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# *"I don't recognize myself", personality characteristics in subjective cognitive impairment and mild cognitive impairment*

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# ABSTRACT

**Background**: Personality changes are common in early stages of many neurodegenerative disorders and often precede cognitive deficits. In individuals with cognitive impairment an increase in feelings of distress and worry (neuroticism) and a decrease in social interpersonal behavior (extraversion) are frequently observed. However, few studies have examined the usefulness of personality assessment in combination with other clinical measurements for the identification of individuals at risk of cognitive decline and dementia. The main aim of the thesis was to examine the significance of personality characteristics in diagnosing prodromal stages of dementia.

**Methods**: The thesis is based on a sample of patients examined for early dementia symptoms at the Memory Clinic, Karolinska University Hospital. The study groups consisted of 35 patients diagnosed with mild cognitive impairment (MCI), 24 with subjective cognitive impairment (SCI) and 26 controls recruited from the community. *Study I* examined patterns of personality across study groups. *Study II* investigated degree of agreement between self- and informant ratings of personality, in relation to cognitive function, in patient groups and controls. *Study III* explored the usefulness of combining personality and cognitive measurements in discriminating patients groups and controls. *Study IV* investigated differences in cognition, personality and CSF biomarkers between memory clinic patients with varying degrees of cognitive impairment. We also analyzed which variables predict conversion to dementia at follow up after three years.

**Results**: *Study I*: Patients with MCI and SCI presented specific patterns of personality with higher scores in traits related to anxiety proneness and aggression-hostility and lower in traits of extraversion, compared to controls. *Study II*: Correlations between patient- and informant ratings of patients' personality were fair to moderate on a majority of personality traits. Measures of incongruence between patients and informants were significantly larger in MCI than in controls across personality scales. Incongruence between raters was negatively correlated with a measure of global cognitive function. *Study III*: Combining cognitive and personality measurements resulted in a better discrimination between groups than any of the measurements used alone. Cognitive tests discriminated MCI from SCI and controls, while personality features separated SCI from controls. *Study IV*: Three years before diagnose, converters to dementia showed a profile of cognitive impairment, higher levels of neuroticism, and lower levels of extraversion and Aβ42, respectively. Low levels of Aβ42 and low results in an episodic memory test predicted conversion to dementia.

**Conclusions:** Patients with MCI and SCI differ in their patterns of personality compared to controls, but not when compared to each other. Disagreement between patients with MCI and their informants may be related to cognitive impairment. Adding personality assessment improves discrimination of patients at risk of cognitive decline. Personality has an independent role early in the disease process, but does not predict disease progression.

# LIST OF PUBLICATIONS

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# CONTENTS

# LIST OF ABBREVIATIONS

| | |
|---|---|
| AD | Alzheimer's disease |
| aMCI | Amnestic mild cognitive impairment |
| ANOVA | Analysis of variance |
| CI | Confidence interval |
| CSF | Cerebrospinal fluid |
| CSDD | Cornell Scale for Depression in Dementia |
| CT | Computed tomography |
| DA | Discriminant analyses |
| DLB | Dementia with Lewy bodies |
| DSM-IV | Diagnostic and Statistical Manual of Mental Disorders 4$^{th}$ edition |
| E | Extraversion |
| EPI/Q | Eysenck Personality Inventory/Questionnaire |
| FFM | Five-Factor-Model |
| FTD | Frontotemporal dementia |
| LP | Lumbar puncture |
| M | Mean |
| MCI | Mild cognitive impairment |
| MCI/P | Mild cognitive impairment with personality features |
| MMSE | Mini-Mental State Examination |
| MRI | Magnetic resonance imaging |
| N | Neuroticism |
| NEO-PI | NEO Personality Inventory |
| NFT | Neurofibrillary tangles |
| OR | Odds ratio |
| PD | Parkinson's disease |
| PET | Positron emission tomography |
| P-tau | Phosphorylated tau |
| RAVLT | Rey Auditory Verbal Learning Test |
| ROCF | Rey Osterrieth complex figure |
| SCI | Subjective cognitive impairment |
| SD | Standard deviation |
| 16 PF | Sixteen Personality Factor Questionnaire |
| SPECT | Single-photon emission computed tomography |
| SSP | Swedish universities Scales of Personality |
| TMT | Trail Making Test |
| T-tau | Total tau |
| VaD | Vascular dementia |
| WAIS-R | Wechsler Adult Intelligence Scale – Revised |
| WHO | World Health Organization |

# 1 INTRODUCTION

This thesis has its origin in my clinical work as a neuropsychologist, examining patients with varying degrees of cognitive impairment, at the Memory Clinic, Karolinska University Hospital in Huddinge, Sweden. In addition to cognitive problems, patients often claimed they didn't recognize themselves, that they had become someone else. In response to weakening memory functions and increased stress vulnerability, they had withdrawn from social interactions, were quieter and less active. Some of them seemed just as worried about the personality changes as cognitive losses. Others appeared more relaxed, finding coping strategies to handle the threat to self-confidence and self-esteem that often follow from diminished intellectual abilities.

Patients' and informants' reports clearly demonstrated that certain personality traits have important implications for the disease process and clinical expression of symptoms, particularly in early stages of dementia. Consequently, one motive to do research in the field is to examine whether patients' experiences of personality change are generalizable to a larger population, another to find out which personality traits that may be of clinical significance when diagnosing patients with mild cognitive impairment (MCI) and subjective cognitive impairment (SCI).

## 1.1 PERSONALITY RESEARCH

Research in older populations has investigated personality in relation to somatic and psychiatric conditions [1], functional abilities [2], life events [3] and mortality [4]. With a growing number of elderly people and increased life expectancy, studies on changes in personality due to normal aging and dementia have come into focus. Numerous studies have demonstrated that specific patterns of personality may be useful for prediction and identification of individuals at risk of cognitive decline and dementia. A summary of studies published within the field of personality, aging and neurodegenerative disorders are presented in table 1.

### 1.1.1 Self- versus informant ratings

Since unawareness of personality change [5] and cognitive disabilities [6-7] are common features in many neurodegenerative disorders, information from a reliable collateral source (e.g. partner, children, employer) is essential during diagnostic dementia work-up. With disease progression a decrease in the accuracy of self-reports can be expected. However, in individuals with minor cognitive deficits it is uncertain whether informant ratings are more accurate than self-reports of personality. In preclinical stages informants may have difficulties noticing subjective and subtle personality changes. As noted in other works and the literature summary in table 1, studies of personality in individuals with MCI and SCI have primarily used self-reports, whereas research on elderly with AD often is based on informant or physician ratings [8-10]. Accordingly, with a gradual loss of insight and memory impairment, a combination of self- and/or or informant reports will probably result in a more comprehensive clinical picture.

Measurements of discrepancy between raters [5] and/or self-other agreement have been used to examine accuracy of perception, or self-awareness, in individuals with cognitive impairment. Self-ratings of personality, by healthy individuals, agree moderately with peer ratings across a variety of personality traits ($r > 0.40$) [11-13]. Yet, in early stages of dementia the degree of self-informant agreement on personality is reduced, with informants reporting larger differences between personality traits than individuals who have the disease themselves [14]. The results indicate that during disease progression the ability to up-date the self-image may be distorted and what remains is the memory of an older version of ones personality.

Earlier research has shown that self-other agreement is adjusted by type of relationship and living conditions. More precise reports of individuals' memory functions [15] and higher agreement on personality have been observed for persons living together [12] and in closer relationships [13]. Features of the situation, the person being rated and the rater, have also been associated with agreement [16-18]. In addition, a higher degree of self-other agreement for ratings of observable, outgoing, behaviors, compared to more emotional personality traits has consistently been demonstrated [19-21]. Thus, when evaluating patients' and informants' reports of cognitive decline, one has to have in mind that a number of factors related to their current lives and common history may bias their perception.

Table 1. Studies on personality, aging and neurodegenerative disorders

| Authors (year) | Personality inventory | Self (S) or Informant (I) rating | Design | Participants (n) | Results |
|---|---|---|---|---|---|
| ***Middle aged participants*** | | | | | |
| Jelicic et al. (2003) | EPQ | S | Cross-sectional, longitudinal | 185 | No relation btw neuroticism and current cognition or cognitive decline |
| Crowe, Pedersen, Andet, Fratiglioni & Gatz (2006) | EPQ | S | Longitudinal, registry study | 4039 | High neuroticism in middle age increased risk of MCI 25 years later |
| ***Healthy elderly*** | | | | | |
| Smith-Gamble et al. (2002) | CAMDEX-R | I | Longitudinal, population based | 3021 | Preclinical personality change doubled risk for dementia |
| Meier, Perrig-Chiello & Perrig (2002) | FPI (N+E-scales) | S | Longitudinal, | 287 | High extra-version and low neuroticism associated with better episodic memory |
| Wilson et al. (2005) | NEO-FFI (N-scale) | S | Longitudinal | 4392 | 30% faster cognitive decline in persons high in distress |
| Wang et al. (2009) | EPI | S | Longitudinal, population based | 506 | Low neuroticism and high extraversion associated with lowest dementia risk |
| Wilson et al. (2011) | A six-item measure of N | S | Longitudinal, cohort study | 785 | Neuroticism related to increased AD risk, decline in memory and speed, but not to neuropathology |

