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Trajectories and the Prognostic Utility of Subjective Memory Complaints in Early Stages of Alzheimer´s Disease – A Retrospective Analysis of a Clinical Sample

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Trajectories and the Prognostic Utility of Subjective Memory Complaints in Early Stages of Alzheimer´s Disease – A Retrospective Analysis of a Clinical Sample

According to the World Health Organization (WHO) dementia refers to an umbrella term including several diseases with impairment of cognitive functions such as memory or processing speed (WHO, 2019). These deteriorating cognitive abilities will result in impaired daily functioning and a loss of independence (McKhann et al., 2011). In 2019, around 50 million people worldwide were diagnosed with dementia, with dementia due to Alzheimer's disease (AD) being the most common form (WHO, 2019). Among the elderly, dementia constitutes one of the major causes of disability and dependency (WHO, 2019), therefore having considerable negative impact on the affected individuals and caregivers, as well as on a societal level. Although there is extensive research on pharmacological treatments, interventions are merely able to slow down the progression of dementia (World Alzheimer Report, 2011). Moreover, a majority of individuals with dementia will not receive timely interventions, as they are diagnosed too late within the progression of the disease (World Alzheimer Report, 2011). Hence, an early diagnose in the course of dementia would be of great benefit.

Additionally, an increasing number of individuals are seeking medical help because of perceived subjective cognitive decline (SCD), although showing unimpaired cognition within objective neuropsychological testing (Garcia-Ptacek et al., 2014; Reid & McLullich, 2006; van der Flier et al., 2018). These solely subjectively impaired individuals show an increased likelihood of having biomarkers of AD pathology and are at increased risk for future objective cognitive decline (Jessen et al., 2020). Hence, subjective reports of cognitive decline moved into the center of interest as an early predictor for later conversion to AD dementia. However, there is a variety of causes and underlying conditions apart from AD pathology that accounts for reporting SCD in cognitively unimpaired individuals. Therefore, a majority of individuals with SCD will not convert to AD dementia, leaving its predictive value still under question. It would be important for early diagnosis to be able to discriminate between elderly with SCD due to AD and elderly with SCD due to other causes.

Because individuals with SCD due to AD most frequently complain about deficits within the memory domain (Jessen et al., 2020), this study focuses on subjective memory complaints (SMC) as an early predictor for future conversion to AD dementia. As there are mixed findings regarding the predictive value of SMC and most previous studies have assessed SMC cross-sectionally (Reid & McLullich, 2006), the present study aimed to contribute additional findings by investigating SMC longitudinally.

Theoretical Background

Dementia due to AD can be seen as a long-lasting disease, as its onset starts years before overt symptoms occur (Jack et al., 2018). Although the initial cognitive decline is too subtle to reach the threshold of objective impairment, this subtle decline may be already subjectively perceived by the individual. Jessen and colleagues (2010) proposed a three-stage-model for conversion to AD dementia. The researchers defined SCD as the first and preclinical stage on the AD continuum, followed by the transitional stage called mild cognitive impairment (MCI). Before going into more detail on the individual stages of the AD continuum, the construct of SMC will be discussed first, as it forms the basis of the preclinical stage and the core of the present study.

Subjective Memory Complaints

Subjective memory is defined as "one´s perceived memory abilities, independent of objective standards or performance" (Bott et al., 2016, p. 1). In the literature, there are several terms used synonymously for SMC, including subjective memory impairment (SMI) and subjective memory decline (SMD). Furthermore, the terms "memory complaint" and "cognitive complaint" are often used synonymously (Edmonds et al., 2014).

Among the elderly, SMC are common. The prevalence rates of SMC estimated within population-based studies vary highly and are within a range from approximately 25% to over 50% (Jonker et al., 2000). The differences are due to sample characteristics and assessment methods. Studies investigating SMC are hardly comparable, as the researchers have applied a variety of different measures for assessing SMC (Reid & MacLullich, 2006). In addition, many studies have applied only one single yes-or-no-question regarding memory complaints (e.g., Liew, 2020). The mixed evidence is partly due to the inconsistency in assessment methods, which make it hard to give clear interpretations and draw definite conclusions.

Associations Between SMC and Other Variables

When investigating the link between SMC and other variables, a review of clinical and population-based studies found a clear association with age over several studies (Jonker et al., 2000). This association can be explained simply by the deteriorating cognitive abilities over age. Moreover, there is extensive research consistently linking SMC to depressive symptoms, indicating a positive association (Lehrner et al., 2014; Reid & MacLullich, 2006). Some researchers suggested that SMC are rather due to depression than reflecting actual objective impairment due to neurodegenerative diseases, as stronger associations of SMC with depression than with objective impairment have been detected (Lehrner et al., 2014). Another

explanation for this link could be that SMC are indeed caused by a cognitive decline too subtle to be detected by neuropsychological testing, but the individual may be subjectively aware of this decline, therefore feeling more depressed (Bott et al., 2016). There could also be a common underlying cause of both SMC and depression, which accounts for the association.

Regarding the association between SMC and objective memory impairment, there is rather mixed evidence (for an overview see the meta-analysis by Crumley et al., 2014). On the one hand, not all individuals with objectively impaired memory performance express SMC (Lenehan et al., 2012). This is often the case in later stages of dementia, where elderly are no longer aware of their cognitive deficits (anosognosia) due to their advanced brain damages (Cacciamani et al., 2020). On the other hand, a great proportion of individuals expressing SMC performs within normal ranges on neuropsychological testing (Garcia-Ptacek et al., 2014; Reid & MacLullich, 2006; van der Flier et al., 2018), which can be explained by a variety of different underlying causes, including AD pathology.

Causes of Subjective Cognitive Complaints

Jessen and colleagues (2014) summarized other causes apart from AD pathology accounting for subjective and/or objective cognitive impairment. These include medication and substance misuse, other forms of dementias (e.g., frontotemporal dementia) and brain diseases (e.g., cerebrovascular disease, head trauma), psychiatric disorders and subclinical psychiatric conditions (e.g., depression, anxiety, sleep disorders), as well as several medical disorders like diabetes, thyroid dysfunction, anemia, etc. Additionally, neuroticism and a general fear of dementia could cause worries about cognitive decline. The perceived cognitive decline could also be due to changes within the normal ageing process and elderly with sensitive self-monitoring may experience these changes even more extensively.

Trajectories of Subjective Cognitive Complaints

Jessen and colleagues (2020) defined different trajectories of subjective complaints and objective impairment depending on the potential underlying causes, including *reversible SCD*, *stable/non-reversible SCD* and *SCD with subsequent progressive cognitive decline to impairment or dementia*. Within reversible SCD, fully remitting subjective complaints occur while objective cognitive performance remains stable. Underlying conditions include for example depression, temporal sleep disturbances or side-effects from medication. Next, stable/non-reversible SCD is again characterized by subjective complaints while objective cognitive performance remains stable. However, in contrast to reversible SCD, the subjective complaints will not remit. This is the case within the normal ageing process. Lastly, SCD with

subsequent progressive cognitive decline to impairment or dementia is characterized by an initial sole subjective complaint with successive objective decline. Underlying conditions include for example neurodegenerative diseases like AD dementia. This SCD trajectory represents the AD continuum, which will be discussed in more detail within the next sections.

The Three-stage Model of the AD Continuum

AD dementia is a syndrome having an insidious onset with a successive cognitive decline (Sachdev et al., 2014). As already mentioned, the AD continuum proposed by Jessen et al. (2010) comprises three stages, starting with SCD, which will proceed to MCI before fully meeting the criteria for AD dementia. It should be noted that this model also accounts for other dementias, not due to AD.

Preclinical Stage: Subjective Cognitive Decline

SCD was defined as the preclinical stage of the AD continuum. Researchers and clinicians of the SCD-Initiative (SCD-I; Jessen et al., 2014) provided a framework for this condition and stated the following two major criteria: (1) self-experienced persistent decline in cognitive capacity as compared to a previously normal cognitive status, which is unrelated to an acute event; and (2) normal performance on standardized cognitive tests adjusted for age, sex and education. Exclusion criteria are being diagnosed with MCI or dementia and the condition may not be explained by psychiatric or neurologic diseases apart from AD, medical disorders, medication, or substance use.

The most frequently expressed cognitive complaints in individuals with SCD due to AD are within the memory domain, but this does not exclude other cognitive domains such as language or processing speed to be affected (Jessen et al., 2020). It should be noted that SCD is not a diagnostic category that can be found in diagnostic tools like the International Classification of Diseases (ICD) or the Diagnostic and Statistical Manual of Mental Disorders (DSM), because of its different courses due to its different causes.

Jessen et al. (2014) suggested that the subjective complaints in elderly with SCD due to AD are caused by an actual subtle objective decline that could not yet be detected by standardized neuropsychological assessments. This objective deterioration remains above the threshold of impairment, enabling the individual to still perform within average ranges as compared to the normative sample data, indicating unimpaired cognition. This initial subtle cognitive deterioration could only be detected via repeated testing of the individual over years. Furthermore, an elderly deteriorating from scores above the average to scores within the average of its reference group of a cognitive test would subjectively perceive his or her

actual and more than subtle cognitive decline. However, this elderly would still perform within normal ranges on standardized neuropsychological testing.

Studies in Europe reported that 25-40% of individuals seeking help for cognitive decline in two memory clinics fulfilled the criteria for SCD (Garcia-Ptacek et al., 2014; van der Flier et al., 2018). Biomarker studies (Jessen et al., 2018; van Harten et al., 2013; Wolfsgruber et al., 2017) found that 7% to 40% of individuals who are seeking medical help because of SCD are considered to be on the AD continuum, indicated by the detection of biomarker abnormalities due to AD.

In recent years, several factors in individuals with SCD have been identified to increase the likelihood of preclinical AD dementia and are defined as *SCD plus features* (Jessen et al., 2020). These include: reporting subjective decline within the memory domain irrespective of function in other cognitive domains; onset of SCD within the past five years; onset of SCD at 60 years and older; worries associated with SCD; persistent SCD over time; seeking medical help and confirmation of cognitive decline by an observer.

