; Demnitz et al., 2016; Desjardins-Crépeau et al., 2014; Donoghue et al., 2012; Hausdorff, Yogeve, Springer, Simon, & Giladi, 2005; MacDonald et al., 2017; Mielke et al., 2013), reasoning (Berkman et al., 1993; Demnitz et al., 2016; Desjardins-Crépeau et al., 2014; Donoghue et al., 2012; Mielke et al., 2013), and dementia status (Atkinson et al., 2010; Auyeung et al., 2008; Clay et al., 2015; Clouston et al., 2013; Cooper et al., 2011; Donoghue et al., 2012; Eggermont et al., 2010; Fitzpatrick et al., 2007; Narazaki et al., 2014; Nieto, Albert, Morrow, & Saxton, 2008; Rosano et al., 2005; Stessman et al., 2017; Vaz-Patto et al., 2017) show inconsistent associations. These inconsistencies occur in part from the complex physical function measure; static balance measures tend to show nonsignificant relationships (Finkel, Ernsth-Bravell, & Pedersen, 2016; Tolea, Morris, & Galvin, 2015), whereas dynamic gait measures show more robust associations (Krall, Carlson, Fried, & Xue, 2014; MacDonald et al., 2017; Stijntjes et al., 2016) .

Longitudinally, weaker baseline grip strength predicts accelerated declines in memory (Fritz et al., 2017; MacDonald, Hultsch, & Dixon, 2011; Praetorius Björk, Johansson, & Hassing, 2016; Sternäng et al., 2016; Stijntjes et al., 2016) and dementia status (Alfaro-Acha et al., 2006; Cooper et al., 2011; Fritz et al., 2017; Stessman et al., 2017; Stijntjes et al., 2016; Taekema, Gussekloo, Maier, Westendorp, & de Craen, 2010); however, there is inconsistent evidence for accelerated declines in speed of processing (Clouston et al., 2013; Ritchie et al., 2016; Sternäng et al., 2016) and reasoning (Clouston et al., 2013; Sternäng et al., 2016). Complex physical function does not predict speed of processing changes (MacDonald et al., 2017), but it predicts changes in memory (Finkel et al., 2016; Krall et al., 2014; MacDonald et al., 2017; Mielke et al., 2013; Stijntjes et al., 2016; Tolea et al., 2015), reasoning (Best et al., 2016; Krall et al., 2014; Mielke et al., 2013; Tolea et al., 2015), and dementia status

(Atkinson et al., 2010; Best et al., 2016; Bullain, Corrada, Perry, & Kawas, 2016; Clouston et al., 2013; Cooper et al., 2011; Krall et al., 2014; Montero-Odasso et al., 2016; K. Park, Hwang, Kim, & Park, 2016; Payette et al., 2011; Taniguchi, Yoshida, Fujiwara, Motohashi, & Shinkai, 2012; Tolea et al., 2015), especially when dynamic (e.g., gait speed) as opposed to static (e.g., standing balance) measures were used (Finkel et al., 2016; Tolea et al., 2015).

Although both static and dynamic balance are related to cognition¹, dynamic balance may have more cognitive demands (e.g., both maintaining postural balance and rapidly allocating resources to reduce falling) and thus more likely to be related to cognitive performance (Barbosa et al., 2016; Kahya, Wood, Sosnoff, & Devos, 2018). In general, baseline objective physical function predicts subsequent objective cognitive function, but the relationship is inconsistent across domains.

When considering the inverse- whether objective cognitive function predicts longitudinal changes in objective physical function- a different pattern of results emerge. There is weak evidence of baseline speed of processing, memory, reasoning, or dementia status predicting subsequent grip strength declines (Clouston et al., 2013); those who found baseline dementia status predicted grip strength declines found this was true for the oldest-old (i.e., 80+) only (Fritz et al., 2017; Stijntjes et al., 2016). Similarly, baseline speed of processing (Gale, Allerhand, Sayer, Cooper, & Deary, 2014), memory (Gale et al., 2014; Krall et al., 2014; Mielke et al., 2013), and reasoning (Best et al., 2016; Gale et al., 2014; Krall et al., 2014; Mielke et al., 2013) did not predict changes in complex physical function. Baseline dementia status predicting subsequent complex physical function declines is rarely examined, but recent evidence found an association (Atkinson et al., 2010; Best et al., 2016; Krall et al., 2014), possibly for the oldest-old only (Stijntjes et al., 2016). See Table 1 for a summary of the observational studies examining cross-sectional and longitudinal associations between objective physical and cognitive function. Notably, it is largely unknown how the relationships differ or change in subjective physical or cognitive function. Examining the subjective physical-cognitive

¹ Static and dynamic balance are related but distinct aspects of balance.

relationship is worth closer examination for several reasons, including the relative ease of (Feuring, Vered, Kushnir, Jette, & Melzer, 2014) and participant comfort with administration compared to objective measures (Quinn, McArthur, Ellis, & Stott, 2011; Tangalos et al., 1996; Woodford & George, 2007), as well as the reliance on subjective evaluations for clinical frailty ratings (Vella Azzopardi et al., 2018).

Table 1. Summary of Observational Relationships between Objective Physical and Cognitive Function in Healthy Older Adults.

Cross-sectional associations				
	Speed of Processing	Memory	Reasoning	Dementia status
Grip strength	~(H. Christensen et al., 2001; Ritchie et al., 2016)	+(Blankevoort et al., 2013)	+(Blankevoort et al., 2013)	+(Atkinson et al., 2010; Auyeung et al., 2008; Blankevoort et al., 2013; Clouston et al., 2013; Cooper et al., 2011; Fritz et al., 2017; Jang & Kim, 2015; Narazaki et al., 2014; Stessman et al., 2017; Vaz-Patto et al., 2017)
Complex lower limb function	+(Demnitz et al., 2016; Desjardins-Crépeau et al., 2014; Donoghue et al., 2012; MacDonald et al., 2017; Rosano et al., 2005)	~(Berkman et al., 1993; Blankevoort et al., 2013; Demnitz et al., 2016; Desjardins-Crépeau et al., 2014; Donoghue et al., 2012; Hausdorff et al., 2005; MacDonald et al., 2017; Mielke et al., 2013; Nieto et al., 2008)	~(Berkman et al., 1993; Demnitz et al., 2016; Desjardins-Crépeau et al., 2014; Donoghue et al., 2012; Mielke et al., 2013; Nieto et al., 2008)	~(Atkinson et al., 2010; Auyeung et al., 2008; Clay et al., 2015; Cooper et al., 2011; Demnitz et al., 2016; Donoghue et al., 2012; Eggermont et al., 2010; Narazaki et al., 2014; Nieto et al., 2008; Rosano et al., 2005; Vaz-Patto et al., 2017)
Longitudinal associations (Physical function = predictor, cognition = outcome)				
	Speed of Processing	Memory	Reasoning	Dementia status
Grip strength	~(Clouston et al., 2013; Ritchie et al., 2016; Sternäng et al., 2016)	+(Fritz et al., 2017; MacDonald et al., 2011; Praetorius Björk et al., 2016; Sternäng et al., 2016; Stijntjes et al., 2016)	~(Alfaro-Acha et al., 2006; Cooper et al., 2011; Fritz et al., 2017; Stessman et al., 2017; Stijntjes et al., 2016; Taekema et al., 2010)	+(Clouston et al., 2013; Sternäng et al., 2016)
Complex lower limb function	~(MacDonald et al., 2017)	+*(Finkel et al., 2016; Krall et al., 2014; MacDonald et al., 2017; Mielke et al., 2013; Stijntjes et al., 2016; Tolea et al., 2015)	+*(Best et al., 2016; Krall et al., 2014; Mielke et al., 2013; Tolea et al., 2015)	+*(Atkinson et al., 2010; Best et al., 2016; Bullain et al., 2016; Clouston et al., 2013; Cooper et al., 2011; Krall et al., 2014; Montero-Odasso et al., 2016; K. Park et al., 2016; Payette et al., 2011; Taniguchi et al., 2012; Tolea et al., 2015)

Longitudinal associations (Cognition = predictor, physical function = outcome)				
	Speed of Processing	Memory	Reasoning	Dementia status
Grip strength	-(Clouston et al., 2013)	-(Clouston et al., 2013)	-(Clouston et al., 2013)	~(Clouston et al., 2013; Fritz et al., 2017; Stijntjes et al., 2016)
Complex lower limb function	~(Gale et al., 2014)	~(Gale et al., 2014; Krall et al., 2014; Mielke et al., 2013)	~(Best et al., 2016; Gale et al., 2014; Krall et al., 2014; Mielke et al., 2013)	~(Atkinson et al., 2010; Best et al., 2016; Clouston et al., 2013; Krall et al., 2014; Stijntjes et al., 2016)

Note. + = consistent significant associations, ~ = inconsistent significant associations, - = consistent nonsignificant associations. *Significance is true for gait parameters, but not balance (See page 3 for possible reasons).

Theories of Physical and Cognitive Function Coupling

Three theories are usually obliquely referenced as mechanisms explaining why there is an increased coupling in older adulthood: (1) speed of processing, (2) common cause, and (3) cognitive reserve. *Speed of processing* theory (Salthouse, 1996) posits that age-related declines in cognitive abilities are largely due to declines in speed of processing. Since speed of processing, or how fast one completes mental operations for relevant tasks (Lu et al., 2011), is a component of higher-order tasks (e.g., reasoning), it is believed that degradations are responsible for poorer performance across a variety of higher-order fluid abilities such as reasoning. Because certain physical function tasks, such as walking speed, incorporate elements similar to cognitive speed tasks (e.g., both are timed tasks), the underlying slowing in older adults is responsible for the increased coupling. *Common cause* theory (H. Christensen et al., 2001) proposes an unnamed common factor as the mechanism for declines across several health domains in older adults. This theory is similar to speed of processing in that there are a few underlying factors (e.g., “common” or “speed of processing” factor) responsible for many of the age-related changes across a breadth of functions. Although the cause itself is unidentified, one of the hallmarks is that the factor should plausibly explain what causes the increased coupling of cognitive and noncognitive measures (H.

Christensen & Mackinnon, 2004). Lastly, *cognitive reserve* is the ability for cognitively healthy older adults (i.e., those without brain damage such as Alzheimer's disease) to maximize or optimize performance through recruitment of brain networks (Stern, 2002, 2013). Reserve mechanisms are various but include education (Stern, 2002) and differential brain activation patterns (discussed below) (Cabeza, 2001; Cabeza, Anderson, Locantore, & McIntosh, 2002; Davis, Dennis, Daselaar, Fleck, & Cabeza, 2008).

Currently, these theories have fallen out of favor due to lack of empirical support (Anstey, Hofer, & Luszcz, 2003; Emery, Finkel, & Pedersen, 2012; Kiely & Anstey, 2015; MacDonald, Hultsch, & Dixon, 2003; Zimprich & Martin, 2002). Notably, the magnitude of the relationships between specific physical and cognitive domains are too inconsistent to implicate one or few mechanistic processes, as well as an overreliance on cross-sectional data to explain longitudinal changes (See Table 1 above). However, newer iterations of these theories specify neurological processes underlying the increased coupling in older adulthood. Specifically, data-driven neuroimaging studies implicate age-related neural dedifferentiation, or reduced brain specialization (Cabeza, 2001; Cabeza et al., 2002; D. C. Park et al., 2004), as the mechanism underlying the increasing physical-cognitive function interrelatedness in older age. In particular, neuroimaging studies demonstrate brain regions primarily associated with speed of processing, attention, and reasoning also show activation in complex physical function tasks such as walking or maintaining balance (Hartley, Jonides, & Sylvester, 2011; Hill, Bohil, Lewis, & Neider, 2013; Rosano et al., 2008; Sleimen-Malkoun, Temprado, & Hong, 2014; van Iersel, Kessels, Bloem, Verbeek, & Olde Rikkert, 2008).

As a result of increased associations across adult development, the role age plays on the physical-cognitive function relationship is believed to be more complex compared to other stages of the lifespan and worth further examination. It is important to note, however, that the utility of chronological age may not be uniform across various demographic factors, particularly those associated with health disparities, such as race or socioeconomic status. For instance, there is

evidence that Black adults experience accelerated aging compared to non-Black adults (Levine & Crimmins, 2014), so the increased physical-cognitive function coupling may occur in earlier life stages, e.g., midlife, compared to White or other non-Black samples. Further complicating the age-physical-cognitive function relationship is the recent reliance on neurological studies to posit mechanisms underlying the increased coupling with age. This is particularly due to the cross-sectional nature of such studies and may violate the age convergence assumption, which states that cross-sectional and longitudinal age differences converge on a common trajectory (Sliwinski, Hoffman, & Hofer, 2010). Explicitly testing this assumption, particularly with refining theories of physical and cognitive aging, is critical because such violations can exaggerate or diminish true aging trajectories.

Age is often treated as a control (Alfaro-Acha et al., 2006), grouping (Al Snih et al., 2002; Sternäng et al., 2016), or moderator (Blankevoort et al., 2013) variable, but accumulating evidence suggests mere statistical control does not fully account for the complex effect of age on older adult function (Clouston et al., 2013; Sprague, Phillips, & Ross, in press). “Age” is an intuitive, easily-assessed proxy of diminished capacity across various metrics, but the within-group variability of older adults is greater than other ages (Sprague, Hyun, & Molenaar, 2017; Stone, Lin, Dannefer, & Kelley-Moore, 2017). That is, it is assumed that (chronological) age is a “cause” of poorer physical and cognitive function, but age may be a correlate, rather than cause of, decreased function. For instance, the average 85-year-old may perform poorer on grip strength compared to a 65-year-old, but there could be 85-year-olds who perform superior in comparison to 65-year-olds. Newer statistical models (described in Chapter 2) allow researchers to test whether the relationship between two variables is stable as a function of age, which can inform if age accounts for the increased coupling of physical and cognitive function in older adulthood.

Understanding age's impact on the physical-cognitive function relationship, especially in observational studies, can inform future interventions through identifying periods when an intervention in one domain are likeliest to transfer, or confer training-related benefits, to other untrained domains. For example, if the relationship magnitude between speed of processing and lower limb balance is greater for 85-year-olds compared to 65-year-olds, this suggests speed of processing interventions may confer more training-related benefits to lower limb balance for the oldest-old and not the young-old. Thoughtful considerations of age beyond a demographic covariate has the possibility of positively influencing future experimental designs through targeting those most likely to benefit from interventions.

Objective Physical and Cognitive Function: Experimental Findings

Physical activity interventions targeting complex physical functions such as balance are frequently implemented to improve cognitive function, but evidence is mixed for cognitive improvement (Kelly et al., 2014b). The cognitive domain most likely to be improved by physical activity interventions is reasoning (Colcombe & Kramer, 2003), but this is not consistent across studies. Although physical activity interventions are useful prevention tools for physical function declines, those unable to complete the intervention protocol are excluded from randomized controlled trials (RCTs). That is, one must have some functional independence in order to participate, so those with limited function (and at increased risk for accelerated decline/disability) are excluded (Barnes et al., 2013; Schättin, Arner, Gennaro, & de Bruin, 2016). This exclusion criterion may exist for several valid reasons, including (1) capturing pre-morbid function and whether the intervention delays or slows down the aging process, (2) ensuring participant safety during the intervention protocol, or (3) increasing the likelihood of retention, but this does limit the extant literature to those with some functional capacity. Furthermore, older adults at highest

risk for further physical function declines may also be less willing or able to engage in physical activity interventions because of previous falls (Jefferis et al., 2014; Klenk et al., 2015) or fear of falling (Murphy, Dubin, & Gill, 2003; Murphy, Williams, & Gill, 2002; Wijlhuizen, de Jong, & Hopman-Rock, 2007).