Table 1. (continued)

| Authors (year) | Personality inventory | Self (S) or Informant (I) rating | Design | Participants (n) | Results |
|---|---|---|---|---|---|
| ***Participants with SCI and MCI*** | | | | | |
| Siegler et al. (1991) | NEO-PI | I | Cross-sectional, retrospective | 35 (MCI) | Higher neuroticism and lower openness extraversion, and conscientiousness compared to premorbid levels |
| Copeland et al. (2003) | Interview | S | Cross-sectional | 112 (MCI)<br>32 (controls) | Increased agitation and passivity in converters to AD |
| Vestberg, Passant, Risberg & Elfgren (2007) | NEO-FFI | S | Cross-sectional | 27 (SMI)<br>30 (MCI) | No personality differences between SCI and MCI |
| Ausén, Edman, Almkvist & Bogdanovic (2009) | SSP | S | Cross-sectional | 24 (SCI)<br>35 (MCI)<br>26 (controls) | Higher stress susceptibility, somatic and psychic anxiety in SCI and MCI than controls |
| Clement, Belleville, Bélanger & Chassé (2009) | EPI | S | Cross-sectional | 30 (MCI)<br>27 (controls) | No difference in personality between MCI and controls |
| Duberstein et al. (2011) | NEO-FFI | S | Longitudinal | 767 (MCI+controls) | High neuroticism, low openness and conscientiousness at age 72 increased risk for AD |
| Kuzma, Sattler, Toro, Schönknecht & Schröder (2011) | NEO-FFI | S | Longitudinal | 66 (MCI)<br>156 (controls) | Higher baseline neuroticism in MCI than in controls; high neuroticism increased risk for MCI 2.24 times |

Table 1. (continued)

| Authors (year) | Personality inventory | Self (S) or Informant (I) rating | Design | Participants (n) | Results |
|---|---|---|---|---|---|
| ***Participants with AD*** | | | | | |
| Jacomb & Jorm (1996) | Goldberg's standard adjective rating scales (short form) | I | Cross-sectional | 50 (AD)<br>167 (UNS)<br>50 (controls) | A global change in personality in AD; increased neuroticism and decreased extraversion, agreeableness, conscientiousness and intellect |
| Wilson et al. (2004) | Goldberg's standard adjective rating scales | I | Longitudinal | 363 (AD) | Premorbid high distress negatively related to episodic memory at baseline, but not to memory decline or other cognitive function |
| Duchek, Balota, Storandt & Larsen (2007) | NEO-FFI | S & I | Cross-sectional | 74 (v mild AD)<br>46 (mild AD)<br>36 (younger controls)<br>131 (older controls) | Higher neuroticism and lower conscientiousness in persons with very mild AD compared to controls |
| Talassi, Cipriani, Bianchetti & Trabucchi (2007) | Brooks and McKinaly's Personality Inventory | I | Longitudinal | 52 (AD)<br>15 (controls) | After AD onset an increase of negative personality traits |
| Archer et al. (2008) | NEO-FFI | I | Retrospective | 213 (AD) | Midlife neuroticism predicted younger age of dementia onset in females, but not in males |

EPQ/I=Eysenck Personality Questionnaire/Inventory; CAMDEX-R=Cambridge Mental Disorders of the Elderly Examination; FPI=Freiburg Personality Inventory; NEO-FFI/PI=NEO Five-Factor Inventory/Personality Inventory; N/E-scale=Neuroticism/Extraversion-scale

### 1.1.2 Personality and cognition

Research on the relationship between personality traits and cognitive functions have generally yielded small, but significant, correlations. Results indicate that personality and cognition are two separate, but interrelated domains of human life. A Seattle based longitudinal study have examined the relationship between personality and cognition since 1956, using a number of cognitive tests and personality questionnaires. In this study correlations ranged from small to modest and the personality factors that were primarily associated with high cognitive performance were Untroubled Adequacy, low Conservatism and low Group Dependency, from Catell's personality dimensions, and Openness to experiences from the NEO Personality Inventory (NEO-PI) [22]. A cross-sectional study found negative correlations between several cognitive tests from the Wechsler Adult Intelligence scale (WAIS-R), and the personality traits Embitterment, Somatic Trait Anxiety, Psychic Trait Anxiety, Stress Susceptibility and Mistrust, from the Swedish universities Scales of Personality (SSP) [23].

There is further evidence that personality has a moderating effect on cognition. Several studies have shown that high levels of neuroticism (proneness to worry and distress) in midlife increase the risk of cognitive decline and dementia in old age [24-25]. Other reports, including older populations, have demonstrated associations between high stress susceptibility, rumination and anxiety, and lower scores in measures of episodic- and working memory [26-27], psychomotor speed [27] and global cognitive functioning [28-29].

The interplay between cognitive and personality dimensions has implications for the progression in neurodegenerative disorders. It has been suggested that a *cognitive reserve* capacity protects against cognitive decline [30] and that high extraversion [31] and a stable or reduced level of neuroticism are associated with better cognitive performance in older individuals [32]. Thus, a stable personality and low neuroticism in particular, equals a *personality reserve* that may have a protective effect against cognitive deterioration.

### 1.1.3 Trait Theory and Factor-Models

#### *1.1.3.1 Introduction*

Classification of personality has a long history. About 400 BC the Greek physician Hippocrates launched a four-factor model of personality. The theory stated that individuals could be characterized according to one of four traits, or temperaments, which were expressions of the so-called body humors; melancholic (black bile), choleric (yellow bile), sanguine (blood) and phlegmatic (phlegm) [33]. The dominance of a body humor resulted in a specific personality type. A melancholic person would be introverted and susceptible to depression, a choleric person assertive and irritable, a sanguine person extraverted and impulsive and a phlegmatic person relaxed and occasionally sluggish. During the following centuries, the physician Galen (200 AD) and others, further developed Hippocrates' model, but in its essence his ideas have had an influence on medicine and the concept of personality until modern times [33].

#### *1.1.3.2 Personality traits*

Personality traits are enduring psychological and biological dispositions that govern how we think, feel and behave in different situations and environments. These dispositions, or patterns of personality, may be inferred from self- or other reports, can be quantified and employed to examine intra- and inter-individual differences, describe particular personality profiles and predict outcome in human behaviors and activities.
Trait theory was developed to examine differences between individuals and has been used in describing current states and developmental changes, i.e. in cross-sectional and longitudinal studies.

#### *1.1.3.3 The lexical approach – a starting point for trait theory*

Discussing the lexical tradition one has to mention Sir Francis Galton, famous for his diverse contributions to the field of psychology. In the late 19$^{th}$ century he was one of the first to recognize that personality traits of importance for inter-individual differences have a direct bearing on the words used to describe them. The more significant the trait is for differentiating people, the more it will result in a precise term in the common language. Galton scanned an English dictionary, registered and grouped about 1000 personality related words describing different aspects of human character [34]. According to a review of trait theory, Galton's work inspired others, but had little impact on contemporary personality research [35].

During the twentieth century the development of scientific and statistical methods resulted in numerous, lexically based, attempts to find a common taxonomy of personality features [36]. The idea was, again, that analyses of language could be the key to advance understanding of human personality. In the end of the 1920s Klages (1926) and Baumgarten (1933) continued Galton's lexical approach, analyzing natural language and dictionaries. They inspired Allport and Oddbert (1936) who collected and sorted 17953 adjectives from the Webster's New International Dictionary into categories. At a point Allport concluded that the amount of words seemed "like a semantic nightmare" [37]. Thus, the list needed further revision.

#### *1.1.3.4 Catell's 16-factor model*

Raymond Catell (1943) edited Allport's wordlist, and ended up with 171 clusters of traits. After ratings of 100 adults and by use of factor analysis he eventually came up with 12 personality factors. By adding another four, from questionnaires, the final result was a model representing 16 bipolar dimensions of personality. Based on his work he developed the Sixteen Personality Factor Questionnaire (16 PF) [36], which has been frequently used in recruitment and personal development.

#### *1.1.3.5 Eysenck's P-E-N-model*

Hans Eysenck (1947) objected to the use of factor analysis as the only way to describing human personality. Furthermore, he was convinced that personality was linked to heredity and physiological brain processes [38]. In contrast to Catell's numerous traits, Eysenck described a model based on two personality factors;

Extraversion (E) and Neuroticism (N). Later he added a third factor; Psychotism (P). The E and N factors have been conceptualized in the Eysenck Personality Inventory (EPI), encompassing 24 items for each subscale and often used in dementia research. The E and N factors encompass dimensions of extraversion-introversion and neuroticism-emotional stability, that was linked to the four Greek temperaments, as well as the E and N dimensions in the later Five-Factor-Model (se below). The P factor added later has been suggested to be a trait of psychopathy or disinhibition [36].

#### *1.1.3.6 The Five-Factor-Model*

Today, the most common framework for examining differences in personality is the Five-Factor-Model (FFM). The FFM was constructed for studies of the normal personality and encompasses five broad personality domains: Neuroticism (easily distressed, problem focused), Extraversion (sociable, positive, confident), Openness for experience (intellectual, imaginative, independent), Agreeableness (friendly, trustful) and Conscientiousness (trustworthy, disciplined) [39]. The FFM describes personality on an abstract, overarching level, but permit a closer examination of human behavior through a number of lower-level traits for each personality domain [39]. For example, Neuroticism can be subclassified into the more specific traits somatic anxiety, psychic anxiety, stress susceptibility and low assertiveness [40]. Finally, item analysis may give an even more detailed description of particular cognitive, affective and behavioral aspects of personality.

Although trait theory does not describe the whole personality, it allows empirical generalizations about how others, with the similar pattern of personality, might act and react and thereby simultaneously offering a joint framework for studying differences between individuals. The FFM has been widely used to describe normal personality development, but also changes due to a variety of disorders. The Revised NEO Personality Inventory (NEO PI-R) is the most prevalent questionnaire representing the FFM, or the “Big-Five”. It exists in a standard form, a short form limited to measuring the global factors; the NEO Five Factor Inventory (NEO-FFI), and an observer version [41]. The Swedish universities Scales of Personality (SSP) used in our studies has been validated against the NEO PI-R [42].