Transitional Stage: Mild Cognitive Impairment

The second stage in the model is MCI. MCI is a diagnostic entity first described by Petersen (1999, 2004) and differs from SCD only by an additional objective impairment in performance on standardized cognitive tests as indicated by scores below the cut-offs. In contrast to dementia, daily functioning and independence is preserved. In patients with MCI, although objectively impaired, the criteria for dementia are not sufficiently met and MCI is considered to be the transitional stage on the course to dementia.

The diagnosis of MCI is subdivided into amnestic MCI (aMCI) and nonamnestic MCI (naMCI, Petersen, 2004). AMCI is diagnosed if the memory domain is impaired, irrespective of impairment in other domains. NaMCI is diagnosed if other cognitive domains apart from the memory domain are affected. Furthermore, the diagnosis is subdivided into MCI – single domain (which will be diagnosed if only one domain is affected) and MCI - multiple domain (which will be diagnosed if more than one domain is affected).

Within the fifth edition of the DSM (DSM-5) provided by the American Psychiatric Association (APA), the following diagnostic criteria were stated: “A. Evidence of modest cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual–motor, or social cognition) based on: 1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a mild decline in cognitive function; and 2. A modest impairment

in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment. B. The cognitive deficits do not interfere with capacity for independence in everyday activities (that is, complex instrumental activities of daily living such as paying bills or managing medications are preserved, but greater effort, compensatory strategies, or accommodation may be required). C. The cognitive deficits do not occur exclusively in the context of a delirium. D. The cognitive deficits are not better explained by another mental disorder (for example, major depressive disorder or schizophrenia)." (APA, 2013, p. 605). However, individuals with MCI will not necessarily proceed to dementia (Sachdev et al., 2014), as the cognitive impairment may be static (e.g., traumatic brain injury).

Petersen et al. (2010) examined prevalence rates in a population-based sample of 1969 non-demented elderly aged between 70 and 89 and found 16% having any type of MCI. If subdivided into aMCI and naMCI, the prevalence rates were 11.1% and 4.9% respectively. There is evidence that especially the aMCI condition constitutes a prodromal stage of dementia due to AD, whereas naMCI more likely precedes to other forms of dementia (Peterson et al., 2004). In a big population-based study conducted by Fischer et al. (2007), the conversion rate to AD dementia after 30 months was higher for the aMCI group (48.7%) than for the naMCI group (28.8%). Likewise, Lehrner et al. (2016) found a higher conversion rate to AD from aMCI than from naMCI in a clinical sample, with five out of the seven MCI patients which converted to AD had been within the aMCI group. The researchers of the study reported an Odds Ratio of 2.0 for the aMCI group converting to AD with a higher probability as compared to the naMCI group.

Final Stage: AD Dementia

Finally, the last stage of the continuum is AD dementia itself. According to the diagnostic criteria of the DSM-5 (APA, 2013) and as compared to MCI, not modest, but substantial cognitive deterioration and impairment have to be ascertained for a dementia diagnosis. This impairment is severe enough to cause problems in daily functioning and therefore a loss of independence. The changes in the brain may also affect behavior and mood. Typically, the first and most affected cognitive domain in dementia specifically due to AD is memory and learning. For an AD dementia diagnosis, at least two cognitive domains have to be impaired and one of these domains has to be memory and learning.

SMC and the Risk for Future Objective Impairment

Several research findings report an increased risk of future objective cognitive decline in elderly with SMC (Jessen et al., 2020). A meta-analysis by Mitchell et al. (2014) showed that elderly with SMC but no objective impairment are twice as likely (relative risk = 2.07) to develop dementia than elderly without SMC. The researchers further found annual conversion rates (ACR) of 6.6% for converting to MCI and 2.3% for converting to dementia (Mitchell et al., 2014). For a period of four years, the rates increased to 26.6% for conversion to MCI and 14.1% for conversion to dementia, compared with 4.6% of elderly without SMC converting to dementia (Mitchell et al., 2014). Specifically, regarding the conversion to dementia due to AD, Lehrner et al. (2005) found an ACR of 3% in elderly with SMC and no objective impairment. However, there are also contradictive findings regarding the prognostic value of SMC for future conversion within the AD continuum. When examining reports of SMC in a clinical sample of 141 patients with SCD or MCI further converting to MCI or dementia, Lehrner et al. (2016) found no differences in baseline SMC between converters and non-converters. In contrast, another study conducted by Lehrner and colleagues (2014) has investigated SMC cross-sectionally in a clinical sample of 581 elderly within the patient group having either SCD or MCI. Their analysis revealed a statistically significant difference in SMC between all diagnostic groups, except for naMCI and the SCD group which did not differ significantly. The aMCI group reported the highest levels of SMC as compared to healthy controls, SCD and naMCI. A recent study conducted by Liew (2020) investigated SCD trajectories longitudinally in a clinical sample of 5661 healthy elderly. The researcher found that elderly reporting stable and persistent subjective complaints within several repeated assessments across four years are at higher risk for MCI and dementia as compared to elderly expressing intermittent or no SCD.

Previous research indicates that the awareness of cognitive deficits declines while proceeding the AD continuum (Lehrner et al., 2015). Lehrner and colleagues examined a clinical sample of 756 elderly and suggested that anosognosia is an important symptom in both AD and aMCI, while individuals with SCD and naMCI tend to overestimate memory dysfunction. The researchers further concluded that a decline of cognitive function is accompanied by a decline of awareness of this cognitive dysfunction, especially in the memory domain. Moreover, this lack of awareness of cognitive deficits in individuals with MCI was recently linked to an increased conversion rate to dementia (Sánchez-Benavides et al., 2018).

The Reliable Change Index

When repeatedly assessing performance within two or more testing points, it can be crucial to evaluate if this change in the reached test scores is reliably due to actual change in performance and not due to systematic errors such as measurement errors or practice effects. One such approach is the Reliable Change Index (RCI), which is a score that can be interpreted as the amount of change that has to occur between the different testing points to be reliably attributed to actual change in performance (Jacobson & Truax, 1991).

The original approach was proposed by Jacobson and Truax (1991). The required values to calculate this RCI include the patients´ individual test scores at time 1 (X) and time 2 (Y), the mean score of normative data or a control group at time 1 (M_X) and time 2 (M_Y) with their respective variances at time 1 and time 2 (S_X and S_Y) as well as the test-retest reliability (r_{XY}) of the normative or control group data (correlation between M_X and M_Y). The researchers calculate their RCI by dividing the simple discrepancy score of the different testing points ($Y - X$) by the standard error of difference (SED). The SED estimates the standard deviation of the difference scores by including the test-retest reliability into its formula: RCI = ($Y - X$) / SED with SED = $\sqrt{2 * S_X(1 - r_{XY})}$. The resulting reliable change (RC) score constitutes a z-score, which subsequently has to be compared with a normal distribution table to detect significance. Setting a 90% confidence interval results in a cut-off score of $\pm$ 1.645 for indicating positive or negative reliable change. As this original RCI approach was proposed in the context of psychotherapy, it does not take into account practice effects. To deal with this potential systematic biases, various different methods expanding the original approach have established in past years (for an overview see Hinton, 2010). The three methods most commonly used in past research have been proposed by Chelune et al. (1993), McSweeny et al. (1993) and Maassen et al. (2006).

Because these RCI methods are calculated on the basis of different values, they differ in the resulting RCIs and are therefore showing differing responsiveness. The responsiveness of a method refers to its ability to detect reliable change over time (Hinton-Bayre, 2016). There is extensive research comparing several RCI models (for an overview see Hinton-Bayre, 2010), but no clear conclusions can be drawn as the results are rather mixed. Regression-based models are found to be more responsive when using clinical data (Hinton-Bayre, 2010). The regression-based model by McSweeny and colleagues was found to be the most responsive to negative change (deterioration) (Hinton-Bayre, 2016). In contrast, when referring to positive change (improvement), the model by Chelune and colleagues was found to be more responsive than the McSweeny model (Levine et al., 2007). However, Duff (2014)

reported a general superiority of the McSweeny model because overall, it is considered to be the most responsive one. The three named RCI methods are introduced within the next sections.

RCI Incorporating Mean Practice Effects

The method by Chelune and colleagues (1993) is typically referred to as RCI_{PE} as it adjusts the original approach to control for practice effects. The RCI_{PE} is calculated by subtracting the mean practice effect of normative data or a control group ($M_Y - M_X$) from the simple discrepancy score of the different testing points and dividing this by the SED: $RCI_{PE} = (Y - X) - (M_Y - M_X)$ / SED. The SED is calculated the same way as within the original approach by Jacobson and Truax (1991; see formula above).

Within this method, the correction for practice effects is made uniformly for all patients, as it uses the mean difference between test and retest scores of a normative or control group. Hence, this method accounts for mean practice effects.

Standardized Regression-based RCI

McSweeny and colleagues (1993) proposed a standardized regression-based (SRB) formula which is commonly referred to as RCI_{SRB}. This method not only accounts for mean practice effects, it expands by adjusting the practice effects for the individual's position relative to the mean of the normative or control group data. The adjustments for the relative position are based on the direction of differential practice, which can be seen as the differences between baseline and retest variances ($S_Y - S_X$) within one patient. Further adjustments are based on the test-retest reliability.

Within this method, linear regression is used to predict the time 2 score (Y') by the time 1 score, following the formula $Y' = b * X + c$, where b represents the regression slope (β weight) of X and c represents the regression intercept (constant). Subsequently, the RCI_{SRB} can be generated by subtracting Y' from the actual observed Y and dividing this difference score by the standard error of the estimate (SEE) of the regression equation: $RCI_{SRB} = (Y - Y') / SEE$.

Additionally, instead of running a regression analysis to generate the required scores, they can be estimated when means, variances and test-retest reliability of the normative or control group are available (Crawford & Garthweite, 2007). The estimated (est) Y' can be obtained using the formular $Y'_{est} = b_{est} * X + c_{est}$ with $b_{est} = r * (S_Y / S_X)$ and $c_{est} = M_Y - b_{est} * M_X$. The SEE can be estimated by $SEE_{est} = S_Y * \sqrt{(1 - r_{XY})}$.