Because of the increasing relatedness of objective physical and cognitive function in older adulthood (Finkel et al., 2016) and ability to perform cognitive training independent of physical mobility (Milman, Atias, Weiss, Mirelman, & Hausdorff, 2014), cognitive interventions are proposed as an additional way to improve physical function. To date, nine randomized controlled trials have examined cognitive training effects on physical function outcomes in healthy older adults at immediate posttest (Azadian, Majlesi, & Jafarnejadgero, 2018; Azadian, Torbati, Kakhki, & Farahpour, 2016; K. Z. H. Li et al., 2010; Marusic et al., 2015; Ng et al., 2015; Smith-Ray et al., 2013; Smith-Ray, Makowski-Woidan, & Hughes, 2014; Verghese, Mahoney, Ambrose, Wang, & Holtzer, 2010) and across five years (Ross, Sprague, Phillips, O'Connor, & Dodson, 2018). Most of the interventions evaluated incorporate components of speed of processing training, also called Useful Field of View (UFOV) training and divided attention training (Ball, Edwards, & Ross, 2007). Such training is conceptualized as a *process-based* training since it aims to decrease the time it takes to complete cognitive processes and includes tasks such as attending to information. Only one study (Ross et al., 2018) evaluated training memory mnemonics (memory training) or pattern identification (reasoning training), types of *strategy-based* training since they aim to improve cognitive function through teaching strategies such as mnemonics or pattern recognition. In general, cognitive training, particularly ones targeting speed of processing, improved gait speed in older adults, with some evidence suggesting that those at greater risk for balance impairment received greater training benefits (Smith-Ray et al., 2014). While there is limited observational work examining the relationship between processing speed and physical function (Table 1), there is strong evidence that speed of processing cognitive training impacts physical function, at least through immediate posttest. Memory and reasoning training show promise as

preserving complex physical functions and are worth further consideration (Ross et al., 2018). Only one study to date has examined long-term transfer to complex lower limb function in a large sample of older adults and found that speed of processing, memory, and reasoning training attenuated declines across five years (Ross et al., 2018). The transfer to other measures of physical function such as grip strength were only examined in one study, where reasoning training conferred benefits five years posttest (Ross et al., 2018).

Dissertation

This dissertation will address three gaps within the literature using the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) trial ($N = 2,802$ older adults 65 – 94 years old). The ACTIVE trial was a four-arm randomized controlled trial that examined the effect of three cognitive training programs on cognitive and everyday function across 10 years. The goal of the first paper was to examine how the subjective physical-memory function relationships differ across the older adulthood continuum (Cosentino, Devanand, & Gurland, 2018). This study is an extension of prior work that evaluated the age-varying association between objective physical (i.e., grip strength and Turn 360) and cognitive (i.e., speed of processing, memory, and reasoning) function. The second project addressed two issues: (1) identify which cognitive training program(s) attenuate age-related declines in physical function (Marusic, Verghese, & Mahoney, 2018), and (2) elucidate potential psychosocial moderators of transfer in cognitive training (Simons et al., 2016). The dissertation studies addressed these burgeoning research areas through providing a more nuanced understanding of the complex interplay between physical and cognitive aging.

Study 1 was designed as a companion piece to a published manuscript (Sprague et al., in press). The primary aim of this study was to implement TVEM to examine the age-varying relationship between subjective physical and memory function in older adults. A supplemental

aim was to explore whether subjective or objective physical function better predicted subjective memory function. **Study 2** evaluated the 10-year effects of cognitive training programs on physical function, serving as a follow-up of a five-year cognitive training paper using intention-to-treat based analyses (Ross et al., 2018). The secondary aim of **Study 2** was to evaluate moderators of training effects to physical function outcomes, specifically cognitive self-efficacy, depressive symptoms, and subjective bodily pain, from cognitive training to physical function outcomes.

Chapter 2: Paper 1

Introduction

Older adulthood is marked by increasing interrelatedness of measures across a breadth of health domains, including objective physical and cognitive function (Clouston et al., 2013; Praetorius Björk et al., 2016; Sprague et al., in press; Sternäng et al., 2016). Recently, the critical role of age on these associations was highlighted (Clouston et al., 2013), indicating that some age-related processes (or merely age itself) underlie the increased coupling in objective function. The degree to which age plays a role on the interrelatedness of subjective physical and cognitive function across older adulthood, however, remain unknown. The overarching goals of this study were to examine age-related differences in the relationship between subjective physical and cognitive function in healthy older adults, as well as identify whether subjective or objective physical function were better at predicting subjective or objective memory. Understanding how age influences the subjective physical-cognitive function relationship can inform which statistical models are appropriate (e.g., should age be an interaction) as well as whether age has relatively more or less influence on subjective evaluations of physical and cognitive health.

Objective physical and cognitive function measures are generally more reliable, valid, and sensitive to change compared to subjective measures (Eekhof, De Bock, Schaapveld, & Springer, 2000), likely due in part to the larger influence of trait-like personality factors on subjective evaluations (Herreen & Zajac, 2018). Despite their utility, objective assessments are not always practical due to time constraints or discomfort with direct observations of everyday function (Quinn et al., 2011; Tangalos et al., 1996; Woodford & George, 2007). As such, it is important to understand and evaluate subjective assessments that correspond to their objective correlates; subjective measures are

easier to implement because they do not require training for test administration and are cost-effective (Feuring et al., 2014).

Understanding whether the relationship between subjective physical and cognitive function is stable across older adulthood is vital for at least two reasons. First, dramatic differences in relationship magnitude may indicate age periods that are more or less susceptible to psychological factors (e.g., subjective age, depressive symptoms). For example, if the relationship is substantially stronger for an 85-year-old than a 65-year-old, this may implicate some psychological factor as driving the increased coupling. It could be that positive perceptions of aging are responsible for positive subjective evaluations across a breadth of domains, thus strengthening the correlation between the two. However, other third variables such as the aging process itself may underlie such coupling. Secondly, comparing the relationship magnitudes against their objective analogs is critical, particularly if they do not behave similarly. If this is the case, it would suggest that subjective assessments may not be appropriate, particularly for certain older adults, and subjective measures should be obtained in conjunction with instead of in lieu of objective measures.

In addition to examining the age-varying relationship between subjective physical and memory function and the impact of depressive symptoms on the relationship strength across older adulthood, it is critical to examine whether subjective (or objective) physical function better predicts subjective (or objective) memory. Subjective physical and cognitive function measures are generally related to their objective analogs (Arvanitakis et al., 2018; Jackson et al., 2017; Langlois & Belleville, 2014), but evidence suggests the correspondence is weak (Burmester, Leatham, & Merrick, 2016; de Winter, Dodou, & Hancock, 2015). As a result, some argue that subjective evaluations may measure something other than pure physical or cognitive function such as depression severity

(Srisurapanont, Suttajit, Eurviriyankul, & Varnado, 2017) or susceptibility to psychological distress (Snitz et al., 2015). This argument is bolstered by evidence that subjective evaluations of physical and cognitive function are influenced by psychological factors such as depression (Bermeo-Ovalle, 2016; Feuring et al., 2014), anxiety (Bermeo-Ovalle, 2016), or stress (Bermeo-Ovalle, 2016). Although psychological factors influence objective physical and cognitive function as well (e.g., depressive symptoms; Geda et al., 2008; Thorpe et al., 2011), evidence suggests factors such as depression or mental well-being have greater influence on subjective performance (Cosentino et al., 2018; Gehring, Taphoorn, Sitskoorn, & Aaronson, 2015). As such, it is worth exploring whether subjective and objective physical function predicts subjective (and objective) memory function similarly.

One way to elucidate disruptions in relationship magnitudes is through time-varying effects modeling, or TVEM (Lanza, Vasilenko, & Russell, 2016). Previously, TVEM has been employed to examine differences in relationship magnitude across different ages (Sprague et al., in press). TVEM is superior to traditional age-interactive models because it relaxes the assumption of constant change (linearity assumption), which is present even in higher-order coefficient terms. Additionally, if there are dramatic changes in relationship magnitude, TVEM provides data-driven instead of researcher-imposed change points. Implementing TVEM in this context is appropriate because evidence suggests age may play a more complex role than can be captured as a covariate only in objective measures of physical and cognitive function (Clouston et al., 2013; Sprague et al., in press). If subjective measures truly reflect their objective correlates, the assumption is that age would also affect the relationship between subjective measures, and TVEM could assess whether this assumption is appropriate. Furthermore, comparing the subjective and objective physical function predictors in this framework could inform whether one assessment tool is consistently more related to an outcome or whether it is age-dependent. For example, it

may be that subjective physical function is better than objective physical function for predicting subjective memory function for older adults 65 to 75, and TVEM would be able to identify such periods if they exist.

Aims and Hypotheses

The goal of the current study is to examine the age-varying relationship between self-reported physical and memory function using two commonly-used questionnaires. Specifically, Aim 1 examined the age-varying relationships between subjective physical (predictor) and memory (outcome) function. We hypothesized a significant positive relationship, and this relationship would be strongest for the oldest-old (85+). A *post-hoc* aim was to examine whether controlling for depressive symptoms changed the relationship magnitude as depressive symptoms influence subjective ratings of health across a variety of domains (Cosentino et al., 2018).

Due to the poor concordance of subjective and objective measures of physical and cognitive function (Burmester et al., 2016; de Winter et al., 2015), Aim 2 considered whether subjective or objective physical function were better predictors of subjective or objective memory function. Specifically, these analyses answered whether: (1) subjective or objective physical function better predicted subjective memory function, and (2) subjective or objective physical function better predicted objective memory function.

Methods

Participant Characteristics

The study consisted of baseline data from the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE, ClinicalTrials.gov identifier NCT00298558) study (Jobe et al., 2001). ACTIVE was a multisite, single-blinded randomized controlled trial designed to evaluate the effects of three cognitive training interventions (speed of processing, memory, and

reasoning) on cognitive and health outcomes in healthy older adults. Individuals were excluded if they: (a) were less than 65 years old at screening, (b) scored less than 23 on the MMSE, (c) required extensive assistance with dressing, bathing, or personal hygiene, (d) had medical conditions likely predisposing participants to immediate functional decline (e.g., recent stroke) or likely to result in mortality within two years, (e) had severe sensory loss, (f) had communicative difficulties so severe participation would be problematic, (g) had recent cognitive training, or (h) were unavailable for testing during the study period. Participants missing any covariates were removed from analyses, leaving an analytic sample of 2,693. See Table 2 for baseline participant information.

Table 2. Participant Characteristics, Study 1, $N = 2,693$.

	<i>n</i> (%) or <i>M</i> (<i>SD</i>)	Range
Women	2,073 (75.64%)	–
White Race	1,969 (72.76%)	–
Education	13.53 (2.70)	4 – 20
Self-Reported General Health	3.37 (0.87)	1 – 5
Age	73.63 (5.91)	65 – 94
SF-36 Physical Function	68.95 (24.06)	0 – 100
MFQ Composite	0.003 (0.59)	-2.06 – 1.47
Turn 360	6.90 (2.02)	1.00 – 31.50
Memory Composite	0.02 (0.90)	-3.90 – 2.06
Depressive Symptoms	5.15 (5.11)	0 – 34

Note. SF-36 = MOS Short-Form-36 Item; MFQ = Memory Functioning Questionnaire. Depressive symptoms $n = 2,686$. Turn 360 $n = 2,631$. Memory composite $n = 2,678$.

Measures

Covariates. Gender (woman = 0, man = 1), race (non-White = 0, White = 1), years of education (0-20, indicating no formal education to a doctoral degree), and self-rated general health served as covariates. The mean age was 73.63 ($SD = 5.91$), 75.64% were women, and 72.76% were White. The average educational attainment was 13.53 years ($SD = 2.70$). Self-rated general health was a single-item question asking, “In general, would you say your health is

excellent, very good, good, fair, or poor?” with higher scores indicating better health ($M = 3.37$, $SD = 0.87$).

Self-reported physical function, the predictor of interest, was measured using the MOS Short-Form (SF-36) physical function subscale (Ware & Sherbourne, 1992). The subscale included 10 questions assessing whether the respondent’s health limits their ability to complete everyday activities in which they might engage. All items were rated such that 1 = yes, limited a lot; 2 = yes, limited a little; and 3 = no, not limited at all; higher total scores indicated better self-reported physical function. Sample items include, “Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports,” “moderate activities, such as moving a table, pushing a vacuum cleaner, bowling or playing golf,” “climbing one flight of stairs,” “walking one block,” or “bathing or dressing yourself.” Total subscale scores were standardized based on the SF-36 manual (Ware, Kosinski, & Keller, 1994) for a possible score of 0 to 100 ($M = 68.95$, $SD = 24.06$; Cronbach’s $\alpha = .895$).

Subjective memory function, the outcome of interest, was measured using a composite of the Memory Functioning Questionnaire (MFQ; Zelinski, Gilewski, & Thompson, 1980). The MFQ assesses how respondents would rate their memory problems generally, as well as identifying specific memory-related problems. Sample questions included, “How would you rate your memory in terms of the kinds of problems that you have,” “How often do personal dates (e.g., birthdays) present a problem for you,” “How often does losing the thread of thought in conversation present a problem for you,” “As you are reading a novel, how often do you have trouble remembering what you have read the paragraph just before the one you are currently reading,” “When you are reading a newspaper or magazine article, how often do you have trouble remembering what you have read three or four sentences before the one you are currently reading,” and “How often do

you make lists of things to do to remind yourself about things?” Scores were z-scored to create a composite and ranged from -2.06 to 1.47 ($M = < .01$, $SD = .59$; Cronbach's $\alpha = .877$). Higher scores indicated better self-reported memory function.

Depressive symptoms were assessed using the Center for Epidemiological Studies-Depression 12-item questionnaire (CES-D; Radloff, 1977). Participants were asked to describe how they felt or behaved during the prior week. Sample statements included, “I felt depressed;” “My sleep was restless;” “I enjoyed life;” or “I could not ‘get going’.” All items were scored on a 0 (never) to 3 (5 - 7 days) Likert scale. Items were summed for a summary score then mean centered for the analyses. The summary scores ranged from 0 to 34 (theoretical maximum = 36; $M = 5.15$, $SD = 5.11$); higher scores indicated more depressive symptoms.

Objective physical function, the other predictor of interest (subjective physical function being the other) for Aim 2, was assessed using Turn 360 (Steinhagen-Thiessen & Borchelt, 1999). Participants were instructed to turn in a complete circle as quickly and safely as possible. If necessary, walking aids were permitted. Scores were the average number of steps across two trials, and higher scores indicated worse performance ($M = 6.90$, $SD = 2.02$). The correlation between the first and second trial was $r = .857$.

Objective memory function, the other outcome of interest (subjective memory function being the other) for Aim 2, was assessed using a composite score of the Rey Auditory-Verbal Learning Test (Rey, 1941) and Hopkins Verbal Learning Test (Brandt, 1991). Both tests are standardized pencil-paper tasks that ask participants to recall lists of 14 words in seven trials or 12 words in three trials, respectively. Each trial recall period was two minutes. Higher scores indicated better performance ($M = 0.02$, $SD = 0.90$, Cronbach's $\alpha = .802$).

Analytic Strategy

Participants aged 85 years and older were collapsed due to insufficient coverage (i.e., power, $n = 81$ participants 86+). Data were analyzed using SAS 9.4 and the TVEM macro 3.1.1 (available from <https://methodology.psu.edu/downloads/tvem>). The TVEM model used the p -spline estimation method and adjusted for gender, race, education, and self-reported general health; covariates were chosen because they are associated with physical function and to allow for comparison against findings with objective physical and cognitive function (Sprague et al., in press). Significance was $p < .05$ for all models; estimates reflected standardized estimates. The final equation tested for Aim 1 was:

$$\text{Subjective Memory}_{ti} = \beta_0(t) + \beta_1(t) \text{SF-36 Physical Function}_{ti} + \beta_2 \text{Gender}_i + \beta_3 \text{White}_i + \beta_4 \text{Education}_i + \beta_5 \text{General Health}_i + \beta_6 \text{Depressive Symptoms}_i + e_{ti}$$

where t indicated any time-varying (i.e., age) variables, and all other variables were invariant. For Aim 2, the same general equations for the full model (i.e., covariates and depressive symptoms) applied. Specifically, all models tested for Aim 2 were:

$$\text{(Equation 1) Subjective Memory}_{ti} = \beta_0(t) + \beta_1(t) \text{SF-36 Physical Function}_{ti} + \beta_2 \text{Gender}_i + \beta_3 \text{White}_i + \beta_4 \text{Education}_i + \beta_5 \text{General Health}_i + \beta_6 \text{Depressive Symptoms}_i + e_{ti}$$

$$\text{(Equation 2) Subjective Memory}_{ti} = \beta_0(t) + \beta_1(t) \text{Turn 360}_{ti} + \beta_2 \text{Gender}_i + \beta_3 \text{White}_i + \beta_4 \text{Education}_i + \beta_5 \text{General Health}_i + \beta_6 \text{Depressive Symptoms}_i + e_{ti}$$

$$\text{(Equation 3) Objective Memory}_{ti} = \beta_0(t) + \beta_1(t) \text{SF-36 Physical Function}_{ti} + \beta_2 \text{Gender}_i + \beta_3 \text{White}_i + \beta_4 \text{Education}_i + \beta_5 \text{General Health}_i + \beta_6 \text{Depressive Symptoms}_i + e_{ti}$$

$$\text{(Equation 4) Objective Memory}_{ti} = \beta_0(t) + \beta_1(t) \text{Turn 360}_{ti} + \beta_2 \text{Gender}_i + \beta_3 \text{White}_i + \beta_4 \text{Education}_i + \beta_5 \text{General Health}_i + \beta_6 \text{Depressive Symptoms}_i + e_{ti}$$

where Equations 1 and 2 tested whether subjective or objective physical function better predicted subjective memory, and Equations 3 and 4 tested whether subjective or objective physical function better predicted objective memory.