#### *1.1.3.7 Limitations of Trait Theory*

There is an agreement that personality can be described in a hierarchical way, with higher-level personality domains at the top. Although several theorists pursue the use of a five-factor solution [41], there is an ongoing debate on how many domains that are needed to get a complete picture of human personality. However, there seems to be an agreement that the traits of Extraversion and Neuroticism are “universal” and therefore recur in most personality questionnaires. Limitations to trait theory concern the risk of not taking the influence of environmental, dispositional and historical factors into account [43]. Critics to the model have also stated that the FFM has limitations in predicting specific behaviors, to give causal explanations of human actions and that it relies on unreliable comparisons of people [44].

#### *1.1.3.8 State or trait*

In dementia, when changes in personality are observed the question may arise whether this is a transient emotional reaction or a permanent characteristic of that person; a state or a trait? This distinction has implications for differential diagnostics and treatment implementation. Traits are stable, enduring patterns of personality, reflecting general dispositions to think, feel and act in certain ways that are roughly coherent across situations [45]. States are transient, often emotional, reactions that tend to be situationally bound. However, as noted in the following section, our personality continues to develop throughout life and often changes in dementia, so the consistency of a behavior may be somewhat difficult to establish. A suggestion is to get an assessment of premorbid personality characteristics, either from the person herself and/or someone who can give a retrospective report.

## 1.2 PERSONALITY AND NORMAL AGING

For long, personality has been considered to be relatively stable after adulthood [46]. However, several studies have reported mean-level changes in personality traits [47], as well as intra-individual differences [48-51], throughout life. Nonetheless, cross-sectional and longitudinal studies of personality development after midlife have shown the same consistent pattern; Agreeableness and Conscientiousness increase and Extraversion and Openness decline, whilst Neuroticism decline or remain stable [22,47, 52]. In older age groups (> 70 years) a negative trend with an increase in Neuroticism [53] and a decrease in Extraversion, Openness, Agreeableness and Conscientiousness [54] has been observed. A cross-sectional study of elderly patients found gender differences with significantly higher levels of Neuroticism, Openness and Agreeableness in women than in men, and significantly higher levels of agreeableness in older participants in general and in older men, compared to younger men, in particular [55].

In sum, studies on personality in healthy aging show generally a positive trend towards emotional wellbeing, friendliness and preserved interest for new experiences. However, in the oldest age groups there is an increase in negative emotionality and a lower interest for social interaction and intellectual demands. These changes might be related to loss of identity and close ones, physical and mental health problems and existential reflections. Despite reports of mean-level personality alterations during the course of life, major personality changes are not expected in healthy aging and should lead to further inquiries about premorbid personality, life events, cognitive functioning and medical status [56].

## 1.3 DEMENTIA AND PERSONALITY CHANGES

### 1.3.1 Alzheimer's disease

The World Health Organization estimates that approximately 36 million people worldwide have a dementing disorder and predict that the number will be tripled by 2050 [57]. Dementia is a syndrome that affects the brain and leads to a gradual

reduction of memory capacity and other intellectual abilities, functional impairment [58] and personality changes [59].

The clinical diagnosis of dementia is established according to criteria in the International Statistical Classification of Diseases and Related Health Problems (ICD-10) [60] or the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [58]. The ICD-10 dementia criteria require a decline in memory (learning, recall) and other cognitive functions, preferably corroborated by an informant or neuropsychological examination. Moreover, there should be evidence of a change in emotional control and social conduct. For a confident clinical diagnosis the symptoms should hamper daily activities and have been present for at least six months, without indication of delirium. Symptom gravity is graded in mild, moderate and sever.

Alzheimer's disease AD is the most common of the neurodegenerative disorders and contributes to about 60% of diagnosed dementia cases [57]. The neuropathological hallmarks of AD are extracellular inclusions of β-amyloid$_{1-42}$ (senile plaques; Aβ42) and intra-cellular aggregates of hyperphosphorylated tau (neurofibrillary tangles; NFTs) [61]. Neuropathological and longitudinal biomarker studies have suggested that amyloid pathology precedes tau pathology and cognitive decline by several years [62-64]. Other pathologic features that have an impact on the clinical presentation of AD are amyloid angiopathy, synaptic dysfunction, neuronal loss, oxidative stress and neuroinflammation [65].

The National Institute on Aging and the Alzheimer's Association work group (NINCDS-ADRDA) have recently proposed new research criteria [66] for AD, taking the pathophysiological process underlying the disorder into account. A body of literature has shown that combining CSF biomarkers with cognitive measures is more effective than using cognitive profiles alone [67-68] and useful for predicting disease progression from MCI to AD [67, 69].

#### *1.3.1.1 Personality changes in AD*

"I have lost myself" are the well-known words expressed by Auguste D, a 51-year old woman who at admission to the Frankfurt hospital in 1901 suffered from severe memory loss, verbal, and visuospatial deficiencies and functional impairment [70]. In 1907 Alzheimer wrote a case report in which he described Auguste D's case and the typical neuropathological findings. According to Alzheimer's description, preceding the cognitive impairment, Auguste D had developed neuropsychiatric symptoms and personality change [71].

Several studies have demonstrated that patients in different stages of AD display an increase in neuroticism and a decrease in extraversion, openness, conscientiousness, and agreeableness, in relation to normal elderly [72-74]. Others have reported patients being quieter, relying on others, disliking of company, unhappy and regressive after onset of AD [75]. Moreover, individuals with AD express more apathy, increased rigidity and less interest in hobbies. They also tend to display more self-centred

behaviour, passivity and agitation during the progression of the disease [76-77]. A recent review examining differences in personality domains before and after diagnosis of AD found a consistent pattern across studies with the most prominent changes in conscientiousness (2-3 SD), followed by neuroticism and extraversion (1-2 SD), openness and agreeableness (> 0.5 SD) [59]. Thus, compared to personality development in healthy aging, which generally is characterized by increased maturity and emotional well being, individuals with AD show a negative development with less drive and increased negative emotionality, as the most prominent features.

#### *1.3.1.2 Mild cognitive impairment*

The prodromal phase during transition from healthy aging to dementia is usually referred to as mild cognitive impairment (MCI), a condition characterized by: (i) cognitive decline reported by the patient and/or informant, (ii) impairment in cognitive functions verified by neuropsychological tests, (iii) preserved abilities to participate in daily activities and (iv) absence of dementia [77-78]. In older populations there is a mean annual conversion rate of 10% (range 2-31%) from MCI to dementia, [79]. This can be compared to 1-2% for healthy elderly people [80].

MCI is a heterogeneous state in which the clinical profile varies depending on the underlying syndrome [81]. In order to handle the heterogeneity, different MCI subtypes have been proposed: amnestic MCI (single and multiple domains) and non-amnestic MCI (single and multiple domains) [77]. A recent study of 1655 MCI patients associations between the existing MCI subgroups (above) and neuropsychiatric, functional and vascular risk factors were investigated. Analyses resulted in several new MCI phenotypes distinguished by prominent cognitive, functional and neuropsychiatric characteristics, or a combination of them all [82]. When MCI due to AD is suspected it is important to exclude other possible neuropsychiatric and somatic disorders that could explain the cognitive decline (e.g. trauma, substance abuse, vascular impairment, long-term exhaustion). A body of literature has demonstrated that MCI characterized by episodic memory impairment, i.e. amnestic MCI (aMCI), elevate the risk of developing subsequent dementia [83-85]. It has also been established that changes in memory and other cognitive abilities, i.e. executive functions, language and visuospatial thinking, can be observed several years before the MCI diagnosis is established [86-87]. It should be noted that MCI due to AD occasionally present with a non-amnestic profile dominated by visual symptoms or language impairment, i.e. posterior cortical atrophy and logopenic aphasia [88].

Low levels of Aβ42 and high T-tau and P-Tau levels in CSF [26-27], structural and functional changes in temporal and parietal regions of the brain, evidenced by imaging techniques, all increase the risk for progression to AD [78]. According to new research criteria these biomarkers are indicative of AD pathology and as such useful for identifying individuals in a prodromal stage of the disease [78].

#### 1.3.1.2.1 Patterns of personality in MCI

Numerous longitudinal studies including elderly people have found associations between higher ratings in traits related to neuroticism and MCI [89]. One of these studies, involving healthy elderly and subjects with MCI, showed a decrease in neuroticism and extraversion in both groups over time. However, those individuals having higher levels of neuroticism at baseline more then doubled the risk for MCI at follow-up. The authors conclude that high premorbid neuroticism may be a risk factor for progression to MCI [89]. In patients with mild to moderate memory impairment low extraversion, openness and conscientiousness, and high neuroticism [26], agitation and passivity was demonstrated [90]. Previously, we have reported that patients with MCI had significantly higher scores in somatic anxiety, psychic anxiety, stress susceptibility and detachment than controls [91]. Yet, others have failed to find differences between patients with MCI and SCI/controls [92-93], as well as associations between neuroticism and MCI [94].

### *1.3.1.3 Subjective cognitive impairment*

There is growing evidence that Alzheimer's disease is preceded by a preclinical, asymptomatic stage, lasting up to 15 years before cognitive symptoms emerges [95]. The concept of SCI, or subjective memory impairment, is currently used to describe a continuum, from normal aging to MCI [95]. SCI denotes a condition where individuals may have occasional word finding difficulties or mild forgetfulness, but perform within normal ranges on neuropsychological tests. SCI is common in the aging population, with prevalence rates from 25% to 56% [96]. Although some individuals with SCI will show no progression, a number of studies have recognized that SCI may be a clinical forerunner of MCI and AD [95,97-98]. A follow-up study over approximately seven years, including healthy elderly and subjects with SCI, reported that 54 % of all SCI participants declined; 79% of those to MCI and 21% to dementia [99].

In cross-sectional and longitudinal studies, SCI in objectively healthy persons have been associated with depression [100], memory impairment [101] and faster cognitive decline [99]. Moreover, in populations with SCI, structural and functional abnormalities in temporal and parietal brain regions [97-98, 102], higher PiB uptake in the right medial prefrontal cortex and precuneus, anterior and posterior cingulate cortex [103], and cerebrospinal fluid (CSF) biomarkers indicative of AD-pathology [104] have been reported.

