UNIVERSITY OF CALIFORNIA, SAN DIEGO

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Anxiety and Cognition in Swedish Twins: Genetic and Environmental Influences

A dissertation submitted in partial satisfaction of the requirements for the degree of

Doctor of Philosophy

in

Clinical Psychology

by

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2014

The Dissertation of Andrew John Petkus is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

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PUBLICATIONS

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1. **Petkus, A. J.**, Gum, A. M., & Wetherell, J. L. (in press). Anxiety is associated with cognitive impairment in homebound older adults. *International Journal of Geriatric Psychiatry.*

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4. Steiner, A., **Petkus, A. J.**, Nguyen, H., & Wetherell, J. L. (in press). Attention bias and SSRI treatment in older adults with Generalized Anxiety Disorder. *Journal of Anxiety Disorders.*

5. **Petkus, A. J.**, & Wetherell, J. L. (2013). Acceptance and Commitment Therapy with older adults: Rationale and considerations. *Cognitive and Behavioral Practice*. *20*, 47-56.

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13. **Petkus, A. J.**, Gum, A. M., Small, B. J., Malcarne, V., Stein, M. B., & Wetherell, J. L. (2010). Evaluation of the factor structure and psychometric properties of the Brief Symptom Inventory – 18 with homebound older adults. *International Journal of Geriatric Psychiatry, 25,* 578-587.

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Book Chapters

1. **Petkus, A. J.**, Merz, C., & Wetherell, J. L. (in press). Developmental pathways to anxiety disorders in older adulthood. In M. G. Emmelkamp & T. Ehring (Eds.), *International Handbook of Anxiety Disorders*. New York: Wiley Blackwell.

2. **Petkus, A. J.**, Lenze, E. J., & Wetherell, J. L. (2013). Anxious depression: Application of the transdiagnostic model to older adults. In M. Sajatovic, H. Lavretsky, and C. F. Reynolds, Eds., *Late Life Mood Disorders*. New York: Oxford University Press.

3. Wetherell, J. L., Ruberg, J., & **Petkus, A. J.** (2010). Generalized anxiety disorder. In K. H. Sorocco & S. Lauderdale (Eds.), *Cognitive behavior therapy with older adults: Innovations across care settings (pp. 157-188).* New York: Springer.

CONFERENCE PRESENTATIONS

1. **Petkus, A.J.**, Wetherell, J.L., Reynolds, C., Kremen, W., & Gatz, M. *Anxiety and cognitive functioning in older adults.* In L. Gerolimatos & B. Edelstein (Chairs), *Late-life anxiety and comorbid cognitive and functional impairment.* Symposium submitted to be presented at the annual meeting of the Gerontological Society of America, New Orleans, LA, November 2013.

2. Bower, E., Merz, C., Wetherell, J.L., **Petkus, A. J.**, & Lenze, E. J. *Psychometric properties of the falling questionnaire in older adults.* Poster submitted to be presented at the annual meeting of the Gerontological Society of America, New Orleans, LA, November 2013.

3. **Petkus, A.J.**, Wetherell, J.L., Reynolds, C., Kremen, W., & Gatz, M. *State anxiety and cognitive functioning in older adults.* Poster to be presented at the annual meeting of the Anxiety Disorders and Depression Association of America, La Jolla, CA, April 2013.

4. Wetherell, J. L., Johnson, K., Chang, D., Ward, S., Merz, C., **Petkus, A. J.**, & Bower, E. S. *Activity, balance, and exposure (ABLE): A new intervention for excessive fear of falling.* Poster to be presented at the annual meeting of the American Association for Geriatric Psychiatry, Los Angeles, CA, March 2013.

5. Wetherell, J. L., **Petkus, A. J.**, & Lenze, E. J. *Fear of falling and rehabilitation outcomes in older adults recovering from hip fracture*. In G. I. Kempen (Chair), *Falls and fear of falling: New findings on determinants and consequences*. Symposium presented at the annual meeting of the Gerontological Society of America, San Diego, CA, November 2012.

6. **Petkus, A. J.**, Wetherell, J. L., Stein, M. B., Craske, M. G., Chavira, D., & Roy-Byrne, P. *Suicidal ideation and response to treatment in older adults with social anxiety disorder.* Paper presented at the annual meeting of the Gerontological Society of America, San Diego, CA, November 2012.

7. Merz, C., **Petkus, A. J.**, Wetherell, J. L., & Lenze, E. J. *The psychometric properties of the falling questionnaire.* Poster presented at the annual meeting of the Anxiety Disorders Association of America, Washington, DC, April 2012.

8. **Petkus, A. J.**, Wetherell, J. L., & Gum, A. M. *Anxiety is associated with cognitive impairment in homebound older adults.* Poster presented at the annual meeting of the Anxiety Disorders Association of America, Washington, DC, April 2012.

9. Wetherell, J. L., **Petkus, A. J.**, Stein, M. B., Craske, M. G., Chavira, D., & Roy-Byrne, P. *Age differences in treatment response to a collaborative care intervention for anxiety disorders in primary care.* Paper presented at the annual meeting of the Anxiety Disorders Association of America, Washington, DC, April 2012.

10. Wetherell, J. L., Johnson, K., Ward, S., Chang, D., & **Petkus, A. J.** *Activity, Balance, Learning, and Exposure (ABLE): A new intervention for excessive fear of falling.* In J. L. Wetherell (Chair), *Body-mind medicine: Rehabilitation interventions to enhance mental health.* Symposium presented at the annual meeting of the American Association for Geriatric Psychiatry, Washington, DC, March 2012.

11. Wetherell, J. L. & **Petkus, A. J.** *Acceptance and Commitment Therapy for chronic pain in older adults.* In H. Lavretsky (Chair), Update on integrative geriatric psychiatry: Is it complementary or alternative? Symposium presented at the annual meeting of the American Association for Geriatric Psychiatry, Washington, DC, March 2012.

12. Sorrell, J. T., Atkinson, J., Afari, N., Rutledge, T., Stoddard, J., **Petkus, A. J.**, Solomon, B., Lehman, D., Liu, L., Lang, A., & Wetherell, J. *ACT and CBT for Chronic Pain: A Randomized, Controlled Trial.* Presentation made at the annual meeting of the American Association of Pain Medicine, Palm Springs, CA, February 2012.

13. **Petkus, A. J.**, Wetherell, J. L., & Lenze, E. J. *Fear of Falling, Physical function, and psychological factors after hip fracture.* Poster presented at the annual Meeting of the Gerontological Society of America, Boston, MA, November 2011.

14. Wetherell, J. L., Johnson, K., Ward, S., Chang, D., & **Petkus, A. J.** *Activity, Balance, Learning, and Exposure (ABLE): A new intervention for excessive fear of falling.* Poster presented at the annual Meeting of the Gerontological Society of America, Boston, MA, November 2011.

15. VanBuskirk, K., **Petkus, A. J.**, & Wetherell, J. L. *Study design and treatment outcomes: The effect of waiting list duration, patient expectations, and patient*

satisfaction. Poster presented at the annual meeting of the Society of Behavioral Medicine, Washington, DC, April 2011.

16. Wetherell, J. L., & **Petkus, A. J.** *Attention bias and treatment outcome in older adults with Generalized Anxiety Disorder.* In J. L. Wetherell (Chair), *Risk factors and predictors of outcome for geriatric anxiety.* Symposium presented at the annual meeting of the Anxiety Disorders Association of America, New Orleans, LA, March 2011.

17. **Petkus, A. J.**, Gum, A. M., & Wetherell, J. L. *Thought suppression is associated with distress in homebound elders.* In J. L. Wetherell (Chair), *Risk factors and predictors of outcome for geriatric anxiety.* Symposium presented at the annual meeting of the Anxiety Disorders Association of America, New Orleans, LA, March 2011.

18. **Petkus, A. J.**, Wetherell, J. L., Stein, M. B., Liu, L., & Barrett-Connor, E. *History of sexual assault is associated with earlier declines in executive functioning in older adults with APOE-4.* Paper presented at the annual meeting of the Gerontological Society of America, New Orleans, LA, November 2010.

19. Wetherell, J. L., Rutledge, T., Sorrell, J., & **Petkus, A. J.** *Acceptance and Commitment Therapy and Cognitive Behavioral Therapy for chronic pain.* Paper presented at the annual meeting of the American Psychological Association, San Diego, CA, August 2010.

20. **Petkus, A. J.**, Ayers, C. R., Liu, L., & Wetherell, J. L. *Life events, avoidant coping, and anxiety in older GAD patients.* Poster session to be presented at the annual meeting of the American Psychological Association, San Diego, CA, August 2010.

21. **Petkus, A. J.**, Gum, A. M., King-Kallimanis, B., & Wetherell, J. L. *History of trauma exposure and physical and psychological well-being of homebound older adults.* Poster session presented at the annual meeting of the American Association for Geriatric Psychiatry, Honolulu, HI, March 2009.

22. Iser, L., **Petkus, A. J.**, & Gum, A. M. *Falls are associated with antidepressant medications and dizziness in homebound older adults.* Poster session presented at the annual meeting of the American Association for Geriatric Psychiatry, Honolulu, HI, March 2009.

23. Gum, A. M., **Petkus, A. J.**, McDougal, S. J., Present, M., & King-Kallimanis, B. *Identification of behavioral health issues in recipients of home-based aging services.* Poster session presented at the annual meeting of the American Association for Geriatric Psychiatry, Orlando, FL, March 2008.

24. Lunsman, M., McFadden, S. H., **Petkus, A.**, & Wolff, A. *The effect of participation in a structured group activity on social behaviors of residents with dementia.* Poster session presented at the annual meeting of the Gerontological Society of America, Dallas, TX, November 2006.

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ABSTRACT OF THE DISSERTATION

Anxiety and Cognition in Swedish Twins: Genetic and Environmental Influences

by

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Doctor of Philosophy in Clinical Psychology

University of California, San Diego, 2013
San Diego State University, 2013

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Cognitive impairment and anxiety disorders are the two most common psychiatric disorders in later life. These problems commonly co-occur and are associated with a range of negative outcomes such as increased functional impairment, greater healthcare utilization, and elevated risk of nursing home placement. Little research has examined the stability of genetic influences on anxiety symptoms in older adults. Similarly, the temporal dynamics of the relationship between cognitive performance and anxiety as well as the extent to which shared genetic factors explain

this association is unclear. The specific goals of this dissertation were to (1) explore the stability of genetic and environmental influences on anxiety in older adulthood, (2) explore the extent to which genetic factors influencing anxiety are also influencing cognitive performance, (3) determine the temporal dynamics of this phenotypic association, and (4) examine the extent to which genetic and environmental factors were driving this association over time.

Design: We examined data from the Swedish Adoption/Twin Study of Aging (SATSA). Between the years 1984 - 2007, 2,018 participants aged 31-98 years completed as many as 7 assessments which included measures of anxiety and cognitive performance. For aim 1, genetic simplex models were fit to examine the stability of genetic and environmental influences on anxiety later in life. For the second aim bivariate Cholesky decompositions were conducted to examine the extent to which shared genetic influences explained the association between anxiety and cognitive performance. For aim 3 we examined the temporal dynamics of the association between anxiety and cognitive performance by fitting bivariate dual change score models (DCSM). For the last aim biometric DCSM models were estimated to examine the temporal dynamics of genetic and environmental contributions.

Results: New genetic contributions to the etiology of anxiety were found beginning at the ages 60-64. New significant unique environmental factors contributed to anxiety symptoms starting after age 70. For aim 2, in males anxiety was associated with worse nonverbal memory, attention, working memory, and aspects of spatial performance.

Anxiety was only associated with worse visuospatial performance and picture memory in females. For males, shared genetic factors were mostly explaining this association. For females unique environmental factors were explaining this association. When examining this association over time, across all cognitive tests worse cognitive performance was a leading indicator of change in anxiety. Anxiety was not associated with subsequent changes in cognitive performance. The biometric models suggested that genetic factors contributing to variance in processing speed and attention were driving variation in anxiety over time. Unique environmental contributions to spatial abilities were driving subsequent variation in anxiety.

Conclusions: The findings from these four studies deepen our understanding of the etiology of late life anxiety and its association with cognitive performance. This information can help to identify older adults at risk for the development of anxiety. The findings from this study also may inform intervention and prevention efforts for older adults experiencing cognitive decline and anxiety.

Anxiety and Cognition in Swedish Twins: Genetic and Environmental Influences

INTRODUCTION

Adults over the age of 65 are the fastest growing segment of the population, with numbers expected to double to an estimated 72 million people, or 20% of the U.S. population by the year 2030 (Jacobsen, Kent, Lee, & Mather, 2011) . Anxiety disorders are the most prevalent psychiatric disorder other than cognitive impairment in older adulthood, with as many as 14% of older adults meeting diagnostic criteria for an anxiety disorder (Wolitzky-Taylor, Castriotta, Lenze, Stanley, & Craske, 2010). Late-life anxiety is associated with negative outcomes such as greater functional impairment (Brenes et al., 2008; Porensky et al., 2009), death ideation (Van Orden, Simning, Conwell, Skoog, & Waern, 2013), more health care utilization (Porensky, et al., 2009; Vasiliadis et al., 2012) , and greater risk for nursing home placement (Gibbons et al., 2002). As the aging population grows so will the importance of understanding anxiety in later life

Symptoms of anxiety in later life are relatively stable and frequently lead to the development of depressive symptoms (Wetherell, Gatz, & Pedersen, 2001). Due to the chronic nature of anxiety, a majority of older adults with anxiety disorders have had these disorders most of their lives (Goncalves & Byrne, 2012a; Kessler et al., 2005). Onset in later life does exist and is relatively common. Chou (2009) found in a large epidemiological study, that almost half of the older adults with Generalized Anxiety Disorder (GAD) had onset after the age of 55. Treatment studies of late life GAD suggest that the disorder may have a bimodal onset with a peak of onset earlier

in life as well as increased rate of incidence after the age of 50 (Le Roux, Gatz, & Wetherell, 2005). It seems as if anxiety is stable across later life with evidence for a later life onset.

What is contributing to this stability over time? Specifically, are the genetic and/or environmental contributions to anxiety symptoms stable across older adulthood? A number of differences exist in the presentation of anxiety later in life compared with to younger adulthood. New physiological (e.g. biological aspects of normal aging, chronic illnesses, and cognitive impairment) or environmental (e.g. role transitions associated with aging, loss of independence, caregiving for significant other, and bereavement) may be unique to the presentation of anxiety later in life (Wolitzky-Taylor, et al., 2010).

Although it is understood that these new physiological and environmental influences may co-occur more frequently with anxiety in later life, little is known about the stability of genetic and environmental contributions to the overall etiology of anxiety across older adulthood. Twin behavioral genetic studies allow for the examination of the overall contribution of genes and environment on a phenotype. Twin studies examining the contribution of genes to the etiology of anxiety suggest that genetic factors explain approximately 34-46% of the variance in anxiety symptoms in younger adults (Kendler, Heath, Martin, & Eaves, 1986). Similar estimates of the genetic contributions to anxiety disorders have been found with research suggesting that one set of genetic influences convey risk across all of the different anxiety disorders (Hettema, Prescott, Myers, Neale, & Kendler, 2005). The

genetic contribution to the respective anxiety disorders have been estimated as follows: GAD = 0.20, Panic = 0.27, Agoraphobia = 0.20, Social Phobia = 0.10, and specific phobia = 0.24. Research examining the variability of depressive disorders and depressive symptoms across the lifespan suggests that new genetic influences may emerge later in life. A longitudinal examination of individuals across the lifespan found new genetic influences on depressive symptoms in females at age 70 (Gillespie et al., 2004). Gatz et al. (1992) found that the heritability of depressive symptoms was greater in adults older than 60 than in adults younger than 60. In another examination, Carmelli et al. (2000) found that genetic influences on depression increased in later life by approximately 25%. These studies examining the genetic contributions to depression have been mixed however, as some studies have reported no moderating effect of age on heritability of depressive symptoms (Johnson, McGue, Gaist, Vaupel, & Christensen, 2002; McGue & Christensen, 2003). It is unknown the extent to which age moderates the heritability of anxiety symptoms.

Identifying the extent to which new genetic factors or environmental stressors contribute to the etiology of anxiety during later life is important for a number of reasons. Identifying these factors may help to identify new targets for psychosocial and pharmacological treatments. A better understanding of the contribution of genes and environment also may aide in identifying older adults who are at particularly high risk for the development of anxiety. Mental health disorders in later life are often undetected by healthcare providers resulting in older adults in need not receiving adequate treatment (Gum et al., 2011). In addition to potentially improving

interventions, learning how genetic and environmental influences are contributing to the stability of symptoms later in life may also improve screening, preventative, and treatment outreach efforts.

The first aim of this dissertation attempted to address this first gap in the literature. Specifically, we aimed to examine the stability of genetic and environmental contributions on anxiety symptoms across older adulthood. We sought to identify if new genetic or environmental influences are contributing to the etiology of anxiety symptoms in older adulthood. Similar to studies with depression, we hypothesized that new genetic innovations will be contributing to the etiology of anxiety in later life.

Although twin studies are beneficial in that they provide an overall estimation of the contribution of genes and environment on a trait, they do not provide information regarding what those specific genetic or environmental contributions are. Examining characteristics that are unique to the presentation of anxiety may shed light onto what these specific genetic or environmental influences might be. As previously described, factors that commonly co-occur with anxiety in older adults more frequently than younger adults are cardiovascular disease, functional impairment, and providing care for a significant other (Chou, 2009).

Cognitive functioning is another factor salient to anxiety in later life (Beaudreau & O'Hara, 2008). Specifically, poorer cognitive performance has been associated with increased anxiety. A number of questions regarding the nature of this association remain unanswered. It is unclear the extent to which shared genetic factors common to both anxiety and cognitive performance are explaining this association.

The directionality of the association is also not clear. Lastly, it is unclear what genetic or environmental factors are driving this longitudinal association.

The cognitive domains that appear most associated with anxiety are domains mediated by the frontal and temporal regions of the brain. Cross-sectional examinations with community dwelling older adults document that higher state anxiety symptoms are associated with worse learning and delayed recall (Bierman, Comijs, Jonker, & Beekman, 2005) as well as set-shifting and delayed recall (Booth, Schinka, Brown, Mortimer, & Borenstein, 2006). Similarly, Beaudreau and O'Hara (2009) found that increased symptoms of anxiety were associated with slower processing speed, poorer set-shifting, and inhibition. This association is also independent of depressive symptoms. Anxiety disorders in late life have also been correlated with worse cognitive abilities. Mantella et al. (2007) found that older adults with Generalized Anxiety Disorder (GAD) had worse memory and executive functioning than participants without GAD. This association has also been found in physically frail older adults who are homebound. Petkus, Gum, & Wetherell (in press) found that anxiety symptoms or meeting criteria for an anxiety disorder was associated with increased likelihood of having cognitive impairment independent of physical health, age, education, and depression in homebound elderly.

Longitudinal studies find that anxiety symptoms and disorders may be associated with cognitive decline over time. Community dwelling older adults with clinically significant symptoms of anxiety may be four times more likely to be identified as cognitively impaired on the Mini Mental Status Exam (MMSE) over the

next three years (Sinoff & Werner, 2003). The cognitive component of anxiety, specifically worry, may be particularly important. Community dwelling older adults experiencing mild worry symptoms had worse performance on tasks of visual and associate learning. Additionally, in this study those with higher worry were more likely to exhibit clinically significant declines in functioning two years later (Pietrzak et al., 2012). Suffering from an anxiety disorder may confer additional risk to cognitive impairment. Depressed older adults with comorbid GAD or Panic disorder had greater declines in memory performance than those without comorbid anxiety (DeLuca et al., 2005). Anxiety also appears to be associated with increased risk of developing cognitive syndromes such as mild cognitive impairment or dementia. Anxiety disorders in men and anxiety symptoms in women were found to be associated with increased risk of new incidence cognitive impairment (Potvin, Forget, Grenier, Preville, & Hudon, 2011). Qureshi et al. (2010) found that older veterans with PTSD were approximately twice as likely to develop dementia when compared to veterans without PTSD. In another retrospective medical records examination, Yaffe et al. (2010) found that 10% of older adults with PTSD went on to develop dementia over a span of seven years compared to 6.6% of those without PTSD. Furthermore, PTSD was associated with being twice as likely to develop dementia over this follow-up period even after controlling for depression, substance abuse, and head injury. There have been some mixed findings, however, with not all research finding an association between anxiety and cognitive decline over time (Wetherell, Reynolds, Gatz, & Pedersen, 2002). Taken together the evidence from cross-sectional and

longitudinal studies document that anxiety and cognition are related and anxiety may be a risk factor for future decline.

Evidence also exists to suggest declining cognitive performance may lead to subsequent increases in anxiety. Rates of psychiatric symptoms such as depression and anxiety are higher in older adults with clinically significant cognitive deficits such as Mild Cognitive Impairment (MCI) or dementia. As many as 29% of older adults with MCI and 69% with dementia suffer from clinically significant symptoms of emotional distress (Lyketsos et al., 2002). Older adults with MCI are three times more likely to have clinically significant anxiety than those with normal cognitive functioning (Geda et al., 2008). Anxiety and worry are some of the most common psychiatric symptoms affecting older adults with dementia (Teri et al., 1999). Anxiety may be an important predictor of future cognitive decline and disease progression from MCI to dementia (Palmer et al., 2007). Compared to younger worriers, older adults may worry more about health (Goncalves & Byrne, 2012b). Lastly, Jajodia and Borders (2011) found that memory decline was associated with subsequent increases in depression; however depression was not associated with future declines in memory. This research with cognitively impaired older adults demonstrates that cognitive decline may be a risk factor for increased emotional distress such as anxiety.

Mechanisms

The hypothalamic-pituitary-adrenal (HPA) axis is a physiological system mediating the hormonal response to stress that is associated with anxiety that may also affect cognition (Carlson, 2004).

Chronic activation of the HPA axis has been shown to be associated with increased risk for chronic physical conditions particularly cardiovascular diseases (i.e. high blood pressure, diabetes, and heart disease). In addition to negatively influencing physical health, chronically elevated cortisol may affect cognitive functioning. Elevated cortisol levels have been shown to damage the hippocampus (Lupien et al., 1998) which in turn may explain deficits in learning and memory. The prefrontal cortex may also be vulnerable to damage from cortisol (Kremen et al., 2010). In this study elevated cortisol was also associated with worse visuospatial ability, abstract reasoning, processing speed, and executive functioning. Furthermore, those with higher cortisol levels had significantly thinner prefrontal cortices.

Anxiety is associated with a dysregulation of this stress response. Individuals with anxiety disorders have repeatedly shown to exhibit a chronic hyperactivation of the HPA axis and elevated cortisol levels (Mantella et al., 2008). Treatment for late life anxiety may result in decreased HPA activation (Lenze et al., 2011). Furthermore, these decreases are correlated with improvements in memory (Lenze et al., 2012). Studies with younger adults suggest that individuals with anxiety disorders may have smaller hippocampal volumes (Stein, Koverola, Hanna, Torchia, & McClarty, 1997) as well as smaller prefrontal cortices (Corbo, Clement, Armony, Pruessner, & Brunet, 2005; Radua, van den Heuvel, Surguladze, & Mataix-Cols, 2010) than those without an anxiety disorder. A study with older adults with PTSD supports this hypothesis that chronically elevated anxiety may be damaging these brain areas (Cardenas et al., 2011). In this study, PTSD was associated with increased atrophy of the prefrontal

cortex over time and the amount of atrophy correlated with changes in cognitive functioning.

Cognitive theories, specifically Eysenck's theory of cognitive processing, may also explain this relationship between cognition and anxiety (M. Eysenck & Calvo, 1992; M. W. Eysenck, Derakshan, Santos, & Calvo, 2007). This theory posits that anxiety is a survival process with the adaptive value of detecting and protecting us from threat. As such, when experiencing anxiety our cognitive and attentional resources are allocated to any threatening stimuli in the environment. Individuals with elevated anxiety tend to be hypervigiliant to task irrelevant and ambiguous stimuli. As a result, cognitive resources are wasted leaving fewer resources to be allocated to the primary task the individual is engaging in. The primary result is an overall deficit in cognitive performance. This theory suggests that older adults may be more vulnerable to the cognitive effects of anxiety. Cognitive functions such as processing speed, executive functioning, and fluid intelligence decline as part of the aging process (Salthouse, 2010). Thus, anxiety may consume already decreasing cognitive resources explaining why anxiety is associated with cognitive deficits later in life.

Cognitive performance may also influence subsequent anxiety levels (Kremen, Lachman, Pruessner, Sliwinski, & Wilson, 2012). Cognitive problems may be a source of worry and anxiety in older adults. Older adults are more likely to worry about developmental salient things such as health (Gould & Edelstein, 2010; Wetherell, Le Roux, & Gatz, 2003). Because anxious older adults worry more about health it is likely that declining cognitive performance may be the content of current and future

worries as well. One aspect of executive functioning is problem solving (Burton, Strauss, Bunce, Hunter, & Hultsch, 2009; Burton, Strauss, Hultsch, & Hunter, 2006). Thus, deficits in problem solving may result in result in ability to deal with current stressors or prevent future stressors from arising in the future. This inability to adequately solve problems may in turn result in the development of anxiety. Research conducted with younger adults support this hypothesis. Higher cognitive performance at age 20 was associated with lower cortisol levels at age 55, suggesting the protective effects of cognition on subsequent stress levels (Franz et al., 2011).

Shared genetic contributions to both anxiety and cognitive functioning later in life may also explain this relationship. It is possible that genetic factors influencing anxiety may be shared with cognitive functioning and cognitive decline. Although findings have been mixed, the short form of the serotonin polymorphism transporter gene (5HTTLPR) appears to be associated with increased risk for a number of psychiatric conditions such as depression (Lotrich & Pollock, 2004), and anxiety (Schinka, Busch, & Robichaux-Keene, 2004). While less research has examined the 5HTTLPR allele in relation to cognitive functioning, there appears to be an association between this allele and cognitive abilities. O'Hara et al. (2007) found that those with the short form of the 5HTTLPR allele had worse memory function and lower hippocampal volume than those with the long allele. Additionally, they found a significant interaction with cortisol in that those with the short allele had higher waking cortisol. Other research found that older adults with the short allele performed significantly worse on a cognitive screening test than those with the long allele

(O'Hara et al., 2012). A large body of research has implicated the apolipoprotein (APOE) ε4 allele as a risk factor for declines in cognitive functioning in later life (Bookheimer & Burggren, 2009; Small, Rosnick, Fratiglioni, & Backman, 2004). Research suggests that the effects of this gene are modified by stress such as anxiety. Carriers of the APOE ε4 allele may be more vulnerable to the adverse effects of stress and cortisol on cognitive functioning (Lee et al., 2008). Older adults with the APOE ε 4 allele who experience a significant stressful life event later in life may have greater declines in cognition than those without this allele (Comijs, van den Kommer, Minnaar, Penninx, & Deeg, 2011). Similarly, older adults with the APOE e4 allele who experienced a sexual assault in adolescence or early adulthood experienced greater and earlier declines in executive functioning later in life (A. J. Petkus, Wetherell, Stein, Liu, & Barrett-Connor, 2012). Carriers of the APOE e4 allele who experience depressive symptoms appear more vulnerable to cognitive decline than those without depressive symptoms (Corsentino, Sawyer, Sachs-Ericsson, & Blazer, 2009). These studies examining specific genes suggest that some of the genetic influences on anxiety and cognition may be shared. The total proportion of the variance in these phenotypes accounted for by shared genetic factors however is unknown.

This review of the literature highlights a number of important areas for future examination on cognition and anxiety. The directionality of the relationship between anxiety and cognitive aging is not clear. Specifically, it is unclear if changes in anxiety occur before future declines in cognitive functioning, if cognitive declines are

occurring before increases in anxiety, or if this is a bi-directional relationship (Kremen, et al., 2012). Additionally, it is unclear the extent to which genetic influences on anxiety vary across middle adulthood into later life. The extent to which genetic influences on anxiety and cognition are shared later in life is also unknown. Understanding how anxiety and cognitive impairment interact with each other can help improve prevention and detection of these problems later in life. Furthermore, understanding how genetic and environmental influences contribute to this association is crucial, as this research can help elucidate biological and environmental mechanisms which than can then be the targets for future interventions.

Current Aims

This dissertation attempted to address these aforementioned gaps in the literature by investigating the temporal dynamics of the association between anxiety and cognitive performance. More specifically, this study aims to:

Specific Aim 1: Explore the variation in the genetic influences on state anxiety across the second half of the lifespan.

Specific Aim 2: Explore the extent to which shared genetic and environmental influences explain the cross-sectional correlation between cognition and anxiety.

Specific Aim 3: Examine the temporal dynamics of the phenotypic association between anxiety and cognitive functioning over time.

Specific Aim 4: Explore the extent to which shared genetic influences explain the correlation between cognition and anxiety over time.

Introduction acknowledgment

The introduction to the dissertation, in part is currently being prepared for submission for publication. The dissertation author was the primary investigator and author of this material. Co-authors to this work include: Julie Wetherell, Ph.D., Chandra Reynolds, Ph.D., William Kremen, Ph.D., Niloofar Afari, Ph.D., Deborah Finkel, Ph.D., and Margaret Gatz, Ph.D.. The dissertation/thesis author was the primary investigator and author of this paper.

METHOD

Participants and recruitment: Archival data was drawn from the Swedish Adoption Twin Study of Aging (SATSA), a subset of the Swedish Twin Registry. The Swedish Twin Registry includes data from all same-sex twin pairs born in Sweden between 1886 and 1958 and is representative of the Swedish population (Cederlof & Lorich, 1978). SATSA contains all twins from the Swedish registry who were separated and reared apart before the age of 11 as well as twins reared together who were matched with the twins reared apart on gender, county of birth, and age (Finkel & Pedersen, 2004; Pedersen, Friberg, Floderus-Myrhed, McClearn, & Plomin, 1984). Beginning in 1984, this study enrolled 2,019 participants (758 complete twin pairs) from the larger Swedish Twin Registry. In 1986, a subsample of those twins aged 50 or older completed an in-person assessment that included a cognitive battery. Participants completed subsequent follow-up assessments every three years. Participants who were younger than 50 years old at the first in-person assessment but turned 50 during the follow-up period were invited to complete the cognitive tests upon their 50th birthday. See figure 1 for flow chart of the assessment schedule with the number of participants and twin pairs at each time point.

This dataset is particularly advantageous as a means for investigating our research question. Due to the fact that half of the twin pairs were reared apart, this dataset has increased power to examine the contribution of shared environmental influences. Participants completed as many as seven assessments over a span of 26 years. This assessment schedule allows for the examination of non-linear trajectories

of the variables of interest over time. For greater detail on the SATSA methods and sample, please see Finkel & Pederson (2004) or Pedersen et al. (1984).

Procedures: Participants were invited to participate in SATSA with the purpose of examining health and cognitive abilities. Between the years of 1984-2007, twin pairs completed both questionnaires and in-person testing assessments (IPTs). Participants completed IPTs and mailed questionnaires approximately every three years. Due to a gap in funding, the fourth IPT was conducted over the phone; thus, cognitive data are not available for this time period. Participants were assessed on the following schedule: IPT1 = 1986-1988; IPT2 = 1989-1991; IPT3 = 1992-1994; IPT4 = 1995-1997; IPT5 = 1999-2001; IPT6 = 2002-2004; IPT7 = 2005-2007. All participants, regardless of age, completed mailed questionnaires every 3 years. Mailed questionnaires included the assessment of anxiety and neuroticism, but did not include cognitive assessments. Participants completed the questionnaires during the following years: Q1 = 1984, Q2 = 1987, Q3 = 1990, Q4 = 1994, Q5 = 2004, Q6 = 2007, & Q 7 = 2010. All participants with at least one assessment were included in the study.

The assessment battery included measures of various cognitive abilities and anxiety. Cognitive measures were administered only during the IPTs. Measures of anxiety were administered during both the IPT and questionnaire assessments. Other data such as demographic information, zygosity (monozygotic vs. dyzygotic), and rearing status (apart vs. together) were evaluated at each participant's Q1 assessment.

Measures:

Anxiety: State anxiety was measured using the state anxiety subscale of the State-Trait Personality Inventory (STPI; Spielberger, 1983). The STPI has been shown to be reliable and valid with community dwelling older adults (Potvin et al., 2011). The STPI was administered at Q1, Q2, Q3, Q4 as well as IPT2 and IPT3.

Neuroticism: Neuroticism was measured using the Eysenck Personality Inventory. The ENI is a 9-item scale in which participants rate dichotomously (No = 0, Yes = 1) if they have been experiencing the item in past two weeks. Higher scores represent more neuroticism. Neuroticism was administered at all the questionnaire time points (Q1-Q7) as well as IPT 2 thru IPT7.

Anxiety Crosswalk: In order to utilize all assessment points in the analyses, a Rasch analysis was conducted to create a crosswalk between the ENI and STPI. The resulting crosswalk score is a calculated STPI score based on the ENI. The similarity of the item content and theoretical association between measures provides the basis of this analysis. Table 1 presents a comparison of the items on the STPI and ENI. Neuroticism is a personality trait common to both anxiety symptoms and disorders (Clark & Watson, 1991; Weinstock & Whisman, 2006). Due to the significant overlap between the constructs of anxiety and neuroticism as well as item overlap of the ENI and STPI, we hypothesized that the ENI and STPI are measuring the same underlying construct. Although these measures have different rating scales they can be linked together and put onto the same metric using Rasch analysis. Additional information on the crosswalk procedure will be provided in the statistical analysis and results section.

The Anxiety Crosswalk variable was computed at each time point the ENI was administered (i.e. Q1-Q7 and IPT2-IPT7).

Cognitive Assessment: The SATSA cognitive battery is designed to measure the cognitive domains of processing speed, nonverbal memory, attention/working memory, and spatial abilities. A total of 9 cognitive tests were administered to measure these four domains of functioning. The proportion of points earned out of the total points possible (0-100) was calculated and used as the outcome for all cognitive tests. Prior SATSA investigations report high reliabilities of these cognitive tests, with alphas ranging from 0.82-0.96 (Finkel, Reynolds, McArdle, Gatz, & Pedersen, 2003; Finkel, Reynolds, McArdle, Hamagami, & Pedersen, 2009; Finkel, Reynolds, McArdle, & Pedersen, 2005, 2007).

Processing Speed:

Symbol Digit: Participants were presented with symbols and participants are asked to verbally report digits that correspond to the symbols (Pedersen, Plomin, Nesselroade, & McClearn, 1992).

Figure Identification (Dureman, Kebbon, & Osterberg, 1971): Participants completed a 60-item pattern-matching test. Each item has five choices, and participants are instructed to identify the item that matches the target item as quickly as possible.

Memory:

Thurstone Picture Memory: (Dureman, et al., 1971) The Thurstone Picture Memory test measures visual recognition memory. Participants are presented with 28

drawings of items for five seconds then are asked to recall which items they had previously seen.

Attention/Working Memory:

Digit Span: (Jonsson & Molander, 1964) Attention and working memory were assessed using the Digit Span test. Participants are asked to repeat strings of 3-9 digits forward and backward. The final score is the sum of the highest number of digits the participant can recall forward and backward. Digit Span forward is a measure of attention while Digit Span backwards measures both attention and working memory (Ramsay & Reynolds, 1995). In this study we analyzed Digit Span both as a composite total score of digits forward and backwards combined and with both subtests separately.

Visuospatial abilities:

Koh's Block Design: (Dureman, et al., 1971) The Block Design task is similar to the WAIS Block Design task. Participants use blocks to create seven designs. Each item is scored from 0-6 based on the amount of time taken to complete the design.

Card Rotations: (Ekstrom, French, & Harman, 1976) Participants are given a target design followed by four items. Participants then rate which of the items was a rotated form of the target. Possible scores range from 0 to 112.

Other Covariates: Depression was measured with the Center for Epidemiological Studies Depression (CES-D) scale (Radloff, 1977). The CES-D has been shown to be reliable and valid with community dwelling older adults (Hertzog, Van Alstine, Usala, Hultsch, & Dixon, 1990). The CESD was administered at each

IPT. Education was assessed at Q1 and was coded on a four-point scale (1 = elementary education to 4 = university or higher).

Zygosity and rearing status: Monozygotic (MZ) twins are genetically identical and share 100% of their genes. Dizygotic twins, on average, share half of their genes. Zygosity was determined using standard serological assay. Twins were classified as being reared apart if they were separated before the age of 11 years old. The majority of twins reared apart were separated before the age of five (82%; Pedersen et al 1991).

