The Psychological Factors and Neural Substrates Associated with Metacognition among
Community-Dwelling and Neurologic Cohorts of Older Adults

Leigh Elizabeth Colvin

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ABSTRACT

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This project consists of three distinct, but sequential studies that explore the psychological factors and neuropathological substrates of *metacognition* or *self-awareness* among older adults. Study 1 examines the premorbid, psychological characteristics associated with metamemory—the mainstay of metacognitive research—in a healthy, community-dwelling cohort of older adults. Study 2 builds on these analyses, and examines the psychological characteristics associated with metacognition, more broadly, in a neurologic cohort of older adults with Essential Tremor (ET). Study 3, which utilizes post-mortem evaluations of participants from Study 2, goes beyond premorbid characteristics and examines whether distortions in metacognition are in part attributable to an underlying disease process. Findings demonstrated that psychological characteristics were associated with metacognitive accuracy in a healthy, community-dwelling cohort of older adults, but not among individuals with ET; further, distortions in metacognition among individuals with ET were better attributable to non-ET specific pathologies, such as amyloid $\beta$, neurofibrillary tangles, and regional-specific atrophy. This project underscores the importance of employing a biopsychosocial approach to understanding the factors that influence metacognition. Ultimately, by understanding and working effectively with awareness phenomena, there is a strong potential to reduce disability and enhance well-being.

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## DEDICATION

To my mother and father – words cannot describe how grateful I am for your love, your endless support, and your humor. Thank you for believing in me during those moments when I doubted myself most.

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CHAPTER I: INTRODUCTION

"I am not yet able, as the Delphic inscription has it, to know myself, so it seems to me ridiculous, when I do not yet know that, to investigate irrelevant things."

—Plato, *Phaedrus* (229E)

This notion that accurate self-knowledge has value and is something to strive for has preoccupied thinkers since Socrates. While self-awareness, as Plato illustrates in the quote above, is not always evident or attainable, it continues to have relevance today for a variety of neurologic conditions, including brain injury, dementias, and movement disorders (Fleming & Dolan, 2012).

*Aim of the Study*

The primary aim of the current research is to investigate the psychological and neuropathological factors associated with metacognition in healthy and neurologic cohorts of older adults. More specifically, this research project consists of three studies: Study 1 examines the psychological factors associated with metamemory—the mainstay of metacognitive research—in a healthy, community-dwelling sample; Study 2, examines metacognition, more broadly, in a neurologic sample of older adults with Essential Tremor (ET); and Study 3 (an extension of Study 2) utilizes postmortem evaluations of older adults with ET to explore the neural substrates of metacognition. These three studies, which were completed in succession, espouse a biopsychosocial approach in an effort to develop a comprehensive understanding of the factors that influence metacognition in the aging brain.

*Research Background and Rationale of Study*

Over the past few decades, numerous studies have highlighted deficits in awareness as an important clinical symptom in various neurocognitive disorders, including stroke, traumatic brain

injury, and Alzheimer's disease (Broadbent et al., 1982; Nelson & Narens, 1990; McKhann et al., 1984; Souchay et al., 2003; Cosentino & Stern, Y., 2005; Barrett et al., 2005; Eslinger et al., 2005; Mendez & Shapira, 2005; Salmon et al., 2006; Burson, Larrick, & Klayman, 2006; Thomas, Lee, & Balota, 2013). Babinski (1914) originated the term, *anosognosia*, to characterize the lack of awareness of left-sided hemiplegia. Since then, its meaning has widened to include unawareness of sensory, perceptual, motor, affective, and cognitive (i.e. metacognitive) deficits (Aalten et al., 2005), the latter of which can vary by both the degree of impairment and the domains affected (Starkstein et al., 1996). In a line of work originating in the field of cognitive psychology and parallel to the clinically-focused research on anosognosia, aspects of self-awareness have been studied as part of the construct of metacognition (Flavell, 1979). Fleming and Frith (2014) proposed that awareness more generally involves the integration of information from both external reality and inner experience—an idea that is reflected in the definition of self-awareness as "the capacity to perceive the self in relatively objective terms whilst maintaining a sense of subjectivity" (Prigatano & Schacter 1991, p. 13). Intact awareness is presumably necessary for high level control of one's own mental process and memories; correspondingly, metacognition, or 'knowing about knowing', refers to a person's ability to monitor, predict, and control his or her own cognitive functions (Nelson & Narens, 1990). It follows that the ability to learn effectively and regulate behavior depends highly on the accuracy and appropriate use of metacognition.

In their seminal papers, Nelson and Narens (1990; 1996) described two primary metacognitive processes: monitoring and control (Figure 1). *Monitoring* relates to knowledge regarding one's own cognitive abilities and performance, while *control* refers to the decisions one makes based on their perception of their abilities or their self-regulation (Nelson & Narens,

1990; Cosentino et al., 2011). In line with this conceptualization, Cosentino and colleagues (2011) have proposed that disordered awareness of memory, or poor metamemory, among individuals with Alzheimer's disease (AD) can be considered a deficit in declarative, episodic memory monitoring. Metamemory refers to the processes whereby people are able to examine the content of their memories, either prospectively or retrospectively, and make judgments or commentaries about them (Metcalfe & Dunlosky, 2008). It is worth noting that there is no single method, or gold standard, for measuring metamemory; rather, metamemory has been operationally defined in a variety of ways—not merely in relation to lack of awareness of memory impairment, but also to memory-related behavioral and functional deficits.

As seen in Figure 2, and as outlined in greater depth by Nelson and Narens (1990), four classic types of judgments have been used to measure memory *monitoring* and have subsequently formed the core of traditional experimental metamemory research: 1) *Ease-of-learning* (EOL) judgments, which occur in advance of information acquisition, are largely inferential, and pertain to items that have not yet been learned. These judgments are predictions about what will be easy or difficult to learn, either in terms of which items will be easiest or in terms of which strategies will make learning easiest; 2) *Judgments of learning* (JOL) occur during or after acquisition and are predictions about future test performance on currently recallable items; 3) *Feeling-of-knowing* (FOK) or tip-of-the-tongue judgments occur during or after acquisition (e.g., during a retention session) and are judgments about whether a currently non-recallable item is known and/or will be identified on a subsequent recognition test; and 4) *Confidence/Accuracy* judgments, which refer to the relationship between a person's predicted or perceived performance and their objective ability. These paradigms generate many objective

metacognitive metrics that can be calculated to measure the relationship between a person's predicted or perceived performance and their objective ability.

One primary approach that is used in classic metacognitive task frameworks, and was applied in the current study, is to examine *calibration bias* or *absolute accuracy of judgments*—that is, the extent to which individuals are generally over or under confident in their perception of their cognitive functioning. This methodology for evaluating metamemory, for example, involves measuring the discrepancy between a person's true, objective memory performance, and stated confidence in his or her memory functioning (i.e., assessed either *online* in the context of a traditional JOL or FOK task, or *offline* in the context of a subjective memory complaints questionnaire—as is done in the current study). Of note, I would like to underscore that metacognitive researchers have suggested there are many flavors of metacognitive report, but all involve the elicitation of subjective beliefs about one's own cognition (Fleming and Dolan, 2014). Thus, an absolute restriction to the aforementioned classic judgments is arbitrary, as metacognition refers to any judgment that is about one's thinking abilities.

Researchers have also found that distortions in metacognition may occur in cognitively normal and impaired people alike. Individuals with unimpaired cognitive functioning may exhibit distorted metamemory if, for example, they are blinded by some illusion due to the circumstances at hand (Dunlosky & Bjork, 1994; Metcalfe and Dunlosky, 2008). That said, disordered metamemory is most often present in those who have experienced stroke, head injury, illness, or neurodegenerative disease (Kashiwa et al., 2005). In AD, the reported prevalence of impaired metacognition ranges between 25% (Reed, Jagust, & Coulter L, 1993) and more than 80% of individuals (Conde-Sala et al., 2013); some of whom may engage in activities well beyond their true functional capacity (Starkstein et al., 2007). Of note, differences in criteria,

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point of measurement, and assessment methods, as well as the multidimensional aspect of awareness contribute to variations in the reported prevalence in dementia. In fact, there is considerable variability in the presentation and severity of disordered metamemory, with unawareness ranging from slight minimization to complete denial of problems (Clare, Marková, Verhey, & Kenny, 2005; Leicht, Berwig, & Gertz, 2010). In dementia, deficits in metacognition, in particular metamemory, have been well associated with worsening cognition and an increase in both dangerous behaviors and neuropsychiatric symptoms (Zanetti et al., 1999; Vogel et al., 2005; Starkstein et al., 2007).

Overestimation of, or overconfidence in memory functioning may explain the association between AD and a higher frequency of motor vehicle accidents (Hunt, Morris, Edwards, & Wilson, 1993; Hunt et al., 1997). Hunt and colleagues (1993; 1997) reported that one-third of these participants, who failed a road test, still considered themselves to be safe drivers. Similarly, patients with AD suffer a relatively high frequency of home and street accidents, and alert caregivers regularly avert many more negative events. Deficits in specific cognitive domains may at least partially account for this phenomenon. For instance, memory deficits may result in patients taking repeated doses of potentially toxic medications, forgetting they left the stove on, and leaving the front door open (a dangerous event in cities with a high-crime rate); spatial disorientation may contribute to patients getting lost in the street, or crossing the roadway recklessly; executive dysfunction may result in important financial losses; and motor vehicle accidents may result from a combination of various neuropsychological impairments. However, to the extent that patients are aware of their cognitive deficits, they may take steps to prevent such accidents from occurring (Hunt, Morris, Edwards, & Wilson, 1993; Hunt et al., 1997; Duchek et al., 1997).

In addition to concerns about patient safety, caregiver burden and mood disturbance also increase with loss of insight as patients become less compliant and harder to manage, often leading to transitions to higher levels of care (Turro-Garriga et al., 2013). A recent study found that a decline in patient insight predicted worse caregiver mood, in addition to burden—even in the Mild Cognitive Impairment (MCI) stage of disease before dementia is diagnosed (Kelleher et al., 2016). Metacognitive researchers have also suggested that the integral role for self-awareness in treatment choices raises the question of whether decisions regarding everyday functions are also compromised by reduced memory awareness. Poor metamemory among individuals with MCI and more progressed dementias may explain why patients who need assistance with daily tasks might make a less than optimal decision as to how to best carry out the task. Numerous studies have demonstrated that memory awareness in MCI and early AD significantly influences decision making abilities and the capacity to provide informed consent for a memory treatment (Cosentino et al., 2011).

Impaired self-awareness in the direction of over-confidence can also be a major problem preventing engagement in rehabilitation from brain injury or stroke. From a clinical perspective, a patient with low levels of self-awareness is likely to be unmotivated or uncooperative in therapy, set unrealistic goals, display poor judgement, or fail to see the need for compensatory strategies (Simmond & Fleming, 2003). Consequently, rehabilitation can be a frustrating exercise for both the patient and rehabilitation team (Sherer, Bergloff, Boake, High, & Levin, 1998; Sherer, Oden, Bergloff, Levin, & High, 1998; Malec & Moessner, 2000; Simmond and Fleming, 2003; Ownsworth, 2005). Contrastingly, individuals with higher levels of self-awareness are more likely to actively participate in rehabilitation, experience stronger therapeutic alliances, and achieve better rehabilitation outcomes in terms of level of community integration, social

functioning, and safety adherence (Leung & Liu, 2011). Of note, while self-awareness is generally regarded as a positive sign for involvement in rehabilitation, improvements in self-awareness have also been linked with the development of emotional distress such as depression and anxiety. For many individuals, self-awareness develops as time passes following injury or onset, and they begin to understand the full impact of their injury as they attempt to return to valued activities. This insight may trigger feelings of despair and hopelessness in patients as the persisting nature of their impairments becomes apparent.

Given the profuse functional implications of disordered awareness, researchers have sought to identify the factors that may impact or be associated with the phenomenon. Neurocognitive explanations of metacognition highlight the nature of brain pathology as the origin of awareness deficits, particularly with regard to lesion localization and cognitive dysfunction (McGlynn & Schacter, 1989). Psychological theories, however, recognize the possible contribution of premorbid mood and personality styles, and the motivated use of psychological defense mechanisms such as *denial* in blocking unpleasant thoughts from awareness (Weinstein, Friedland, & Wagner, 1994). Other explanations suggest that in some cases, or to some degree, unawareness of illness or cognitive dysfunction, might be a product of social and environmental factors. The multi-faceted and complex nature of awareness calls for a broad conceptual framework, encompassing a diverse range of possible influences when seeking to understand awareness-related phenomena in clinical situations. Therefore, theoretical models of unawareness may have greater clinical utility if they allow for the possibility of integrating neurological, psychological, and socioenvironmental levels of explanation (Clare et al., 2011a).

In accordance with a biopsychosocial approach, the following three studies, which comprise this dissertation, explore the psychological and neuropathological factors associated with

metacognition. Study 1 examines the psychological characteristics associated with metamemory in a healthy, community-dwelling cohort of older adults. Study 2 goes beyond metamemory, and examines the association between these psychological characteristics and metacognition more broadly (i.e. metalanguage and meta-executive function) in a neurologic cohort of older adults with Essential Tremor (ET). Study 3 utilizes postmortem neuropathological evaluations of the ET participants from Study 2, in an effort to investigate the neural substrates that may contribute to disordered awareness. All three experiments are novel in concept, design, and statistical approach.

CHAPTER II: STUDY 1: EXAMINING THE ASSOCIATION BETWEEN METAMEMORY AND PSYCHOLOGICAL CHARACTERISTICS IN A HEALTHY, COMMUNITY-DWELLING COHORT OF OLDER ADULTS

As discussed in the introduction, overestimation of memory functioning has been shown to have important clinical implications for both the patient and caregiver; indeed the same may hold true for underestimation of one's abilities. Disordered metamemory, in the direction of under-confidence, among older adults may have particular implications for the diagnosis of Subjective Cognitive Decline (SCD)—a state hypothesized to precede objectively apparent cognitive symptoms of Alzheimer's disease, and hold promise as a preclinical indicator of AD (Buckley et al., 2016). SCD is generally characterized by subjective memory deficits, which may or may not be indicative of an underlying degenerative illness. Recent work has suggested that in the context of mild cognitive impairment (MCI), reliance on subjective memory complaints as a diagnostic criterion contributes to false classifications among the worried well (Jessen et al., 2014; Edmonds et al., 2014). Further, studies have long shown an inconsistent relationship between subjective memory complaints (SMC) and objective memory performance (OMP)— both of which are considered to be the building blocks of metamemory—among participants with MCI (Roberts, Clare, & Woods, 2009; Lenehan, Klekociuk, & Summers, 2012; Buckley et

al., 2013; Studer, Donati, Popp, & von Gunten, 2014). According to Edmonds and colleagues (2014), there are multiple factors that could account for this disparity between SMCs and OMP, including the possibility that the relationship is explained in part by emotional factors and personality features (Reid & MacLullich, 2006; Studer, Donati, Popp, & von Gunten, 2014).

Indeed, in non-demented older adults, researchers have demonstrated that psychological variables are associated with the perception of cognition, SMCs, and objective cognitive performance (OCP) individually (e.g. Comijs et al., 2002; Steinberg et al., 2013). Specifically, meta-analyses have revealed associations between increased SMCs and affective distress, depression, and anxiety—even when objective cognitive measures were normal (Binder, Storzbach, Rohlman, Campbell, & Anger, 1999; Pereira et al., 2010; Balash et al., 2012).

In regards to specific personality characteristics, a recent study utilizing the NEO-FFI indicated that impaired OCP in older adults is associated with high neuroticism, whereas high conscientiousness and openness and lower extraversion were associated with better memory performance concurrently and less decline over time (Luchetti et al., 2015). Neuroticism in particular, which is the tendency to experience negative emotions and involves difficulties with impulse control, has been related to poorer performance on cognitive tasks across a number of studies; researchers have also postulated that trait anxiety relates to negative bias in selective attention and other cognitive functions (Williams et al., 2010; Eysenck, 1967; Meier, Perrig-Chiello, & Perrig, 2002; Booth et al., 2006; Boyle et al., 2010; Soubelet & Salthouse, 2011).

Unfortunately, due to the multifarious approaches to personality research, the literature is large, but poorly integrated (e.g., Pearman & Storandt, 2004). There does not appear to be consensus regarding the relationship between SMCs and personality traits; however, many studies have suggested that individuals low in extraversion and high in neuroticism, for example,

tend to report more complaints about their memory (Geerlings, Jonker, Bouter, Adèr, & Schmand, 1999; Steinberg et al., 2013). Importantly, these findings make sense when viewed through the lens of self-evaluation schemas. Self-evaluation schemas represent stable psychological traits, which encompass individuals' subconscious, fundamental evaluations about themselves, their own abilities and their own control. People who have more positive self-evaluations will think positively of themselves and be confident in their own abilities. Conversely, those with more negative core self-evaluations will have a negative appraisal of themselves and may lack confidence (Judge, Locke & Durham, 1998).

While numerous studies have demonstrated the association between psychological variables and subjective cognition (SC), to the best of my knowledge, no research study has examined the relationship between psychological variables and the *accuracy* of SC (i.e., metacognition) in non-demented older adults. Clare and colleagues (2011a) examined this question in dementia, finding that a larger discrepancy score between self-ratings of cognitive performance and caregiver report (indicating lower awareness) was associated with higher levels of anxiety and depression among participants. However, such studies have typically only utilized subjective ratings of cognitive functioning (i.e. clinical ratings of anosognosia or a discrepancy score between caregiver and self-ratings) rather than comparing self-report to an objective measure of performance (Clare, Marková, Roth, & Morris, 2011c; Clare et al. 2011b). Thus, little is known about the extent to which premorbid, psychological factors such as mood and personality traits influence metamemory accuracy prior to any metacognitive impairment that emerges in the context of dementia (i.e., unawareness of memory loss) or neural injury. The current study addresses whether a composite of both personality and mood (CPM) is associated with an offline, objective measure of metamemory in a community-based sample of older adults.

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## HYPOTHESES AND PREDICTIONS

*Prediction 1*: Are there distinct patterns of mood and personality that relate to metamemory confidence accuracy?

*Hypothesis 1:* Patterns of high extraversion, low anxiety, low depression, and low neuroticism will be associated with more accurate metamemory; while patterns of low extraversion, high anxiety, high depression, and high neuroticism will be associated with less accurate metamemory in the direction of under-confidence in cognitive functioning.

*Hypothesis 2:* Demographic factors, including age, education, and gender might influence these associations. Ethnicity is excluded from analyses given the relative homogeneity of the sample in Study 1.

## METHOD

### PARTICIPANTS

Data were obtained from the Nathan Kline Institute Rockland Sample Initiative (NKI-RSI), a community-ascertained lifespan sample (approx. N = 1,200) from the northern suburban area of New York City, USA. Ethnic and economic demographics of Rockland, and the surrounding counties, resemble those of the United States (U.S. Census Bureau, 2009)—increasing the generalizability of the NKI-RSI to the broader U.S. population. Participants were recruited via advertisements flyer mailings, posting of materials in local shops, community talks, street fairs, and various meeting places. Enrollment efforts were used to avoid over-representation of any portion of the community, and to ensure faithful representation of Rockland County. For a full description of the methodology of collection and sampling procedures, see Nooner and colleagues (2012). This study is in compliance with the Columbia University Institutional Review Board (IRB).

*NKI-RSI Exclusion Criteria.* General NKI-RSI study criteria included residents of Rockland, Bergen, Orange and Westchester counties, aged 6-85, who were fluent in English with capacity to understand the study and provide informed consent. General NKI-RSI exclusions were assessed over a screening phone call or determined at the time of study participation by the research team, and included chronic medical illness, history of neoplasia requiring intrathecal chemotherapy or focal cranial irradiation, history of leukomalacia or static encephalopathy, other serious neurological (specific or focal) or metabolic disorders, including epilepsy (except for resolved febrile seizures), history of traumatic brain injury, stroke, aneurysm, HIV, carotid artery stenosis, encephalitis, dementia, Huntington's Disease, Parkinson's, hospitalization within the past month, contraindication for MRI scanning (metal implants, pacemakers, claustrophobia, metal foreign bodies or pregnancy), or inability to ambulate independently. Individuals with an Estimated FSIQ below 66 (WASI-2nd Edition; Wechsler, 2011) determined at study visit were excluded from the study. Other exclusionary criteria included acute unipolar depression, bipolar disorder, autism spectrum disorders, psychosis or suicidal/homicidal ideation; a history of chronic or acute substance dependence disorder; history of psychiatric hospitalization, and suicide attempts requiring medical intervention, which were determined through self-report at screening or at study visit via diagnostic interview (SCID-I/NP) (First, Spitzer, Gibbon, & Williams, 2002). The current study participants were drawn from the larger NKI-RSI data set and consist of a community-representative sample of 157 older adults aged 50-85 years, (mean 64.48; SD = 8.79; median = 65.00 years). A score of 23 or above on the Montreal Cognitive Assessment (MoCA) (Trzepacz, Hochstetler, Wang, Walker, & Saykin, 2015) was also required for inclusion in these analyses. For full demographics and clinical information about the sample, see Table 1.

**MEASURES**

*Demographics*. The demographics questionnaire (DEMOS) is a self-report measure collecting age, sex (Male or Female), race (American Indian or native Alaskan, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other Race) and native language (English, Spanish, Asian dialect, African dialect, Indian dialect, Other).

*Cognitive Failures Questionnaire (CFQ)*. The CFQ is a 25-item self-report questionnaire assessing failures in perception, memory, and motor function in the completion of everyday tasks in the past 6 months. Individuals are asked to rate the frequency of experiences and behaviors on a 5-point scale: 0-Never, 1-Very rarely, 2-Occasionally, 3-Quite often, and 4-Very often. A higher score on the CFQ suggests that the individual has a higher number of cognitive complaints (Broadbent, Cooper, FitzGerald, & Parkes, 1982).