In contrast to biomarker evidence of SCI, as a preclinical stage of AD, other researchers have emphasized that subjective cognitive complaints, in the absence of objective cognitive deficits, could be related to personality traits and psychiatric symptoms, rather then cognitive impairment *per se* [100, 105]. This notion is to some extent contradicted by studies showing that individuals who worry about their memory are at a higher risk of cognitive decline and dementia, than those who don't [79,103,106]. The latter finding means that worrying about cognitive problems may have a predictive value in its own, even in the absence of objective cognitive deficits.

#### 1.3.1.3.1 Patterns of personality in SCI

Few studies have examined personality changes in relation to SCI. A prospective longitudinal study of non-demented older adults found a doubled risk for dementia in those who reported preclinical symptoms of any change in personality, including less concern for others, increased apathy, irritability and stubbornness [107]. Another longitudinal study reported increased rigidity, irritability, apathy, egocentricity and a reduced capacity for emotional control in non-demented persons who later progressed to dementia. In this study preclinical personality changes correlated to AD pathology at autopsy [108]. A recent study reported higher levels of somatic anxiety, psychic anxiety and stress susceptibility, and lower levels of adventure seeking for SCI compared to controls, but no personality differences between patients with SCI and MCI [109]. Earlier work has shown that low mood in healthy elderly precedes MCI [110] and that psychiatric symptoms increase in early stages of cognitive impairment [111], particularly in females [91].

### 1.3.2 Personality and other disorders

#### *1.3.2.1 Dementia*

A 2007 study reported that a passive factor, featuring less emotional responsiveness, diminished interest for hobbies, apathy and purposeless hyperactivity, significantly discriminated patients with Lewy Body Dementia (DLB) from those with AD [112]. Studies of patients with Parkinson's disease (PD) have found correlations between a reduction in social behaviour and prefrontal functioning and a general negative change in the "Big-Five" personality dimensions [113-114]. In frontotemporal dementia (FTD) are personality change and impairment in social conduct part of the diagnostic criteria [115-116]. Individuals with FTD display higher levels of regression and impulsivity, less self-awareness and insight, disinhibition and stereotypic behaviour when compared to others diagnosed with AD [117-119]. A study of subjects with vascular dementia (VaD) and AD found differences between groups that could be related to the underlying pathology, with VaD subjects being more at ease, tender and showing more apathy than those with AD [120].

#### *1.3.2.2 Neuropsychiatric diseases*

Neuropsychiatric symptoms, like depression, anxiety, apathy and irritability are reported in 35-75% of individuals with MCI [121]. Higher levels of anxiety in elderly subjects with MCI have been associated with increased risk for cognitive decline [122] and earlier progression to AD [123-124]. However, opposite results have also been reported [125]. In elderly people with varying levels of cognitive impairment the prevalence of anxiety and depressive symptoms, alone and combined, increased in early stages of cognitive decline and decreased with disease progression [111].

Depression has been associated with increased risk of dementia, but it remains unclear whether depression is a risk factor or a prodrome to AD. In depressed elderly, CSF biomarkers indicative of AD (Aβ42 in plasma) have been associated with lower results in test of memory, visuospatial ability and executive functions, implying an

"amyloid-associated depression" [126]. In subjects with memory impairment, personality change, but not depressive symptoms, was related to functional decline [90].

## 1.4 NEURAL CORRELATES OF PERSONALITY

By use of brain imaging techniques and biochemistry analyses several studies have demonstrated associations between personality traits and neural correlates. Neuroticism and extraversion have both been associated with cortical thickness and neural activity in prefrontal and temporal regions [127-128], the hippocampus, the midbrain [128], and frontostriatal circuits [129]. Moreover, Positron emission tomography (PET) studies have presented correlations between dopaminergic biomarkers and the personality traits detachment [130], novelty seeking [131], social desirability [132], anxiety and irritability [133]. These findings confirm relationships between several personality traits and structures supporting emotion regulation, social functioning and cognition, often affected by aging and neurodegenerative disorders [134].

A study of 214 patients with different neurodegenerative diseases found correlations between traits related to agency (directness toward others) and grey matter volume in left, frontotemporal, dorsolateral brain regions, whereas traits related to affiliation (emotional responsiveness) were correlated to right frontotemporal, ventromedial parts of the brain [135]. The relationship between neuroticism (chronic distress) and cognitive impairment has furthermore been discussed in terms of a dysregulation of the HPA-axis, causing higher levels of glucocorticoids (cortisol), reduced hippocampal volume and lower episodic memory performance [136]. Proneness to distress has been correlated with cognitive impairment and risk of dementia, but not to any type of neuropathological changes, i.e. senile plaques, NFTs, Lewy bodies or cerebral infarctions, on post mortem examination [137]. A retrospective cohort study found that apathy, a common feature late in AD, correlated with a higher NFT accumulation in the anterior cingulate gyrus [138].

To date there is strong evidence for associations between specific personality traits, cognitive impairment and dementia. However, knowledge about relationships between personality traits, cognitive functions and their neurobiological underpinnings in preclinical dementia are limited. Further studies of associations between personality changes and the AD pathophysiological process are warranted.

## 1.5 AIMS

With reference to the growing evidence that specific personality traits are of importance for the clinical picture in early stages of neurodegenerative disorders, the overall aim of the thesis was to examine the significance of personality characteristics in diagnosing prodromal stages of dementia. Specifically:

I. To investigate differences in patterns of personality in patients with MCI, SCI and controls;

II. To investigate degree of agreement between self- and informant ratings of personality, in relation to cognitive function, in patients with MCI, SCI and controls;

III. To investigate the usefulness of combining personality and cognitive measurements in discriminating patients with MCI and SCI from controls;

IV. To investigate differences in cognition, personality and CSF biomarkers between memory clinic patients with varying degrees of cognitive impairment, and to analyse which variables predict conversion to dementia at follow up after three years.

# 2 MATERIAL AND METHODS

## 2.1 SUBJECTS

### 2.1.1 General background

The participants in study I-IV were consecutively recruited during 2004-2005 among patients examined for early dementia symptoms at the Memory Clinic at the Karolinska University Hospital, Huddinge, Sweden. Patients were referred from general practitioners, occupational health services and other specialist, e.g. psychiatrists or neurologists. Moreover, patients and informants could get an appointment at the clinic through self-referral. A majority (50/59) of the subjects participated in a longitudinal European multi-centre study; Development of screening guidelines and diagnostic criteria for predementia Alzheimer's disease (DESCRIPA) [139]. To enlarge the study sample nine more patients were consecutively enrolled from the clinical population.

#### *2.1.1.1 Study I-IV*

Twenty-four (24) patients diagnosed with SCI and 35 with MCI were consecutively recruited to the present study with the aim to examine personality in relation to cognitive impairment and conversion to Alzheimer's disease. Inclusion criteria at baseline were ≥ 55 years of age and no cognitive impairment due to substance abuse, history of head trauma or other major physical or psychiatric disorder. Results from the same clinical groups were used in study I-IV.

In addition to the patient population a group of 26 controls were drafted by word of mouth and through advertising in different public locations, i.e. community centers, churches and hospitals. The somatic and cognitive health status was checked by an in-house telephone interview by the author. If the controls reported no subjective memory complaints and met the inclusion criteria listed above they were enrolled in the study. At separate visits, all controls were assessed with the same cognitive, personality and depression tests as the patient groups. Demographic and clinical data for patient groups and controls are presented in table 2.

Table 2. Demographic and clinical data presented as means (M) and standard deviations (SD) for the participants

| | Control (n= 26) | | SCI (n= 24) | | MCI (n= 35) | |
|---|---|---|---|---|---|---|
| | M | SD | M | SD | M | SD |
| Sex (% female) | 65 | | 46 | | 43 | |
| Age (years) | 64.7 | 8.54 | 62.5 | 4.89 | 67.3 | 7.17 |
| Education (years) | 16.0 | 4.84 | 12.5 | 3.46 | 12.1 | 4.29 |
| MMSE (score) | 29.2 | 1.04 | 28.9 | 0.97 | 27.5 | 1.72 |
| Cornell (score) | 3.4 | 2.83 | 4.9 | 4.71 | 5.2 | 5.83 |

Note. MMSE = Mini-Mental State Examination; Cornell = Cornell Scale for Depression in Dementia

*2.1.1.2 Study II*

In order to study self-other agreement in personality ratings, reports from a reliable informant for all participants were collected. Due to lack of informant and missing responses the final study groups consisted of 23 dyads of patients/informants with SCI, 32 patients/informants with MCI and 22 dyads of controls/informants.

The mean age of the informants were 59 years (SD 12.8) and 61% were women. Eighty-seven percent (87%) of the informants filled out the personality questionnaire at home and returned it by mail. A majority of the informants were spouses (69%), followed by children or children in-law (21%), siblings, other relatives or friends (10%). Analysis of living status showed that 65% of patients with SCI, 56% of those with MCI and 73% of controls were co-resident with their informants.

*2.1.1.3 Study IV – Follow-up*

All patients were followed-up as part of clinical routines with the aim to monitor progression of cognitive decline, to implement therapy and ensure differential diagnostic accuracy. The mean duration of follow-up in this study was 38.0±11.0 months (range 7-55). During follow-up one MCI patient died and another seven patients (3 SCI, 4 MCI) declined further participation. At follow up 47% of patients with MCI had converted to AD, 3% to other dementia diagnoses and the rest, 50%, remained MCI. In the SCI group, 5% converted to dementia (BLD), 62% to MCI, and 33% showed no progression (Figure 1). Thus, the final population in study IV encompassed 51 patients (30 MCI, 21 SCI): 15 patients that at follow-up had received a dementia diagnosis (converters), 36 that were not demented (non-converters) and 26 controls. Since CSF biomarkers were missing in 9 out of 51 patients (5 converters, 4 non-converters), these cases were excluded in the analyses comparing for CSF differences between converters and non-converters.