Statistical Analyses

Analyses were performed using the following programs: Open MX (Boker et al., 2011), classic MX version 1.7.03 (Neale, Boker, Xie, & Maes, 2003), MPLUS version 6.12 (Muthen & Muthen, 2010), SAS version 9.3, and WINSTEPS version 3.74 (Linacre, 2012). In sections describing the specific analysis for each aim will indicate what software was used to perform the analysis described.

Genetic Analyses

Standard biometrical genetic model-fitting methods were used for all genetically informed analyses (aims one, two and four). Twin studies are especially informative because they allow for the decomposition of the variance of a phenotype into the following components: the additive genetic variance (A), non-additive/dominance genetic variance (D), shared environmental variance (C), and non-shared environmental variance including error (E). It is not mathematically possible to estimate all four variance components of variance in the same model. We fit ACE and ADE models for aim one. Research suggests little influence of common environment

on anxiety (Gillespie, et al., 2004) or cognitive performance later in life (Reynolds et al., 2005). Results from the first aim of this dissertation did not find any significant contributions of shared environment on anxiety. Thus, in order to reduce the number of models run for later aims we fit an ADE model and did not examine shared environmental contributions.

For the ACE models four sets of equations were used. Equations are based on whether the twin pair is monozygotic reared together ($covMZT = V_a + V_c + V_e$), monozygotic reared apart ($covMZA = V_a + V_e$), dizygotic reared together ($covDZT = 0.5*V_a + V_c + V_e$), or dizygotic reared apart ($covDZA = 0.5*V_a + V_e$). The coefficient for monozygotic twins is 1.0 because monozygotic twins share 100% of their genes. The coefficient for dizygotic twins is set to 0.50 because these twins share 50% of their genes on average. Four different covariance matrices were created for each twin type: MZA, MZT, DZA, and DZT. Twins before the age of 11 have been classified as reared apart in prior SATSA examinations. Environmental events early in life (before the age 11) can have important impact on the development of cognitive abilities and anxiety later in life. To ensure we were modeling early shared environment correctly, sensitivity analyses were run in which rearing status was not accounted for. In these models only two different covariance structures were used: one for MZ twins and one for DZ twins. For the ADE models two sets of equations were used in each model. The equations are based solely on the zygosity of the twin pair. The equation for MZ and DZ twins in the ADE model were written as:

$$covMZ = V_a + V_{d+} V_e$$

$$covDZ = 0.50*V_a + 0.25*V_d + V_e$$

See figure 2 for a depiction of these associations between twins. Important assumptions of biometric twin models include the following: 1) the environment in which the trait is examined is the same for DZ and MZ twins (i.e. DZ and MZ twins are treated the same way), 2) mating is random, 3) no epistasis or dominance, 4) no gene by environment interaction or correlations are present, and 5) effects of natural selection or genetic mutations are too small to affect the results (Verweij, Mosing, Zietsch, & Medland, 2012).

One assumption of these models is that the data is missing at random. We are unable to establish whether this assumption is met due to the fact that complete mortality data is not available. Previous SATSA studies have examined characteristics of participants who dropped out during the course of the study (Pederson & Reynolds, 1998; Finkel & Pederson, 2004; Finkel et al. 2007). These studies have found that those participants remaining in the study are significantly different than those who have dropped out. Older participants were more likely to have to have three or more assessment points when compared to younger participants.

Remaining analyses were conducted according to the Specific Aims outlined below.

Rasch anxiety crosswalk

Common person-item equating was employed to create the crosswalk to link the ENI and STPI. Creating a crosswalk requires the following: (1) common items across the two measures and (2) a sample who have completed both measures

(Velozo, Byers, Wang, & Joseph, 2007). Table 1 presents the items and rating scales of the two measures. Both measures contain similar items assessing “worry”, “anxiousness”, “nervousness”, and “restlessness”. This suggests that substantial overlap exists in the content of these two instruments. Additionally, the other items of the ENI (making decisions late, feeling tired, deep in thought, sensitivity) are also common symptoms of anxiety providing further face validity of the ENI as a measure of anxiety. A direct one-to-one correspondence between items is not necessary for completion of a Rasch item linking (Bond & Fox, 2007). All that is necessary is a substantial commonality of items across the measures to suggest the same underlying construct is being assessed. At Q1 a total of 1,322 participants completed both the ENI and the STPI. The Rasch modeling program WINSTEPS version 3.74 (Linacre, 2012) was used for the crosswalk analysis. The procedure used by past research (Velozo, et al., 2007) was followed to link the scales. The specific steps used to link the two tests are described next.

Step 1: Convert ENI ratings to match STPI ratings

Before conducting the Rasch analysis we conducted item transformations to ensure conceptual consistency between the two scales. Some items of the STPI (items 1, 3,7,9) were initially rated with higher scores representing lower anxiety. These items were reversed scored in order to be consistent with the rest of the items from the STIP and ENI. Following the item recoding, a higher score represented more anxiety for all items across both measures.

Step2: Remove Invalid Data

The conversion between two measures should only be done with valid data (Bond & Fox, 2007). One criterion for valid data is that participants have similar scores on both measures. A participant endorsing low anxiety on the STPI should also endorse low neuroticism on the ENI. The steps outlined in Bond and Fox (2007) for assessing this assumption were conducted. First, a separate Rasch analysis of the STPI and ENI was conducted. The ability estimates and standard errors for each participant were saved. A scatterplot of ability estimates was created with ENI on the X axis and STPI on the Y axis. The standard errors were then used to create a 95% confidence interval around the scatterplot. Person measures falling outside the 95% confidence intervals were removed for the subsequent calibration analyses.

Step 3: Generate ENI and STPI Cocalibrated Item and Rating-Scale Measures

We conducted a Rasch model by bringing together all of the items from both measures in a WINSTEPS Rasch analysis. A Partial Credit Model was used to account for the differences in rating scales between the two measures. The person-item map was examined to compare the difficulty of each item. Additionally, Cronbach's alpha, item-total correlations, as well as infit and outfit mean squares were examined to assess adequacy of fit. The infit and outfit mean squares are indicators of how well an item is fitting in the Rasch model. The infit mean square is weighted to give more influence towards persons who are closer to the mean. The outfit mean square is unweighted which increases the influence of outlying scores (Bond & Fox, 2007) . For clinical instruments, Wright and Linacre (1994) propose that acceptable mean squares range from 0.50 to 1.70. A lower mean square means that participants exhibited too

little variation in how they responded (e.g. an item in which almost all participants responded yes therefore minimizing the amount of helpful information provided by the item). A higher mean square represents an item that was too haphazard resulting in too much variation in responses (i.e. an item that participants were too unpredictable in response pattern). The following criterion were used to determine if an ENI should be removed from further analysis: 1) Poor face validity with STPI items 2) both infit and outfit mean squares below 0.50 or above 1.7 or 3) ability estimates of ENI items not lining up with the STPI items on the item map. Items that met this criterion were removed and step 3 was repeated. The item and step measures from this cocalibrated Rasch analysis were then saved and each used as anchors for subsequent analyses.

Step 4: Anchor Separate ENI and STPI Rasch Analyses to Item and Step Measures from the Cocalibrated Analysis

Separate Rasch analyses were then conducted for the ENI and STPI. Both of these analyses were anchored with the item and step measures from the previous step. The score file which links the measures raw score with the predicted ability score was saved for both measures. The raw scores for each that corresponded to the same ability score were then linked to create a raw-score conversion table. This table allows for ENI raw scores to be translated to the equivalent STPI raw score.

Step 5: Correlate Anxiety Crosswalk Score with STPI True Score

The last step consisted of computing the Anxiety Crosswalk score from the ENI score via the raw-score conversion table for each participant. The Anxiety

Crosswalk at Q1 and Q2 were correlated with Q1 and Q2 STPI scores to assess the association between the two scales.

Specific Aim 1: Examine the variation in the genetic influences on state anxiety across the second half of the lifespan.

Aim 1 included the 1,477 participants who had completed at least one STPI or Anxiety Crosswalk. Participant's age was calculated and classified to be in one of nine age intervals: 54.9 and under, 55-59.9, 60-64.9, 65-69.9, 70-74.9, 75-79.9, 80-84.9, or 85+. If participants were assessed twice during one of these periods only the first observation was used. See table 2 for the total number of complete and partial twin pairs by zygosity, rearing status, and age group. The average age of participants at the Q1 assessment was 60 (SD = 13.0) years old. The phenotypic correlation for the STPI between MZ twins was 0.369 and 0.048 for DZ twins. The phenotypic correlation for MZ twins was more than twice the correlation of DZ twins, which is suggestive of both additive genetic as well as potential dominant genetic influences.

Simplex models were fit to examine the stability of genetic and environmental influences on anxiety symptoms over time. Simplex models allow for the analysis of the longitudinal nature of the data and allow for inferences of causation (Boomsma, Martin, & Molenaar, 1989) . This type of modeling allows for discrimination of genetic/environmental factors that are persistent across time and factors that are unique to a certain age. Genetic simplex models are autoregressive in which scores are predicted on the basis of the previous time point. Figure 3 displays the full simplex model that was estimated. The anxiety score at age 55-59.99 can be expressed by the

following equation: $anx_{55\text{-}59} = \beta_{54} * anx_{54} + \zeta_{55\text{-}59}$. In this equation $anx_{55\text{-}59}$ term represents the latent variable of anxiety for those 55-59 years old. The β_{54} is the regression of the latent factor on the preceding latent factor of anxiety for those 54 or younger (anx_{54}). The parameter $\zeta_{55\text{-}59}$ is the new genetic innovation for those between the ages of 55-59. The equation for the measurement model for those 54 and under was written as $ANX_{54} = \lambda_{54} * anx_{54} + \varepsilon_{54}$. In this equation ANX_{54} represents the raw anxiety score for someone at this age group, λ_{54} represents the factor loading of this raw score on the latent variable anx_{54}, and ε_{54} represents the measurement error of the observed variables. The innovation term (ζ) in the structural equation represents genetic or environmental factors that significantly explain variance at that age group as well as every subsequent age. For example, if genetic innovations at the age 54 and younger are observed, those genetic innovations would continuously explain variance at all subsequent time points. Likewise, if significant genetic innovations were observed at the age of 70-74, this would indicate that new genetic influences explain additional variance in anxiety at this age as well as all subsequent ages. These genetic factors in this 70-74 innovation however, would not explain variance in participants younger than 70. The error terms for the last two time points were constrained to be equal. This constraint is needed in order for the model to be identified and converge.

The models were fit using standard biometric fitting approaches. We examined three full models: 1) ACE accounting for rearing status (apart or together), 2) an ACE model without accounting for rearing status, and 3) an ADE model to test for dominance. In total, the full ACE or ADE model estimated 60 parameters

consisting of: seven error terms ($\varepsilon_{54} - \varepsilon_{80}$), eight means ($\mu_{54} - \mu_{85}$), eight innovations ($\zeta$) and eight regression coefficients (β) for each source of variation (A, C/D, or E). We examined the effect of dropping the shared environment parameter (C) on model fit by dropping this term and estimating an AE model. Likewise, we also examined the effect of dropping the genetic dominance parameter (D) on model fit by dropping this term. Model comparisons were done by comparing the difference between the negative log likelihood between models. Parameters were kept in the model if dropping the parameter from the model resulted in significantly worse fit ($p < 0.05$) when compared to the full model. After determining if an ACE, ADE, or AE model best explained the data we examined the effect of genetic and environmental innovations at each specific time point. To do this we systematically dropped each genetic and environmental innovation term one by one for each time point starting at the age 55-59 group. Again, the log-likelihood difference test was used to compare the submodel to the best fitting model from the prior step. Innovations were kept in the model if dropping the parameter resulted in significantly worse model fit. The goal was to develop the most parsimonious model that best explains the data.

Prior research suggests that the genetic and environmental determinants of anxiety may vary by gender (Gillespie, et al., 2004). Due to limited sample size we were unable to fit the simplex models separately for males and females to examine sex differences. Models were run for each anxiety outcome separately. Because the STPI was administered at fewer time points than the Anxiety Crosswalk, the total number of twin pairs aged 85 and older was small (N = 80; only 12 complete twin pairs). Due to

the limited number of participants in this age group simplex models for the STPI did not include twins 85 and older. Models were fit using the program Open Mx (Boker, et al., 2011).

Specific Aim 2: Explore the extent to which shared genetic influences explain the correlation between cognition and anxiety.

For specific aim 2 we analyzed STPI and cognition data from the second in-person assessment. The second in-person assessment was chosen for this cross-sectional analysis because it contained the largest sample of participants who completed both the cognitive assessment and STPI.

As described in aim 1, twin data allowed for the decomposition of variance into three components: additive genetic (A), non-additive genetic (D), and non-shared environment (E). We examined both the specific and shared influences on anxiety and cognitive performance by using bivariate structural equation modeling with a full bivariate Cholesky decomposition.

In order to examine how sex modified the variance structure of each phenotype was, a univariate sex-limitation ADE model for the STPI and cognitive tests was fit. The full ADE sex limitation model estimated separate A, D, and E components for males and females. A nested model where A, D, and E components were constrained to be equal across sexes was then estimated. These two models were compared using the log-likelihood test to determine if significant sex differences existed. After determining if separate models were needed for males and females, univariate submodels were fit in which the respective variance components were dropped. An

AE submodel and E submodel were estimated. These submodels were compared to the full ADE model.

The phenotypic correlation between the STPI and each measure of cognitive performance was examined next. Because results from the prior univariate models suggested sex differences in the variance structure of the STPI the phenotypic correlation was also examined for males and females separately. For cognitive tests that were significantly associated with anxiety we ran bivariate Cholesky decompositions. Bivariate Cholesky decomposition allowed us to estimate the degree of overlap in genetic and environmental contributions on anxiety and cognitive performance. We estimated a total of six bivariate models between anxiety and each cognitive test.

Figure 4 displays the bivariate Cholesky model. The genetic factor A1 influences both anxiety and cognitive performance. Genetic factor A2 only influences only cognitive performance. The factor A2 represents the additive genetic contribution on cognitive performance after partialling out the genetic effects on anxiety. The pathway a21 represents the additive genetic contribution of anxiety on cognitive performance. The e21 pathway represents the environmental contribution of anxiety on cognitive performance. Genetic (r_a) and environmental (r_e) correlations were also estimated in order to estimate the extent to which genetic and environmental factors overlap. A high genetic correlation indicates that the genetic factors influencing anxiety are also influencing cognitive performance. Likewise, a high environmental correlation indicates a large overlap in the environmental factors influencing both

anxiety and cognition. The proportion of the phenotypic correlation explained by shared genetic factors is a function of the genetic correlation and two genetic factors (A1 & A2). This proportion was calculated via the following equation:

$$\frac{\sqrt{A^2_{anxiety}} * r_a * \sqrt{A^2_{cognition}}}{r_{pheno\ anxiety,cognition}}$$

Similarly, the proportion of the phenotypic correlation explained by unique environmental factors that are shared between anxiety and cognitive performance can be explained by the same equation but substituting the E variance components and environmental correlation.

First, a full ADE model that estimated the A, D, and E components as well as the overlap between anxiety and cognition were fit. Next, AE and E models were fit in order to identify the most parsimonious full model. Model comparisons were done using the log-likelihood difference test. After determining the most parsimonious full model we examined the statistical significance of the shared pathways (a21 and e21). This was done by removing these pathways in a stepwise fashion and examining change in model fit compared to the full model. For example, if removing path a21 from the model does not result in degradation of the model it is suggestive of no significant shared genetic influences on anxiety and cognitive performance. Lastly, a model dropping both shared components was run. If dropping both shared parameters did not result in worse model fit the AIC fit index was used to determine the best fitting model. The trait-specific and shared variance components from the full model were used to calculate the proportion of the phenotypic variance explained by shared

genetic and unique environmental factors. All bivariate Cholesky decompositions were fitted using the Open Mx structural equation modeling program (Boker, et al., 2011).

Specific Aim 3: Examine the temporal dynamics of the phenotypic association between anxiety and cognitive functioning over time.

For aim 3 we examined the longitudinal phenotypic association between cognitive functioning and anxiety. Advances in structural equation modeling allow for the examination of the dynamic association between two variables longitudinally (McArdle & Hamagami, 2003). These models enabled the examination of how change in one variable lead to changes in another variable. In this study, we used DCSMs to investigate the extent to which change in anxiety was associated with change in cognitive performance over time. The reverse was also examined; to what extent do changes in cognitive abilities lead to changes in anxiety over time. DCSMs have been used in other longitudinal examinations investigating the association between processing speed and cognitive ability (Finkel, et al., 2007), openness to experience and cognition (Sharp, Reynolds, Pedersen, & Gatz, 2010), and depression and cognitive performance (Jajodia & Borders, 2011).

Anxiety data gathered during the Q1 and Q4 assessments as well as IPT 2, 3, 5, 6 and 7 assessments were analyzed. Cognitive performance data from IPT's 1-3 and 5-7 were included in the analysis. See Table 3 for the number of participants who completed anxiety and cognitive data in each age group. To ease the computational burden of the model and ensure convergence of the models, the anxiety crosswalk and

cognitive data were standardized into T-scores. The mean and standard deviation at the first time these variables were measured (Q1 for anxiety crosswalk and IPT1 for cognitive measures) were used for standardization. Standardizing both variables on the same scale also aids in the interpretation of the dynamic coupling between the two variables and is common practice in DCSM analyses (Finkel, et al., 2009; Finkel, et al., 2007; Infurna, Gerstorf, Ryan, & Smith, 2011).

Univariate models were fit to identify and confirm the trajectory of each variable over time. Bivariate models were fit next. All participants with at least one assessment were included in each analysis. Due to the fact that participants were twins, the statistical assumption of independence of data was violated. To account for the twin pair dependency participants were clustered on twin pair across all models. Additionally, in all models, age was modeled as a time variable. Prior SATSA investigations (Finkel, et al., 2003; Finkel, et al., 2009; Finkel, et al., 2007) have suggested that using a 3-year interval maximizes the age range for which trajectories can be examined. Thus, age was modeled as 50-52, 53-55, 56-58, and so on, up to 86-88. Lastly, possible confounding variables (education, sex, initial depression symptoms) were added as covariates in the model and regressed upon the latent intercept and slope variables.

Univariate DCSMs: Univariate DCSMs were estimated to examine trajectories of anxiety and the respective cognitive measures separately. In these models, latent difference scores were estimated based on changes in scores from one latent age score to the next. The goal of these analyses was to model the trajectory of change over

time. Linear change and nonlinear proportional change were estimated. In DCSM models, constant linear change is represented with α, the slope of the latent factor is represented as y_s, and β represents the proportional or non-linear change from one time point to the next. The equation representing change in cognitive performance at age A can thus be written as follows: $\Delta cog[A] = \alpha * cog_s + \beta_y * (cog[A-1])$. The equation representing change in anxiety at age A is written as: $\Delta anx[A] = \alpha * anx_s + \beta_y * (anx[A-1])$. In these models, α is set to a value of one while parameter β is estimated. The intercept (cog_0) and slope (cog_s) were included in each model, along with the variance around the intercept ($б_0$), slope ($б_s$). Lastly, the correlation between intercept and slope were also estimated (r_{0s}). DCSM investigations assume that α and β parameters are consistent across time (Finkel, et al., 2009; Finkel, et al., 2007). First, a full model estimating both linear and proportional change was fit. A second model constraining β to zero and only estimating linear change was estimated. Due to the clustered nature of the data the standard difference in negative log-likelihood and degrees of freedom test could not be conducted. The maximum likelihood estimation with robust standard errors (MLR) was used to compare models. The difference between two MLR log-likelihoods does not follow a chi-square distribution. This resulted in the need for scaling correction factors when comparing differences using MLR (Sharp, et al., 2010). In order to compare models this chi-square difference tests with scaling factor corrections was used (see http://www.statmodel.com/chidiff.shtml).

Bivariate DCSMs: After estimating the univariate DCSMs, bivariate DCSMs were fit to examine the dynamic relationships between anxiety and cognitive

performance. The bivariate DCSMs contain the same parameters that were estimated in the univariate models. The bivariate DCSM models also included two coupling parameters, designated by γ, which link cognitive performance and anxiety. The first coupling parameter estimated how much change in cognitive performance depended on the previous value of anxiety ($\gamma_{COG*ANX}$). The opposite coupling parameter estimated how much change in anxiety depended on the previous value of cognitive performance ($\gamma_{ANX*COG}$). Therefore, the equation representing the modeling of cognitive performance in relation to prior levels of anxiety builds on the univariate model and can be written as: $\Delta cog[A] = \alpha*cog_s + \beta_y*cog[A-1]+\gamma_{anx*cog}*anx[A-1]$. The equation representing the modeling of anxiety in relation to prior levels of cognitive performance can be written as: $\Delta anx[A]=\alpha*anx_s+\gamma_{COG*ANX}*cog[A-1]$. Results from the univariate model suggested no significant proportional change in anxiety over time. Thus, the bivariate equation for anxiety only estimated linear change over time. Similar to the α and β parameters, γ is assumed to be constant across all ages. As in the univariate model, bivariate DCSMs estimate the intercepts (anx_0 & cog_0), slopes (anx_s & cog_s), variance of the intercepts ($anx\text{б}_0$ & $cog\text{б}_0$) and slopes ($anx\text{б}_s$ & $cog\text{б}_s$) as well as correlation between all latent growth factors. Covariates were also regressed upon the intercept and slope similar to the univariate models.

Past research, as well as findings from second aim of this dissertation, found sex differences in the association between anxiety and cognitive performance. To examine potential sex differences a multigroup DCSM model that estimated different change parameters (specifically: β_{cog} , $\gamma_{COG*ANX,}$ $\gamma_{ANX*COG}$) for males and females,

without covariates added in the model was fit. This full model was compared to a model that constrained the change parameters to be equal for each sex. No significant sex differences were found across all DCSM models so all subsequent models contained both males and females together in a single group.

To examine the dynamic change hypothesis, five nested models were compared for each cognitive domain and state anxiety in a stepwise fashion. First, we examined a full model estimating both coupling parameters $\gamma_{ANX*COG}$ and $\gamma_{COG*ANX}$. The second model examined the dynamic relationship in one direction only, with anxiety being a leading indicator of change in cognitive performance. This was done by constraining the $\gamma_{COG*ANX}$ parameter to zero while estimating the $\gamma_{ANX*COG}$ parameter. The third model examined the dynamic association in the other direction, with cognitive performance as a leading indicator of change in anxiety. This was done by constraining the $\gamma_{ANX*COG}$ parameter to zero and estimating the $\gamma_{COG*ANX}$ parameter. The fourth model examined a no coupling model in which both coupling parameters were set to zero ($\gamma_{ANX*COG}= \gamma_{COG*ANX}=0$). Model comparison was done using the MLR comparison with scaling factors. Figure 6 provides a conceptual illustration of the full bivariate DCSM. All phenotypic DCSM models were conducted using the structural equation modeling program MPLUS version 6.12 (Muthen & Muthen, 2010).

Specific Aim 4: Examine the extent to which shared genetic influences explain the correlation between cognition and anxiety over time.

For the last aim we conducted biometric DCSM models to examine the temporal dynamics of genetic and environmental contributions on cognitive

performance and anxiety. Again all participants were included if they had completed at least one anxiety or cognitive assessment. See table 4 for the number of complete and incomplete twin pairs in each category.

Biometric Univariate DCSMs: The procedure for estimating the biometric univariate DCSMs is the same as described in Aim 3, but the variance around the intercept and slope will be decomposed into genetic and environmental effects. For all models, additive genetic, dominant genetic, and nonshared environmental effects of the intercept (a_0,d_0, e_0), the slope (a_s,d_s, e_s), and the correlation between intercept and slope were estimated (a_{0s},d_{0s}, e_{0s}). A total of eleven sets of models were fit, one for each anxiety and cognitive test pair. Ten separate nested models were estimated for each anxiety and cognitive test pair to determine which genetic and environmental effects were significantly different than zero. First, a full model estimated all of the genetic and environmental contributions to the slope, intercept, and correlation between slope and intercept. A second model tested the significance of the anxiety on cognitive performance coupling parameter ($\gamma_{ANX*COG}$) by removing this parameter and examining change in the negative log-likelihood. A third model examined the significance of the cognitive performance on anxiety coupling parameter ($\gamma_{COG*ANX}$). The fourth model tested dominant genetic influences on anxiety by removing all dominant genetic effects (d_0,d_s, d_{0s}) on anxiety. The fifth model examined dominant genetic influences on the cognitive variable by removing all of these d pathways (d_0,d_s, d_{0s}) and examining change in model fit. The sixth model examined the effect of dropping all dominant genetic influences on both anxiety and cognitive performance

simultaneously. The seventh model tested the additive genetic influences on anxiety slope by removing the a_s pathway. The eight model examined the additive genetic influences on cognitive performance by removing the a_s pathway on the cognitive performance slope latent variable. The ninth model examined the effect of additive genetic influences on the anxiety slope that are acting through the additive genetic influences on the intercept of anxiety (a_{Os}). The last model tested the additive genetic effects on the correlation between cognitive performance intercept and slope by dropping this pathway (a_{sOs}). See figure 6 for the full biometric DCSM model. Similar to the prior aims, model fit was assessed using the negative log-likelihood and change in degrees of freedom test to assess which genetic and environmental effects were statistically significant.

In order to visualize the temporal dynamics of the genetic and environmental contributions on anxiety and cognitive performance, the estimated additive genetic and environmental variance components were calculated and plotted. We examined the effect of adding the coupling parameters on the estimated genetic and environmental variance. When no coupling between anxiety and cognitive performance is included in the model, the estimates for the genetic and environmental variance components at each age group are not linked between variables. The contribution of genetic factors that cognitive performance has on anxiety over time can then be visualized by examining differences in the genetic and environmental variance at each age when coupling is in the model versus when it is not. Biometric DCSM models were fit using

the classic Mx structural equation modeling program version 1.7.03 (Neale, et al., 2003).

Methods chapter acknowledgment

The methods of the dissertation, in part is currently being prepared for submission for publication. The dissertation author was the primary investigator and author of this material. Co-authors to this work include: Julie Wetherell, Ph.D., Chandra Reynolds, Ph.D., William Kremen, Ph.D., Niloofar Afari, Ph.D., Deborah Finkel, Ph.D., and Margaret Gatz, Ph.D.. The dissertation/thesis author was the primary investigator and author of this paper.

RESULTS

Rasch Anxiety Crosswalk

Figure 7 displays the scatterplot of participant ability scores on the ENI and STPI measures. Of the 1,322 participants, 177 fell outside the 95% confidence interval and were eliminated from further Rasch analyses. The final sample for the crosswalk analyses consisted of 1,145 participants.

Figure 8 displays the item-person map for the co-calibrated scale. Table 5 presents the mean square and item total correlations. Person measures are presented on the far left (each # represents 7 participants, each "." Represents 1-6 participants). The ENI item measures are listed in middle and the STPI item measures are on the far right. The central axis represents the natural logarithm odds unit. Items that fall lower on the scale are "easier" items in that the participants were more likely to endorse. Items that fall higher on the item map are "harder" items and less likely to be endorsed. Three of the items from the ENI (Sensitive, happy or sad without reason, and worry when embarrassing oneself in a social situation) were easier to endorse than the other items and did not line up with the STPI items. The face validity of these items was also questionable. The ENI item "happy or sad without reason" may be a better indicator of depression than anxiety. The item regarding worry following an embarrassing situation may capture the construct of social anxiety rather than general state anxiety. Given that these three items had questionable face validity and were not matching up with the rest of the STPI items they were removed from further analyses. The item map from the Rasch analysis with these items removed is presented in figure

9. The cocalibarated ENI and STPI analysis were re-run with these three items removed. The abbreviated measure had good person and item level psychometric properties. Person reliability of the measure was high (Cronbach's alpha = 0.82). Table 6 displays the mean infit and outfit for each item. The average item infit was 0.99 (ideal mean infit is 1.00) and person infit was 1.04. Only one item (make decisions late) exhibited poor outfit at the suggested cut point of 1.70. This item had acceptable infit mean square of 1.26 and was kept in the measure. See table 7 for the crosswalk table linking the ENI and STPI raw scores. The raw scores were linked through the person measures that were generated from the separate ENI and STPI anchored analyses. Results of the crosswalk suggested that an ENI raw score of zero corresponds to a STPI raw score of 12 because both of these raw scores shared a common person ability measure of -2.87 logits. Likewise, an ENI raw score of one corresponded to a STPI raw score of 16 because both of these scores shared the common person ability measure of -1.52 logits.

Lastly, the Anxiety Crosswalk score was computed at Q1 and Q2 from the ENI scores. The correlation between the Anxiety Crosswalk and STPI at Q1 was significant ($r = 0.49$, $p < 0.001$). The STPI and Anxiety Crosswalk at Questionnaire assessment two were also highly correlated ($r = 0.60$, $p < 0.001$).

Specific Aim 1: Examine the variation in the genetic influences on state anxiety across the second half of the lifespan.

See table 8. for a summary of the model fitting results for the longitudinal simplex model of the STPI. Three separate full models were fitted first: an ACE model

accounting for rearing status, an ACE model not accounting for rearing, and an ADE model to examine potential dominant genetic effects. Across all models we were able to drop the drop all shared environment or genetic dominance components without experiencing worse model fit ($p > 0.53$).

Genetic innovations starting at age 55-59 were dropped one by one in a stepwise fashion. Compared to the full AE model there was a significant deterioration in model fit when the genetic innovation at age 60 was dropped (Δfit = 4.07, Δdf = 1, $p = 0.04$). Genetic influences at age 55 and 65-80 were all dropped without a significant deterioration in model fit. Next, unique environmental innovations were dropped one by one in a stepwise fashion. Deterioration in model fit occurred when the unique environmental innovation at age 75 was dropped (Δfit = 5.13, Δdf = 1, $p = 0.02$). There were no significant changes in model fit when the unique environment innovations were dropped one at a time at age 55, 60, 65, 70, 80, and 85. Simultaneously removing all of these non-significant genetic and unique environmental innovations did not produce a significantly worse model fit (Δfit = 8.14, Δdf = 10, $p = 0.62$). The best fitting model required additional genetic innovations at age 60 as well as non-shared environmental innovations at age 75. Figure 10. presents the best fitting simplex model. Figure 11. presents the proportion of variance accounted for by genetic and environmental factors estimated from this model at each age group. The proportion of variance accounted for at each age group is a function of both the innovation and transmission parameters. At age 54 and younger additive genetic factors explain 32% of the variance in STPI symptoms. From

age 55 to 65 genetic factors significantly decrease and explain 23% of the variance at age 60-65. From 65-79 proportion of variance accounted for by genetic factors returns to similar levels seen before age 54 (27%-36%). Genetic factors increase in saliency at age 80 explaining 49% of the variance.

Simplex models examining the anxiety crosswalk measure were run next. See table 9 for a summary of model fit and comparisons. Similar to the STPI simplex models no common environmental influences or genetic dominance effects were present as the most parsimonious model was the AE model. This was true if rearing status was accounted for in the model or not.

Similar to the STPI models, no new significant genetic innovations were present at ages 55, 65, 70, 75, 80 or 85. We were not able to drop the genetic innovation at age 60 without a significant decrease in model fit (Δfit = 6.79, Δdf = 1, $p < 0.01$). Dropping the unique environmental innovations at age 55,60,65,70,80 or 85 did not result in a degradation of model fit. Dropping the unique environmental innovation at age 75 resulted in a significant decrease in the fit of the model (Δfit = 5.28, Δdf = 1, $p < 0.02$). Simultaneously removing all of these non-significant genetic and unique environmental innovations did not produce a significantly worse fitting model (Δfit = 11.75, Δdf = 12, $p = 0.47$). Similar to the STPI model, the most parsimonious simplex model for the anxiety crosswalk measure included new genetic innovations at age 60-64, as well as non-shared environmental innovations at age 75-79. See figure 12 for a diagram of the best fitting model. The proportion of variance

accounted for by genetic and non-shared environment for each age group was calculated and is presented in figure 13.

Specific Aim 2: Examine the cross-sectional correlation between anxiety and cognitive performance and explore the extent to which shared genetic influences explain the association.

Univariate Cholesky decomposition

Table 10 presents the univariate ADE cholesky decomposition model results for STPI and cognitive measures. The most parsimonious univariate model for the STPI was the AE model with sex limitation effects. The sex limitation effects suggest that males and females had significantly different variance structure. The most parsimonious univariate model for all cognitive measures was the AE models without sex limitation.

Phenotypic correlations between STPI and cognitive performance

Table 11 displays the phenotypic means and correlations between STPI, Crosswalk Anxiety, and cognitive measures. Higher STPI scores were associated with worse performance on the Thurstone Picture Memory ($r = -0.14$; $p < 0.01$), Block Design ($r = -0.15$; $p < 0.01$), Rotations ($r = -0.09$; $p < 0.04$), and Figure Logic ($r = -0.09$; $p = 0.04$). Similarly, higher Crosswalk Anxiety scores were associated with worse performance on Thurstone Picture Memory ($r = -0.13$; $p < 0.01$), Block Design ($r = -0.14$; $p <0.01$), Rotations ($r = -0.11$; $p = 0.01$), Figure Logic ($r = -0.11$; $p =0.02$), as well as Symbol Digit ($r = -0.09$; $p = 0.04$). As expected the STPI was also highly correlated with the Anxiety Crosswalk ($r = 0.53$; $p < 0.001$).

Bivariate Cholesky Decompositions

Bivariate Cholesky decompositions were fit next to examine the extent to which shared genetic and environmental factors explained the correlation between STPI and the respective cognitive measures. Because sex limitation effects were found on the STPI, the bivariate Cholesky models were run separately for males and females and are presented in table 12. Bivariate Cholesky decompositions were only run for those cognitive measures that had a significant phenotypic correlation with anxiety. For males bivariate Cholesky decompositions were run examining STPI and the following cognitive tests: Digit Span Total, Digit Span Forward, Digit Span Backwards, Thurstone, Block Design, and Rotations. For females bivariate Cholesky decompositions were fit examining STPI and Thurstone, as well as STPI and Block Design.

The correlation matrix between STPI and Digit Span Total for male MZ and DZ twins is presented in table 13. Model fitting results are presented in table 14. Similar to univariate models, no significant dominant genetic effects were found on STPI or Total Digit Span. Dropping the shared genetic pathway did not significantly decrease model fit (Δfit = 0.05, Δdf = 1, p = 0.82), while dropping the E12 pathway did result in a significant degradation of model fit (Δfit = 3.77, Δdf = 1, p = 0.05). The correlation between unique environmental latent factors in the full model was -0.26, suggesting that 87.5% of the unique environmental variance affecting STPI is shared with the unique environmental influences on Digit Span Total.

The correlation matrix between STPI and Digit Span Forward for MZ and DZ twins is presented in table 15 while model fitting results are presented in table 16. Again, no dominant genetic effects were found for both STPI and Digit Span Forward. Dropping the shared component of the additive genetic variance did not result in a significant worse fitting model (Δfit = 0.26, Δdf = 1, p = 0.61). There was a significant decrease in model fit when the shared unique environmental component was dropped (Δfit = 4.30, Δdf = 1, p = 0.04). The unique environmental correlation was -0.27 while the genetic correlation was 0.13. Problems arise in calculating the proportion of variance accounted for when the genetic and environmental correlations are in different directions. This is most likely the result of low variance in Digit Span Forwards performance as well as the small phenotypic correlation. Constraining the shared genetic variance pathway to zero does not significantly reduce model fit, suggesting that no significant shared genetic factors exist which contribute to both Digit Span Forward and anxiety.

The correlation matrix between STPI and Digit Span backwards for male MZ and DZ twins is presented in table 17 while model fitting results are presented in table 18. Again, no dominant genetic effects were found for both STPI and Digit Span Backwards. Dropping either the shared component of the additive genetic variance (Δfit = 0.26, Δdf = 1, p = 0.61) or the shared unique environmental variance (Δfit = 0.26, Δdf = 1, p = 0.61) did not result in a significant decrease in model fit. However, dropping both of the shared components in the same model resulted in significantly worse fit (Δfit = 0.26, Δdf = 1, p = 0.61). This suggested that some shared genetic and

unique environmental variance between anxiety and digit span backwards was present. The correlation between the latent unique environmental components was -0.11 while the correlation between latent genetic components was -0.24. The AE model suggests that 60.4% of the genetic variance affecting anxiety resulted from genetic influences that also contribute to Digit Span Backwards performance. Additionally, 39.6% of the unique environmental variance affecting anxiety in males is shared with the unique environmental influences on Digit Span Backwards.