*Cognitive Failures Questionnaire-Memory (CFQ-M)*. For the purposes of the current study, a seven-item subscale was compiled on both theoretical and empirical bases to assess judgments specifically about the frequency of memory failures. 7 items (2, 6, 12, 16, 17, 20, 23) were selected based on their content as memory-related (i.e., Do you find you forget appointments?), and their overlap with items included in a validated memory complaint scale (Subjective Memory Complaints Questionnaire; Youn et al., 2009). Additionally, a Confirmatory Factor Analysis in the current study found that these seven items loaded highly on one factor (Table 2). The Kaiser-Meyer-Olkin measure of sampling adequacy was .78, above the recommended value of .6, and Bartlett's test of sphericity was significant ($\chi^2$ (21) = 227.43, $p < .01$). Individuals' total score was calculated as the sum of the seven items. This score was converted to a z score based on the mean and SD of the current sample and, for ease of interpretation, the score was then

inverted such that higher z-scores suggest that the individual perceives him or herself as higher functioning or having fewer memory complaints.

*Rey Auditory Verbal Learning Test (RAVLT).* The RAVLT (Rey, 1941) is a sensitive and commonly used measure of verbal learning and memory—assessing a person's ability to encode, consolidate, and retrieve verbal information (see Roberts & Schmidt, 1996, for a review; e.g. Butters, et al., 1985; Bigler et al., 1989). Performance on the RAVLT is reported to be generally insensitive to depression and anxiety with scores that do not differ meaningfully from healthy peers (e.g., Query & Megran, 1983; Davidoff et al., 1990; Roberts & Schmidt, 1996; Schoenberg et al., 2006). During the test, the examiner reads aloud a list of 15 words. The participant is then asked to repeat all words from the list that he/she can remember. This procedure is carried out six times to create a total Immediate Recall score. After an interference trial and a 20-minute delay, the participant is again asked to recall as many words as possible from the first list (i.e., Delayed Recall score). Scores were calculated as the average performance of Immediate and Delayed Recall, and then converted to z-scores based on the mean and standard deviation (SD) of the current sample.

*Metamemory Index (MMI).* The global, *offline* MMI was computed as the discrepancy between the CFQ-M and RAVLT z-scores (CFQ-M – RAVLT) with higher scores reflecting over confidence and lower scores reflecting under-confidence. I utilized an *offline* evaluation (i.e. a retrospective, crystallized notion of what their memory abilities are) as opposed to an online evaluation (i.e. perception of memory abilities while engaged in a memory task), due to its rich reflection of everyday, real world levels of awareness (Fleming & Frith, 2014; Cosentino, Metcalfe, Cary, De Leon, & Karlawish, 2011).

*Personality Measure.* The NEO Five Factor Inventory (NEO-FFI-3) is a 60-item psychological inventory that was used to assess the five major dimensions of personality: Openness to Experience, Conscientiousness, Extraversion, Agreeableness, and Neuroticism. Participants are asked to select the response that best represents their opinion on a 5-point scale: 0-Strongly Agree, 1-Agree, 2-Neutral, 3-Disagree, 4-Strongly Disagree. Scores were standardized, controlling for gender (McCrae & Costa, 2010).

*State Trait Anxiety Inventory (STAI).* The STAI is a 40-Item self-report questionnaire designed to separately evaluate state (A-State) and trait (A-Trait) anxiety in adults. The test is divided into two sections, each with twenty questions. The first subscale measures state anxiety; the second measures trait anxiety. Each 20-question measure uses ratings on a 4-point scale: 1-Almost never, 2-Sometimes, 3-Often, and 4-Almost always. Affectivity ranges from immediate, transitory emotional states, through longer-lasting mood states, through dynamic motivational traits, ranging up to relatively enduring personality traits (Boyle, Saflofske, & Matthews, 2015).

*Geriatric Depression Scale (GDS).* The GDS is a 30-item self-report assessment used to identify depression in the elderly (ages 65 and older). The participant is asked to respond "Yes" or "No" to a series of questions about how they have felt over the past week. Participants are then scored as normal (with total score of 0-9); mild to moderate depressives (10-19); or severe depressives (20-30) (Yesavage et al., 1982; 1986).

*Beck Depression Inventory (BDI-II).* The BDI-II is a 21-item self-report questionnaire assessing the current severity of depression symptoms in adolescents and adults (ages 13 and up). It is not designed to serve as an instrument of diagnosis, but rather to identify the presence and severity of symptoms consistent with the criteria of the DSM-IV. Questions assess typical symptoms of depression such as mood, pessimism, or sense of failure. Participants are asked to pick a

statement on a 4-point scale that best describes the way they have been feeling during the past two weeks. A total score of 0-10 is considered within the normal range, 11-30 is mild to moderate, and 31+ is severe (Beck, Steer, & Brown, 1996).

*Depression Composite Score (DCS).* Due to the nature of the data procedure, 72 participants in our sample were administered the GDS and 80 were administered the BDI-II. Given that studies (Stiles & McGarrahan, 1998) have demonstrated the high correlation and convergent validity between the GDS and BDI-II, participants were assigned to one of three groups based on the interpretive label they received on either the GDS or BDI-II: normal (0), mild to moderate (1), or severe (2). Both the GDS and BDI-II been shown to have high content, construct, and criterion validity, and high internal consistency.

## DATA ANALYSIS PLAN

The primary goal of this analysis is to examine the relationship between the composite of mood and personality (CPM) and the global, offline metamemory index (MMI).

I first performed a Latent Class Analysis (LCA) using MPLUS 7.1 (Muthén & Muthén, 1998) to identify discrete, heterogeneous patterns of personality traits and mood (i.e. anxiety and depression scores). LCA models latent clusters of subjects (or classes) using robust maximum likelihood estimation, such that the classes explain the relationship between multivariate variables (i.e. the probability of the variables scores breaks down into a product of univariate response probabilities conditional on the latent classes). I compared nested unconditional LCA models characterized by a progressive number of classes. All variables were standardized to assist model convergence. The optimal number of classes was estimated combining information from conventional model fit indices (Nylund, Asparouhov, & Muthén, 2007), including Bayesian

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Information Criterion (BIC), sample-size adjusted Bayesian Information Criterion (SSBIC), and Aikaike information criterion (AIC). Greatest weight was placed on the BIC and SSBIC due to evidence that they are the strongest indicator of relative fit under these analytic circumstances (Muthén & Muthén, 2006). The least weight was placed on the AIC because of evidence that it tends to favor over specification (Henson, 2007). Additionally, relative Entropy indicated the clarity of class specification, with scores ranging from 0 to 1. Entropy values closer to 1 suggest better fit of the data into the prescribed class structure (Duncan, Duncan, & Strycker, 2006). Furthermore, the nested models were compared using the Lo-Mendell-Rubin Adjusted Likelihood Ratio Test (LMR), and Bootstrapped Likelihood Ratio Test (BLRT). The LMR compares improvement of fit between nested model solutions with an increasing $k$ number of classes (Lo, Mendell, & Rubin, 2001). LMR significance is derived from the comparison of the derivatives of a $k$ class model's likelihood ratio chi-square test with those of the $k$-1 class model. Similarly, the BLRT (McLachlan, & Peel, 2004) is a bootstrapped comparison of the loglikelihood difference of the nested models (Nylund, Asparouhov, & Muthén, 2007). Non significance of either the LMR or BLRT suggests that the one less class solution is a better fit for the data (Asparouhov & Muthén, 2012). Lastly, explanatory properties, parsimony and interpretability were also considered to determine the optimal number of classes (Muthén, 2004).

I then performed a GLM to examine whether MMI (as a continuous variable) differed as a function of the participants' LCA class membership assignments. I investigated the associations of metamemory (confidence/accuracy judgments) with CPM by regressing MMI on the derived classes while controlling for age, gender, and education. Finally, I ran one sample t-tests on metamemory scores in the LCA classes, to determine whether the scores for each class

differed significantly from zero (i.e. whether each class was significantly over, under, or accurate in their perception of memory). I used an alpha level of .05 for all statistical tests.

## RESULTS

Table 3 displays relative model fit from 1 to 3 class solutions for the unconditional LCA. Results indicated that the LMR likelihood ratio test was not significant for the three class solution. As such, the LMR suggested that the two class model was a more appropriate fit for the data than its neighboring three class solution. Among the remaining solutions, the two class model was the one with the best fit in terms of AIC, BIC, SSBIC, and higher relative entropy; furthermore, the LMR and BLRT for the two class solution were both significant. Taken together, information from the fit indices proved that the two class model was the optimal solution. Figure 3 displays the two class solution, characterized by distinct patterns of mood and personality scores. The best log-likelihood value of the model replicated, indicating successful convergence. The first CPM Class (N= 118, 74.4% sample) was characterized by predominantly low neuroticism and low anxiety, and high extraversion and high conscientiousness. The second CPM Class (N= 39, 24.6%) was characterized by predominantly high neuroticism and high anxiety, and low extraversion and low conscientiousness.

A generalized linear model (GLM) was performed to examine whether MMI differed as a function of the emergent CPM class membership, while covarying for age, education, and gender (for full estimates, see Table 4). The model was significant ($F_{(4,151)} = 5.54$, $p < .001$) and accounted for 13.2% of the variance ($\eta2=0.13$). Separate one sample t-tests (Table 4a) indicated that individuals assigned to Class 1 demonstrated accurate metamemory (M = 0.19, SD = 1.26; t(111) = .12, $p$ = 0.12), while individuals in Class 2 demonstrated under-confidence (M = -0.52, SD = 1.41; t(38) = -2.32, $p$ = 0.02). Results suggest that individuals who exhibit characteristics

of low neuroticism and low anxiety, and high extraversion and high conscientiousness tend to be accurate in their perception of their memory functioning; whereas, individuals who exhibit characteristics of high neuroticism and high anxiety, and low extraversion and low conscientiousness tend to underestimate their cognitive functioning. Further analysis (Table 4b) revealed gender differences such that men significantly overestimated their memory abilities (M = 0.44, SD = 1.33), t (44) = 2.24, $p$ = 0.03, whereas women tended to be accurate in their perception of their memory abilities (M = -0.18, SD = 1.29), t (105) = -1.45, $p$ = 0.15. Levene's test of equality of error variance was not significant (F (1, 149) = 1.17, $p$ = 0.28).

## DISCUSSION

Study 1 investigated the association between metamemory and characteristics of personality and mood (CPM). The ability to estimate one's own performance accurately has been shown to be important for managing everyday situations safely and effectively, and for remaining independent (West, Dennehy-Basile, & Norris, 1996; Clare, Marková, Roth, & Morris, 2011). Metamemory may also be important for psychological well-being, since overestimation of ability carries risk of failure, while underestimation could lead to avoidance of activities and further loss of skills and confidence. For individuals in the mild to severe stages of AD, when distortions in evaluative judgments intensify, interventions (i.e. provision of contextual cues and environmental support) could aim to improve accuracy of performance monitoring in real life situations to support more effective coping with deficits (Clare, Marková, Roth, & Morris, 2011). For those who significantly underestimate their functioning—and express greater concerns that they may not be remembering as well as before—clinicians should pay careful attention to objective measures of performance (i.e. to reduce the prevalence of

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misdiagnosis of amnestic MCI), and might consider explicitly conveying the differences between normal and abnormal aging to their patients.

Ultimately, I examined metamemory by comparing offline, *global* estimations (i.e. retrospective assessments of general performance in a given area) to objective memory performance in order to determine the extent to which individuals overestimated, underestimated, or made accurate estimations of their memory abilities. The multi-faceted and complex nature of awareness calls for a broad conceptual framework—encompassing a diverse range of possible influences when seeking to understand awareness-related phenomena in clinical situations. This study was designed to explore whether latent classes of mood and personality explain a significant proportion of the variance in metamemory. Although previous research in non-demented elders has found that individual psychological factors are associated with SMCs (e.g. Binder, Storzbach, Rohlman, Campbell, & Anger, 1999; Balash et al., 2013), I sought to take a holistic approach and examine both the stable and changeable psychological characteristics that might influence the accuracy of SMCs (i.e. metamemory). The current results indeed yielded two primary mood and personality patterns—the first of which was characterized by predominantly high extraversion, with low anxiety and low neuroticism. Contrary to hypotheses, rather than low depression, the final component of the profile was high conscientiousness (i.e. all of which together comprises Class 1). Of note, I found that the sample exhibited normal to mild depressive affect, which may explain in part why depression did not differ significantly across the two classes. The second class was characterized primarily by high anxiety and high neuroticism, and low extraversion and low conscientiousness. Our findings substantiated our primary hypothesis that distinct patterns of mood and personality are associated with metamemory accuracy, as I found that Class 1 and Class 2 differed significantly in this

regard. Moreover, I found that individuals who exhibited characteristics of low neuroticism and low anxiety, and high extraversion and high conscientiousness tended to be accurate in their perception of their memory functioning. In contrast, individuals who exhibit characteristics of high neuroticism and anxiety and low extraversion and conscientiousness tend to underestimate their cognitive functioning. These results underscore the need for clinicians to take into consideration psychological characteristics, like mood and personality in their evaluation of the factors that may contribute to variability in patients' metamemory.

Our findings regarding latent classes of mood and personality are generally consistent with the literature—that is, studies have repeatedly demonstrated a positive correlation between anxiety and neuroticism, and a negative correlation between extraversion and these two constructs across the lifespan (Costa & McCrae, 1992; Timoney & Holder, 2013). In Clark and Watson's (1991) tripartite model, they assert that anxiety and depression not only have a shared component of negative affect or general distress (potentially corresponding to the construct of neuroticism) but also maintain the unique components of "anxious arousal" (autonomic hyperactivity) and "anhedonic depression" (low positive affect). A likely interpretation of the high correlations observed among indices of anxiety and neuroticism is that they tap, at least in part, into a common underlying construct (Bishop & Forster, 2012).

Previous research has also suggested that mood and personality traits (as measured by the NEOFFI) may be associated with different styles by which individuals guide their self-evaluation schemas (Judge, Locke, Durham, & Kluger, 1998). The stable patterns of mood and personality elucidated in this study may represent or map onto biases in self-evaluation, which may in turn distort the accuracy of estimations about cognitive functioning. Although previous studies provide important insights into how different traits are associated with SMCs and self-evaluation

schemas, they fail to establish what the association is between these premorbid characteristics and the integrity of metamemory processes. Furthermore, studies examining metamemory with online, objective paradigms (e.g. FOK and JOL) have largely dismissed these factors in their studies. Thus, I attempted to bridge the gap, and examine the extent to which personality traits and mood factors could explain variance in memory knowledge. I discuss in brevity the relationships between these premorbid characteristics, self-evaluation schemas, and metamemory accuracy.

**Neuroticism and STAI.** The domain of neuroticism consists of such negative affect states as anxiety, angry hostility, self-consciousness, vulnerability, and depression. Individuals who are highly neurotic may possess limited social networks and demonstrate difficulties coping with psychological stress and regulating negative affect (Costa & McCrae, 1992). At the opposite end of the spectrum, individuals who score low on neuroticism are more emotionally stable, less reactive to stress and—though low in negative emotion—not necessarily high in positive emotion; importantly, these individuals tend to report higher levels of well-being and life satisfaction (Passer & Smith, 2011). Research on self-evaluation schemas suggest that individuals with high anxiety and elevated levels of neuroticism (i.e. Class 2) may develop a greater sensitivity to negative outcomes, and subsequently maintain a negative self-appraisal. Studies have demonstrated that neuroticism and anxiety are highly correlated with pessimism, and negatively correlated with optimism and self-esteem (Williams, 1992; Amirkhan, Risinger & Swickert, 1995). Data from the current study may suggest that persons high on neuroticism and anxiety may be more likely to draw on negative conceptions about themselves (i.e. regarding declining memory) irrespective of their actual level of functioning, and may subsequently underestimate their true ability.

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**Conscientiousness.** Individuals high in conscientiousness (Class 1) are distinguished as being organized, persistent, goal-oriented, and disciplined (McCrae & Costa, 2003). Though extraversion (discussed below) and neuroticism seem to have the largest effect on subjective well-being, conscientiousness has also been shown to correlate with positive affect and optimism (DeNeve, & Cooper, 1998; Steel, Schmidt, & Shultz, 2008). Conscientiousness, which often develops in childhood and remains unchanged in adulthood, manifests in characteristic behaviors such as being thorough and deliberate in one's actions (McCrae, 2004). When taken to extremes, these individuals are often labeled as "perfectionists," "workaholics," or compulsive in their behavior (Carter, Guan, Maples, Williamson, & Miller, 2016). Through a self-evaluation lens, those who are higher on conscientiousness may be more meticulous in nature, and subsequently accurate in their perception of their cognitive abilities.

**Extraversion/Introversion.** Extraversion refers to a wide variety of traits including warmth, gregariousness, assertiveness, activity, excitement seeking, and of greatest relevance: a tendency to experience positive affect (Costa & McCrae, 1992; McCrae & Costa, 2003). Conversely, individuals who score lower on extraversion or higher on introversion (i.e. Class 2), are typically more reserved and self-reflective (Sipps & Alexander, 1987). Psychologists like Jung have characterized introverts as people whose energy tends to expand through reflection and dwindle during interaction. Eysenck (1963) similarly characterized extraversion/introversion as the degree to which a person is outgoing and interactive with the world. He postulated that these behavioral variances are presumed to be the result of underlying differences in brain physiology (Eysenck, 1963). While extraverts seek excitement and social activity in an effort to heighten their arousal level and positive affect, introverts tend to avoid social situations in an effort to keep such arousal to a minimum. He theorized that extraversion is a combination of two

major tendencies: impulsiveness and sociability—later adding such traits as liveliness, activity level, and excitability. Extraversion has been repeatedly understood as a facilitator of social interactions (McCrae & Costa, 1991; Zelenski & Larsen, 1999; Lucas, Le, & Dyrenforth, 2008) since low cortical arousal may result in extraverts seeking more social situations in an effort to increase arousal (Eysenck, 1967). In accordance with Eysenck (1967), McCrae and Costa (1991) put forth the *social activity hypothesis* to explain the greater subjective well-being among extraverts. They suggest that higher extraversion (as seen in Class 1) helps in the creation of life circumstances, which in turn promote higher levels of positive affect and a more positive self-evaluation schema than does high introversion, high anxiety, and/or high neuroticism (Class 2). The strong correlation demonstrated in numerous studies between extraversion and both positive self-schemas and optimism aligns with our findings that individuals with a more extraverted profile—though accurate in their metacognitive abilities —tend more towards overestimation rather than underestimation (Williams, 1992; Amirkhan, Risinger & Swickert, 1995).

Investigating the long standing or "premorbid" characteristics of an individual that influence biases in self-related judgments, not only provides information about how self-judgments are formed, but informs the factors that contribute to impaired metamemory in the context of aging and disease (Cosentino, Metcalfe, Steffener, Holmes, & Stern, 2011). The present study supports a biopsychosocial approach to understanding self-assessment and examining awareness in a healthy aging population (Clare, Marková, Roth, & Morris, 2011). In the context of SCD, our research lends credence to concerns that SMCs alone are not sufficient indicators of cognitive decline, and may in fact contribute to misdiagnosis of MCI. Indeed, Jessen and colleagues (2014), in their consensus report on the diagnosis of SCD, point to the association between SCD and both mood and personality traits. They acknowledge the

previously reported link between SCD and neuroticism and anxiety, and the inverse association with openness and conscientiousness. The current work provides additional information in this regard, directly showing that not only are certain psychological variables associated with cognitive complaints, but such complaints are on average, inaccurate underestimations of actual functioning. Current results highlight the psychological variables that come into play within the biopsychosocial framework and provide evidence for the hypothesis that metamemory processes are subject to a range of influencing factors that may constitute barriers to accurate self-knowledge (Greenwald, 1980; Gergen, 1984).

**Limitations and Future Directions.** The current study has both strengths and limitations. A significant strength, which I discussed earlier, is that this is the first attempt to our knowledge to both uncover discrete classes of mood and personality in an aging population, and to study whether metamemory is associated with distinct patterns of mood and personality. However, there are a few limitations to this study that are important to address.  First, our selected subjective memory instrument was a modified version of an existing SCC questionnaire (i.e., CFQ), thus potentially raising questions about the reliability and validity of the modified scale. However, in creating the CFQ-M, I used factor analysis to ensure the items plotted onto a single construct (memory) and also ensured that the items selected were consistent with those found in a reliable and validated memory complaint scale (Subjective Memory Complaints Questionnaire) developed by Youn et al. (2009). Second, though a strength of this study is that it utilizes an objective measure of metamemory by comparing memory ratings directly to memory performance, I acknowledge that the metamemory rating was an offline evaluation (i.e. a crystallized notion of what their memory abilities are) as opposed to an online evaluation of metamemory experience (i.e. perception of memory abilities while engaged in an ongoing

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memory task). It remains unknown in which way the emergent classes of mood and personality would relate to an online metamemory evaluation like FOK or JOL. That said, it has been shown that online and offline measures are correlated in individuals with AD, and that there may be significant benefits to using an offline, global subjective measure (Cosentino, Metcalfe, Butterfield, & Stern, 2007). For example, the offline measure is rich in its reflection of everyday, real world levels of awareness. In some respects, offline scores may be better able to inform practically and clinically relevant issues including the extent to which participants appreciate their need for assistance or devise strategies for completing cognitively demanding activities (Cosentino, Metcalfe, Cary, De Leon, & Karlawish, 2011; Fleming & Frith, 2014). An area of debate related to this limitation is that there remains some question as to the convergent validity between subjective cognitive questionnaires (e.g. CFQ-M or an Activities of Daily Living Questionnaire) and task-specific, neuropsychological measures of cognition (e.g. RAVLT). This is an issue that unfortunately plagues many metacognitive studies, which utilize neuropsychological measures with questionable ecological validity. It remains unclear to what extent the clinically-relevant questions in our CFQ-M map conceptually and directly onto the RAVLT; said differently, a reasonable area of contention is whether there is adequate convergence between a long term list-learning task and a comprehensive evaluation of common, everyday memory complaints. For this reason, I do not operationalize our MKI as memory *monitoring*, but instead characterize the construct I am measuring as a more generalized knowledge of memory abilities. Nonetheless, the significant difference, and the direction of the difference in average metamemory confidence across LCA groups, suggests that individuals with certain personality features tend more towards underestimation of abilities than those without such features—regardless of the absolute agreement that is to be expected between the subjective

and objective measurements of memory in the general population. Third, our use of a Depression Composite Score (DCS) rather than a single, consistent measure of depression is a limitation in this retrospective study, and any extrapolation should be made carefully. Ideally, the BDI or a more comprehensive measure of depression would have been available in all participants. Our decision to group participants based on the interpretive label they received on the GDS and BDI-II aligns with numerous studies that have demonstrated a high correlation and convergent validity between these two measures of depression. In addition, our sample was fairly homogeneous (see Table 1), and results may not generalize to a larger and more diverse population. A final limitation is the cross sectional nature of the study. Based on previous personality literature, I made the assumptions that 1) personality is a stable, lifelong construct that is not subject to change significantly without deliberate intervention and 2) metacognition is something that can be changed in the context of the aging brain. Future research might consider exploring CPM and metamemory at multiple points in time to determine whether change in one predicts change in the other.