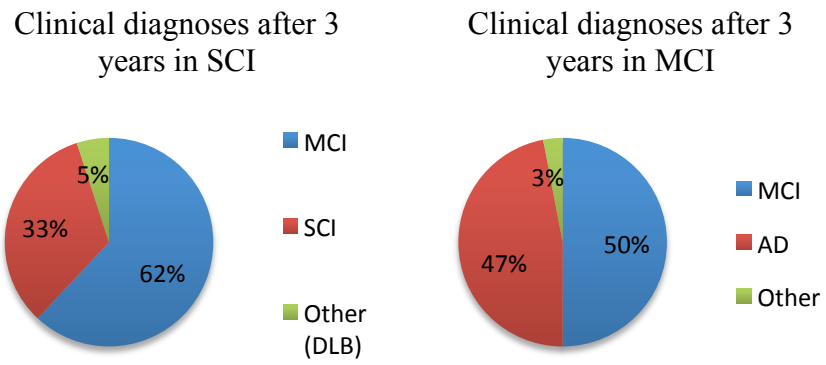


Figure 1. Conversion rates of clinical diagnoses at follow-up after 3 years

## 2.2 STUDY PROCEDURES

### 2.2.1 Clinical evaluation

All participants eligible for the study underwent a standardized comprehensive medical examination including patient- and informant interview, physical, mental and neurological status, brain imaging (computed tomography (CT), single-photon emission computed tomography (SPECT) and/or magnetic resonance imaging (MRI)) and biochemistry of blood, urine and cerebrospinal fluid (T-tau, P-tau and Aβ42). A neuropsychological examination including tests of language, visuospatial thinking, attention/psychomotor speed and episodic memory was performed. The Mini-Mental State Examination (MMSE) was used to measure global cognitive function [140] and the Cornell Scale for Depression in Dementia to evaluate level of depression (CSDD) [141]. In addition to the clinical examination, personality was assessed with the Swedish universities Scales of Personality (SSP) [40].

### 2.2.2 Diagnostic procedure

To identify and diagnose patients with cognitive impairment and early-stage dementia a multidisciplinary approach is required. Diagnoses were decided at clinical rounds where representatives from different professions were present, i.e. physicians, neuropsychologists, speech pathologists, occupational therapists, social workers and nurses. MCI was diagnosed according to Winblad et al. consensus criteria [77], i.e. patients were considered neither normal for their age, nor demented according to or DSM-IV or ICD-10 criteria for dementia, had objective signs of cognitive decline and preserved ability to participate in activities of daily living. AD was diagnosed according to ICD-10 criteria and Dementia with Lewy Bodies (DLB) according to McKeith et al. consensus criteria [142]. Patients who were referred to the clinic because of a subjective experience of cognitive decline, but after a clinical examination were found to have no objective signs of cognitive impairment, measured by neuropsychological tests, brain imaging and laboratory analyses, were diagnosed as SCI.

## 2.3 METHODS

## 2.4 NEUROPSYCHOLOGICAL EXAMINATION

*2.4.1.1 Test setting*

To optimize cognitive performance and increase the ecological validity a working alliance between the patient and the neuropsychologist/examiner has to be established. This collaborative approach, referred to as therapeutic neuropsychological assessment [143], does not compromise standard test routines, but may additionally increase patients' self-esteem [144] and boost coping strategies. In brief, during the session patients were asked to describe their cognitive deficits and how they affect daily life. They were informed that the purpose of the examination was to examine cognitive strengths and weaknesses, which function each test is supposed to measure and how these may relate to everyday situations. Finally, patients evaluated their performance and received feedback on their results, on a global level, in relation to their subjective problems and the question for which they had been referred to the clinic.

#### *2.4.1.2 Neuropsychological assessment*

The neuropsychological examination in this study encompassed a test battery covering a spectrum of cognitive functions, often used in the diagnostic work-up of early dementia syndromes. In line with MCI criteria [77] the neuropsychological examination aimed at: (1) establish whether patients had a memory impairment and/or (2) deficits in other cognitive domains, e.g. verbal, visuospatial and executive functions. Identifying type of memory impairment (storage, retrieval, recall) objectivizes patients' subjective complaints and may generate hypotheses about the underlying disorder [145]. However, for clinical diagnostic purposes it is important to evaluate memory problems in relation to changes in other cognitive functions, the entire neuropsychological profile [146] and additional anamnestic information.

The examination at baseline was conducted by an experienced neuropsychologist (BA) and included tests of: *Language*: Information and Similarities (Wechsler Adult Intelligence Scale – Revised, WAIS-R) [147]; V*isuospatial function*: Block design (WAIS-R) [147] and Rey-Osterrieth Complex Figure (ROCF), copying [148]; *perceptual speed/flexibility*: Trail Making Test (TMT) A & B [149] and Digit Symbol (WAIS-R) [147]; V*erbal episodic memory*: Rey Auditory Verbal Learning Test (RAVLT) total score (learning trials 1-5) and delayed recall (30 minutes) [150]; V*isual memory*: ROCF, retention [148]. Test results were standardized by z-transformations using a healthy control group [151].

#### *2.4.1.3 The Mini-Mental State Examination*

The Mini-Mental State Examination (MMSE) is a screening tool aimed at measuring cognitive mental status, with questions related to orientation, memory, attention, naming, the ability to follow verbal and written commands, writing a full sentence and copying two overlapping pentagons. The test is not time limited and the maximum score is 30 [140]. The MMSE is generally denoted a measure of global cognitive function, in memory clinic examinations and in clinical trials [139]. Moreover, the level of MMSE scores is often used for staging of both prodromal conditions and dementia severity, to follow disease progression and treatment outcome. The MMSE scores for healthy individuals and those with SCI are in the range 29-30, for MCI 26-29, mild dementia 21-25, moderate dementia 11-20 and severe dementia 0-10 [153]. Studies of MMSE sensitivity and specificity values have suggested that it should be used in conjunction with a more profound neuropsychological examination, particularly in cognitively well functioning and educated individuals [152].

#### *2.4.1.4 Cornell Scale for Depression in Dementia*

The Cornell Scale for Depression in Dementia (CSDD) [141] is an inventory constructed to examine symptoms of major depression in patients with dementia. The CSDD consists of 19 items with three response alternatives: "absent", "mild or intermittent" and "severe". The answers are based on interviews with both the patient and an informant and focus on symptoms present the week before the interview. Additionally, the clinician does an independent CSSD rating. A total score below 6 equals no depression, above 10 a probable major depression and a score of 19 and higher a definite major depression. The CSSD has been found to be valid for use also

with non-demented persons [154], reliable and suitable for screening of depression symptoms in memory clinic patients [155].

### 2.4.2 Personality Assessment

#### *2.4.2.1 Swedish universities Scales of Personality*

The personality assessment was completed at the same visit as the neuropsychological examination and in presence of the author, ready to answer upcoming questions. To assess personality the Swedish universities Scales of Personality (SSP), a self-report personality inventory was used. The SSP is a revised version of the Karolinska Scales of Personality (KSP) [40]; a questionnaire developed to study neurobiological underpinnings of some psychiatric disorders. The SSP comprises 91 items, rated on a four-point Likert scale from "does not apply at all" to "applies completely". Items are categorized into 13 subscales, with seven items in each. Factor analysis of the SSP has resulted in three personality factors: Anxiety proneness, Extraversion and Aggression-Hostility. However, the internal distribution of some traits has varied in studies of the same or related personality inventories [156-157]. Factors, subscales and item examples are presented in table 3.

To obtain current personality characteristics the original SSP instructions were modified so that patients were asked to give the answers that best described their present personality, rather than how they usually feel or act. The SSP is standardized on a representative sample from the general Swedish population, for men and women. Scale scores were summed and transformed to T scores (M= 50, SD = 10).
An informant version of the SSP was used to measure personality in patients and controls. It was a parallel version of the original SSP in which the wording was changed from "I" to "NN" in all items, i.e. "NN easily gets impatient" instead of "I easily get impatient". All informants were asked to give the answers that best described the patient's/control person's present personality.

#### *2.4.2.2 Self-rated personality change*

In addition to the SSP questionnaire a structured interview was conducted with the patient groups. Both patients and their informants were asked if they felt that the patient, in relation to cognitive deficits, had changed in his/her personality. If yes, they were asked to describe in which way their personality had changed.

Table 3. SSP factors, subscales and item examples

**Swedish universities Scales of Personality**

| Personality scales | Item example | Characteristics of high scorers |
|---|---|---|
| *Anxiety Proneness* | | |
| Somatic Trait Anxiety | "Sometimes my heart pounds hard or irregularly for no apparent reason" | Somatic symptoms under stress |
| Psychic Trait Anxiety | "I worry far in advance when I'm going to get started on something" | Low self-confidence, worried, experience anticipatory anxiety |
| Stress Susceptibility | "I get tired and hurried too easily". | Easily fatigued and uneasy when urged to speed up |
| Low Assertiveness | "I find it difficult to assert my opinions" | Low ability to speak up and be self-assertive in social situations |
| *Extraversion* | | |
| Impulsivity | "I usually talk before I think" | Act on the spur of the moment, difficulties planning ahead |
| Adventure Seeking | "I prefer people who do exciting and unexpected things" | Need for change and action, avoid routines |
| Detachment | "I feel best when I keep people at a certain distance" | Withdrawn, avoid involvement in others |
| Embitterment | "I have often got into trouble even when it was not my fault" | Unsatisfied, blaming and envying others, self-victimized |
| Social Desirability | "I'm always polite, even to unpleasant people" | Socially conformed, friendly, helpful, conciliated |
| *Aggression-Hostility* | | |
| Verbal Trait Aggressivity | "I often get into arguments with people who disagree with me" | Get into arguments, criticize people when annoyed |
| Physical Trait Aggressivity | "I sometimes get so angry that people around me think I'll start to fight" | Get into fights, start fights, hit back |
| Trait Irritability | "I'm easily annoyed with people" | Lack patience, irritable |
| Mistrust | "It's hard for me to trust other people" | Suspicious, distrust others' motives |

### 2.4.3 Analyses of CSF bio markers

Lumbar puncture (LP) was used to collect CSF samples. During LP the needle was inserted into the intervertebral space L3/L4 or L4/L5, and 10-12 ml CSF was tapped and collected in sterile polypropylene tubes. The CSF samples was analysed for Aβ42, T-tau and P-tau [139].