Adjusted Standardized Regression-based RCI

Maassen and colleagues (2006) further expanded this simple regression approach. While still accounting for mean practice and making adjustments for the individual's relative position and inequality of variances, their predicted retest score is not affected by test-retest reliability. The adjusted predicted retest score (Y'_{adj}) can still be calculated by $Y'_{adj} = b_{adj} * X + c_{adj}$ with $b_{adj} = S_Y/S_X$ and $c_{adj} = M_Y - b_{adj} * M_X$. Again, the adjusted RCI_{SRB} can subsequently be calculated by subtracting the adjusted predicted retest score from the actual observed retest score and dividing this difference by the adjusted SED: $RCI_{SRBadj} = (Y - Y'adj) / SED_{adj}$ with $SED_{adj} = \sqrt{(S_X^2 + S_Y^2) * (1 - r_{XY})}$.

Aims of the Study

To sum it up, there is evidence that individuals reporting SMC but showing no objective cognitive impairment are at the preclinical stage of the AD continuum defined as SCD, indicated by biomarker evidence due to AD and increased conversion rates to MCI and AD dementia (Jessen et al., 2020). However, a majority of individuals with SCD will not show future objective cognitive decline. Hence, the predictive value of SMC is still under question. More research is needed to investigate SMC in elderly with SCD to evaluate clinical utility. As the mixed evidence results partly due to mixed assessment methods, often comprising solely one single question to assess SMC (Reid & MacLullich, 2006) the present study used a more comprehensive measure comprising 16 items to assess SMC. Because early diagnosis is crucial for slowing down the progression of dementia, the main objective of the present study was to investigate SMC as assessed via the Forgetful Assessment Inventory (FAI; Lehrner et al., 2014) in elderly with SCD as an early predictor for future conversion to aMCI and naMCI. Given that most previous studies investigated subjective complaints cross-sectionally (Reid & MacLullich, 2006), the present study was interested in the course of SMC longitudinally over two measurement points, following the aim to provide additional findings regarding early stages of the AD continuum. Additionally, there is evidence regarding discrepancies depending on whether a raw score or standardized *z*-score resulting from psychometric tests are used for interpretation (Bondi et al., 2003). Therefore, the present study further aimed to evaluate the predictive value of a raw score and a standardized *z*-score of SMC separately. Because previous studies found associations between SMC and other variables (Jonker et al., 2000), the current study was interested in finding correlations between SMC and demographic and clinical variables. Moreover, the present study aimed to investigate the FAI as a valid tool for discriminating between converters to aMCI and non-converters to aMCI, as the aMCI

group is of most interest within AD dementia research. Finally, the last objective was to calculate and compare the three most widely used methods for assessing reliable change.

Research Questions

To reach the study aims, the following research questions and hypotheses were formulated. The first research question asked (1) if a raw score of SMC does predict the conversion from SCD to aMCI and naMCI. The hypothesis was that a raw score of SMC does predict the conversion from SCD to aMCI and naMCI (hypothesis 1). Analogue to this, the second research question asked (2) if an age-, sex- and education-adjusted standardized *z*-score of SMC does predict the conversion from SCD to aMCI and naMCI. The hypothesis again was that a standardized *z*-score of SMC does predict the conversion from SCD to aMCI and naMCI (hypothesis 2). Next, the third and fourth research questions asked whether the different diagnostic groups as classified after follow-up testing (non-converters/SCD, converters to aMCI and converters to naMCI) show different courses over time of (3) a raw score of SMC and (4) an age-, sex- and education-adjusted standardized *z*-score of SMC respectively. The hypotheses were that the diagnostic groups show differing courses of the raw score (hypothesis 3) and the age-, sex- and education-adjusted standardized *z*-score (hypothesis 4) of SMC. Moreover, the fifth research question asked (5) if there is a difference in the course of objective cognitive performance over time between elderly reporting high SMC and elderly reporting low SMC. The corresponding hypothesis was that there is a difference in the course of cognitive performance over time between elderly reporting high SMC and elderly reporting low SMC (hypothesis 5).

Additionally, several exploratory research questions were formulated asking (6) whether there are associations between SMC and the demographical and clinical variables included into this study (sex, age, education, interval, depressive symptoms, verbal IQ and objective cognitive performance); (7) if the Forgetful Assessment Inventory constitutes a valid tool to discriminate between converters to aMCI and non-converters to aMCI; and lastly (8) whether there are differences in the resulting RCIs as assessed via the methods by Chelune et al. (1993), McSweeny et al. (1993) and Maassen et al. (2006).

Methods

Data Collection

The present quasi-experimental and longitudinal study was performed within the "Viennese Conversion to Dementia Study" (EK 174/2008) at the Medical University of

Vienna. The data was analyzed retrospectively and had already been collected at the outpatient memory clinic of the department of neurology between June 2001 and October 2018. All participants conducted complete neuropsychological assessments as well as psychometric tests at baseline (T1) and follow-up (T2).

Regarding ethical aspects, the present study was approved by the Ethics Committee of the Medical University of Vienna (EK number: 1889/2020). In terms of data protection, the retrospectively analyzed dataset was pseudonymized. The original dataset resides within a secure databank of the Medical University of Vienna at the Department of Neurology, only accessible by authorized personnel via password.

Sample

The sample consisted of $N = 81$ participants, divided into a patient group (PG) and a healthy control group (HCG). The PG included individuals who sought medical help for perceived cognitive decline and were either self-referred or referred by physicians to the outpatient memory clinic. Only individuals classified as having SCD after baseline investigation were included into the PG. Inclusion criteria were: (1) age of 50 years or older, (2) Mini Mental State Examination (MMSE) score higher than 23, (3) no neurological diseases (e.g., stroke or traumatic brain injury), (4) no current major psychiatric diagnosis according to ICD-10 (excluding depression), (5) no objective cognitive impairment at baseline, as indicated by neuropsychological testing, (6) no language, motor, auditory or visual deficits, or other medical conditions that would influence patient's cognitive performance. Reporting depressive symptoms was not considered to be an exclusion criterion, as depressive symptoms are very common among the elderly (Lehrner et al., 2014). The HCG was self-recruited from the general population via advertisements based on the same inclusion criteria. Solely the MMSE score had to be above 27. Only participants which completed the whole testing procedure at both testing points were included into the analysis. All participants gave written informed consent.

The PG ($n = 36$) comprised more men ($n = 21$, 58.3%) than women ($n = 15$; 41.7%) Participants in the PG were aged between 50 and 82 years, with a mean age of 66.50 ($SD = 8.98$) and had absolved 8 to 20 years of education ($M = 12.97$, $SD = 3.57$). The HCG ($n = 45$) comprised more men ($n = 30$, 66.7%) than women ($n = 15$, 33.3%) as well. The healthy controls were aged between 51 and 76 years ($M = 60.49$, $SD = 5.32$) and absolved between 6 and 24 years of education ($M = 13.03$, $SD = 4.97$).

Instruments

Mini Mental Status Examination (MMSE)

The MMSE (Folstein et al., 1975) is a screening tool for an initial assessment of cognitive deficits. In the current study, the German version of the MMSE, the Mini-Mental-Status-Test (MMST; Kessler et al., 2000), was used to prescreen the participants. The MMSE score was used for descriptive statistics. A maximum of 30 points can be reached. The MMSE consists of 20 questions and short exercises measuring various cognitive functions. These include for example temporal (e.g., "*Which year do we have?*") and spatial orientation (e.g., "*Where are we here?*"), memory (e.g., little exercise where the participant has to recall three words. These words were introduced two exercises prior, were the participant simply got the instruction to repeat these three words, without explicit instruction to memorize the words.), as well as performing verbal and written commands (e.g., the patient has to repeat a sentence verbally given by the test administrator). The MMSE lasts approximately 5 minutes and the resulting points can be summed for scoring, with a higher score meaning better performance. Kessler et al. (2000) reported a good interrater reliability (r = .83).

Vienna Visuo-Constructional Test (VVT) 3.0 Screening

The VVT 3.0 screening (Lehrner, 2015) was used to screen for visuo-constructive performance. The results were used for descriptive statistics. Within the VVT, the participant has to copy three given symbols (a clock, two overlapping pentagons and a three-dimensional cube). The drawings are later evaluated within 10 items (three for the clock, three for the pentagons, and four for the cube) regarding the completeness and the precision of the copies. In total, 10 points can be reached with a higher score indicating better visuo-constructive performance. The duration for executing the VVT is set at approximately 5 minutes. Numrich et al. (2017) reported a good internal consistency with a Cronbach´s alpha (α) of .84 and a good interrater reliability (r = .84).

Neuropsychological Test Battery Vienna (NTBV)

For comprehensive neuropsychological assessment, the NTBV (Lehrner et al., 2007) was applied. The results of the NTBV were used to determine whether the patient has objective cognitive impairment. The NTBV was designed to detect dementia and assesses cognitive function in the domains of attention, memory, language and executive functioning. Evaluating the domain of attention include the Alters-Konzentrationstest (AKT; Gatterer, 2008), the symbol counting subtest from the Cerebral Insufficiency (C.I.) Test (Lehrl & Fischer, 1997),

the Digit-Symbol subtest of the WAIS-R (Tewes, 1994), part B of the Trail Marking Test (TMT; Reitan, 1979) and the score difference of part A and part B of the TMT. The memory domain is assessed via the Verbal Selective Reminding Test (VRST; Lehrner et al., 2007), consisting of the subtests *immediate recall*, *total recall*, *delayed recall* and *recognition of prior presented foods*. Within the language domain, lexical verbal fluency is assessed by the Phonematic Verbal Fluency Test (Goodglass & Kaplan, 1983), as well as by naming as many words with the letters b, f and l as possible within one minute each. Additionally, verbal fluency is investigated by using the Semantic Verbal Fluency Test (Goodglass & Kaplan, 1983) and the modified Boston Naming Test (BNT; Morris et al., 1989). To investigate executive functions, the Five-Point Test (Regard et al., 1982), part A of the TMT (Reitan, 1979), the Stroop and the Maze subtests from the Nürnberger Aging Inventory (NAI; Oswald & Fleischmann, 1997) and the Interference subtest from the C.I. Test (Lehrl & Fischer, 1997) are applied. For more detailed information of the NTBV see: https://kpfg.meduniwien.ac.at/wissenschaft-forschung/psychologische-verfahren/. Executing the whole test battery lasts approximately 45 to 60 Minutes. An age-, sex- and education-adjusted standardized *z*-score for each domain, as well as a total *z*-score across all domains can be calculated out of the raw scores of each test. For a group of demented patients, Lehrner et al. (2007) reported a good internal consistency (Cronbach´s α = .87 - .89). The correlation coefficients of the test-retest reliability ranged from r = .69 - .94. (Hitzl, 2015; Lehrner et al., 2007; Macher, 2013).