These issues notwithstanding, our results reveal that discrete patterns of mood and personality are associated with metamemory accuracy within a community-dwelling, non-demented cohort of older adults. More research is needed to explore questions about the extent to which metamemory changes as a function of these premorbid characteristics both across the lifespan and across a range of neurodegenerative diseases, including dementias and movement disorders.

CHAPTER III: STUDY 2: EXAMINING THE ASSOCIATION BETWEEN
METACOGNITION AND PSYCHOLOGICAL CHARACTERISTICS IN A NEUROLOGIC
COHORT OF OLDER ADULTS WITH ESSENTIAL TREMOR

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The purpose of Study 2 is to contribute to our understanding of the psychological characteristics associated with metacognition in a neurologic sample of older adults. Study 2 builds upon Study 1, which found that latent classes of mood and personality accounted for a significant proportion of the variance in metamemory. However, given that the sample from Study 1 is distinct from the sample in the final two studies, these initial findings serve only as the conceptual bedrock—no direct statistical comparison will be made between these two cohorts.

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Essential Tremor (ET) is the most common pathological tremor in humans; in some studies, twenty times more prevalent than Parkinson's disease (Rautakorpi et al., 1982). In the United States alone, thirteen million people are estimated to be affected, and the condition is clearly global, affecting human beings in a variety of settings, ranging from remote to urban areas (Lundervold & Poppen, 1995). ET is a deceivingly simple clinical syndrome that is associated with a complex web of clinical, pathological, and genetic phenomena (Elble, 2013). Despite being such a common disease, little progress was made up until the last few decades in terms of understanding the underlying mechanisms.

The traditional view of ET is as a *mono-symptomatic* condition characterized by action, or kinetic, tremor. However, over the past two decades, researchers have learned that this picture is an oversimplification. The emerging view of ET is that it is a pathologically heterogeneous neurological disease characterized by a number of motor and non-motor features that accompany the recognizable kinetic tremor (Louis et al., 2001; Lombardi et al., 2001). It is debated whether

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the non-motor manifestations—most prominenctly, psychological and cognitive changes—in ET

result from widespread neurodegeneration beginning with cerebellar compromise, or are merely

secondary to impaired motor functions and reduced quality of life resulting from tremor. That

said, there is growing literature supporting the hypothesis that ET patients have characteristic

personality traits and mood changes (i.e. increased anxiety and depression), as well as

impairment in several domains of cognition that is dissociable from tremor severity itself. Before

discussing the literature on the cognitive profile of ET, I briefly review the psychiatric features

associated with the disease.

**Essential Tremor and Psychiatric Features.** The hypothesis that ET is more than a motor

disorder has become established in recent years, with many studies highlighting the cognitive

changes in patients; however, studies have only begun to explore the psychological profile of ET

(Chatterjee, Jurewicz, Applegate, & Louis, 2004). Of the few studies (e.g. Chatterjee et al., 2004;

Thenganatt et al., 2012) that have examined personality traits in ET, a tridimensional personality

questionnaire (i.e. harm avoidance, novelty seeking and reward dependence) was utilized rather

than the more traditional five factor model implemented in this study. Lorenz and colleagues

(2006) employed a revised version of the Eysenck Personality Questionnaire (EPQ-R) in a

German population; the EPQ-R measures three dimensions of personality: extraversion (E),

neuroticism (N), and psychoticism (P). They reported a significantly lower score on the P-scale

of the EPQ-R, suggesting that ET patients are kinder, more tender-minded, and less aggressive

than the normal cohort. Other studies lend support to the hypothesis that ET patients are more

anxious and depressed compared to controls, and that anxiety significantly affects their ability to

perform daily activities (E.g. Louis et al. 2001; Dogu et al., 2005). Lombardi and colleagues

(2010) reported higher levels of depression in persons with ET as compared to normal controls,

and Duane and Vermilion (2002) described prevalence rates of 49% for depression and 55% for anxiety in those diagnosed with ET. However, there have been conflicting reports regarding the correlation of self-reported anxiety and depression with tremor scores, and it remains unclear whether high negative affect among ET patients is due to underlying ET pathology, a secondary pathological diagnosis (e.g. AD), or if it is a derivative phenomenon (i.e. a response to the tremor) (Schuurman et al., 2002; Huey et al., 2018). Thus, the lack of consensus makes it difficult to determine whether there is a consistent psychological profile related to ET.

**Essential Tremor and Cognition.** During the past decade, clinical literature has supported the hypothesis that the cerebellum might be centrally involved in ET. First, cerebellar-like problems, with abnormalities in tandem gait and balance, have been repeatedly described in ET patients (Singer, Sanchez-Ramos, Weiner, 1994; Hubble et al., 1997; Stolze et al., 2001; Klebe et al., 2005; Parisi, Heroux, Culham, & Norman, 2006). Intention tremor of the hands occurs in 58% of ET patients (Deuschl et al., 2000; Koster et al., 2002), and, in 10% of ET patients, intention tremor spreads to the head (Leegwater-Kim et al., 2006). Second, unilateral cerebellar stroke has been reported to abruptly terminate ipsilateral arm tremor in ET (Dupuis, Delwaide, Boucquey, & Gonsette, 1989) and cerebellar outflow pathways are the target of deep brain stimulation, which is an effective treatment for ET (Benabid et al., 1993; Schuurman et al., 2000). In addition, numerous neuro-imaging studies have provided evidence of cerebellar hemispheric dysfunction in ET, including functional magnetic resonance imaging (fMRI) (Bucher et al., 1997), positron emission tomography (e.g. Colebatch et al., 1990), and magnetic resonance spectroscopic imaging (MRSI) studies (e.g. Louis et al., 2002).

With regard to the nature of cognitive changes in ET, clinic-based and population-based studies have consistently shown deficits in attention, executive function, and memory in ET

cases that are greater than expected for age (e.g. Lombardi, Woolston, Roberts, & Gross, 2001;

Lacritz, Dewey, Giller, & Cullum, 2002; Troster et al., 2002; Sahin et al., 2006; Higginson et al.,

2008; Benito-Leon et al., 2011; Kim et al., 2009; Sinoff & Badarny, 2014). It is generally

proposed that the anatomical basis of such deficits is a disconnection between cortical, thalamic,

and cerebellar regions (Lombardi et al., 2001; Troster et al., 2002), sometimes referred to as a

cortico-cerebellar, or frontal-subcortical syndrome (Higginson et al., 2008). However, four out of

six studies that evaluated recognition memory, a measure of memory storage, document

impairment in patients with ET (Kim et al., 2009; Lacritz et al., 2002; Lombardi et al., 2001;

Sahin et al., 2006; Sinoff & Badarny, 2014; Troster et al., 2002). This type of deficit is often

considered a primary component of an amnestic syndrome, and is not typically expected in the

context of cortico-cerebellar or fronto-subcortical syndromes (Daum & Ackerman, 1997; Neau,

Arroyo-Anllo, Bonnaud, Ingrand, & Gil, 2000). Recognition memory deficits are typically more

consistent with mesial temporal, or hippocampal dysfunction, a cardinal feature of AD (Pillon et

al., 1993; Pillon, Deweer, Agid, & Dubois, 1993; Deweer, Lehericy, & Pillon, 1995; Lekeu et al.,

2003; Manns, Hopkins, & Squire, 2003; Hamilton et al., 2004; Remy, Mirrashed, Campbell, &

Richter, 2005; Beyer et al., 2013). The presence of this cognitive deficit in a subset of ET

individuals is consistent with their increased risk of developing MCI and AD reported in

epidemiologic studies of ET (Thawani et al., 2009; Benito-León, Louis, Mitchell, Bermejo-

Pareja, 2011).

**Essential Tremor and Metacognition.** Given that research has demonstrated an increased risk

for AD as well as metacognitive impairment among individuals with more progressed ET, it has

become imperative to explore the features of the disease that may be contributing to deficits in

awareness in this population. As discussed in the introduction, limited awareness of cognitive

dysfunction is a frequent feature of MCI, dementia, and neurodegenerative diseases such as AD—and one that compromises early diagnosis, patient safety, quality of life, and caregiver burden. Investigating awareness of cognitive impairment in ET is particularly important as physicians may not refer patients with ET for neuropsychological assessment without cognitive complaints by the patients themselves. Moreover, as physicians in general may not be aware of the recent reports of cognitive difficulties associated with ET, they may not query patients about such deficits or they may dismiss them as age- rather than disease-associated—leading them to under-query and under-appreciate these deficits (Azar et al., 2017).

To the best of my knowledge, only one study, which analyzed the same data set that was used in Studies 2 and 3, has examined metacognition in Essential Tremor. In this study, Azar and colleagues (2017) sought to examine to what extent patients with ET, who develop clinically significant cognitive impairment, accurately perceive their cognitive changes. Awareness was assessed by comparing self-rated functioning in three specific cognitive domains (memory, language, and executive functioning) to objectively measured performance in these areas. They found that ET patients with normal cognition made largely accurate assessments—as defined by discrepancy scores not statistically different from zero—in the domains of language and executive functioning. While estimations for memory performance reflected some degree of overconfidence, the authors considered this a "normal" estimation style as it is what is observed in this group of cognitive healthy older adults with ET. In contrast, ET patients with cognitive impairment (i.e. MCI to demented) demonstrated limited awareness of their deficits— significantly over-estimating their performance in all three domains as indicated both by discrepancy scores significantly greater than zero, as well as by discrepancy scores that were significantly greater (i.e., more positive) than the cognitively healthy group. Of note, although

the study combined MCI and demented participants in the same group, they found that the demented participants were driving these differences.

Study 2 builds on these analyses (Azar et al., 2017) as well as the findings from Study 1 to examine whether psychological characteristics are associated with distortions in metacognition among cognitively diverse, but non-demented adults (i.e. those with normal cognition and MCI) with ET. Determining the factors that influence integrity of awareness in individuals with ET will have important implications for how and when to screen cognition in patients with ET, and for identifying individuals who are at risk for unsafe behaviors.

## HYPOTHESES AND PREDICTIONS

*Prediction 1a*: Are there distinct patterns of mood and personality that relate to confidence accuracy in a non-demented, neurologic cohort of older adults with Essential Tremor?

*Prediction 1b.* Is the CPM that emerges in a non-demented ET cohort similar to the CPM that emerged in a non-demented, community-dwelling sample of older adults (Study 1)?

*Hypothesis 1.* Patterns of high extraversion and high conscientiousness, and low anxiety, low depression, and low neuroticism will be associated with less accurate metamemory in the direction of over-confidence; while patterns of low extraversion and low conscientiousness, and high anxiety, high depression, and high neuroticism will be associated with less accurate metamemory in the direction of under-confidence in cognitive functioning.

*Hypothesis 2.* Patterns of high extraversion and high conscientiousness, and low anxiety, low depression, and low neuroticism will be associated with more accurate metalanguage; while patterns of low extraversion and low conscientiousness, and high anxiety, high depression, and

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high neuroticism will be associated with less accurate metalanguage in the direction of under-confidence in cognitive functioning.

*Hypothesis 3.* Patterns of high extraversion and high conscientiousness, and low anxiety, low depression, and low neuroticism will be associated with more accurate meta-executive functioning; while patterns of low extraversion and low conscientiousness, and high anxiety, high depression, and high neuroticism will be associated with less accurate meta-executive functioning in the direction of under-confidence in cognitive functioning.

*Hypothesis 4.* Demographic factors, including age, education, and gender might influence the above associations. Ethnicity is excluded from analyses given the relative racial and ethnic homogeneity of the sample in Study 2.

## METHOD

### PARTICIPANTS

Data were obtained from the Clinical Pathological Study of Cognitive Impairment in Essential Tremor (CPSCI-ET) N INDS R01NS086736, which commenced enrollment in July 2014. The goal of this prospective, longitudinal study is to clinically and pathologically characterize a cohort of ET patients using motor, neuropsychiatric, and neuropsychological measures across three assessments (baseline, after 18 months and after 36 months). **Please note**, the following paragraph was taken directly from the R01NS086736 grant proposal: *Cases also enrolled as brain donors. Participants were recruited using an advertisement posted on a study website and other websites (International Essential Tremor Foundation) that described a study whose purpose is "to learn more about brain functioning in patients with ET" and that listed the following eligibility criteria: 1) diagnosis of ET, 2) ≥ 50 years old, 3) did not have deep brain stimulation surgery for ET, 4) willingness to perform "pencil and paper tests in a number of areas*

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*including reading comprehension, problem-solving, planning, attention, language, and perception" and 5) willingness to become a brain donor. Participants received an in-person, in-home clinical assessment during which a trained research assistant administered an extensive paper and pencil neuropsychological test battery and a videotaped neurological examination. The entire assessment required approximately 4 hours to complete and typically was broken into two 2-hour sessions to minimize fatigue. Cases also designated an informant, who participated in a short telephone interview consisting of questions about each case's behavior. The Yale University and Columbia University Internal Review Boards approved study procedures. Signed informed consent was obtained upon enrollment.*

The current study included baseline data from participants enrolled in CPSCI-ET. A total of 223 non-demented, community-dwelling adults with ET, aged 56-97 (mean = 78; SD = 9.37; median = 79) were included in the analyses. Participants with a "dementia" classification were excluded from analyses (See "**Normal, MCI, and Dementia Classification**" for more information). All participants were fluent in English with capacity to understand the study and provide informed consent. For full demographics and clinical information about the sample, see Table 5.

**Diagnosis of Essential Tremor in CPSCI-ET**

Each participant underwent a videotaped neurological examination, which included a detailed assessment of postural tremor, five tests for kinetic tremor, and the motor portion of the Unified Parkinson's Disease Rating Scale (UPDRS) (Goetz et al., 2007). A senior movement disorders neurologist (Elan Louis M.D.) reviewed all videotaped examinations. Rest tremor, dystonia, and other movements were noted as present vs. absent on that examination, and the severity of postural and kinetic tremors were rated (0-3), resulting in a total tremor score (range

0-36 [maximum])—a measure of the severity of the action tremor. Based on the videotaped examination, the senior movement disorders neurologist confirmed ET diagnoses using reliable (Louis, Ford, & Bismuth, 1998) and valid (Louis et al., 1999) diagnostic criteria (moderate or greater amplitude kinetic tremor on ≥3 tests or head tremor, in the absence of Parkinson's Disease (PD), dystonia or another known cause). None of the ET cases had a history of (1) traumatic brain injury, (2) exposure to medications known to cause cerebellar damage, or (3) heavy ethanol use, as previously defined (Louis et al., 2017).

**Normal, MCI, and Dementia Classification**

Cognitive diagnoses (e.g., normal cognition, MCI, or dementia) were assigned by trained experts (Stephanie Cosentino [S.C.], Ph.D. and Edward Huey, M.D.) on the basis of neuropsychological test scores and information regarding the participant's level of everyday functioning discussed during a diagnostic case conference.  A comprehensive neuropsychological test battery (described below) was designed specifically for the study by a neuropsychologist (S.C.). Tests were selected to require minimal motor activity so as to reduce the effect of tremor on performance. Raw test scores were converted to scaled scores (z-scores) using demographically adjusted, published normative data. Information about everyday functioning was ascertained using the Clinical Dementia Rating Score (CDR) (Morris, 1993). Informants designated by study participants were queried via telephone regarding the participant's level of functioning in the six domains outlined in the CDR (Morris, 1997). Additionally, the Neuropsychiatric Inventory (Cummings et al., 1994), the Frontal Behavioral Inventory (Kertesz, Davidson, & Fox, 1997), and the Lawton Instrumental Activities of Daily Living Scale (Lawton & Brody, 1969) were completed. If an informant was not available, CDR was determined by participant self-report as well as through examiner impression over the course

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of the lengthy study interview. CDR was confirmed through consultation during a diagnostic case conference with trained experts (EDH and SC), during which a cognitive diagnosis was determined for each participant. Functional difficulties in everyday life secondary to motor or mood issues was not considered to be functional impairment as measured on the CDR, as this instrument seeks to identify functional disturbances due to cognitive problems specifically.

For this particular study, only community-dwelling individuals with a CDR score of 0 (no impairment) through 0.5 (reflecting mild concern from the patient or informant) on neuropsychological testing were included in analyses. Individuals met criteria for dementia if they demonstrated cognitive impairment in multiple ($\geq$2) cognitive domains and scored $\geq$1 on the CDR.

**Cognitive Assessment**

For the purposes of this study, the following three measures were selected to assess memory, language, and executive function, respectively: 1) California Verbal Learning Test-II (CVLT-II) [Delis, Kramer, Kaplan, & Ober, 2000]; 2) Delis-Kaplan Executive Function System (D-KEFS) [Delis, Kaplan, & Kramer, 2001] Phonemic Fluency; and 3) D-KEFS Verbal Fluency Switching Task.

**MEASURES**

*Demographics*. The demographics questionnaire is a self-report measure collecting age, gender (Male or Female), and years of education.

*Subjective Cognition (Self-ratings).* Participants completed a modified version of the Brief Anosognosia Scale (Cosentino et al., 2007) in which they are asked to rate their ability to perform 14 different cognitive, motor, emotional, and functional abilities. For each item,

participants rated their ability on a 5-point scale including values of: (1) very impaired, (2) below average, (3) average, (4) above average, or (5) excellent. This self-rating scale, originally developed by Reid et al., (2006) has been used in previous studies from my lab and is correlated with other forms of cognitive self-assessment. Of the 14 items, I focused on three abilities including the ability to 1) *remember,* 2) *find the right word when speaking, and* 3) *multitask,* which mapped onto cognitive abilities measured objectively in our study in the domains of memory, language, and executive functioning, respectively (Azar et al., 2017).

*Objective Measures of Cognition.* In order to derive measures of awareness in the domains of memory, language, and executive functioning, the three self-ratings were paired in an a priori manner to objective neuropsychological tests commonly used to assess these cognitive domains. In addition to the theoretical bases for pairing the individual ratings and tests, I considered a significant bivariate association between the paired ratings and tests (i.e., memory rating and memory test) along with an absence of an association between the non-paired tests (i.e., memory rating and language test) to be empirical support for the pairing. Test scores were converted to demographically adjusted standardized scores (z-scores or scaled scores depending on the normative scores provided) using published normative data. In order to compare performance on the objective tests directly with the subjective ratings described below, standardized scores were then converted to ordinal scores and then to z scores (Table 6), which correspond broadly to common interpretations of standardized test score values (Graham et al., 2005; Azar et al., 2017).

**Memory.** Participants' subjective rating of *remembering* (SubjMem) was examined in relation to performance on the 16-word CVLT-II, a commonly used word list learning test assessing short and long term free recall and recognition (Woods et al., 2006). In the current study, long delay free was used as the dependent variable.

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**Language.** Participants' subjective rating of *finding the right word when speaking* (SubjLang) was examined in relation to performance on the D-KEFS Phonemic Fluency test. This test assesses participants' ability to rapidly generate words beginning with specified letters. The dependent variable for this test is the total number of words generated across three 60-second trials.

**Executive Function.** Participants' subjective rating of *multitasking* (the ability to do more than one task at the same time) (SubjEF) was examined in relation to performance on the D-KEFS Verbal Fluency Switching Task. Multitasking in everyday life requires the ability to rapidly and efficiently shift attention between different tasks. The D-KEFS fluency switching task was designed to assess one's ability to shift attentions between two competing tasks, requiring the participant to generate as many words as possible in 60 seconds, alternating between words from two specified semantic categories. Performance on this task has been shown to correlate with other forms of task switching (Schmitter-Edgecombe & Sanders, 2009). The dependent variable for this test is the total number of words accurately generated (Jardim de Paula & Costa, 2015).

*Metacognition Indices.* The global, offline metacognitive indices were computed as a discrepancy score by subtracting objective cognitive performance on memory, language, and executive functioning tasks from self-ratings in each domain. As in Study 1, a discrepancy z score of zero reflects accurate self-assessment whereas negative discrepancy scores ($z \leq$ -0.5) reflect under-confidence and positive scores ($z \geq 0.5$) reflect over-confidence.

**Metamemory (MM) Index.** The global, *offline* MM was computed as the discrepancy between the SubjMem and CVLT long delay z-scores (SubjMem – CVLT-LD) with higher scores reflecting over confidence and lower scores reflecting under-confidence.

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**Metalanguage (ML) Index.** The global, *offline* ML was computed as the discrepancy between the SubjLang and D-KEFS Phonemic Fluency (SubjLang – D-KEFS-PF) with higher scores reflecting over confidence and lower scores reflecting under-confidence.

**Meta-Executive Functioning (MEF) Index.** The global, *offline* MEF was computed as the discrepancy between the SubjEF and D-KEFS Verbal Fluency Switching (SubjEF – D-KEFS-VFS) with higher scores reflecting over confidence and lower scores reflecting under-confidence.

*Measures of Mood and Personality*

**The NEO Five Factor Inventory (NEO-FFI-3).** The NEO-FFI-3 is a 60-item psychological inventory that was used to assess the five major dimensions of personality: Openness to Experience, Conscientiousness, Extraversion, Agreeableness, and Neuroticism. Participants are asked to select the response that best represents their opinion on a 5-point scale: 0-Strongly Agree, 1-Agree, 2-Neutral, 3-Disagree, 4-Strongly Disagree. Scores were standardized, controlling for gender (McCrae & Costa, 2010).

**Geriatric Depression Scale (GDS).** See *Chapter II: Measures* for a review.

**Generalized Anxiety Disorder-7 (GAD-7).** The GAD-7 is a seven item measure often used in clinical practice and research to screen for and assess the severity of Generalized Anxiety Disorder. The GAD-7 score is calculated by assigning scores of 0, 1, 2, and 3, to the response categories of 'not at all', 'several days', 'more than half the days', and 'nearly every day', respectively, and adding together the scores for the seven questions. Scores of 5, 10, and 15 are taken as the cut-off points for mild, moderate and severe anxiety, respectively (Spitzer et al., 2006).

## DATA ANALYSIS PLAN

The primary goal of this analysis is to examine the relationship between the composite of mood and personality (CPM) and global, offline metacognitive indices.