## 2.5 STATISTICAL ANALYSIS

The statistical methods used in our studies were $\chi^2$–test, analysis of variance (ANOVA), t-test and corresponding non-parametric techniques (Kruskal-Wallis, Kendall's tau rank correlation coefficient), intra-class correlations (ICC) and logistic (stepwise, forward) regressions [158]. Demographic data were presented with standard

descriptive methods, i.e. means and standard deviations. The level of statistical significance was set at $p<0.05$.

#### *2.5.1.1 Study I*

One-way analyses of variance (ANOVA), followed by the Tukey honestly significant difference (HSD) test were conducted to investigate differences between patients with MCI, SCI and controls in demographic data and personality traits. Since there were age differences between groups, age was entered as a covariate in the analysis of personality. Due to unequal variances between groups in the MMSE and Cornell scale for depression in dementia the non-parametric Kruskal-Wallis test was used to re-examine group differences. A $\chi^2$–test was conducted to examine the distribution of females and males in the groups.

#### *2.5.1.2 Study II*

Intra-class correlations (ICC) were calculated to examine agreement between dyads of patients/controls and their informants, when both had rated the patients'/controls' personality. The output, that is ICC coefficients, was transformed to z-values and mean-correlations were computed. ICC coefficients reflect level of agreement between raters, where 1 represents complete agreement and 0 no agreement. ICC values are often interpreted as follows: 0-0.2 = poor agreement, 0.3-0.4 = fair agreement, 0.5-0.6 = moderate agreement, 0.7-0.8 = strong agreement and > 0.8 almost perfect agreement.
Additionally, an index to measure incongruence between raters was constructed. First, the difference between participants' and their informants' personality ratings was computed. Thereafter the standard deviation of this difference between raters was extracted. With total agreement between raters the index would be zero (0).
In order to validate obtained differences between patients/controls and their informants, that is to find a possible cause to their disagreement, correlations between the incongruence index and a measure of general cognitive function (MMSE) was calculated with the Kendall's tau rank correlation coefficient. T-tests was used to examine whether differences in the incongruence index was related to demographic variables between groups (patients/controls vs informants).

#### *2.5.1.3 Study III*

Discriminant function analyses were performed to examine which variables discriminate between patients with MCI, SCI and controls. Data from cognitive tests and personality assessments were used, separately and in combination. Standardized canonical discriminant function coefficients were calculated and Jack-knifed classification, a cross-validation technique, was used to classify cases into predicted groups. The larger the standardized coefficient, the greater is the contribution of the particular variable to the discrimination between groups. Mean values of canonical discriminant functions (group centroids) were computed to illustrate intergroup relations along two discriminant canonical functions. The larger the distance between the means, the less error there will be in classification.
An alternative way to characterize the discriminant functions is to examine the factor structure. Factor structure coefficients are correlations between each discriminating

variable and the canonical discriminant functions. Thus, in addition to identifying specific variables of importance for group separation, the factor structure analysis was used to label the discriminant functions, i.e. cognition and personality.

#### *2.5.1.4 Study IV*

A one-way Anova, followed by the Tukey honestly significant difference (HSD) test was conducted to examine differences between groups in personality traits and cognitive functions. Due to unequal variances in cognition, differences between groups were re-examined using the Kruskal-Wallis test. Statistical (stepwise, forward) logistic regressions were performed to find out which variables predict conversion to dementia at follow-up after three years in patients with SCI and MCI.

## 2.6 ETHICAL CONSIDERATIONS

There are ethical issues that need to be considered in studies including patients with varying levels of cognitive impairment. Diminished cognitive resources may reduce understanding and affect patients' ability to make autonomous decisions about partaking in research. The participants in this study were all cognitively well functioning, which to some extent ensured preserved decision making ability. However, since early cognitive impairment may lead to reduced awareness [159], the aims of the study and possible negative consequences were thoroughly discussed beforehand. In addition to the communication during clinical examinations, all participants got written and oral information about the study and gave their written consent. The local Ethics Committee at the Karolinska Institutet approved study I-IV (Forskningsetikkommitté Syd, 407/03, 2006/861-32).

# 3 RESULTS

## 3.1 STUDY I

This study compared differences in personality between memory clinic patients with MCI, SCI and controls. Our aim was to examine patterns of personality in diagnostic groups at risk of cognitive decline and dementia, compared to controls.

### 3.1.1 Personality differences

When corrected for age, significant differences between groups were seen in Somatic Trait Anxiety ($F(2, 81) = 11.964$, $p < 0.001$), Psychic Trait Anxiety ($F(2, 81) = 10.806$, $p < 0.001$), Stress Susceptibility ($F(2, 81) = 9.030$, $p < 0.001$), Adventure Seeking ($F(2, 81) = 3.553$, $p = 0.033$), Detachment ($F(2, 81) = 3.473$, $p = 0.036$), Verbal Trait Aggressivity ($F(2, 81) = 3.302$, $p = 0.042$) and Trait Irritability ($F(2, 81) = 3.369$, $p = 0.039$). Post hoc analyses showed that patients with SCI and MCI exhibited significantly higher levels of anxiety than the healthy controls. There were no significant differences between patients with SCI and MCI, although patients with MCI consistently showed a higher degree of anxiety than patients with SCI. Compared to controls, patients with SCI were significantly less prone to Adventure Seeking, while the MCI group expressed a significantly higher degree of Detachment. Personality profiles for all groups are presented in Figure 2.

In sum, patients with MCI and SCI presented higher scores in traits related to anxiety proneness and aggression-hostility and lower in traits of extraversion. Differences followed a sequential pattern in the order controls<SCI<MCI. The results suggest that patterns of personality may be related to degree of cognitive impairment.

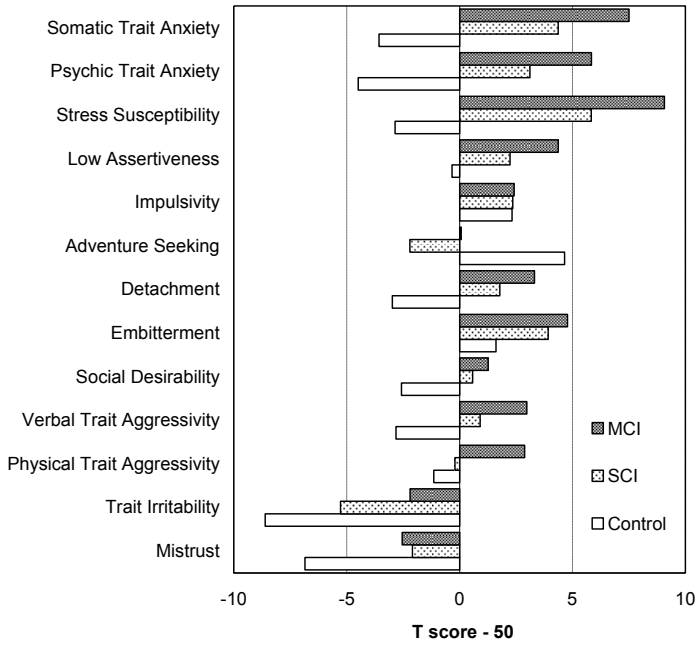


Figure 2. Differences in personality profiles for patients with MCI, SCI and controls

## 3.2 STUDY II

The aim of this study was to examine degree of agreement between self- and informant ratings of personality, in relation to cognitive function, in patients with MCI, SCI and controls.

### 3.2.1 Self- and informant agreement

ICCs between MCI patients' self-reports and those of their informants' ranged from ri = 0.03 to 0.55, were moderate in 2 out of 13 scales and significant in 7 (Somatic Trait Anxiety, Low Assertiveness, Impulsivity, Detachment, Social Desirability, Physical Trait Aggressivity and Mistrust). ICCs between SCI patients' self-reports and that of their informants' ranged from ri = 0.13 to 0.61, were moderate in 5 of 13 scales and significant in 5 (Somatic Trait Anxiety, Social Desirability, Verbal Trait Aggressivity, Trait Irritability and Mistrust). ICCs between controls' self-reports and those of their informants' ranged from ri = 0.10 to 0.76, were moderate to strong in 5 of 13 scales and significant in 5 (Somatic Trait Anxiety, Stress Susceptibility, Low Assertiveness, Impulsivity and Adventure Seeking).

### 3.2.2 The incongruence index

The analyses of the incongruence index were controlled for age and education. The mean of the incongruence index was 1.18 (SD = 0.23) for patients with MCI, 1.08 (SD = 0.22) for patients with SCI and 0.95 (SD = 0.18) for the controls. There was a significant difference between groups in the incongruence index [$F(2,74) = 7.591$, $p = 0.001$]. Post hoc analyses showed that patients with MCI exhibited a significantly higher incongruence index, i.e. lesser agreement between patient and informant, than the HC and their informants. Moreover, there was a significant negative correlation between the incongruence index and the MMSE ($r = –0.219$, $p = 0.011$) when all subjects were included in the analysis, meaning that low scores in MMSE will result in higher incongruence between patients' and informants' reports of the patients' personality. There were no significant differences in the incongruence index between the groups in living status [$t(74) = 0.559$, $p = 0.578$] or gender of patient [$t(75) = –0.249$, $p = 0.804$] and informant [$t(75) = 0.623$, $p = 0.535$], meaning that the degree of agreement did not seem to be related to whether they lived together or to the gender of the patient or informant.