The correlation matrix between STPI and Thurstone performance for male MZ and DZ twins is presented in table 19. Model comparison and variance component estimates are presented in table 20. No significant dominant genetic effects were found for both STPI and Thurstone. Dropping the shared component of the additive genetic variance resulted in a significantly worse fitting model (Δfit = 4.37, Δdf = 1, p = 0.04), while dropping the shared unique environmental variance pathway did not result in a significantly worse fitting model (Δfit = 0.13, Δdf = 1, p = 0.71). From the full AE model, the correlation between latent genetic components was -0.49 while the correlation between latent unique environmental components was 0.05. A genetic correlation that is negative with a positive environmental correlation often occurs when the phenotypic association is small or not statistically significant (Hansen et al., 2007). Because constraining the shared unique environment path to zero did not reduce model fit we do not have evidence for significant shared unique environmental influences on this correlation.

See table 21 for the correlation matrix between STPI and Thurstone performance for female MZ and DZ twins. Model fitting results are presented in table 22. No significant dominant genetic contributions on either the STPI or Thurstone. Unlike males, dropping either the shared component of the additive genetic variance (Δfit = 0.29, Δdf = 1, p = 0.59) or the shared unique environmental variance (Δfit = 1.80, Δdf = 1, p = 0.18) did not result in worse model fit. However, there was a significant deterioration in model fit when both of these shared components were dropped in the same model (Δfit = 6.41, Δdf = 2, p = 0.04). Examination of the AIC fit index suggests that the most parsimonious model included shared environmental factors. The correlation between latent genetic components from the full model was -0.11 and -0.18 between latent unique environmental components. The full AE model suggested that 32.3% of the genetic variance affecting anxiety symptoms result from genetic influences that also affect Thurstone performance. Additionally, 67.7% of the unique environmental variance affecting anxiety in females is shared with the unique environmental influences on performance on the Thurstone.

See table 23 for the correlation matrix between STPI and Block Design performance for male MZ and DZ twins. Model fitting results are presented in table 24. No significant dominant genetic effects were found on either STPI or Block Design. Dropping either the shared component of the additive genetic variance (Δfit = 3.03, Δdf = 1, p = 0.08) or the shared unique environmental variance (Δfit = 0.19, Δdf = 1, p = 0.66) did not result in worse model fit. Likewise, there was no significant deterioration in model fit when both of these shared components were dropped in the

same model (Δfit = 5.62, Δdf = 2, p = 0.06). Examination of the AIC model fit index suggested that the best fitting model included a shared genetic component only. The correlation between latent genetic components was -0.27. The full AE model suggested that 85.4% of the genetic variance contributing to Block Design performance resulted from genetic influences that also affect symptoms of anxiety.

See table 25 for the correlation matrix between STPI and Block design performance for female MZ and DZ twins. Model fitting results are presented in table 26. No significant genetic dominance effects were found for either STPI and Block Design performance. Dropping either the shared component of the additive genetic variance (Δfit = 0.33, Δdf = 1, p = 0.57) or the shared unique environmental variance (Δfit = 2.23, Δdf = 1, p = 0.14) did not result in worse model fit. However, there was a significant deterioration in model fit when both of these shared components were dropped in the same model (Δfit = 7.00, Δdf = 2, p = 0.03). Examination of the AIC fit index suggested that the model including shared unique environmental components without shared genetic components was most parsimonious. The correlation between latent unique environmental components was -0.14. The full AE model suggests that 66.0% of the unique environmental variance affecting anxiety symptoms resulted from unique environmental influences that also affect Block Design performance.

The correlation matrix between STPI and Card Rotations for male MZ and DZ twins is presented in table 27 while model fitting results are presented in table 28. Again, no dominant genetic effects were found for both STPI and Card Rotations. Dropping the shared component of the additive genetic variance resulted in a

significantly worse fitting mode (Δfit = 5.88, Δdf = 1, p = 0.02) while dropping the shared unique environmental component did not decrease model fit (Δfit = 0.68, Δdf = 1, p = 0.68). The correlation between the latent unique environmental components was 0.14 while the genetic correlation was -0.45. When the genetic and environmental correlations are in different directions the overall proportion of variance accounted for by shared genes or environment cannot be calculated. Constraining the shared unique environmental variance pathway to zero does not significantly reduce model fit, suggestive of no significant shared unique environmental influences contributing to this correlation. Table 29 displays a summary of the significant phenotypic correlations between STPI and cognitive measures as well as the estimated proportion of this correlation due to shared additive genetics and unique environment.

Specific Aim 3: Examine the temporal dynamics of the phenotypic association between anxiety and cognitive performance over time.

Univariate Dual Change Score Models

A univariate DCSM was fit to each of the cognitive variables as well as the anxiety crosswalk. The purpose behind the univariate models was to verify the trajectory shape over age as well as to gather parameter estimates to use as start values in the bivariate models. Two models were fit for each variable: a full model which estimated proportional change over time and a restricted model in which the β parameter is constrained to zero. In the full model a total of 12 parameters were estimated. Parameter estimates for the most parsimonious best fitting models as well as model comparison statistics are presented in table 30.

For the Anxiety Crosswalk the reduced model in which β was set to zero did not produce a degradation of fit (Δ-2LL (Δdf) = 0.22 (1) ; $p > 0.05$). This suggests that Anxiety Crosswalk exhibited only linear change over time. For all measures of processing speed (Symbol Digit, Figure Identification tests), nonverbal memory (Thurston), and visuospatial abilities (Block Design, Card Rotations, and Figure Logic) removing the proportional change parameter resulted in significantly worse model fit ($p < 0.01$). For Total Digit Span Total, Forwards, and Backwards, however, the restricted model was not significantly worse than the full model thus proportional change was dropped.

When interpreting change using DCSM, change parameters need to be viewed in the context of the proportional change parameter β. All cognitive tests (with the exception of Digit Span) estimated a positive β parameter with a negative slope. A positive β parameter represents accelerated change with advancing age, while a negative slope parameter signifies declining performance with age. The combination of these two parameters estimates suggested small decreases initially in cognitive performance with accelerating declines later with advancing age. Higher proportional change estimation represents greater acceleration of declines. The equation representing change in Symbol Digit performance as estimated from the univariate models can be written as:

Δ Symbol Digit[*A*] = -6.55 + 0.10 X Symbol Digit[A-1].

In this equation change at age "A" equals a combination of linear change (-6.55) for each advancing time plus 0.10 times Symbol Digit performance at the prior age. For

the Anxiety Crosswalk as well as Digit Span, proportional change was not statistically significant. Change in these variables was linear with change during each time period equaling the slope estimation. See figures 14-23 for the trajectories of the Anxiety Crosswalk and performance on all cognitive tests as estimated from these univariate models.

Bivariate Dual Change Score Models

The bivariate analysis examining the association between anxiety and Symbol Digit performance was examined first. Parameter estimates with standard errors and fit statistics from model comparisons are presented in table 31. First, a multigroup bivariate DCSM was fit to examine sex differences in proportional change as well as the coupling parameter. A full multigroup model was run estimating unique coupling parameters ($\gamma_{\text{anx-sym digit}}$ and $\gamma_{\text{sym digit-anx}}$) and proportional change for males and females separately. The restricted model which constrained these change parameters to be equal across genders did not result in worse model fit (Δfit = 1.23, Δdf = 3, *ns*). This suggested that the bivariate association was not significantly different for males and females. The full bivariate single group model was estimated and compared to the restricted models. Model fitting indicated that the dynamic effect of anxiety on Symbol Digit performance could be dropped from the model without reduced model fit (Δfit = 0.13, Δdf = 1, *ns*). The converse was not the same. The dynamic effect of Symbol Digit performance on anxiety was both statistically significant ($\gamma_{\text{sym digit-anx}}$ = -0.07, SE = 0.02, $p < 0.01$) and unable to be removed from this from the model without

significantly worse model fit (Δfit = 27, Δdf = 1, $p < 0.01$). Change at time *t* for Symbol Digit and anxiety can be calculated by the following equations:

Δ Symbol Digit[*A*] = -6.56 + 0.10 X symbol digit[A-1] + 0.04 X anxiety[A-1]

Δ anxiety[*A*] = 3.18 – 0.08 X Symbol Digit[A-1]

The equation for Symbol Digit demonstrated that change in Symbol Digit performance over time is a function of constant linear change (-6.56), previous performance on Symbol Digit and to a lesser extent prior levels of anxiety (although this parameter was not statistically significant). The equation for anxiety demonstrates that change in anxiety over time was a function of constant linear change (3.18) and prior performance on Symbol Digit. Figure 24 presents a graphical depiction of this association in a vector field plot. Each arrow in Figure 24 presents the expected change at time *A+1* for the pair of latent anxiety and symbol digit scores at time *A* with longer arrows signifying greater changes.

The bivariate analysis examining the association between anxiety and Figure Identification was examined next. Parameter estimates with standard errors and fit statistics from model comparisons are presented in table 32. The multigroup model indicated that the bivariate association between anxiety and Figure Identification was not significantly different for males and females (Δfit = 0.52, Δdf = 3, *ns*). The single group full model suggested that the dynamic effect of anxiety on Figure Identification performance could be dropped without a reduction in fit (Δfit = 1.73, Δdf = 1, *ns*). The same was not true in reverse. The dynamic effect of Figure Identification performance on anxiety was both statistically significant ($\gamma_{\text{figure ID-anx}} = -0.07$, SE = 0.02, $p < 0.01$)

and we were unable to drop this parameter from the model without significantly worse model fit (Δfit = 18.49, Δdf = 1, $p < 0.01$). Change at time *A* for figure identification and anxiety can be calculated by the following equations:

Δ Figure Identification[*A*] = -14.90 + 0.11 X Figure Identification[A-1] + 0.16 X anxiety[A-1]

Δ anxiety[*t*] = 3.28 – 0.07 X Figure Identification[t-1]

The equation for Figure Identification demonstrates that change in performance over time is a function of constant linear change (-7.35), previous performance on Figure Identification, and prior anxiety symptoms (although not statistically significant). The equation for anxiety demonstrates that change in anxiety over time is a function of constant linear change (3.28) and prior performance on Figure Identification. Figure 25 presents a vector field plot of this association.

The association between anxiety and Thurstone picture memory was examined next. Parameter estimates with standard errors and fit statistics from model comparisons are presented in table 33. The multigroup model suggested that the bivariate association was not significantly different by sex (Δfit = 0.52, Δdf = 3, *ns*). The single group model suggested that the dynamic effect of anxiety on Thurstone performance could be dropped from the model without reduced model fit (Δfit = 0.39, Δdf = 1, *ns*). The Thurstone on anxiety coupling parameter was both statistically significant ($\gamma_{\text{Thurstone-anx}} = -0.19$, SE = 0.06, $p < 0.01$) and unable to drop this parameter from the model without significantly worse model fit (Δfit = 7.55, Δdf = 1, $p < 0.01$).

Change at time *A* for Thurstone and anxiety can be calculated by the following equations:

$$\Delta \text{ Thurstone}[A] = -25.85 + 0.45 \text{ X Thurstone}[A-1] + 0.08 \text{ X anxiety}[A-1]$$

$$\Delta \text{ anxiety}[A] = 8.69 - 0.19 \text{ X Thurstone}[A-1]$$

The equation for the Thurstone demonstrated that change in performance over time is a function of constant linear change (-7.35), previous performance on Thurstone, and previous anxiety symptoms (although not statistically significant). The equation for anxiety demonstrated that change in anxiety over time is a function of constant linear change (3.28) and prior performance on the Thurstone. A vector field plot of this dynamic association is presented in figure 26.

Parameter estimates with standard errors and fit statistics from the bivariate DCMS examining Digit Span Total and anxiety are presented in table 34. Because the univariate model did not find evidence of proportional change for Digit Span over time this parameter was not estimated in the bivariate model. The multigroup model comparisons indicate that the bivariate association between anxiety and Total Digit Span did not differ by sex (Δfit = 2.28, Δdf = 3, *ns*). The dynamic effect of anxiety on Total Digit Span performance could be dropped from the model without reduced model fit (Δfit = 0.03, Δdf = 1, *ns*). The Total Digit Span on anxiety coupling parameter was both statistically significant ($\gamma_{\text{digit span-anx}}$ = -0.20, SE = 0.05, $p < 0.01$) and we were unable to drop this parameter from the model without significantly worse model fit (Δfit = 12.19, Δdf = 1, $p < 0.01$). Change at time *A* for total digit span and anxiety can be calculated by the following equations:

Δ Total Digit Span[*A*] = -0.08 – 0.01 X anxiety[A-1]

Δ anxiety[*A*] = 9.43 – 0.20 X Total Digit Span[A-1]

The equation for the digit demonstrates that change in Total Digit Span performance over time is a function of constant linear change (-0.08) and prior anxiety (although not statistically significant). The equation for anxiety demonstrated that change in anxiety over time is a function of constant linear change (9.43) and prior performance on Total Digit Span. Figure 27 presents a vector field plot illustrating this dynamic association.

Parameter estimates with standard errors and fit statistics from the bivariate DCMS examining Digit Span Forward and anxiety are presented in table 35. The proportional change parameter for Forward Digit Span was not estimated in the models based off findings from the univariate models showing lack of proportional change. The multigroup model comparisons indicated that the bivariate association between anxiety and Digit Span Forward did not differ by gender (Δfit = 1.05, Δdf = 2, *ns*). The single group model suggested that the dynamic effect of anxiety on Digit Span Forward performance could be dropped from the model without reduced model fit (Δfit = 1.04, Δdf = 1, *ns*). The Digit Span Forward on anxiety coupling parameter was both statistically significant ($\gamma_{\text{digit span-anx}}$ = -0.26, SE = 0.08, $p < 0.01$) and we were unable to drop this parameter from the model without significantly worse model fit (Δfit = 9.10 Δdf = 1, $p < 0.01$). Change at time *A* for Digit Span Forward and anxiety can be calculated by the following equations:

Δ Digit Span Forward[*A*] = 3.30 – 0.08 X anxiety[A-1]

Δ anxiety[*A*] = 12.20 – 0.26 X Digit Span Forward[A-1]

Figure 28 is a vector field plot depicting this dynamic association.

Parameter estimates with standard errors and fit statistics from the bivariate DCMS examining Digit Span Backward and anxiety are presented in table 36. The proportional change parameter for Digit Span Backwards was not estimated in the models. This parameter was not estimated due to findings from the univariate models suggesting no significant proportional change time. The multigroup model comparisons indicated that the bivariate association between anxiety and Digit Span Backward did not differ by sex (Δfit = 0.72, Δdf = 2, *ns*). The single group model suggested that the dynamic effect of anxiety on Digit Span Backwards performance could be dropped from the model without reduced model fit (Δfit = 0.08, Δdf = 1, *ns*). The Digit Span Backwards on anxiety coupling parameter was both statistically significant ($\gamma_{\text{digit span-anx}}$ = -0.21, SE = 0.06, $p < 0.01$) and dropping this parameter from the model resulted in significantly worse model fit (Δfit = 10.80 Δdf = 1, $p < 0.01$). Change at time *A* for Digit Span Backward and anxiety can be calculated by the following equations:

Δ Digit Span Backward[*t*] = -1.79 + 0.02 X anxiety [t-1]

Δ anxiety[*t*] = 9.95 – 0.21 X Digit Span Backwards[t-1]

Figure 29 graphically depicts this dynamic association in a vector field plot.

Parameter estimates with standard errors and fit statistics from the bivariate DCSM examining Block Design and anxiety are presented in table 37. The multigroup model comparisons indicated that the bivariate association between anxiety and Block

Design did not differ significantly by sex (Δfit = 1.42, Δdf = 2, *ns*). The single group model suggested that the dynamic effect of anxiety on Block Design could be dropped from the model without reduced model fit (Δfit = 0.38, Δdf = 1, *ns*). The Block Design on anxiety coupling parameter was both statistically significant ($\gamma_{blocks\text{-}anx}$ = -0.12, SE = 0.03, $p < 0.01$) and dropping this parameter from the model resulted in significantly worse model fit (Δfit = 17.04 Δdf = 1, $p < 0.01$). Change at time *A* for Block Design and anxiety can be calculated by the following equations:

Δ Block Design[*A*] = -12.53+0.20 X Block Design[A-1]+0.04 X anxiety[A-1]

Δ anxiety[*A*] = 5.77 – 0.12 X Block Design[A-1]

The equation for the Block Design demonstrates that change in performance over time is a function constant linear change (-12.53), Block Design performance at the previous age, and anxiety symptoms at the previous age. The equation for anxiety demonstrates that change in anxiety over time is a function of constant linear change (5.77) and prior performance on Block Design. See Figure 30 for a vector field plot of this association.

Parameter estimates with standard errors and fit statistics from the bivariate DCMS examining Card Rotations performance and anxiety are presented in table 38. The multigroup model comparisons indicated that the bivariate association between anxiety and Card Rotations did not differ significantly by sex (Δfit = 0.16, Δdf = 2, *ns*). The single group model suggested that the dynamic effect of anxiety on Card Rotations could be dropped from the model without reduced model fit (Δfit = 0.07, Δdf = 1, *ns*). The Card Rotations on anxiety coupling parameter was both statistically

significant ($\gamma_{rotations\text{-}anx}$ = -0.11, SE = 0.03, $p < 0.01$) and dropping this parameter from the model resulted in significantly worse model fit (Δfit = 15.68 Δdf = 1, $p < 0.01$). Change at time *A* for Card Rotations and anxiety can be calculated by the following equations:

Δ Card Rotations[*t*] = -6.74 + 0.14 X Card Rotations[t-1] – 0.04 X anxiety[t-1]

Δ anxiety[*t*] = 5.30 – 0.11 X Card Rotations[t-1]

The equation for Card Rotations demonstrated that change in performance is a function constant linear change (-0.69), Card Rotations performance at the previous age, and anxiety at the prior age (although not statistically significant). The equation for anxiety demonstrates that change in anxiety over time is a function of constant linear change (9.95) and prior performance on Card Rotations. See Figure 31 for a vector field plot of this association.

Parameter estimates with standard errors and fit statistics from the bivariate DCMS examining anxiety and Figure Logic performance are presented in table 39. The multigroup model indicated that the bivariate association between anxiety and Figure Logic did not differ significantly by sex (Δfit = 1.06, Δdf = 3, *ns*). The single group model suggested that the dynamic effect of anxiety on Figure Logic could be dropped from the model without reduced model fit (Δfit = 0.17, Δdf = 1, *ns*). The Figure Logic on anxiety coupling parameter was both statistically significant ($\gamma_{figure\ logic\text{-}anx}$ = -0.14, SE = 0.05, $p < 0.01$) and dropping this parameter from the model resulted in significantly worse model fit (Δfit = 8.18 Δdf = 1, $p < 0.01$). Change at time *A* for figure logic and anxiety can be calculated by the following equations:

Δ Figure Logic[*A*] = -13.10+0.28 X Figure Logic[A-1] – 0.05 X anxiety[A-1]

Δ anxiety[*A*] = 7.02 – 0.14 X Figure Logic[A-1]

The equation for Figure Logic demonstrates that change in performance was a function constant linear change (-13.10), Figure Logic performance at the previous age, and to a lesser prior anxiety (although not statistically significant). The equation for anxiety demonstrates that change in anxiety over time is a function of constant linear change (7.02) and prior performance on Figure Logic. Figure 32 presents a vector field plot of this association.

Specific Aim 4: Explore the temporal dynamics underlying the genetic covariation between anxiety and cognitive abilities.

The association between anxiety and Symbol Digit performance was examined first. The parameter estimates from the full model are presented in table 40. Inconsistent with the results from the phenotypic analysis, evidence for bidirectional coupling was found. The estimates of both coupling parameters were small; however, removing them from the model resulted in significantly worse model fit. Strong genetic influences on the intercept were found for both Symbol Digit and anxiety. No significant dominant genetic effects were found on either variable as these effects were able to be dropped without reducing model fit (Δfit = 3 Δdf = 6, $p < ns$). For anxiety no significant genetic effects on the slope were found. For Symbol Digit the only significant genetic effects on the slope acted through genetic influences on the intercept (Δfit = 34 Δdf = 1, $p < 0.01$). Model parameters were used to calculate the expected variance components over the age range. Figure 33 presents the estimated

variance components from the full AE model with and without coupling. Comparing the results of the age based variance components demonstrated the effect of coupling. Figure 33? shows little difference between the coupling and no coupling models for anxiety and Symbol Digit. The small difference in model estimates reflects the modest estimate of the coupling parameter. The figure indicates increasing genetic variance in anxiety over time while the genetic variance in Symbol Digit remains relatively stable. When coupling is introduced in the model the amount of genetic variance in anxiety increases compared to the model without coupling. This suggests that genetic variance in Symbol Digit is driving genetic variance in anxiety. Similarly, the amount of variance in Symbol Digit performance accounted for no unique environmental factors increases over time. When coupling was introduced in the model unique environmental variance in symbol digit increased over time. This increase suggests that unique environmental variance in anxiety was contributing to subsequent unique environmental variance in symbol digit performance.

The association between anxiety and Figure Identification performance was examined next. The parameter estimates from the full model are presented in table 41. Consistent with the results from the phenotypic analyses, evidence for unidirectional coupling of Figure Identification on anxiety was found. The anxiety on Figure Identification coupling parameter was not statistically significant and dropping this model did not result in a degradation of model fit. Conversely, removing the Figure Identification on anxiety coupling resulted in worse model fit when removed from the model. No significant dominant genetic effects were found on either Figure

Identification performance or anxiety. For anxiety no significant genetic effects on the slope were found. For Figure Identification significant additive genetic effects were present directly on the slope as well as acting through genetic influences on the intercept. Model parameters were used to calculate the expected variance components over the age range. Figure 34? shows little difference between the coupling and no coupling models for anxiety and Figure Identification. The small difference in model estimates reflects the modest estimate of the coupling parameter. The figure suggests increasing genetic variance in anxiety as well as Figure Identification over time. Furthermore, when coupling is introduced into the model the unique environmental variance component for anxiety exhibits slightly greater increases over time compared to the no coupling model. Although the magnitude of the difference between the two models is small, it is statistically significant given the significance of the coupling parameter. Thus, we can say unique environmental influences on Figure Identification performance are driving variance in anxiety symptoms over time. When examining the figures the estimated genetic variance for Figure Identification over time is greater when coupling is introduced into the model. Although the magnitude of this difference appears greater than the unique environmental variance for anxiety, this difference is not statistically significant due to the non-significant anxiety on Figure Identification coupling parameter.

We examined the association between anxiety and Total Digit Span performance next. The parameter estimates from the full model are presented in table 43. Consistent with the results from the prior aim, evidence for unidirectional coupling

of Total Digit Span on anxiety was found. The anxiety on Total Digit Span coupling parameter was not statistically significant and dropping this model did not result in a degradation of model fit. Conversely, we were unable to remove the Total Digit Span on anxiety coupling without a worse fitting model. No significant dominant genetic effects were found on either Total Digit Span performance or anxiety. Similarly, no significant additive genetic effects were found on the slope directly or acting through the additive genetic influences on the intercept for both anxiety and Digit Span Total. Model parameters were used to calculate the expected variance components over the age range. Figure 36 shows little difference between the coupling and no coupling models for anxiety and Total Digit Span. The figure indicates increasing genetic variance in anxiety over time and decreasing genetic variance in Total Digit Span over time. The amount of additive genetic variance in anxiety is greater when coupling is introduced in the model. Similarly the amount of unique environment variance decreased when coupling was introduced in the model. This suggests that genetic factors driving variance in Digit Span Total are also driving genetic variance in anxiety.

Table 44 presents the parameter estimates from the biometric models examining anxiety and Digit Span Forward. Unlike previous models, no evidence for coupling was found. Dropping the anxiety on Forward Digit Span coupling did not reduce model fit. Dropping the Digit Span Forward on anxiety coupling also did not reduce model fit. No significant dominant genetic influences were found on either

anxiety or Digit Span Forward. For both anxiety and Digit Span Forwards the only significant additive genetic contributions were present on the intercept.

Table 45 presents the parameter estimates from the biometric models examining anxiety and Digit Span Backwards. Again, evidence for unidirectional coupling was found. Dropping the anxiety on Digit Span Backwards parameter did not result in a worse fitting model. Dropping the Digit Span Backwards on anxiety parameter resulted in a significant deterioration of model fit. No significant dominant genetic influences were found on either anxiety or Digit Span Backwards. The only significant additive genetic contribution found on anxiety was on the intercept. Significant additive genetic contributions on Digit Span Backwards were found on the intercept, and on the slope through the intercept. Figure 37 shows little difference between the coupling and no coupling models for anxiety and Digit Span Backwards. The figure suggests that unique environmental contributions to Digit Span Backwards were driving the variation in anxiety over time.

Next, we examined the association between anxiety and Block Design performance. The parameter estimates from the full model are presented in table 46. Consistent with the results from aim 3, evidence for unidirectional coupling of Block Design on anxiety was found. Dropping the anxiety on Block Design coupling did not result in a degradation of model fit. Conversely, we were unable to remove the Block Design on anxiety coupling without a worse fitting model. No significant dominant genetic effects were found on either anxiety or Block Design performance. No significant genetic influences were found on the slope of anxiety. The only significant

additive genetic contribution on the slope of Block Design acted through the additive genetic influences on the intercept. Figure 38 compares the estimations of the additive genetic and unique environmental variance at each age. The figure demonstrates that unique environmental variance in Block Design was driving variation in anxiety symptoms. Although the magnitude is small it is statistically significant.

The association between anxiety and Card Rotations performance was examined next. The parameter estimates from the full model are presented in table 47. Evidence for unidirectional coupling of rotations performance on anxiety was found. Dropping the anxiety on Card Rotations performance coupling did not result in a degradation of model fit. Removing the Card Rotations performance on anxiety coupling resulted in a worse fitting model. No significant dominant genetic effects were found on either anxiety or Card Rotations performance. No significant genetic influences were found on the slope of anxiety. The only significant additive genetic contribution on the slope of Card Rotations acted through the additive genetic influences on the intercept. Figure 39 compares the estimations of the additive genetic and unique environmental variance at each age. The figure demonstrates that unique environmental variance in Card Rotations was driving variation in anxiety symptoms. Although the magnitude is small it is statistically significant given the significant coupling parameter.

Lastly, biometric models examining the association between anxiety and Figure Logic were fitted. Parameter estimates from the full model are present in table 48. Removing the anxiety on Figure Logic coupling did not significantly decrease

model fit. Conversely, removing the Figure Logic on anxiety coupling resulted in a significantly worse fitting model. Like previous models, all significant additive genetic influences on anxiety were through the intercept. Significant additive genetic contributions were present on the intercept as well as on the slope through the intercept. Figure 40 presents age-based estimation of the additive genetic and unique environmental variance for model with and without coupling. Unique environmental variance on figure logic was driving unique environmental variance in anxiety.

Results Chapter acknowledgment

The results section of the dissertation, in part is currently being prepared for submission for publication. The dissertation author was the primary investigator and author of this material. Co-authors to this work include: Julie Wetherell, Ph.D., Chandra Reynolds, Ph.D., William Kremen, Ph.D., Niloofar Afari, Ph.D., Deborah Finkel, Ph.D., and Margaret Gatz, Ph.D.. The dissertation/thesis author was the primary investigator and author of this paper.

DISCUSSION

The broad focus of this dissertation was to examine the developmental trajectory of anxiety across later life and its association with cognitive performance. This project addressed aforementioned gaps in the literature and hoped to answer four main questions: (1) How stable are the genetic and environmental contributions on symptoms of anxiety throughout older adulthood? (2) To what extent do shared genetic and environmental factors explain the association between anxiety and cognitive performance in later life? (3) What is the directionality of the association between anxiety and cognitive performance? (4) What are the temporal dynamics of genetic and environmental influences on this association? To examine these questions, longitudinal anxiety and cognitive performance data gathered over a span of 23 years from a nationally representative twin population were examined. We anticipated that given changes associated with aging (both physiological and environmental) new genetic or environmental contributions to the etiology of anxiety symptoms would arise in later life. Given prior findings documenting single genes that may influence both cognition and anxiety we hypothesized that some shared genetic influences would explain the correlation between anxiety and cognitive performance. We then examined the directionality of the association between cognitive performance and anxiety over time. We did not have a hypothesis regarding the directionality of the association between anxiety and cognitive performance, as research to date suggests that it may be in either direction. Lastly, we examined the temporal dynamics of genetic and environmental influences driving this association.

We found some support for our hypotheses. Specifically, we found evidence for new additive genetic and unique environmental influences on the etiology of anxiety in later life. We also found evidence for shared genetic influences impacting both anxiety and cognitive performance. Findings also suggest that the association between anxiety and cognitive performance is unidirectional. Poorer cognitive performance was associated with subsequent increases in anxiety; however, increased anxiety was not associated with subsequently greater declines in cognitive performance.

The first aim of this study was to examine the stability of genetic and environmental influences on anxiety across older adulthood. Although genetic innovations in younger adulthood (age 54 and younger) explained much of the genetic variance throughout later life, we did find evidence for differences in the genetic determinants of anxiety arising around the age of 60. Similarly, although the unique environmental influences on anxiety in younger adulthood explained much of the unique environmental variance in later life evidence for new unique environmental determinants of anxiety were found arising between age 70 and 80. The finding that genetic and unique environmental influences in younger life explain most of the variance in anxiety symptoms later in life is consistent with prior research (Gillespie, et al., 2004). We also did not find evidence of dominant genetic or shared environmental factors in the etiology of anxiety later in life. This is also consistent with a large body of literature (Kendler et al., 2011).

New significant genetic contributions were found at age 60-64 for both measures of anxiety. This finding suggests that starting at this age new biological factors may be contributing to the etiology of anxiety symptoms. New genetic contributions on anxiety may exist not only at this age but at all subsequent ages. These new genetic factors were small, but statistically significant. This finding of new genetic contributions in later life is somewhat consistent with prior research that found new increased heritability of depression later in life (Gatz, et al., 1992; Gillespie, et al., 2004). As described previously, cardiovascular disease and other chronic health conditions are commonly comorbid with anxiety in older adulthood. The incidence and prevalence of cardiovascular diseases (e.g. hypertension, heart disease, heart failure, and stroke) increase substantially after the age of 60 (Go et al., 2013). Recent epidemiological research has documented the association between physical health and anxiety (Mackenzie, El-Gabalawy, Chou, & Sareen, 2013). This study found that poor physical health was a predictor of persistent mood and anxiety disorders in older adults. While not unique to older adults, chronic medical conditions typically occur with greater frequency in older than younger adults. Other pathophysiologies unique to late life anxiety may also explain this new genetic innovation. Genes contributing to cognitive decline may explain this genetic innovation seen at age 60. Cognitive performance typically starts to decline a greater rate, starting around the age of 60 (Salthouse, 2010).

New unique environmental factors were contributing to the etiology of anxiety at ages 70-74 for the STPI and ages 75-79 for the Anxiety Crosswalk measure. The

new unique environmental influences on anxiety at this age may reflect some of the stressful life events that are associated with the aging process that commonly arise during these ages. Providing care for a significant other who is chronically ill or cognitively impaired may be one of these environmental events associated with anxiety at this age. Additionally, during the course of SATSA the life expectancy in Swedish population ranged from 73-83 years (U.S. Census Bureau, 2012). The likelihood of experiencing significant bereavement from having a spouse or close friend pass away is quite high. Although research has consistently demonstrated that the prevalence of anxiety and depression decreases in later life and most people are resilient following the death of a significant other (Bonanno, 2004), some individuals have difficulty coping with these significant environmental stressors (Miller, 2012). These stressors may explain the significant unique environmental contributions to anxiety symptoms that were found starting at these ages.

The heritability of anxiety symptoms estimated in the first study was accounted for by a combination of the genetic innovations and autoregressive transmission factors. For both measures of anxiety we found that genetic influences on anxiety symptoms decreased modestly (from 35-40% to about 20%) while participants were in their 60's. This decrease was largely due to a decrease in magnitude of transmission factors from age 55 to age 60. While we found that the mean level of anxiety did not decrease during this age span environmental factors became more salient in the etiology of symptoms. The ages of 60-65 are commonly a period of significant transition in social roles, specifically transitioning from working to retirement. While

most people experience increased well-being and life satisfaction following retirement, this life transition may be challenging for some. Thus, it is possible that stressors associated with retirement may be accounting for the increased salience of environmental factors at this age period. This is consistent with the developmental psychopathology model of psychopathology (Cicchetti, 2006). This model, while previously mostly applied to children and early life transitions, posits that transitional periods may be particularly salient in the development of psychopathology. The increased importance of environmental factors during this time period may reflect retirement and the transition into older adulthood.

In sum, the first question of this dissertation asked how stable are the genetic and environmental contributions to anxiety in later life? We found that genetic and environmental influences are mostly stable with some evidence for new genetic factors impacting the etiology of anxiety symptoms starting at ages 60-64. It is unclear what these new genetic influences are at this age. One hypothesis is given association between cognitive performance and anxiety in later life (Beaudreau & O'Hara, 2008), genetic influences contributing to cognitive performance may also be influencing anxiety. This may potentially explain the new genetic innovation on anxiety that was detected at age 60. The extent to which shared genetics or environment contribute to the association between cognitive performance and anxiety later in life is largely unknown. We aimed to answer this question with the second study of this dissertation.

Results from this second study provide evidence that higher anxiety was associated with worse cognitive performance in the domains of attention, working

memory, nonverbal recognition memory, and visuospatial abilities. Contrary to our hypotheses, we did not find any association between anxiety and processing speed. Also, unexpectedly we found an association between anxiety and visuospatial abilities. Sex differences did emerge with this association being higher in males than in females. Additionally, differences between the sexes were found in the variance structure of genetic and environmental risk factors underlying this association. For males we found significant shared genetic vulnerabilities, while in females shared unique environmental factors explained the association.

Univariate sex-limitation models were estimated first to examine sex differences in the variance structure of anxiety and cognitive performance. The univariate models found evidence that the variance structure in anxiety symptoms differed by sex. Specifically, we found that the overall variance in anxiety symptoms was greater for males than females. The overall proportion of variance accounted for by additive genetic factors was similar for males (35%) and females (38%). Consistent with prior research, no sex differences in the variance structures were found in cognitive performance (Finkel, Reynolds, Berg, & Pedersen, 2006). There was also no evidence for significant contributions of dominant genetic effects on anxiety symptoms or cognitive performance.

For males, higher anxiety was associated with worse performance on tests of attention (Digit Span Forward), working memory (Digit Span Backwards), nonverbal memory (Thurstone picture memory), and aspects of visuospatial functioning (Block Design, and Card Rotations). In females, anxiety was associated with worse nonverbal

memory and visuosptatial abilities. Inconsistent with our initial hypotheses and past research, we did not find any significant association between anxiety and processing speed in both males and females. Additionally, inconsistent with our hypothesis, anxiety was associated with worse visuospatial performance. Future research needs to examine the association between anxiety and visuospatial functioning in greater detail. The Block Design task has a speed component to performance. Higher scores are representative of a faster performance. It is possible that the speed aspect of this test may be driving the association between Block Design and anxiety. Significant associations were also found on a different test of visuospatial performance (Card Rotations), suggesting an association between visuospatial abilities and anxiety. Future research needs to examine the association between anxiety and visuospatial processing in greater depth.

The extent to which genetic and environmental factors explain the correlation between anxiety and cognitive performance differed by sex and cognitive domain. For males, the association between basic attention and anxiety was explained primarily by shared unique environmental factors. Conversely, shared genetic contributions explained the association between the more demanding working memory (Digit Span Backwards). Sex differences emerged on tests of nonverbal memory and visuospatial performance. For females, the association between anxiety, nonverbal memory, and visuospatial abilities was explained primarily by unique environmental factors. For males, shared additive genetic factors primarily explained this association.

One explanation as to why genetic factors may be more salient in males is the role of cardiovascular disease. Not only is cardiovascular disease more prevalent in males (Perez-Lopez, Larrad-Mur, Kallen, Chedraui, & Taylor, 2010) but genetic contributions to specific cardiovascular diseases such as hypertension also appear to be greater in males (Biino et al., 2013). Cardiovascular diseases are associated with both anxiety and poorer cognitive performance. Therefore, genetic contributions influencing vascular health might be explaining the shared genetic contributions on anxiety and cognitive performance. The potential protective role of estrogen on cognition also may contribute to these sex differences. Research, primarily in animal models, has found that the hormone estrogen may have a positive effect on cognition especially in the domains of learning and memory (Pompili, Arnone, & Gasbarri, 2012). Estrogen receptors have been implicated in the brain's stress response pathways (Ter Horst, Wichmann, Gerrits, Westenbroek, & Lin, 2009) and might be protective to neurons from the harmful effects of cortisol (Hulshof, Novati, Luiten, den Boer, & Meerlo, 2012). Similarly, Dumas et al. (2012) found that estrogen was associated with less negative reactivity to stress in older women. The potential protectiveness of estrogen against the harmful effects of stress on brain physiology may explain why unique environmental factors contribute more to the association between anxiety and cognitive performance in females.