Wortschatztest (WST)

The WST (Schmidt & Metzler, 1992) is a vocabulary test that was applied to assess verbal intelligence of the participants in order to use it as a control variable in statistical analysis. Six words in a row are presented to the participant. However, only one constitutes a real existing word and the other five were freely made up. Within 40 items, the participant has to identify the real word out of the other fake one´s (example item in German: Renek – Skerk – Erenk – Kern – Nerk – Lersk). The participant is introduced not to make a guess if the correct word cannot be found. The WST lasts about 5 to 10 minutes. All correct items are scored with one point and finally summed to a maximum of 40. An intelligence quotient (IQ) score can be calculated out of the raw score. Schmidt & Metzler (1992) reported an excellent internal consistency (Cronbach´s α = .92).

The Forgetful Assessment Inventory

SMC were assessed via the FAI (Lehrner et al., 2014), which is a self-report questionnaire. The FAI consists of 16 items, asking for perceived change on memory function in the everyday life of the past four weeks (e.g., "*How often did you have problems during the past 4 weeks remembering names of people*"). The items are rated on a 5-point Likert scale ranging from 1 (*never*) to 5 (*very often*). The FAI lasts approximately 5 minutes. For scoring, the items can be summed and divided by the number of items answered. A higher score indicates more reported SMC. The internal consistency of the FAI can be interpreted as excellent with a Cronbach´s α of .93 (Lehrner et al., 2014). The FAI can be obtained from www.psimistri.com.

Beck Depression Inventory-II (BDI-II)

Depressive symptoms were assessed via the German version of the BDI-II (Hautzinger et al., 2009; original version from Beck et al., 1996) to use it as a control variable for statistical analysis. The BDI-II is a self-report questionnaire consisting of 21 items regarding depressive symptoms. The participant has to choose one out of four statements (4-point Likert scale from 0 to 3), which best describes the participant's feelings during the last two weeks (e.g., "(0) *I am not sad*, (1) *I am sad*, (2) *I am sad all the time and I can´t get away from it*, (3) *I am so sad or unhappy that I can hardly stand it anymore"*). The resulting points have to be summed for scoring, with a maximum of 63. A higher score indicates stronger depression. The BDI-II lasts about 5 to 10 minutes. Segal et al. (2008) reported a good internal consistency (Cronbach´s α = .86), as well as given convergent and discriminant validity.

Study Design and Testing Procedure

All participants firstly attended anamnesis to assess demographic characteristics (age, sex and education), clarify the patients (medical) history and reveal exclusion criteria. Afterwards, the participants conducted short screening for cognitive deficits (using MMSE and VVT 3.0 screening), before neuropsychological assessment (via NTBV). Lastly, the participants completed the remaining psychometric tests and measurements (WST, FAI, BDI-II). As already mentioned, conducting the NTBV lasts approximately 45 to 60 minutes. Adding the time needed for the remaining measurements, the whole testing procedure took about 70 - 120 minutes. After the baseline investigation took place, the participants conducted follow-up examination between 12 and 48 months later, using the same testing procedure. Depending on the diagnosis that resulted from the follow-up examination, the PG was divided into the following diagnostic groups: (1) non-converters/SCD (all patients still classified as SCD), (2)

converters to aMCI (all patients which converted from SCD to aMCI), (3) converters to naMCI (all patients which converted from SCD to naMCI).

Criteria for Assignment to the Diagnostic Groups

The patients were assigned to the diagnostic groups based on the results of the neuropsychological assessment via NTBV and judgement of clinicians. The raw scores of the NTBV were transformed into standardized *z*-scores to be adjusted for age, sex and education. SCD criteria (based on the recommendations of the SCD-I; Jessen et al., 2014) were experiencing subjective decline in any cognitive domain and an unimpaired objective cognition, as indicated by *z*-scores above -1.5 *SD* for each domain measured. MCI was defined based on criteria proposed by Petersen (2004): (1) reports of subjective cognitive complaints by the patients and/or their caregivers, (2) no significant functional impairment in the daily life, (3) objective cognitive decline in at least one domain, as indicated by *z*-values below -1.5 *SD*, and (4) no present dementia diagnosis. Participants classified as MCI were further subdivided into the groups aMCI and naMCI. AMCI was diagnosed if the *z*-value of the memory domain was below -1.5 *SD*, irrespective of cognitive deficits in other domains. NaMCI was diagnosed if the *z*-value of one or more domains other than memory were below -1.5 *SD*.

Statistical Analysis

Statistical analysis was conducted using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corporation, 2019). The significance level (p) was set at 5% (two-tailed). Therefore, a $p \leq .05$ indicates a significant result. First, the dataset was checked for plausibility and completeness, yielding 61.7% missing values within the VVT. This is because the VVT was implemented at a later date during data collection. As the results of the VVT were only used for descriptive statistics, the reported values were calculated based on the available VVT values. Moreover, age-, sex- and education-adjusted standardized *z*-scores for FAI (FAI_z) were derived out of the FAI raw scores (FAI_raw) for each participant based on normative sample data using a GAMLSS (Generalized Additive Models for Location, Scale and Shape) model. Next, a categorial variable was generated, defining the diagnostic group after the follow-up testing, including the three categories: (0) non-converters (labeled *SCD*), (1) converters to naMCI (labeled *naMCI*) and (2) converters to aMCI (labeled *aMCI*). Demographic characteristics and clinical variables were descriptively analyzed. The variable labeled *interval* represents the elapsed months between T1 and T2. Additionally, conversion rates from SCD to naMCI or aMCI were calculated using the following formula: (number of

converted patients / total number of patients) * 100. Next, before conducting the main analyses, the corresponding test assumptions for the statistical methods were checked and are reported in the following within the respective sections.

Multinomial Logistic Regression

In order to answer the first and second research questions, which are asking whether a raw score of SMC (FAI_raw) and an age-, sex- and education-adjusted standardized *z*-score of SMC (FAI_z) respectively can predict conversion from SCD to naMCI or aMCI, multinomial logistic regression analyses were conducted. Multinomial logistic regression expands the method of binary logistic regression by predicting the probability of more than two different possible categories within a categorial outcome variable (Field, 2018). To calculate multinomial logistic regression, one category of the outcome variable has to be defined as the reference category, consequently comparing all other categories separately with this reference category. In other words, multinomial logistic regression estimates the probability of a case belonging to a certain category of the outcome variable as compared to the reference category, depending on the given value of one or more predictor variable/s.

In the present study, two multinomial logistic regressions were conducted for the PG (N = 36). The continuous independent variables were FAI_raw and FAI_z, respectively at T1, predicting the diagnostic group as the categorial dependent variable with its three categories (0) SCD, (1) naMCI and (2) aMCI. Each regression was calculated twice. At first, SCD was set as the reference group (to allow for the comparisons 1 vs. 0 and 2 vs. 0) and secondly, aMCI was set as the reference group (to additionally allow for the comparison 2 vs. 1). Sex, age, education, WST-IQ and BDI-II were used as control variables. All variables were entered simultaneously using the enter method. To calculate how much additional outcome variance can be explained by the final model as opposed to the original model without predictors, the change in the log-likelihood was interpreted. A smaller log-likelihood value indicates less unexplained variance (Field, 2018). Hence, a significant *p*-value indicates a better fit of the final model as opposed to the original model without predictors. To further assess the model fit, Nagelkerke´s R^2 as well as Cox and Snell´s R^2 are reported, estimating the amount of explained variance. These values lie between 0 and 1, with a higher value indicating more explained variance and consequently a better model fit (Field, 2018). Moreover, if the overall logistic regression model turns out to be significant, reporting the Odds Ratio (OR) is crucial for the interpretation of the results. The OR quantifies the change in odds for the relevant outcome category as compared to the reference category if the predictor value changes by one

unit (Field, 2018). An OR greater than 1 indicates that as the value of the predictor variable increases, the odds for the relevant outcome category also increases as compared to the reference category. In contrast, an OR smaller than 1 indicates that as the value of the predictor variable increases, the odds for the relevant outcome category decreases as compared to the reference category.

The first test assumption of multinomial logistic regression is having a linear relationship between the independent variable and the logit of the outcome variable (linearity of the logit; Field, 2018). This assumption was met, indicated by non-significant interaction terms of FAI_raw and FAI_z respectively with its own natural log transformation (*p*-values of the regression coefficients of FAI_raw * ln[FAI_raw] and FAI_z * ln[FAI_z] > .05). To meet the second test assumption, the predictors within the regression should not correlate too strongly with each other (no multicollinearity; Field, 2018). Collinearity diagnostics were assessed to test for linear relationships between the predictor variables. A tolerance value smaller than 0.1 and VIF (variance inflation factor) higher than 10 indicate problems with multicollinearity. As all tolerance (for all variables > 0.1) and VIF (for all variables < 10) values fell within these cuff-offs, no problems with multicollinearity were being detected for the present study.

Mixed Design ANCOVA for FAI

To test whether the diagnostic groups show different courses of FAI_raw and FAI_z respectively across the two testing points, two separate mixed design ANCOVAs had been conducted, including the individuals of the PG ($N = 36$). A mixed design model is used to combine repeated measures (within-subject variable) and independent measures (between-subject variable; Field, 2018). In the present study, the within-subject factor was *time* with two measurement points (T1 and T2) and the within-subject variables were FAI_raw and FAI_z respectively at T1 and at T2. The between-subject-factor was the diagnostic group after T2 with its three categories (0) SCD, (1) naMCI and (3) aMCI. Sex, age, education, WST-IQ and BDI-II were added as covariates. After calculating main and interaction effects, pairwise comparisons were performed using the Šidak correction to control the familywise error rate in multiple testing. For the overall ANCOVA, partial eta squared (η_p^2), which can be interpreted as the amount of explained variance, is reported as a measure of effect size. An $\eta_p^2 \geq .01$, $\eta_p^2 \geq .06$ and $\eta_p^2 \geq .14$ indicates a small, moderate and large effect respectively (Kirk, 1996). Additionally, Cohen´s *f* is reported as effect size for significant pairwise comparisons. Following Cohen´s criteria (1988), a $f \geq 0.1$, $f \geq 0.25$ and $f \geq 0.4$ indicates a small, moderate and large effect respectively.