To conclude, correlations between self and informant ratings were fair to moderate on a majority of SSP scales and significant in 44%. The incongruence between patient and informant ratings was significantly larger in MCI than in controls across SSP scales. Incongruence between raters was negatively correlated with a measure of global cognitive function (MMSE), for all groups. Accordingly, disagreement between patients and informants indicates cognitive impairment.

### 3.2.3 Self-rated personality change

In the structured interview 69 % of all patients (equal for MCI and SCI) and 56% of the informants reported an overall personality change, in the patient, in relation to the intellectual problems for which they had come to the clinic. Patents described changes

in temperament, anxiety and depressive symptoms, increased stress susceptibility, low self-esteem and social withdrawal, lack of energy, being slower and more passive. They said: " I have become critical and grumpy", "… it's worse, I'm more sentimental and have difficulties getting things done" and " I have become a sensitive, quiet and pessimistic person". However, a few also reported positive changes like " I 'm more daring, think things through and don't get that excited anymore".

Informants described increased irritability and impatience, low mood, tiredness and lack of energy. They also reported loss of interest and ambition, increased dependence and stress susceptibility. In contrast to the negative cognitive development, some experienced that their partners had become more calm and listening.[1]

## 3.3 STUDY III

This study explored the utility of personality assessment in the delineation of patients with MCI, SCI and controls.

### 3.3.1 Cognitive and personality measurements

A canonical discriminant function analysis using cognitive data from 10 neuropsychological tests as predictors was significant ($\lambda$= .527, $\chi^2$= 51.62, df= 4, p< .001) with one discriminant canonical function that accounted for 99% of the between group variability. The function was based on two predictors, RAVLT (delayed recall) and TMT A. The standardized coefficients for the variables were 0.824 for RAVLT and 0.587 for TMT A. With the use of jackknifed classification procedure for the total sample of subjects, 54% were correctly classified; 13 out of 26 controls, 6 out of 24 patients with SCI and 26 out of 34 patients with MCI.

When SSP data was used the analysis was significant ($\lambda$= .799, $\chi^2$= 18.15, df= 2, p< .001) with one discriminant canonical function that accounted for 100% of the between group variability. The function was based on one predictor, Psychic Trait Anxiety (standardized coefficient 1.00). The jackknife procedure showed that 46 % of subjects were correctly classified; 18 out of 26 controls, 4 out of 24 patients with SCI and 17 out of 34 patients with MCI.

The analysis using a combination of cognitive and SSP data resulted in a significant outcome ($\lambda$=.370, $\chi^2$=79.05, df= 8, p< .001) with two discriminant canonical functions. The two functions accounted for 88 % and 12 % of the between group variability and were based on the predictors RAVLT (delayed recall), TMT A, Somatic Trait Anxiety and Adventure Seeking. In the first discriminant canonical function good episodic memory (RAVLT) and perceptual speed (TMT A), as well as low Somatic Trait Anxiety were the strongest predictors for group allocation. In the second discriminant canonical function the strongest predictors were low Adventure Seeking, high Somatic Trait Anxiety and moderate episodic memory (RAVLT). The jackknife procedure showed that 68% of subjects were correctly classified, 14 out of 26 controls, 15 out of

[1] Unpublished data

24 patients with SCI and 28 out of 34 with MCI. The larger the standardized coefficient, the greater is the contribution of the particular variable to the discrimination between groups.

In order to label the discriminant functions we examined the factor structure. According to the significant loadings in the factor matrix, cognitive tests (god episodic memory and perceptual speed) defined the first discriminant canonical function and personality traits (low adventure seeking and high somatic anxiety) the second function.

The separation between groups using function 1 and function 2 data is illustrated in figure 3. By plotting individual scores and group means for each function (centroids) we illustrated intergroup separation along two discriminant canonical functions. All three groups were separated along the first (cognitive) function with the MCI group, as expected, having lower scores than both the SCI group and controls. In relation to the second (personality) function four different patterns were distinguished. Along the midline the MCI group was delineated in two equally large subgroups; one characterized by cognitive impairment and higher scores in personality ratings (MCI/P) and the other by cognitive impairment only. Preserved cognition and higher scores in personality ratings distinguished the SCI group. The controls showed no deviations in cognition or personality.

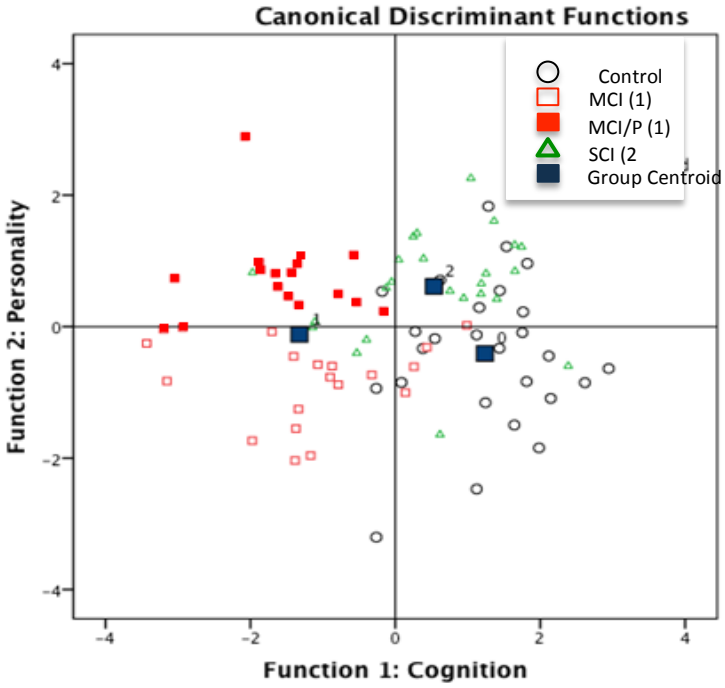


Figure 3. Illustration of discrimination between diagnostic groups using discriminant functions 1 (cognition) and 2 (personality). The scatterplot also shows the group means (centroids) for each group

In conclusion, adding personality assessment has potential clinical implications in the delineation of memory clinic subgroups and identification of individuals at risk of cognitive impairment. Since high neuroticism affects emotional well-being and

cognitive performance, leads to faster cognitive decline and increased risk of dementia, early detection and primary prevention strategies are of significant importance.

## 3.4 STUDY IV

The objective in study IV was twofold: first, to investigate differences in cognition, personality and CSF biomarkers (Aβ42, T-tau, P-tau) between memory clinic patients with varying degrees of cognitive impairment, but not dementia; second, to analyse which variables predict conversion to dementia at follow up after three years. Patient groups were compared to controls in cognition and personality.

### 3.4.1 Differences between converters and non-converters

A one-way ANOVA showed significant differences on a group level in most cognitive tests: Similarities [$F(2,71) = 5.291$, $p = 0.007$]; Digit symbol [$F(2,67) = 7.356$, $p = 0.001$]; TMT A [$F(2,72) = 5.657$, $p = 0.005$]; TMT B [$F(2,72) = 4.831$, $p = 0.011$]; RAVLT (learning) [$F(2,72) = 6.390$, $p = 0.003$]; RAVLT (delayed recall) [$F(2,71) = 8.885$, $p < 0.001$] and ROCF (retention) [$F(2,71) = 10.839$, $p < 0.001$]. Post hoc analyses showed that converters differed significantly from non-converters and controls, with lower scores in Similarities, Digit symbol, TMT A, TMT B, RAVLT (learning, delayed recall) and ROCF (retention). The non-converters had significantly lower scores than the controls in Similarities, Digit symbol, TMT A, TMT B, and RAVLT (learning).

Due to unequal variances group differences were re-examined by a Kruskal-Wallis ANOVA. Again, the analysis showed a significant effect of diagnostic group for Similarities ($\chi^2$=7.040, df=2, p=0.030), Digit Symbol ($\chi^2$ =11.639, df=2, p=0.003), TMT A ($\chi^2$ =8.737, df=2, p= 0.013), TMT B ($\chi^2$ =10.379, df=2, p=0.006), RAVLT (learning) ($\chi^2$ =10.843, df=2, p=0.004), RAVLT (delayed recall) ($\chi^2$ =12.790, df=2, p=0.002) and ROCF (ret) ($\chi^2$ =13.483, df=2, p=0.001).

A one-way ANOVA demonstrated significant differences between groups at baseline with respect to a number of personality variables: Somatic Trait Anxiety [$F(2,74) = 9.180$, $p < 0.001$]; Psychic Trait Anxiety [$F(2,74) = 9.696$, $p < 0.001$]; Stress Susceptibility [$F(2,74) = 6.308$, $p = 0.003$]; Detachment [$F(2,74) = 3.887$, $p = 0.025$]; Verbal Trait Aggressivity [$F(2,74) = 4.486$, $p = 0.014$] and Mistrust [$F(2,74) = 3.436$, $p = 0.037$]. Post hoc tests showed that the converters and non-converters had significantly higher scores in Somatic Trait Anxiety, Psychic Trait Anxiety, Stress Susceptibility, Detachment and Verbal Trait Aggressivity than the controls. Converters had furthermore significantly higher scores than the non-converters in Detachment, while non-converters had significantly higher scores than converters in Verbal Trait Aggressivity.

Further analyses revealed significantly lower levels of Aβ42 for converters to dementia than non-converters [$t(40) = -4.425$, $p < 0.001$], while levels of T-tau [$t(40) = 1.876$, $p = 0.068$] and P-tau[$t(40) = -1.010$, $p = 0.318$] were not significant between groups.