Interpretation. Instead of traditional point estimates, the output for time-varying predictors are graphically represented in TVEM. The solid black line was the estimated coefficient. Positive relationships were represented by a confidence band above zero, and the relationship strength was indicated by the coefficient value. Higher absolute values indicated stronger relationships. The light grey band was the 95% confidence band. It is important to note the band width was not constrained to be equal across the time continuum. In traditional regression, the 95% confidence interval is assumed to be constant across all values. Instances where the 95% confidence band “fans out” were likely due to few data points. For instance, this dataset had fewer adults at the extreme end of the age range (at least 86 years old, $n = 81$), so the confidence band was wider. There were no specific p -values reported for the time-varying variables beyond the significance value set at $p < .05$. Although there were no output statistics to compare within-group differences, one way to ascertain if the relationship magnitude was similar for different ages is to compare the confidence bands. If the confidence band for one age was included in the confidence band of the second age, the relationship magnitude would be considered equal. Comparisons between subjective and objective results were qualitative and done by examining whether the relative influence of age across both models were similar. For example, if the relationship between subjective physical and cognitive function was significantly higher for those 85+, there would be a qualitative evaluation of the objective relationship to examine whether a similar increase in relationship magnitude was present in the same age group.

Power. Current statistical packages cannot estimate power for TVEM. However, the number of participants per age (e.g., 66, 67) ranged from 43 to 189. Additionally, the power analysis for a multiple linear regression with six parameters (covariates, subjective physical function, and age) revealed that with 80% power and an effect size of .103 (adjusted R^2 obtained from regression), a minimum sample size of 131 was necessary. Because TVEM relies on nearby ages to obtain its coefficient curve, there was sufficient power for this analysis.

Results

Aim 1

The null model demonstrated that better SF-36 physical function predicted significantly better MFQ scores across all ages and was stable in magnitude (Figure 1a). Adding covariates did not appreciably impact the relationship stability except for adults 65-66, where the relationship became nonsignificant (Figure 1b). For example, the standardized β for a 70-year old ($\beta = .004$, 95% CI = .003, .006) did not significantly differ from that of an 85-year old ($\beta = .005$, 95% CI = .003, .008). White race ($\beta = .07$, $p = .005$) and higher general health ($\beta = .10$, $p < .001$) were associated with higher MFQ scores. Gender ($\beta = .05$, $p = .08$) and education ($\beta = .004$, $p = .32$) did not significantly predict MFQ scores. After including depressive symptoms as an age-invariant covariate ($\beta = -.026$, $p < .001$), there was no difference in the coefficient curve (Figure 1c). Compared to the null model, the fully-adjusted model (demographics and CES-D) demonstrated significantly different relationship strengths in those aged 67 to 75. That is, the relationship between subjective physical and memory function was significant after adjusting for all covariates but was significantly smaller compared to the null model (see Appendix A for graphical illustration).

Aim 2

The bivariate correlation between the subjective measures and their objective correlates were weak. The correlation between subjective and objective physical function was $r = -.324$, indicating that better subjective physical function was associated with fewer steps (i.e., better performance). The correlation between subjective and objective memory function was $r = .253$, indicating that better subjective memory function was associated with better memory composite scores.

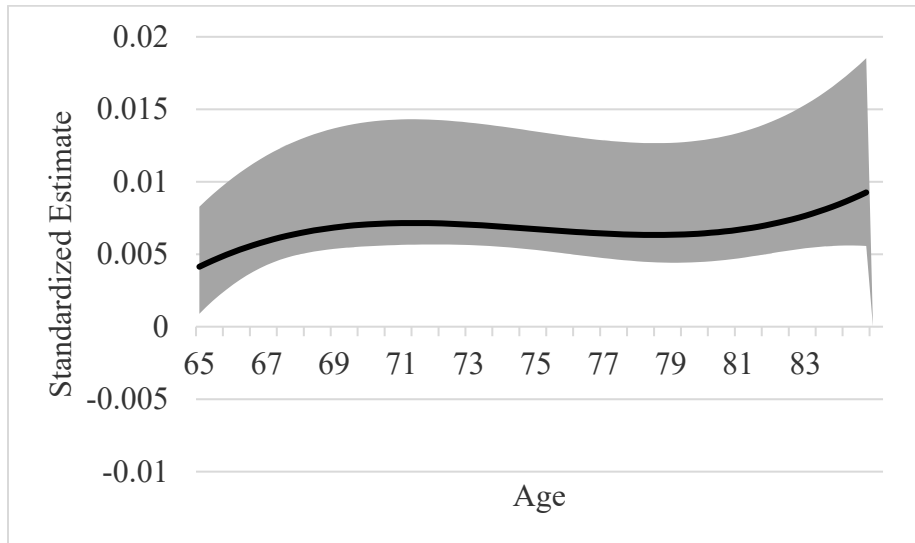
Subjective memory as outcome. The relationship between subjective physical function and subjective memory was small but significant and positive across adults 66 – 85 ($p < .05$) where better subjective physical function predicted better subjective memory function. In comparison, the relationship between objective physical function and subjective memory was nonsignificant across all ages. Although this indicated the SF-36 physical function subscale was a better predictor of subjective memory across older adults 66 to 85 (Figure 2), the confidence intervals overlapped with objective physical function across all ages. That is, although the SF-36 physical function subscale was a significant predictor, it was not significantly different than objective physical function predicting subjective memory ($p > .05$).

Objective memory as outcome. The relationship between subjective physical function and objective memory was nonsignificant for 65 to 66 year-olds, as well as 71- to 82-year olds ($p > .05$). For older adults 66-71 and 82+, there was a weak positive relationship indicating that better subjective physical function predicted better objective memory ($p < .05$). In comparison, there was a significant negative relationship between objective physical and memory function in adults 67 – 85 ($p < .05$) indicating that better Turn 360 predicted significantly better objective memory. Coupled with the substantially larger absolute value of the coefficient curve across all ages, this

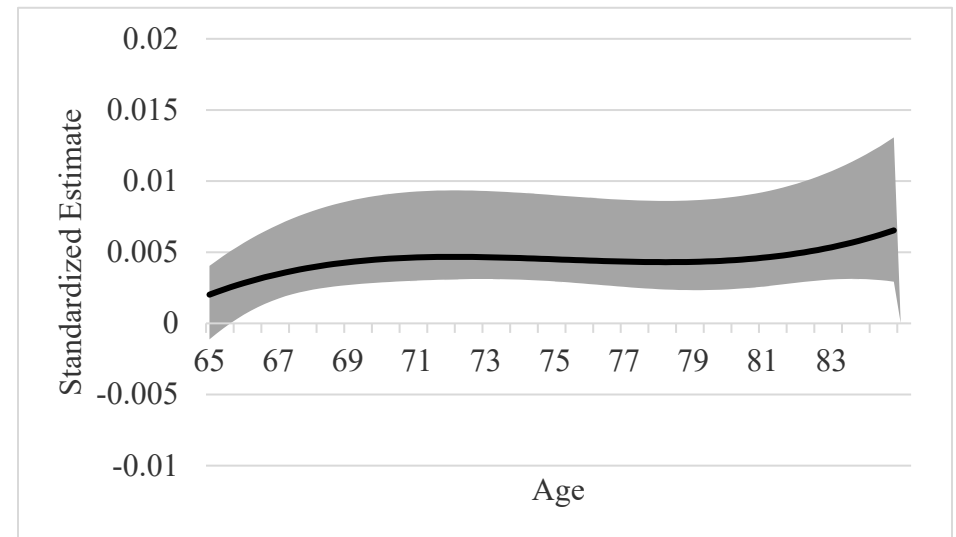
suggests Turn 360 was a better predictor of objective memory across adults 67 to 85 after controlling for demographic characteristics and depressive symptoms (Figure 2).

Figure 1. Standardized Coefficient Curve of SF-36 Physical Function on MFQ.

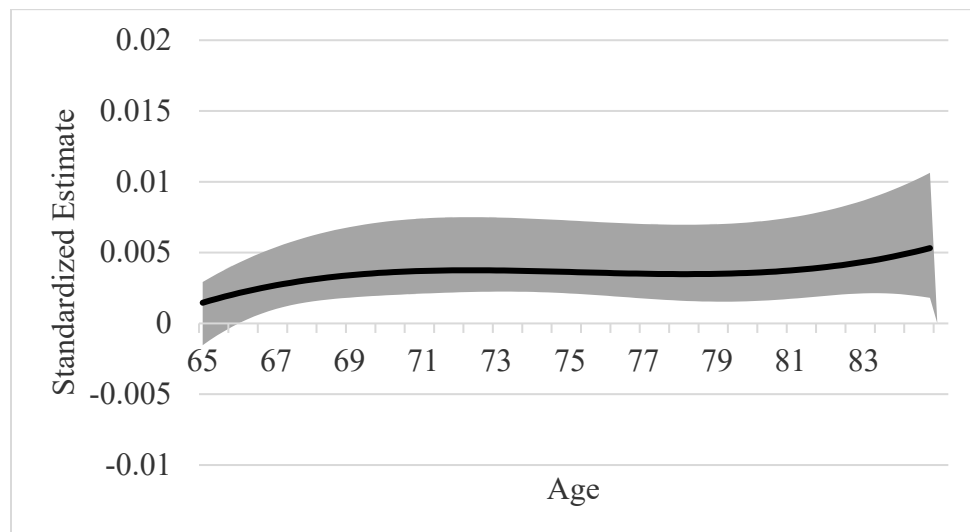
a.



b.



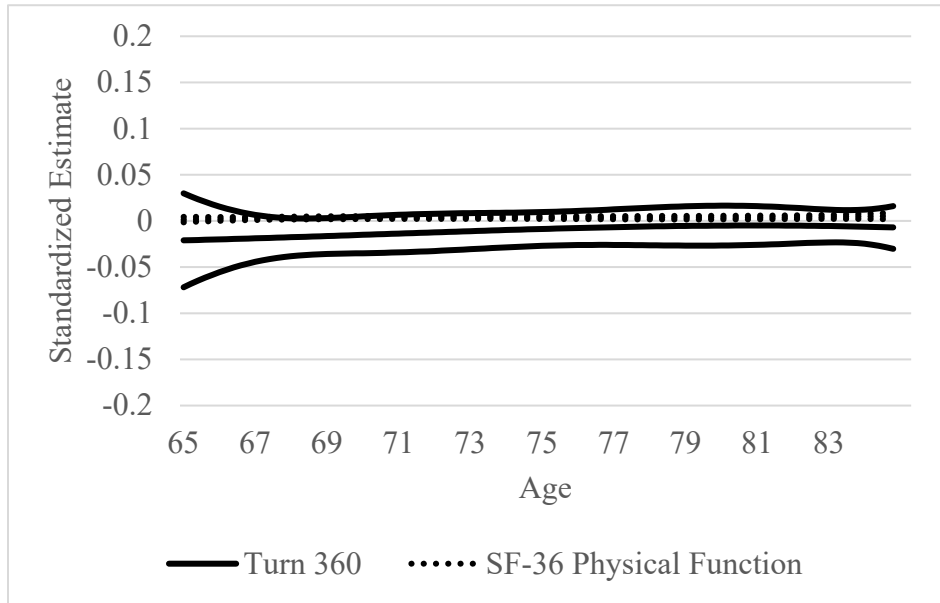
c.



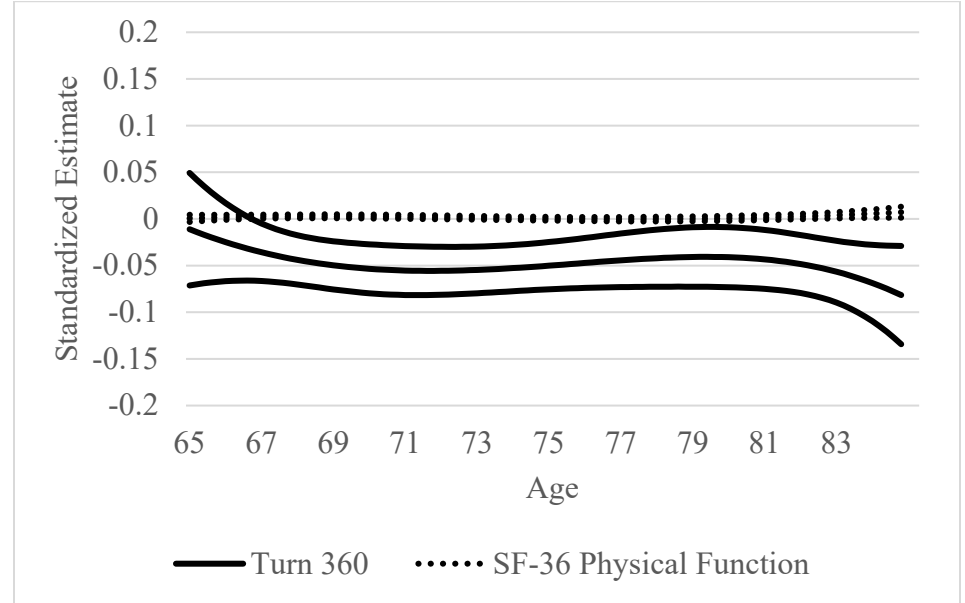
Note. SF-36 = Short Form-36-Item Physical Function Subscale; MFQ = Memory Functioning Questionnaire. 1a = Unconditional model; 1b = Covariates (gender, race, education, general health) without depressive symptoms; 1c = Covariates (gender, race, education, general health) + depressive symptoms. Relationships are nonsignificant ($p > .05$) when grey or black lines intersect x-axis. Grey lines = 95% confidence interval; solid line = point estimate. See Appendix A for a direct comparison of 1a vs. 1c.

Figure 2. Standardized Coefficient Curve of (a) Physical Function on MFQ and (b) Memory Composite.

a.



b.



Note. MFQ = Memory Functioning Questionnaire. Relationships are nonsignificant ($p > .05$) when lines intersect x-axis. Larger absolute values indicate stronger absolute magnitude. Higher Turn 360 scores indicate worse performance.

Discussion

The goals of the current study were to evaluate the age-varying association between subjective physical and memory function in older adulthood and explore whether subjective or objective physical function was a better predictor of subjective or objective memory across this period. The current results demonstrated that the relationship between subjective physical and memory function was significant and stable across older adulthood (i.e., 66+), even after controlling for depressive symptoms. Furthermore, while subjective physical function significantly predicted subjective memory (and objective physical function did not), it was not a significantly better predictor. When examining objective memory as the outcome, objective physical function was a significantly better predictor than subjective physical function for adults 67 to 85 years old. This is only the second study, to our knowledge, to evaluate the relationship between subjective physical and cognitive function in older adults (Cosentino et al., 2018), and it was the first to examine this relationship as a function of continuous age instead of a covariate only. These results are in line with prior work establishing a relationship between better subjective physical and memory function (Cosentino et al., 2018). Overall, the physical-cognitive function relationship extends to subjective evaluations and warrants future study.