Before conducting the main analysis, test assumptions were checked. First, all continuous variables included into the analysis should be normally distributed within all categories of the independent variable (Field, 2018). To test this, a Shapiro-Wilk-Test was conducted, which revealed normally distributed variables within all diagnostic groups: FAI_raw at T1 (p = .278 - .441), FAI_raw at T2 (p = .528 - .993), FAI_z at T1 (p = .186 - .629), FAI_z at T2 (p = .426 - .968), age (p = .284 - .983), education (p = .162 - .995), WST-IQ (p = .188 - .857) and BDI-II (p = .273 - .629). As the Shapiro-Wilk-Test depends on sample size and therefore may be biased, histograms and P-P-plots were visually checked as well in order to detect deviations from normal distribution. These show similar patterns and are largely in accordance with the Shapiro-Wilk-Test. Next, the variances of the dependent variable should be equal across groups (homogeneity of variances; Field, 2018). This assumption was checked via Levene-Test, which revealed non-significant for FAI_raw at T1 [$F(2,33) = 0.61$, p = .547] and T2 [$F(2,33) = 0.82$, p = .450] as well as for FAI_z at T1 [$F(2, 33) = 0.05$, p = .949] and T2 [$F(2, 33) = 0.88$, p = .424], indicating homogeneity of variances. The next assumption refers to the required independency between the covariates and the independent variable (Field, 2018). This assumption was met (all $p > .05$), as the diagnostic groups did not differ significantly in sex [$F(2, 33) = 0.532$, p = .592], age [$F(2, 33) = 0.14$, p = .869], education [$F(2, 33) = 2.83$, p = .074], WST-IQ [$F(2, 33) = 0.76$, p = .447] and BDI-II [$F(2, 33) = 1.73$, p = .193]. Another test assumption refers to the relationship between the dependent variable and the covariates, which should be the same for all categories of the independent variable (homogeneity of the regression slopes; Field, 2018). This assumption was met (all $p > .05$), indicated by non-significant interaction effects (independent variable * covariate) for the diagnostic group with every single covariate: age [$F(1) = 0.00$, p = .965], sex [$F(1) = 0.04$, p = .835], education [$F(1) = 0.40$, p = .534], WST-IQ [$F(1) = 0.20$, p = .659] and BDI-II [$F(1) = 0.04$, p = .844].

Mixed Design ANCOVA for NTBV

Another mixed design ANCOVA was conducted for the whole sample (N = 81) to test whether there are different courses of objective cognitive performance over time depending on FAI_z and the sample group. The sample group was divided into (0) the HCG (n = 45) and the PG (n = 36). Regarding FAI_z, a new dichotomous variable labeled *SMC group* was created, including the two categories (0) *high SMC* (all participants with a z-score of FAI ≤ -1.5, thereby having reported more SMC than the average 50%, n = 9) and (1) *low SMC* (all participants with a z-score of FAI > -1.5, thereby including all participants within or above the average 50%, n = 72).

The within-subject factor was *Time*, having NTBV_z at T1 and at T2 as within-subject variables. The between-subject factors were the sample group (HCG vs. PG) and the SMC group (low SMC vs. high SMC). Sex, age, education, WST-IQ and BDI-II were added as covariates. Again, pairwise comparisons were performed using the Šidak correction. As measures of effect size, η_p^2 is reported for the overall ANCOVA and Cohen´s *f* is reported for pairwise comparisons.

At first, test assumptions were checked. Shapiro-Wilk-Test was conducted to test for normality of distribution for all variables split for the sample group. Within the PG, the variables FAI_raw ($p = .376$), FAI_z ($p = .831$), NTBV_z ($p = .073$), WST-IQ ($p = .146$), age ($p = .178$) and education ($p = .051$) were nearly normally distributed, whereas the variables MMSE ($p = .001$) and BDI-II ($p = .024$) diverge from normal distribution. Within the HCG, normal distribution was given for the variables FAI_raw ($p = .147$), FAI_z ($p = .667$), NTBV_z ($p = .725$) and WST-IQ ($p = .128$), whereas normal distribution was not given for the variables age ($p < .001$), education ($p = .001$), MMSE ($p < .001$) and BDI-II ($p < .001$). Normality of distribution for the variables split for low SMC and high SMC are reported next. For the dependent variables, normality of distribution was given both in the high SMC group (NTBV_z at T1: $p = .971$, NTBV_z at T2: $p = .758$); and in the low SMC group (NTBV_z at T1: $p = .430$, NTBV_z at T2: $p = .129$). Furthermore, Shapiro-Wilk-Test indicated normality of distribution for all covariates in the high SMC group ($p = .052$ - $.912$), whereas deviation from normal distribution was indicated for all covariates in the low SMC group ($p = .046$ - $\leq .001$). Histograms and P-P-Plots showed similar results and are in accordance with the Shapiro-Wilk-Test. Moreover, Levene-Test indicated homogeneity of variances for both NTBV_z at T1, $F(3, 77) = 2.06$, $p = .112$, and NTBV_z at T2, $F(3, 77) = 0.85$, $p = .469$. Next, independency between the covariates and the sample group was given for sex [$F(1, 79) = 0.59$, $p = .447$], education [$F(1, 79) = 0.00$, $p = .951$], WST-IQ [$F(1, 79) = 1.65$, $p = .202$] and not given for age [$F(1, 79) = 14.03$, $p = < .001$] and BDI-II [$F(1, 79) = 13.18$, $p = .001$]. Regarding the SMC group, independency with all covariates was given: sex [$F(1, 79) = 0.06$, $p = .810$], age [$F(1, 79) = 0.57$, $p = .453$], education [$F(1, 79) = 0.00$, $p = .965$], WST-IQ [$F(1, 79) = 0.20$, $p = .653$] and BDI-II [$F(1, 79) = 0.41$, $p = .523$]. Lastly, the assumption of homogeneity of regression slopes had been checked and revealed as given for all covariates in the sample groups: sex [$F(1) = 0.19$, $p = .662$], age [$F(1) = 0.46$, $p = .502$], education [$F(1) = 0.17$, $p = .679$], WST-IQ [$F(1) = 3.18$, $p = .079$] and BDI-II [$F(1) = 1.10$, $p = .299$] as well as in the SMC groups: sex [$F(1) = 0.01$, $p = .906$], age [$F(1) = 0.01$, $p = .921$], education [$F(1) = 0.39$, $p = .536$], WST-IQ [$F(1) = 0.05$, $p = .831$] and BDI-II [$F(1) = 0.15$, $p = .702$].

Correlation Analysis

As the first exploratory research question aims to find associations between SMC and other relevant variables, a correlation analysis was conducted for the whole sample ($N = 81$). The correlation coefficient was calculated for associations between FAI_raw and FAI_z respectively with sex, age, education, interval, WST-IQ, BDI-II and NTBV_z. All variables included into this analysis originate from the baseline examination, except for interval. According to Cohen (1988), a small effect is indicated by $r \geq .10$, a moderate effect is indicated by $r \geq .30$ and a strong effect is indicated by $r \geq .50$.

To test for normality of the distribution for the relevant variables within the whole sample, a Shapiro-Wilk-Test was conducted. Normality of distribution was almost given for the variables FAI_raw ($p = .358$), FAI_z ($p = .842$), NTBV_z ($p = .414$) and WST-IQ ($p = .077$). For the variables age, education, MMSE and BDI-II, normal distribution was not given (all $p < .001$). Histograms and P-P-Plots showed similar results and are in accordance with the Shapiro-Wilk-Test. Because of the lack of normal distribution in some variables, Spearman correlation coefficient (r_s) was calculated.

Receiver Operating Characteristic (ROC) Analysis

The next exploratory research question refers to the FAI being a valid tool for discriminating between the diagnostic groups. To answer this, ROC analysis was conducted with FAI_raw and FAI_z respectively as the testing variable and the diagnostic group as the state variable ($N = 36$). AMCI was set as the positive condition, resulting in the groups (0) non-converters to aMCI (comprising of the diagnostic groups SCD and naMCI; $n = 31$) and (1) converters to aMCI ($n = 5$). First, an ROC curve was obtained by plotting sensitivity vs. 1 - specificity of all individuals in the PG. The sensitivity refers to the probability that a test result will be positive, given the disease is in fact present (Wirtz, 2019c). The specificity of a test refers to the probability that a test result will be negative, given the diagnosis is in fact absent (Wirtz, 2019c). The ROC curve was evaluated and interpreted by calculating the *area under the curve* (AUC), which reveals how well the participants are classified into the diagnostic groups (Linden, 2006). The AUC value lies between 0 and 1. A test making only correct classifications is indicated by an AUC of 1 and a test making only false classifications is indicated by an AUC of 0. An AUC of .50 means that classifications are made randomly. The ROC analysis further provides calculated sensitivity and specificity of a test at different cut-off points. The optimal cut-off score was derived by determining the combination of sensitivity and specificity producing the greatest Youden Index (J) by using the formula (J =

sensitivity + specificity – 1; Youden, 1950). Applying the chosen cut-off score enables to produce classification tables illustrating the number of patients being correctly diagnosed as positive (true positive [TP]) or negative (true negative [TN]), as well as the number of patients being incorrectly diagnosed as positive (false positive [FP]) or negative (false negative [FN]). As a next step, positive predictive value (PPV = TP / [TP + FP]), negative predictive value (NPV = TN / [TN + FN]), positive likelihood ratio (LR+ = sensitivity / [1 – specificity]) and negative likelihood ratio (LR- = [1 – sensitivity] / specificity) were calculated. The PPV refers to the probability that the disease is present when the test is positive (Wirtz, 2019b), whereas the NPV refers to the probability that the disease is absent when the test is negative (Wirtz, 2019a). The LR+ represents the change in the odds of having a disease over not having a disease when the test is positive, whereas the LR- represents the change in odds of not having a disease over having a disease when the test is negative (Gessner & Arndt, 2019a/2019b). The likelihood ratios were interpreted as proposed by Jaeschke et al. (1994): convincing diagnostic evidence is indicated by LR+ > 10 and LR- < 0.1; high diagnostic evidence is indicated by LR+ > 5 - ≤ 10 and LR- ≥ 0.1 - < 0.2; weak diagnostic evidence is indicated by LR+ > 2 - ≤ 5 and LR- ≥ 0.2 - < 0.5; and scarce diagnostic evidence is indicated by LR+ > 1 - ≤ 2 and LR- ≥ 0.5 - < 1.