Limitations of this dissertation are discussed in greater detail later in this section, but one important limitation of correlational research is the inability to draw inferences of causation or directionality. Based on these cross-sectional correlations it

is unclear if individuals experiencing higher anxiety are then subsequently experiencing greater declines in cognitive performance or if the opposite is true. Participants experiencing declining cognitive performance might be subsequently becoming more anxious. This question we sought to answer with the third study of this dissertation was: "What are the temporal dynamics of this association between anxiety and cognitive functioning?" We sought to elucidate the directionality of this association. Specifically we sought to find out if anxiety was associated with subsequent declines in cognitive performance or if declining cognitive performance was a leading indicator of changes in anxiety.

To attempt to answer this third question we examined the complex association between cognitive performance and anxiety symptoms by fitting dual change score models of change. Univariate models indicated that anxiety was stable throughout later life with a small but significant linear decline over older adulthood. This finding is consistent with prior research (Wetherell, et al., 2001). Although anxiety was fairly stable we found significant variability in this linear trajectory of anxiety over age. Also consistent with prior research, univariate models documented significant declines in all cognitive abilities examined during the second half of life (Salthouse, 2010). With the exception of digit span, all measures of cognitive performance exhibited significant proportional changes over time. This proportional change suggested that the rate of declines in cognitive performance increased with age.

Anxiety symptoms at one age did not predict subsequent changes cognitive performance. Cognitive performance did however predict future changes in anxiety.

Specifically, across all cognitive outcomes, worse performance was associated with increased anxiety three years later. Similarly, better cognitive performance was associated with less anxiety three years later. These findings are consistent with a prior study utilizing dual change modeling to examine the dynamic association between depression and memory over time (Jajodia & Borders, 2011). Unlike the prior aim we did not find any evidence of sex differences in this association.

This dynamic association between anxiety and cognitive performance was present even after controlling for depression, education, and sex. Not surprisingly symptoms of depression were associated with symptoms of anxiety as well as many cognitive abilities. Higher depressive symptoms were associated with faster linear declines in processing speed, nonverbal memory, and visuospatial functioning over age. Depressive symptoms were also associated with greater initial anxiety symptoms but were not associated with changes over age.

Psychological processes may explain this association between cognitive performance and future anxiety symptoms. Noticeable declines in cognitive ability may become a source of worry and distress leading to increased anxiety three years later. Declines in cognitive performance may impact social functioning. Declines in memory, attention, and processing speed all may contribute to feeling anxious about performance in social settings. Declining spatial functioning may result in worry about engaging in activities far from home due to fear of being unsure of surroundings. This anxiety may result in avoidance of these situations reinforcing their concerns. This potential social withdrawal may result in the emergence of emotional distress such as

anxiety or depression. Another possibility is that declining cognitive performance may hinder one's ability to respond and cope with life stressors. This potential decreased problem solving ability may result in the prolongation of stressors or inability to prevent stressors. The prolongation of stressors may be contributing to the future emergence of anxiety.

Biological processes may explain this association. Declines in cognitive ability initially followed by subsequent increases in anxiety may be the sequelae of a larger pathophysiological process. One potential process is cardiovascular disease and chronic medical illness. Cardiovascular disease, specifically hypertension, causes hyperintensities of the white matter tracts in the brain. These changes to the white matter pathways of the brain are associated with worse cognitive performance particularly slower processing speed. Recent research has also shown a positive association between white matter hyperintensities, avoidance behaviors, and trait anxiety symptoms (Montag, Reuter, Weber, Markett, & Schoene-Bake, 2012; Westlye, Bjornebekk, Grydeland, Fjell, & Walhovd, 2011) as well as late-life depression (Santos et al., 2012). It is possible that cognitive decline and anxiety may be sequelae of cardiovascular disease.

These findings have important clinical implications. Clinicians working with older adults need to monitor and assess anxiety when working with older adults who are experiencing objective declines in cognitive abilities. Most older adults in need of mental health care seek treatment through their primary care doctor and not in specialized settings (Gum, Iser, & Petkus, 2010). Older adults suffering from anxiety,

or other psychiatric conditions commonly do not have insight into their symptoms (Gum et al., 2009). The end result being that the majority of older adults in need of mental health care do not receive adequate treatment (Garrido, Kane, Kaas, & Kane, 2011). Primary care providers have limited time and resources for screening of these problems are scarce. Thus, screening efforts need to be targeted to optimize resources. The findings that changes in cognitive performance typically precede increased anxiety may improve the effectiveness of detection of anxiety in healthcare settings. Initial assessment and continued monitoring of anxiety in individuals experiencing cognitive declines may be helpful in improving the detection of these problems.

Education on normal cognitive aging has been identified as important to the prevention of dementia (Middleton & Yaffe, 2009). The findings from this study confirm the potential importance of psychoeducation with older adults. If the hypothesis that psychological factors are contributing to subsequent increases in anxiety, namely cognitive abilities become a target of worry, then psychoeducation may be preventative in the future development of anxiety. If older adults are educated about normal cognitive aging they may be less likely to worry about their own current level of functioning. Additionally, psychoeducation may be beneficial if a physiological mechanism such as cardiovascular disease is contributing to declining cognitive abilities and increased anxiety. Education about cardiovascular disease and other risk factors for future cognitive declines may potentially decrease both anxiety and some of the risk factors for future cognitive declines. Research suggests that older

adults are satisfied with and can improve knowledge through programs designed to increase knowledge about cognitive aging (Norrie et al., 2011).

The last aim of this dissertation sought to increase our knowledge base around the question of the mechanisms driving this association between cognitive decline and future anxiety. Specifically we aimed to determine if genetic or environmental factors were driving this association over time. As discussed, this association can be explained by a number of potential scenarios. Specifically we investigated three possible scenarios: (1) genetic or environmental factors impacting anxiety are driving variation in cognitive performance (2) genetic or environmental factors impacting cognitive performance are driving variation in anxiety symptoms, or (3) if a bidirectional association exists.

The results from these biometric models demonstrate the complex association between anxiety and cognitive performance. We found that for some cognitive domains genetic factors influencing cognitive performance were driving variation anxiety. Primarily for processing speed and attention, genetic factors contributing to cognitive performance were driving variation in anxiety over time. In other domains, specifically spatial abilities, unique environmental variation of spatial functioning was driving variation in anxiety. Across all of these biometric analyses the effect was small.

Genetic factors explaining variance in measures of processing speed (Symbol Digit) and working memory/attention (Digit Span Total) were driving variation in anxiety symptoms. This provides support for the hypothesis that physiological

mechanisms driving changes in processing speed are subsequently driving increases in anxiety. The APOE gene may be one candidate gene influencing both changes in processing speed followed by increased anxiety. Older adults with the higher neuroticism and the APOE ε4 allele may have worse cognitive functioning than those without the APOE ε4 allele (Dar-Nimrod et al., 2012). White matter changes are another potential physiological mechanism. Late life depression has been also been associated with periventricular white matter changes (Nebes et al., 2001). It is possible that white matter changes occurring in the frontal lobe may be first cause slower cognitive processing (Kerchner et al., 2012) followed by emotional distress such as depression or anxiety. Changes in the frontal lobe have been implicated in both depression and anxiety later in life. Future research needs to investigate this further.

Contrary to processing speed, unique environmental contributions to visuospatial performance were driving variation in anxiety. These findings suggest that different mechanism driving the association between anxiety and cognitive performance varies by domain. Physiological mechanisms do not appear to be driving the association between anxiety and visuospatial abilities. Referring back to a potential explanation posited in the discussion of the phenotypic analysis, these findings potentially provide some support for the idea that cognitive changes may be resulting in activity restriction. Individuals experiencing declining abilities in this domain might be less confident or willing to engage in new activities outside of the home due to fear of getting lost. This potential social withdrawal may result in decreased engagement in value consistent and pleasant activities resulting in the development of emotional

distress such as anxiety or depression. Prior SATSA examinations have documented that genetic variance driving processing speed drives variation in spatial abilities (Finkel, et al., 2009). Thus, it is possible that genetic factors influencing processing speed may be causing variation in anxiety through spatial processing.

Limitations

The studies conducted in this dissertation have a number of limitations that need to be discussed. First, global limitations that are present across all aims will be discussed. This will be followed with a discussion of limitations specific to each of the study aims.

The measurement of anxiety across studies was not optimal and is a significant limitation of this work. The anxiety crosswalk measure converted face valid items initially intended to measure the construct of neuroticism to a corresponding score on a validated anxiety measure (STPI). While the constructs of anxiety and neuroticism significantly overlap, and a widely used statistical approach was implemented to link these instruments (Rasch crosswalk analysis), no data exsit outside this study on the psychometrics of this created crosswalk scale. Although the Anxiety Crosswalk scale had a similar mean to the STPI as well as a similar cross-sectional correlation with cognitive performance at IPT2, a more well-validated measure of anxiety would have been optimal. The computed crosswalk scale also had a restricted number of possible scores due to the dichotomous nature of the ENI items. As a result of the limited scores, the crosswalk measure may not have been able to capture the more subtle differences in anxiety.

The cognitive battery used in these studies poses another limitation. The initial SATSA cognitive assessment took place in the year 1986. While the cognitive battery used in this examination is both valid and reliable and captures a number of domains of functioning, it does not measures some cognitive abilities that have been associated with anxiety. Mainly, the lack of an assessment of verbal memory and executive functioning is a major limitation of this work. The battery only had a measure of nonverbal memory (Thurstone picture memory). The Thurstone only measures recognition abilities and not recall abilities which is another limitation of this test. Additionally, in order to best assess change in a measure over time the same measure needs to be administered at every assessment point. This means that the measures administered at the beginning of the study should be used throughout at each follow-up assessment. This poses a potential problem in studies whose duration is several years or even decades like SATSA. While the cognitive assessments used in this study are reliable and valid, the field of neuropsychological assessment has grown exponentially since the onset of the study. New measures have been developed that may be more sensitive to change and better able to measure the cognitive processes of interest have been developed since the inception of SATSA.

It is unclear how these findings would translate to older adults with anxiety disorders or older adults experiencing clinically significant cognitive deficits. A strength of the study is that it includes a nationally representative sample, participants were endorsing minimal levels of anxiety and were not included in the analysis if they met criteria for dementia. However, it is not known if these patterns of findings remain

true for older adults experiencing clinically significant anxiety. The directionality of the anxiety-cognition association may be different in clinically anxious older adults. As discussed in the introduction, evidence does exist suggesting that diagnosed anxiety disorders such as PTSD are associated with increased risk for cognitive impairment in the future (Yaffe et al., 2011). Future research needs to examine these relationships in a clinically anxious sample of older adults.

Some specific limitations in the first study include the inability to examine potential sex differences in the simplex models. Prior research has demonstrated that the genetic and environmental contributions to anxiety symptoms may be different for men and women over time (Gillespie et al., 2004). We also found evidence for sex differences in the univariate Cholesky decompositions in the second aim of this project. Future research needs to replicate these findings with the examination of sex differences. The limited number of participants at both ends of the age distribution is another limitation of the simplex models. For the Anxiety Crosswalk only 33 total twin pairs and 133 partial twin pairs were aged 86 or older. As a result our statistical power to examine the stability of anxiety symptoms in the oldest old was limited. The population of the oldest old (typically defined as 85 or older) is growing at an exponential rate (Papalia, Sterns, Feldman, & Camp, 2007). Given the increasing importance of this population future research needs to examine the stability of anxiety symptoms in this age group.

Important limitations exist in the phenotypic and biometric dual change score statistical models used in the third and fourth study. Structural equation models such

as the DCSM model have assumptions that inter and intra individual variance are equivalent and missing data are missing at random (Finkel, et al., 2007). Although the DCSM models minimize this bias through the use of both latent variables and latent change scores, the more reliable measure might be assigned as the leading indicator of change. Thus, it is possible that the finding that cognition was a leading indicator of change in anxiety is a result of the fact that the cognitive tests were psychometrically more sound than the anxiety crosswalk.

Inconsistencies between the parameter estimates from the biometric and phenotypic DCSM models were also found. Two different computer programs were needed to fit the phenotypic (MPLUS) and biometric (classic Mx) models. While the results were largely consistent some slight inconsistencies emerged. First, the estimated trajectories for all variables differed slightly by software program. Second, while the bivariate associations between variables were largely consistent, this was not true for all bivariate associations. For the bivariate association between Symbol Digit and anxiety, the phenotypic models suggested that unidirectional coupling was occurring, namely Symbol Digit was associated with subsequent anxiety symptoms. The biometric models suggested bidirectional coupling, with evidence for both Symbol Digit associated with subsequent anxiety, as well as anxiety associated with subsequent Symbol Digit performance. Similarly, with the models examining Digit Span Forward and anxiety, the phenotypic models suggested unidirectional coupling while the biometric models found no significant coupling. Future examination of these models needs to be done to clarify these discrepancies.

Summary

In sum, evidence was found for new genetic and environmental influences arising in the etiology of anxiety symptoms in older adulthood. Cross-sectionally, anxiety was associated with poorer working memory, figure memory, and spatial abilities. The association was stronger in males than females. Genetic factors explained the association in males whereas shared unique environmental factors were more salient in females. When examining the directionality of this association over time, worse cognitive performance was predictive of higher anxiety. Genetic factors contributing to processing speed appear to be driving the variation in anxiety, whereas unique environmental factors contributing to spatial abilities were driving the variation in anxiety. These findings have important clinical implications for identifying targets for interventions and preventative efforts. Future research needs to examine the role of vascular health and how this may be impacting these results. Additionally, future research needs to examine the role of target genes such as the APOE and serotonin transporter allele as potential specific genes driving this association.

Discussion chapter acknowledgment

The discussion chapter of the dissertation, in part is currently being prepared for submission for publication. The dissertation author was the primary investigator and author of this material. Co-authors to this work include: Julie Wetherell, Ph.D., Chandra Reynolds, Ph.D., William Kremen, Ph.D., Niloofar Afari, Ph.D., Deborah Finkel, Ph.D., and Margaret Gatz, Ph.D.. The dissertation/thesis author was the primary investigator and author of this paper.

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APPENDIX 1: TABLES AND FIGURES

Table 1. Item comparison of the state anxiety scale for the state trait personality inventory (STPI) and the Eyesnck neuroticism inventory (ENI).

	STPI	ENI
1.	I feel calm	Are you often anxious and feel that you want something but you don't know what?
2.	I feel tense	Are you sometimes happy or sad without any particular reason?
3.	I feel satisfied	Often make decisions too late?
4.	I am worried in case I fail	Often feel tired or listless without particular reason?
5.	I feel nervous	Do you often find yourself deep in thought?
6.	I feel shaky	Are extra sensitive in certain situations?
7.	I feel relaxed	Are you so restless sometimes that you cannot sit still?
8.	I am anxious	Do you have nervous troubles?
9.	I feel harmonious	Do you usually worry too long after a very embarrassing experience?
10.	I feel frightened	
Rating Scale	1 = Fits me exactly 2 3 4 5 = Does not fit me at all	0 = No 1 = Yes

Table 2. Number of complete and incomplete twin pairs who completed a STPI and anxiety crosswalk assessment by age interval, zygosity, and rearing status.

	54 younger		55-59		60-64		65-69		70-74		75-79		80-84		85 and older	
	●●	●○	●●	●○	●●	●○	●●	●○	●●	●○	●●	●○	●●	●○	●●	●○
STPI																
1.MZ	75	32	64	24	71	40	76	63	67	71	38	69	14	46	5	26
2.DZ	111	103	104	76	115	105	149	117	109	167	81	127	21	101	7	42
1.MZT	52	19	42	9	48	17	47	32	38	39	20	39	7	25	4	12
2.MZA	23	13	22	15	23	23	29	31	29	32	18	30	7	21	1	14
3.DZT	46	40	40	29	49	42	77	49	63	79	46	58	13	42	6	19
4.DZA	65	63	64	47	66	63	72	68	46	88	35	69	8	59	1	23
Total	186	135	168	100	186	145	225	180	176	238	119	196	35	147	12	68
Anxiety Crosswalk																
1.MZ	95	24	84	24	98	43	107	62	98	79	70	87	40	54	12	46
2.DZ	169	80	139	84	160	124	201	154	172	204	125	178	53	150	21	109
1.MZT	66	10	58	11	65	19	64	30	59	43	40	53	20	32	7	26
2.MZA	29	14	26	13	33	24	43	35	32	36	30	32	20	22	5	20
3.DZT	72	33	56	32	73	48	98	64	87	92	63	79	25	68	16	50
4.DZA	97	47	83	52	87	76	103	87	85	112	62	99	28	82	5	59
Total	264	104	223	108	256	167	308	216	270	283	195	265	93	204	33	155

Note: ●● = complete twin pair ; ●○ = incomplete twin pair; MZ = Monozygotic twin pair; DZ = Dizygotic twin pair; MZT = Monozygotic pair raised together; MZA = Monozygotic pair raised apart; DZT = Dizygotic pair raised together; DZA = Dizygotic pair raised apart

Table 3. Number of participants who completed anxiety and cognitive data at each age group (N = 801). Note that the assessment schedule for anxiety crosswalk and cognitive performance were not identical resulting in different N's for the anxiety and cognitive data.

Age (Years)	Anxiety Crosswalk (N)	Cognitive Performance (N)
50.00-52.99	139	81
53.00-55.99	194	157
56.00-58.99	238	195
59.00-61.99	256	236
62.00-64.99	319	293
65.00-67.99	353	353
68.00-70.99	345	339
71.00-73.99	310	304
74.00-76.99	289	288
77.00-79.99	243	223
80.00-82.99	169	169
83.00-85.99	112	105
86 and older	63	68

Table 4. Number of twin pairs who completed cognitive data at each age group (N = 801) broken down by zygosity.

	MZ		DZ	
	●●	●○	●●	●○
50-52.99	14	0	23	8
53.00-55.99	25	2	48	8
56.00-58.99	34	6	51	19
59.00-61.99	37	9	68	15
62.00-64.99	52	8	73	32
65.00-67.99	60	13	92	35
68.00-70.99	44	21	83	51
71.00-73.99	40	19	75	46
74.00-76.99	32	29	66	49
77.00-79.99	31	24	41	44
80.00-82.99	19	19	24	49
83.00-85.99	6	19	9	39
86.00-88.99	2	16	5	22

Table 5. Item-total correlations and infit/outfit mean squares estimates for Rasch analysis of all items of the STPI and ENI.

		Infit		Outfit		
		MNSQ	STD	MNSQ	STD	Corr
STPI Items						
1.	I feel calm	0.80	-4.2	0.75	-5.2	0.70
2.	I feel tense	0.82	-3.8	0.76	-4.1	0.70
3.	I feel satisfied	1.09	1.8	1.11	2.2	0.64
4.	I am worried in case I fail	1.38	7.5	1.40	6.9	0.60
5.	I feel nervous	0.62	-9.0	0.57	-7.9	0.74
6.	I feel shaky	0.98	-0.3	0.74	-2.8	0.59
7.	I feel relaxed	0.96	-0.8	1.07	1.5	0.71
8.	I am anxious	0.90	-2.2	1.00	0.1	0.70
9.	I feel harmonious	0.93	-1.4	1.01	0.2	0.71
10.	I feel frightened	0.82	-3.2	0.72	-3.3	0.64
ENI Items						
1.	Anxious	0.91	-1.8	0.77	-1.9	0.46
2.	Happy or sad	1.14	4.6	1.36	5.8	0.45
3.	Make decisions late	1.21	4.8	1.70	5.9	0.33
4.	Tired	0.95	-1.0	1.09	0.8	0.44
5.	Deep in thought	1.10	2.8	1.29	3.7	0.44
6.	Sensitive	1.20	6.1	1.42	6.6	0.43
7.	Restless	1.09	2.2	1.28	2.5	0.39
8.	Nervous	0.82	-2.8	0.64	-2.2	0.45
9.	Worry	1.17	5.3	1.37	5.7	0.43

STPI = State subscale of the State Trait Personality Inventory
MNSQ = Mean Square
STD = Standard deviation
Corr = Item-total score correlation

Table 6. Item total correlations and infit/outfit mean squares for Rasch analysis of all STPI items and misfitting items of ENI removed.

		Infit		Outfit		
		MNSQ	STD	MNSQ	STD	Corr
STPI Items						
1.	I feel calm	0.80	-3.9	0.75	-5.1	0.71
2.	I feel tense	0.85	-3.1	0.81	-3.2	0.70
3.	I feel satisfied	1.16	2.9	1.21	3.7	0.65
4.	I am worried in case I fail	1.48	8.8	1.56	9.0	0.61
5.	I feel nervous	0.61	-8.6	0.58	-7.5	0.74
6.	I feel shaky	0.96	-0.60	0.73	-2.9	0.60
7.	I feel relaxed	1.00	0.01	1.14	2.5	0.72
8.	I am anxious	0.92	-1.6	1.05	0.90	0.71
9.	I feel harmonious	0.98	-0.4	1.08	1.6	0.72
10.	I feel frightened	0.85	-2.7	0.84	-1.7	0.63
ENI Items						
1.	Anxious	0.91	-1.6	0.83	-1.1	0.45
2.	Make decisions late	1.26	5.6	2.08	7.7	0.33
3.	Tired	0.94	-1.2	1.43	2.8	0.44
4.	Deep in thought	1.17	4.7	1.64	6.8	0.42
5.	Restless	1.10	2.2	1.67	4.7	0.40
6.	Nervous	0.81	-3.0	0.89	-0.5	0.45

STPI = State subscale of the State Trait Personality Inventory
MNSQ = Mean Square
STD = Standard deviation
Corr = Item-total score correlation

Table 7. Crosswalk table linking STPI and the shortened 6 item ENI scale.

STPI Raw Score	LOGIT	ENI Raw Score
12	-2.87	0
16	-1.52	1
23	-0.59	2
31	0.12	3
39	0.84	4
46	1.78	5
49	3.16	6

Table 8. Simplex Model Fitting Results for the STPI

Model	-2LL	df	AIC	Compare	Δ -2LL	Δ df	*p*	
1.ACE-4 groups	22239.06	3279	15681	-	-	-	-	
2.ACE-2 groups	22248.60	3279	15690	-	-	-	-	
3.ADE	22248.45	3279	15690	-	-	-	-	
4.AE	22252.23	3292	15668	1	13.17	13	0.99	
5.E	22300.76	3305	15690	4	48.53	13	<0.01	**
AE simplex sub-models								
Drop Ai55	22252.27	3293	15666	4	0.04	1	0.84	
Drop Ai60	22256.30	3293	15670	4	4.07	1	0.04	*
Drop Ai65	22252.37	3293	15666	4	0.15	1	0.70	
Drop Ai70	22252.23	3293	15666	4	0.00	1	1.00	
Drop Ai75	22253.90	3293	15667	4	1.68	1	0.20	
Drop Ai80	22252.23	3293	15666	4	0.00	1	1.00	
Drop Ai55 and Ai65-Ai80	22254.09	3297	15660	4	1.86	5	0.87	
Drop Ei55	22252.23	3293	15666	4	0.00	1	1.00	
Drop Ei60	22252.79	3293	15666	4	0.56	1	0.45	
Drop Ei65	22254.47	3293	15668	4	2.24	1	0.13	
Drop Ei70	22257.35	3293	15671	4	5.13	1	0.02	*
Drop Ei75	22252.23	3293	15666	4	0	1	1.00	
Drop Ei80	22252.68	3293	15666	4	0.45	1	0.50	
Drop Ei55-Ei70 and Ei80-Ei80	22261.36	3297	15667	4	9.13	5	0.10	
Drop all A & E non-significant innovations	22260.37	3302	15656	4	8.14	10	0.62	

Note: -2LL = -2 * Log likelihood; Ai = additive genetic innovation at a specific age group; Ei = unique environmental innovation at an age group; Compare =indicates the full model being that submodel is being compared with; significant innovations at p <0.05 are designated with an *

Table 9. Simplex Model Fitting Results for the Anxiety Crosswalk

Model	-2LL	df	AIC	Compare	Δ -2LL	Δ df	*p*
1.ACE-4 groups	33763.43	4722	24319	-	-	-	-
2.ACE-2 groups	33765.39	4722	24321	-	-	-	-
3.ADE	33771.1	4722	24327	-	-	-	-
4.AE	33781.56	4737	24307	1	16.17	15	0.37
5.E	33880.91	4752	24376	4	99.36	15	<0.01**
AE simplex sub-models							
Drop Ai55	33784.97	4738	24308	4	3.42	1	0.06
Drop Ai60	33788.35	4738	24312	4	6.79	1	0.01*
Drop Ai65	33781.56	4738	24305	4	0	1	0.98
Drop Ai70	33781.58	4738	24305	4	0.03	1	0.87
Drop Ai75	33782.94	4738	24306	4	1.39	1	0.24
Drop Ai80	33782.35	4738	24306	4	0.80	1	0.37
Drop Ai85	33781.56	4738	24305	4	0.0	1	0.97
Drop Ai55 and Ai65-Ai85	33787.39	4743	24301	4	5.84	6	0.44
Drop Ei55	33781.56	4738	24305	4	0	1	1
Drop Ei60	33781.56	4738	24305	4	0	1	1
Drop Ei65	33781.56	4738	24305	4	0	1	1
Drop Ei70	33784.18	4738	24308	4	2.62	1	0.11
Drop Ei75	33786.83	4738	24310	4	5.28	1	0.02*
Drop Ei80	33781.82	4738	24305	4	0.26	1	0.61
Drop Ei85	33781.82	4738	24305	4	0.26	1	0.61
Drop Ei55-Ei70 and Ei80-Ei85	33784.48	4743	24298	4	2.92	6	0.82
Drop all A & E non-significant innovation	33793.31	4749	24295	4	11.75	12	0.47

Note: -2LL = -2 * Log likelihood; Ai = additive genetic innovation at a specific age group; Ei = unique environmental innovation at an age group; Compare = indicates the full model being that submodel is being compared with; significant innovations at p <0.05 are designated with an *

Table 10. Univariate models for STPI and cognitive measures.

	-2LL	df	AIC	ΔX2	Δdf	p	Compare		A	D	E
STPI models											
1. ADE- Sex Limitation	3820.41	562	2696.41	-	-	-	-				
								Male	0.01	0.41	0.59
								Female	0.31	0.08	0.61
2. ADE-Sex equal	3847.28	565	2717.28	26.87	3	<0.01*	Model 1		0.16	0.25	0.60
3. AE-Sex Limitation	3821.32	564	2693.32	0.91	2	0.63	Model 1				
								Male	0.35	-	0.65
								Female	0.38	-	0.62
Symbol digit models											
1. ADE-Sex Limitation	3854.13	506	2842.13	-	-	-	-				
								Male	0.81	0	0.19
								Female	0.76	0	0.24
2. ADE-Sex equal	3854.89	509	2836.89	0.76	3	0.76	Model 1		0.78	<0.01	0.22
3. AE-Sex equal	3584.89	510	2834.89	0	1	>0.99	Model 2		0.78	-	0.22
Figure identification models											
1. ADE-Sex Limitation	4149.71	522	3105.71	-	-	-	-				
								Male	0.65	<0.01	0.34
								Female	0.11	0.56	0.33
2. ADE-Sex equal	4150.90	525	3100.90	1.19	3	0.76	Model 1		0.38	0.28	0.33
3. AD-Sex equal	4151.61	526	3099.61	0.71	1	0.40	Model 2		0.66	-	0.34
Thurstone models											
1. ADE-Sex Limitation	4387.81	518	3351.81	-	-	-	-				
								Male	0.49	<0.01	0.51
								Female	0.48	0.03	0.49
2. ADE-Sex equal	4389.85	521	3347.85	2.04	3	0.57	Model 1		0.49	<0.01	0.51
3. AE- Sex equal	4389.85	522	3345.85	0	1	>0.99	Model 2		0.49	-	0.51
Digit span total											
1. ADE-Sex Limitation	4319.19	547	3225.19	-	-	-	-				
								Male	0.19	0.36	0.46
								Female	0.56	<0.01	0.44
2. ADE-Sex equal	4319.61	550		0.42	3	0.94	Model 1		0.41	0.14	0.45
3. AE-Sex equal	4319.79	551		0.19	1	0.67	Model 2		0.54	-	0.46
Digit Span Forward											
1. ADE-Sex Limitation	4423.61	547	3329.61	-	-	-	-				
								Male	0.03	0.33	0.64
								Female	0.51	<0.01	0.49
2. ADE-Sex equal	4426.33	550	3326.33	2.72	3	0.44	Model 1		0.42	0.02	0.56
3. AE- Sex equal	4426.33	551	3324.33	0	1	0.96	Model 2		0.43	-	0.57
Digit Span Backward											
1. ADE-Sex Limitation	4603.41	547	3509.41	-	-	-	-				
								Male	0.35	0.11	0.53
								Female	0.37	0.06	0.57
2. ADE-Sex equal	4605.53	550	3505.53	2.12	3	0.55	Model 1		0.36	0.09	0.55
3. AE- Sex equal	4605.6	551	3503.60	0.07	1	0.79	Model 2		0.44	-	0.56
Figure logic models											
1. ADE-Sex Limitation	4216.5	523	3170.50	-	-	-	-				
								Male	0.37	0.11	0.52
								Female	<0.01	0.34	0.65
2. ADE-Sex equal	4217.58	526	3165.58	1.09	3	0.78	Model 1		0.21	0.18	0.61
3. AE-Sex equal	4217.84	527	3163.84	0.25	1	0.61	Model 2		0.37	-	0.63
Block design models											
1. ADE-Sex Limitation	4423.52	528	3367.52	-	-	-	-				
								Male	0.79	<0.01	0.21
								Female	0.65	0.05	0.30
2. ADE-Sex equal	4425.53	531	3363.53	2	3	0.57	Model 1		0.74	<0.01	0.26
3. AE-Sex equal	4425.53	532	3361.53	0	1	>0.99	Model 2		0.75	-	0.26
Rotations models											
1. ADE-Sex Limitation	4142.26	491	3160.26	-	-	-	-				
								Male	0.72	<0.01	0.28
								Female	0.44	0.20	0.37
2. ADE-Sex equal	4145.84	494	3157.84	3.57	3	0.31	Model 1		0.60	0.07	0.33
3. AE-Sex equal	4145.89	495	3155.89	0.05	1	0.82	Model 2		0.67	-	0.33

2LL = -2 * Log likelihood; AIC = Akaike information criterion; A = proportion of variance accounted for by additive genetics; D = proportion of variance accounted for by genetic dominance; E = proportion of variance accounted for by unique environment; Sex Limitation models estimated variance components for males and females separately; Sex Equal models estimated variance structure for males and females pooled together; Compare = indicates the full model being that submodel is being compared to.

Table 11. Means and phenotypic correlations between STPI, anxiety crosswalk, and cognitive performance for males and females pooled together.

		Mean	STPI		Anxiety Crosswalk	
Cognitive Domain	Variable	(SD)	r	p	r	p
Processing Speed						
	Symbol Digit	38.0 (11.4)	-0.08	0.07	-0.09	0.04*
	Figure Identification		-0.05	0.27	-0.06	0.16
Attention/Working Memory						
	Digit Span Forward	64.3 (13.4)	-0.07	0.08	-0.06	0.14
	Digit Span Backwards	52.2 (16.0)	-0.06	0.17	-0.05	0.21
	Digit Span Total	58.6 (12.5)	-0.08	0.07	-0.07	0.11
Memory						
	Thurstone	74.4 (16.4)	-0.14	<0.01*	-0.13	<0.01*
Visuospatial						
	Block's	45.4 (16.5)	-0.15	<0.01**	-0.14	<0.01**
	Rotations	46.0 (17.0)	-0.12	<0.01**	-0.11	0.01*
	Figure Logic	60.6 (13.2)	-0.09	0.04*	-0.11	0.02*
Anxiety						
	STPI	17.8 (7.3)	-	-	0.53	<0.001**
	Anxiety Crosswalk	17.4 (8.1)	0.53	<0.001**	-	-

Notes: STPI = State Anxiety subscale of the State Trait Personality Inventory;
** denotes correlations significant at $p < 0.01$
* denotes correlations significant at $p < 0.05$

Table 12. Means and phenotypic correlations between STPI, anxiety crosswalk, and cognitive performance for males and females examined separately.

	Males				Females			
	STPI		Anxiety Crosswalk		STPI		Anxiety Crosswalk	
	r	p	r	p	r	p	r	p
Processing Speed								
Symbol Digit	-0.09	0.20	-0.05	0.49	-0.08	0.17	-0.13	0.03*
Figure Identification	-0.11	0.09	-0.01	0.93	-0.04	0.45	-0.11	0.07
Attention/Working Memory								
Digit Span Forward	-0.13	0.04*	-0.14	0.04*	-0.05	0.33	-0.20	0.72
Digit Span Backwards	-0.16	0.02*	-0.09	0.15	0.01	0.84	-0.02	0.69
Digit Span Total	-0.17	<0.01**	-0.14	0.04*	-0.02	0.68	-0.03	0.65
Memory								
Thurstone	-0.17	0.01**	-0.03	0.63	-0.16	<0.01**	-0.21	<0.01**
Visuospatial								
Block's	-0.16	0.02*	-0.07	0.27	-0.15	<0.01**	-0.18	<0.01**
Rotations	-0.17	0.01**	-0.09	0.21	-0.04	0.54	-0.12	0.04
Figure Logic	-0.11	0.10	-0.02	0.74	-0.04	0.48	-0.14	<0.01**

Notes: STPI = State Anxiety subscale of the State Trait Personality Inventory;
** denotes correlations significant at $p < 0.01$
* denotes correlations significant at $p < 0.05$

Table 13. Correlation matrix for STPI and Digit Span Total.

Male MZ	STPI Twin 1	Digit Span Twin 1	STPI Twin 2	Digit Span Twin 2
STPI Twin 1	1.00	-	-	-
Digit Span Twin 1	-0.36	1.00	-	-
STPI Twin 2	0.43	-0.14	1.00	-
Digit Span Twin 2	-0.06	0.58	-0.04	1.00

Male DZ	STPI Twin 1	Digit Span Twin 1	STPI Twin 2	Digit Span Twin 2
STPI Twin 1	1.00	-	-	-
Digit Span Twin 1	-0.05	1.00	-	-
STPI Twin 2	0.11	-0.04	1.00	-
Digit Span Twin 2	0.13	0.16	-0.19	1.00

Table 14. Bivariate Cholesky decomposition of STPI and digit span total for males.

	-2LL	df	Versus	p	AIC		A	D	E	rA	rE
1.ADE	3360.33	467	-	-	2426						
						STPI	0.04	0.37	0.59	-	-
						Digit Span	0.21	0.33	0.45		
2.AE	3361.72	470	1	0.71	2421					-0.05	-0.26
						STPI	0.35	-	0.65		
						Digit Span	0.52	-	0.48		
3.E	3389.02	473	1	<0.01*	2443						
4.Drop A12	3361.77	471		0.82	2419					-	-0.28
						STPI	0.35	-	0.65		
						Digit Span	0.52	-	0.48		
5.Drop E12	3365.49	471	2	0.05*	2423					-0.32	-
						STPI	0.36	-	0.64		
						Digit Span	0.52	-	0.48		
6.Drop A12 and E12	3369.95	472	2	0.02*	2425					-	-
						STPI	0.35	-	0.65		
						Digit Span	0.52	-	0.48		

Table 15. Correlation matrix of STPI and digit span forward for males.

Male MZ	STPI Twin 1	Forward Span Twin 1	STPI Twin 2	Forward Span Twin 2
STPI Twin 1	1.00	-	-	-
Forward Span Twin 1	-0.36	1.00	-	-
STPI Twin 2	0.43	-0.14	1.00	-
Forward Span Twin 2	-0.06	0.58	-0.04	1.00

Male DZ	STPI Twin 1	Forward Span Twin 1	STPI Twin 2	Forward Span Twin 2
STPI Twin 1	1.00	-	-	-
Forward Span Twin 1	-0.05	1.00	-	-
STPI Twin 2	0.11	-0.04	1.00	-
Forward Span Twin 2	0.13	0.16	-0.19	1.00

Table 16. Bivariate Cholesky decomposition of STPI and digit span forward for males.