Our hypothesis that the relationship magnitude would be significantly higher for the oldest-old was not supported, indicating that the influence of age on the relationship between subjective physical and memory function is such that including it as a covariate should be sufficient. That is, no higher-order age parameters such as age^2 are necessary in such models. However, there are instances where there are higher order age effects present. In particular, the relationship between grip strength and speed of processing, memory, and reasoning was

significantly stronger with increased age (Sprague et al., in press). The current evidence suggests this may not be true for subjective physical and memory function.

Interestingly, the inclusion of depressive symptoms in our *post-hoc* Aim 1 analysis did not impact the relationship between subjective physical function and memory, although it did significantly predict subjective memory scores. This suggests that while depressive symptoms are related to subjective memory evaluations, the relationship between subjective physical function and memory is largely independent of depressive symptomology in healthy samples. Importantly, this was a largely healthy sample with low reported depressive symptoms, so it remains unclear how this relationship would occur in clinically depressed older adults. However, this pattern of results may be more indicative of a generally healthy older adult population.

Aim 2 demonstrated that while subjective physical function significantly predicted subjective memory function, it was not significantly different than when objective physical function was a predictor. That is, while subjective physical and memory function were related, the relationship was relatively weak and may not be practically significant. When objective memory was the outcome, objective physical function was a significantly better predictor for older adults 67 to 85. This suggests the relationship between objective measures of physical and memory function were stronger than subjective physical and memory function. While the current study cannot elucidate why this is true, it may be that the subjective measures did not adequately reflect their objective analogs as evidenced by the weak correlations. Subjective measures with greater correspondence to their objective analogs may be significantly better at predicting subjective outcomes. Further development of subjective measures that better correlate with their hypothesized objective analogs is warranted.

There are a few notable limitations. These results can only be generalized to healthy older adults without dementia ($MMSE \geq 23$), so it remains unclear how the age-varying relationship would appear to those with dementia or are otherwise in poor health. Additionally, the data were collected in the late 1990s. Because there is a noted trend of cohort differences in physical, cognitive, and psychosocial factors (K. Christensen et al., 2013; Gerstorf et al., 2015), it is unknown how these relationships would appear in more recent cohorts. TVEM could be implemented to examine the resultant coefficient curves across different cohorts; this may be of interest if one were interested in evaluating the impact of both age and cohort on either subjective or objective performance.

A second limitation is that we were unable to examine many of the psychological factors believed to impact subjective evaluations. Including depressive symptoms, a known correlate of subjective function (Carrasco et al., 2017), did not affect the relationship significance or age-varying pattern, highlighting the fact that, in this sample, depressive symptoms were related to but not a proxy of subjective function. This may be partly due to the health of the sample; the average score on the CES-D ($M = 5.15$) was well below the recommended cutoff for probable clinical depression (Vilagut, Forero, Barbaglia, & Alonso, 2016). Samples with greater depressive symptoms may demonstrate that depressive symptoms attenuate subjective relationships, and future research should replicate this finding in those with more depressive symptoms. Future work is needed to explore the age-varying relationships between such factors- such as well-being (Benito-León, Mitchell, Vega, & Bermejo-Pareja, 2010)- and subjective physical and cognitive evaluations to identify ages that may be particularly vulnerable (or resilient) and modifiable to promote optimal aging. Emerging evidence suggests that psychological factors such as subjective age can be experimentally manipulated and manifest improvements in objective physical function (Stephan, Chalabaev, Kotter-

Gruhn, & Jaconelli, 2013). It would be fair to assume that such manipulations to subjective age would impact subjective evaluations maybe more than it impacts objective function. Lastly, we had to collapse our analysis of adults 85+ for interpretability, so trends cannot be extrapolated beyond that age. The data suggest that the relationship magnitude may be significantly stronger with increased age, but we were unable to reliably draw this conclusion because of limited power. Future work should replicate this with a larger sample of the oldest-old to examine whether these trends are similar across the older adulthood continuum.

Despite the limitations, there were strengths of this study. Ours was only the second study to compare a significant association between subjective physical and memory function in older adults (Cosentino et al., 2018), suggesting that subjective evaluations affect a breadth of health measures. Lastly, these results demonstrated the utility in implementing TVEM to test assumptions about the role of age on older adult health. If the data lend themselves to this analysis, it is superior to age-moderation models because of its flexibility in exploring higher-order or nonparametric relationships. It may not be appropriate in all instances, but TVEM is an easy-to-use exploratory tool to better understand the aging process. Future work should continue examining subjective measures of physical and cognitive function in healthy older adults (ideally, subjective evaluations of different domains of physical and cognitive health such as grip strength or reasoning), evaluate whether this relationship is similar in newer cohorts of older adults, and consider how these relationships unfold over time.

Chapter 3: Paper 2

Introduction

Physical function is critical for maintaining independence in older adulthood (Cesari et al., 2004), and its degradations are associated with myriad poor health measures. For instance, poorer physical function is associated with loss of functional independence (Cesari et al., 2004), increased risk of hospitalization (Cesari et al., 2004), disability (Buchman et al., 2016), poorer cognitive function (Montero-Odasso et al., in press; Robitaille, Piccinin, Hofer, Johansson, & Muniz-Terrera, in press; Spedden, Malling, Andersen, & Jensen, 2017), and mortality (Al Snih et al., 2002; Cesari et al., 2004; Nofuji et al., 2016; Sabia et al., 2014). Previous interventions targeting physical function were aimed at rehabilitating specialized samples such as those with Parkinson's disease or previous stroke(s) (Pichierri, Wolf, Murer, & de Bruin, 2011), but there is increasing emphasis on preventing or delaying decline in functionally independent, healthy older adults rather than rehabilitating lost abilities. Emphasizing impairment prevention is important because it may reduce costly downstream effects by reducing outcomes such as falls (Mangani et al., 2008), everyday function disability (Gobbens & van Assen, 2014), and hospital length of stay (van Aalst, Oosterhof, Nijhuis-van der Sanden, & Schreurs, 2014).

The most common behavioral intervention for physical function is exercise, particularly exercises emphasizing balance (Brach, Simonsick, Kritchevsky, Yaffe, & Newman, 2004; Chou, Hwang, & Wu, 2012). However, individual characteristics such as obesity (Buford et al., 2012), age (Layne et al., 2017), or experiencing a barrier to physical activity (Bethancourt, Rosenberg, Beatty, & Arteburn, 2014) may affect who benefits from exercise programs, leading some to argue that exercise may be necessary but insufficient to prevent physical function decline or disability (Keysor & Brembs, 2011). Additionally, there are barriers to exercise engagement that are necessary to address. Although older adults with poor physical function can participate in exercise interventions (de Labra, Guimaraes-Pinheiro, Maseda, Lorenzo, & Millán-Calenti, 2015; Helbostad, Sletvold, & Moe-Nilssen, 2004; Peel, Utsey, & MacGregor, 1999) and

recognize its health benefits (Tuvemo Johnson, Martin, Anens, Johansson, & Hellström, 2018), they may be disinclined to participate due to barriers such as perceived or previous falling or injury (Jefferis et al., 2014; Klenk et al., 2015; Murphy et al., 2003; Murphy et al., 2002) (See Chapter 4 for an in-depth discussion).

This is problematic as fear of falls (Choi, Jeon, & Cho, 2017), previous falls (Kronzer et al., 2016), and decreased exercise (Paterson & Warburton, 2010) are risk factors for subsequent functional decline, leading to a cycle of excess disability. Additionally, exercise detraining, or loss in training-related gains resulting from exercise cessation, may limit any long-term gains in physical function (Henderson et al., 2018). Significant detraining effects on cardiorespiratory fitness occur weeks post-cessation (Coyle et al., 1984; Madsen, Pedersen, Djurhuus, & Klitgaard, 1993; Mujika & Padilla, 2000; Neuffer, 1989), suggesting that continual engagement is necessary to maintain training gains.

Because older adults tend to cease engagement within one year of exercise intervention (Christie et al., 2017; Henderson et al., 2018), non-exercise interventions with long-term improvements that do not require continual engagement hold potential. Such intervention could also be used to reach those who are severely physically limited, may not likely adhere to exercise interventions (Picorelli, Pereira, Pererira, Felício, & Sherrington, 2014), be afraid, or unable to participate in such interventions.

Although exercise is the most promising avenue for physical function maintenance (Marusic & Grosprêtre, 2018), cognitive training impacts physical function in older adults (Azadian et al., 2018; Azadian et al., 2016; K. Z. H. Li et al., 2010; Marusic et al., 2015; Marusic et al., 2018; Ng et al., 2015; Ross et al., 2018; Smith-Ray et al., 2013; Smith-Ray, Irmiter, & Boulter, 2016; Smith-Ray et al., 2014; Verghese et al., 2010). Generally, speed of processing training transfers to attenuations in complex lower limb function such as gait speed, but recent work extends this to specific cognitive domain training, as well as both gross and fine motor upper limb function across five years (Ross et al., 2018). Only one study has evaluated the impact of strategy-based interventions such as teaching memory mnemonics or pattern recognition on physical function (Ross et al., 2018). The mechanisms underlying transfer have not

been empirically tested, but neuroimaging studies suggest the relationship between physical and cognitive function occurs in part from neural dedifferentiation, or the age-related reduced specialization of brain regions (D. C. Park et al., 2004; Sleimen-Malkoun et al., 2014). Differentiation may reflect compensation for reduced neural resources (Cabeza et al., 2002), so cognitive training may capitalize on this compensatory process through improving brain regions associated with physical and cognitive function. For example, brain regions associated primarily with speed of processing and reasoning, e.g., dorsolateral prefrontal cortex, are activated when older adults walk (Hartley et al., 2011; Hill et al., 2013; Rosano et al., 2008), indicating that these different domains are related, even when speed of processing or other cognitive tasks are not explicitly performed. Indeed, complex physical functions such as walking require speed of processing to rapidly and continually allocate motor and cognitive resources while moving through space to react to visuospatial demands (van Iersel et al., 2008). These associations are more pronounced in older adults than younger adults (Spedden et al., 2017), suggesting increased coupling (possibly through dedifferentiation) between physical and cognitive function with age. Taken together, this suggests cognitive training, particularly those training speed of processing (also called Useful Field of View or UFOV, processing speed, or speed of processing/divided attention) and reasoning training, may confer benefits to physical function, especially complex lower limb function. It is notable that memory training does have promise for attenuating declines in physical function, but only one study has implemented strategy-based memory training (Ross et al., 2018).

Despite emerging, consistent evidence of transfer from cognitive *training* to physical function (Azadian et al., 2018; Azadian et al., 2016; K. Z. H. Li et al., 2010; Marusic et al., 2015; Marusic et al., 2018; Ng et al., 2015; Ross et al., 2018; Smith-Ray et al., 2013; Smith-Ray et al., 2016; Smith-Ray et al., 2014; Verghese et al., 2010), there

are remaining gaps in the extant literature. A major limitation is that all but one trial (Ross et al., 2018) had small (e.g., < 100 participants) who were selected because they were at risk of future falls. While the ability to demonstrate transfer with such few, vulnerable individuals highlights how effective training can be for risky populations, the tradeoff is that the generalizability to a wider community-dwelling sample who may not be at risk is unknown. Additionally, only one study to date assessed long-term physical function, suggesting attenuations up to five years post-training (Ross et al., 2018). Speed of processing, maintained or improved everyday function measures such as dementia risk (Edwards et al., 2017) and self-reported instrumental activities of daily living (along with reasoning training) (Rebok et al., 2014), as well as reduced risk of driving cessation (Ross, Freed, Edwards, Phillips, & Ball, 2017) 10 years post-training. Therefore, training effects may extend to physical function across at least 10 years.

Psychosocial Moderators of Training Gains

Psychosocial factors such as higher self-efficacy and fewer depressive symptoms have a well-documented relationship to better physical function (Briggs, Carey, Kenney, & Kennelly, 2018; Demakakos et al., 2013; dos Santos Gomes et al., 2014; Helmes & Klinger, 2017; Lee, 2015; Lemke, Wendorff, Mieth, Buhl, & Linnemann, 2000; Lever-van Milligen, Lamers, Smit, & Penninx, 2017; M. Li & Dong, 2017; Lim & Noh, 2015; McAuley, Szabo, Gothe, & Olson, 2011; Raji, Ostir, Markides, & Goodwin, 2002; Sanders, Bremmer, Deeg, & Beekman, 2012; Santos, Fernandes, Reis, Coqueiro, & Rocha, 2012; but see Verghese, Wang, Allai, Holtzer, & Ayers, 2016). The directionality of association between these psychosocial factors (i.e., self-efficacy and depressive symptoms) and physical function are unclear (Gayman, Turner, & Cui, 2008; Sanders et al., 2012), but evidence suggests psychosocial factors indirectly impact later physical function through decreased exercise (A. J. Brown et al., 2017; Penninx, Leveille, Ferrucci, van Eijk, & Guralnik, 1999; Perrino, Mason, Brown, & Szapocznik, 2010). That is, if individuals believe they can accomplish some task or have few depressive symptoms, they are likelier to engage in exercise, which is associated with physical function (Buford, Anton,

Clark, Higgins, & Cooke, 2014). Behavioral depression interventions such as cognitive behavioral therapy or aerobic exercise have been shown to improve physical function (Callahan et al., 2005; Penninx et al., 2002), so other interventions that have far transfer (i.e., training-related improvement in untrained domains such as improvements in physical function from non-physical interventions) to psychosocial factors such as self-efficacy and depression may have indirect effects on physical function.

Not only are self-efficacy and depressive symptoms related to physical function, but they are also associated with cognitive function (Anderson, Cochrane, Golding, & Nowicki, 2018; Brewster, Peterson, Roker, Ellis, & Edwards, 2017; B. R. Brown & Granick, 1983; Geda et al., 2008; Neupert & Allaire, 2012; O'Shea et al., 2016; Wilson et al., 2002; Zahodne, Nowinski, Gershon, & Manly, 2014; Zahodne, Watson, Seehra, & Martinez, 2018; Årdal & Hammar, 2011). Similar to physical function, the directionality between these psychosocial factors and cognitive function are unclear (Perrino, Mason, Brown, Spokane, & Szapocznik, 2008; Zahodne et al., 2018), but some argue that such factors may contribute to one's cognitive reserve (Ganguli, 2009; Zahodne et al., 2014) and could be responsible for downstream effects such as perseverance in challenging tasks (Bandura, 1989), e.g., cognitive training (Zahodne et al., 2015). In turn, experimental work demonstrates engagement in challenging tasks is associated with better cognitive function (D. C. Park et al., 2014), and better cognitive function is associated with higher positive psychosocial measures (Allerhand, Gale, & Deary, 2014) and fewer depressive symptoms (Gale, Allerhand, & Deary, 2012). The bidirectional associations indicates there are multiple avenues for intervention in older adults. Evidence suggests cognitive training particularly speed of processing, can increase cognitive self-efficacy (Wolinsky et al., 2010) and reduce depressive symptoms (Nouchi, Saito, Nouchi, & Kawashima, 2016; Wolinsky, Mahncke, et al., 2009; Wolinsky, Vander Weg, Howren, Jones, & Dotson, 2015; Wolinsky, Vander Weg, et al., 2009) in older adults, and such improvements are present even five years after the training program. It remains unclear why speed of processing training specifically confers such

psychosocial benefits when other cognitive training (i.e., memory or reasoning) do not consistently demonstrate similar benefits. Wolinsky and colleagues (2009) posit that speed of processing training may indirectly affect such factors through positively impacting quality of life (Wolinsky, Unverzagt, Smith, Jones, Stoddard, et al., 2006; Wolinsky, Unverzagt, Smith, Jones, Wright, et al., 2006), driving behaviors (Ross et al., 2016; Ross, Freed, Phillips, Edwards, & Ball, 2017)- a known predictor of depressive symptoms-, everyday function (Edwards et al., 2002; Edwards et al., 2005) and directly through training-related changes in brain regions related to mood and reward. That is, there may be an interaction between speed of processing training and psychosocial factors that enhance or diminish training-related gains in physical function.