Thus, patients who converted to dementia differed from non-converters in level of Aβ42 already at baseline about three years before diagnosis. Moreover, they had higher levels of T-tau and P-tau. The following cut off levels for CSF Aβ42, T-tau and P-tau in AD, using the ELISA technique, was proposed: Aβ42 < 500 pg/ml; T-tau >450 pg/ml (age 51-70) and P-tau >60 pg/ml [160]. Differences between groups in CSF biomarkers are presented in table 4.

Table 4. CSF biomarkers for non-converters and converters to dementia

| | *Non-converters (n=32)* | *Converters (n=10)* |
|---|---|---|
| *CSF biomarkers* | *M (SD)* | *M(SD)* |
| Aβ42 | 801 (186) | 491 (219) |
| Total tau (T-tau) | 331 (166) | 452 (215) |
| Phosphorylated tau (P-tau) | 53 (22) | 61 (23) |

CSF values are expressed as means of picograms per millilitre

### 3.4.2 Predictors of conversion to dementia

Logistic regression analyses were conducted to examine associations between personality traits, cognitive test and CSF-biomarkers, at baseline, with conversion to dementia, after three years follow-up. Two factors, lower scores in episodic memory (ROCF, retention) *OR* 0.351 (95% CI, 0.136-0.908) and lower levels of Aβ42 *OR* 0.991 (95% *CI*, 0.984-0.998) showed small, but significant, associations with conversion to dementia. Using the model, 100% of non-converters were correctly classified and 70% of the converters, overall 92.9%. There were no associations between baseline personality traits and dementia at follow-up.

In sum, our study demonstrates that three years before diagnose, converters to dementia showed a profile of cognitive impairment, higher levels of neuroticism, and lower levels of extraversion and Aβ42, respectively. Personality has an independent role early in the disease process, but is not directly associated with disease progression. Predictors of dementia at follow-up were Aβ42 and episodic memory, but not personality.

# 4 DISCUSSION

## 4.1 FINDINGS AND REFLECTIONS

The overall aim of this thesis was to examine the significance of personality characteristics in diagnosing prodromal stages of dementia. More precisely, we investigated patterns of personality in subjects with MCI, SCI and controls; level of patient- informant agreement on personality ratings, in relation to cognitive function; the usefulness of personality assessment in discriminating preclinical and prodromal patient groups and lastly, which clinical tests that may predict conversion to dementia at follow up after three years.

Personality changes are common in early stages of AD, but seldom fully recognized in the dementia work-up. In study I we demonstrated that subgroups of memory clinic patients diagnosed with MCI and SCI diverged in their personality profiles, compared to controls. There were no significant differences between patient groups, but gradually higher scores from a healthy state to SCI and MCI, indicating a progressive change in personality that could be related to degree of cognitive impairment. Our patients reported significantly higher levels of somatic anxiety, psychic anxiety and stress susceptibility. Additionally, patients with MCI had higher ratings in detachment, reflecting a reduced interest for social interaction, while patients with SCI scored lower on adventure seeking, meaning a loss of interest for getting new experiences. The results are consistent with numerous studies showing an increase in personality traits related to neuroticism and a decrease in extraversion in subjects with cognitive impairment [26, 89]. Furthermore, both patient groups had higher, although not significantly, levels of depressive symptoms compared to controls. Neuropsychiatric symptoms are well-known features in aging and neurodegenerative disorders, with depression, apathy, anxiety and irritability being the most common [121].

In times of reduced healthcare capacity the challenge in diagnosing patients with MCI and SCI might be to distinguish transitional states, e.g. depressive symptoms, from constitutional changes in personality. Enough time and reliable questionnaires are needed to collect information about patients' premorbid personality. This distinction has important implications for treatment implementation. A recent study showed that high neuroticism was correlated with medication non-adherence in elderly included in a clinical memory study [161]. Moreover, personality screening has a value when discussing coping strategies to handle loss of cognitive abilities. As mentioned previously, having a stable personality, with low neuroticism and high extraversion may improve cognitive functioning and even delay cognitive decline. Thus, to improve emotional well-being and optimize cognitive functioning, coping strategies should focus on reducing negative thinking patterns and support an active life. How these strategies can be implemented in memory clinic populations warrants further studies.

The reliability of patient reports was considered in study II. Due to loss of memory and reduced awareness, information about patients referred to memory clinics most often

has to be corroborated by an informant. We found that agreement between our subjects and their informants was fair to moderate in most personality traits (range: 0.03-0.76) and significant in 44%. Interestingly, dyads with MCI had the highest number of significant correlations; most of them for highly visible traits, i.e. somatic anxiety, low assertiveness, impulsivity, detachment, social desirability, physical aggressivity and mistrust. On the other hand, using an incongruence index, MCI dyads also reported significantly higher incongruence between raters, compared to controls. In our study the difference in agreement was negatively related to MMSE scores, meaning that a low MMSE ratings will result in greater incongruence between raters.

Using informant reports in patients with only minor cognitive deficits relate to matters concerning autonomy and integrity. When should informants be involved? Awareness in not an all-or-non-matter, but has been shown to vary across cognitive domains and functional abilities [14,17]. As mentioned previously and according to a huge body of literature, agreement between raters will be affected numerous factors like degree of acquaintanceship, if they live together, contextual characteristics and the type of behavior being rated [12-13, 16-17]; the more extraverted and visible the behavior, the easier to rate [19-21]. A consequence of our findings is that reports from informants are important to confirm changes in overt personality traits, but in order to catch more subtle emotional changes patients' self-reports are indispensible.

The main finding in study III was that personality assessment is useful for identifying individuals at risk of cognitive decline. The combination of cognitive and personality measurements, compared to using cognitive test alone, improved classification of subjects with MCI from 76% to 82% and SCI from 25% to 62%. As expected, tests of verbal episodic memory and perceptual speed predicted group separation between MCI and SCI/controls, whereas the personality traits somatic anxiety and adventure seeking predicted differences between SCI and controls. Another important result was the identification of subgroups, indicating that patients with MCI and SCI encompass different phenotypes characterized by distinctive features. The results are in line with previous work and have implications for differential diagnostics and patient selection for clinical trials.

One may speculate whether higher levels of distress and anxiety in subjects with SCI reflect preclinical symptoms of future cognitive decline, or neuropsychiatric symptoms related to other disorders or emerging life events. It could be both. SCI has been found to increase the risk for cognitive decline [95] and correlated to several neuropathologic features indicative of dementia [97-99, 102-103]. However, in absence of biomarker evidence, personality assessment, in conjunction with neuropsychological examinations and amnestic information, may result in a more comprehensive clinical profile and improve group discrimination.

In study IV we focused on differences in clinical measures between memory clinic patients with varying degrees of cognitive impairment. We also examined predictors for conversion to dementia at follow-up after three years. A first finding was that

converters to dementia could be separated from non-converters and controls already at baseline. Their profile was characterized by lower results in test of verbal, executive and episodic memory functions and higher levels of somatic anxiety, psychic anxiety, stress susceptibility, detachment and verbal aggressivity. Moreover, they had significantly lower levels of Aβ42. The non-converters, a mixed group of patients with MCI and SCI, differed from controls in the same cognitive and personality measurements as the converters, but showed no abnormalities in CSF levels. A second finding was that low scores in a visual episodic memory test and low Aβ42, but no personality traits, predicted conversion to dementia three years before diagnose. Previous work has shown that low Aβ42 in subjects with MCI increase the risk for conversion to AD [68].

Despite strong evidence for associations between measures of personality and different levels of cognitive impairment, few studies have found significant correlations between personality traits and CSF biomarkers indicative of AD [136]. A conclusion is that personality has an independent, moderating role early in the disease process, but is not directly associated with disease progression. The clinical challenge today is early identification of individuals at risk of developing the cognitive and pathophysiological AD profile. We suggest that by adding personality assessment and controlling for high levels neuroticism and low levels of extraversion, we may further shift the timely diagnostic procedure to an even earlier stage.

## 4.2 LIMITATIONS

First, the sample size is small, reducing the ability to detect minor, but consistent differences between groups. Despite the lack of power, our data corroborate previous findings from longitudinal studies with bigger groups, indicating that our sample is representative for this population. Secondly, since our subjects were recruited from a memory clinic there might be a risk for selection bias, reducing the external generalizability of the results. However, the aim of this study was to examine useful diagnostic tools for this specific population, i.e. internal generalizability. Thirdly, cross-sectional studies are limited to the present level of functioning. In order to identify which variables that correlate with cognitive decline, longitudinal studies with preclinical assessments are needed. Finally, since all subjects were initially diagnosed with the same neuropsychological tests that were used as predictors, there was a risk of circular reasoning. However, the point was not to validate cognitive tests, but to examine the utility of using a combination of personality and cognitive measurements to separate diagnostic groups.

## 4.3 CONCLUSIONS AND FUTURE DIRECTIONS

- Despite the small sample sizes and the cross-sectional design we found significant differences between diagnostic groups and controls, confirming that personality assessment may contribute to the description and delineation of memory clinic patients at risk of cognitive decline. Further research on larger populations and longer follow-up periods are needed to confirm generalizability.

- It has been discussed to which extent community based controls are representative of the larger population and concluded that they may have different reasons for partaking in studies (e.g. worries about memory problems). Follow-up of our control group is suggested to investigate their cognitive and personality profiles, longitudinally, to find out how they develop, compared to our patient groups.

- Based on our findings, we suggest that a short form of the SSP, encompassing traits related to anxiety proneness/neuroticism and extraversion should be implement on a regular basis in the diagnostic dementia work-up. Both a patient- and/or an informant version could be used to investigate which is the most appropriate test for use in memory clinic settings when examining patients with dementia, MCI and SCI, respectively.

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