Reliable Change Analysis

To address the last exploratory research question, a RC analysis was conducted to compare the three different methods by Chelune et al. (1994), McSweeny et al. (1993) and Maassen et al. (2006). At first, mean, standard deviation and test-retest reliability of the HCG were calculated. Afterwards, the respective RC scores were assessed using the Reliable Change Calculator 1.0 provided by Dr. Hinton-Bayre at the University of Western Australia. This calculator assesses the respective RCIs based on the formulas provided within the theoretical background section. The RCI by McSweeny and colleagues was obtained using the formulas for the estimated values. The resulting RC scores have then to be compared with a critical *z*-score to detect significance. However, with a control group sample size smaller than 50, Hinton-Bayre (2010) suggested using a critical *t*-score instead of a *z*-score. As this is the case in the present study, an RC score ± 1.684 is considered statistically significant at the 90% confidence level. Based on the RC values, individuals in the PG were further classified into the following groups: (→) no change group, comprising all patients with non-significant RC scores; (↑) gain group, comprising all patients with a reliable increase as indicated by

significant positive RC scores; and (↓) loss group, comprising all patients with a reliable decrease as indicated by significant negative RC scores.

Results

Descriptive Statistics

Sample characteristics at baseline for the whole sample, as well as split into the sample groups (PG and HCG) are shown in table 1. When descriptively analyzing the sample characteristics, the ratio of males to females (m:f) was quite well-balanced in both the PG (58:42) and the HGC (50:50). The PG had a higher mean age and rated depressive symptoms on average more than twice as high as the HCG. Apart from that, both groups showed similar baseline characteristics.

Conversion rates from SCD to aMCI or naMCI for the PG after the follow-up examination were calculated. Out of the 36 individuals, at total of 14 patients (38.89%) converted to MCI, out of which 5 patients (13.89%) converted to aMCI and 9 patients (25%) converted to naMCI. Consequently, 22 patients (61.11%) were non-converters and stayed SCD.

Additionally, sample characteristics at baseline for the PG split into the diagnostic groups as classified after follow-up are reported in table 2. The descriptive statistics for FAI and

Table 1

Sample Characteristics at T1

Variable	Total (N = 81)	PG (n = 36)	HCG (n = 45)
Sex (m/f)	51/30	21/15	30/15
Age [a]	63.16 (7.74), 50-82	66.50 (8.98), 50-82	60.49 (5.32), 51-76
Education [a]	13.01 (4.38), 6-24	12.97 (3.57), 8-20	13.03 (4.97), 6-24
WST-IQ	114.65 (11.61), 88-139	116.50 (11.69), 88-133	113.18 (11.45), 90-139
BDI-II	6.52 (6.77), 0-31	9.36 (6.60), 0-31	4.24 (6.06), 0-29
MMSE	28.73 (1.14), 26-30	28.53 (1.34), 26-30	28.89 (0.94), 27-30
VVT	9.84 (0.37), 9-10	9.80 (0.41), 9-10	9.88 (0.34), 9-10
Interval [b]	29.70 (12.14), 12-48	29.81 (11.00), 13-48	29.62 (13.10), 12-42

Note. M (*SD*), Range. T1 = baseline; PG = patient group; HCG = healthy control group; m = male, f = female; WST = Wortschatztest; BDI = Beck Depression Inventory; MMSE = Mini Mental State Examination; VVT = Vienna Visuo-Constructional Test.

[a] in years. [b] interval between baseline and follow-up in months.

Table 2

Sample Characteristics for the Patient Group at T1 Split Into the Diagnostic Groups

Variable	SCD (*n* = 22)	naMCI (*n* = 9)	aMCI (*n* = 5)
Sex (m/f)	12/10	5/4	4/1
Age [a]	66.64 (8.53), 53-82	65.33 (9.85), 50-81	68.00 (11.14), 53-82
Education [a]	13.64 (3.61), 8-19	10.67 (2.18), 8-14	14.20 (4.15), 9-20
WST-IQ	117.14 (12.87), 88-133	112.78 (9.65), 99-129	120.40 (9.34), 107-133
BDI-II	7.77 (5.52), 0-20	12.11 (4.54), 6-21	11.40 (11.97), 1-31
MMSE	28.45 (1.30), 26-30	28.78 (1.39), 26-30	28.40 (1.67), 26-30
VVT	9.71 (0.49), 9-10	9.80 (0.45), 9-10	10.00 (0.00), 10-10
Interval [b]	27.91 (10.65), 13-47	36.33 (11.67), 13-48	26.40 (7.86), 19-39

Note. M (*SD*), Range. *N* = 36. T1 = baseline; SCD = subjective cognitive decline; naMCI = non-amnestic mild cognitive impairment; aMCI = amnestic mild cognitive impairment; m = male, f = female; WST = Wortschatztest; BDI = Beck Depression Inventory; MMSE = Mini Mental State Examination; VVT = Vienna Visuo-Constructional Test.

[a] in years, [b] interval between baseline and follow-up in months.

NTBV at baseline and follow-up for the whole sample and the sample group, as well for the PG split into the diagnostic groups are shown in table 3 and table 4 respectively.

Multinomial Logistic Regression: Predicting Conversion by SMC

Multinomial logistic regressions were conducted separately for FAI_raw and FAI_z respectively at T1 as independent variable predicting the diagnostic group, while controlling for sex, age, education, WST-IQ and BDI-II. All participants of the PG (*N* = 36) were included in this analysis. Regarding the model including FAI_raw, the decrease of the log-likelihood from the baseline model (66.36) to the final model (51.81) was non-significant with χ^2 (12) = 14.55, *p* = .267. Furthermore, looking at the goodness-of-fit statistics revealed a good model fit, as indicated by non-significant values of the Pearson (*p* = .467) and Deviance (*p* = .703) statistic. Nagelkerke´s R^2 was .40 and Cox and Snell´s R^2 was .33. The non-significant likelihood-ratio-tests showed that none of the variables in the model was able to predict the diagnostic group; sex: χ^2 (2) = 1.30, *p* = .522; age: χ^2 (2) = 3.56, *p* = .166; education: χ^2 (2) = 5.40, *p* = .067; BDI-II: χ^2 (2) = 2.15, *p* = .341; WST-IQ: χ^2 (2) = 0.44, *p* = .805; FAI_raw: χ^2 (2) = 1.82, *p* = .402. Additionally, the model including FAI_z as the predictor variable showed similar patterns. The decrease of the log-likelihood from the

Table 3

Descriptive Statistics of FAI and NTBV at T1 and T2

Group	T	FAI_raw	FAI_z [a]	NTBV_z [a]
Total	T1	2.50 (0.69), 1.00-4.50	-0.28 (1.04), -2.94-2.49	0.32 (0.51), -1.17-1.37
(*N* = 81)	T2	2.40 (0.72), 1.00-4.26	-0.05 (1.16), -3.29-2.81	0.35 (0.52), -1.07-1.38
PG	T1	2.78 (0.62), 1.50-4.50	-0.65 (.90), -2.53-1.52	0.36 (0.36), -0.21-1.12
(*n* = 36)	T2	2.71 (0.74), 1.25-4.26	-0.52 (1.18), -3.29-1.55	0.33 (0.45), -0.40-1.26
HCG	T1	2.27 (0.66), 1.00-4.5	0.02 (1.05), -2.94-2.49	0.28 (0.60), -1.17-1.37
(*n* = 45)	T2	2.15 (0.61), 1.00-3.56	0.32 (1.01), -1.71-2.81	0.36 (0.58), -1.07-1.38

Note. M (*SD*), Range. FAI = Forgetful Assessment Inventory; NTBV = Neuropsychological Test Battery Vienna; T = time; T1 = baseline; T2 = follow-up; PG = patient group; HCG = healthy control group.

[a] age-, sex- and education-adjusted standardized score, higher values indicate less subjective memory complaints (FAI_z) or better objective performance (NTBV_z).

Table 4

Descriptive statistics of FAI and NTBV at T1 and T2 for the Patient Group Split Into the Diagnostic Groups

Group	T	FAI_raw	FAI_z [a]	NTBV_z [a]
SCD	T1	2.72 (0.55), 1.50-3.69	-0.57 (0.89), -1.83-1.52	0.38 (0.40), -0.21-1.12
(*n* = 22)	T2	2.83 (0.77), 1.25-4.26	-0.69 (1.23), -3.29-1.55	0.39 (0.44), -0.25-1.27
naMCI	T1	3.04 (0.70), 2.31-4.50	-1.02 (0.87), -2.53-0.09	0.44 (0.29), 0.10-0.89
(*n* = 9)	T2	2.42 (0.64), 1.50-3.25	-0.10 (1.01), -1.27-1.47	0.40 (0.38), -0.07-1.16
aMCI	T1	2.60 (0.76), 1.5-3.31	-0.33 (0.97), -1.15-1.00	0.14 (0.24), -0.08-0.55
(*n* = 5)	T2	2.71 (0.79), 1.67-3.69	-0.48 (1.22), -1.72-1.46	-0.10 (0.45), -0.41-0.68

Note. M (*SD*), Range. *N* = 36. FAI = Forgetful Assessment Inventory; NTBV = Neuropsychological Test Battery Vienna; T = Time; T1 = baseline; T2 = follow-up; SCD = subjective cognitive decline; naMCI = nonamnestic mild cognitive impairment; aMCI = amnestic mild cognitive impairment.