Bodily Pain and Physical Function

In addition to psychosocial factors, physical health markers such as bodily pain influence physical function in older adults (Aghdam, Kolahi, Hasankhani, Behshid, & Varmaziar, 2013; Hennig et al., 2013; Kwan, Lin, Chen, Close, & Lord, 2011; Lord, Murray, Chapman, Munro, & Tiedemann, 2002; Tiedemann, Sherrington, & Lord, 2007). In fact, disease-related pain, especially arthritis, may prevent participants from completing specific physical function tests if the pain location is associated with the relevant task. For instance, those with arthritis or reported wrist pain in the previous three months may be excluded from completing the grip strength task (Jobe et al., 2001). As a result, it is difficult to ascertain the degree to which these measures are related over time. Preliminary evidence suggests a possible longitudinal correspondence between baseline bodily pain and changes in subjective physical function (Karayannis, Sturgeon, Chih-Kao, Cooley, & Mackey, 2017; Patel et al., 2016), but the longitudinal relationship to objective physical function is unknown (Estévez-López, 2017). Because evidence suggests cognitive *training* reduces age-related decline in physical function (K. Z. H. Li et al., 2010; Marusic & Grosprêtre, 2018; Marusic et al., 2018; Ross et al., 2018; Smith-Ray et al., 2013; Smith-Ray et al., 2014; Verghese et

al., 2010), it may be true that training-related changes differ based on subjective bodily pain. To date, however, this has not been empirically evaluated.

Aims and Hypotheses

The first aim of this study was to examine the 10-year effects of three cognitive training programs (speed of processing, memory, or reasoning) on physical function (grip strength, Digit Symbol Copy, and Turn 360) in a large, community-dwelling sample of older adults. Similar to prior work across five years (Ross et al., 2018), we hypothesized that the age-related declines in Digit Symbol Copy and Turn 360 would be attenuated in all training groups, and the reasoning training would continue to be associated with attenuation in all three measures (Ross et al., 2018). The second aim was to identify which baseline moderators (i.e., cognitive self-efficacy, depressive symptoms, or subjective bodily pain) impacted training effects. We hypothesized that those with better baseline cognitive self-efficacy, fewer depressive symptoms, and less bodily pain would be associated with greater attenuations in physical function decline across 10 years.

Methods

Participants

This study used secondary data from the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) study, a multi-site, randomized clinical trial investigating the effect of three cognitive training programs on health and functional outcomes across a 10-year period. Physical function was an *a priori* identified secondary outcome of the ACTIVE trial. Inclusion criteria were: age 65 or older, visual acuity $\geq 20/50$, Mini-Mental State Examination score ≥ 23 , no health conditions associated with cognitive impairment, verbal communication skills, no difficulties performing basic activities of daily living, and no recent participation in cognitive training. Eligible participants ($N = 2,802$) completed a baseline assessment and then randomly

assigned to either a cognitive training or control condition. Participants were randomized to speed of processing, memory, or reasoning training or the no-contact control arm. At baseline, participants were an average of 73.60 years old ($SD = 5.90$), were predominantly women ($n = 2,121$; 75.83%), reported an average of 13.5 years of education ($SD = 2.70$), and were predominantly White ($n = 2,051$, 73.33%). Sample descriptive statistics for each arm are presented in Table 3. Extensive details about ACTIVE can be found elsewhere (Jobe et al., 2001), ClinicalTrials.gov Identifier NCT00298558.

Table 3. Demographics by Study Arm, Study 2 ($N = 2,802$ for ITT Analysis).

Variable	No-contact control ($n = 698$)	Speed of processing training ($n = 702$)	Memory training ($n = 703$)	Reasoning training ($n = 694$)
Grip strength, M (SD)	24.03 (8.07)	23.98 (8.34)	24.00 (8.37)	24.37 (8.44)
Digit Symbol Copy, M (SD)	108.09 (73.18)	102.53 (30.28)	104.64 (34.87)	104.82 (34.22)
Turn 360, M (SD)	6.95 (2.11)	6.90 (1.97)	6.89 (1.99)	7.01 (2.26)
Age, M (SD)	74.05 (6.05)	73.42 (5.78)	73.53 (6.02)	73.56 (5.77)
Men, n (%)	184 (26.36%)	164 (23.36%)	166 (23.61%)	162 (23.34%)
White, n (%)	503 (72.06%)	523 (74.50%)	524 (74.54%)	501 (72.19%)
Education, M (SD)	13.37 (2.71)	13.65 (2.68)	13.59 (2.73)	13.51 (2.68)
SF-36 Physical Function	74.05 (6.05)	73.42 (5.78)	73.53 (6.02)	73.56 (5.77)
Cognitive Self-Efficacy (Raw Score)	30.00 (4.50)	29.98 (4.43)	30.00 (4.55)	29.94 (4.53)
Depressive Symptoms (Raw Score)	5.06 (4.87)	5.11 (5.00)	4.99 (5.32)	5.54 (5.37)
SF-36 Bodily Pain (Scaled Score)	26.03 (21.22)	24.69 (20.45)	25.20 (20.98)	20.98 (21.13)

Note. Chi-square and ANOVAs revealed that study arms did not differ on any variables at baseline. SF-36 is the MOS Short-Form 36-Item scale.

Study Design and Procedures

Baseline assessments for the ACTIVE study were conducted between 1998 and 1999. Prior to randomization, baseline cognitive, physical function, lifestyle factors, and health assessments were conducted. The initial cognitive training interventions consisted of 10 60-to-75-minute sessions administered over six weeks. Certified trainers conducted the training using

standardized procedures in groups of three or four participants. All training condition participants received individualized feedback after each block of trials and experienced the same amount of social contact with trainers. Follow-up assessments were conducted approximately two months (posttest), one year, two years, three years, five years, and 10 years after baseline testing. Grip strength and Turn 360 were not assessed at the immediate posttest or one-year post-intervention. Compliant training arm participants (i.e., completed at least eight of ten training sessions) were further randomized to either receive four booster sessions prior to assessments in years one and three (totaling eight possible booster sessions) or receive no booster training.

Speed of processing training arm. This was process-, computer-based training that focused on improving the display speeds at which participants could correctly identify increasingly complex displays of visual information. In the literature, this training is also called UFOV or divided attention training. The exercises emphasized speed of processing (identifying stimuli), divided attention, selective attention (divided attention and inhibition of irrelevant stimuli), and selective attention with a central discrimination task (Jobe et al., 2001). For each task, the score was the shortest presentation time needed to perform the task correctly 75% of the time. For example, a participant was presented a central stimulus with a peripheral stimulus. After the image disappeared from the screen, the participant would be asked what the central stimulus was (car or truck) as well as where the peripheral distractor was located. Training was completed in a group setting.

Memory training arm. This was pencil-and-paper training designed to mnemonic strategies focused on verbal episodic memory. This included practice and feedback with organizing materials into meaningful categories that would promote transfer to everyday function. Example categories include remembering lists of errands or grocery shopping (Jobe et al.,

2001). The tasks were adapted over the intervention trial but not explicitly documented.

Participants practiced in both individual and group exercises.

Reasoning training arm. This was pencil-and-paper training that focused on improving problem solving and included practice and feedback on identifying patterns or sequences. For example, training activities included finding the pattern in a series of repeating letters or identifying dosage patterns of medications (Jobe et al., 2001). There were two levels of reasoning training provided for participants that differed in three ways: (1) task difficulty/complexity in the early training sessions, (2) pacing and instructional time on tasks, and (3) emphasis on the modeling and demonstration of strategy use. Reasoning training occurred in both individual and group settings.

No-contact control arm. Participants randomized to the no-contact control arm came to the study site for all assessments, and no intervention was conducted.

Measures

Physical function. *Grip strength*, a measure of gross upper limb muscle strength, was assessed using the Jamar hydraulic hand dynamometer (Lafayette Instruments). Handheld dynamometers have been shown to be reliable and valid instruments in older adults, even in those with cognitive impairment (Al Snih et al., 2002; Syddall, Cooper, Martin, Briggs, & Aihie Sayer, 2003). Participants were instructed to squeeze as hard as they comfortably could in their dominant hand, and the assessment was completed twice. If participants reported recent worsening of pain or arthritis in their wrists, had tendonitis, or had hand or arm surgery during the prior three months, they did not complete the standardized grip strength protocol. Scores indicated the output strength in kilograms rounded to the nearest whole number and were averaged across the two trials to yield a composite measure of grip strength. Scores were then baseline-adjusted by

subtracting the baseline mean and dividing by the baseline standard deviation. Higher scores indicated greater grip strength.

Digit Symbol Copy (Wechsler, 1981) was used as a measure of fine visuomotor coordination and motor speed (Kreiner & Ryan, 2001). After successfully completing four practice items, participants copied 93 symbols as quickly as possible into empty boxes below the symbols. Scores indicated the time to complete the task. Scores were then baseline-adjusted by subtracting the baseline mean and dividing by the baseline standard deviation. Higher scores indicated worse performance.

Turn 360, a measure of complex lower limb function, was assessed (Steinhagen-Thiessen & Borchelt, 1999). Participants were instructed to turn in a complete circle as quickly and safely as possible. If necessary, walking aids were permitted. Scores were the average number of steps across two trials. Scores were then baseline-adjusted by subtracting the baseline mean and dividing by the baseline standard deviation. Higher scores indicated worse performance. Figure 2 presents the raw means of grip strength, digit symbol copy, and Turn 360 across the 10-year period. The raw means for all outcomes are presented in Figure 3, and the baseline correlation between outcome variables are presented in Appendix B.

Training. Intention-to-treat (ITT) multilevel models assessed the effect of randomization on training regardless of adherence. Training groups were separately compared against the no-contact control group using effects coding. For example, memory training was coded as 1, and the no-contact was coded as -1. In addition, pseudo-ITT models where only those who were compliant in the initial trial (i.e., at least eight of 10 sessions) or the no-contact control group were analyzed to examine whether receiving the treatment impacted physical function. Follow-up analyses with only those completing the booster (i.e., at least 11 training sessions) were

completed to assess whether training gains were similar to the main compliance analyses. For the compliance models, participants receiving the minimum amount of training sessions (i.e., eight for the main compliance or at least 11 for the dosage) or control group were analyzed using the same approach as the ITT analyses. That is, the covariates and effects coding were the same, and the critical difference was the number of participants in each analyses were smaller than the full ITT (see Tables 4-6 for compliance analytic samples).

Baseline psychosocial moderators. All baseline moderators evaluated whether baseline status attenuated 10-year physical function slopes. *Cognitive self-efficacy* was assessed using the Personality in Intellectual Contexts-36 item (PIC-36) internal locus of control subscale (Lachman, Baltes, Nesselroade, & Willis, 1982), which consisted of six items assessing one's ability to (re)learn unfamiliar materials. Sample questions included, "There would be ways for me to learn how to fill out a tax form if I really wanted to;" "If I forgot my friend's zip code I'd be able to learn it again;" and "I'd be able to keep an accurate record of my expenses so as to avoid financial problems." All items were scored on a 1 (strongly agree) to 6 (strongly disagree) Likert scale. Items were summed for a summary score then mean centered for the analyses. The summary scores ranged from 8 to 36; higher scores indicated higher cognitive self-efficacy.

Depressive symptoms were assessed using the Center for Epidemiological Studies-Depression 12-item questionnaire (CES-D-12) (Radloff, 1977). Participants were asked to describe how they felt or behaved during the prior week. Sample statements included, "I felt depressed;" "My sleep was restless;" "I enjoyed life;" or "I could not 'get going'." All items were scored on a 0 (never) to 3 (5 - 7 days) Likert scale. Items were summed for a summary score then mean centered for the analyses. The summary scores ranged from 0 to 34 (theoretical maximum = 36); higher scores indicated more depressive symptoms.

Baseline subjective bodily pain. Bodily pain was assessed using the SF-36 two-item bodily pain subscale (Ware & Sherbourne, 1992). Participants were asked whether they experienced bodily pain during the previous four weeks and whether the pain interfered with their normal work. Raw scores were transformed to standardized scores based on the scoring manual (Ware et al., 1994) using the equation $((\text{Raw Score} - 2)/10) * 100$. The standardized scores ranged from 0 to 90 (theoretical maximum = 100), with higher scores indicating more bodily pain.

Covariates. Self-reported *baseline age*, *gender* (woman = 0; man = 1), *race* (non-White = 0 or White = 1), and *education* (0 - 20) were included as covariates because work demonstrated older age (Clouston et al., 2013), women (Blankevoort et al., 2013), non-White race (Rantanen et al., 1998), and lower educational attainment (Honjo, Iso, Ikeda, Inoue, & Tsugane, 2009) predicted lower physical function. Baseline age and education were grand mean centered at baseline such that higher scores indicated older age and more education, respectively. Additionally, *baseline self-reported physical function* using the SF-36 physical function subscale was included because perceptions of physical function may indicate underlying health conditions affecting both physical and cognitive function. Scores were transformed to standardized scores based on the SF-36 scoring manual (Ware et al., 1994) using the equation $((\text{Raw Score} - 10)/20) * 100$. Scores were then centered based on the sample mean; higher scores indicated better self-reported function.

Analytic Strategy

Chi-square and ANOVAs were used to test baseline differences; there were no differences in any characteristics of interest by intervention group. All multilevel models will use restricted maximum-likelihood estimation with an unstructured covariance matrix and were conducted with SPSS, version 25 (IBM Corporation). All estimates were unstandardized, and significance was evaluated at $p < .05$. To examine changes in physical function, all outcome

variables were standardized by first subtracting the baseline mean and dividing by the baseline standard deviation. Time was scaled to reflect the number of months since the baseline assessment (i.e., the number of months since baseline that corresponded to 1-, 2-, 3-, 5-, and 10-year follow-ups). Similar to prior work (Ross et al., 2016; Ross et al., 2018), base models were developed using the control arm of the study ($n = 698$) and included all demographics, physical function, and time*covariate interactions. The full general multilevel model for the ITT analysis for the Aim 1 was:

For assessment j of individual i

$$\text{Level 1: Baseline-Adjusted Physical Function}_{ji} = \beta_{0i} + \beta_{1i}\text{Month}C_{ji} + \beta_{2i}\text{Month}C_{ji}^2 + e_{ji}$$

$$\text{Level 2: } \beta_{0i} = \gamma_{00} + \gamma_{01}\text{Age}C_i + \gamma_{02}\text{Gender}_i + \gamma_{03}\text{Race}_i + \gamma_{04}\text{Education}C_i + \gamma_{05}\text{SF-36 Physical Function}C_i + u_{0i}$$

$$\beta_{1i} = \gamma_{10} + \gamma_{11}\text{Age}C_i + \gamma_{12}\text{Gender}_i + \gamma_{13}\text{Race}_i + \gamma_{14}\text{Education}C_i + \gamma_{15}\text{SF-36 Physical Function}C_i + \gamma_{16}\text{Training Group}_i + u_{1i}$$

$$\beta_{2i} = \gamma_{20} + \gamma_{21}\text{Training Group}_i$$

The β_{0i} equation examined whether age (γ_{01}), gender (γ_{02}), race (γ_{03}), education (γ_{04}), or SF-36 physical function (γ_{05}) significantly predicted differences in baseline physical function. The β_{1i} equation examined whether age (γ_{11}), gender (γ_{12}), race (γ_{13}), education (γ_{14}), SF-36 physical function (γ_{15}), or training group assignment (γ_{16}) significantly predicted changes in physical function across time. The γ_{21} coefficient examined whether there were significant differences in acceleration over time by training group assignment. Together, the γ_{16} and γ_{21} coefficients specifically tested the first aim. Variables that end with C denoted centered variables; all variables except time were baseline grand mean centered. Month was centered at the overall grand mean. Random intercept (u_{0i}) and slope (u_{1i}) were included to test whether there was significant variability in those parameters. Nonsignificant covariates and interactions were removed, resulting in different covariates for each physical function outcome measure. The β_{2i}

estimate was small (e.g., $< .00001$) but significant, so model comparisons using AIC and BIC were used to determine whether its inclusion was appropriate. The same models were conducted to analyze complaint participants. Participants completing at least eight of the initial sessions were included in the compliance analyses.