	-2LL	Df	Versus	P value	AIC		A	D	E	rA	rE
1.ADE	3420.44	467	-	-	2486						
						STPI	0.01	0.42	0.58		
						Forward Span	0.03	0.34	0.63		
2.AE	3422.01	470	1	0.67	2482					0.13	-0.27
						STPI	0.36	-	0.64		
						Forward Span	0.34	-	0.66		
3.E	3438.80	473	1	0.01**	2492						
4.Drop A12	3422.27	471	2	0.61	2480					-	-0.23
						STPI	0.37	-	0.63		
						Forward Span	0.35	-	0.65		
5.Drop E12	3426.31	471	2	0.04*	2484					-0.26	-
						STPI	0.36	-	0.64		
						Forward Span	0.34	-	0.66		
6.Drop A12 and E12	3428.31	472	2	0.04*	2484					-	-
						STPI	0.35	-	0.65		
						Forward Span	0.33	-	0.66		

Table 17. Correlation matrix of STPI and backwards digit span for males.

Male MZ	STPI Twin 1	Backward Span Twin 1	STPI Twin 2	Backward Span Twin 2
STPI Twin 1	1.00	-	-	-
Backward Span Twin 1	-0.35	1.00	-	-
STPI Twin 2	0.43	-0.18	1.00	-
Backward Span Twin 2	-0.14	0.45	0.01	1.00

Male DZ	STPI Twin 1	Backward Span Twin 1	STPI Twin 2	Backward Span Twin 2
STPI Twin 1	1.00	-	-	-
Backward Span Twin 1	0.01	1.00	-	-
STPI Twin 2	0.11	-0.03	1.00	-
Backward Span Twin 2	0.09	0.23	-0.25	1.00

Table 18. Bivariate Cholesky decomposition of STPI and digit span backward for males.

	-2LL	Df	Versus	P value	AIC		A	D	E	rA	rE
1.ADE	3459.34	467	-	-	2486						
						STPI	0.05	0.36	0.53		
						Backward Span	0.30	0.17	0.53		
2.AE	3460.88	470	1	0.67	2482					-0.24	-0.11
						STPI	0.36	-	0.64		
						Backward Span	0.45	-	0.55		
3.E	3480.98	473	1	0.01**	2492					-	-
4.Drop A12	3461.99	471	2	0.29	2480					-	-0.13
						STPI	0.33	-	0.67		
						Backward Span	0.43	-	0.57		
5.Drop E12	3461.52	471	2	0.42	2484					-0.37	-
						STPI	0.36	-	0.64		
						Backward Span	0.46	-	0.54		
6.Drop A12 and E12	3466.68	472	2	0.04*	2484					-	-
						STPI	0.35	-	0.65		
						Backward Span	0.45	-	0.55		

Table 19. Correlation matrix of STPI and Thurstone for males.

Male MZ	STPI Twin 1	Thurstone Twin 1	STPI Twin 2	Thurstone Twin 2
STPI Twin 1	1.00	-	-	-
Thurstone Twin 1	-0.37	1.00	-	-
STPI Twin 2	0.50	-0.13	1.00	-
Thurstone Twin 2	-0.28	0.44	-0.07	1.00

Male DZ	STPI Twin 1	Thurstone Twin 1	STPI Twin 2	Thurstone Twin 2
STPI Twin 1	1.00	-	-	-
Thurstone Twin 1	-0.24	1.00	-	-
STPI Twin 2	0.09	-0.16	1.00	-
Thurstone Twin 2	-0.25	0.30	-0.18	1.00

Table 20. Bivariate Cholesky decomposition of STPI and Thurstone for males.

	-2LL	Df	Versus	P value	AIC		A	D	E	rA	rE
1.ADE	3433.04	457	-	-	2525					-	-
						STPI	0.05	0.36	0.59		
						Thurstone	0.30	0.17	0.53		
2.AE	3433.99	460	1	0.81	2513					-0.49	0.05*
						STPI	0.34	-	0.66		
						Thurstone	0.47	-	0.53		
3.E	3453.97	463	1	0.01**	2527						
4.Drop A12	3438.36	461	2	0.04	2516					-	-0.10
						STPI	0.32	-	0.68		
						Thurstone	0.45	-	0.55		
5.Drop E12	3434.12	461	2	0.71	2512					-0.43	-
						STPI	0.34	-	0.66		
						Thurstone	0.47	-	0.53		
6.Drop A12 and E12	3440.79	462	2	0.03*	2516					-	-
						STPI	0.35	-	0.65		
						Thurstone	0.49	-	0.51		

Table 21. Correlation matrix of STPI and Thurstone for females.

Female MZ	STPI Twin 1	Thurstone Twin 1	STPI Twin 2	Thurstone Twin 2
STPI Twin 1	1.00	-	-	-
Thurstone Twin 1	0.10	1.00	-	-
STPI Twin 2	0.44	-0.05	1.00	-
Thurstone Twin 2	0.08	0.47	-0.27	1.00

Female DZ	STPI Twin 1	Thurstone Twin 1	STPI Twin 2	Thurstone Twin 2
STPI Twin 1	1.00	-	-	-
Thurstone Twin 1	-0.08	1.00	-	-
STPI Twin 2	0.13	-0.07	1.00	-
Thurstone Twin 2	0.08	0.24	-0.11	1.00

Table 22. Bivariate Cholesky decomposition of STPI and Thurstone for females.

	-2LL	Df	Versus	P value	AIC		A	D	E	rA	rE
1.ADE	4761.86	617	-	-	3527					-	-
						STPI	0.29	0.36	0.61		
						Thurstone	0.45	0.17	0.49		
2.AE	4761.94	620	1	0.99	3521					-0.11	-0.18
						STPI	0.38	-	0.62		
						Thurstone	0.50	-	0.50		
3.E	4789.03	623	1	0.01**	3543						
4.Drop A12	4762.23	621	2	0.59	3520					-	-0.23
						STPI	0.37	-	0.63		
						Thurstone	0.49	-	0.51		
5.Drop E12	4763.74	621	2	0.18	3521					-0.30	-
						STPI	0.39	-	0.61		
						Thurstone	0.52	-	0.48		
6.Drop A12 and E12	4768.35	622	2	0.04*	3524					-	-
						STPI	0.38	-	0.62		
						Thurstone	0.51	-	0.49		

Table 23. Correlation matrix of STPI and Block Design for males.

Male MZ	STPI Twin 1	Blocks Twin 1	STPI Twin 2	Blocks Twin 2
STPI Twin 1	1.00	-	-	-
Blocks Twin 1	-0.09	1.00	-	-
STPI Twin 2	0.41	-0.03	1.00	-
Blocks Twin 2	-0.20	0.76	-0.22	1.00

Male DZ	STPI Twin 1	Blocks Twin 1	STPI Twin 2	Blocks Twin 2
STPI Twin 1	1.00	-	-	-
Blocks Twin 1	-0.20	1.00	-	-
STPI Twin 2	0.14	-0.17	1.00	-
Blocks Twin 2	-0.04	0.59	-0.17	1.00

Table 24. Bivariate Cholesky decomposition of STPI and Block Design for males.

	-2LL	Df	Versus	P value	AIC		A	D	E	rA	rE
1.ADE	3392.43	459	-	-	2474					-	-
						STPI	0.02	0.39	0.59		
						Blocks	0.79	0.002	0.21		
2.AE	3393.35	462	1	0.82	2469					-0.27	-0.17
						STPI	0.35	-	0.65		
						Blocks	0.79	-	0.21		
3.E	3456.21	465	1	0.01**	2526						
4.Drop A12	3396.38	463	2	0.08	2470					-	-0.20
						STPI	0.32	-	0.68		
						Blocks	0.77	-	0.23		
5.Drop E12	3393.54	463	2	0.66	2467					-0.30	-
						STPI	0.35	-	0.65		
						Blocks	0.79	-	0.21		
6.Drop A12 and E12	3398.97	464	2	0.06	2470					-	-
						STPI	0.35	-	0.65		
						Blocks	0.79	-	0.21		

Table 25. Correlation matrix of STPI and Blocks for females.

Male MZ	STPI Twin 1	Blocks Twin 1	STPI Twin 2	Blocks Twin 2
STPI Twin 1	1.00	-	-	-
Blocks Twin 1	0.01	1.00	-	-
STPI Twin 2	0.48	-0.04	1.00	-
Blocks Twin 2	0.04	0.72	-0.05	1.00

Male DZ	STPI Twin 1	Blocks Twin 1	STPI Twin 2	Blocks Twin 2
STPI Twin 1	1.00	-	-	-
Blocks Twin 1	-0.20	1.00	-	-
STPI Twin 2	0.14	-0.06	1.00	-
Blocks Twin 2	0.16	0.30	-0.21	1.00

Table 26. Bivariate Cholesky decomposition of STPI and Blocks for females.

	-2LL	Df	Versus	P value	AIC		A	D	E	rA	rE
1.ADE	4837.88	625	-	-	3587					-	-
						STPI	0.11	0.39	0.59		
						Blocks	0.48	0.002	0.30		
2.AE	4838.89	628	1	0.80	3582					-0.10	-0.14
						STPI	0.38	-	0.62		
						Blocks	0.69	-	0.32		
3.E	4890.74	631	1	0.01**	3628						
4.Drop A12	4839.22	629	2	0.57	3581					-	-0.12
						STPI	0.36	-	0.64		
						Blocks	0.67	-	0.33		
5.Drop E12	4841.12	629	2	0.14	3583					-0.25	-
						STPI	0.40	-	0.60		
						Blocks	0.71	-	0.29		
6.Drop A12 and E12	4845.89	630	2	0.03*	3585					-	-
						STPI	0.38	-	0.62		
						Blocks	0.70	-	0.30		

Table 27. Correlation matrix of STPI and Card Rotations for males.

Male MZ	STPI Twin 1	Rotations Twin 1	STPI Twin 2	Rotations Twin 2
STPI Twin 1	1.00	-	-	-
Rotations Twin 1	-0.30	1.00	-	-
STPI Twin 2	0.50	-0.24	1.00	-
Rotations Twin 2	-0.39	0.69	-0.26	1.00

Male DZ	STPI Twin 1	Rotations Twin 1	STPI Twin 2	Rotations Twin 2
STPI Twin 1	1.00	-	-	-
Rotations Twin 1	-0.12	1.00	-	-
STPI Twin 2	0.11	-0.22	1.00	-
Rotations Twin 2	-0.05	0.38	-0.14	1.00

Table 28. Bivariate Cholesky decomposition of STPI and Card Rotations for males.

	-2LL	Df	Versus	P value	AIC		A	D	E	rA	rE
1.ADE	3333.08	446	-	-	2441					-	-
						STPI	0.08	0.32	0.60		
						Rotations	0.72	0.001	0.28		
2.AE	3333.92	449	1	0.84	2435					-0.45	0.14
						STPI	0.35	-	0.65		
						Rotations	0.72	-	0.28		
3.E	3373.89	452	1	0.01**	2469						
4.Drop A12	3339.80	450	2	0.02*	2439					-	-0.13
						STPI	0.32	-	0.68		
						Rotations	0.71	-	0.29		
5.Drop E12	3334.60	450	2	0.68	2434					-0.30	-
						STPI	0.34	-	0.66		
						Rotations	0.72	-	0.28		
6.Drop A12 and E12	3340.72	451	2	0.03*	2439					-	-
						STPI	0.35	-	0.65		
						Rotations	0.72	-	0.28		

Table 29. Phenotypic correlations between STPI and cognitive outcomes with estimated proportion of phenotypic correlation accounted for by shared additive genetic and unique environmental factors.

	r_{pheno}	r_A	r_E	Proportion of r_{pheno} due to shared genetics	Proportion of r_{pheno} due to shared unique environment
Male Total Digit Span	-0.17	-0.05	-0.26	12.5%	87.5%
Male Forwards Digit	-0.13	0.13	-0.27	Not Computable	Not Computable
Male Backwards Digit	-0.16	-0.24	-0.11	60.4%	39.6%
Male Thurstone	-0.17	-0.49	0.05	Not Computable	Not Computable
Female Thurstone	-0.16	-0.11	-0.18	32.3%	67.7%
Male Blocks	-0.16	-0.27	-0.17	85.4%	14.6%
Female Blocks	-0.15	-0.10	-0.14	34.0%	66.0%
Male Rotations	-0.17	-0.45	0.14	Not Computable	Not Computable

r_{pheno} = phenotypic correlation between cognitive performance measure and STPI; r_A = genetic correlation; r_E = unique environmental correlation

Note for male forward digit span, male Thurstone, and male Rotations the proportion due to shared genetics and shared unique environment is not computable. This is due to genetic and environmental correlations that are in opposite directions. If we attempted to calculate the proportion it the proportion will be over 100%.

Table 30. Parameter estimates and fit statistics from the univariate dual change score models.

	Anxiety Crosswalk		Symbol Digit		Figure ID	
	Est	SE	Est	SE	Est	SE
Constant Change,	1	-	1	-	1	-
Proportional Change,	-	-	0.10	0.02**	0.12	0.03**
Mean Intercept,	49.75	0.69**	54.08	0.80**	54.06	0.97**
Mean Slope,	-0.32	0.10**	-6.55	0.87**	-7.36	1.61**
Intercept Deviation	38.47	7.07**	46.95	4.56**	64.86	6.30**
Slope Deviation	0.58	0.16**	0.70	0.19**	1.51	0.45**
Intercept-slope Covariance	-2.79	1.02**	-5.40	1.00**	-9.38	1.81**
Error Deviation	38.69	2.35**	20.20	1.29**	30.15	1.55**
Covariates:						
Gender on Intercept	-1.29	0.77	1.40	0.79	3.26	0.91**
Sex on Slope	0.39	0.12	-0.03	0.13	-0.41	0.18*
CESD on Intercept	0.44	0.06**	-0.16	0.05**	-0.07	0.07
CESD on Slope	-0.01	0.01	0.01	0.01	-0.004	0.02
Education on Intercept	-0.07	0.41	3.26	0.43**	2.23	0.54**
Education on Slope	-0.01	0.07	-0.29	0.11**	-0.20	0.16
	Misfit / parameters	Scaling factor	Misfit / parameters	Scaling factor	Misfit / parameters	Scaling factor
Full Modal	20798/13	1.79	17768/13	1.34	18752/13	1.42
Set β = 0	20799/12	1.71	17531/12	1.32	18784/12	1.39
-2LL test	0.22/1		26/1**		13/1**	

	Anxiety Crosswalk		Symbol Digit		Figure ID	
	Est	SE	Est	SE	Est	SE
Constant Change,	1	-	1	-	1	-
Proportional Change,	-	-	0.10	0.02**	0.12	0.03**
Mean Intercept,	49.75	0.69**	54.08	0.80**	54.06	0.97**
Mean Slope,	-0.32	0.10**	-6.55	0.87**	-7.36	1.61**
Intercept Deviation	38.47	7.07**	46.95	4.56**	64.86	6.30**
Slope Deviation	0.58	0.16**	0.70	0.19**	1.51	0.45**
Intercept-slope Covariance	-2.79	1.02**	-5.40	1.00**	-9.38	1.81**
Error Deviation	38.69	2.35**	20.20	1.29**	30.15	1.55**
Covariates:						
Gender on Intercept	-1.29	0.77	1.40	0.79	3.26	0.91**
Sex on Slope	0.39	0.12	-0.03	0.13	-0.41	0.18*
CESD on Intercept	0.44	0.06**	-0.16	0.05**	-0.07	0.07
CESD on Slope	-0.01	0.01	0.01	0.01	-0.004	0.02
Education on Intercept	-0.07	0.41	3.26	0.43**	2.23	0.54**
Education on Slope	-0.01	0.07	-0.29	0.11**	-0.20	0.16
	Misfit / parameters	Scaling factor	Misfit / parameters	Scaling factor	Misfit / parameters	Scaling factor
Full Modal	20798/13	1.79	17768/13	1.34	18752/13	1.42
Set β = 0	20799/12	1.71	17531/12	1.32	18784/12	1.39
-2LL test	0.22/1		26/1**		13/1**	

Parameter	Block Design		Card Rotations		Figure Logic	
	Est	SE	Est	SE	Est	SE
Constant Change,	1	-	1	-	1	-
Proportional Change,	0.20	0.03**	0.14	0.04**	0.28	0.08**
Mean Intercept,	52.64	0.80**	57.20	0.95**	53.02	0.88**
Mean Slope,	-11.07	1.22**	-8.58	1.82**	-15.13	3.79**
Intercept Deviation	62.68	4.61**	70.31	6.19**	45.61	5.08**
Slope Deviation	2.85	0.66**	1.54	0.76*	3.89	1.95*
Intercept-slope Covariance	13.30	1.78**	-10.37	2.78**	-13.28	3.68**
Error Deviation	17.78	1.11**	33.17	1.48**	48.29	2.20**
Covariates:						
Sex on Intercept	-0.06	0.86	-5.90	1.00**	-2.30	0.81**
Sex on Slope	0.05	0.20	0.99	0.27**	0.68	0.27*
CESD on Intercept	-0.25	0.05**	-0.11	0.06	-0.18	0.04**
CESD on Slope	0.06	0.01**	0.01	0.01	0.05	0.02**
Education on Intercept	3.22	0.41**	1.91	0.54**	3.36	0.44**
Education on Slope	-0.65	0.13**	-0.23	0.14	-0.94	0.32**
	Misfit / parameters	Scaling factor	Misfit / parameters	Scaling factor	Misfit / parameters	Scaling factor
Full Modal	17818/13	1.32	17387/13	1.34	19475/13	1.25
Set β = 0	17901/12	1.34	17420/12	1.24	19510/12	1.22
-2LL test	78/1**		19/1**		23/1**	

Note: Est = parameter estimate, SE = standard error, misfit = 2 x the negative logliklihood, CESD = first Center for Epidemiological Studies Depression Score; Set β = 0 are results of submodel where proportional change is constrained to zero.

Table 31. Parameter estimates and goodness-of-fit statistics from the full bivariate dual change score model of Anxiety Crosswalk and Symbol Digit score.

Model	Misfit	Scaling factor	Compare	Δ-2LL/ Parameters
1.Sex unequal	40148/37	1.78	-	-
2.Sex equal	40148/34	1.55	Model 1	1.23/3
3.Full single group	38257/31	1.46	-	-
4.Set Anx →Cog =0	38257/30	1.40	Model 3	0.13/1
5.Set Cog →Anx =0	38275/30	1.48	Model 3	27.4/1**
6.No Coupling	38275/29	1.40	Model 3	8.45/2*

	Anxiety		Symbol Digit	
Parameter	Est	SE	Est	SE
Constant Change	1	-	1	-
Proportional Change	-	-	0.10	0.02**
Coupling Anx → Cog	-	-	0.04	0.12
Coupling Cog → Anx	-0.08	0.02**	-	-
Mean Intercept	51.11	0.82**	54.08	0.81**
Mean Slope	3.18	0.94**	-6.56	0.88**
Intercept deviation	38.55	6.97**	47.47	4.58**
Slope deviation	0.83	0.24**	0.73	0.19**
Error deviation	38.36	2.35**	20.11	1.27**
Covariates				
Sex on Intercept	-1.23	0.76	1.57	0.93
CESD on Intercept	0.45	0.07**	-0.016	0.05**
Edu on Intercept	-0.20	0.46	3.29	3.29**
Sex on Slope	0.50	0.13**	-0.05	0.15
CESD on Slope	-0.02	0.01	-0.01	0.05
Edu on Slope	0.27	0.11*	-0.28	0.11*

Notes: Est = parameter estimate; CESD = initial Center for Epidemiological Studies Depression Scale score; Edu = education level. Sex unequal model is multigroup model where change parameters were estimated separately for males and females; Sex equal model is multigroup model where change parameters for males and females were constrained to equality; Coup Anx → Cog = coupling parameter $\gamma_{ANX*SYMBOL\ DIGIT}$; Coup Cog → Anx = coupling parameter $\gamma_{SYMBOL\ DIGIT*ANX}$

** denotes $p < 0.01$

* denotes $p < 0.05$

Table 32. Parameter estimates and goodness-of-fit from the full bivariate dual change score model of Anxiety Crosswalk and Figure Identification performance.

Model	Misfit	Scaling factor	Compare	Δ-2LL/ Δparameter
1.Sex unequal	41329/37	1.59	-	-
2.Sex equal	41330/34	1.52	Model 1	0.52/3
3.Full single group	39517/31	1.46	-	-
4.Set Anx →Cog =0	39521/30	1.44	Model 3	1.73/1
5.Set Cog →Anx =0	39533/30	1.48	Model 3	18.49/1**
6.No Coupling	39536/29	1.44	Model 3	10.05/2**

	Anxiety		Figure ID	
Parameter	Est	SE	Est	SE
Constant Change	1	-	1	-
Proportional Change	-	-	0.11	0.04**
Coupling Anx → Cog	-	-	0.16	0.13
Coupling Cog → Anx	-0.08	0.03**	-	-
Mean Intercept	50.63	0.86**	53.35	1.02**
Mean Slope	3.35	1.18**	-14.90	5.99**
Intercept deviation	35.38	7.13**	69.57	7.10**
Slope deviation	0.81	0.33*	2.28	1.23
Error deviation	38.56	2.41**	29.71	1.49**
Covariates				
Sex on Intercept	-0.95	0.77	3.83	1.03**
CESD on Intercept	0.45	0.06**	-0.08	0.08
Edu on Intercept	-0.11	0.44	2.25	0.56**
Sex on Slope	0.56	0.15**	-0.50	0.22
CESD on Slope	-0.01	0.01	-0.07	0.06
Edu on Slope	0.18	0.11	-0.17	0.17

Notes: Est = parameter estimate; CESD = initial Center for Epidemiological Studies Depression Scale score; Edu = education level. Sex unequal model is multigroup model where change parameters were estimated separately for males and females; Sex equal model is multigroup model where change parameters for males and females were constrained to equality; Coup Anx → Cog = coupling parameter $\gamma_{ANX \cdot FIGURE\ ID}$; Coup Cog → Anx = coupling parameter $\gamma_{FIGURE\ ID \cdot ANX}$

** denotes $p < 0.01$

* denotes $p < 0.05$

Table 33. Parameter estimates and goodness-of-fit from the full bivariate dual change score model of Anxiety Crosswalk and Thurstone performance.

Model	Misfit	Scaling factor	Compare	Δ-2LL/ Δparameter
1.Sex unequal	41218/37	0.97	-	
2.Sex equal	41224/34	1.37	Model 1	1.44/3
3.Full single group	39335/31	1.35	-	-
4.Set Anx →Cog =0	39336/30	1.35	Model 3	0.39/1
5.Set Cog →Anx =0	39349/30	1.34	Model 3	7.55/1**
6.No Coupling	39349/29	1.35	Model 3	9.67/2**

	Anxiety		Thurstone	
Parameter	Est	SE	Est	SE
Constant Change	1	-	1	-
Proportional Change	-	-	0.45	0.07**
Coupling Anx → Cog	-	-	0.08	0.58
Coupling Cog → Anx	-0.19	0.06**	-	-
Mean Intercept	50.40	0.80**	48.60	0.76**
Mean Slope	8.62	2.94**	-25.85	7.01**
Intercept deviation	36.54	6.55**	56.21	5.10**
Slope deviation	2.46	1.33	11.21	3.30**
Error deviation	38.53	2.35**	32.03	1.64**
Covariates				
Sex on Intercept	-1.05	0.81	3.86	0.80**
CESD on Intercept	0.44	0.06**	-0.24	-0.24**
Edu on Intercept	-0.22	0.41	2.52	2.52**
Sex on Slope	1.04	0.29**	-1.69	0.43**
CESD on Slope	-0.05	0.02*	0.07	0.07
Edu on Slope	0.49	0.19**	-1.11	0.26**

Notes: Est = parameter estimate; CESD = initial Center for Epidemiological Studies Depression Scale score; Edu = education level. Sex unequal model is multigroup model where change parameters were estimated separately for males and females; Sex equal model is multigroup model where change parameters for males and females were constrained to equality; Coup Anx → Cog = coupling parameter $\gamma_{ANX*THURSTONE}$; Coup Cog → Anx = coupling parameter $\gamma_{THURSTONE*ANX}$

** denotes $p < 0.01$

* denotes $p < 0.05$

Table 34. Parameter estimates and goodness-of-fit from the bivariate dual change score model of Anxiety Crosswalk and Digit Span Total performance.

Model	Misfit	Scaling factor	Compare	Δ-2LL/ Δparameter
1.Sex unequal	42455/37	1.35	-	-
2.Sex equal	42458/34	1.36	Model 1	2.28/3
3.Full single group	40496/30	1.35	-	-
4.Set Anx →Cog =0	40496/29	1.35	Model 3	0.03/1
5.Set Cog →Anx =0	40516/29	1.34	Model 3	12.19/1**
6.No Coupling	40514/28	1.35	Model 3	14.30/2**

	Anxiety		Digit Span Total	
Parameter	Est.	SE	Est.	SE
Constant Change	1	-	1	-
Proportional Change	-	-	-	-
Coupling Anx → Cog	-	-	-0.01	0.07
Coupling Cog → Anx	-0.20	0.05**	-	-
Mean Intercept	51.21	0.85**	52.16	0.97**
Mean Slope	9.51	2.57**	-0.08	3.47
Intercept deviation	36.73	7.31**	66.44	7.25**
Slope deviation	2.41	1.11*	0.01	0.11
Error deviation	38.41	2.37**	39.94	1.76**
Covariates				
Sex on Intercept	-1.34	0.82	-0.21	1.08
CESD on Intercept	0.46	0.07*	-0.11	0.06
Edu on Intercept	-0.22	0.43	2.51	0.56**
Sex on Slope	0.43	0.18	0.15	0.13
CESD on Slope	-0.03	0.02*	0.01	0.03
Edu on Slope	0.52	0.16**	-0.01	0.07

Notes: Est = parameter estimate; CESD = initial Center for Epidemiological Studies Depression Scale score; Edu = education level. Sex unequal model is multigroup model where change parameters were estimated separately for males and females; Sex equal model is multigroup model where change parameters for males and females were constrained to equality; Coup Anx → Cog = coupling parameter $\gamma_{\text{ANX*DIGIT SPAN TOTAL}}$; Coup Cog → Anx = coupling parameter $\gamma_{\text{DIGIT SPAN TOTAL*ANX}}$
** denotes $p < 0.01$* denotes $p < 0.05$

Table 35. Parameter estimates and goodness-of-fit from the bivariate dual change score model of Anxiety Crosswalk and Digit Span Forwards performance.

Model	Misfit	Scaling factor	Compare	Δ-2LL/ Δparameter
1.Sex unequal	42661/35	1.35	-	-
2.Sex equal	42662/33	1.34	Model 1	1.05/2
3.Full single group	40886/30	1.31	-	-
4.Set Anx →Cog =0	40888/29	1.32	Model 3	1.04/1
5.Set Cog →Anx =0	40906/29	1.28	Model 3	9.10/1**
6.No Coupling	40906/28	1.30	Model 3	13.52/2**

	Anxiety		Forward Span	
Parameter	Est.	SE	Est.	SE
Constant Change	1	-	1	-
Proportional Change	-	-	-	-
Coupling Anx → Cog	-	-	-0.08	0.08
Coupling Cog → Anx	-0.26	0.08**	-	-
Mean Intercept	51.13	0.92**	51.38	0.95**
Mean Slope	12.65	3.67**	-3.30	4.11**
Intercept deviation	36.50	7.67**	62.66	6.82**
Slope deviation	4.16	2.12*	0.07	0.32
Error deviation	38.34	2.38**	49.38	1.96**
Covariates				
Sex on Intercept	-1.41	0.87	0.53	1.09
CESD on Intercept	0.45	0.07**	-0.12	0.06*
Edu on Intercept	-0.23	0.45	2.14	0.55**
Sex on Slope	0.66	0.23	0.12	0.13
CESD on Slope	-0.04	0.02	0.04	0.04
Edu on Slope	0.60	0.20	-0.01	0.07

Notes: Est = parameter estimate; CESD = initial Center for Epidemiological Studies Depression Scale score; Edu = education level. Sex unequal model is multigroup model where change parameters were estimated separately for males and females; Sex equal model is multigroup model where change parameters for males and females were constrained to equality; Coup Anx → Cog = coupling parameter $\gamma_{\text{ANX*FORWARD SPAN}}$; Coup Cog → Anx = coupling parameter $\gamma_{\text{FORWARD SPAN*ANX}}$ ** denotes p <0.01 * denotes $p < 0.05$

Table 36. Parameter estimates and goodness-of-fit from the bivariate dual change score model of Anxiety Crosswalk and Digit Span Backwards performance.

Model	Misfit	Scaling factor	Compare	Δ-2LL/ Δparameter
1.Sex unequal	42622/35	1.48	-	-
2.Sex equal	42623/33	1.47	Model 1	0.72/2
3.Full single group	40842/30	1.41	-	-
4.Set Anx →Cog =0	40842/29	1.41	Model 3	0.08/1
5.Set Cog →Anx =0	40859/29	1.40	Model 3	10.80/1**
6.No Coupling	40860/28	1.42	Model 3	14.35/2**

	Anxiety		Backwards Span	
Parameter	Est.	SE	Est.	SE
Constant Change	1	-	1	-
Proportional Change	-	-	-	-
Coupling Anx → Cog	-	-	0.02	0.08
Coupling Cog → Anx	-0.21	0.06**	-	-
Mean Intercept	51.28	0.87**	52.58	0.99**
Mean Slope	9.83	2.95**	-1.79	3.99
Intercept deviation	38.65	7.69**	42.84	7.80**
Slope deviation	1.68	0.86*	0.02	0.25
Error deviation	38.24	2.36**	52.66	2.80**
Covariates				
Sex on Intercept	-1.46	0.84	-1.05	1.05
CESD on Intercept	0.47	0.07**	-0.06	0.06
Edu on Intercept	-0.18	0.44	2.08	0.54**
Sex on Slope	0.29	0.17	0.18	0.14
CESD on Slope	-0.03	0.02	-0.02	0.04
Edu on Slope	0.43	0.15**	-0.01	0.08

Notes: Est = parameter estimate; CESD = initial Center for Epidemiological Studies Depression Scale score; Edu = education level. Sex unequal model is multigroup model where change parameters were estimated separately for males and females; Sex equal model is multigroup model where change parameters for males and females were constrained to equality; Coup Anx → Cog = coupling parameter $\gamma_{ANX*BACKWARD\ SPAN}$; Coup Cog → Anx = coupling parameter $\gamma_{BACKWARD\ SPAN*ANX}$

Table 37. Parameter estimates and goodness-of-fit from the bivariate dual change score model of Anxiety Crosswalk and Block Design performance.

Model	Misfit	Scaling factor	Compare	Δ-2LL/ Δparameter
1.Sex unequal	40496/37	1.42	-	-
2.Sex equal	40498/34	1.39	Model 1	1.42/2
3.Full single group	38625/31	1.36	-	-
4.Set Anx →Cog =0	38625/30	1.37	Model 3	0.38/1
5.Set Cog →Anx =0	38643/30	1.37	Model 3	17.04/1**
6.No Coupling	38643/29	1.38	Model 3	16.82/2**

	Anxiety		Block Design	
Parameter	Est.	SE	Est.	SE
Constant Change	1	-	1	-
Proportional Change	-	-	0.20	0.02**
Coupling Anx → Cog	-	-	0.04	0.06
Coupling Cog → Anx	-0.12	0.03**	-	-
Mean Intercept	50.87	0.82**	52.53	0.81**
Mean Slope	5.80	1.59**	-12.53	2.80**
Intercept deviation	37.35	7.07**	63.21	4.64**
Slope deviation	1.43	0.54*	2.72	0.63**
Error deviation	38.47	2.35**	17.75	1.11**
Covariates				
Sex on Intercept	-1.22	0.79	0.04	0.88
CESD on Intercept	0.44	0.06**	-0.25	0.05**
Edu on Intercept	-0.18	0.42	3.22	0.41**
Sex on Slope	0.37	0.15*	0.04	0.20
CESD on Slope	-0.03	0.02*	0.04	0.03
Edu on Slope	0.41	0.14**	-0.63	0.12**

Notes: Est = parameter estimate; CESD = initial Center for Epidemiological Studies Depression Scale score; Edu = education level. Sex unequal model is multigroup model where change parameters were estimated separately for males and females; Sex equal model is multigroup model where change parameters for males and females were constrained to equality; Coup Anx → Cog = coupling parameter $\gamma_{ANXIETY*BLOCKS}$; Coup Cog → Anx = coupling parameter $\gamma_{BLOCKS*ANXIETY}$
** denotes $p < 0.01$ * denotes $p < 0.05$

Table 38. Parameter estimates and goodness-of-fit from the bivariate dual change score model of Anxiety Crosswalk and Card Rotations performance.

Model	Misfit	Scaling factor	Compare	Δ-2LL/ Δparameter
1.Sex unequal	39742/37	1.50	-	-
2.Sex equal	39742/34	1.42	Model 1	0.16/2
3.Full single group	38055/31	1.40	-	-
4.Set Anx →Cog =0	38055/30	1.36	Model 3	0.07/1
5.Set Cog →Anx =0	38072/30	1.40	Model 3	15.68/1**
6.No Coupling	38072/29	1.35	Model 3	8.69/2**

	Anxiety		Rotations	
Parameter	Est	SE	Est	SE
Constant Change	1	-	1	-
Proportional Change	-	-	0.14	0.03**
Coupling Anx → Cog	-	-	-0.04	0.16
Coupling Cog → Anx	-0.11	0.03**	-	-
Mean Intercept	51.13	0.88**	57.38	1.18**
Mean Slope	5.35	1.56**	-6.74	7.05
Intercept deviation	39.05	8.13**	69.13	6.89**
Slope deviation	1.43	0.57*	1.67	1.05
Error deviation	38.21	2.37**	33.24	1.49**
Covariates				
Sex on Intercept	-1.42	0.82	-6.08	1.20**
CESD on Intercept	0.46	0.07**	-0.11	0.06
Edu on Intercept	-0.28	0.45	1.92	0.54**
Sex on Slope	-0.18	0.22	1.04	0.35**
CESD on Slope	-0.02	0.01	0.03	0.07
Edu on Slope	0.25	0.11*	-0.25	0.15

Table 39. Parameter estimates and goodness-of-fit from the bivariate dual change score model of Anxiety Crosswalk and Figure Logic performance.

Model	Misfit	Scaling factor	Compare	Δ-2LL/ Δparameter
1.Sex unequal	42293/37	1.55	-	-
2.Sex equal	42298/34	1.38	Model 1	1.06/3
3.Full single group	40301/31	1.36	-	-
4.Set Anx →Cog =0	40302/30	1.35	Model 3	0.17/1
5.Set Cog →Anx =0	40315/30	1.35	Model 3	8.18/1**
6.No Coupling	40315/29	1.35	Model 3	9.84/2**

	Anxiety		Figure Logic	
Parameter	Est	SE	Est	SE
Constant Change	1	-	1	-
Proportional Change	-	-	0.28	0.08**
Coupling Anx → Cog	-	-	-0.05	0.13
Coupling Cog → Anx	-0.14	0.05**	-	-
Mean Intercept	50.79	0.90**	53.28	0.91**
Mean Slope	6.98	2.45**	-13.10	5.42**
Intercept deviation	40.17	7.80**	45.95	5.14**
Slope deviation	1.36	0.67*	4.20	2.58
Error deviation	38.54	2.38**	47.92	2.12**
Covariates				
Sex on Intercept	-1.34	0.88	-2.54	0.88**
CESD on Intercept	0.45	0.07**	-0.17	0.05**
Edu on Intercept	-0.21	0.42	3.33	0.44**
Sex on Slope	0.07	0.19	0.76	0.32*
CESD on Slope	-0.03	0.02*	0.07	0.06
Edu on Slope	0.50	0.20*	-0.97	0.36**

Table 40. Parameter estimates and goodness-of-fit from the bivariate biometric dual change score model of Anxiety Crosswalk and Symbol Digit performance.

Model	-2LL	Df	Compare	Δ-2LL/Δdf
1. Full ADE	38679	5724	-	-
2. Drop coupling Anxiety → Symbol Digit	38686	5725	Model 1	7/1**
3. Drop coupling Symbol Digit → Anxiety	38690	5725	Model 1	12/1**
4. Drop all D on anxiety	38679	5727	Model 1	1/3
5. Drop all D on symbol digit	38680	5727	Model 1	2/1
6. Drop D on both	38681	5730	Model 1	3/3
7.Drop Anxiety a_s → Anxiety Slope	38682	5731	Model 6	1/1
8.Drop Symbol Digit a_s -> Slope	38683	5731	Model 6	2/1
9.Drop anxiety a_0 → Slope	38681	5731	Model 6	1/1
10. Drop Symbol Digit a_0 → Slope	38715	5731	Model 6	33/1**

Parameters	Anxiety	Symbol Digit
Fixed effects		
Mean intercept	48.90	56.78
Mean slope	0.96	-6.21
Constant change	1	1
Proportional change	-	0.10
Coupling, Anxiety →Symbol Digit	-	-0.01
Coupling, Symbol Digit → Anxiety	-0.02	-
Random effects		
Intercept		
A	3.74	7.06
D	2.62	2.01
E	5.57	2.32
Slope		
A	< 0.01	<-0.01
D	<-0.01	< -0.01
E	0.42	0.20
Slope on level		
A	0.11	-0.87
D	-0.54	<-0.01
E	-0.41	-0.29
Error	6.23	4.49

Notes: -2LL = 2 * the negative log likelihood of the model, df = degrees of freedom from the model; Compare indicated the comparison model; Est = parameter estimates; a_s = additive genetic variance of slope; a_0 = additive genetic variance of intercept
** denotes $p < 0.01$ * denotes $p < 0.05$

Table 41. Parameter estimates and goodness-of-fit from the bivariate biometric dual change score model of Anxiety Crosswalk and Figure Identification performance.