As in Study 1, I first performed a Latent Class Analysis (LCA) using MPLUS 7.1 (Muthén & Muthén, 1998) to identify discrete, heterogeneous patterns of personality traits and mood (i.e. anxiety and depression scores). See **Chapter I: Data Analysis** section for a review of the procedure.

I then performed separate GLMs to examine whether 1) metamemory, 2) metalanguage, and 3) meta-executive functioning (as continuous variables) each differ as a function of the participants' LCA class membership assignments. I investigated the associations of metacognition (confidence/accuracy judgments) with CPM by regressing 1) MM, 2) ML, and 3) MEF on the derived classes while controlling for age, gender, and education. An alpha level of .05 was used for all statistical tests.

## RESULTS

Table 7 displays relative model fit from 1 to 3 class solutions for the unconditional LCA. Results indicated that the LMR likelihood ratio test was not significant for the three class solution. As such, the LMR suggested that the two class model was a more appropriate fit for the data than its neighboring three class solution. Among the remaining solutions, the two class model was the one with the best fit in terms of AIC, BIC, SSBIC, and higher relative entropy; furthermore, the LMR and BLRT for the two class solution were both significant. Taken together, information from the fit indices proved that the two class model was the optimal solution. Figure 4 displays the two class solution, characterized by distinct patterns of mood and

personality scores. The best log-likelihood value of the model replicated, indicating successful

convergence. The first CPM Class (N= 203, 91% sample) was characterized by largely average

levels of mood and personality constructs with mildly lower anxiety, depression, and

neuroticism. The second CPM Class (N= 20, 9%) was characterized by predominantly high

neuroticism, high depression, and high anxiety, and low conscientiousness and low openness.

Three separate GLMs were performed to examine whether awareness of (1) memory, (2)

language, and (3) executive functioning differed as a function of the emergent CPM class

membership, while covarying for age, education, and gender (for full estimates, see Tables 8, 9,

and 10). The models were not significant. Further exploratory analyses revealed that only

awareness of executive functioning and the independent construct of *Conscientiousness* from the

NEOFFI were significantly correlated, r (221) = .184, $p < .05$.

Regarding demographics variables, one sample t-tests (Table 8a) revealed that

metamemory accuracy differed significantly across gender, such that men tended to overestimate

(M = 0.45, SD = 1.59) and women tended to underestimate (M = -0.36, SD = 1.37) their memory

abilities, t (181) = -3.57, $p < .05$.

Age emerged as a significant predictor of meta-executive functioning abilities.

Subsequently, I divided the cohort based on theoretical and statistical (i.e. mean and median of

the sample) reasoning into two groups (Young Old: 78 years and under; and Very Old: 79 years

and older). T-tests (Table 10a) revealed that individuals in the Young Old cohort had lower MEF

scores such that they underestimated their executive functioning abilities (M = -0.32, SD = 1.36)

as compared to the Very Old who tended to be accurate in their assessment of their executive

functioning (M = 0.22, SD = 1.72). Overall, these results suggest that among a neurologic cohort

of older adults with ET, composites of mood and personality constructs do not significantly influence likelihood of metacognitive accuracy.

## DISCUSSION

Study 2 investigated the association between metacognition and characteristics of personality and mood (CPM). As discussed previously, the ability to estimate one's own performance accurately has been shown to be important for managing everyday situations safely and effectively. Studies have consistently demonstrated strong associations between overestimation of cognitive functioning and poor medication adherence, higher caregiver burden, and a greater frequency of motor vehicle accidents. Conversely, underestimation of cognitive functioning may result in avoidance of activities and further loss of skills or confidence; perhaps even most interestingly, under-confidence—manifesting clinically as subjective cognitive complaints (SCC)—has been associated with a higher rate of misdiagnosis of mild cognitive impairment, and subsequent improper treatment (e.g. recommendation of Aricept rather than CBT). For these reasons, and many others, it is imperative that we continue to develop a comprehensive understanding of the factors that influence metacognition.

In line with Study 1, which examined the psychological factors associated with distorted metamemory in a healthy cohort of older adults, Study 2 explores whether the same psychological constructs continue to explain variability in metacognition among a neurologic cohort of community-dwelling older adults with Essential Tremor (ET). I examined metacognition by comparing offline, *global* estimations (i.e., assessments of one's 1) ability to remember, 2) ability to find the right word, and 3) ability to multitask) to objective memory, language, and executive functioning performance (respectively) in order to determine the extent to which individuals overestimated, underestimated, or made accurate estimations of their

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memory, language, or executive functioning abilities. In accordance with the findings of Study 1 that higher negative affect (i.e. anxiety and neuroticism) was significantly associated with underestimation of memory functioning, whereas lower negative affect was associated with more accurate awareness, I hypothesized that 1) two classes of mood and personality would emerge among older adults with ET and 2) that negative affect would again be associated with underestimation of cognitive functioning. The current results indeed yielded two primary mood and personality patterns—Class 1 was characterized by significantly lower anxiety, lower depression, and lower neuroticism as compared to anxiety, depression, and neuroticism levels seen in Class 2. However, in contrast to Study 2 hypotheses and the findings of Study 1, this first class was characterized by average levels of mood and personality constructs across the board (i.e. $0.5 \geq z \geq -0.5$). Consistent with Study 2 hypotheses and the findings of Study 1, Class 2 was characterized by high anxiety, high depression, high neuroticism, and low consciousness. However, rather than low extraversion, the final component of the profile was low openness (i.e. all of which comprise Class 2).

Contrary to Study 1 outcome and Study 2 hypotheses (i.e. that distinct patterns of personality and mood would be associated with metacognitive accuracy in a neurologic cohort of older adults with ET), I found that CPM did not significantly predict variability in awareness of memory, language, or executive functioning abilities. Of note, the age of the sample was significantly higher than that of Study 1, and age was a significant contributor to variability in meta-executive functioning accuracy in the current study. However, analyses revealed that the "Very Old" participants ($\geq 79$ years) were not more likely than the "Young Old" ($\leq 78$ years) to exhibit overconfidence in executive functioning.

With that said, consistent with Study 1, analyses revealed that metamemory differed across gender, such that men tended to be more confident in their memory functioning than women. However, in contrast to Study 1 findings (i.e. that women were largely accurate in their perception of their memory functioning), women in the current study significantly underestimated their memory abilities. It is worth noting that there were not significant differences in objective cognitive performance (OCP) between gender groups in either Study 1 or Study 2 cohorts; although qualitatively, women performed slightly better than men on both the RAVLT and CVLT long delay. This was consistent with literature that indicates women tend to perform better on average than men on verbal measures (e.g. Schmidt, 1996; Maccoby & Jacklin, 1974). While there is a dearth of studies that examine gender differences in subjective memory complaints (SMCs), findings from Study 1 and Study 2 are largely in agreement with previous research (e.g. Pallier, 2003), which has demonstrated a tendency for men to overestimate and women to underestimate their cognitive abilities. Potential differences in self-concept and "stereotype threat" may explain this discrepancy, and is certainly a fruitful avenue for future research.

Subsequent exploratory analyses that examined the relationship between metacognition and individual mood and personality constructs (e.g. metamemory and neuroticism alone)—rather than utilizing LCA—similarly did not produce significant relationships between these variables. That being said, a weak, but significant association was found between higher conscientiousness and accurate awareness of executive functioning. Overall, these results while contrary to my hypotheses, are nonetheless clinically interesting. Before discussing potential interpretations of the findings, it is important to first consider some limitations of the current study.

**Limitations and Future Directions.** The current study has both strengths and limitations. A significant strength is that this is the first attempt to my knowledge to both uncover discrete classes of mood and personality in a neurologic cohort, and to investigate whether these premorbid characteristics are associated with variability in metacognitive accuracy among older adults with ET. Another strength is that the current study obtained a large sample of individuals diagnosed with ET who received consensus diagnoses of normal cognition, MCI, and dementia based on clinical consideration of performance on a comprehensive objective neuropsychological testing battery as well as detailed interviews of the patients' everyday functioning. Moreover, all participants were well characterized both neurologically and cognitively, and the neuropsychological tests were chosen to minimize motor demands. However, there are a few limitations to this study that are important to address. First, in comparison to Study 1, which included a comprehensive offline evaluation of subjective cognitive functioning, the selected self-ratings of cognitive function used in the current study were based on a single item for each of the three cognitive domains. As a result, the ratings may be less reliable and robust than ratings based on multiple items for each domain. Similarly, as discussed in the previous chapter, an area of debate related to this limitation is that there remains some question as to the convergent validity between subjective cognitive complaints and task-specific, objective neuropsychological measures of cognition. Said differently, it may be unclear to what extent clinically-relevant questions from the modified version of the Brief Anosognosia Scale (e.g. rate your ability to remember from [1] Very Impaired to [5] Excellent) map conceptually and directly onto the objective measures of cognition (e.g. performance on the CVLT long delay). That being said, in order to ensure that the *a priori* pairings of subjective ratings with specific objective tests were reasonable, Azar and colleagues (2017), who previously

utilized this same data set ran bivariate correlations between test scores and subjective ratings within an ET normal cognition group. The CVLT long-delay free recall scores were significantly associated with ratings of one's ability to remember ($r = 0.18$, $p < 0.05$), the VFT Letter task scores were associated with ratings of one's ability to find the right word when speaking ($r = 0.18$, $p < 0.05$) and VFT switching scores were associated with the ratings of one's ability to multitask ($r = 0.29$, $p < 0.001$). Relatedly, though a strength of this study is that it utilizes an objective measure of metamemory by comparing memory ratings directly to memory performance rather than informant report, I acknowledge that the metamemory rating was an offline evaluation (i.e. a crystallized notion of what their memory abilities are) as opposed to an online evaluation of metamemory experience (i.e. perception of memory abilities while engaged in an ongoing memory task). As discussed in Study 1, it remains unknown in which way the emergent classes of mood and personality would relate to an online metamemory evaluation like FOK or JOL. That said, it has been shown that online and offline measures are highly correlated and that there may be significant benefits to using an offline, global subjective measure (Cosentino, Metcalfe, Butterfield, & Stern, 2007). For example, the offline measure is rich in its reflection of everyday, real world levels of awareness. In some respects, offline scores may be better able to inform practically and clinically relevant issues including the extent to which participants appreciate their need for assistance or devise strategies for completing cognitively demanding activities (Cosentino, Metcalfe, Cary, De Leon, & Karlawish, 2011; Fleming & Frith, 2014).

A second limitation involves the current research procedure. In Studies 1 and 2, older participants were asked by a young research coordinator to rate their ability to remember, to find the right word, and to multitask on a 5-point scale from (1) very impaired, (2) below average, (3)

average, (4) above average, to (5) excellent. Although this methodology is consistently utilized in metacognitive research, it is important to consider the impact of this research paradigm on the reliability of an individual's responses. Social Expectancy Theory (SET) posits that cultural values shape how individuals perceive and evaluate others, and this influences how others evaluate themselves. Based on this theory, ageism may shape older individuals' self-evaluations. In the presence of a younger individual, they may, for example, be more likely to overestimate their cognitive functioning; whereas in the presence of someone their age or older, they may provide a more accurate or honest evaluation of their functioning. Moreover, perceptions of an individual's own age (i.e., subjective age) may influence evaluations and judgments. For these reasons, future studies may benefit from 1) incorporating a Self-Concealment Scale (e.g. Larson and Chastain, 1990), which measures the degree to which a person tends to conceal personal information perceived as negative or distressing, 2) including a measure of perceived age ("How old do you feel?"), 3) asking participants to rate their abilities relative to their peers, and 4) lastly, if asked, for example, to rate their ability to remember, ensuring that a younger research coordinator is not present during this questionnaire.

A third limitation of Study 2 involves the characteristics of the sample. Class 2, which was characterized by high neuroticism, high anxiety, and high depression, represented only 9% (N = 20) of the sample. Given that in Study 1 we found that only individuals who tended towards higher negative affect demonstrated under-confidence in their cognitive functioning—whereas those who had lower negative affect were accurate in their perception of their cognitive functioning—it is possible that one reason we are not seeing a replication of these findings is that the statistical power is limited. Perhaps, if there were a more even distribution across CPM or if Class 2 was larger, a significant relationship might emerge between metacognition and

psychological characteristics. Moreover, the mean age and standard deviation (SD) of the participants in Study 2 (Table 5) are significantly greater than the mean age and SD in Study 1 (Table 1). Given the majority of this sample was quite old ($\geq$79 years), it is possible that age has influenced or colored these results. Indeed, while we did not find that the mean of the very old (VO) group differed significantly from zero, we did find that age was in fact a significant predictor of meta-executive functioning accuracy with young-old (YO) individuals underestimating their functioning. Thus, inclusion of more YO participants who are comparable in age to Study 1 may have resulted in a larger number of individuals significantly underestimating their functioning—which one might conjecture could alter the sample size of Class 2 and the outcome of the current study.

A final and critical limitation of Study 2 is the absence of a control group. While I have made qualitative, observational comparisons between the findings of Studies 1 and 2, a non-ET normal control (NC) group is needed to determine statistically whether CPM differs in healthy and neurologic cohorts of older adults. Moreover, a comparison group would provide further information regarding whether the difference in findings across groups are due to age, limited power (e.g. of Class 2), or are in fact attributable to the presence of ET pathology. Including non-ET groups as a point of comparison would allow a clearer depiction of the way in which disordered awareness may manifest specifically in ET and would provide a richer understanding of the factors that may differentially influence awareness in these two groups.

With these limitations in mind, it remains possible that the differences in outcome between Studies 1 and 2 reflect true differences in the association between psychological variables and metacognition in healthy and neurologic cohorts. Moreover, these findings offer an alternative theory—that is, perhaps the presence of a disease process like ET influences the

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extent to which premorbid characteristics relate to metacognitive accuracy. One possibility is that age- or disease-related neuroanatomical changes among individuals in this sample may more strongly explain differences in metacognitive accuracy than psychological characteristics alone. Along these lines, several researchers have proposed that there is a specific neural basis for metacognition and that metacognitive efficiency may decrease linearly as we age and develop neuropathological burden (Fleming, Weil, Nagy, Dolan, & Rees, 2010; Rounis, Maniscalco, Rothwell, Passingham, & Lau, 2010; Yokoyama et al., 2010; Fleming, Huijgen, & Dolan, 2012; Palmer, David, & Fleming, 2014). With regard to the mechanism underlying metacognitive disturbance in aging, studies have highlighted deterioration in frontal and temporal regions, including the hippocampus, dorsolateral prefrontal cortex, the anterior cingulate cortex, the orbital frontal cortex, and the insula (e.g. Fernandez-Duque, Baird, & Posner, 2000; Souchay, Isingrini, & Espagnet, 2000; Souchay et al., 2003; Perrotin, Isingrini, Souchay, Clarys, & Taconnat, 2006; Palmer, David, & Fleming, 2014). Similarly, many researchers have championed a bio-genetic approach to metacognition—positing that accumulation of biomarker profiles, such as amyloid beta (Aβ), neurofibrillary tangles, and Lewy bodies, for example, may account for varying levels of awareness. However, these associations between age, neuroanatomical changes, and metacognition have not been consistently replicated across studies with some authors asserting that factors like age do not mediate deficits in monitoring abilities— instead, supporting the argument that greater life experience may lead to more accurate self-knowledge and greater metacognitive efficiency even among individuals with a neurologic disease (e.g. Lachman, Lachman, & Thronesbery, 1979; Dodson et al., 2007). As mentioned previously, these inconsistencies in the literature likely reflect differences across studies in the

conceptualization of awareness, the object of awareness selected, the type of measure used, and the point of progression of the disease process.

While some researchers have maintained a preference for the neuropathological approach to metacognition over the psychological, the lack of consensus described previously may suggest that each predictive model is insufficient on its own. Although psychological characteristics were not significantly associated with metacognition in the current neurologic sample—these negative findings yield perhaps an even more compelling question: Does ET pathology or a clinically-dormant comorbid neurodegenerative process, rather than premorbid characteristics, better explain the variability in awareness? Directions for future research might include exploring 1) the neuroanatomical biomarkers of metacognition among older adults with ET, 2) the extent to which premorbid characteristics differ between individuals with ET and NC, and 3) whether metacognition varies depending on the *severity* of ET pathology. By adopting a comprehensive, biopsychosocial approach to factors that influence metacognition, there is a strong potential to gain further insight into the awareness deficits associated with ET and the clinical implications for patients, caregivers, and physicians.

## CHAPTER IV: STUDY 3: THE NEUROPATHOLOGY OF METACOGNITION IN ESSENTIAL TREMOR

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The previous two studies investigated the psychological factors associated with metacognition in healthy and neurologic cohorts of community-dwelling older adults. Contrary to my hypotheses, Study 2 found that among individuals with ET, mood and personality constructs did not significantly explain variability in metacognitive accuracy. In light of these findings, Study 3 hypothesizes that distortions in metacognition may be better explained by an underlying disease process. Thus, Study 3 seeks to go beyond premorbid characteristics and examines whether

neuropathological substrates, including dysfunction or death of Purkinje cells and structural changes in the white and gray matter areas of the brain may influence an individual's ability to accurately perceive his or her cognitive functioning. Furthermore, the following study examines whether a secondary, comorbid neuropathological process (e.g., neuropathologic changes consistent with AD and cortical atrophy) may be associated with distortions in metacognition.

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Given the clinical heterogeneity of ET, it has been proposed that ET represents a family of diseases rather than a single clinical-pathological entity (Louis et al., 2014). As the disease advances, tremor (1) becomes more severe, resulting in functional difficulties; (2) may become more varied, with the development of rest and intention tremors; and (3) often becomes anatomically widespread (Cohen and others 2003; Sternberg and others 2013). As discussed in the introduction to Study 2, there is a growing literature that suggests ET is associated with a variety of non-motor symptoms, most prominently: cognitive deficits (i.e. MCI or dementia) as well as personality and mood changes. Importantly several of these non-motor manifestations have been seen in many other neurodegenerative conditions such as Parkinson's disease (PD), Progressive Supranuclear Palsy (PSP), Dementia with Lewy Body (DLB), and most notably, Alzheimer's disease (AD).

Greater interest in ET research in the recent decade has resulted in fresh knowledge of this disorder and a new formulation of disease pathophysiology. This new formulation proposes that ET may be a disease of the cerebellum and, more specifically, the Purkinje cell (PC) population (Grimaldi and Manto, 2013; Louis, 2014). Indeed, some investigators have even proposed that ET may be a "Purkinjopathy" (Grimaldi & Manto, 2013)—this term refers both to degeneration of PCs and the formation of torpedoes, which are swellings of the proximal,

unmyelinated segment of the Purkinje cell axon and are believed to be secondary markers related to PC degeneration. Controlled postmortem ET studies in recent years have documented a growing number of structural changes in the cerebellum (or in the brainstem neurons that synapse with PC) and none in other brain regions, further substantiating the notion that the "seat of the disease" is the cerebellum (Louis, 2014). Studies have also strongly implicated Lewy bodies and neuronal loss in the locus coeruleus (LC) in the progression of ET; of note, atrophy of the LC and related "purkinjopathy" have also been shown to be present in the brains of patients with other neurodegenerative disorders (e.g., PD or AD) in which distorted awareness is a common clinical feature—but not nearly to the same degree as occurs in ET (Louis et al., 2009).

However, the pathophysiology of ET may be more complex than the above formulation. Recent epidemiological studies demonstrate an association between ET (particularly with onset after age 65) and increased risk for cognitive impairment and dementia. Although existing studies have generally conceptualized cognitive changes in ET as consistent with a 'frontosubcortical' or 'corticocerebellar' profile, results from these same studies suggest that cognitive impairment in ET may in fact be more heterogeneous and widespread (Lombardi et al., 2001; Troster et al., 2002; Higginson et al., 2008). Furthermore, the underlying mechanisms remain uncertain. Thus, cognitive changes could be a byproduct of the cerebellar dysfunction of ET itself; alternately, they may be a feature of concomitant neurodegenerative diseases like AD.

The idea that cognitive impairment in ET may reflect either the distal effects of cerebellar changes via cortical-thalamic and subcortical networks is consistent with growing literature documenting the role of the cerebellum in facilitating cognitive, psychological, and learning activities (Watson, 1978; Schmahmann and Sherman, 1998; Middleton and Strick, 2000; Lombardi et al. 2001; Peterburs et al. 2010). Moreover, many reports of

neuropsychological performance in patients with ET have highlighted patterns of both executive and amnestic dysfunction that is analogous to that observed in neurodegenerative diseases affecting both subcortical white matter and basal ganglion structures as well as the hippocampal region, respectively (Lafosse et al. 1997; Tierney et al. 2001; Schmidtke and Hull, 2002; Traykov et al. 2002).

Furthermore, clinicians have long observed that there seems to be a tendency for ET patients to develop incident AD, PD, PSP, or DLB—raising questions about links between ET and these neurological diseases. Indeed, the considerable evidence for 1) an association between ET and diseases characterized by neurofibrillary tangles and neuritic plaques, as well as the fact that 2) elderly-onset ET increases the risk of developing AD nearly twofold, suggests that ET may share pathogenic mechanisms with these disorders (Benito-León, Louis, & Bermejo-Pareja, 2006; Louis et al., 2007).

As discussed in the introduction, it has been long recognized that a significant proportion of patients with such neurodegenerative diseases as AD, PSP, and DLB display some degree of unawareness for disease-related cognitive impairment. The high co-morbidity rates of ET with these diseases, has incited researchers to explore whether individuals with ET are likely to exhibit distortions in awareness. A recent study by Azar and colleagues (2017) found that among individuals with ET, only those with severe cognitive impairment exhibited impaired metacognition. These findings call into question whether the observed distortions in awareness were due to ET pathology or a secondary, underlying disease process (e.g., AD, neurofibrillary tangles, or hippocampal sclerosis).

In line with a biopsychosocial approach to understanding the factors which influence metacognition, this final study extends beyond psychological and demographic characteristics

and explores the neurological substrates of awareness. The aims of the current study are to determine whether distorted metacognition is associated with 1) ET-specific, cerebellar pathology; 2) neuropathological changes consistent with Alzheimer's disease; or 3) other neuropathological substrates and regional specificity of disease burden.

## HYPOTHESES AND PREDICTIONS

*Prediction 1:* Does overconfidence in cognitive functioning map onto the presence of the following ET-specific, cerebellar pathologies: (a) global reduction in Purkinje count and (b) torpedo formation.