All baseline psychosocial moderation and bodily pain analyses were analyzed in separate regressions. For example, depressive symptoms was not included as a covariate in the same model with bodily pain. This was done to simplify interpretation of the results. Moderation analyses were completed using ITT instead of compliance samples as a conservative test of differential training benefits. Using depressive symptoms as an example, the general model for Aim 2 was:

For assessment j of individual i

$$\text{Level 1: Baseline-Adjusted Physical Function}_{ji} = \beta_{0i} + \beta_{1i}\text{Month}C_{ji} + \beta_{2i}\text{Month}C_{ji}^2 + e_{ji}$$

$$\text{Level 2: } \beta_{0i} = \gamma_{00} + \gamma_{01}\text{Age}C_i + \gamma_{02}\text{Gender}_i + \gamma_{03}\text{Race}_i + \gamma_{04}\text{Education}C_i + \gamma_{05}\text{SF-36 Physical Function}C_i + u_{0i}$$

$$\beta_{1i} = \gamma_{10} + \gamma_{11}\text{Age}C_i + \gamma_{12}\text{Gender}_i + \gamma_{13}\text{Race}_i + \gamma_{14}\text{Education}C_i + \gamma_{15}\text{SF-36 Physical Function}C_i + \gamma_{16}\text{Training Group}_i + \gamma_{17}\text{Depressive Symptoms}C_i + \gamma_{18}\text{Training Group}_i * \text{Depressive Symptoms}C_i + u_{1i}$$

$$\beta_{2i} = \gamma_{20} + \gamma_{21}\text{Training Group}_i$$

γ_{18} specifically examined the effect of the interaction of baseline psychosocial factors and training group assignment on physical function across time (i.e., Aim 2). For example, it answered whether participants with higher depressive symptoms and assigned to memory training had greater changes in physical function.

Effect sizes were calculated such that positive numbers indicated greater pre- to 10-year gains for the training group relative to the control group. For all outcomes, Cohen's d was calculated as:

$$d = \frac{(M_{\text{post,Treatment}} - M_{\text{pre,Treatment}}) - (M_{\text{post,Control}} - M_{\text{pre,Control}})}{SD_{\text{pre}}}$$

The pooled pre-training standard deviation (SD_{pre}) was calculated as:

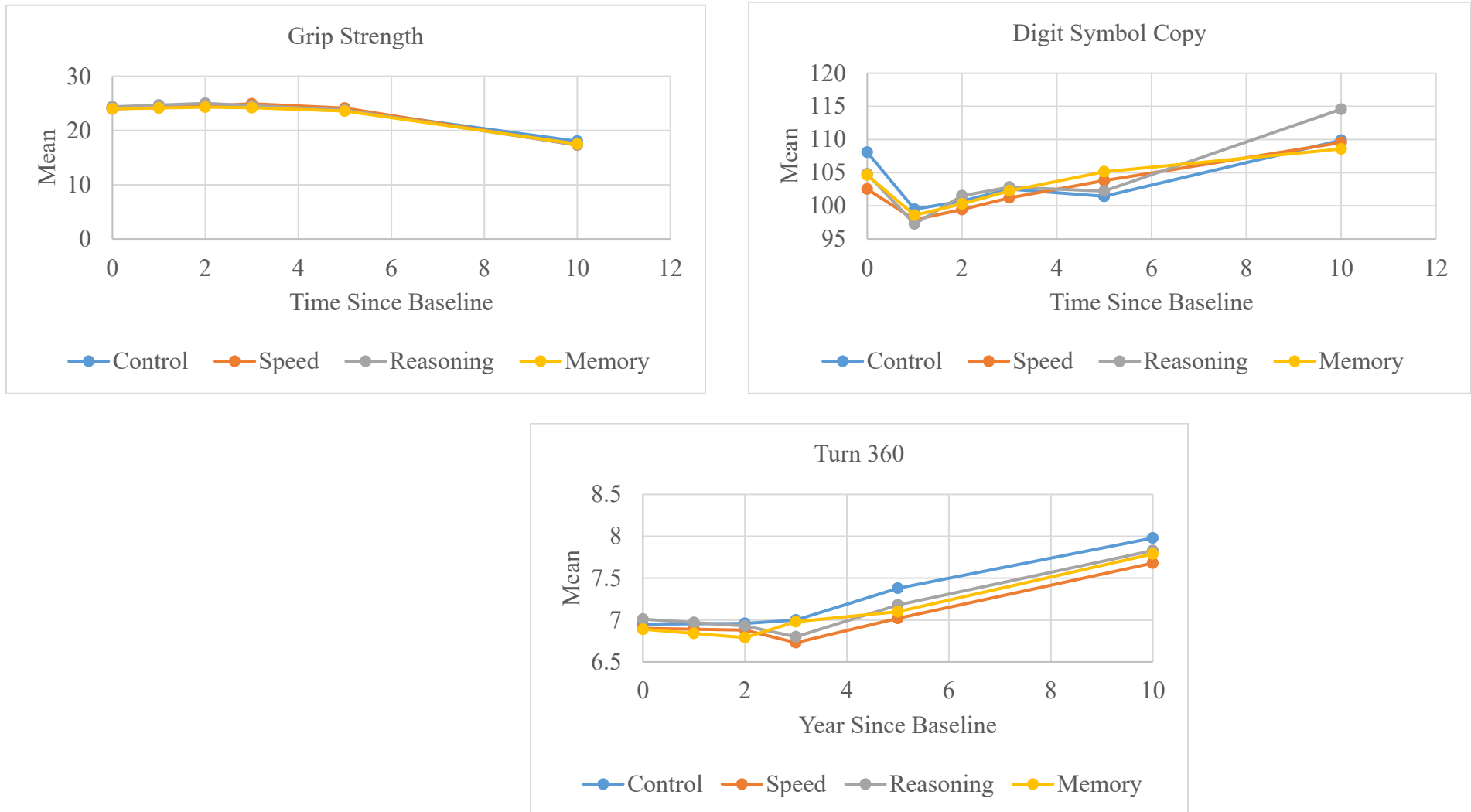
$$SD_{\text{pre}} = \sqrt{\frac{(N_{\text{Treatment}} - 1)SD_{\text{pre,Treatment}}^2 + (N_{\text{Control}} - 1)SD_{\text{pre,Control}}^2}{N_{\text{Treatment}} + N_{\text{Control}} - 2}}$$

$N_{\text{Treatment}}$ and N_{Control} represented the sample sizes of the training and control groups that had available data for baseline and the 10-year measures, respectively. In addition to Cohen's d , Hedges' g , which corrects for small sample size bias (as recommended by Morris, 2007), was calculated as:

$$g = d \left[1 - \frac{3}{4(N_{\text{Treatment}} + N_{\text{Control}} - 2) - 1} \right]$$

Both effect sizes for the treatment-received models (unadjusted for covariates) are presented.

Figure 3. Raw means of grip strength, digit symbol copy, and Turn 360 across 10 years.



Note. 0 = baseline; numbers represent years posttest. Points indicate when data were collected (i.e., baseline, 2, 3, 5, and 10 years posttest). There were no significant differences at baseline ($p > .05$).

Results

Base Models

The base model for grip strength indicated that younger age (est. = $-.04$, $p < .001$), men (est. = -1.49 , $p < .001$), non-White participants (est. = $.36$, $p < .001$), and those with better baseline self-reported physical function (est. = $.01$, $p < .001$) had better grip strength. Grip strength significantly weakened over time (est. = $-.004$, $p < .001$). Model fit indices suggested time² better fit the data and were included. In the base model, there was accelerated decline over time (est. $< .001$, $p < .001$).

The base model for Digit Symbol Copy demonstrated that younger age (est. = $.02$, $p = .001$), women (est. = $-.22$, $p = .02$), White participants (est. = $.46$, $p < .001$), and those with better baseline self-reported physical function (est. = $-.01$, $p < .001$) had better Digit Symbol Copy. There was no main effect of time (est. $< .001$, $p = .52$).

The base model for Turn 360 indicated that older age (est. = $.041$, $p < .001$), White participants (est. = $-.16$, $p = .01$) and those with better physical function (est. = $-.01$, $p < .001$) had better Turn 360. Over time, Turn 360 scores significantly declined (est. = $.007$, $p < .001$). Lastly, there was a significant age*time interaction such that over time, those who were older had accelerated decline (est. $< .001$, $p = .002$).

Grip Strength

Aim 1a: ITT models. Assignment to speed of processing (est. = $< .001$, $p = .454$), memory (est. $< .001$, $p = .647$), or reasoning training (est. = $.001$, $p = .251$) did not significantly predict better grip strength relative to the control group. Additionally, assignment to speed of processing (est. = $< .001$, $p = .478$), memory (est. = $< .001$, $p = .684$), or reasoning training (est. = $< .001$, $p = .984$) did not predict differences in accelerated grip strength weakness over time.

Aim 1b: Compliance models. Compliance in speed of processing (est. = $<-.001$, $p = .356$; $d = .104$; $g = .104$), memory (est. = $<.001$, $p = .620$; $d = .053$; $g = .053$), and reasoning (est. = $.001$, $p = .239$; $d = .097$; $g = .097$) training did not significantly predict grip strength relative to the control group (Table 4). Furthermore, compliance in speed of processing (est. = $<.001$, $p = .630$), memory (est. = $<-.001$, $p = .740$), or reasoning (est. $<.001$, $p = .905$) training did not predict differences in accelerated grip strength weakness over time. The same pattern of results held when constraining the analyses to those who received booster sessions only (i.e., 11 or more sessions total).

Aim 2: Psychosocial moderators and bodily pain. Baseline cognitive self-efficacy, depressive symptoms, or bodily pain did not moderate the relationship between training group assignment and grip strength for speed of processing, memory, or reasoning training ($p > .05$). See Table 5 for a visual summary.

Table 4. Effects of Cognitive Training on Grip Strength, Compliant Participants.

	Speed of processing training ($n = 598$) vs. no-contact control ($n = 616$)		Memory training ($n = 603$) vs. no-contact control ($n = 616$)		Reasoning training ($n = 592$) vs. no-contact control ($n = 616$)	
	Est. (<i>SE</i>)	95% CI	Est. (<i>SE</i>)	95% CI	Est. (<i>SE</i>)	95% CI
Fixed effects						
γ_{00} Intercept	.998 (.038)***	.924, 1.072	.939 (.038)***	.864, 1.015	1.064 (.037)***	.992, 1.137
γ_{16} <i>Training Group Assignment*Month</i>	<.001 (.001)	-.001, .002	<.001 (<.001)	-.001, .001	.001 (.001)	<-.001, .002
γ_{21} <i>Training Group Assignment*Month²</i>	<.001 (<.001)	<-.001, <.001	<-.001 (<.001)	<-.001, <.001	<.001 (<.001)	<-.001, <.001
γ_{01} Age	-.041 (.003)***	-.047, -.035	-.034 (.003)***	-.040, -.028	-.039 (.003)***	-.045, -.032
γ_{02} Gender	-1.488 (.041)***	-1.570, -1.407	-1.425 (.042)***	-1.059, -1.342	-1.555 (.041)***	-1.635, -1.474
γ_{03} Race	.346 (.042)***	.263, .428	.385 (.042)***	.302, .467	.326 (.041)***	.245, .406
γ_{05} SF-36 Physical Function	.005 (.001)***	.004, .007	.006 (.001)***	.004 (.007)	.004 (.001)***	.002, .005
γ_{10} Month	-.004 (<.001)***	-.005, -.003	-.004 (<.001)***	-.005, -.003	-.004 (<.001)***	-.005, -.003
γ_{20} Month ²	<-.001 (<.001)***	<-.001, <-.001	<-.001, (<.001)***	<-.001, <-.001	<-.001 (<.001)***	<-.001, <-.001
Random effects						
e_{ij} Residual	.171 (.006)***	.160, .183	.166 (.005)***	.156, .177	.172 (.006)***	.161, .183
u_{0i} Intercept	.310 (.017)***	.279, .345	.322 (<.001)***	.290, .356	.300 (.016)***	.270, .332
u_{1i} Month	<.001 (<.001)***	<.001, <.001	<.001 (.001)***	<.001, <.001	<.001 (<.001)***	<.001, <.001
$r_{u_{0i}, u_{1i}}$ Covariance (intercept, month)	<.001 (<.001)	<-.001, <.001	<.001 (<.001)	<-.001, <.001	<-.001 (<.001)	<-.001, <.001

Note. Higher grip strength scores indicate better performance. The parameter notation reflects those from the full model (pp. 39-40; Appendix D for pruned equation). CI = Confidence Interval, *SE* = Standard Error. *** $p < .001$, ** $p < .01$, * $p < .05$. Bolded and italicized parameters tested Aim 1b.

Table 5. Visual Schematic of Psychosocial Moderators and Bodily Pain Results.

Grip Strength			
	Speed of Processing	Memory	Reasoning
Cognitive Self-Efficacy	X	X	X
Depressive Symptoms	X	X	X
Bodily Pain	X	X	X
Digit Symbol Copy			
	Speed of Processing	Memory	Reasoning
Cognitive Self-Efficacy	-	-	-
Depressive Symptoms	X	NA	-
Bodily Pain	X	X	X
Turn 360			
	Speed of Processing	Memory	Reasoning
Cognitive Self-Efficacy	X	X	X
Depressive Symptoms	X	X	X
Bodily Pain	-	X	X

Note. + = interaction with dosage was significant, - = main effect was significant only, X = neither interaction nor main effect was significant. NA indicates the model failed to converge on a solution.

Digit Symbol Copy

Aim 1a: ITT models. Assignment to speed of processing (est. = $-.002$, $p = .168$), memory (est. = $-.001$, $p = .199$), or reasoning training (est. = $-.002$, $p = .054$) did not significantly predict better digit symbol copy relative to the control group.

Aim 1b: Compliance models. Compliance in speed of processing (est. = $-.002$, $p = .179$; $d = .047$; $g = .047$), memory (est. = $-.002$, $p = .150$; $d = .055$; $g = .055$), and reasoning (est. = $-.002$, $p = .060$; $d = -.012$; $g = -.012$) training did not significantly predict better digit symbol copy time scores compared to the control group (Table 6). Notably, the reasoning training compliance effects were trending. The same pattern of results held when constraining the analyses to those who received booster sessions only (i.e., 11 or more sessions total).

Aim 2: Psychosocial moderators and bodily pain. Baseline cognitive self-efficacy, depressive symptoms, or bodily pain did not moderate the relationship between training group assignment and grip strength for speed of processing, memory, or reasoning training ($p > .05$). Interestingly, the effect of training group assignment became significant after controlling for the impact of depressive symptoms on the intercept for the reasoning group only. Specifically, those assigned to receive reasoning training had greater improvements in digit symbol copy over time compared to those in the control group (est. = $-.002$, $p = .038$). See Table 5 for a visual summary.

Table 6. Effects of Cognitive Training on Digit Symbol Copy, Compliant Participants.

	Speed of processing training ($n = 701$) vs. no-contact control ($n = 694$)		Memory training ($n = 723$) vs. no-contact control ($n = 694$)		Reasoning training ($n = 692$) vs. no-contact control ($n = 694$)	
	Est. (SE)	95% CI	Est. (SE)	95% CI	Est. (SE)	95% CI
Fixed effects						
γ_{00} Intercept	.044 (.052)	-.059, .146	.078 (.055)***	-.029, .186	.136 (.060)*	.020, .253
γ_{16}Training Group Assignment*Month	<i>-.002 (.001)</i>	<i>-.005, .001</i>	<i>-.002 (.001)</i>	<i>-.004, .001</i>	<i>-.002 (.001)</i>	<i>-.004, <.001</i>
γ_{01} Age	.024 (.004)***	.015, .033	.023 (.004)***	.014, .032	.027 (.005)***	.015, .037
γ_{02} Gender	-.171 (.058)**	-.285, -.057	-.217 (.061)***	-.337, -.098	-.268 (.067)***	-.399, -.137
γ_{03} Race	.450 (.058)***	.337, .564	.498 (.059)***	.382, .615	.455 (.065)***	.327, .583
γ_{05} SF-36 Physical Function	-.008 (.001)***	-.010, -.006	-.008 (.001)***	-.010, -.006	-.009 (.001)***	-.011, -.006
γ_{10} Month	.002 (.001)**	.001, .004	.003 (.001)**	.001, .005	.003 (.001)***	.002, .005
Random effects						
e_{ij} Residual	.179 (.005)***	.170, .188	.228 (.006)***	.216, .240	.196 (.005)***	.186, .206
u_{0i} Intercept	.683 (.051)***	.589, .791	.717 (.052)***	.622, .827	.960 (.070)***	.833, 1.015
u_{1i} Month	<.001 (<.001)***	<.001, <.001	<.001 (<.001)***	<.001, <.001	<.001 (<.001)***	<.001, <.001
$r_{u_{0i}, u_{1i}}$ Covariance (intercept, month)	.002 (.001)**	.001, .003	.002 (.001)**	.001, .003	.002 (.001)**	.001, .003

Note. Higher scores on Digit Symbol Copy indicate worse performance. The parameter notation reflects those from the full model (pp. 39-40; Appendix D for pruned equation). CI = Confidence Interval, SE = Standard Error. *** $p < .001$, ** $p < .01$, * $p < .05$. Bolded and italicized parameter tested Aim 1b.