Model	-2LL	Df	Compare	Δ-2LL/Δdf
1. Full ADE	38130.0	5561	-	-
2. Drop coupling Anxiety → Figure ID	38133.5	5562	Model 1	3.5/1
3. Drop coupling Figure ID → Anxiety	38142.8	5562	Model 1	12.8/1**
4. Drop all D on Anxiety	38131	5564	Model 1	1/3
5. Drop all D on Figure ID	38132	5564	Model 1	2/3
6. Drop D on both	38133	5567	Model 1	3/6
7.Drop Anxiety a_s on Slope	38135	5568	Model 6	2/1
8.Drop Figure ID a_s on Slope	38139	5568	Model 6	6/1**
9.Drop Anxiety a_0 on Slope	38134	5568	Model 6	1/1
10. Drop Figure ID a_0 on Slope	38162	5568	Model 6	29/1**

Parameters	Anxiety	Figure Identification
Fixed effects		
Mean intercept	48.21	56.83
Mean slope	0.54	-7.60
Constant change	1	1
Proportional change	-	0.14
Coupling, Anxiety →Figure ID	-	-0.01
Coupling, Figure ID → Anxiety	-0.02	-
Random effects		
Intercept		
A	4.09	7.21
D	2.68	2.27
E	5.62	3.92
Slope		
A	<0.01	<0.01
D	<0.01	-0.20
E	-0.43	-0.17
Slope on level		
A	0.05	-1.15
D	-0.58	-0.11
E	-0.38	-0.67
Error	5.56	5.49

Notes: -2LL = 2 * the negative log likelihood of the model, df = degrees of freedom from the model; Compare indicated the comparison model; a_s = additive genetic variance of slope; a_0 = additive genetic variance of intercept
** denotes $p < 0.01$ * denotes $p < 0.05$

Table 42. Parameter estimates and goodness-of-fit from the bivariate biometric dual change score model of Anxiety Crosswalk and Thurstone picture memory.

Model	-2LL	Df	Compare	Δ-2LL/Δdf
1. Full ADE	39964.8	5721	-	-
2. Drop coupling Anxiety → Thurstone	39965.1	5722	Model 1	0.3/1
3. Drop coupling Thurstone → Anxiety	39971.6	5722	Model 1	6.8/1**
4. Drop all D on Anxiety	39964.9	5724	Model 1	0.1/1
5. Drop all D on Thurstone	39965.5	5724	Model 1	0.7/1
6. Drop D on both	39965.5	5727	Model 1	0.7/3
7.Drop Anxiety a_s on Slope	39965.6	5728	Model 6	0.1/1
8.Drop Thurstone a_s on Slope	39965.7	5728	Model 6	0.2/1
9.Drop Anxiety a_0 on Slope	39966.0	5728	Model 6	0.5/1
10. Drop Thurstone a_0 on Slope	40145.5	5728	Model 6	180/1**
Parameters	**Anxiety**	**Thurstone**		
Fixed effects				
Mean intercept	49.68	52.10		
Mean slope	0.74	-24.18		
Constant change	1	1		
Proportional change	-	0.46		
Coupling, Anxiety →Thurstone	-	<0.001		
Coupling, Thurstone → Anxiety	-0.02	-		
Random effects				
Intercept				
A	4.30	6.86		
D	1.33	4.16		
E	6.13	2.39		
Slope				
A	<-0.01	<0.01		
D	<-0.01	<0.01		
E	0.50	0.04		
Slope on level				
A	0.12	-3.18		
D	-0.27	-1.97		
E	-0.62	-1.08		
Error	6.14	5.68		

Notes: -2LL = 2 * the negative log likelihood of the model, df = degrees of freedom from the model; Compare indicated the comparison model; a_s = additive genetic variance of slope; a_0 = additive genetic variance of intercept

** denotes $p < 0.01$ * denotes $p < 0.05$

Table 43. Parameter estimates and goodness-of-fit estimates from the bivariate biometric dual change score models of Anxiety Crosswalk and Total Digit Span.

Model	-2LL	Df	Compare	Δ-2LL/Δdf
1. Full ADE	40858.7	5841	-	-
2. Drop coupling Anxiety → Total Dspan	40858.8	5842	Model 1	0.1/1
3. Drop coupling Total Dspan → Anxiety	40870.9	5842	Model 1	12.2/1**
4. Drop all D on Anxiety	40859.7	5845	Model 1	0.1/3
5. Drop all D on Total Dspan	40859.8	5845	Model 1	1.1/3
6. Drop D on both	40860.9	5848	Model 1	2.2/6
7.Drop Anxiety a_s on Slope	40862.1	5849	Model 6	1.2/1
8.Drop Total Dspan a_s on Slope	40861.1	5849	Model 6	0.2/1
9.Drop Anxiety a_o on Slope	40860.9	5849	Model 6	0.1/1
10. Drop Total Dspan a_o on Slope	40864.5	5849	Model 6	3.6/1

Parameters	Anxiety	Digit Span Total
Fixed effects		
Mean intercept	48.62	53.02
Mean slope	1.04	-4.48
Constant change	1	1
Proportional change		0.07
Coupling, anxiety →Total Dspan	-	0.002
Coupling, Total Dspan → anxiety	-0.02	-
Random effects		
Intercept		
A	3.83	6.53
D	2.64	3.62
E	5.50	4.19
Slope		
A	< -0.01	< -0.01
D	<-0.01	< -0.01
E	0.40	0.06
Slope on level		
A	0.09	-0.62
D	-0.56	-0.21
E	-0.38	-0.40
Error	6.23	6.28

Notes: -2LL = 2 * the negative log likelihood of the model, df = degrees of freedom from the model; Compare indicated the comparison model; a_s = additive genetic variance of slope; a_o = additive genetic variance of intercept

** denotes $p < 0.01$ * denotes $p < 0.05$

Table 44. Parameter and goodness-of-fit estimates from the bivariate biometric dual change score model of Anxiety Crosswalk and Digit Span Forward performance.

Model	-2LL	Df	Compare	Δ-2LL/Δdf
1. Full ADE	41502.4	5849	-	-
2. Drop coupling Anxiety → Forward Span	41502.8	5850	Model 1	0.4/1
3. Drop coupling Forward Span → Anxiety	41504.9	5850	Model 1	2.5/1
4. Drop all D on Anxiety	41502.8	5852	Model 1	0.4/3
5. Drop all D on Forward Span	41503.0	5852	Model 1	0.6/3
6. Drop D on both	41503.1	5855	Model 1	0.7/6
7.Drop Anxiety a_s on Slope	41503.2	5856	Model 6	0.1/1
8.Drop Forward Span a_s on Slope	41503.1	5856	Model 6	0.1/1
9.Drop Anxiety a_0 on Slope	41503.1	5856	Model 6	0.1/1
10. Drop Forward Span a_0 on Slope	41504.6	5856	Model 6	1.5/1

Parameters	Anxiety	Digit Span Forwards
Fixed effects		
Mean intercept	49.42	52.98
Mean slope	0.51	-3.08
Constant change	1	1
Proportional change	-	0.05
Coupling, Anxiety →Forward Span		0.005
Coupling, Forward Span → Anxiety	-0.01	-
Random effects		
Intercept		
A	4.83	7.26
D	2.10	<0.01
E	5.81	4.37
Slope		
A	<0.01	<0.01
D	<0.01	<0.01
E	-0.41	<0.01
Slope on level		
A	0.04	-0.50
D	-0.42	<-0.01
E	-0.43	-0.27
Error	6.42	6.86

Notes: -2LL = 2 * the negative log likelihood of the model, df = degrees of freedom from the model; Compare indicated the comparison model; a_s = additive genetic variance of slope; a_0 = additive genetic variance of intercept

** denotes $p < 0.01$ * denotes $p < 0.05$

Table 45. Parameter and goodness-of-fit estimations from the bivariate dual change score model of Anxiety crosswalk and Digit Span Backwards performance.

Model	-2LL	Df	Compare	Δ-2LL/Δdf
1. Full ADE	41464.9	5841	-	-
2. Drop coupling Anxiety → Backward Span	41465.9	5842	Model 1	1/1
3. Drop coupling Backward Span → Anxiety	41472.4	5842	Model 1	7.5/1**
4. Drop all D on Anxiety	41465.3	5844	Model 1	0.4/3
5. Drop all D on Backward Span	41465.6	5844	Model 1	0.7/3
6. Drop D on both	41466.0	5847	Model 1	1.1/6
7.Drop Anxiety a_s on Slope	41466.0	5848	Model 6	0.1/1
8.Drop Backward Span a_s on Slope	41466.0	5848	Model 6	0.1/1
9.Drop Anxiety a_0 on Slope	41466.1	5848	Model 6	0.1/1
10. Drop Backward Span a_0 on Slope	41467.5	5848	Model 6	0.9/1

Parameters	Anxiety	Digit Span Backwards
Fixed effects		
Mean intercept	49.26	53.17
Mean slope	1.33	-3.93
Constant change	1	1
Proportional change	-	0.06
Coupling, Anxiety →Backward Span	-	<0.01
Coupling, Backward Span → Anxiety	-0.03	-
Random effects		
Intercept		
A	4.46	6.36
D	1.78	-1.37
E	6.04	2.29
Slope		
A	<0.01	<-0.01
D	<0.01	<-0.01
E	-0.46	<-0.01
Slope on level		
A	0.06	-0.57
D	-0.39	-0.12
E	-0.55	-0.09
Error	6.37	7.33

Notes: -2LL = 2 * the negative log likelihood of the model, df = degrees of freedom from the model; Compare indicated the comparison model; a_s = additive genetic variance of slope; a_0 = additive genetic variance of intercept

** denotes $p < 0.01$ * denotes $p < 0.05$

Table 46. Parameter and goodness-of-fit estimates from the bivariate biometric dual change score model of Anxiety Crosswalk and Block Design performance.

Model	-2LL	Df	Compare	Δ-2LL/Δdf
1. Full ADE	39403.0	5794	-	-
2. Drop coupling Anxiety → Blocks	39403.1	5795	Model 1	0.1/1
3. Drop coupling Blocks → Anxiety	39416.2	5795	Model 1	13.2/1**
4. Drop all D on Anxiety	39403.6	5797	Model 1	0.6/3
5. Drop all D on Blocks	39403.0	5797	Model 1	0.1/3
6. Drop D on both	39403.6	5800	Model 1	0.9/6
7.Drop Anxiety a_s on Slope	39403.7	5801	Model 6	0.1/1
8.Drop Blocks a_s on Slope	39404.6	5801	Model 6	0.9/1
9.Drop Anxiety a_0 on Slope	39403.6	5801	Model 6	0.1/1
10. Drop Blocks a_0 on Slope	39452.3	5801	Model 6	48.7/1**
Parameters	**Anxiety**	**Block Design**		
Fixed effects				
Mean intercept	49.47	54.67		
Mean slope	0.95	-10.40		
Constant change	1	1		
Proportional change	-	0.18		
Coupling, Anxiety →Blocks	-	-<0.001		
Coupling, Blocks → Anxiety	-0.02	-		
Random effects				
Intercept				
A	4.49	8.24		
D	1.84	<0.01		
E	5.95	2.24		
Slope				
A	<-0.01	-0.13		
D	<-0.01	<-0.01		
E	-0.47	<0.01		
Slope on level				
A	0.06	-1.60		
D	-0.40	<-0.01		
E	-0.47	-0.36		
Error	5.98	4.28		

Notes: -2LL = 2 * the negative log likelihood of the model, df = degrees of freedom from the model; Compare indicated the comparison model; a_s = additive genetic variance of slope; a_0 = additive genetic variance of intercept

** denotes $p < 0.01$ * denotes $p < 0.05$

Table 47. Parameter and goodness-of-fit estimates from the bivariate dual change score model of Anxiety Crosswalk and Card Rotations performance.

Model	-2LL	Df	Compare	Δ-2LL/Δdf
1. Full ADE	38860.0	5542	-	-
2. Drop coupling Anxiety → Rotations	38860.7	5543	Model 1	0.7/1
3. Drop coupling Rotations → Anxiety	38864.2	5543	Model 1	4.2/1*
4. Drop all D on Anxiety	38860.5	5545	Model 1	0.5/3
5. Drop all D on Rotations	38860.6	5545	Model 1	0.6/3
6. Drop D on both	38860.7	5548	Model 1	0.7/6
7.Drop Anxiety a_s on Slope	38860.8	5549	Model 6	0.8/1
8.Drop Rotations a_s on Slope	38861.6	5549	Model 6	0.9/1
9.Drop Anxiety a_0 on Slope	38860.7	5549	Model 6	0.1/1
10. Drop Rotations a_0 on Slope	38882.2	5549	Model 6	21.4/1**

Full Model Parameters	Anxiety	Rotations
Fixed effects		
Mean intercept	48.72	54.87
Mean slope	0.72	-8.16
Constant change	1	1
Proportional change	-	0.15
Coupling, Anxiety →Rotations	-	-0.009
Coupling, Rotations → Anxiety	-0.01	-
Random effects		
Intercept		
A	3.79	8.00
D	2.74	2.56
E	5.46	3.54
Slope		
A	<-0.01	<0.01
D	<-0.01	<0.01
E	-0.42	<0.01
Slope on level		
A	0.10	-1.31
D	-0.56	-0.29
E	-0.38	-0.50
Error	6.23	5.75

Notes: -2LL = 2 * the negative log likelihood of the model, df = degrees of freedom from the model; Compare indicated the comparison model; a_s = additive genetic variance of slope; a_0 = additive genetic variance of intercept

** denotes $p < 0.01$ * denotes $p < 0.05$

Table 48. Parameter and goodness-of-fit estimates from the bivariate dual change score model of Anxiety Crosswalk and Figure Logic performance.

Model	-2LL	Df	Compare	Δ-2LL/Δdf
1. Full ADE	40950.4	5756	-	-
2. Drop coupling Anxiety → Fig Log	40950.7	5757	Model 1	0.3/1
3. Drop coupling Fig Log → Anxiety	40954.7	5757	Model 1	4.3/1*
4. Drop all D on Anxiety	40951.1	5759	Model 1	0.7/3
5. Drop all D on Fig Log	40950.6	5759	Model 1	0.2/3
6. Drop D on both	40951.3	5762	Model 1	0.7/6
7.Drop Anxiety a_s on Slope	40951.6	5763	Model 6	0.3/1
8.Drop Fig Log a_s on Slope	40951.3	5763	Model 6	0.1/1
9.Drop Anxiety a_0 on Slope	40951.3	5763	Model 6	0.1/1
10. Drop Fig Log a_0 on Slope	41009.5	5763	Model 6	57.9/1**
Full Model Parameters	**Anxiety**	**Figure Logic**		
Fixed effects				
Mean intercept	49.64	53.86		
Mean slope	0.70	-17.44		
Constant change	1	1		
Proportional change	-	0.32		
Coupling, Anxiety →Fig Log		-0.002		
Coupling, Fig Log → Anxiety	-0.02			
Random effects	6.33	6.99		
Intercept				
A	4.53	7.33		
D	2.26	3.06		
E	5.90	1.78		
Slope				
A	<-0.01	<-0.01		
D	<-0.01	<-0.01		
E	0.47	0.13		
Slope on level				
A	0.08	-2.46		
D	-0.47	-0.99		
E	-0.51	-0.53		
Error	6.30	5.82		

Notes: -2LL = 2 * the negative log likelihood of the model, df = degrees of freedom from the model; Compare indicated the comparison model; a_s = additive genetic variance of slope; a_0 = additive genetic variance of intercept

** denotes $p < 0.01$ * denotes $p < 0.05$

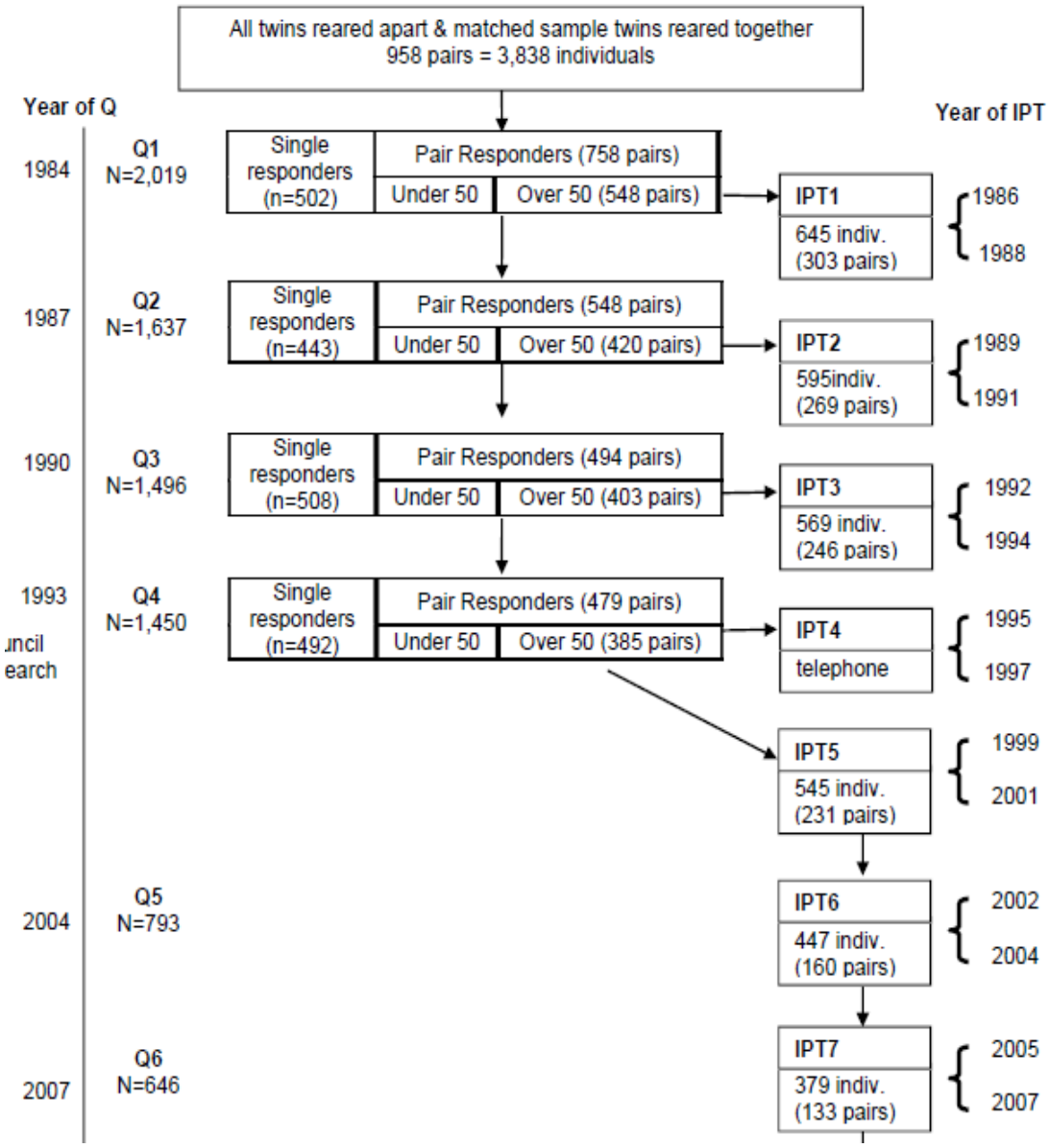

Figure 1. SATSA assessment schedule with number of participants and twin pairs assessed at each time point.

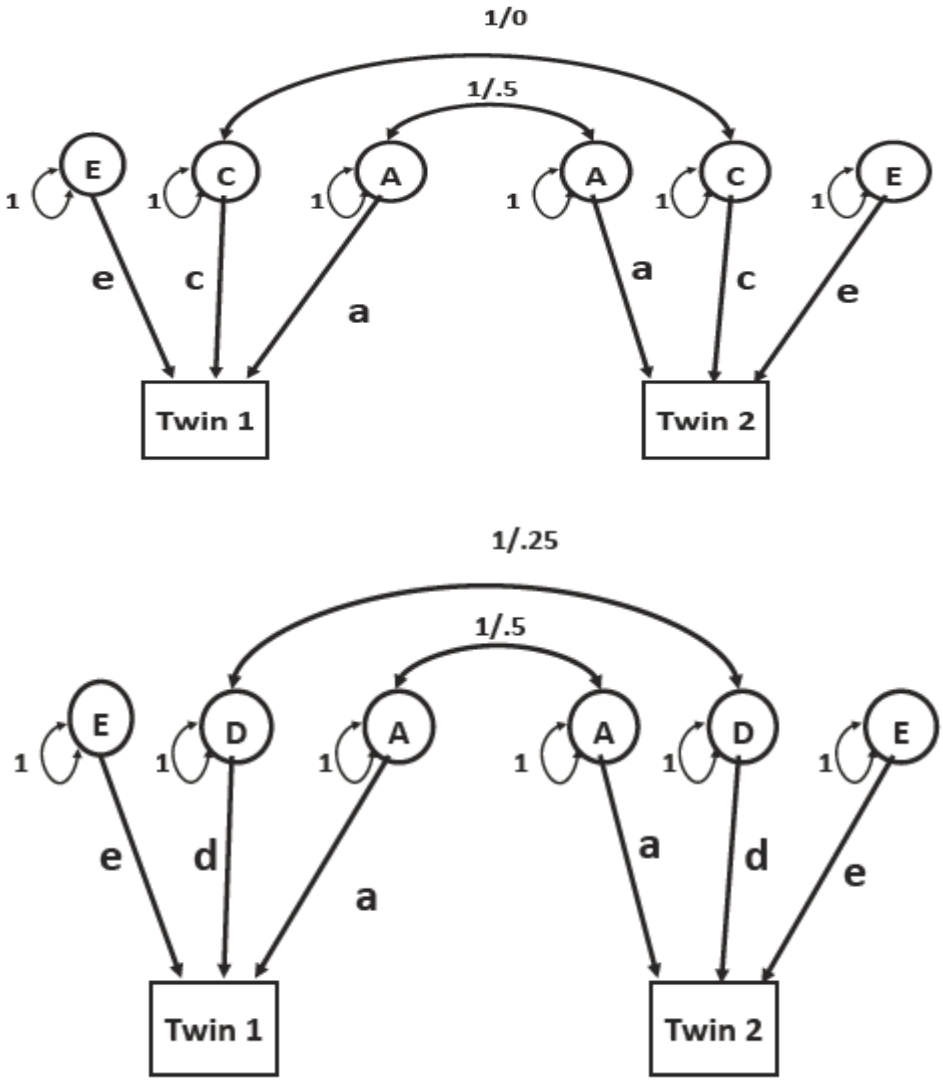

Figure 2. Conceptual depiction of the decomposition of variance between twins.

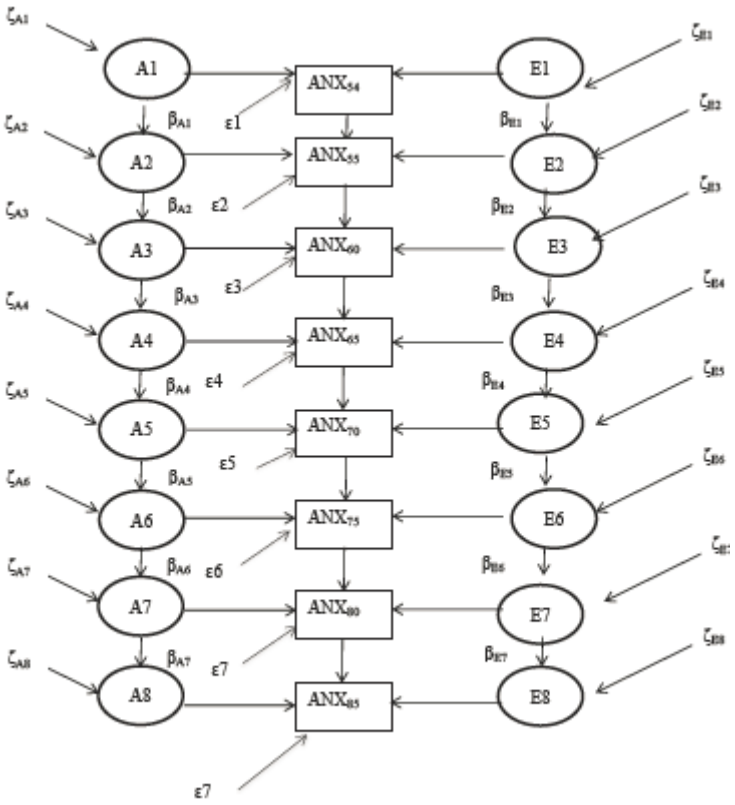

Figure 3. Diagram of the full AE simplex model. Please note that the shared environment (C) or genetic dominance factors (D) were not included in this picture for clarity.

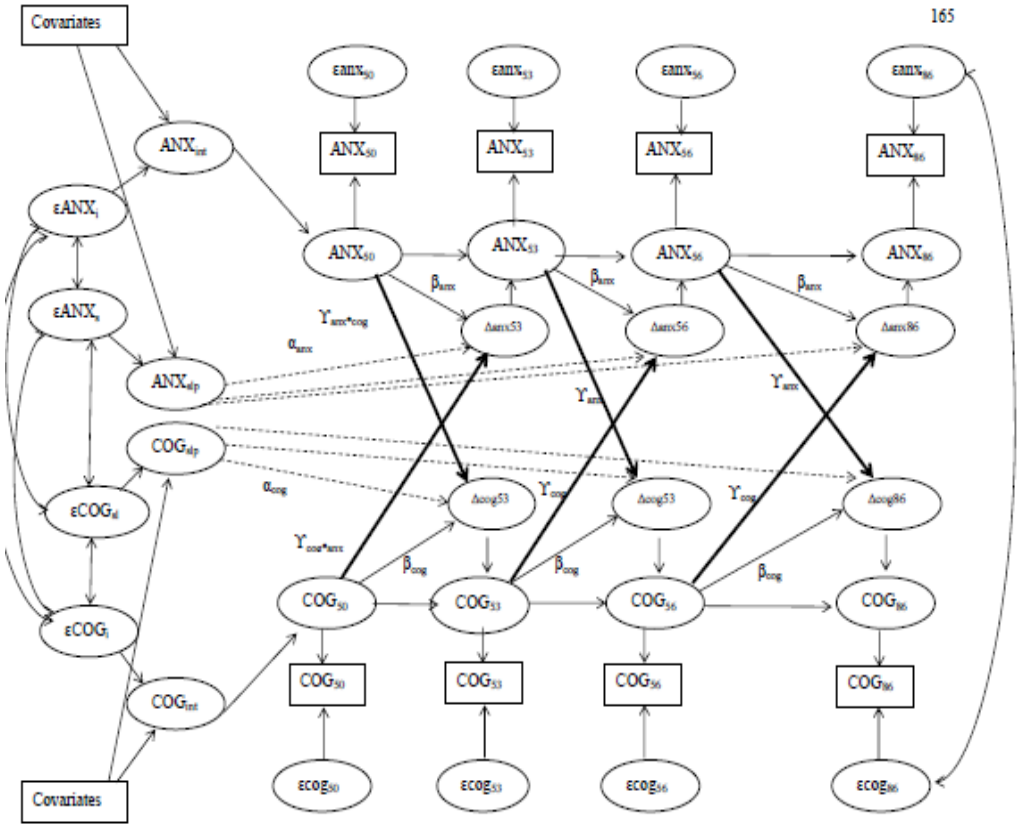

Figure 4. Diagram of the full phenotypic dual change score model examining dynamic change between anxiety and cognitive performance over time.

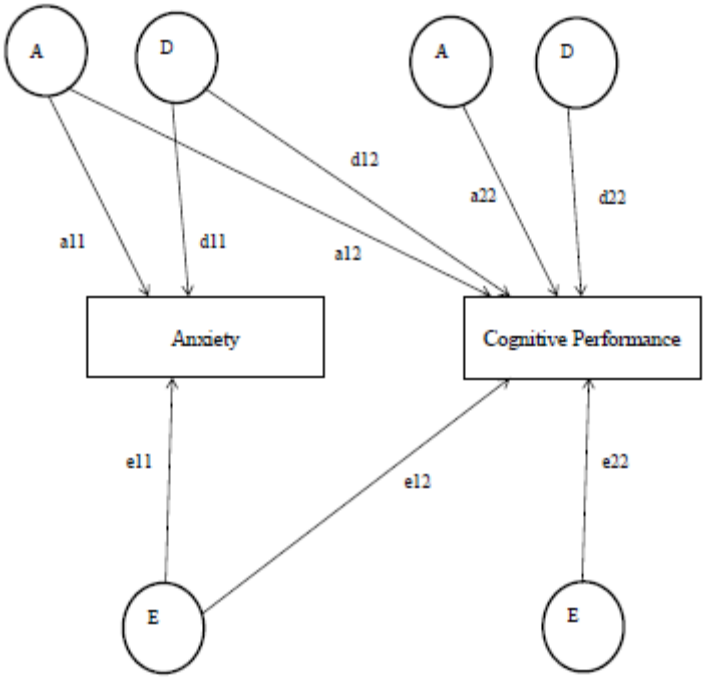

Figure 5. Diagram of the full ADE bivariate Cholesky decomposition examining shared genetic and environmental influences between anxiety and cognitive functioning.

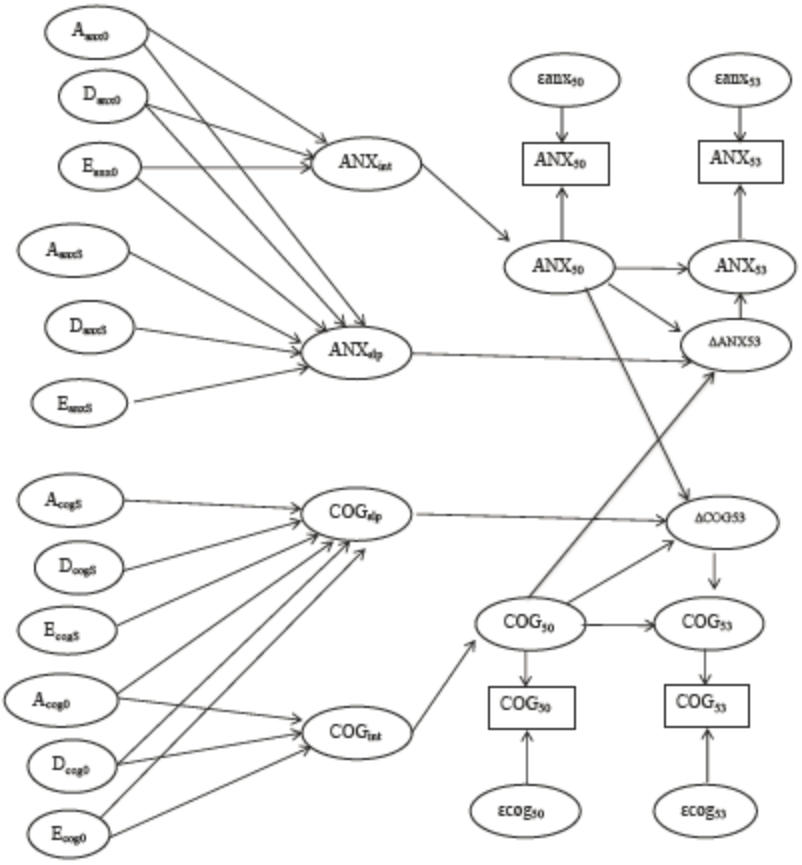

Figure 6. Diagram of the full ADE biometric dual change score model. In order to make the diagram easier to understand only the first two time points were included. The model continues until age 86.

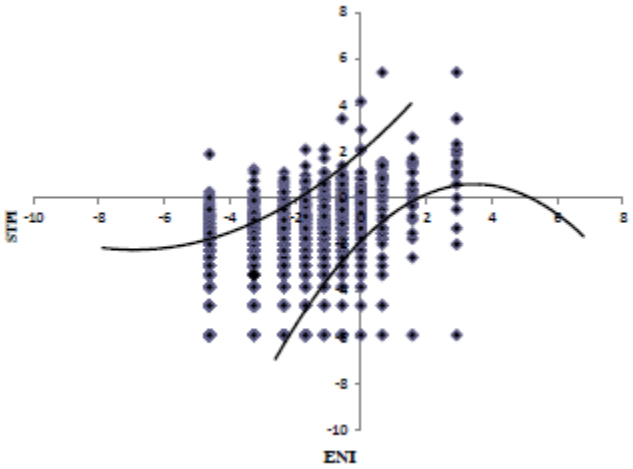

Figure 7. Scatterplot with 95% confidence interval of the estimated performance estimates for the STPI (Y-Axis) and the ENI (X-Axis) from the full Rasch analysis.

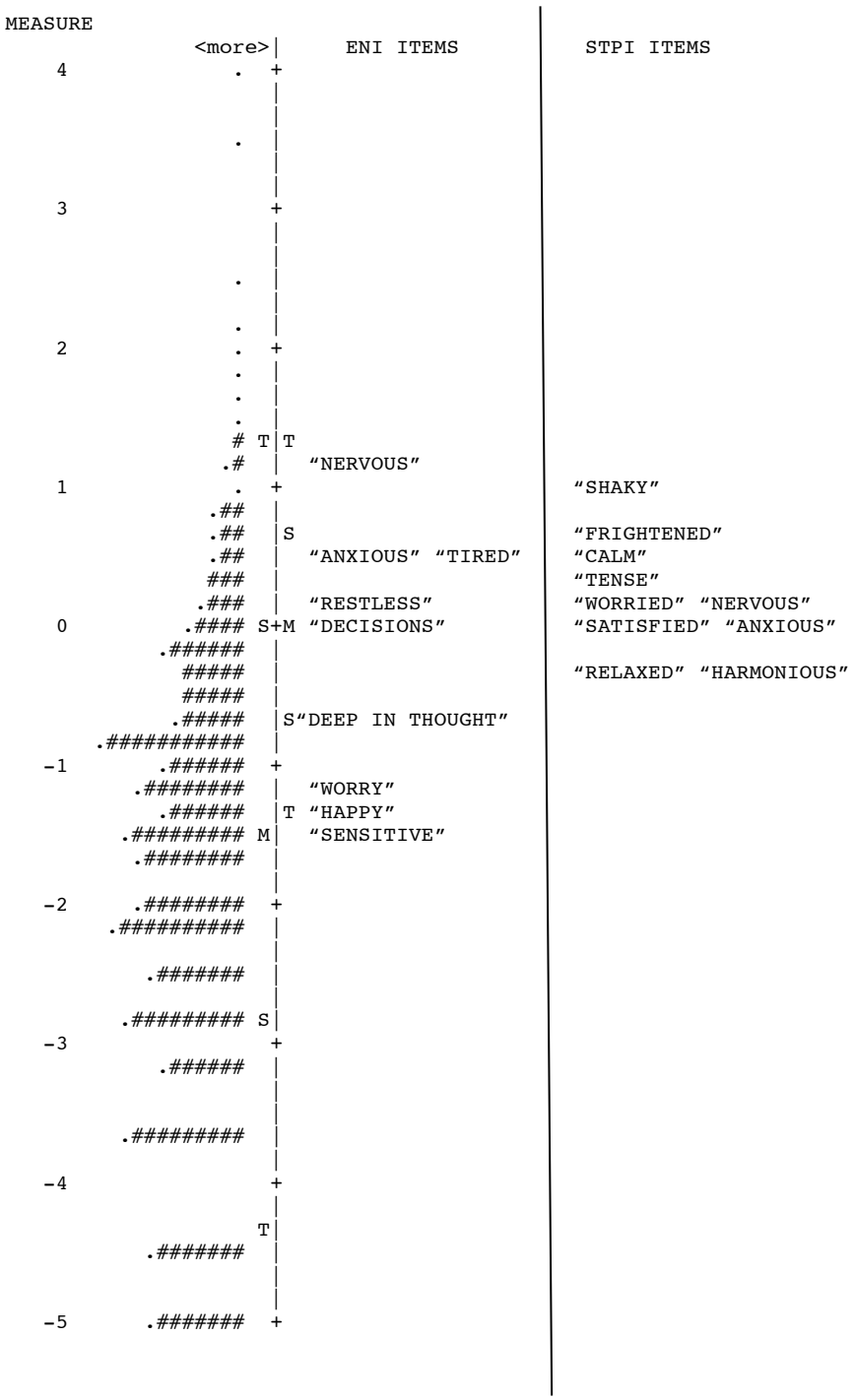

Figure 8. Item map from the Rasch analysis of all valid ENI and STPI items.