*Hypothesis 1.* Distorted metacognition, in the direction of overconfidence, will be significantly associated with cerebellar pathology (i.e., Purkinje cell axonal swellings or torpedo formation).

Briefly, the locus coeruleus (LC)—a neighboring region of the cerebellum—has been identified as the principal site for the brain's synthesis of the neuromodulator, norepinephrine (noradrenaline). Noradrenaline has its origin in the brainstem nuclei and projects broadly to cortical and subcortical regions, including the prefrontal cortex and the hippocampus (Hauser et al., 2016). The LC, and the areas of the central nervous system affected by the norepinephrine it produces, are described collectively as the locus coeruleus-noradrenergic system or LC-NA system. Degeneration of this system has been associated with different neurodegenerative diseases, including AD, Progressive Supranuclear Palsy (PSP), and Parkinson's Disease (PD)— of which distorted awareness is a common clinical symptom (e.g. Heneka et al., 2006; Uchikado et al. 2006; Ross et al. 2015, Delaville et al., 2011). Correspondingly, activation of the LC-NA has been implicated in metacognitive control processes such as attentional modulation, learning and memory retention, and the regulation of goal-directed versus exploratory behaviors (Usher et

al., 1999; Aston-Jones and Cohen, 2005; Yu & Dayan, 2005; De Martino et al., 2008; Eldar et al., 2013). The LC—in addition to having noradrenergic properties—has major efferent connections to cerebellar Purkinje cells. It has been proposed that the locus ceruleus-cerebellar pathway is important for the normal function of Purkinje cells and their inhibitory output (Hoffer et al., 1973; Moises and Woodward, 1980; Moises et al., 1981). Further, researchers have indicated that neuronal depletion in the LC may lead to Purkinje cell loss in the cerebellum (Louis and Vonsattel, 2008).

Although on a less consistent basis, neuroimaging studies have demonstrated an association between monitoring of cognitive abilities and increased activation in the cerebellum (Blakemore, Frith, & Wolpert, 2001; Molenberghs et al., 2016). Moreover, researchers have found that cerebellar activation correlates highly with activation of a region of the frontal lobe (i.e. DLPFC) that has been repeatedly associated with higher order, metacognitive ability (Allen et al., 2005). In sum, taking into consideration both frontocerebellar connections as well as the strong relationship between the LC-NA network and Purkinje cells, I hypothesize that ET-specific, cerebellar pathologies will be associated with distorted metacognitive functioning.

*Prediction 2:* Are individuals, who exhibit over-confidence in their cognitive functioning more likely to have comorbid, neuropathological change consistent with Alzheimer's disease than those who do not demonstrate over-confidence?

*Hypothesis 2:* Overconfidence in cognitive functioning will be associated with the presence of neuropathological change consistent with AD.

Briefly, as a review, it has been long recognized that a significant proportion of patients with such neurodegenerative conditions, such as Alzheimer's disease, display some degree of unawareness for cognitive impairment. The high co-morbidity rates of ET with AD, have incited

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researchers to explore whether individuals with ET are likely to exhibit distortions in awareness. A recent study by Azar and colleagues (2017) found that among individuals with ET, only those with severe cognitive impairment exhibited impaired metacognition. These findings call into question whether the observed distortions in awareness are better explained by a secondary disease process like AD than by ET pathology alone.

*Prediction 3:* Is overconfidence in cognitive functioning associated with specific neuropathologies?

*Hypothesis 3:* Overconfidence in cognitive functioning will be associated with greater (a) likelihood of an Alzheimer's-type pathology diagnosis (amyloid β deposits, neurofibrillary tangles (NFT), and neuritic plaques), (b) specificity of hyperphosphorylated tau burden in the hippocampus, mid-temporal cortex, and frontal cortex, (c) cortical atrophy in the temporal and frontal lobes, (d) cerebral amyloid angiopathy, and (e) cerebrovascular disease burden.

## METHOD

**PARTICIPANTS**

As described in the R01NS042859 grant: *Data were obtained through a currently-funded project at Columbia University, whose aim is the study the basic neuropathology of ET (the Essential Tremor Centralized Brain Repository, ETCBR, R01NS042859, E. Louis). Participants in this study are a self-motivated group that responded to advertisements in ET-society newsletters (e.g., International Essential Tremor Foundation) and live throughout the United States. Each subject has a personalized brain donor plan set up by one of the ETCBR nurse coordinators. This includes the names of next of kin, the name of a pathologist at a nearby*

*hospital, contact people at the funeral home. The details of these plans are re-reviewed with the cases every six months and updated if necessary.*

Twenty one postmortem evaluations of participants were collected from the same Clinical Pathological Study of Cognitive Impairment in Essential Tremor (CPSCI-ET) data set utilized in Study 2; however, in contrast to Study 2, participants diagnosed with cognitive impairment (i.e. MCI to dementia) were included in this final, autopsy study. Given that postmortem evaluations were conducted one year after baseline, the mean age of the derived sample at baseline (mean = 88.67; SD = 4.66; median = 89) and autopsy (mean = 89.84; SD = 4.71; median = 90) is significantly older than the mean in Study 2. The implications of this discrepancy will be discussed in detail in the **Discussion** section for Study 3. As mentioned in Study 2, these cases reside in various US regions (Northeast, Southeast, North Central, South Central, Northwest, and Southwest). Participants were fluent in English with capacity to understand the study and provide informed consent. For full demographics and clinical information about the sample, see Table 11.

**MEASURES**

*Metacognition Indices.* Metamemory, Metalanguage, and Meta-executive functioning indices were calculated using the same measures of subjective and objective cognition utilized in Study 2 (Please refer to Study 2: **Measures** section for a review) and the same procedure (i.e. a discrepancy z score) implemented in both Studies 1 and 2. Briefly, global, offline metacognitive indices were computed as a discrepancy score by subtracting objective cognitive performance on memory, language, and executive functioning tasks from single-item self-ratings in each domain. However, in contrast to Studies 1 and 2—which utilized a continuous measure of metacognition as the dependent variable—Study 3 utilizes a categorical measure of metacognition. To

elaborate, participants were divided into two groups (i.e. "Overconfident" vs. "Not Overconfident, Normal to Under-confident"). Those with a positive discrepancy z score greater than or equal to 0.5 were deemed over-confident; those with a discrepancy score below 0.5 were considered either accurate in their estimations of their cognitive functioning or significantly under confident in their abilities. The rationale for utilizing a categorical measure of metacognition rather than a continuous measure, is twofold: First, the aforementioned study by Azar and colleagues (2017), which examined the same participants seen in Study 2, found that among those showing distortions in metacognitive accuracy, these individuals were largely overestimating their abilities rather than underestimating their cognitive functioning. Second, while I hypothesize that increased pathology burden is associated with over-confidence in cognitive functioning, given that the pathology measures described below are largely continuous, I did not want to make the assumption of linearity—that is, as pathology *decreases*, participants would become under-confident in their abilities. For these reasons, Study 3 focuses primarily on the relationship between overconfidence and underlying neuropathologies. See Table 12 for a description of the relative distributions of metacognition in this sample as compared to metacognitive distributions in Studies 1 and 2.

**Categorical Metamemory (CMM) Index.** The global, *offline* MM was computed as the discrepancy between the Subjective Memory and CVLT long delay z-scores (SubjMem – CVLT-LD). Participants were labelled as "Overconfident" if $z \geq 0.5$.

**Categorical Metalanguage (CML) Index.** The global, *offline* ML was computed as the discrepancy between the Subjective Language and D-KEFS Phonemic Fluency z-scores (SubjLang – D-KEFS-PF). Participants were labelled as "Overconfident" if $z \geq 0.5$.

**Categorical Meta-Executive Functioning (CMEF) Index.** The global, *offline* MEF was computed as the discrepancy between the Subjective Executive Functioning and D-KEFS Verbal Fluency Switching z-scores (SubjEF – D-KEFS-VFS). Participants were labelled as "Overconfident" if z ≥ 0.5.

*ET-Specific Pathology*

**Purkinje Cells (PC).** Purkinje cells, also called Purkinje neurons, are neurons located in the cerebellar cortex of the brain. Purkinje cell bodies are shaped like a flask and have many threadlike extensions called dendrites, which receive impulses from other neurons called granule cells. Each cell also has a single projection called an axon, which transmits impulses to the part of the brain that controls movement, the cerebellum. Purkinje cells are inhibitory neurons that participate in the processes of motor control and learning; they secrete neurotransmitters that bind to receptors that inhibit or reduce the firing of other neurons. In the current study, Purkinje cells were calculated as the total number of PCs counted in the cerebellum.

**Torpedoes.** PCs are an unusual central nervous system neuron because they are particularly resistant to degeneration after axotomy; in such settings, the response of PCs to stress is a partly degenerative and partly compensatory response. This process involves the formation of *Torpedoes*, as well as other structural changes in the axon (e.g., recurrent collateral formation, axonal branching, and terminal axonal sprouting). Torpedoes are attenuated fusiform swellings of the proximal, unmyelinated segment of the Purkinje cell axon that are believed to be secondary markers related to the degeneration and death of Purkinje cells (Louis, 2016). They are found in small numbers in the normal human cerebellum, and have been observed to a similar extent across a wide range of ages (i.e., they do not accumulate with age). Increased torpedo formation seems to occur as a standard cerebellar response to injury, and may represent a cellular compensatory

mechanism in the setting of PC stress. Previous studies have shown that in ET the number of torpedoes is increased several-fold compared with control brains (e.g. Louis, 2014). Torpedoes stained with Luxol fast blue/hematoxylin and eosin (LHE-T) were calculated as total number of torpedoes in the cerebellum.

*Alzheimer's disease pathologies and other neuropathologies.*

In addition to ET specific pathologies examined in the cerebellum, several other neuropathologies were quantified as part of the standard neuropathological examination. There are several characteristic neuropathologic changes of AD that can be measured as described below:

**Thal Phase (Aβ plaque score).** Thal stages refer to the anatomical location of amyloid beta (Aβ)-immunopositivity or presence of amyloid plaques. The "amyloid hypothesis" that the plaques are responsible for the pathology of Alzheimer's disease, is accepted by the majority of researchers, but is by no means conclusively established. Aβ deposits are morphologically diverse and also include non-neuritic structures called diffuse plaques, cored plaques, amyloid lakes and subpial bands. The situation is further complicated because different types of plaques tend to develop in different brain regions, and even though all genetic causes of AD have Aβ deposits, they do not invariably have many neuritic plaques (Crook et al., 1998). Further, Aβ peptides are diverse proteins with heterogeneous lengths, amino- and carboxy-termini and assembly states that span from small oligomers and protofibrils to fibrils with the physical chemical properties of amyloid (Walsh et al., 2007). Amyloid beta protein was identified by molecularly-specific immunohistochemistry and quantified by image analysis. Value is percent area of cortex occupied by amyloid beta. Aβ plaques were then assessed on an ordinal scale of 0-Negative, 1-Mild, 2-Moderate, and 3-Severe. The *Aβ Thal score* was calculated as a severity score: A0 - no Aβ or amyloid plaques; A1- Thal phases 1 or 2; A2 - Thal phase 3; A3 - Thal phases 4 or 5.

**Braak Stage.** Braak Stage is a semi quantitative measure of severity of neurofibrillary tangle (NFT) pathology. Neurofibrillary tangles are formed by hyperphosphorylation of a microtubule-associated protein known as tau, causing it to aggregate, or group, in an insoluble form. These aggregations of hyperphosphorylated tau protein are commonly known as a primary marker of Alzheimer's disease. However, the precise mechanism of tangle formation is not completely understood, and it is still controversial whether tangles are a primary causative factor in disease or play a more peripheral role. *Braak NFT* burden was assessed on an ordinal scale of 0-Negative, 1-Mild, 2-Moderate, and 3-Severe. Braak stages were based upon the distribution and severity of NFT pathology: Braak stages I and II indicate NFTs confined mainly to the entorhinal region of the brain; Braak stages III and IV indicate involvement of limbic regions such as the hippocampus; Braak stages V and VI indicate moderate to severe neocortical involvement. Diagnosis includes algorithm and neuropathologist's opinion.

Bielschowsky silver stain was also used to capture NFT count on a continuous scale in the *Entorhinal Cortex, Hippocampus, Mid-Temporal Cortex, Inferior Parietal Cortex, Mid-Frontal Cortex,* and overall *Cerebral NFT Burden.*

**CERAD (Neuritic Plaques).** CERAD score is a semi quantitative measure of neuritic plaques. Neuritic, or senile plaques, are another major component of AD neuropathologic change; they are extracellular deposits of the Aβ peptide, but their nomenclature and morphologic features are complex. Indeed, neuritic plaques have been considered to be most closely associated with neuronal injury as they are defined by dystrophic neurites within or around deposits of Aβ, and are characterized by greater local synapse loss and glial activation. *Neuritic plaques* were assessed on an ordinal scale of 0-Negative, 1-Mild, 2-Moderate, and 3-Severe.

While AD pathologies are quite common and can exist in "pure" form, they commonly co-exists with non-specific pathologic changes (i.e., atrophy) or changes of other diseases that also can contribute to cognitive impairment.

**Cerebral Cortical Atrophy.** Cortical Atrophy is a common feature of many of the diseases that affect the brain. Atrophy of tissue means a decrement in the size of the cell due to loss of neurons and the connections between them. Cortical atrophy in the Frontal, Parietal, Temporal, and Occipital lobes was measured on a severity scale: 0 – Negative, 1 – Mild, 2 – Moderate, and 3 – Severe. Total *Cerebral Cortical Atrophy* was then calculated as an aggregate sum of atrophy severity in all four cortical regions of the cerebrum.

**Cerebrovascular Disease Burden (CVD-B).** Cerebrovascular Disease (CVD) includes a variety of medical conditions that affect blood vessels of the brain and cerebral circulation, including atherosclerosis, arteriolosclerosis, and cerebral amyloid angiopathy (described below). Vascular Brain Injury (VBI), which describes parenchymal damage from CVD (as well as systemic dysfunction like prolonged hypotension or hypoxia), is typically characterized as infarcts or hemorrhages. CVD was measured on a severity scale with 0 – Negative, 1 – Mild, 2 – Moderate, and 3 – Severe; VBI was measured as 1- Positive and 0 – Negative. *Cerebrovascular Burden* was then calculated as the aggregate sum of CVD and VBI.

**Cerebral Amyloid Angiopathy (CAA).** CAA is a form of angiopathy in which Aβ deposits form in the walls of the blood vessels of the central nervous system. Numerous autopsy studies have suggested that CAA is associated with cognitive impairment (e.g. global cognitive decline and episodic memory loss) and risk for dementia. Indeed, CAA is an important determinant of AD dementia in particular as they often share the APOE ε4 allele (Boyle et al., 2015). That being said, CAA has many manifestations including intracerebral hemorrhage,

microbleeds, and white matter hyperintensities. The presence of CAA interweaves AD and VBI, as Aβ-positive CAA often occurs together with the other neuropathologic changes of AD. *Cerebral Amyloid Angiopathy* was measured on a severity scale: 0 – Negative, 1 – Mild, 2 – Moderate, and 3 – Severe.

*Neuropathological Diagnosis*

In addition to receiving a clinical diagnosis (i.e. Normal, MCI, Dementia) participants were assigned a Neuropathological Diagnosis based on the observed neuropathological change. Such diagnoses could include: 1) *AD-NP change*, 2) *Primary Age-Related Tauopathy* (PART), 3) *Hippocampal Sclerosis* (HS), 4) *Progressive Supranuclear Palsy* (PSP), and 5) *Lewy Body Disease* (LBD), for example.

**AD Neuropathological Diagnosis.** (Per ETCBR, R01NS042859) The modified NIA-Reagan score is based on consensus recommendations for postmortem diagnosis of Alzheimer's disease (See Hyman et al., 2012 for a review of NIA Guidelines). The criteria rely on both neurofibrillary tangles (Braak) and neuritic plaques (CERAD). The criteria is modified because the neuropathological evaluation is done without knowledge of clinical information, including a diagnosis of dementia. The neuropathologist determines the level of AD pathology (1-High, 2-Intermediate, 3-Low, and 4-No AD). Those with intermediate or high fulfill criteria for having a pathologic diagnosis of AD (i.e. neuropathological changes consistent with AD). To elaborate, AD pathology burden is a quantitative summary of AD pathology derived from counts of three AD pathologies discussed below: diffuse amyloid plaques, neurofibrillary tangles, and neuritic plaques—as determined by microscopic examination of silver-stained slides. Each regional count is scaled by dividing by the corresponding standard deviation. The regional measures for each type of pathology are then averaged to obtain summary measures (Thal, Braak, and CERAD scores).

These 3 summary measures are then averaged to obtain the measure of global AD pathology. A neuropathologic diagnosis is made of no AD, possible AD, probable AD, or definite AD based on semiquantitative estimates of neuritic plaque density as recommended by the Consortium to Establish a Registry for Alzheimer's disease (CERAD), modified to be implemented without adjustment for age and clinical diagnosis. CERAD neuropathologic diagnosis of AD required moderate (probable AD) or frequent neuritic plaques (definite AD) in one or more neocortical regions. Diagnosis includes algorithm and neuropathologist's opinion, blinded to age and all clinical data.

*Alzheimer's Disease Neuropathic Change (AD-NP Change).* AD-NP was operationalized as the presence of neuropathological changes considered consistent with Alzheimer's disease, (i.e., both plaques and tangles), but the degree of changes may not be enough to contribute to cognitive impairment.

**Primary age-related Tauopathy (PART).** PART recently described neuropathological designation used to describe the neurofibrillary tangles (NFT) that are commonly observed in the brains of normally aged individuals that can occur independently of the amyloid plaques of Alzheimer's disease (AD) (Crary et al., 2014). Since introduction of PART as a possible neurological disorder, 18% of dementia in normal and 5% of cognitively impaired elderly cases have been attributed to it (Josephs et al., 2017). Patients with severe PART typically exhibit mild cognitive impairment or an amnestic dementia. At autopsy, they display Alzheimer's-type NFT, predominantly in the medial temporal lobe, but no amyloid-beta (Aβ42) peptide accumulation in plaques. Participants who had NFT burden without the presence of Aβ were diagnosed with PART.

**Hippocampal Sclerosis (HS).** HS is a neuropathological condition with severe neuronal cell loss and gliosis in CA1 and subiculum of the hippocampus that is out of proportion to AD-type pathology in the same areas. Individuals with hippocampal sclerosis have similar initial symptoms (e.g. episodic memory loss) and rates of dementia progression to those with Alzheimer's disease (AD), and therefore are frequently misclassified as having Alzheimer's disease. Participants with the presence of clinically significant hippocampal sclerosis were labelled as HS-Positive; those without hippocampal sclerosis were labelled HS-Negative.

**Progressive Supranuclear Palsy (PSP).** PSP is one of a number of subcortical degenerative diseases collectively known as Parkinson's Plus syndrome—featuring the classical signs of Parkinson's disease (tremor, rigidity, akinesia/bradykinesia, and postural instability) with additional symptoms that distinguish them from simple idiopathic Parkinson's disease (PD). In addition to Parkinsonism, PSP is characterized primarily by cognitive and behavioral changes and visual symptoms (e.g. downward gaze palsy). Although the etiology is unknown, the pathophysiology involves the degeneration of neurons and glial cells primarily in the basal ganglia, Supranuclear brainstem, frontal lobes, dentate nucleus, and the spinal cord. Tufts of tau protein in astrocytes, or tufted astrocytes, are also considered diagnostic. PSP diagnosed based clinical diagnosis and on the presence of tufted astrocytes and glial cytoplasmic inclusions.

**Lewy Body Disease.** LBD is a subcortical degenerative disease characterized by changes in behavior, cognition, and movement. The cardinal features of dementia with Lewy bodies are REM sleep behavior disorder, non-threatening visual hallucinations, Parkinsonism, and fluctuations in attention or alertness. LBD is a subset of diseases that shares the feature of abnormal accumulation of α-synuclein in regions of brain. Lewy bodies (LB) are immunoreactive for α-synuclein and are frequent in the setting of moderate to severe levels of

AD neuropathologic change. LB are considered to be independent in some circumstances, since not all cases with LB have AD pathology; however, there appears to be a strong relationship as most individuals with LB burden have concomitant AD neuropathologic change. Pathologic diagnosis of Lewy Body disease describes 4 stages of distribution of α-synuclein in the brain based on algorithm and neuropathologist's opinion. Sections (6 μm) of paraffin-embedded brain tissue (from midfrontal, midtemporal, inferior parietal, anterior cingulate, entorhinal and hippocampal cortices, basal ganglia and midbrain) were stained for α-synuclein immunostain (Zymed; 1:50). Immunohistochemistry was performed using the VECTASTAIN ABC method with alkaline phosphatase as the color developer. McKeith criteria (McKeith et al., 1996) were modified to assess the following categories of Lewy body disease: 0 – not present; 1- nigral-predominant; 2-limbic type; 3-neocortical type. Nigral Lewy bodies were identified as round, intracytoplasmic structures with a darker halo. In the cortex, Lewy bodies were identified as round intracytoplasmic structures, often lacking any halo and with an eccentric nucleus. Only intracytoplasmic Lewy bodies were used as an indicator of positive staining. Note: Both limbic type and neocortical Lewy body disease - are considered "cortical" Lewy body disease; however in ETCBR study (and others) only neocortical are related to dementia. For Study 3, *Lewy Body disease* was determined based on presence of nigral, limbic, or neocortical type LBs.

**PROCEDURE**

The post-mortem neuropathologic evaluation includes a uniform structured assessment of AD pathology, cerebral infarcts, Lewy body disease, and other pathologies common in aging and dementia. The procedures follow those recommended by the National Alzheimer's Disease Coordinating Center (NACC). Pathologic diagnoses of AD use NIA-Reagan and modified CERAD criteria, and the staging of neurofibrillary pathology uses Braak Staging.

**Please note,** the following section is taken directly from <u>R01NS042859 and RO1NS086736</u> grant proposals, and includes information on autopsy procedure and how brain pathology was evaluated:

*Neuropathological Assessment*

**Procedure at the Time of Death.** At the time of death, the brain was removed by a local pathologist, and then the intact, fresh brain was tightly double bagged, placed in a pail containing wet-ice and water, and immediately shipped to the New York Brain Bank according to the Bank's protocol (Vonsattel, Amaya, Cortes, Mancevska, & Keller, 2008).