Turn 360

Aim 1a: ITT models. Assignment to speed of processing (est. = .001, $p = .133$), memory (est. = $<.001$, $p = .867$), or reasoning training (est. = .001, $p = .186$) did not significantly predict better Turn 360 relative to the control group.

Aim 1b: Compliance models. Compliance in speed of processing (est. = .001, $p = .059$; $d = .216$; $g = .215$), memory (est. $<.001$, $p = .778$; $d = .057$; $g = .056$), and reasoning (est. = $-.001$, $p = .188$; $d = .210$; $g = .209$) training did not significantly predict better Turn 360 relative to the control group (Table 7). Speed of processing training, however, was trending toward significance. The same pattern of results held when constraining the analyses to those who received booster sessions only (i.e., 11 or more sessions total).

Aim 2: Psychosocial moderators and bodily pain. Baseline cognitive self-efficacy, depressive symptoms, and bodily pain did not moderate the relationship between dosage and grip strength for speed of processing, memory, or reasoning training ($p > .05$). See Table 5 for a visual summary.

Table 7. Effects of Cognitive Training on Turn 360, Compliant Participants.

	Speed of processing training ($n = 684$) vs. no-contact control ($n = 681$)		Memory training ($n = 688$) vs. no-contact control ($n = 681$)		Reasoning training ($n = 678$) vs. no-contact control ($n = 681$)	
	Est. (<i>SE</i>)	95% CI	Est. (<i>SE</i>)	95% CI	Est. (<i>SE</i>)	95% CI
Fixed effects						
γ_{00} Intercept	.247 (.026)***	.195, .299	.256 (.026)***	.204, .307	.250 (.027)***	.198, .303
γ_{16}Training Group Assignment*Month	.001 (.001)	<-.001, .003	<.001 (.001)	-.001, .002	.001 (.001)	<-.001, .003
γ_{01} Age	.056 (.004)***	.047, .064	.051 (.004)***	.043, .060	.055 (.004)***	.047, .063
γ_{03} Race	-.108 (.047)*	-.202, -.015	-.102 (.047)*	-.194, -.010	-.126 (.048)*	-.220, -.031
γ_{05} SF-36 Physical Function	-.012 (.001)***	-.013, -.010	-.012 (.001)***	-.014, -.010	-.012 (.001)***	-.013, -.010
γ_{10} Month	.005 (.001)***	.004, .006	.007 (.001)***	.005, .008	.006 (<.001)***	<.001, <.001
γ_{11} Age*Month	<.001 (<.001)**	<.001, <.001	<.001 (<.001)**	<.001, <.001	<.001 (.001)**	<.001, <.001
Random effects						
e_{ij} Residual	.411 (.013)***	.387, .437	.389 (.012)***	.366, .414	.421 (.013)***	.396, .447
u_{0i} Intercept	.434 (.028)***	.383, .494	.433 (.028)***	.381, .492	.442 (.028)***	.389, .502
u_{1i} Time	<.001 (<.001)***	<.001, <.001	<.001 (<.001)***	<.001, <.001	<.001 (<.001)***	<.001, <.001
$r_{u_{0i}, u_{1i}}$ Covariance (intercept, month)	.002 (<.001)***	.002, .003	.002 (<.001)***	.002, .003	.002 (<.001)***	.001, .003

Note. Higher scores on Turn 360 indicate worse performance. The parameter notation reflects those from the full model (pp. 39-40; Appendix D for pruned equation). CI = Confidence Interval, *SE* = Standard Error. *** $p < .001$, ** $p < .01$, * $p < .05$. Bolded and italicized parameter tested Aim 1b.

Discussion

Cognitive training is increasingly viewed as a viable intervention strategy for older adult physical function (Azadian et al., 2018; Azadian et al., 2016; K. Z. H. Li et al., 2010; Marusic & Grosprêtre, 2018; Marusic et al., 2015; Marusic et al., 2018; Ng et al., 2015; Ross et al., 2018; Smith-Ray et al., 2013; Smith-Ray et al., 2014; Verghese et al., 2010). This study extends this work by examining ITT-based models of cognitive training across 10 years and found a lack of attenuation in physical function, suggesting that more continual engagement is necessary to maintain training-related gains. Although the mechanistic pathways by which cognitive training attenuates age-related physical function decline are unknown, neuroimaging studies identify neural dedifferentiation as a candidate mechanism. Neural dedifferentiation is associated with normative aging and is a candidate explanation for the increased relatedness of physical and cognitive function in older adults (Cabeza, 2001; Reuter-Lorenz, 2002; Sleimen-Malkoun et al., 2014). This process may also explain why cognitive interventions improve complex physical function (Cabeza, 2001; Reuter-Lorenz, 2002; Sleimen-Malkoun et al., 2014). Complex physical function is associated with brain regions primarily responsible for cognitive speed of processing such as the dorsolateral prefrontal cortex (Hausdorff et al., 2005; Heuninckx, Wenderoth, Devaere, Peeters, & Swinnen, 2005; Rosano et al., 2008) which is required to rapidly and continually allocate motor or cognitive resources while moving through space and reacting to visuospatial demands (van Iersel et al., 2008). Of the cognitive interventions, those targeting speed of processing historically have the strongest evidence for impacting complex physical function (K. Z. H. Li et al., 2010; Ross et al., 2018; Smith-Ray et al., 2013; Smith-Ray et al., 2014; Verghese et al., 2010) even across five years (Ross et al., 2018), but this may be due to the fact that it is the most frequently-used cognitive intervention type and memory and reasoning training are not typically evaluated as interventions for physical function outcomes. Speed of processing and reasoning training positively impact other measures of everyday function such as driving cessation and subjective instrumental activities of daily living

(Rebok et al., 2014; Ross, Freed, Edwards, et al., 2017), demonstrating the utility of cognitive training for maintaining long-term older adult independence even if such effects were not observed across ten years of physical function in these analyses.

Despite accumulating evidence that grip strength and cognition are related in healthy older adults, cognitive training did not confer any benefit to grip strength in this study. These results are similar to prior work that found grip strength was only improved in reasoning training after five years (Ross et al., 2018). This may be due to the health of the sample. Since weaker grip strength is associated with mortality (Granic et al., 2017; Strand et al., 2016), those who may be likeliest to receive benefits could have died during the follow-up period. As a result, the remaining participants with better grip strength may perform similarly to those with cognitive training. Relatedly, older adults healthy enough for in-person assessments after 10 years were unlikely to be frail (119/1594 or 7.46% available for 10 year data), so between-group differences may be more pronounced in frail older adults.

The second goal of this study was to evaluate baseline moderators of training effects. Despite the hypothesized relationship between person-specific characteristics such as cognitive self-efficacy and cognitive training benefits (Simons et al., 2016), this study found that cognitive self-efficacy, depressive symptoms, and bodily pain did not moderate training effects on any physical function outcome, nor did they consistently predict physical function when included as a covariate only. These results were unsurprising since prior work found that baseline cognitive self-efficacy did not explain training gains from speed of processing training (Sharpe, Holup, Hansen, & Edwards, 2014). Furthermore, subjective bodily pain did not predict training effects, nor was it a significant covariate of physical function. This may be partly due to the inclusion criteria, since participants who reported pain in their arm or wrist could not participate in the grip strength

protocol. However, these participants were able to complete the other physical function tasks, so exclusion does not fully explain the lack of moderation. This set of findings highlights that the experience of pain may be independent of one's capability to complete physical tasks. It may also be that other physical function tasks such as Timed Up and Go, gait speed, or dynamic balance tasks with longer duration (e.g., one-leg balance test, Short Physical Performance Battery) would be better predicted by pain. That is, the short duration of the physical function tasks may have reduced the likelihood that bodily pain would interfere with task performance.

Taken together, this study demonstrates that the attenuation of physical function decline due to cognitive training is lost by 10 years post-training in ITT-based analyses. While this study does *not* imply that cognitive training is ineffective for attenuating age-related declines in these abilities, it suggests that more continual engagement may be necessary to maintain training benefits. One limitation of this study is the usage of ITT and ITT-based analyses only. While such analyses provide valuable information such as how interventions could behave under real-world conditions with suboptimal compliance, it fails to consider whether dosage impacts training-related gains. For example, adaptation (i.e., increase in difficulty across time) is a hallmark of effective cognitive training (Kelly et al., 2014a). While the ACTIVE trial was adaptive, the processing speed training group was not uniformly adaptive across the intervention trial; the first five sessions (of 10) were not adaptive to the individual but rather training participants to a standardized, specified level of complexity (Ball et al., 2007). That is, the compliance-based models only would consider those receiving “half-dose” processing speed training and does not consider the “full treatment effect.” Future work should evaluate dosage-based models to determine which dosage is necessary to attenuate long-term physical function declines, as the current study had a lower dosage compared to other cognitive training programs (Smith-Ray et al., 2013; Smith-Ray et al., 2014).

There were no significant differences in intervention effectiveness based on baseline psychosocial and subjective pain characteristics, indicating that psychosocial beliefs and experiences unrelated to physical function are unlikely to impact training gains. Future research should continue exploring the complex, dynamic relationship between physical and cognitive function with an emphasis on interventions that can simultaneously improve both health domains. For instance, some propose that combining physical and cognitive training may confer the greatest benefits to both physical and cognitive health and warrant future exploration (Marusic et al., 2018). Identifying effective, time-efficient interventions are important to promote older adults' health, independence, and well-being.

Chapter 4: General Discussion

The relationship between physical and cognitive function in older adulthood is well-documented, but recent work highlights important unresolved issues such as the subjective relationship (Cosentino et al., 2018) and a better understanding of non-physical interventions (e.g., cognitive training) for improving or maintaining physical function (K. Z. H. Li et al., 2010; Marusic & Grosprêtre, 2018; Marusic et al., 2018; Ross et al., 2018; Smith-Ray et al., 2013; Smith-Ray et al., 2014; Verghese et al., 2010). The two studies in this dissertation directly address these gaps in the literature by examining the relationship between subjective physical and memory function and the long-term effects of different cognitive training interventions on multiple measures of physical function.

Study 1 extended the literature by demonstrating that subjective physical and memory function are related to each other across older adults aged 65-85. Adjusting for demographic factors and depressive symptoms only partially attenuated this relationship, suggesting there is a relationship that cannot fully be explained by depressive symptoms. Interestingly, the relationship magnitude was not significantly different than using objective physical function as a (nonsignificant) predictor of subjective memory function. This highlights that while the relationship between subjective physical and memory function was significant, it was weak. Furthermore, including age as a covariate only should be sufficient to control for age effects on physical and cognitive function in similar samples.

Study 2 examined the 10-year effects of different cognitive training interventions on multiple measures of objective physical function and found that being assigned to receive speed of processing, memory, or reasoning training did not predict attenuations in physical function decline across time. Relatedly, constraining the analyses to only those who were compliant did not change the pattern of results. In general, the training gains were not moderated by

psychosocial factors or bodily pain, suggesting the lack of benefits were equivalent regardless of one's baseline score on these measures. This extends the literature by examining the longest follow-up period of any cognitive training study on physical function (Azadian et al., 2018; Azadian et al., 2016; K. Z. H. Li et al., 2010; Marusic et al., 2015; Ng et al., 2015; Ross et al., 2018; Smith-Ray et al., 2013; Smith-Ray et al., 2014; Verghese et al., 2010) and suggests that while there may be short-term attenuations in physical function decline, researchers should not assume these training gains will be maintained to the same degree as other everyday assessments (Rebok et al., 2014). This knowledge is essential for developing and implementing interventions for those who cannot engage in physical activity interventions.

Subjective Physical and Memory Function.

This dissertation applied novel methods (to gerontology) (Sprague et al., in press) to study the relationship between subjective physical and memory function in older adults. Unlike prior work that included aging as a moderator (Blankevoort et al., 2013), covariate (Alfaro-Acha et al., 2006), or grouping variable (Al Snih et al., 2002; Sternäng et al., 2016), our study evaluated whether the strength of this relationship differed as a function of continuous age and found there was a significant relationship between subjective physical and memory function across older adults aged 66 to 85, and the relationship magnitude was stable (i.e., statistically similar) across this age range. Furthermore, subjective physical function better predicted subjective memory, and objective physical function better predicted objective memory. This suggests that when modeling the relationship between subjective physical and memory function, including age as a covariate with no higher-order age interactions should be sufficient to capture the effect of age on the relationship. It also suggests that subjective physical function better predicts subjective memory, and objective physical function better predicts objective memory. That is, subjective and objective measures provide unique and more holistic information about older adult function than

relying solely on subjective or objective assessments alone. Future work should consider examining longitudinal changes in this relationship, such as whether the relationship magnitude strengthens as one approaches death.

Cognitive Training and Physical Function.

Physical activity is believed to be the most effective method of improving older adult physical function (Brach et al., 2004). Despite this, there are several barriers to engagement, including feeling intimidated by equipment or group workouts (Bethancourt et al., 2014), lack of enjoyment (Bethancourt et al., 2014; van Stralen, De Vries, Mudde, Bolman, & Lechner, 2009), fear of injury (Baert, Gorus, Mets, Geerts, & Bautmans, 2011; Bethancourt et al., 2014; Booth, Owen, Bauman, Clavisi, & Leslie, 2000; Costello, Kafchinski, Vrazel, & Sullivan, 2011), cost (Baert et al., 2011), physical limitations (Bethancourt et al., 2014), or lack of time (Baert et al., 2011). Furthermore, less than 20% of older adults report meeting the federal physical activity guidelines (National Health Interview Survey, 2018) despite knowledge from care providers and news sources (Friedman et al., 2015; Friedman, Laditka, Laditka, & Price, 2011; Friedman et al., 2013) that engagement is important for both physical and brain health. The percent of adults 65+ meeting the recommended aerobic activity levels are both lower compared to the national average across all adults 18+ (52.9%) and is lower compared to any other age group (National Health Interview Survey, 2018). Complicating this is the fact that some care providers feel ill-equipped to provide physical activity counseling or do not have the institutional support, such as reimbursement or organizational policies, to do so (AuYoung et al., 2016). In addition to the person-specific barriers, older adults may be reluctant to engage in physical activity if the advisor (e.g., care provider) is not physically active themselves (Lobelo & Garcia de Quevedo, 2016). Even if older adults intend to engage in physical activity, there is a well-documented intention-behavior gap such that those with high intention to exercise do not necessarily adhere to engagement (Godin & Conner, 2008).

Not only does observational work consistently find that most older adults fail to engage in the recommended physical activity levels, but intervention research demonstrates that when older adults are in physical activity interventions, there is modest adherence (e.g., ~ 65-86 %; Evers, Klusmann, Ziegelmann, Schwarzer, & Heuser, 2012; Picorelli et al., 2014). Those who do adhere tend to be both physically and cognitively healthier (Picorelli et al., 2014), exacerbating extant health disparities in older adults. Supervised or group-based interventions generally have greater adherence (Picorelli et al., 2014; Zaleski et al., 2016), but this is problematic because of the increased cost of maintaining staff for such supervision. While technology-based physical activity interventions that could be administered at home (e.g., Nintendo Wii) show promise for improving adherence, long-term adherence remains unknown (Valenzuela, Okubo, Woodbury, Lord, & Delbaere, 2018). Understanding long-term adherence is critical as continual engagement is necessary to maintain gains, and detraining (i.e., loss in training-related gains) can occur within weeks of physical activity cessation (Coyle et al., 1984; Madsen et al., 1993; Mujika & Padilla, 2000; Neuffer, 1989). Therefore, identifying non-physical alternatives that reduce barriers to engagement (Marusic & Grosprêtre, 2018; Marusic et al., 2018), do not require supervision (Edwards et al., 2013), and do not require continual engagement for benefits (Rebok et al., 2014; Ross, Freed, Edwards, et al., 2017; Ross et al., 2018; Willis et al., 2006) are important for maintaining or improving older adult health. Because the relationship between physical and cognitive function is bidirectional (Finkel et al., 2016), this suggests that cognitive training, particularly training in domains that share common neurological pathways with physical functions, would transfer to improved physical function.