Figure 9. Item map from the Rasch analysis of the STPI and the ENI with items worry, happy or sad for no reason, and sensitive removed.

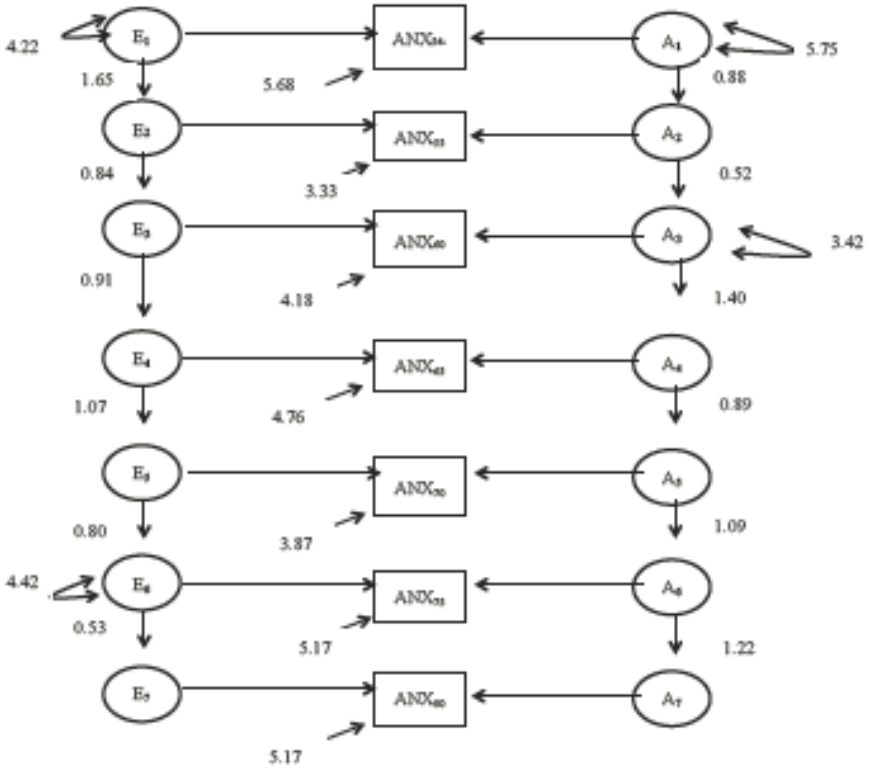

Figure 10. Diagram of the best STPI simplex model with unstandardized variance components and path coefficients.

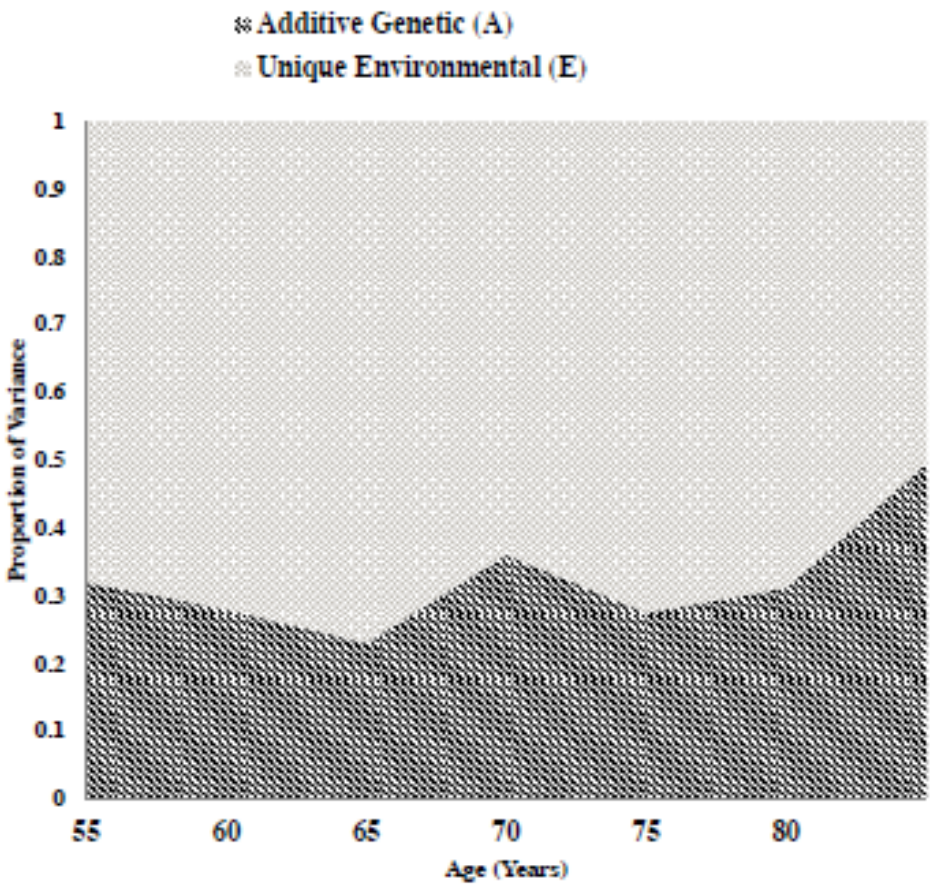

Figure 11. Graph of the estimated proportion of variance in STPI accounted for by additive genetic (A) and unique environmental (E) factors from the simplex model.

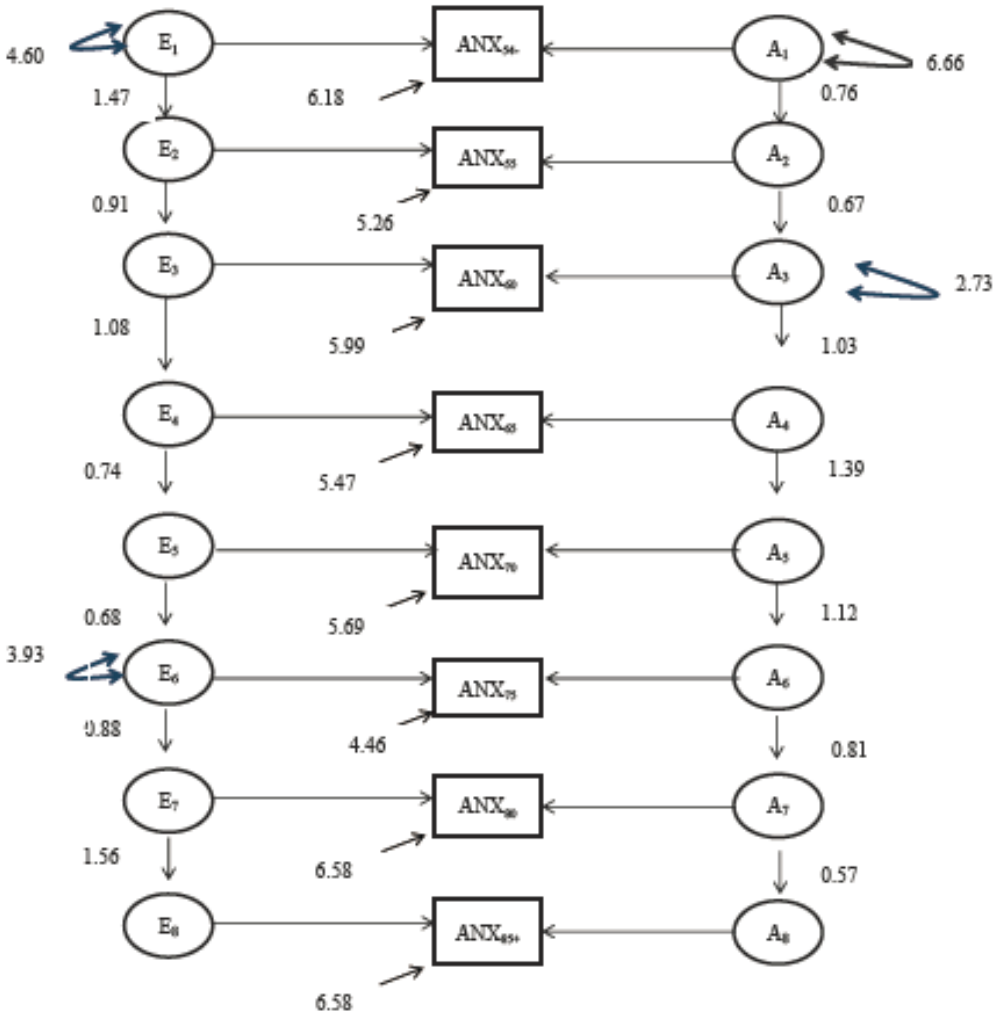

Figure 12. Diagram of the best fitting Anxiety Crosswalk simplex model with unstandardized variance components and path coefficients.

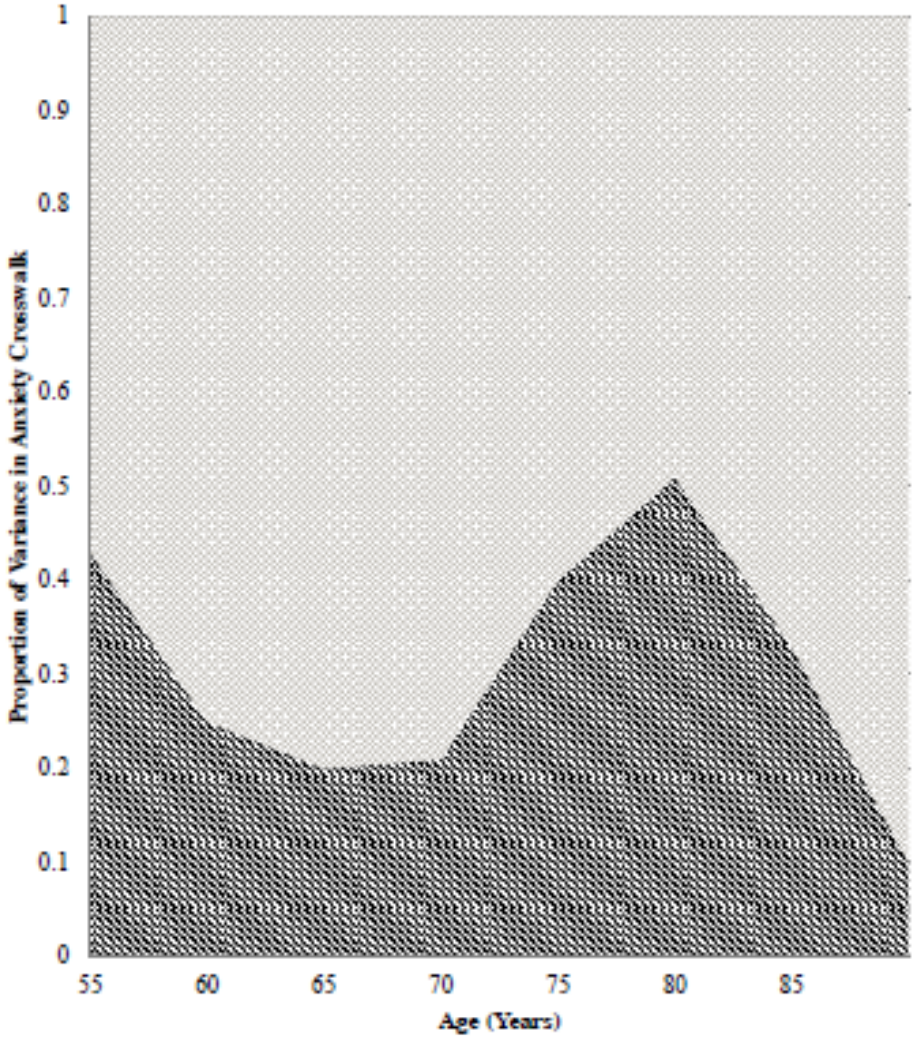

Figure 13. Graph of the estimated proportion of variance in the anxiety crosswalk measure accounted for by additive genetic (A) and unique environmental (E) factors from the simplex model.

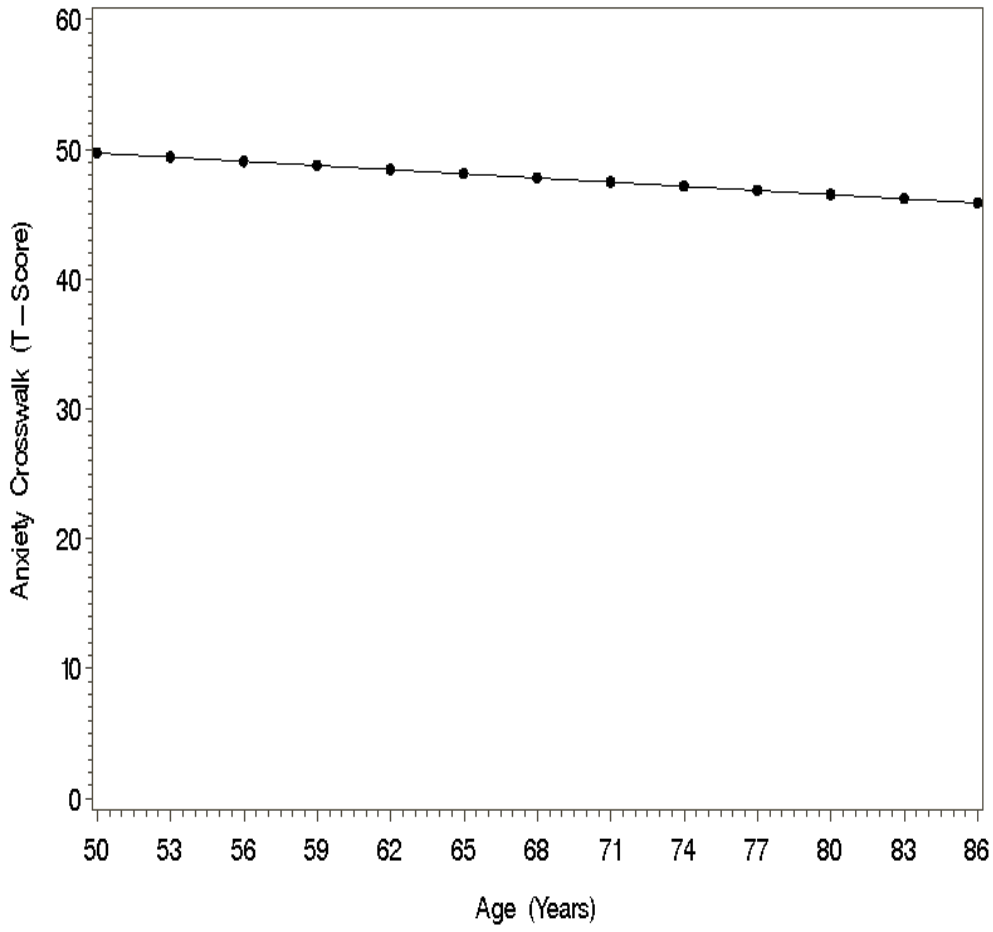

Figure 14. Graph of the estimated anxiety crosswalk trajectory over age from the univariate DCMS.

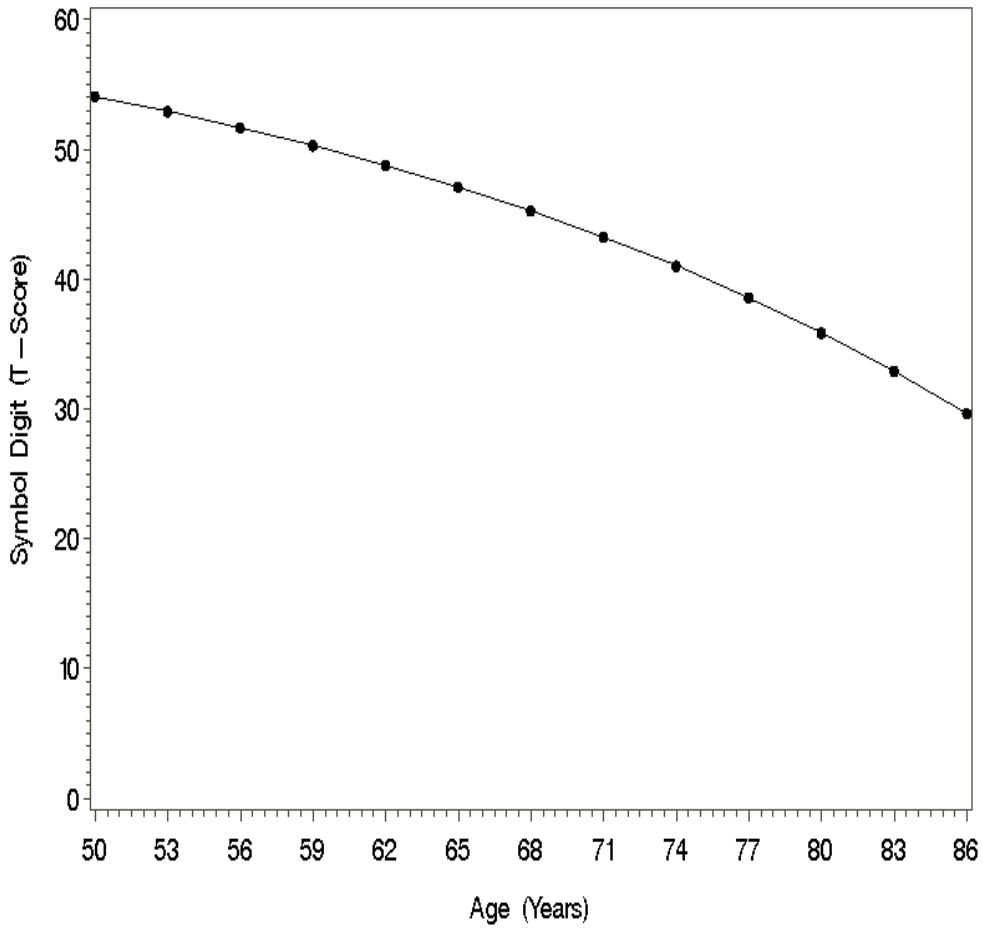

Figure 15. Graph of the estimated Symbol Digit trajectory over age from the univariate DCMS.

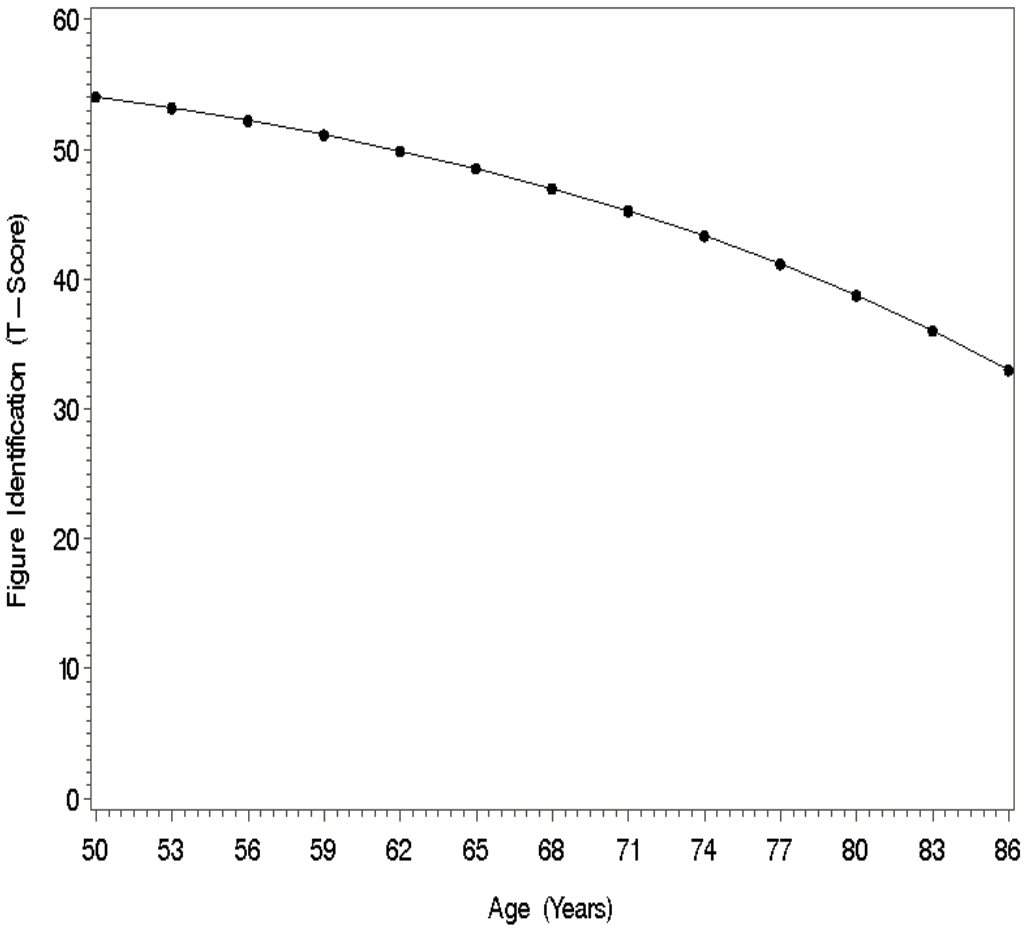

Figure 16. Graph of the estimated Figure Identification trajectory over age from the univariate DCMS.

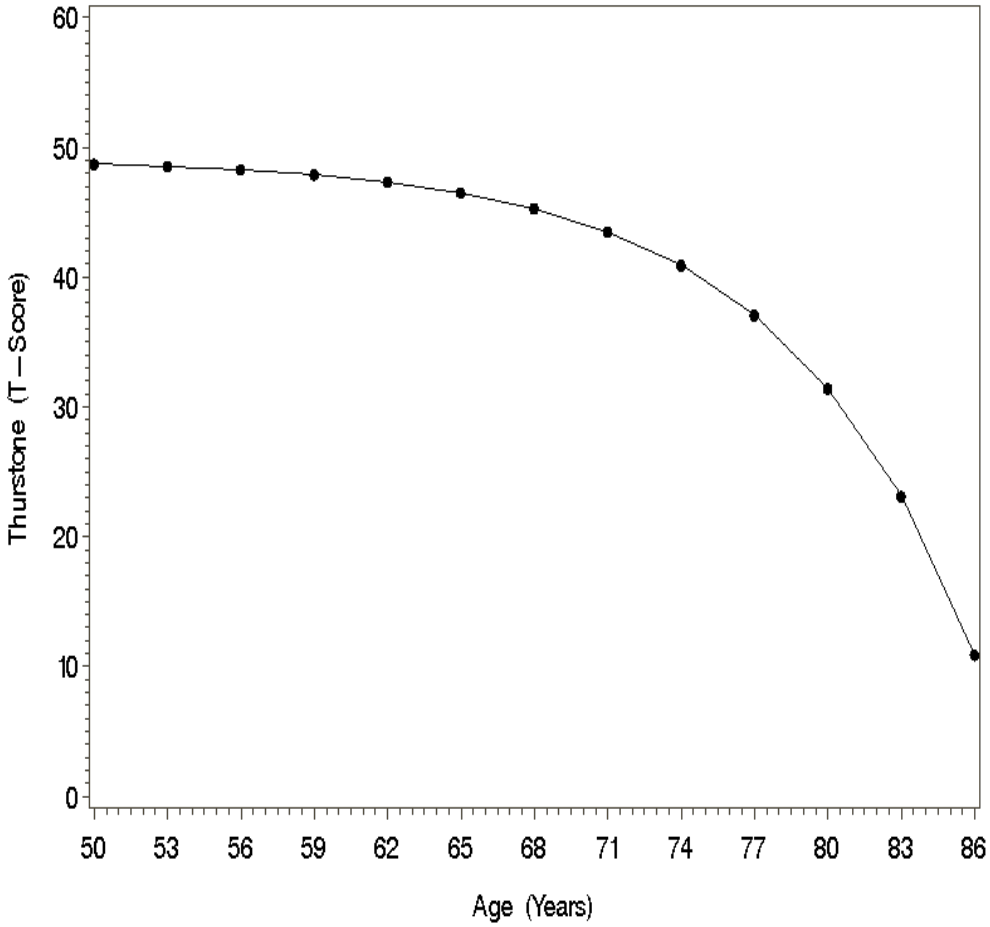

Figure 17. Graph of the estimated Thurstone trajectory over age from the univariate DCMS.

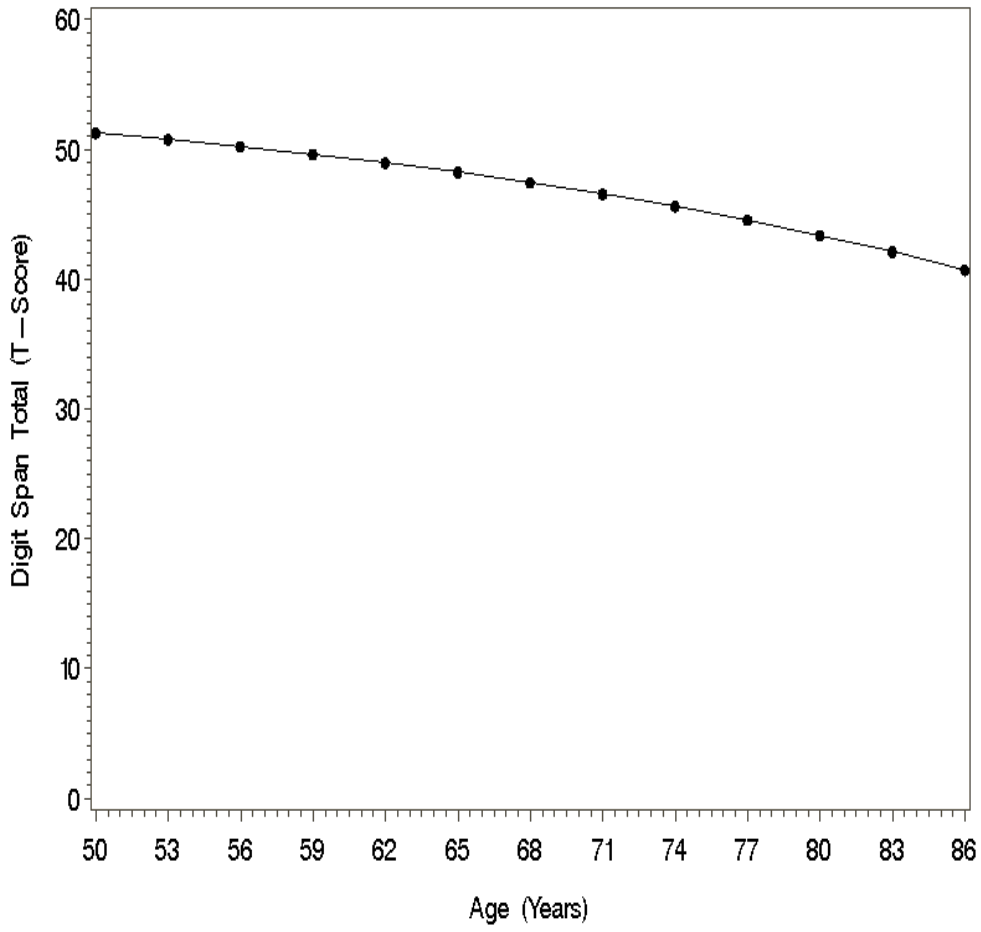

Figure 18. Graph of the estimated total Digit Span trajectory over age from the univariate DCMS.

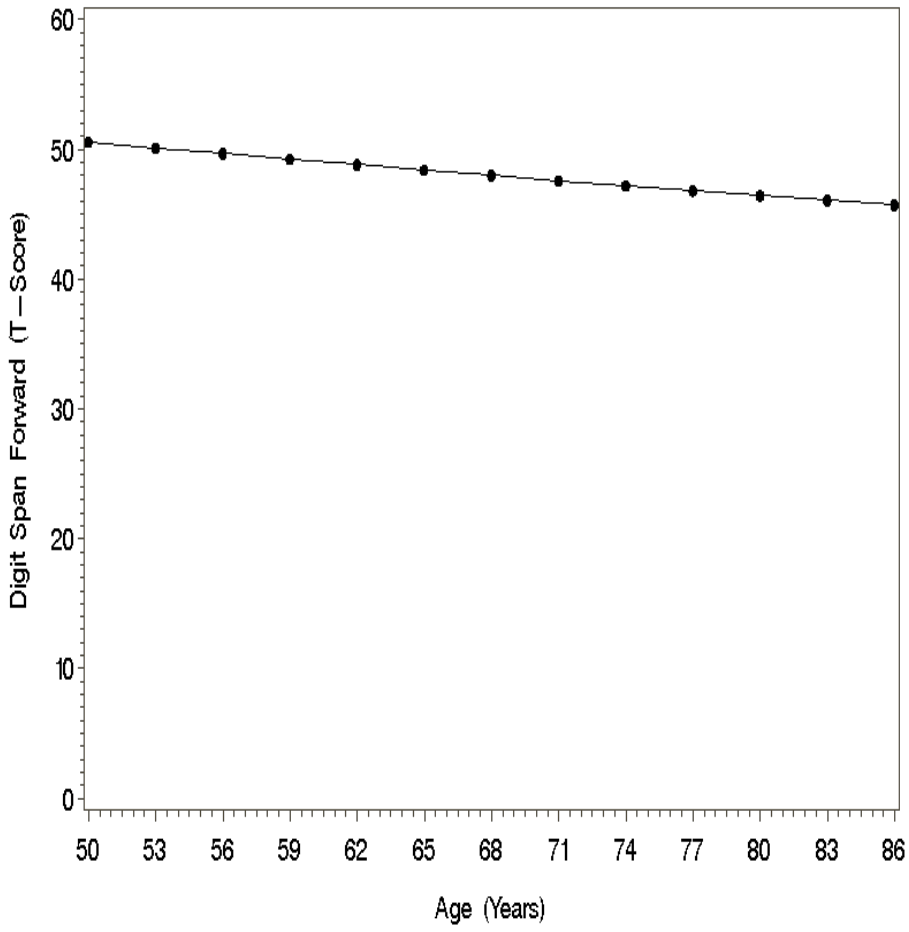

Figure 19. Graph of the estimated forward Digit Span trajectory over age from the univariate DCMS.

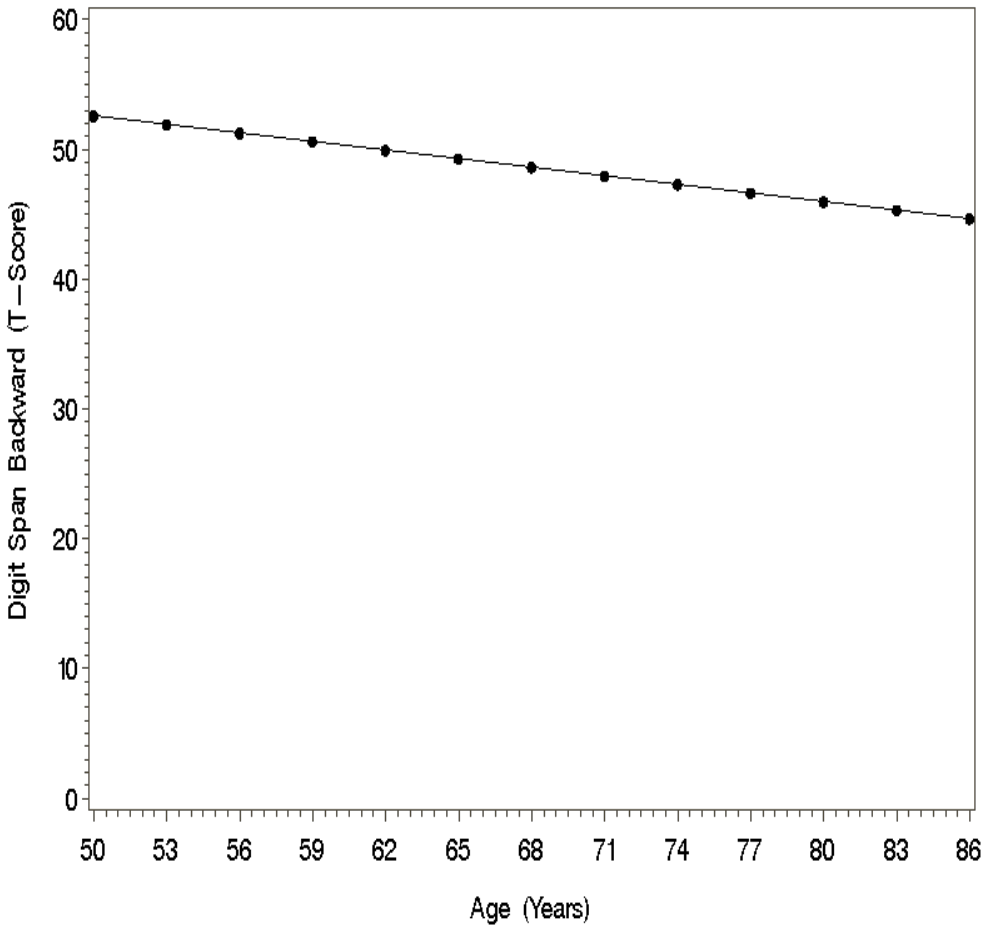

Figure 20. Graph of the estimated backward Digit Span trajectory over age from the univariate DCMS.

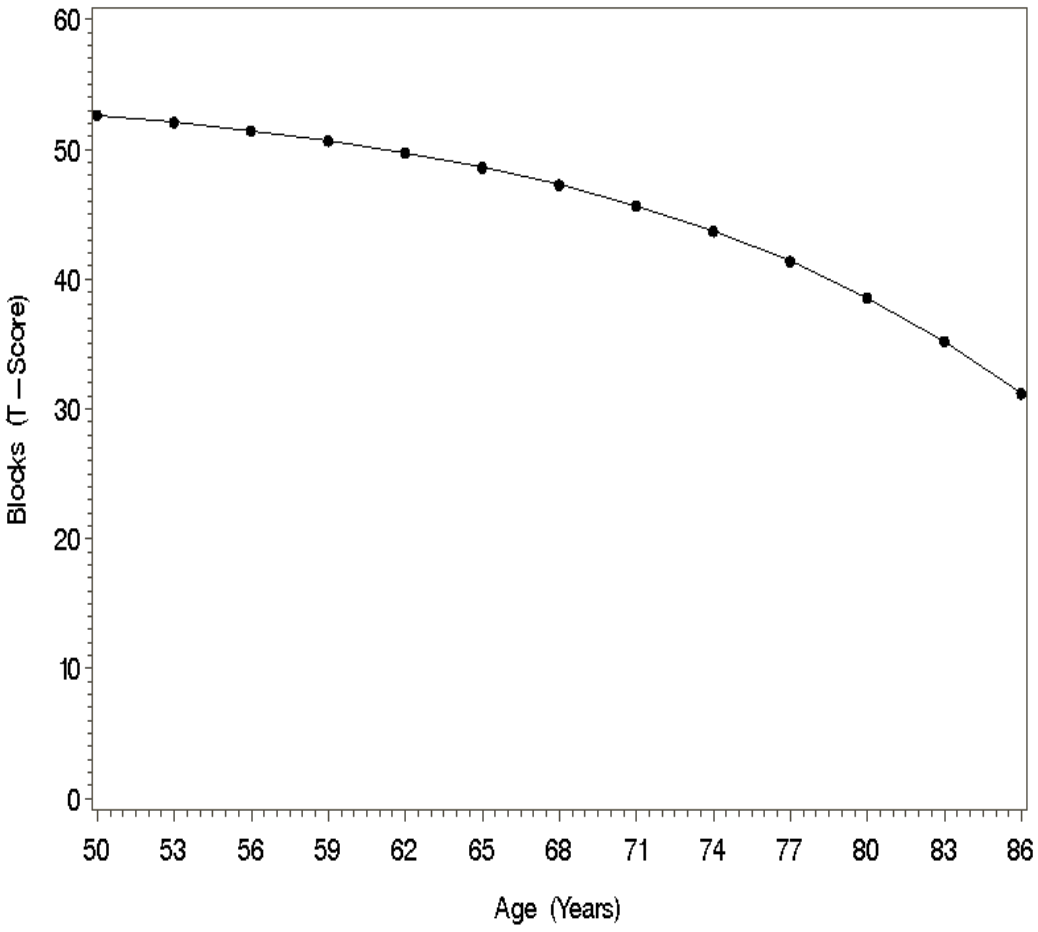

Figure 21. Graph of the estimated Block Design trajectory over age from the univariate DCMS.