**Standard Neuropathological Evaluation.** A minimum of 17 standardized blocks were harvested from each brain and processed (Vonsattel, Del Amaya, & Keller, 2008). Brains underwent a complete neuropathological assessment and all evaluations reported here were performed at the New York Brain Bank. Standardized measurements of brain weight (in grams) and postmortem interval (hours between death and placement of brain in a cold room or on ice) were recorded. Paraffin embedded blocks from standardized brain regions were sectioned at 7-μm and stained respectively with Luxol fast blue and hematoxylin and eosin (LH&E) for general tissue survey and assessment of myelin, and the modified Bielschowsky silver stain for axons and neurofibrils. Additional sections were processed with peroxidase-antiperoxidase methods for α-synuclein-, β–amyloid-, and for tauopathic-burdens.

*Quantification of ET-Related Neuropathological Changes:* A standard 3 × 20 × 25 mm parasagittal, formalin-fixed, tissue block was harvested from the neocerebellum; the block included the cerebellar cortex, white matter, and dentate nucleus (Babij et al., 2013; Choe et al., 2016). The block contained the anterior quadrangulate lobules in the anterior lobe of the cerebellar cortex, which are involved in motor control (Stoodley &

Schmahmann, 2009). Using a LH&E stained 7-µm thick section (Babij et al., 2013; Choe et al., 2016), a senior neuropathologist (P.L.F.) blinded to clinical information quantified torpedoes in the entire section. Using the same section, P.L.F. counted Purkinje cell bodies in fifteen 100x fields. The fields were selected as follows: (i) non-adjacent fields representing different regions of the section, and (ii) fields that were between but not inclusive of the base of the fissure and the apex of the folium. The counts obtained above, from fifteen 100x fields, were divided by the length of the Purkinje cell layer centered in the microscopic field (cells/mm). This resulted in a measure of Purkinje cell linear density.

Calbindin$_{D28k}$ immunohistochemistry was performed in free-floating 100 m thick, formalin-fixed vibratome sections of cerebellar cortex to visualize Purkinje cell axonal morphology. The sections were heated at 37°C for 10 min in 20 µg/ml Proteinase K (Roche Applied Science) in 10 mM Tris, 0.1 mM EDTA, pH 8, followed by 1% hydrogen peroxide in PBS for 30 min and serum blocking solution (10% normal goat serum, 1% IgG-free bovine serum albumin [Jackson Immunoresearch], 1% Triton™X-100, in PBS) for 1 hour. Rabbit polyclonal anti-calbindin D28k (1:1000, Swant) was applied overnight at 4°C in antibody diluent (1% IgG-free bovine serum albumin, 1% Triton™X-100 in PBS). Secondary antibody (1:200, 2 hours, biotin-SP goat-anti-rabbit [Fisher Scientific]), followed by streptavidin-horseradish peroxidase (1:200, 1 h, AbD Serotec, for biotinlyated antibodies) was developed with 3,3′ diaminobenzidene chromogen solution (Dako). Purkinje cell axonal morphology in 10 randomly-selected 100X images was quantified: axon recurrent collaterals (an axon with at least a 90° turn back towards the Purkinje cell layer from its initial trajectory) and Purkinje cell axonal

branching (any Purkinje cell axon with at least one branch point; multiple bifurcations on the same axon were not separately counted). The raw counts of Purkinje cell axonal features were normalized to the total length of the Purkinje cell layer length (Babij et al., 2013; Kuo et al., 2016; Louis et al., 2017).

ETCBR lab technicians then followed the recently revised National Institute on Aging–AD Association guidelines for the neuropathologic assessment of AD neuropathologic change (Montine et al., 2012). Core features are: (1) assigning an "ABC" score for AD neuropathologic change that incorporates histopathologic assessments of amyloid β deposits (see Thal et al., 2002) (i.e., "A" in "ABC"), staging of neurofibrillary tangles (see Braak et al. 2006) (i.e., "B" in "ABC"), and scoring of neuritic plaques (see Mirra, 1997) (i.e., "C" in "ABC") (see Montine et al., 2012), (2) a detailed approach for assessing common co-morbid conditions such as cerebrovascular burden (volume and location of macroscopic and microscopic lesions), Lewy body disease (i.e., classification based on alpha-synuclein immunohistochemistry into five categories) and hippocampal sclerosis, and (3) a guide for a minimum sampling of brain regions (see Montine et al., 2012). As recommended, "ABC" scores are transformed into one of four levels of AD neuropathologic change: Not, Low, Intermediate, or High. ETCBR lab also followed neuropathological criteria for PSP (Hauw et al., 1994); and collected data on neuropathological changes in the cerebellum (including heterotopic Purkinje cell counts) (Kuo et al., 2011; Erickson-Davis et al., 2010; Axelrad et al., 2008).

Stained sections from formalin-fixed paraffin embedded blocks are examined as part of a general neuropathologic survey. In brief, 7μm thick sections are stained with hematoxylin and eosin (H&E) and Luxol fast blue/H&E. In addition, selected sections are

stained with the Bielschowsky method for evaluation of neuritic plaques and neurofibrillary neuronal or glial tangles; and with several antibodies (calbindin D28k to evaluate Purkinje cells; monoclonal antibodies to glial fibrillary acidic protein to examine gliosis; alpha-synuclein for Lewy bodies or cytoplasmic glial inclusions; AT8 for hyperphosphorylated tau; ubiquitin to determine either cytoplasmic, nuclear, or neuropil ubiquitinated burden; Fused in Sarcoma [FUS]; and beta-amyloid for amyloid burden). Lewy bodies and Lewy neurites are assessed using quantitative measures on alpha synuclein immunostained sections of locus coeruleus, substantia nigra, and other brain regions. Consortium to Establish a Registry for Alzheimer's Disease (CERAD) plaque score and Braak stage are assigned to each brain.

The formalin fixed tissue was assessed histologically (i.e., hematoxylin and eosin/Luxol fast blue and Bielschowsky silver stain) and immunohistochemically (i.e., antisera targeting b-amyloid, phospho-tau, a-synuclein, and ubiquitin). Cases were assigned a Braak neurofibrillary tangle score categorized by NIA Reagan and CERAD criteria. Sampled brain regions include the frontal cortex (BA9), parietal cortex, primary motor cortex (BA4), visual cortex (BA17), anterior cingulated gyrus, hippocampal formation (at the level of the lateral geniculate nucleus or anterior hippocampus), amygdala, caudate/putamen/globus pallidus, thalamus, cerebellum, substantia nigra, medulla and pons with locus coeruleus and spinal cord. Neuropathological variables included CERAD plaque frequency (none, sparse, moderate, frequent), CERAD NFT frequency, CERAD age-adjusted plaque score (0, A, B, C), CERAD neuropathological diagnosis (possible, probable, definite AD), Braak NFT stage, NIA Reagan classification, CAA score, TDP-43 positivity, a-synuclein positivity and argyrophilic grain positivity.

Manual counts and a custom computer aided macro were also used to quantify various pathology in specific regions of interest (ROIs).

## DATA ANALYSIS PLAN

The goals of these analyses are to examine the relationship between 1) ET-specific, cerebellar pathologies and metacognition, 2) neuropathological changes consistent with AD and metacognition, and finally to explore the relationship between 3) non-ET specific neuropathology and metacognition.

First, I performed individual Mann-Whitney U tests to determine whether overconfidence in memory, language, and executive functioning maps onto the presence of two ET-specific pathologies: 1) Purkinje cell count (PCC) and 2) LHE Torpedoes (LHE-T). I regressed the dependent variables of PCC and LHE-T on the three categorical measures of metacognition (i.e. presence vs. absence of overconfidence in cognitive functioning). Second, I ran a Chi Square Test of Independence to determine whether individuals with AD-NP, neuropathological changes consistent with AD, were more likely than those without AD-NP to be over-confident in their memory, language, and executive functioning abilities. Third, I performed individual Mann-Whitney U tests to determine whether overconfidence in cognitive functioning was associated with a higher degree of (a) individuals Alzheimer's pathologies (amyloid β deposits, neurofibrillary tangles (NFT), and neuritic plaques), (b) specificity of hyperphosphorylated tau burden in the hippocampus, mid-temporal cortex, and frontal cortex, (c) cortical atrophy in the temporal and frontal lobes, (d) cerebral amyloid angiopathy and (e) cerebrovascular disease burden. Please note, the rationale for utilizing nonparametric analyses (i.e. Mann-Whitney U tests) to assess the relationship between specific neuropathologies and metacognition is that the dependent variables were ordinal or continuous, but not normally distributed (Fields, 2013).

Also, given that 1) fewer than 20 participants were in each metacognitive group (i.e. over confident vs. not overconfident) and that 2) the method used to calculate $p$ values does not correct for ties in data (i.e., when two or more participants have identical values on the dependent variable), the asymptotic p-value will be reported.

## RESULTS

Individual Mann-Whitney U tests (Tables 13, 14, and 15) were performed to examine whether the degree of ET-specific, cerebellar pathologies differed between those who were overconfident and those who were not overconfident in their cognitive functioning. Specifically, Mann-Whitney U tests were conducted to examine whether overconfidence in (1) memory, (2) language, and (3) executive functioning were associated with (a) PCC and (b) LHE-T. The relationship between PCC and metamemory ($U = 16$, $p = 1.00$, $r = 0.00$), metalanguage ($U = 13$, $p = .487$, $r = 0.20$), and meta-executive functioning ($U = 21$, $p = .360$, $r = 0.26$) was not significant. The relationship between LHE-T and metamemory ($U = 39$, $p = .066$, $r = -0.55$), metalanguage ($U = 5$, $p = .346$, $r = -0.28$), and meta-executive functioning ($U = 13$, $p = .850$, $r = -0.06$) was not significant. These results suggest that distortions in metacognition in the direction of overconfidence in cognitive functioning are not attributable to ET-specific, cerebellar pathologies.

Three Chi Square Tests of Independence (Tables 16, 17, and 18) were performed to examine the relationship between overconfidence in (1) memory, (2) language, and (3) executive functioning and the diagnosis of AD-NP. The relationship between the diagnosis of AD-NP and overconfidence in memory functioning was not significant, $\chi^2$ (2, N = 21) $= .081$, $p = 0.78$ (Fisher's Exact Test, $p = 0.59$). The relationship between the diagnosis of AD-NP and

overconfidence in language functioning was not significant, $\chi^2$ (2, N = 21) = .420, $p$ = 0.52 (Fisher's Exact Test, $p$ = 0.45). The relationship between the diagnosis of AD-NP and overconfidence in executive functioning was not significant, $\chi^2$ (2, N = 21) = 2.35, $p$ = 0.13 (Fisher's Exact Test, $p$ = 0.15). These findings suggests that individuals diagnosed on autopsy with neuropathological changes consistent with AD are not more likely than those with a different pathological diagnosis to exhibit over-confidence in memory, language, or executive functioning.

Individual Mann-Whitney U tests (Tables 13, 14, and 15) were performed to examine whether the degree of non-ET specific neuropathologies (regardless of pathological diagnosis) differed between those who were overconfident and those who were not over confident in their cognitive functioning. Specifically, Mann-Whitney U tests were conducted to determine whether individuals who were overconfident in (1) memory, (2) language, and (3) executive functioning abilities exhibited a higher degree of (a) Alzheimer's pathology (amyloid β deposits, neurofibrillary tangles (NFT), and neuritic plaques), (b) specificity of NFTs in the hippocampus, mid-temporal cortex, and frontal cortex, (c) cortical atrophy in the temporal and frontal lobes, (d) cerebral amyloid angiopathy (CAA), and (e) cerebrovascular disease burden. For brevity, only test statistics of significant Mann-Whitney U tests are reported in this section (please refer to Tables 13-15 for additional statistics). Analyses revealed that the degree of hypothesized pathologies (a-e) did not differ significantly between those who were overconfident in their memory abilities as compared to those who were not over-confident in their memory abilities. Overall, these findings suggest that individuals who overestimate their memory abilities are not more likely than those who do not overestimate their memory abilities to exhibit greater non-ET specific neuropathological burden.

Analyses revealed that of the hypothesized pathologies only degree of Thal Aβ ($U = 66.5$, $p = .018$, $r = -0.28$), NFTs in the mid-temporal lobe ($U = 67$, $p = .009$, $r = 0.59$), and CAA ($U = 63.5$, $p = .025$, $r = 0.49$) differed significantly between those who were overconfident in their language abilities as compared to those who were not over-confident in their language abilities. These findings suggest that overestimation of language functioning is associated with increased neurological burden of amyloid plaques, neurofibrillary tangles particularly in the mid-temporal lobe, and cerebral amyloid angiopathy, but not with other non-ET specific pathologies.

Analyses revealed that of the hypothesized pathologies only degree of temporal atrophy ($U = 81$, $p = .034$, $r = 0.46$) differed significantly between those who were overconfident in their executive functioning abilities as compared to those who were not over-confident in their executive functioning abilities. These findings suggest that overestimation of executive functioning is associated with increased temporal atrophy, but not with other non-ET specific pathologies.

## DISCUSSION

Study 3 investigated the neuropathological substrates of awareness among older adults with Essential Tremor (ET). In an effort to develop a more comprehensive understanding of metacognition, the current study examines not only metamemory, but also metalanguage and meta-executive functioning. As discussed in the conclusion of Study 2, our incomplete understanding of what drives the dramatic variability in awareness deficits that emerge in the context of disease underscores the importance of expanding the scope of research into the factors that influence self-awareness more broadly. Despite progress in the definition and measurement of metacognition, the psychological and neural underpinnings of metacognitive accuracy remain ill understood. In tandem with Study 2, which examined whether psychological characteristics

explain variability in awareness among those with ET, the current study serves as the neurological piece towards completing a greater metacognitive puzzle.

Consistent with the procedures of Studies 1 and 2, I measured metacognition by comparing offline, *global* estimations (i.e., subjective assessments of general performance) to objective performance in three domains of cognitive functioning. In contrast to the previous two studies I conducted, a dichotomized rather than continuous measure of metamemory, metalanguage, and meta-executive functioning was utilized. As discussed earlier, the rationale for dividing participants into two groups (i.e. Overconfident and Not Overconfident) was twofold: first, a previous study conducted by Azar and colleagues (2017) using the same sample of older adults with ET (as in Studies 2 and 3), found that among those who exhibited distortions in metacognition, these individuals tended to overestimate rather than underestimate their functioning; this finding is in line with previous metacognitive and subjective cognitive decline (SCD) studies which have demonstrated that individuals with neurological disorders (e.g. stroke, Alzheimer's disease, and frontotemporal dementia) tend to be over-confident as opposed to under-confident in their abilities, particularly when controlling for such symptoms as depression and anxiety (e.g. Shany-Ur, 2014). Second, while I postulated that increased pathology burden is associated with over-confidence in cognitive functioning, I did not want to make a specious assumption that as pathology decreases, individuals become under-confident in their abilities.

Ultimately, the aims of the current study were to determine whether disordered metacognition in the direction of overconfidence in cognitive functioning was associated with 1) an increased burden of ET-specific, cerebellar pathology, 2) a postmortem diagnosis of neuropathological changes consistent with Alzheimer's disease (AD-NP), or 3) the degree of other neuropathological substrates and regional specificity of disease burden. As a brief review,

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Study 1 found that premorbid, psychological characteristics did in fact explain a significant proportion of the variability in awareness among healthy, community-dwelling older adults. However, when examining mood and personality constructs in a neurologic cohort of community-dwelling older adults with ET in Study 2, these findings were not replicated. Although there are certainly various explanations for these disparate findings (e.g. differences in measurement of metacognition), one consideration involves the neurologic characteristic of the sample. Study 2 begs the question: Are methodological limitations (e.g. the measures used to calculate metacognition) obstructing our view of the true impact of mood and personality on awareness or does neuropathology better explain variability in accuracy of metacognition in this population?

**Essential Tremor and Alzheimer's Disease Pathology.** Contrary to hypotheses, I found that overconfidence in memory, language, and executive functioning abilities was not associated with ET-specific cerebellar pathologies (i.e. decreased Purkinje cell count and increased LHE torpedoes). Given the high comorbidity rates of ET and AD as well as the observation that approximately 70% of the sample received a neuropathological diagnosis of neuropathological changes consistent with AD (AD-NP), I examined whether distorted awareness might be explained by the presence of this secondary neurodegenerative condition. Contrary to hypotheses, individuals who overestimated their memory, language, or executive abilities were not more likely than those who did not overestimate their functioning to be diagnosed with AD-NP. Although these findings diverge from my hypotheses, they are nonetheless clinically remarkable. In the aforementioned study by Azar and colleagues (2017), the researchers found that in this neurologic sample of older adults with Essential Tremor, individuals with normal cognitive functioning made largely accurate assessments of their memory, language, and

executive functioning; whereas, individuals with cognitive impairment were largely responsible for inaccurate estimations in the direction of overconfidence. Thus, one possible explanation for the null findings is that clinical diagnosis of cognitive functioning (i.e. normal, MCI, or dementia) might better account for metacognitive variability than ET or AD-NP. In fact, subsequent exploratory analyses (Tables 19 and 20) found that individuals who exhibited objective cognitive impairment tended to be overconfident in their memory ($\chi^2$ (2, N = 21) = 10.09, p <.01) and executive functioning abilities ($\chi^2$ (2, N = 21) = 7.88, p <.01), but not their language functioning. Moreover, as described in Table 11, individuals with AD-NP were relatively evenly distributed in terms of cognitive or clinical status; given that only approximately 60% of individuals with AD pathology exhibited cognitive impairment, it is possible that the remaining 40%, who were diagnosed as cognitively normal, had not yet reached a critical threshold in which clinical symptoms (e.g. anosognosia, cognitive deficits) become manifest. This theory aligns with the notion of *brain reserve*, which was proposed to account for the frequently seen discrepancy between pathological and clinical status, and is defined as the brain's resilience or its ability to cope with increasing structural damage while functioning adequately. This threshold model presumes the existence of a fixed cut-off point, which once reached, would herald the emergence of symptoms of dementia (e.g. Mori et al., 1997). Thus, as we progress towards a multifactorial, biopsychosocial model of awareness—it may be argued that clinical diagnosis is a more sensitive biomarker of disordered metacognition than the neural substrates of ET and AD.

While I did not find that ET-specific pathologies or the diagnosis of neuropathological changes consistent with AD were associated with overconfidence in cognitive functioning, I sought to examine whether the degree of specific AD pathologies as well as other pathological

changes—including (a) amyloid β deposits, neurofibrillary tangles (NFT), and neuritic plaques, (b) specificity of hyperphosphorylated tau burden in the hippocampus, mid-temporal cortex, and frontal cortex, (c) cortical atrophy in the temporal and frontal lobes, and (d) cerebral amyloid angiopathy, and (e) cerebrovascular disease burden—differed in severity between those who were overconfident and those who were not overconfident in their memory, language, and executive functioning. The following sections briefly discuss the findings of this third and final research question.

**Metamemory and Neuropathology.** The current study measured awareness of memory functioning by comparing an individual's subjective rating of his or her ability to remember to objective performance on a measure of delayed recall. Contrary to hypotheses, I found that individuals who overestimated their memory abilities were not more likely than those who did not overestimate their memory abilities to exhibit a greater degree of specific neuropathologies. While these findings may align with the aforementioned theory of *brain reserve*—that is, participants with such pathologies may not have reached a clinical threshold at which point they would exhibit distortions in metamemory—it is important to consider whether the small sample size of this study (N = 21) and reduced power may prevent us from detecting an effect when there is in fact an effect to be detected. With more people in each confidence group, we might be able to see the true impact of these hypothesized disease pathologies on metamemory accuracy. That said, this interpretation is less convincing considering that we found differences in degree of neuropathology within metalanguage and meta-executive functioning domains. Thus, perhaps a more apt explanation for null findings might be that the metamemory discrepancy score (i.e. subjective rating of ability to remember – objective performance on CVLT long delay) maps less precisely or reliably onto neuropathological changes than our other discrepancy scores.

Alternatively, the specific pairing of subjective and objective measures to assess memory awareness may be less valid or reliable than the pairings for language and executive functioning awareness. Future studies might consider investigating the association between neuropathologies and metacognitive metrics at the task level—that is, whether the types of metric used for measuring metacognition (i.e. single vs. multiple item subjective measure of cognitive functioning) differ in their sensitivity to detecting underlying neuropathological changes.

**Metalanguage and Neuropathology.** The current study measured awareness of language functioning by comparing an individual's subjective rating of his or her ability to find the right word to objective performance on a measure of verbal fluency. My hypotheses were only partially confirmed such that overestimation of language functioning was associated with increased burden of amyloid plaques, neurofibrillary tangles particularly in the mid-temporal lobe (MT-NFT), and cerebral amyloid angiopathy (CAA), but not with other neurological changes. While numerous studies have demonstrated an association between these pathologies and SCD (Perrotin et al., 2009), there is a dearth of and inconsistencies in the literature regarding their association with metacognitive ability. Again, this inconsistency or variability is likely attributable to multiple factors including differences in measurement of awareness and point of disease progression.

Diffuse amyloid plaques, MT-NFTs, and CAA have long been recognized as morphological hallmarks of AD (e.g. Janson, 2015; Visser et al., 2004). Although we did not find that the formal diagnosis of AD-NP was associated overconfidence—likely because the size and distribution of the confidence groups was quite limited and the majority of the sample had this diagnosis —the degree of certain individual AD neuropathologies appears to be independently associated with disordered awareness of language functioning. Future studies should therefore

investigate whether overconfidence in metalanguage may be an earlier or more sensitive

indicator of AD neuropathological changes than metamemory and (as discussed below) meta-

executive functioning disturbance. These findings, in conjunction with the null findings

described in the previous paragraph, may also suggest that there are separate pathways of

awareness. Said differently, these results call into question whether discrete neuropathologies

affect metacognition differentially across cognitive domain. I made the assumption in my

hypotheses that metamemory, metalanguage, and meta-executive functioning have shared

neuropathological underpinnings; however, the outcome of this study challenges this notion. An

area of future research might be to explore whether structural changes in the brain are

differentially associated with levels of awareness across different domains of cognitive

functioning and among various neurodegenerative disorders.