There is a growing literature examining the effect of cognitive training on physical function in older adults, but a limitation of the extant work is the failure to examine multiple cognitive training programs. It is important to evaluate cognitive training program separately

(e.g., speed of processing vs. memory training) instead of treating them as a homogenous intervention type because different conclusions may be drawn. For instance, reasoning training attenuated age-related declines in grip strength, Digit Symbol Copy, and Turn 360 across five years, whereas speed of processing and memory training only attenuated age-related declines in Digit Symbol Copy and Turn 360 (Ross et al., 2018). This suggests that while any of the three cognitive training programs impacted fine visuomotor coordination/motor speed and complex lower limb function, something specific to reasoning training affects gross upper limb muscle strength. Given that the results did not replicate in the 10-year results, future studies should replicate this training protocol to ensure that there are real short-term attenuations in grip strength from reasoning training and that these results were not spurious. Understanding which cognitive training programs impact which physical functions would allow for intervention tailoring based on an individual's goals.

A second limitation of the current literature is the failure to include multiple physical function outcomes. While various physical functions are related to each other, the association is weak (Harris-Love, Benson, Leasure, Adams, & McIntosh, 2018), so measures of one physical function (e.g., grip strength) cannot be assumed to be a proxy for other measures of physical function (e.g., lower limb function). Separately analyzing physical function outcomes can identify which interventions are most effective for specific outcomes, and interventionists could combine intervention components to maximize benefits across a breadth of physical functions. For example, if speed of processing only transferred to grip strength and reasoning training only transferred to Turn 360, a training program including elements of both interventions could confer benefits to both grip strength and Turn 360.

This study extended prior work by both addressing these limitations, as well as extending the follow-up period beyond immediate posttest only. While there was no evidence of long-term transfer from speed of processing, memory, and reasoning training to physical function across 10 years, it is notable because the follow-up period was substantially longer (10 years) compared to long-term follow-up in physical activity interventions (two years; Finnegan, Seers, & Bruce, in press). Additionally, this was among the first to examine “who benefits” from cognitive training to physical function (Smith-Ray et al., 2013) and found that there were no differential effects after accounting for baseline cognitive self-efficacy, depressive symptoms, or subjective bodily pain. Future work should consider mechanisms of transfer to elucidate what is responsible for the short-term benefit to physical function. This would allow researchers to create an intervention that would have larger effects on physical function.

Limitations and Strengths.

Despite the innovations of these studies, several limitations should be considered. The dataset consisted of healthy older adults who were able to complete a cognitive training protocol, so it is unclear how these findings would replicate in older adults with poor mobility. Relatedly, baseline data were collected in the late 1990s, limiting our ability to generalize to newer cohorts of older adults. Physical function is known to be related to early life experiences (Alastalo et al., 2013) and differ by cohorts (K. Christensen et al., 2013); future work should replicate these findings in more recent older adult cohorts (e.g., Baby Boomers). Relatedly, future studies should also assess early life experiences to identify early-life predictors of late-life function. Lastly, there was substantial (~55%) dropout in the ACTIVE trial, which may lead to survival effects in the database (see Appendix C). That is, those older adults contributing data for the longitudinal conclusions may be different (i.e., healthier) than the general population, further highlighting the importance to

replicate this study in older adults with poorer baseline health. However, dropout in the ACTIVE trial is remarkably low compared to interventions with shorter follow-up periods. For example, physical activity interventions have reported dropout rates ranging from 22% to 76% (Jancey et al., 2007; Prohaska, Peters, & Warren, 2000; Schmidt, Gruman, King, & Wolfson, 2000). Most attrition occurs within the first six months (Dishman, 1991, 1994; Ettinger et al., 1997; Mullen et al., 2013; Resnick, Palmer, Jenkins, & Spellbring, 2000; Schmidt et al., 2000; van der Deijl, Etman, Kamphuis, & van Lenthe, 2014) and tends to occur in those who have poorer baseline health (Viken et al., in press); while no physical activity trial to date has the long-term follow-up period similar to ACTIVE, it is fair to assume that the retention would be substantially lower 10 years later. Even among those who complete a physical activity intervention, the adherence rates are around 66%- lower than that of the ACTIVE trial (Dishman, 1991; Linke, Gallo, & Norman, 2011).

Despite these limitations, there are strengths worth noting. The ACTIVE trial is the largest cognitive intervention trial with the longest follow-up to date. The trial design allows for separate evaluation of cognitive domain training, which is critical for understanding which cognitive domains are responsible for improving cognitive, physical, and everyday function outcomes. For instance, the finding that controlling for baseline depressive symptoms made the reasoning training ITT analysis for Digit Symbol Copy significant would not be readily apparent in cognitive training that incorporated speed of processing, memory, and reasoning training in one program.

Overall Conclusion.

Physical and cognitive function are interrelated in older adulthood, and this dissertation extended prior work by examining the age-varying relationship between subjective physical and cognitive function (Cosentino et al., 2018). Additionally, this dissertation added to the cognitive

intervention literature by demonstrating a lack of 10-year transfer of cognitive training to physical function. Future work should replicate these findings in diverse samples of newer cohorts of older adults who are at greater risk of health decline.

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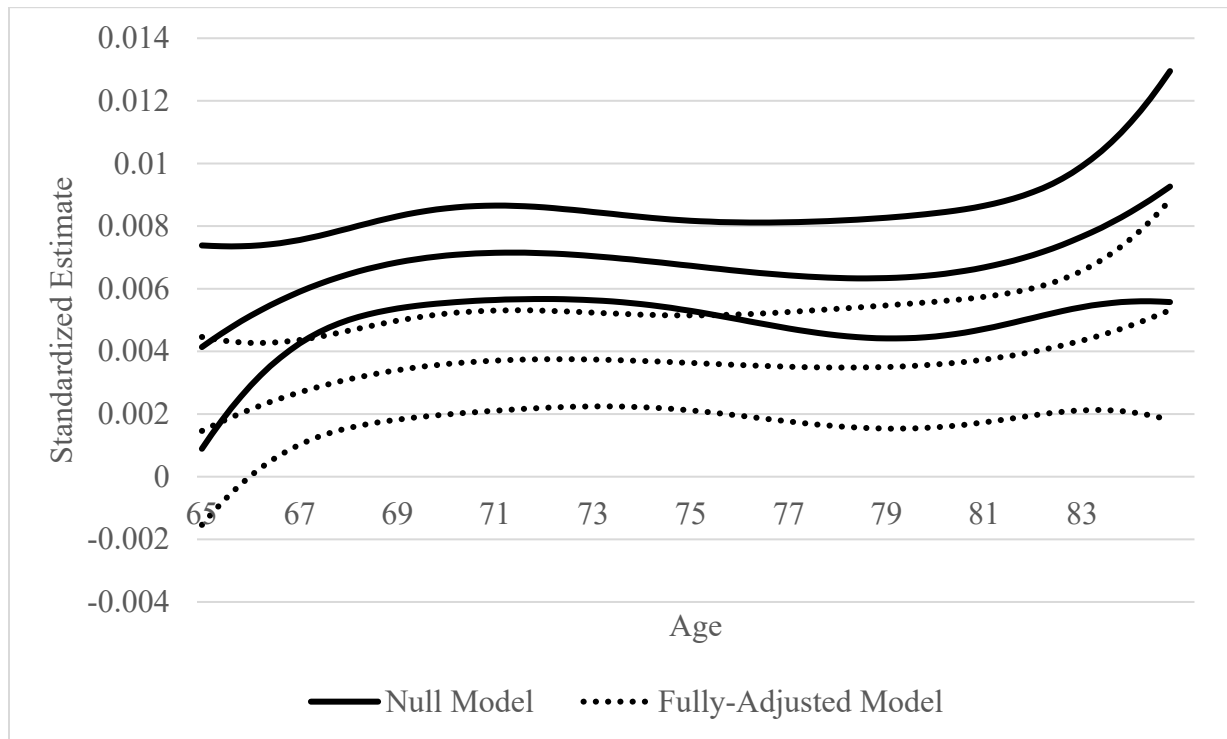
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Appendices

Appendix A. Comparison of Null Model to Fully-Adjusted Model, Paper 1.



Note. Relationships are nonsignificant ($p > .05$) when lines intersect x-axis. Solid lines = estimate and 95% confidence band for null model. Dotted lines = estimate and 95% confidence band for covariate-adjusted model. Adjusting for demographic covariates nonsignificantly reduced the relationship between subjective physical and memory function.

Appendix B. Correlations Between Objective Physical Function Outcomes, Paper 2.

	Grip Strength	Digit Symbol Copy	Turn 360
Digit Symbol Copy	-.041	1.00	--
Turn 360	-.208	.157	1.00

Appendix C. Final Models for Aim 1a and 1b, Paper 2.

	General Equation		
Grip Strength	<p>Level 1: Grip Strength_{ji} = $\beta_{0i} + \beta_{1i}\text{Month}_{ji} + \beta_{2i}\text{Month}_{ji}^2 + e_{ji}$</p> <p>Level 2: $\beta_{0i} = \gamma_{00} + \gamma_{01}\text{Age}_i + \gamma_{02}\text{Gender}_i + \gamma_{03}\text{Race}_i + \gamma_{05}\text{SF-36 Physical Function}_i + \gamma_{06}\text{SpeedvsControl}_i + u_{0i}$</p> <p>$\beta_{1i} = \gamma_{10} + \underline{\gamma_{17}\text{SpeedvsControl}_i} + u_{1i}$</p> <p>$\beta_{2i} = \gamma_{20} + \underline{\gamma_{21}\text{SpeedvsControl}_i}$</p>	<p>Level 1: Grip Strength_{ji} = $\beta_{0i} + \beta_{1i}\text{Month}_{ji} + \beta_{2i}\text{Month}_{ji}^2 + e_{ij}$</p> <p>Level 2: $\beta_{0i} = \gamma_{00} + \gamma_{01}\text{Age}_i + \gamma_{02}\text{Gender}_i + \gamma_{03}\text{Race}_i + \gamma_{05}\text{SF-36 Physical Function}_i + u_{0i}$</p> <p>$\beta_{1i} = \gamma_{10} + \underline{\gamma_{17}\text{MemvsControl}_i} + u_{1i}$</p> <p>$\beta_{2i} = \gamma_{20} + \underline{\gamma_{21}\text{MemvsControl}_i}$</p>	<p>Level 1: Grip Strength_{ji} = $\beta_{0i} + \beta_{1i}\text{Month}_{ji} + \beta_{2i}\text{Month}_{ji}^2 + e_{ji}$</p> <p>Level 2: $\beta_{0i} = \gamma_{00} + \gamma_{01}\text{Age}_i + \gamma_{02}\text{Gender}_i + \gamma_{03}\text{Race}_i + \gamma_{05}\text{SF-36 Physical Function}_i + u_{0i}$</p> <p>$\beta_{1i} = \gamma_{10} + \underline{\gamma_{17}\text{ReasvsControl}_i} + u_{1i}$</p> <p>$\beta_{2i} = \gamma_{20} + \underline{\gamma_{21}\text{ReasvsControl}_i}$</p>
Digit Symbol Copy	<p>Level 1: Digit Symbol Copy_{ji} = $\beta_{0i} + \beta_{1i}\text{Month}_{ji} + e_{ji}$</p> <p>Level 2: $\beta_{0i} = \gamma_{00} + \gamma_{01}\text{Age}_i + \gamma_{02}\text{Gender}_i + \gamma_{03}\text{Race}_i + \gamma_{04}\text{Education}_i + \gamma_{05}\text{SF-36 Physical Function}_i + u_{0i}$</p> <p>$\beta_{1i} = \gamma_{10} + \underline{\gamma_{17}\text{SpeedvsControl}_i} + u_{1i}$</p>	<p>Level 1: Digit Symbol Copy_{ji} = $\beta_{0i} + \beta_{1i}\text{Month}_{ji} + e_{ji}$</p> <p>Level 2: $\beta_{0i} = \gamma_{00} + \gamma_{01}\text{Age}_i + \gamma_{02}\text{Gender}_i + \gamma_{03}\text{Race}_i + \gamma_{04}\text{Education}_i + \gamma_{05}\text{SF-36 Physical Function}_i + u_{0i}$</p> <p>$\beta_{1i} = \gamma_{10} + \underline{\gamma_{17}\text{MemvsControl}_i} + u_{1i}$</p>	<p>Level 1: Digit Symbol Copy_{ji} = $\beta_{0i} + \beta_{1i}\text{Month}_{ji} + e_{ji}$</p> <p>Level 2: $\beta_{0i} = \gamma_{00} + \gamma_{01}\text{Age}_i + \gamma_{02}\text{Gender}_i + \gamma_{03}\text{Race}_i + \gamma_{04}\text{Education}_i + \gamma_{05}\text{SF-36 Physical Function}_i + u_{0i}$</p> <p>$\beta_{1i} = \gamma_{10} + \underline{\gamma_{17}\text{ReasvsControl}_i} + u_{1i}$</p>
Turn 360	<p>Level 1: Turn 360_{ji} = $\beta_{0i} + \beta_{1i}\text{Month}_{ji} + e_{ji}$</p> <p>Level 2: $\beta_{0i} = \gamma_{00} + \gamma_{01}\text{Age}_i + \gamma_{03}\text{Race}_i + \gamma_{05}\text{SF-36 Physical Function}_i + u_{0i}$</p> <p>$\beta_{1i} = \gamma_{10} + \gamma_{11}\text{Age}_i + \underline{\gamma_{17}\text{SpeedvsControl}_i} + u_{1i}$</p>	<p>Level 1: Turn 360_{ji} = $\beta_{0i} + \beta_{1i}\text{Month}_{ji} + e_{ji}$</p> <p>Level 2: $\beta_{0i} = \gamma_{00} + \gamma_{01}\text{Age}_i + \gamma_{03}\text{Race}_i + \gamma_{05}\text{SF-36 Physical Function}_i + u_{0i}$</p> <p>$\beta_{1i} = \gamma_{10} + \gamma_{11}\text{Age}_i + \underline{\gamma_{17}\text{MemvsControl}_i} + u_{1i}$</p>	<p>Level 1: Turn 360_{ji} = $\beta_{0i} + \beta_{1i}\text{Month}_{ji} + e_{ji}$</p> <p>Level 2: $\beta_{0i} = \gamma_{00} + \gamma_{01}\text{Age}_i + \gamma_{03}\text{Race}_i + \gamma_{05}\text{SF-36 Physical Function}_i + u_{0i}$</p> <p>$\beta_{1i} = \gamma_{10} + \gamma_{11}\text{Age}_i + \underline{\gamma_{17}\text{ReasvsControl}_i} + u_{1i}$</p>

Note. For all models, assessment j of individual i . Bolded and underlined parameters indicate the parameters used to evaluate Aim 1's analyses. Aim 1a was a true ITT model, and Aim 1b was filtered to only those who completed at least eight of the 10 initial training sessions. Aim 2 models were the same as Aim 1a models except the inclusion of cognitive self-efficacy, depressive symptoms, or bodily pain parameters in the β_{1i} equation. See Chapter 2, analytic strategy for more detail.

Sprague Vitae

PEER-REVIWED MANUSCRIPTS

- Sprague, B. N.**, Freed, S. A., Webb, C. E., Phillips, C. B., Hyun, J., & Ross, L. A. (in press). The impact of behavioral interventions on cognitive function in healthy older adults: A systematic review. *Ageing Research Reviews*.
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