[a] age-, sex- and education-adjusted standardized score, higher values indicate less subjective memory complaints (FAI_z) or better objective performance (NTBV_z).

baseline model (66.36) to the final model (51.64) was again non-significant with χ^2 (12) = 14.73, p = .257. The goodness-of-fit statistic revealed a good model fit, again indicated by non-significant values of the Pearson (p = .487) and Deviance (p = .709) statistics. Nagelkerke´s R^2 was .40 and Cox and Snell´s R^2 was .34. Again, the non-significant likelihood-ratio-tests showed that none of the variables in the model was able to predict the diagnostic group; sex: χ^2 (2) = 1.09, p = .258; age: χ^2 (2) = 2.71, p = .550; education: χ^2 (2) = 5.62, p = .060; BDI-II: χ^2 (2) = 2.12, p = .346; WST-IQ: χ^2 (2) = 0.46, p = .794; FAI_z: χ^2 (2) = 2.00, p = .368. The results of the parameter estimates for both the models with FAI_raw and FAI_z are shown simultaneously in tables 5-7.

Table 5

Multinomial Logistic Regression of FAI Comparing aMCI vs. SCD, Parameter Estimates

Variable		*B* (*SE*)	Wald	*p*	Exp(*B*)	95%-CI for Exp(*B*)
FAI_raw	Constant	-3.75 (7.88)	0.23	.634	-	-
	Sex [a]	0.86 (1.47)	0.34	.560	0.43	0.02 - 7.54
	Age	0.05 (0.09)	0.38	.536	1.06	0.89 - 1.25
	Education	0.16 (0.33)	0.23	.635	1.17	0.62 - 2.22
	WST-IQ	-0.02 (0.07)	0.05	.825	0.98	0.85 - 1.13
	BDI-II	1.15 (0.11)	1.86	.173	1.16	0.94 - 1.44
	FAI	-1.04 (1.15)	0.82	.367	0.35	0.04 - 3.38
FAI_z	Constant	-5.31 (8.12)	0.43	.513	-	-
	Sex [a]	-0.88 (1.46)	0.36	.546	0.42	0.02 – 7.20
	Age	0.04 (0.08)	0.28	.599	1.05	0.89 – 1.23
	Education	0.18 (0.33)	0.28	.597	1.19	0.62 – 2.28
	WST-IQ	-0.02 (0.07)	0.08	.780	0.98	0.85 – 1.13
	BDI-II	0.15 (0.11)	1.85	.174	1.16	0.94 – 1.44
	FAI	0.64 (0.67)	0.91	.341	1.89	0.51 – 7.05

Note. Effects hold for amnestic mild cognitive impairment (aMCI, n = 5), the reference group is subjective cognitive decline (SCD, n = 22). Degrees of freedom = 1. FAI = Forgetful Assessment Inventory; Exp(*B*) = the exponential of *B;* CI = confidence interval; WST = Wortschatztest; BDI = Beck Depression Inventory.

[a] effect for females compared to males.

Table 6

Multinomial Logistic Regression for FAI Comparing naMCI vs. SCD, Parameter Estimates

Variable		*B* (*SE*)	Wald	*p*	Exp(*B*)	95% - CI for Exp(*B*)
FAI_raw	Constant	6.49 (6.62)	0.96	.327	-	-
	Sex [a]	1.12 (1.09)	1.06	.303	0.33	0.04-2.76
	Age	-0.10 (007)	2.25	.134	0.91	0.80-1.03
	Education	-0.53(0.29)	3.35	.067	0.59	0.34-1.04
	WST-IQ	0.04 (0.06)	0.31	.580	1.04	0.92-1.17
	BDI-II	0.01 (0.09)	0.02	.897	1.01	0.84-1.22
	FAI	0.64 (0.82)	0.60	.439	1.89	0.38-9.42
FAI_z	Constant	7.21 (6.36)	1.28	.257	-	-
	Sex [a]	-1.01 (1.11)	0.85	.358	0.36	0.04 – 3.16
	Age	-0.09 (0.06)	1.81	.178	0.92	0.81 – 1.04
	Education	-0.53 (0.29)	3.40	.065	0.59	0.34 – 1.03
	WST-IQ	0.03 (0.06)	0.29	.590	1.03	0.92 – 1.17
	BDI-II	0.02 (0.09)	0.03	.872	1.02	0.85 – 1.22
	FAI	-0.50 (0.62)	0.65	.419	0.60	0.18 – 2.05

Note. Effects hold for nonamnestic mild cognitive impairment (naMCI, $n = 9$), the reference group is subjective cognitive decline (SCD, $n = 22$). Degrees of freedom = 1. FAI = Forgetful Assessment Inventory; Exp(*B*) = the exponential of *B;* CI = confidence interval; WST = Wortschatztest; BDI = Beck Depression Inventory.

[a] effect for females compared to males.

Mixed design ANCOVA: Trajectories of SMC

Two separate mixed design ANCOVAs were conducted for the PG ($N = 36$). The analysis included FAI_raw and FAI_z respectively at T1 and T2 as within-subject variables and the diagnostic group as between-subject factor. Sex, age, education, WST-IQ and BDI-II were included as covariates. The results of both models (for FAI_raw and FAI_z) are reported simultaneously. The label *FAI* refers to both FAI_raw and FAI_z at once.

The tests of between-subject effects were non-significant for all variables in both models. The results are displayed in table 8. Moreover, the tests of within-subjects-effects revealed a significant interaction effect between FAI and the diagnostic group, indicating that the profile of FAI ratings across the two measurement points differed within the diagnostic groups,

Table 7

Multinomial Logistic Regression for FAI Comparing naMCI vs. aMCI, Parameter Estimates

Variable		*B* (*SE*)	Wald	*p*	Exp(*B*)	95% - CI for Exp(B)
FAI_raw	Constant	10.23 (9,57)	1.14	.285	-	-
	Sex [a]	-0.27 (1.67)	0.03	.873	0.77	0.03 – 20.34
	Age	-0.15 (0.10)	2.25	.134	0.88	0.71 – 1.05
	Education	-0.68 (0.40)	2.83	.092	0.51	0.23 – 1.12
	WST-IQ	0.05 (0.09)	0.34	.559	1.05	0.89 – 1.25
	BDI-II	-0.14 (0.12)	1.41	.236	0.87	0.69 – 1.10
	FAI_raw	1.68 (1.32)	1.61	.205	5.35	0.40 – 71.49
FAI_z	Constant	12.52 (9.62)	1.69	.193	-	-
	Sex [a]	-0.14 (1.67)	0.01	.934	0.87	0.03 – 23.00
	Age	-0.13 (0.10)	1.74	.187	0.88	0.72 – 1.07
	Education	-0.70 (0.41)	2.99	.084	0.50	0.23 – 1.10
	WST-IQ	0.05 (0.09)	0.39	.535	1.06	0.89 – 1.25
	BDI-II	-0.13 (0.12)	1.35	.245	0.88	0.70 – 1.10
	FAI_z	-1.14 (0.85)	1.79	.181	0.32	0.06 – 1.70

Note. Effects hold for non-amnestic mild cognitive impairment (naMCI, $n = 9$), the reference group is amnestic mild cognitive impairment (aMCI, $n = 5$). Degrees of freedom = 1. FAI = Forgetful Assessment Inventory; Exp(*B*) = the exponential of *B;* CI = confidence interval; WST = Wortschatztest; BDI = Beck Depression Inventory.

[a] effect of females compared to males.

FAI_raw: $F(2) = 5.39$, $p = .010$, partial $\eta^2 = .278$; FAI_z: $F(2) = 5.45$, $p = .010$, partial $\eta^2 = .280$. The main effect of FAI, as well as interaction effects between FAI and all covariates included into the analysis were non-significant. The results are displayed in table 9. To further evaluate the interaction effect of FAI with the diagnostic group, marginal means of FAI at both testing points adjusted for the covariates based on the following values were estimated: sex = .42, age = 66.50, education = 12.97, WST-IQ = 116.50 and BDI-II = 9.36.

Next, pairwise comparisons were calculated, comparing FAI at T1 with FAI at T2 within the diagnostic groups (within-group comparisons). The estimated marginal means and the

Table 8

Mixed Design ANCOVA for FAI, Tests of Between-subject-effects

Variable	FAI_raw			FAI_z		
	F	*p*	η_p^2	*F*	*p*	η_p^2
Constant	2.73	.110	.089	0.42	.521	.015
Sex	1.38	.250	.047	1.95	.173	.065
Age	0.95	.338	.033	0.00	.968	.000
Education	0.23	.634	.008	0.09	.772	.003
WST-IQ	0.02	.904	.001	0.09	.767	.003
BDI-II	1.36	.254	.046	0.82	.374	.028
Diagnostic group	0.59	.562	.040	0.53	.597	.036

Notes. $N = 36$. All degrees of freedom (df) = 1, except for diagnostic group (df = 2); FAI = Forgetful Assessment Inventory; η_p^2 = partial eta squared; WST = Wortschatztest; BDI = Beck Depression Inventory. The diagnostic group comprises three categories: subjective cognitive decline (SCD) vs. nonamestic mild cognitive impairment (naMCI) vs. amnestic mild cognitive impairment (aMCI).

Table 9

Mixed Design ANCOVA for FAI, Tests of Within-subject-effects

Variable	FAI_raw			FAI_z		
	F	*p*	η_p^2	*F*	*p*	η_p^2
FAI	0.79	.383	.027	0.92	.346	.032
FAI * sex	3.90	.058	.122	4.07	.053	.127
FAI * age	0.50	.509	.016	0.40	.533	.014
FAI * education	2.12	.156	.070	2.30	.141	.076
FAI * WST-IQ	0.23	.637	.008	0.17	.683	.006
FAI * BDI-II	0.99	.328	.034	1.11	.302	.038
FAI * diagnostic group	**5.39**	**.010**	**.278**	**5.46**	**.010**	**.280**

Notes. $N = 36$. All degrees of freedom (df) = 1, except for FAI*diagnostic group (df = 2); FAI = Forgetful Assessment Inventory; η_p^2 = partial eta squared; WST = Wortschatztest; BDI = Beck Depression Inventory. The diagnostic group comprises three categories: subjective cognitive decline (SCD) vs. nonamestic mild cognitive impairment (naMCI) vs. amnestic mild cognitive impairment (aMCI).

mean differences with the respective standard errors, significance levels and confidence intervals are displayed in table 10. A significant mean difference between FAI at T1 and T2 could be detected for naMCI, indicating a significant strong decrease of FAI between the two testing points, FAI_raw: $F(1, 28) = 10.54$, $p = .003$, $f = .61$; FAI_z: $F(1, 28) = 11.35$, $p = .002$, $f = .64$.