**Meta-Executive Functioning and Neuropathology.** Awareness of executive

functioning was measured by comparing an individual's subjective rating of his or her ability to

multitask to objective performance on a measure of task switching. My hypotheses were only

partially supported such that overestimation of executive functioning was associated with

increased temporal atrophy, but not with other neuropathological changes. While I have

remarked that such factors as reduced power of the sample, neuropathological distribution, and

measurement of metacognition may be preventing us from detecting additional effects, this result

is nonetheless clinically interesting. Briefly, the temporal lobe is involved in numerous cognitive

functions, including memory and emotional processing. Of note, neuroimaging studies have

established the presence of strong cortical connectivity between the temporal lobe and

neocortical regions of the brain including the dorsolateral prefrontal cortex and the anterior

cingulate cortex—areas that have been repeatedly associated with higher order, metacognitive

ability as well as executive functioning (e.g. Allen et al., 2005; Lacruz et al., 2007). Thus, one interpretation of this result is that temporal atrophy may lead to reduced connectivity with specific frontal regions that are largely responsible for maintaining metacognitive accuracy. Furthermore, given the absence of an association between overconfidence in meta-executive functioning and amyloid pathology (e.g. CAA and amyloid plaques), one possibility is that meta-executive disturbance may be a more sensitive indicator of PART—a Tauopathy that occurs independently of the amyloid plaques of Alzheimer's disease. Thus, when taken together, a potential interpretation of the current study—and an exciting area for future research—is that overconfidence in meta-executive and metalanguage functioning may be sensitive or early indicators of PART and AD pathology, respectively.

<p style="text-align:center">***</p>

Overall, while I found some convergence around temporal lobe conservation in language and executive functioning awareness, I did not find that meta-executive functioning, metalanguage, and metamemory shared many neuropathological substrates. These results are nonetheless clinically informative and could begin to teach us about what supports these different metacognitive networks. These findings suggest that some indicators of Alzheimer's disease, and possibly, PART may be more closely associated with metacognitive changes than others, and that measures of metalanguage and meta-executive functioning may in fact map better than the metamemory measure onto certain pathological outcomes.

**Limitations and Future Directions.** The current study has both strengths and limitations. A significant strength is that this is the first study of its kind that utilizes post mortem evaluations to examine the neuropathological substrates of metacognition among individuals with Essential Tremor (ET). That said, there are a few limitations that are important to address.

First, as discussed in detail in Study 2, the use of a single-item subjective measure of cognitive functioning to calculate metacognitive discrepancy scores is likely a limitation of the study. While the three self-ratings were paired in an *a priori* manner (and confirmed using bivariate correlations) to objective neuropsychological tests commonly used to assess these cognitive domains, they may be less robust and reliable than ratings based on multiple items for each domain. A second limitation is the relatively small size of the sample, which may preclude us from detecting existing effects. Similarly, the neuropathological homogeneity (i.e. majority exhibited AD-NP) of the sample is another limitation. That said, given that this is the first year in which autopsy data were available in this longitudinal study, the relationships between neuropathological substrates and metacognition will continue to be explored in the coming months and years. Thus, we should be careful when extrapolating from these early findings as significant differences could emerge in the context of a larger autopsy sample. A final limitation of this study involves the diagnosis of ET. While Purkinje cell count and LHE torpedoes were utilized as biomarkers of ET severity, there is no measure of the clinical progression of ET—that is, perhaps some participants may exhibit greater ET functional burden than others. Future studies might consider including a measure that assesses the clinical severity of ET given that functional impairment due to ET symptomatology (i.e. reduction in basic and instrumental activities of daily living) could have a profound impact on one's perception of their cognitive or daily functioning.

In sum, the current study represents an important step towards understanding the specific neuropathological substrates that are associated with metacognition among older adults with Essential Tremor. This study raises intriguing questions about the discrete pathways of awareness as well as the extent to which different metacognitive metrics may be more sensitive

indicators of neuropathological change. As we continue to collect neuropathological data and increase both sample size and heterogeneity, we may begin to build a multifactorial model of awareness that takes into consideration such factors as cognitive diagnosis, psychological characteristics, age, education, and neural substrates to better predict disordered awareness. Using this information, we can develop proposals for identifying and intervening with individuals at risk for engaging in unsafe behaviors—leading to a more positive outcome for older adults with ET and other neurodegenerative disorders.

## CHAPTER V: Conclusion

Ultimately, my objective for this dissertation was to contribute to a developing picture of the factors that influence awareness. Key theoretical challenges for future research will be to identify the distinct influences and contributions of both neurocognitive and socio-environmental factors, and to clarify which awareness phenomena are amenable to appropriate and sensitive intervention. Moreover, to properly account for their heterogeneous contributions, future research should measure the influence of these factors on individuals directly within the mixture model estimations. Moving forward, this research may be applied towards developing a multifactorial biopsychosocial equation for predicting disordered metacognition. Obstacles for clinical practice will be to identify where it is appropriate to attempt to increase awareness and where it is preferable to find ways of managing unawareness, and to help caregivers understand the nature and extent of the person's awareness and tailor their interactions accordingly. By understanding and working effectively with awareness phenomena there is a strong potential to reduce disability and enhance wellbeing. Therefore, further knowledge in this area should be vigorously pursued. My hope is that by espousing a biopsychosocial approach, and identifying the psychological characteristics and neuropathological substrates associated with distortions in

awareness, we may be better equipped to facilitate appropriate interventions, enhance decision

making capacity, and maintain individual autonomy among older adults.

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APPENDIX A

**TABLE 1. Study 1: Demographic, Cognitive, and Clinical information (*N=157*)**

|  | **Mean (SD)** | **Range** |
|---|---|---|
| **Demographics** | | |
| Age | 64.48 (8.79) | 50 - 85 |
| Education | 16.26 (2.60) | 0 - 24 |
| Gender (female/male %) | 67/23% | - |
| Race (Asian/Black/White %) | 3/9/88% | - |
| **Cognitive and Clinical Information** | | |
| *RAVLT age corrected Z scores\** | | |
| Trial 1 | -.16 (.98) | -2.80 - 3.00 |
| Trial 2 | .72 (.77) | -1.39 - 2.30 |
| Trial 3 | .03 (1.07) | -2.89 - 2.48 |
| Trial 4 | -.44 (1.06) | -3.37 - 1.89 |
| Trial 5 | -.25 (1.04) | -3.86 - 1.96 |
| Trial 6 | .09 (.35) | -.50 - 2.15 |
| Delay | -.04 (1.37) | -2.92 - 3.33 |
| *Current and past psychiatric diagnosis* | | |
| No diagnosis or condition on Axis I (%) | 69 % | - |
| Major Depressive Disorder (%) | 8 % | - |
| Depressive Disorder NOS | 2 % | - |
| Anxiety Disorder | 5 % | - |

*Note.* RAVLT, Rey Auditory Verbal Learning Test. *RAVLT scores in the sample are calculated based on published, age-adjusted normative data (Roberts & Schmidt, 1996).

**TABLE 2. Principal Component Matrix of seven memory–related items (CFQ-M) from the Cognitive Failures Questionnaire (*N*=157)**

| | |
|---|---|
| COGFQ_02: Do you find you forget why you went from one part of the house to the other? | .623 |
| COGFQ_06: Do you find you forget whether you've turned off a light or a fire or locked the door? | .683 |
| COGFQ_12: Do you find you forget which way to turn on a road you know well but rarely use? | .683 |
| COGFQ_16: Do you find you forget appointments? | .597 |
| COGFQ_17: Do you forget where you put something like a newspaper or a book? | .722 |
| COGFQ_20: Do you find you forget people's names? | .513 |
| COGFQ_23: Do you find you forget what you came to the shops to buy? | .711 |

*Note*. COGFQ, Cognitive Failures Questionnaire

**TABLE 3. Model fit indices for one to three class solutions of the mood and personality (*N*=157)**

| Fit Indices | 1 Class | 2 Classes* | 3 Classes |
|---|---|---|---|
| AIC | 3124.65 | 2872.19 | 2796.02 |
| BIC | 3173.55 | 2948.59 | 2899.93 |
| SSBIC | 3122.90 | 2869.46 | 2792.31 |
| Entropy | - | .919 | .883 |
| Lo-Mendell-Rubin Adjusted LRT | - | 264.64 | 92.148 |
| *P-value* | - | *<0.0001* | *.651* |
| Bootstrapped LRT *P*-value | - | *<0.0001* | *<0.0001* |

*Note.* AIC, Akaike information criterion; BIC, Bayesian information criterion; SSBIC, sample size adjusted Bayesian information criterion.

**TABLE 4. General Linear Model Examines Metamemory as a Function of the Composite of Personality and Mood, Covarying for Age, Gender, and Education**

| Source | df | Mean Square | F | Sig.[b] | Partial Eta Squared | Observed Power |
|---|---|---|---|---|---|---|
| Corrected Model | 4 | 9.21 | 5.42 | <.001 | .13 | .97 |
| Intercept | 1 | 0.01 | .01 | .93 | .00 | .05 |
| Age | 1 | 4.43 | 2.61 | .11 | .02 | .36 |
| Gender | 1 | 10.03 | 5.89 | .02 | .04 | .67 |
| Education | 1 | 1.46 | .86 | .36 | .01 | .15 |
| Class Membership LCA | 1 | 17.15 | 10.09 | .002 | .06 | .88 |

b. Alpha = .05

**TABLE 4a. T-Test Compares Metamemory In Each LCA Group Against Zero**

| LCA Groups | N | Mean (SD) | $t$ | df | Sig. |
|---|---|---|---|---|---|
| Class 1 | 112 | 0.18 (1.26) | 1.59 | 111 | .116 |
| Class 2 | 39 | -0.52 (1.41) | -2.32 | 38 | 0.02* |

*Note.* Class 1, Low Negative Affect. Class 2, High Negative Affect. *One Sample T-tests were conducted to determine whether mean metamemory scores for Classes 1 and 2 differed significantly from zero.

**TABLE 4b. T-Test Compares Metamemory In Each Gender Against Zero**

| Gender | N | Mean (SD) | $t$ | df | Sig. |
|---|---|---|---|---|---|
| Male | 45 | 0.44 (1.33) | 2.24 | 44 | 0.03* |
| Female | 106 | -0.18 (1.29) | -1.45 | 105 | .151 |

*Note.* One Sample T-tests were conducted to determine whether mean metamemory scores for males and females differed significantly from zero.

**TABLE 5. Study 2: Demographic, Cognitive, and Clinical Information (*N = 223*)**

|  | Mean (SD) | Range |
|---|---|---|
| **Demographics** | | |
| Age | 79 (9.37) | 56-97 |
| Education | 15.62 (2.73) | 9 - 20 |
| Gender (female/male %) | 61.3/36.6% | - |
| Race (Asian/Black/White %) | 1/1/81.2% | - |
| *Current and past psychiatric diagnosis* (N)* | | |
| Depressive Disorder NOS | 7 | - |
| Generalized Anxiety Disorder | 44 | - |

*Note.* * Psychiatric Diagnoses are based on the Generalized Anxiety Disorder-7 ($\geq$10) and Geriatric Depression Scale ($\geq$10).

**Table 6. Conversion of Objective Standardized Scores**

| Standardized Objective Test Scores | | Ordinal Scores |
|---|---|---|
| **z-scores** | **Scaled Scores** | |
| $\geq$ 2.0 | $\geq$16 | Excellent |
| > 1.0 and < 2.0 | $\geq$ 13 and $\leq$15 | Above Average |
| > - 1.0 to $\leq$ 1.0 | $\geq$7 and $\leq$15 | Average |
| > -2.0 and $\leq$ - 1.0 | $\geq$4 and $\leq$6 | Below Average |
| $\leq$ -2.0 | $\leq$3 | Very Impaired |

**TABLE 7. Model fit indices for one to three class solutions of the mood and personality (*N*=223)**

| Fit Indices | 1 Class | 2 Classes* | 3 Classes |
|---|---|---|---|
| AIC | 3707.38 | 3554.67 | 3484.88 |
| BIC | 3755.08 | 3629.63 | 3587.10 |
| SSBIC | 3710.71 | 3559.90 | 3492.02 |
| Entropy | - | 0.92 | 0.80 |
| Lo-Mendell-Rubin Adjusted LRT | - | 164.90 | 83.85 |
| *P-value* | - | *0.05* | *0.38* |
| Bootstrapped LRT *P*-value | - | *<0.0001* | *<0.0001* |

*Note.* AIC, Akaike information criterion; BIC, Bayesian information criterion; SSBIC, sample size adjusted Bayesian information criterion.

**TABLE 8. General Linear Model Examines Metamemory as a Function of the Composite of Personality and Mood, Covarying for Age, Gender, and Education**

| Source | df | Mean Square | F | Sig.[b] | Partial Eta Squared | Observed Power |
|---|---|---|---|---|---|---|
| Corrected Model | 4 | 7.88 | 3.45 | .010 | .074 | .850 |
| Intercept | 1 | .591 | .259 | .611 | .001 | .080 |
| Age | 1 | 3.05 | 1.34 | .249 | .008 | .210 |
| Gender | 1 | 22.06 | 9.67 | .002 | .053 | .871 |
| Education | 1 | 3.18 | 1.39 | .239 | .008 | .217 |
| Class Membership LCA | 1 | .010 | .004 | .948 | .000 | .050 |

b. Alpha = .05

**TABLE 8a. T-Test Compares Metamemory In Each Gender Against Zero**

| Gender | N | Mean (SD) | *t* | df | Sig. |
|---|---|---|---|---|---|
| Male | 75 | 0.45 (1.59) | 2.95 | 74 | .004* |
| Female | 108 | -0.36 (1.37) | -2.26 | 107 | .027* |

*Note.* *One Sample T-tests were conducted to determine whether mean metamemory scores for males and females differed significantly from zero.

**TABLE 9. General Linear Model Examines Metalanguage as a Function of the Composite of Personality and Mood, Covarying for Age, Gender, and Education**

| Source | df | Mean Square | F | Sig.[b] | Partial Eta Squared | Observed Power |
|---|---|---|---|---|---|---|
| Corrected Model | 4 | 2.33 | 1.07 | .375 | .024 | .331 |
| Intercept | 1 | .657 | .300 | .585 | .002 | .085 |
| Age | 1 | 4.72 | 2.16 | .144 | .012 | .309 |
| Gender | 1 | .583 | .266 | .606 | .002 | .081 |
| Education | 1 | 3.35 | 1.53 | .217 | .009 | .234 |
| Class Membership LCA | 1 | .990 | .452 | .502 | .003 | .103 |

b. Alpha = .05

**TABLE 10. General Linear Model Examines Meta-Executive Functioning as a Function of the Composite of Personality and Mood, Covarying for Age, Gender, and Education**

| Source | df | Mean Square | F | Sig.[b] | Partial Eta Squared | Observed Power |
|---|---|---|---|---|---|---|
| Corrected Model | 4 | 7.29 | 2.97 | .021 | .063 | .786 |
| Intercept | 1 | 1.55 | .633 | .427 | .004 | .124 |
| Age | 1 | 15.29 | 6.24 | .013 | .034 | .700 |
| Gender | 1 | 7.27 | 2.96 | .087 | .016 | .402 |
| Education | 1 | 7.69 | 3.14 | .078 | .017 | .421 |
| Class Membership LCA | 1 | 1.04 | .424 | .516 | .002 | .009 |

b. Alpha = .05

**TABLE 10a. One Sample T-Test Compares Meta-Executive Functioning Within Each Age Group Against Zero**

| Age | N | Mean (SD) | t | df | Sig. |
|---|---|---|---|---|---|
| Y-M Age | 82 | -0.32 (1.36) | -2.15 | 81 | .034* |
| VO Age | 105 | 0.22 (1.72) | 1.28 | 104 | .203 |

*Note.* Y-M Age, Young-Middle Old Age (≤78 years); VO Age, Very Old Age (≥79 years). Age groups were determined by mean and median of sample as well as qualitative analysis of mean plots. *One Sample T-tests were conducted to determine whether mean meta-executive functioning scores for Y-M and VO groups differed significantly from zero.

**TABLE 11. Study 3: Demographic, Clinical, and Neuropathological Information (*N = 21*)**

|  | Mean (SD) | Range |
|---|---|---|
| **Demographics** | | |
| Age at Baseline | 88.67 (4.66) | 73 – 94 |
| Age at Autopsy | 89.84 (4.71) | 74 – 95 |
| Education | 16.26 (2.60) | 9 - 20 |
| Gender (female/male %) | 61.9/38.1% | - |
| Race (White %) | 100% | - |
| **Clinical Diagnoses* *(N)*** | | |
| Normal Cognition | 7 | - |
| Cognitive Impairment | 14 | - |
|     Mild Cognitive Impairment | 8 | - |
|     Dementia | 6 | - |
| **Neuropathological Diagnosis** *(N)*** | | |
| Alzheimer's Type Pathology | 15 | - |
|     Normal Cognition | 6 | |
|     Mild Cognitive Impairment | 5 | |
|     Dementia | 4 | |
| Primary Age-Related Tauopathy | 3 | - |
| Hippocampal Sclerosis | 1 | - |
| Progressive Supranuclear Palsy | 1 | - |
| Lewy Body Disease | 1 | - |
| **Specific Neuropathologies** | | |
| Nft Hippocampus | 28.62 (38.97) | 0 – 153 |
| Nft Entorhinal Cortex | 27.21 (32.31) | 3 – 121 |
| Nft Mid Temporal Cortex | 6.05 (14.45) | 0 – 64 |
| Nft Mid Frontal Cortex | 2.55 (2.89) | 0 – 8 |

| | | |
|---|---|---|
| Nft Inferior Parietal Cortex | 0.94 (1.26) | 0 – 5 |
| Total NFT Severity | 62.24 (75.40) | 8 – 310 |
| Frontal Atrophy | 1.24 (0.44) | 0 – 1 |
| Parietal Atrophy | 0.81 (0.51) | 0 – 2 |
| Temporal Atrophy | 1.38 (0.74) | 0 – 2 |
| Occipital Atrophy | 1.05 (1.07) | 0 – 4 |
| Cortical Atrophy Severity | 4.48 (1.91) | 1 – 9 |
| THAL Aβ | 2 (1) | 0 – 3 |
| CERAD | 1.95 (1.02) | 0 – 3 |
| BRAAK | 1.9 (0.77) | 0 – 3 |
| Lewy Bodies | 0.1 (0.30) | 0 – 1 |
| Cerebral Amyloid Angiopathy | 0.71 (1.01) | 0 – 3 |
| Cerebrovascular Disease Burden | 3.57 (0.87) | 1 – 4 |
| LHE Torpedoes | 55.41 (52.36) | 5 – 195 |
| Purkinje Cell Count | 0.04 (0.01) | 0 – 0 |
| **Metacognition Distribution** | | |
| Metamemory (*N, % Overconfident*) | 13, 61.9% | - |
| Metalanguage (*N, % Overconfident*) | 5, 23.8% | - |
| Meta-executive functioning (*N, % Overconfident*) | 9, 42.9% | - |

*Note.* MCI, Mild Cognitive Impairment; LHE Torp, Torpedoes in the cerebellar hemisphere stained using Luxol fast blue and counterstained with hematoxylin-eosin; Thal Aβ, Amyloid β plaque deposits; Braak, Staging of Neurofibrillary tangles; CERAD, Scoring of Neuritic Plaques; Nft, Neurofibrillary tangles. *Clinical diagnoses are based on clinical case conferences with a licensed neuropsychologist and neurologist. **Neuropathological diagnoses are identified by a neuropathologist during autopsy.

**TABLE 12. Studies 1-3: Descriptive Statistics and Distributions of Metacognition**

| | | Mean | SD | Median | Range |
|---|---|---|---|---|---|
| Study 1 (N=157) | Metamemory | 0.01 | 1.33 | 0.14 | -3.99 – 2.64 |
| Study 2 (N=223) | Metamemory | 0.12 | 1.55 | 0.11 | -3.95 – 4.79 |
| | Metalanguage | -0.12 | 1.48 | -0.25 | -3.75 – 3.41 |
| | Meta-Executive | -0.02 | 1.59 | -0.06 | -3.17 – 4.92 |
| Study 3 (N=21)* | Metamemory (61.9%**) | 0.86 | 1.50 | 0.75 | -1.66 – 4.49 |
| | Metalanguage (24%) | -0.26 | 1.11 | -0.47 | .2.15 – 1.52 |
| | Meta-Executive (43%) | -0.02 | 1.93 | -0.54 | -4.46 – 2.79 |

*Note*. *Descriptive statistics for Study 3 are based on a continuous measure of metamemory, metalanguage, and meta-executive functioning. **Values in parentheses are percentage of participants who were overconfident in their cognitive functioning.