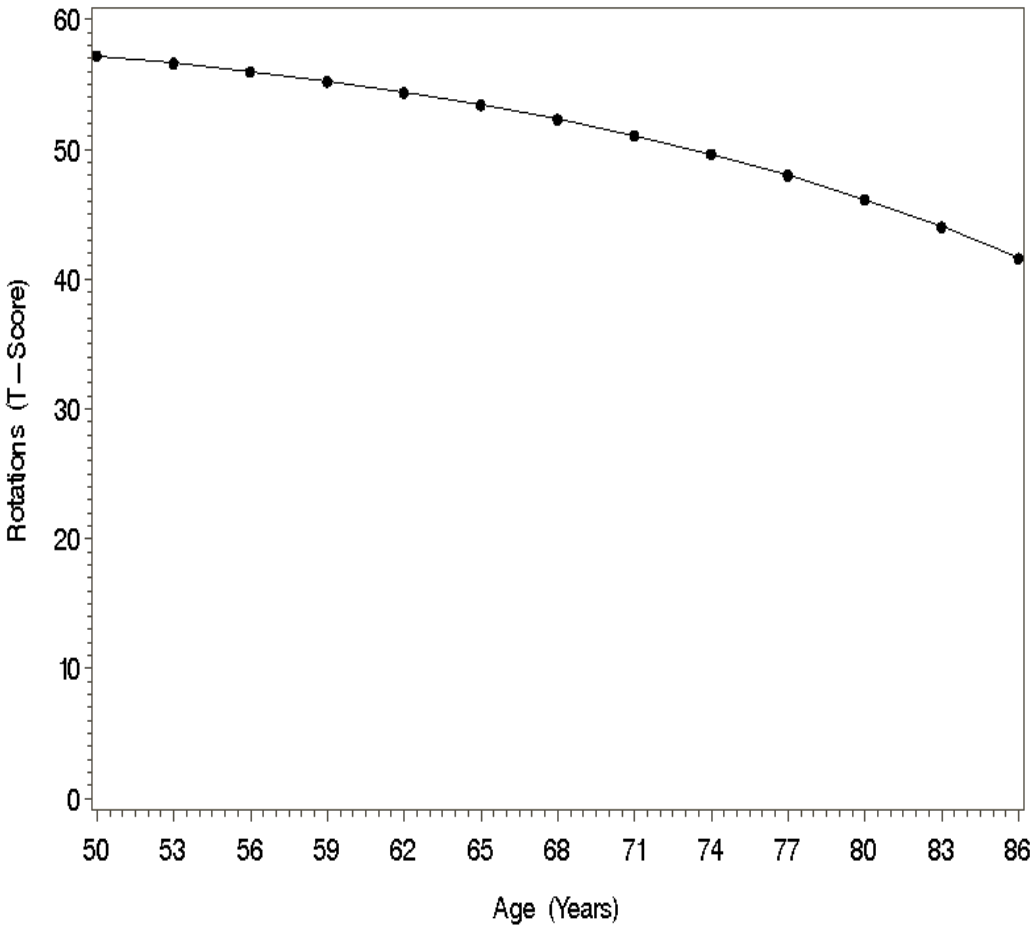

Figure 22. Graph of the estimated Card Rotations trajectory over time from the univariate DCMS.

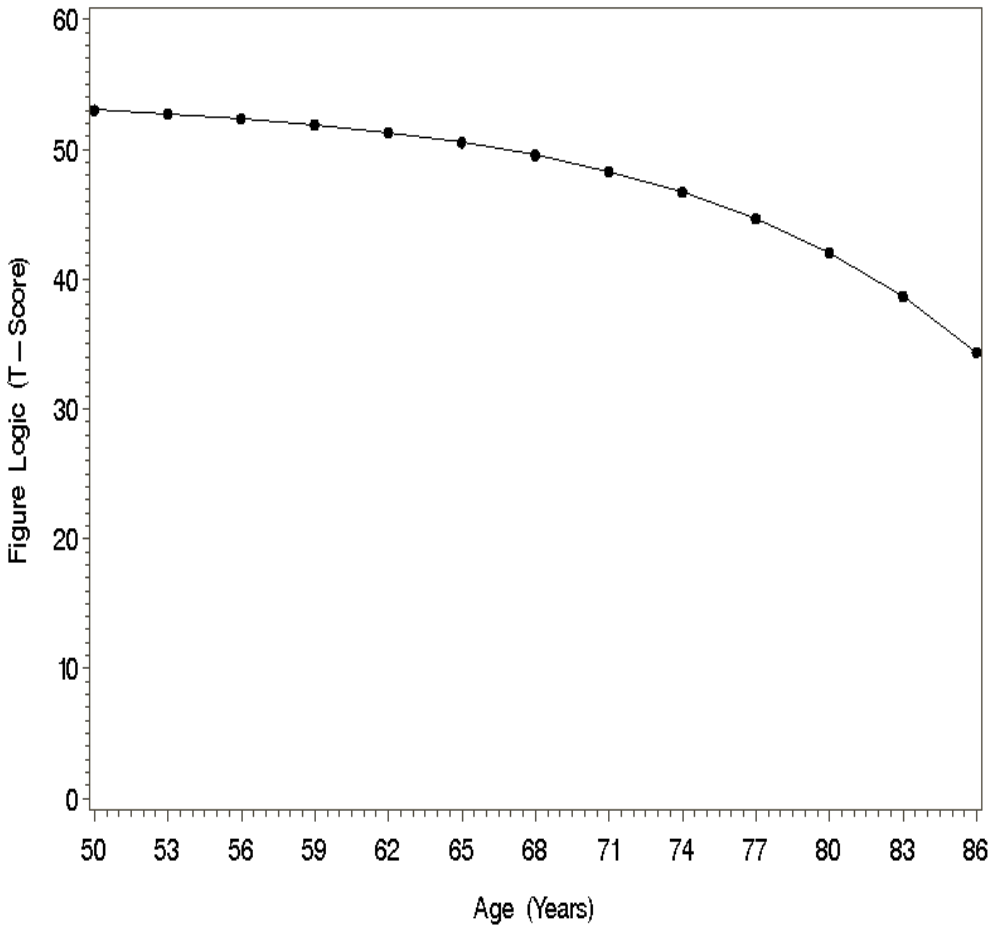

Figure 23. Graph of the estimated Figure Logic trajectory over time from the univariate DCMS.

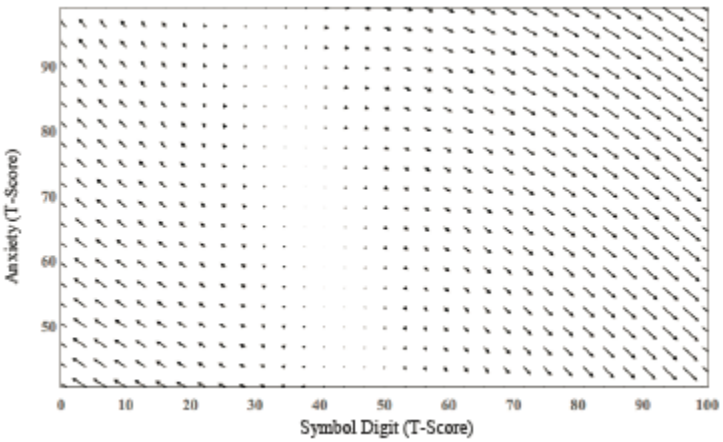

Figure 24. Vector field plot depicting the dynamic association between changes in anxiety and changes in Symbol Digit performance from the full bivariate DCMS model.

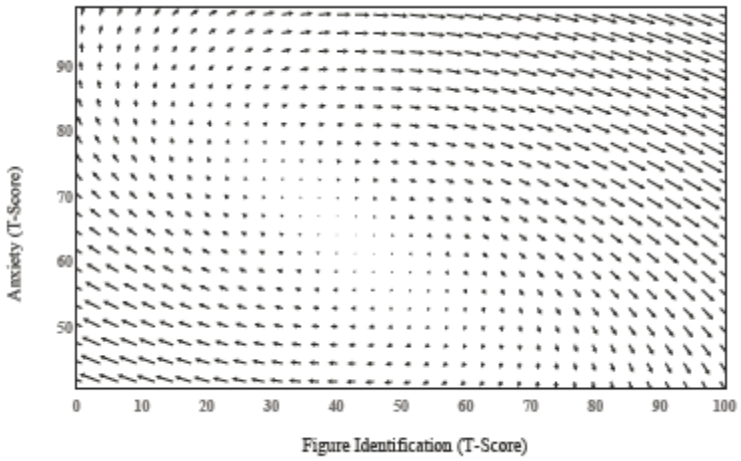

Figure 25. Vector field plot depicting dynamic association between changes in anxiety and changes in Figure Identification performance from the full bivariate DCMS model.

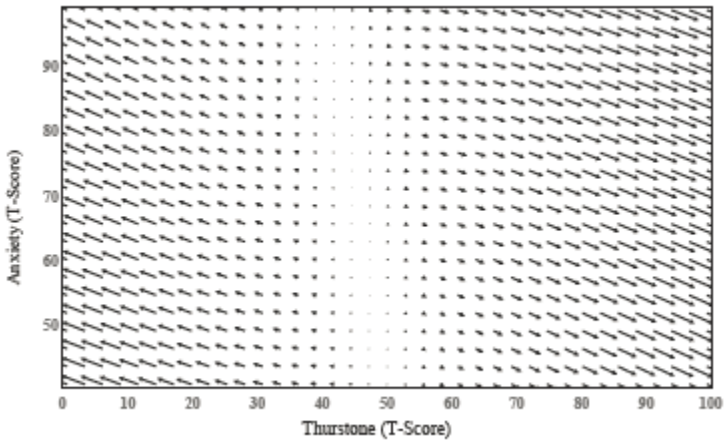

Figure 26. Vector field plot depicting the dynamic association between changes in anxiety and changes in Thurstone performance from the full bivariate DCMS model.

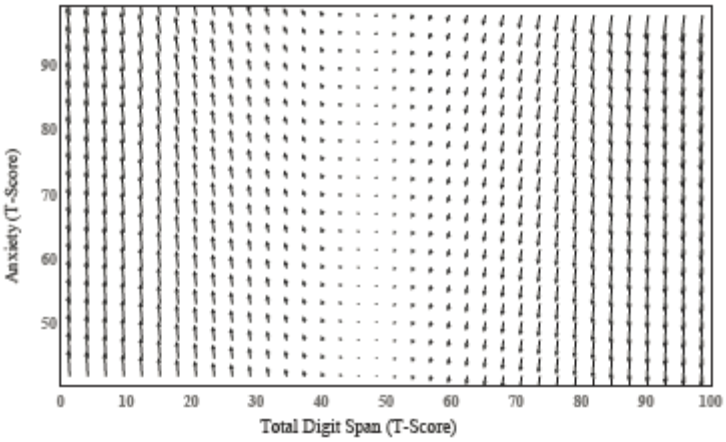

Figure 27. Vector field plot depicting the dynamic association between changes in anxiety and changes in total Digit Span performance from the full bivariate DCMS model.

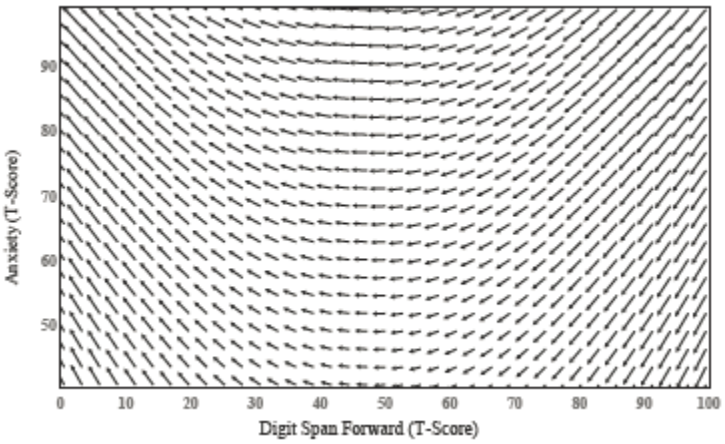

Figure 28. Vector field plot depicting the dynamic association between changes in anxiety and changes in Digit Span forward performance from the full bivariate DCMS model.

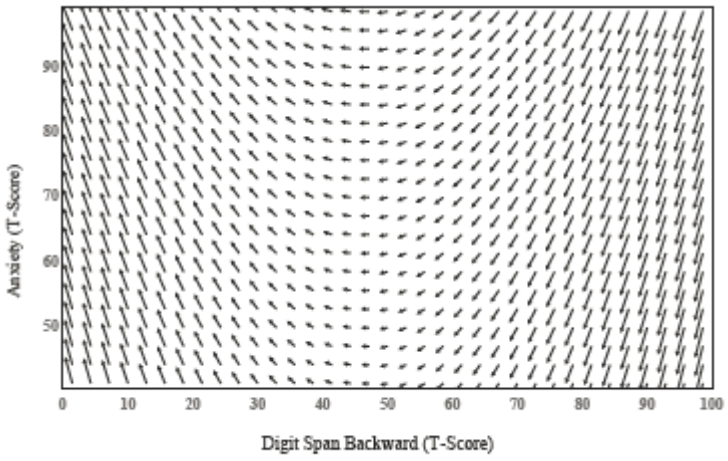

Figure 29. Vector field plot depicting dynamic the association between changes in anxiety and changes in Digit Span backwards performance from the full bivariate DCMS model.

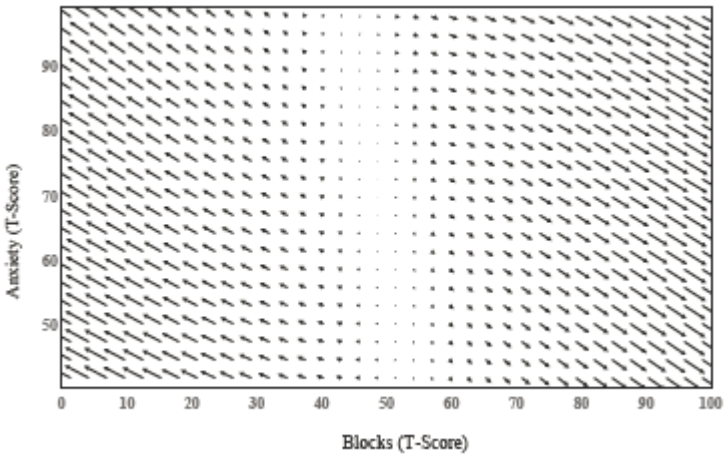

Figure 30. Vector field plot depicting the dynamic association between changes in anxiety and changes in Block Design performance from the full bivariate DCMS model.

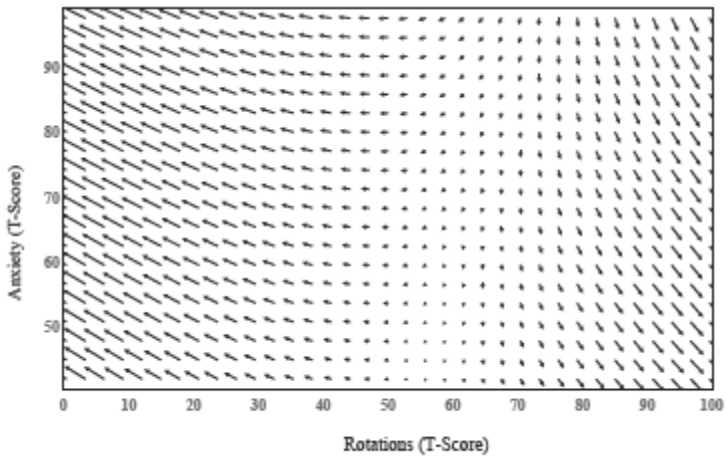

Figure 31. Vector field plot depicting the dynamic association between changes in anxiety and changes in Card Rotations performance from the full bivariate DCMS model.

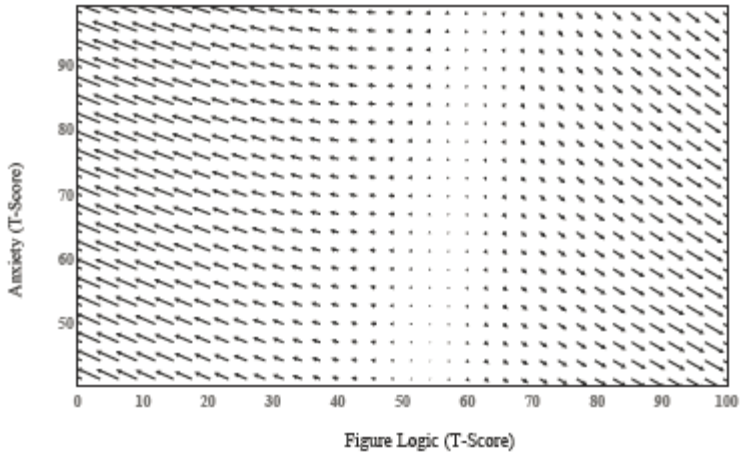

Figure 32. Vector field plot depicting the dynamic association between changes in anxiety and Figure Logic performance from the full bivariate DCMS model.

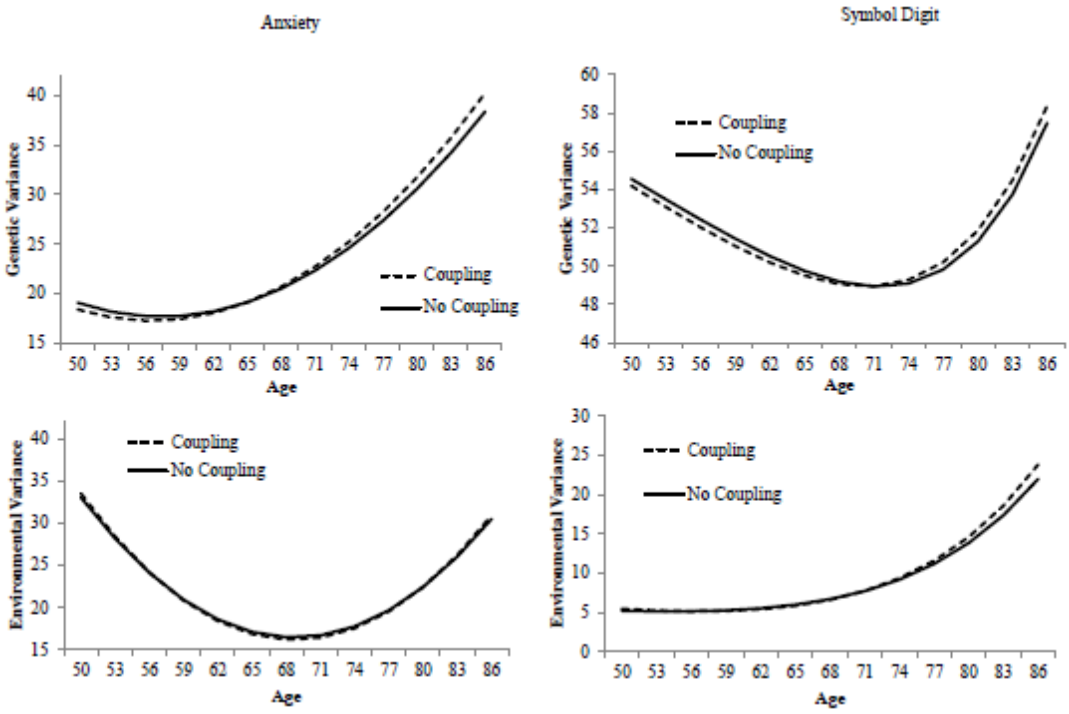

Figure 33. Estimated age-based genetic and unique environmental variance of anxiety (left) and Symbol Digit (right) variables, with and without full coupling.

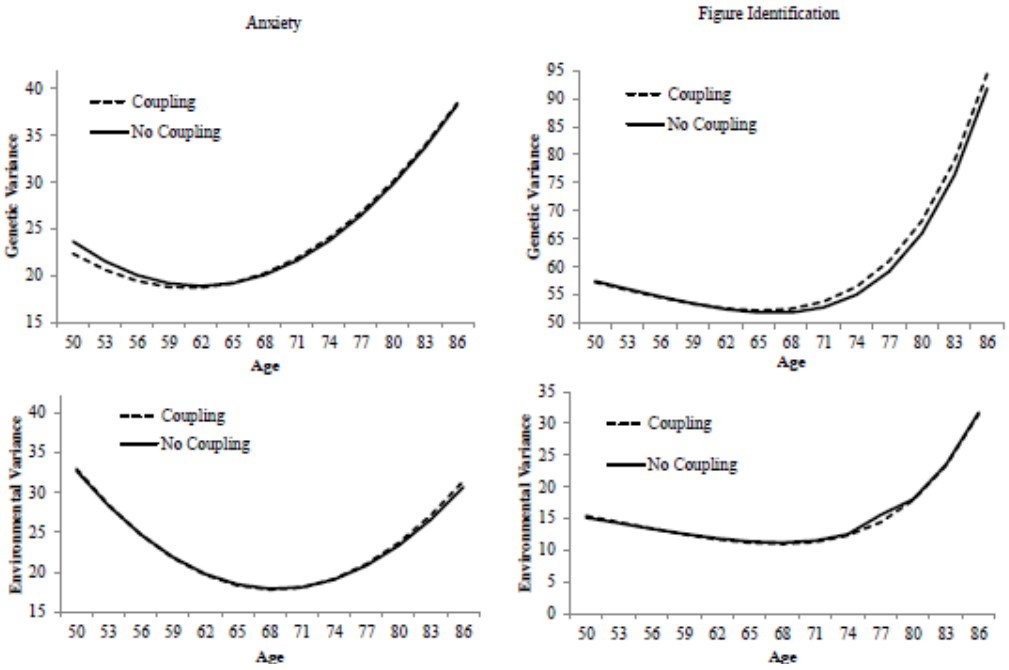

Figure 34. Estimated age-based genetic and unique environmental variance of anxiety (left) and Figure Identification (right) variables, with and without full coupling.

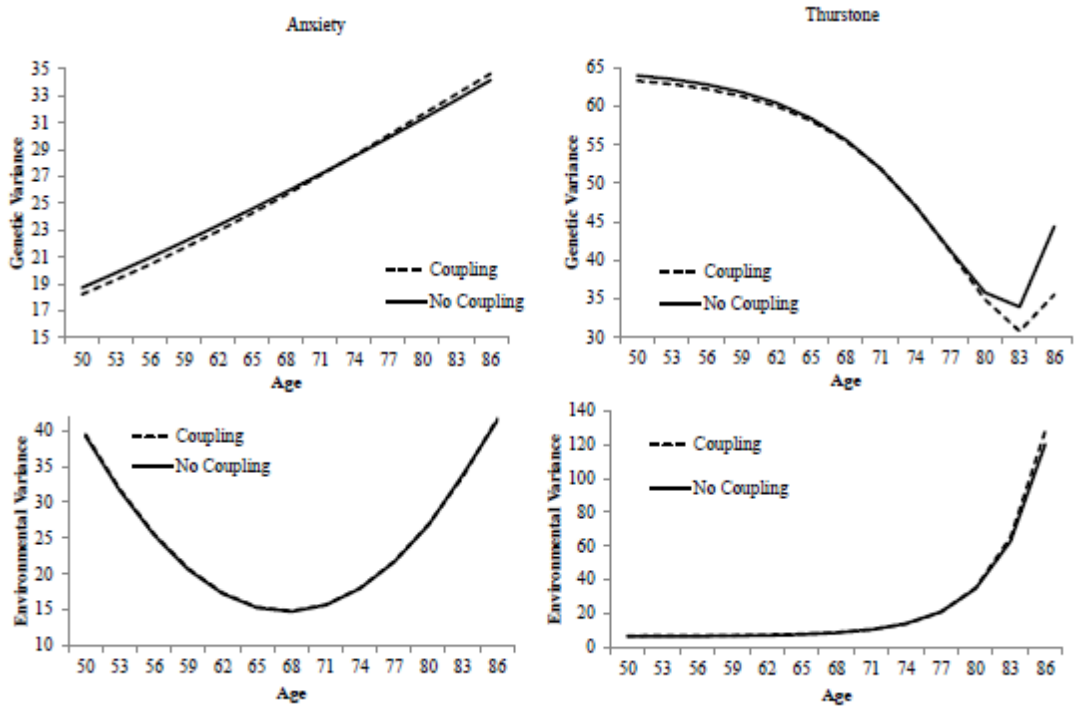

Figure 35. Estimated age-based genetic and unique environmental variance of anxiety (left) and Thurstone (right) variables with and without full coupling.

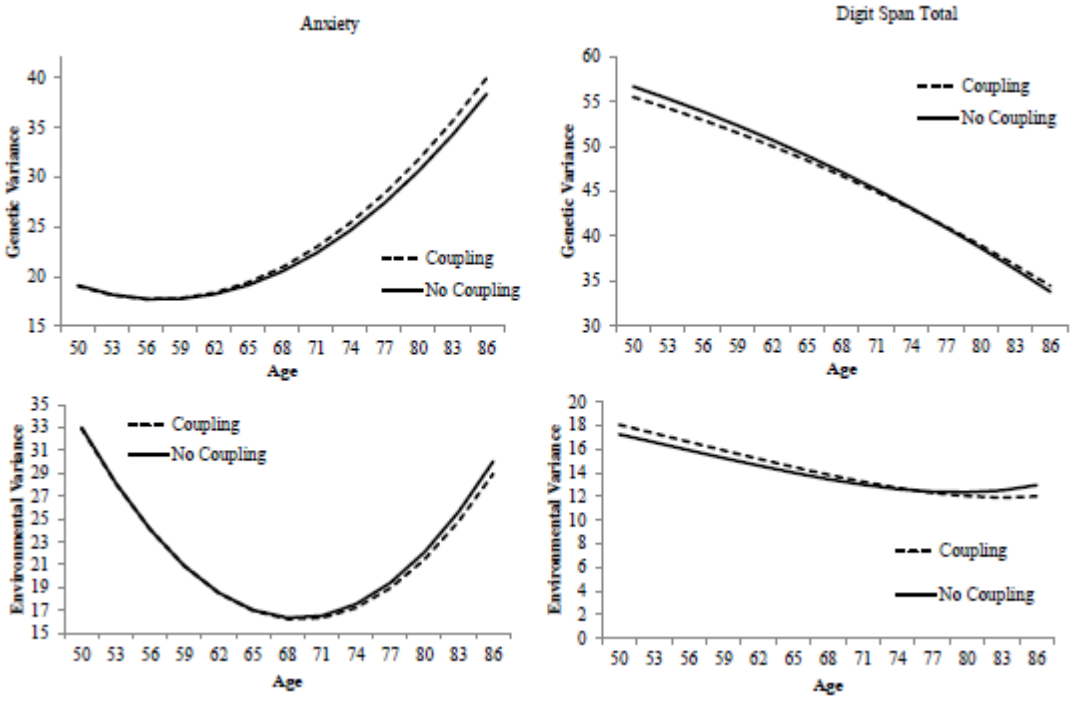

Figure 36. Estimated age-based genetic and unique environmental variance of anxiety (left) and Digit Span total (right) variables, with and without full coupling.

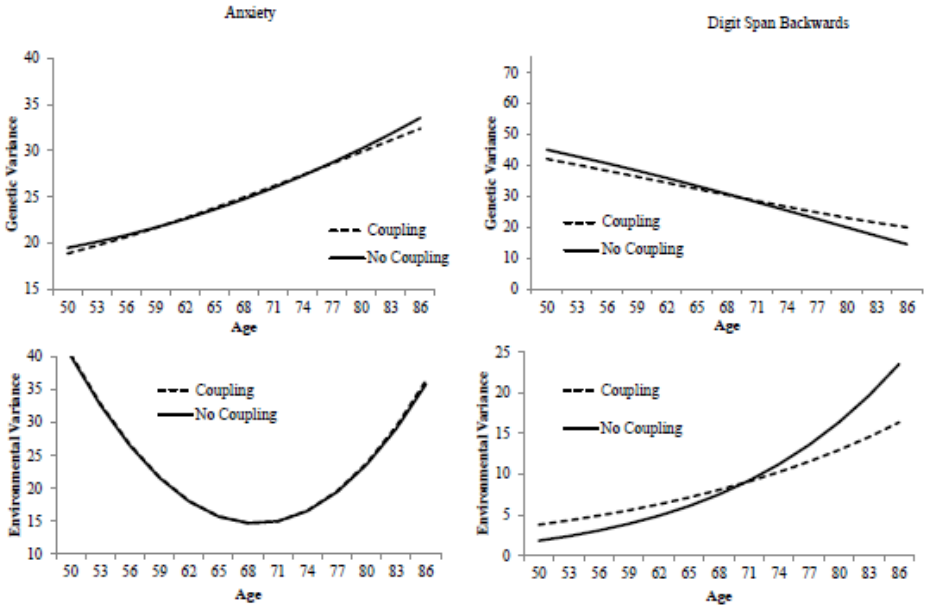

Figure 37. Estimated age-based genetic and unique environmental variance of anxiety (left) and Digit Span Backwards (right) variables, with and without full coupling.

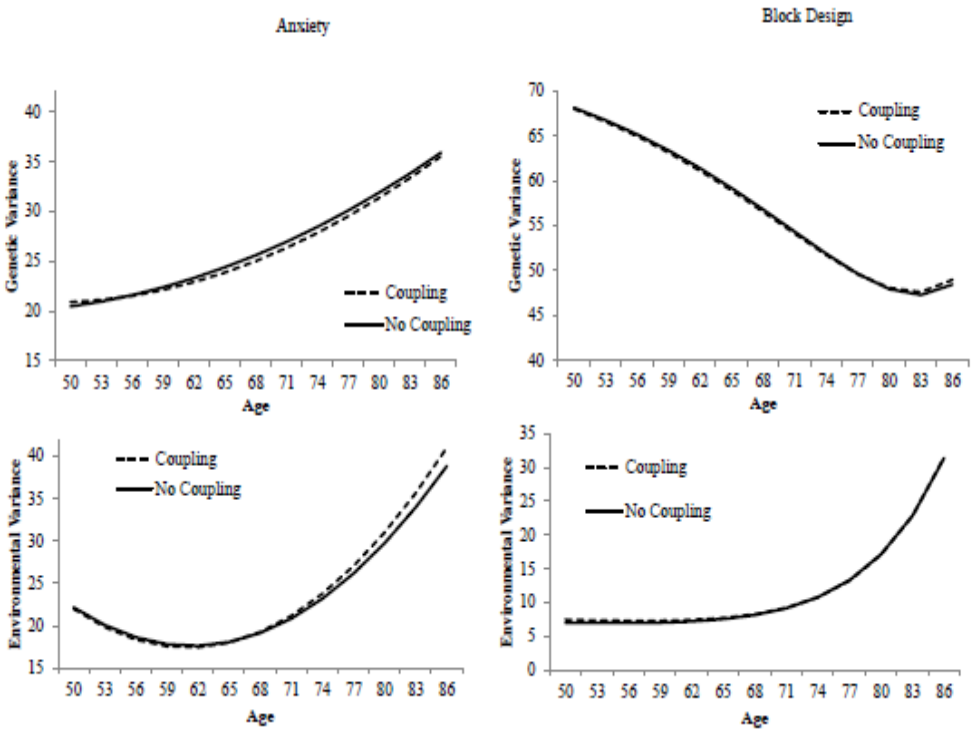

Figure 38. Estimated age-based genetic and unique environmental variance of anxiety (left) and Block Design (right) variables, with and without full coupling.

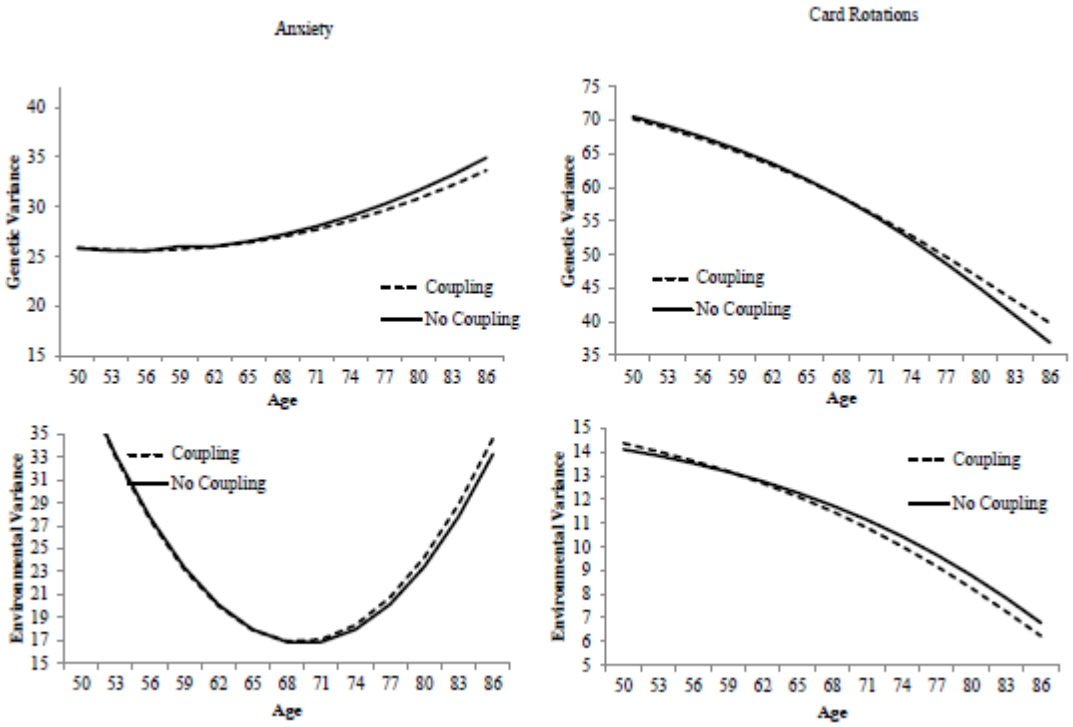

Figure 39. Estimated age-based genetic and unique environmental variance of anxiety (left) and Card Rotations (right) variables, with and without full coupling.

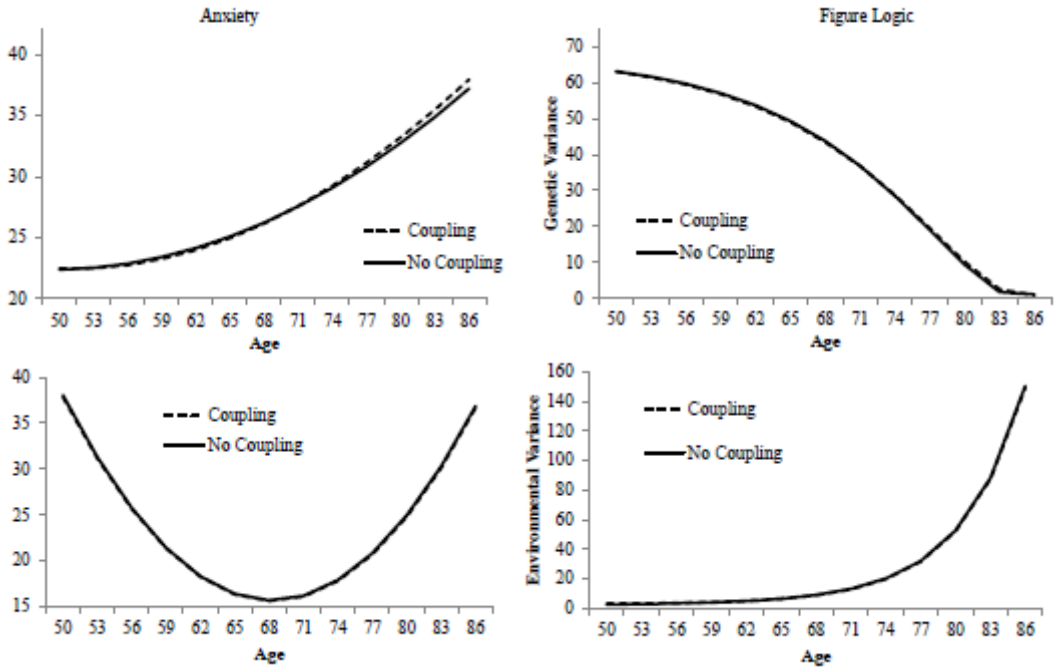

Figure 40. Estimated age-based genetic and unique environmental variance of anxiety (left) and Figure Logic (right) variables, with and without full coupling.