**TABLE 13. Mann-Whitney U Tests Examine the Relationship between Overconfidence in Memory Functioning and Neuropathological Features**

| Neuropathology | | Mean Rank (N) | | U | Z | p-value | r (effect size) |
|---|---|---|---|---|---|---|---|
| | | N-OC | OC | | | | |
| ET-Specific Pathology | LHE Torpedoes | 9 (3) | 4.88 (8) | 39 | -1.84 | .066 | -0.55 |
| | Purkinje Cell Count | 6.5 (4) | 6.5 (8) | 16 | .000 | 1.00 | 0.00 |
| ABC Score | Thal Aβ | 10 (8) | 11.62 (13) | 60 | .627 | .531 | 0.14 |
| | Braak | 10.19 (8) | 11.50 (13) | 58.5 | .526 | .599 | 0.11 |
| | CERAD | 10.31 (8) | 11.42 (13) | 57.5 | .424 | .672 | 0.09 |
| Tangle Counts | Nft Hippocampus | 9.12 (8) | 12.15 (13) | 67 | 1.08 | .277 | 0.24 |
| | Nft Mid-Temp Cortex | 9.62 (8) | 11.08 (12) | 55 | .549 | .583 | 0.12 |
| | Nft Mid-Frontal Cortex | 12.56 (8) | 9.12 (12) | 31.5 | -1.31 | .191 | -0.29 |

| | | N-OC | OC | | | | |
|---|---|---|---|---|---|---|---|
| | Nft Entorhinal Cortex | 9.75 (8) | 10.18 (11) | 46 | .166 | .869 | 0.04 |
| | Nft IPC | 8.43 (7) | 10.18 (11) | 46 | .727 | .467 | 0.17 |
| | Total Nft Cortex | 10.88 (8) | 11.08 (13) | 53 | .072 | .942 | 0.02 |
| Cortical Atrophy | Frontal Atrophy | 9.81 (8) | 11.73 (13) | 61.5 | .932 | .352 | 0.20 |
| | Temporal Atrophy | 9.13 (8) | 12.15 (13) | 67 | 1.20 | .230 | 0.26 |
| | Parietal Atrophy | 11.50 (8) | 10.69 (13) | 48 | -.367 | .714 | -0.08 |
| | Occipital Atrophy | 9.94 (8) | 11.65 (13) | 60.5 | .741 | .459 | 0.16 |
| | Total Cortical Atrophy | 9.88 (8) | 11.69 (13) | 61 | .663 | .507 | 0.14 |
| Other Conditions | CAA | 8.38 (8) | 12.62 (13) | 73 | 1.76 | .079 | 0.38 |
| | CVD-B | 9.44 (8) | 11.96 (13) | 64.5 | 1.21 | .225 | 0.26 |
| | Lewy Bodies | 10 (8) | 11.62 (13) | 60 | 1.14 | .255 | 0.25 |

*Note.* N-OC, Not Overconfident in memory functioning; OC, Overconfident in memory functioning; LHE Torp, Torpedoes in the cerebellar hemisphere stained using Luxol fast blue and counterstained with hematoxylin-eosin; ABC Score, Amyloid, Braak, and CERAD staging scores were calculated by a neuropathologist at autopsy to determine the presence of neuropathological changes consistent with Alzheimer's disease; Thal Aβ, Amyloid β plaque deposits; Braak, Staging of Neurofibrillary tangles; CERAD, Scoring of Neuritic Plaques; Nft Hippocampus, Neurofibrillary tangle count in the hippocampus; Nft Mid-Temp Cortex, Neurofibrillary tangle count in the Mid-Temporal Cortex; Nft Mid-Frontal Cortex; Neurofibrillary tangle count in the Mid-Frontal Cortex; Nft Entorhinal Cortex, Neurofibrillary tangle count in the Entorhinal Cortex; Nft IPC, Neurofibrillary tangle count in the Inferior Parietal Cortex; Total Nft Cortex, Total Neurofibrillary tangle count in the cerebral cortex; CAA, Cerebral Amyloid Angiopathy; CVD-B, Cerebrovascular Disease Burden.

**TABLE 14. Mann-Whitney U Tests Examine the Relationship between Overconfidence in Language Functioning and Neuropathological Features**

| Neuropathology | | Mean Rank (N) | | U | Z | p-value | r (effect size) |
|---|---|---|---|---|---|---|---|
| | | N-OC | OC | | | | |
| ET-Specific Pathology | LHE Torpedoes | 6.44 (9) | 4 (2) | 5 | -.934 | .346 | -0.28 |
| | Purkinje Cell Count | 6.20 (10) | 8 (2) | 13 | .695 | .487 | 0.20 |
| ABC Score | Thal Aβ | 9.34 (16) | 16.30 (5) | 66.5 | 2.37 | .018* | 0.52 |
| | Braak | 9.84 (16) | 14.70 (5) | 58.5 | 1.71 | .088 | 0.37 |
| | CERAD | 10.16 (16) | 13.7 (5) | 53.5 | 1.19 | .235 | 0.26 |
| Tangle Counts | Nft Hippocampus | 10.38 (16) | 13 (5) | 50 | .827 | .408 | 0.18 |
| | Nft Mid-Temp Cortex | 8.53 (15) | 16.40 (5) | 67 | 2.62 | .009* | 0.59 |
| | Nft Mid-Frontal Cortex | 10.20 (15) | 11.40 (5) | 42 | .404 | .686 | 0.09 |
| | Nft Entorhinal Cortex | 9.71 (14) | 10.80 (5) | 39 | .371 | .711 | 0.09 |
| | Nft IPC | 9.65 (13) | 9.10 (5) | 30.5 | -.211 | .833 | -0.05 |
| | Total Nft Cortex | 10.09 (16) | 13.09 (5) | 54.5 | 1.19 | .231 | 0.26 |
| Cortical Atrophy | Frontal Atrophy | 11.12 (16) | 10.60 (5) | 38 | -.224 | .823 | -0.05 |
| | Temporal Atrophy | 10.31 (16) | 13.20 (5) | 51 | 1.01 | .315 | 0.22 |
| | Parietal Atrophy | 11.62 (16) | 9 (5) | 30 | -1.05 | .296 | -0.23 |
| | Occipital Atrophy | 10.62 (16) | 12.20 (5) | 46 | .596 | .551 | 0.13 |
| | Total Cortical Atrophy | 10.56 (16) | 12.40 (5) | 47 | .588 | .557 | 0.13 |

| Other Conditions | CAA | 9.53 (16) | 15.70 (5) | 63.5 | 2.24 | .025* | 0.49 |
|---|---|---|---|---|---|---|---|
| | CVD-B | 11 (16) | 11 (5) | 40 | .000 | 1.00 | 0.00 |
| | Lewy Bodies | 111.31 (16) | 10 (5) | 35 | -.811 | .417 | -0.18 |

*Note.* N-OC, Not Overconfident in language functioning; OC, Overconfident in language functioning; LHE Torp, Torpedoes in the cerebellar hemisphere stained using Luxol fast blue and counterstained with hematoxylin-eosin; ABC Score, Amyloid, Braak, and CERAD staging scores were calculated by a neuropathologist at autopsy to determine the presence of neuropathological changes consistent with Alzheimer's disease; Thal Aβ, Amyloid β plaque deposits; Braak, Staging of Neurofibrillary tangles; CERAD, Scoring of Neuritic Plaques; Nft Hippocampus, Neurofibrillary tangle count in the hippocampus; Nft Mid-Temp Cortex, Neurofibrillary tangle count in the Mid-Temporal Cortex; Nft Mid-Frontal Cortex; Neurofibrillary tangle count in the Mid-Frontal Cortex; Nft Entorhinal Cortex, Neurofibrillary tangle count in the Entorhinal Cortex; Nft IPC, Neurofibrillary tangle count in the Inferior Parietal Cortex; Total Nft Cortex, Total Neurofibrillary tangle count in the cerebral cortex; CAA, Cerebral Amyloid Angiopathy; CVD-B, Cerebrovascular Disease Burden.

**TABLE 15. Mann-Whitney U Tests Examine the Relationship between Overconfidence in Executive Functioning and Neuropathological Features**

| Neuropathology | | Mean Rank (N) | | $U$ | Z | *p-value* | *r (effect size)* |
|---|---|---|---|---|---|---|---|
| | | N-OC | OC | | | | |
| ET-Specific Pathology | LHE Torpedoes | 6.14 (7) | 5.75 (4) | 13 | -.189 | .850 | -0.06 |
| | Purkinje Cell Count | 5.88 (8) | 7.75 (4) | 21 | .916 | .360 | 0.26 |
| ABC Score | Thal Aβ | 11.33 (12) | 10.56 (9) | 50 | -.308 | .758 | -0.07 |
| | Braak | 10.62 (12) | 11.50 (9) | 58.5 | .357 | .721 | 0.08 |
| | CERAD | 9.08 (12) | 13.56 (9) | 77 | 1.74 | .082 | 0.38 |
| Tangle Counts | Nft Hippocampus | 9.29 (12) | 13.28 (9) | 74.5 | 1.46 | .144 | 0.32 |
| | Nft Mid-Temp Cortex | 10.95 (11) | 11.06 (9) | 54.5 | .386 | .699 | 0.09 |
| | Nft Mid-Frontal Cortex | 11.32 (11) | 9.50 (9) | 40.5 | -.703 | .482 | -0.16 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Nft Entorhinal Cortex | 8.88 (12) | 11.93 (7) | 55.5 | 1.14 | .253 | 0.26 |
| | Nft IPC | 9.10 (10) | 10 (8) | 44 | .380 | .704 | 0.09 |
| | Total Nft Cortex | 10 (12) | 12.33 (9) | 66 | .854 | .393 | 0.19 |
| Cortical Atrophy | Frontal Atrophy | 12 (12) | 9.67 (9) | 42 | -1.16 | .248 | -0.25 |
| | Temporal Atrophy | 8.75 (12) | 14 (9) | 81 | 2.12 | .034* | 0.46 |
| | Parietal Atrophy | 11.17 (12) | 10.78 (9) | 52 | -.180 | .857 | -0.04 |
| | Occipital Atrophy | 9.33 (12) | 13.22 (9) | 74 | 1.71 | .087 | 0.37 |
| | Total Cortical Atrophy | 9.42 (12) | 13.11 (9) | 73 | 1.37 | .170 | 0.30 |
| Other Conditions | CAA | 10.08 (12) | 12.22 (9) | 65 | .903 | .367 | 0.20 |
| | CVD-B | 10.92 (12) | 11.11 (9) | 55 | .095 | .924 | 0.02 |
| | Lewy Bodies | 10 (12) | 12.33 (9) | 66 | 1.68 | .094 | 0.39 |

*Note.* N-OC, Not Overconfident in executive functioning; OC, Overconfident in executive functioning; LHE Torp, Torpedoes in the cerebellar hemisphere stained using Luxol fast blue and counterstained with hematoxylin-eosin; ABC Score, Amyloid, Braak, and CERAD staging scores were calculated by a neuropathologist at autopsy to determine the presence of neuropathological changes consistent with Alzheimer's disease; Thal Aβ, Amyloid β plaque deposits; Braak, Staging of Neurofibrillary tangles; CERAD, Scoring of Neuritic Plaques; Nft Hippocampus, Neurofibrillary tangle count in the hippocampus; Nft Mid-Temp Cortex, Neurofibrillary tangle count in the Mid-Temporal Cortex; Nft Mid-Frontal Cortex; Neurofibrillary tangle count in the Mid-Frontal Cortex; Nft Entorhinal Cortex, Neurofibrillary tangle count in the Entorhinal Cortex; Nft IPC, Neurofibrillary tangle count in the Inferior Parietal Cortex; Total Nft Cortex, Total Neurofibrillary tangle count in the cerebral cortex; CAA, Cerebral Amyloid Angiopathy; CVD-B, Cerebrovascular Disease Burden.

**Table 16. Results of Chi-square Test Examining the Association between AD-NP Diagnosis and Overestimation of Memory Functioning**

| | Neuropathological Diagnosis | |
|---|---|---|
| Over-Estimation | AD-NP Change | Other NP Change |
| No | 2 (33.3) | 4 (66.7) |
| Yes | 6 (40) | 9 (60) |

*Note*. AD-NP, Alzheimer's Disease-Neuropathological change; NP, Neuropathological change; $\chi^2$ = .081, df = 1, $p$ = 0.78. Numbers in parentheses indicate percentages.

**Table 17. Results of Chi-square Test Examining the Association between AD-NP Diagnosis and Overestimation of Language Functioning**

| | Neuropathological Diagnosis | |
|---|---|---|
| Over-Estimation | AD-NP Change | Other NP Change |
| No | 4 (66.7) | 2 (33.3) |
| Yes | 12 (80) | 3 (20) |

*Note.* AD-NP, Alzheimer's Disease-Neuropathological change; NP, Neuropathological change; $\chi^2$ = .420, df = 1, $p$ = 0.52. Numbers in parentheses indicate column percentages.

**Table 18. Results of Chi-square Test Examining the Association between AD-NP Diagnosis and Overestimation of Executive Functioning**

| | Neuropathological Diagnosis | |
|---|---|---|
| Over-Estimation | AD-NP Change | Other NP Change |
| No | 5 (83.3) | 1 (16.7) |
| Yes | 7 (46.7) | 8 (53.3) |

*Note.* $\chi^2$ = 2.35, df = 1, $p$ = 0.13. Numbers in parentheses indicate column percentages.

**Table 19. Results of Chi-square Test Examining the Association between Clinical Diagnosis and Overestimation of Memory Functioning**

| | Clinical/Cognitive Diagnosis | |
|---|---|---|
| Over-Estimation | Normal Cognition | Cognitive Impairment |
| No | 6 (75%) | 2 (25%) |
| Yes | 1 (7.7%) | 12 (92.3%) |

*Note.* $\chi^2$ = 10.09, df = 1, $p$ = .001. Numbers in parentheses indicate column percentages.

**Table 20. Results of Chi-square Test Examining the Association between Clinical Diagnosis and Overestimation of Executive Functioning**

| | Clinical/Cognitive Diagnosis | |
|---|---|---|
| Over-Estimation | Normal Cognition | Cognitive Impairment |
| No | 7 (58.3%) | 5 (41.7%) |
| Yes | 0 (0%) | 9 (64.3.3%) |

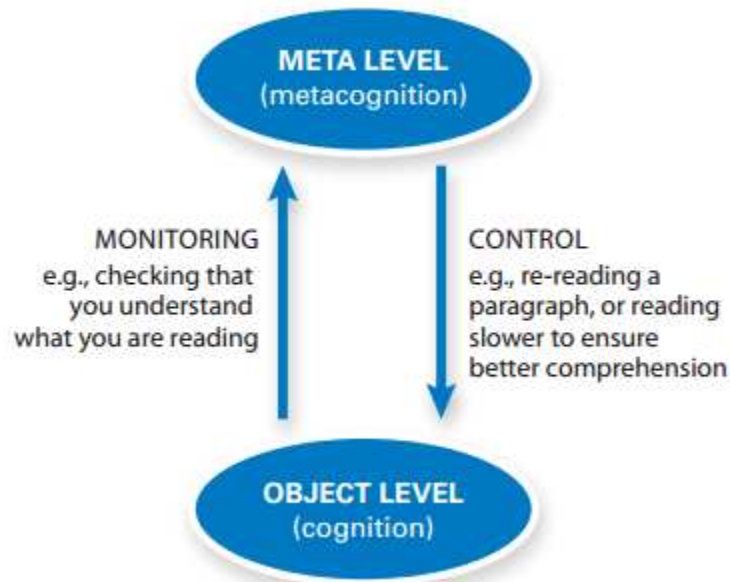*Note.* $\chi^2$ = 7.88, df = 1, $p$ = .005. Numbers in parentheses indicate column percentages.

Figure 1. Nelson and Narens' (1990) Model of Metacognition. The object level is where cognitive processes or 'one's thinking' occurs. The higher order metacognitive level is where your 'thinking about thinking' takes place; this meta-level both monitors and controls the contents of the object level.
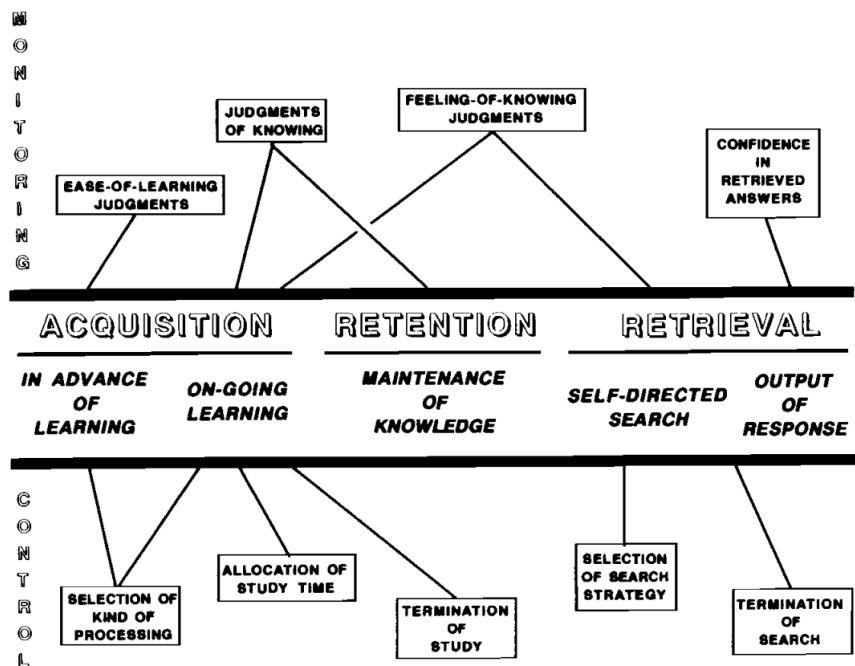


Figure 2. Main stages in theoretical memory framework from Nelson and Narens (1990).
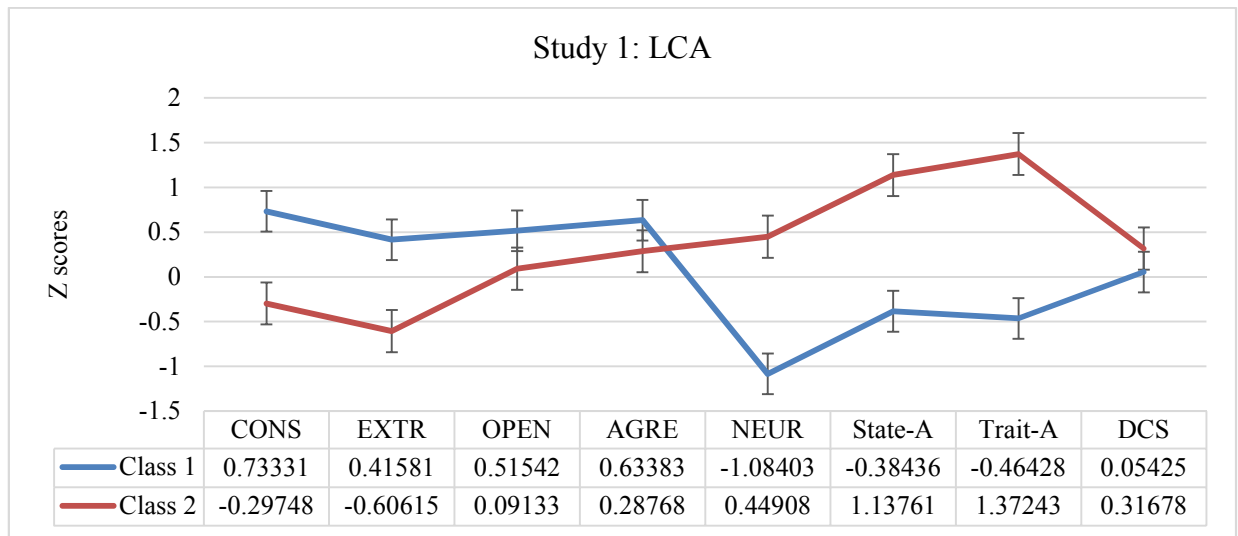
Figure 3. CONS, Conscientiousness; EXTR, Extraversion; OPEN, Openness; AGREE, Agreeableness; NEUR, Neuroticism; State-A, State Anxiety; Trait-A, Trait Anxiety; DCS, Depression Composite Scale

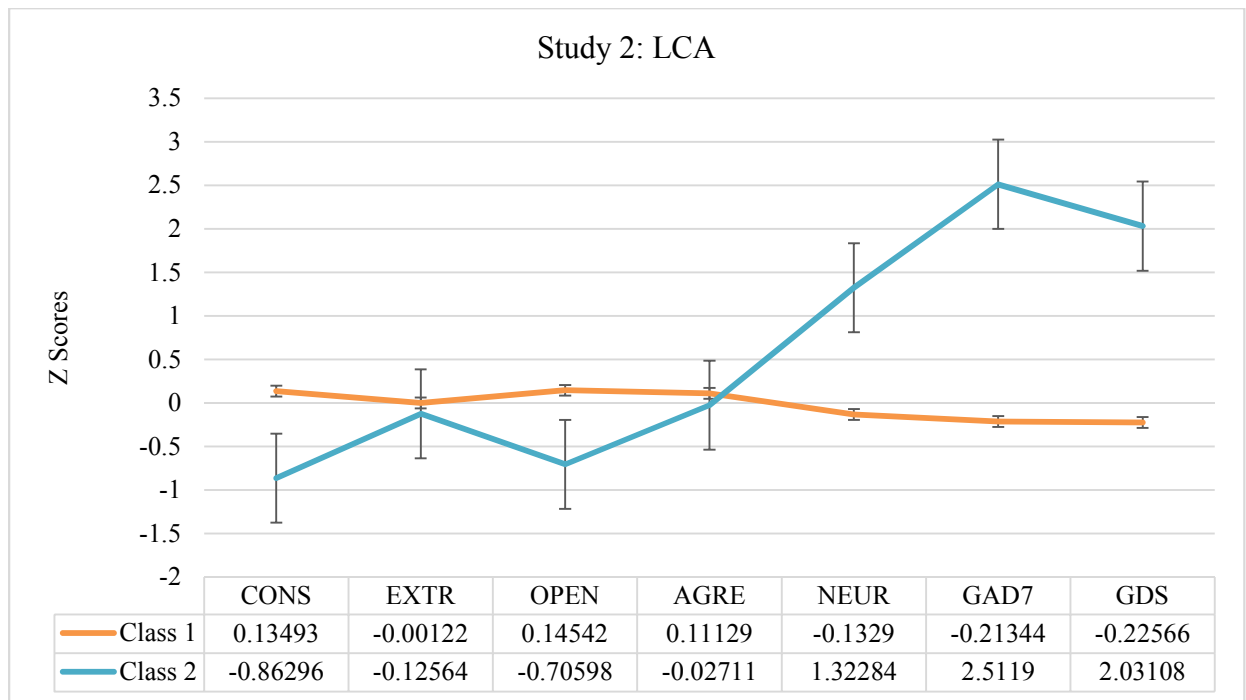| | CONS | EXTR | OPEN | AGRE | NEUR | State-A | Trait-A | DCS |
|---|---|---|---|---|---|---|---|---|
| Class 1 | 0.73331 | 0.41581 | 0.51542 | 0.63383 | -1.08403 | -0.38436 | -0.46428 | 0.05425 |
| Class 2 | -0.29748 | -0.60615 | 0.09133 | 0.28768 | 0.44908 | 1.13761 | 1.37243 | 0.31678 |



Figure 4. CONS, Conscientiousness; EXTR, Extraversion; OPEN, Openness; AGREE, Agreeableness; NEUR, Neuroticism; GAD-7, Generalized Anxiety Disorder 7-Item Scale; GDS, The Geriatric Depression Scale

| | CONS | EXTR | OPEN | AGRE | NEUR | GAD7 | GDS |
|---|---|---|---|---|---|---|---|
| Class 1 | 0.13493 | -0.00122 | 0.14542 | 0.11129 | -0.1329 | -0.21344 | -0.22566 |
| Class 2 | -0.86296 | -0.12564 | -0.70598 | -0.02711 | 1.32284 | 2.5119 | 2.03108 |