Additionally, pairwise comparisons were calculated to assess if the diagnostic groups differ in FAI at T1 and T2 respectively (between-group comparisons). The results are displayed in table 11. All comparisons turned out to be non-significant, indicating that the diagnostic groups did not differ significantly in FAI at T1 and T2 respectively. Lastly, two separate line diagrams for the interaction effect were plotted to visually demonstrate the courses of FAI over the two measurement points within the different diagnostic groups. The graphs for FAI_raw and FAI_z are displayed in figure 1 simultaneously.

Table 10

Estimated Marginal Means and Within-subject Comparisons of FAI at T1 and T2 for the Patient Group Split Into the Diagnostic Groups

Variable	Group	T1	T2	T2 – T1		
		M (*SE*)	*M* (*SE*)	*M* (*SE*)	*p*	95%-CI
FAI_raw	SCD	2.76 (0.14)	2.92 (0.16)	0.16 (0.14)	.264	-0.12 - 0.43
	naMCI	**3.00 (0.23)**	**2.26 (0.27)**	**-0.74 (0.23)**	**.003**	**-1.21 - -0.27**
	aMCI	2.50 (0.28)	2.64 (0.33)	0.14 (0.28)	.629	-0.44 - 0.72
FAI_z [a]	SCD	-0.63 (0.20)	-0.81 (0.26)	-0.18 (0.20)	.355	-0.58 - 0.22
	naMCI	**-0.97 (0.34)**	**0.14 (0.44)**	**1.10 (0.33)**	**.002**	**0.43 - 1.77**
	aMCI	-0.18 (0.43)	-0.38 (0.55)	-0.19 (0.41)	.639	-1.03 - 0.64

Notes. $N = 36$. Reported means are adjusted for covariates: sex = .42, age = 66.50, education: 12.97, Wortschatztest = 116.50, Beck Depression Inventory = 9.36. Šidak correction for multiple comparisons. CI = confidence interval for the mean difference; FAI = Forgetful Assessment Inventory; T1 = baseline; T2 = follow-up; SCD = subjective cognitive decline ($n = 22$); naMCI = nonamnestic mild cognitive impairment ($n = 9$); aMCI = amnestic mild cognitive impairment ($n = 5$).

[a] age-, sex- and education-adjusted standardized score, lower values in FAI_z indicate higher rated subjective memory complaints.

Table 11

Pairwise Between-group Comparisons of *FAI at T1 and T2*

Variable	Time	Comparison	Mean Difference (*SE*)	*p*	95%-CI
FAI_raw	T1	SCD vs. aMCI	0.26 (0.31)	.791	-0.53 – 1-06
		SCD vs. naMCI	-0.23 (0.28)	.789	-0.94 – 0.47
		aMCI vs. naMCI	-0.50 (0.37)	.468	-1.44 – 0.44
	T2	SCD vs. aMCI	0.28 (0.37)	.839	-0.66 – 1.22
		SCD vs. naMCI	0.66 (0.33)	.150	-0.17 – 1.49
		aMCI vs. naMCI	0.38 (0.44)	.773	-0.73 – 1.49
FAI_z	T1	SCD vs. aMCI	-0.45 (0.47)	.731	-1.65 – 0.76
		SCD vs. naMCI	0.34 (0.42)	.814	-0.73 – 1.40
		aMCI vs. naMCI	0.78 (0.56)	.436	-0.64 – 2.20
	T2	SCD vs. aMCI	-0.44 (0.61)	.861	-1.99 – 1.12
		SCD vs. naMCI	-0.95 (0.54)	.246	-2.32 – 0.42
		aMCI vs. naMCI	-0.51 (0.72)	.863	-2.35 – 1.32

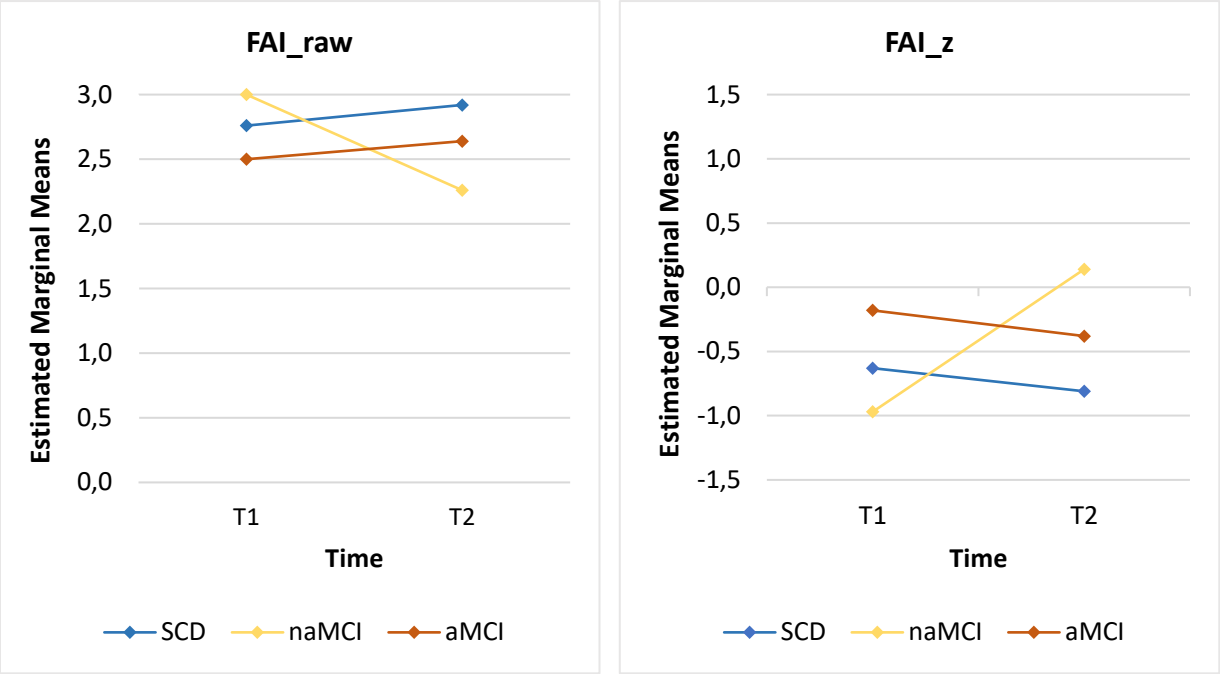
Notes. $N = 36$. Comparisons are based on the estimated marginal means (see table 10). Šidak correction for multiple comparisons. FAI = Forgetful Assessment Inventory; T1 = baseline; T2 = follow-up; CI = confidence interval for the mean difference; SCD = subjective cognitive decline ($n = 22$); naMCI = nonamnestic mild cognitive impairment ($n = 9$); aMCI = amnestic mild cognitive impairment ($n = 5$).

Mixed design ANCOVA: Trajectories of Objective Cognitive Performance

One more mixed design ANCOVA was conducted for the whole sample ($N = 81$) with NTBV_z at T1 and T2 as within-subject variables. The between-subject factors were the sample group and the SMC group. Again, sex, age, education, WST-IQ and BDI-II were added as covariates. The results of the tests of between-subject effects are displayed in table 12. The main effects of the SMC group and the sample group, as well as their interaction effect were non-significant. Similarly, the included covariates turned out to be non-significant, except for WST-IQ having a significant small effect on NTBV performance, $F(1) = 4.11$, $p = .046$, $\eta_p^2 = .054$. This effect was further evaluated by looking at the parameter estimates predicting NTBV_z separately at T1 and T2. WST-IQ showed a significant moderate positive effect on NTBV_z only at T2 ($b = 0.01$, $p = .029$, 95%-CI [.00 - .03],

Figure 1

Interaction Between FAI and the Diagnostic Group



Note. The course of FAI_raw and FAI_z from baseline (T1) to follow-up (T2) split for the diagnostic groups. The interaction was significant for the naMCI group. The values are based on the estimated marginal means adjusted for covariates (see table 10). FAI_z is an age-, sex- and education-adjusted standardized score, lower values in FAI_z indicate higher rated subjective memory complaints. FAI = Forgetful Assessment Inventory; SCD = subjective cognitive decline; naMCI = nonamnestic mild cognitive impairment; aMCI = amnestic mild cognitive impairment.

f = .26). The effect of WST-IQ on NTBV_z at T1 was non-significant (*b* = 0.01, p = .100, 95%-CI [-.00 - .02]).The tests of within-subject effects were non-significant for all variables and their interactions. The results are displayed in table 13. For the sake of completeness, estimated marginal means and pairwise comparisons are reported in tables 14 and 15. To illustrate the course of NTBV_z over time separately for the sample groups split into the SMC groups, a graph was plotted based on the estimated marginal means and is displayed in figure 2.

Correlation Analysis

To assess associations between FAI_raw and FAI_z at baseline with FAI_raw, FAI_z, NTBV_z (at T1 and T2), demographical (age, sex, education) and clinical (WST-IQ, BDI-II)

Table 12

Mixed Design ANCOVA for NTBV: Tests of Between-subject-effects

Variable	*F*	*p*	η_p^2
Constant	1.04	.312	.014
Sex	0.63	.431	.009
Age	0.08	.782	.001
Education	0.00	.978	.000
WST-IQ	**4.11**	**.046**	**.054**
BDI-II	2.86	.095	.038
SMC group	0.40	.532	.005
Sample group	0.28	.597	.004
SMC group * sample group	0.20	.660	.003

Note. N = 81. Degrees of freedom = 1. NTBV = Neuropsychological Test Battery Vienna; η_p^2 = partial eta squared; WST = Wortschatztest; BDI = Beck Depression Inventory; SMC = subjective memory complaints. The SMC group comprises high SMC vs. low SMC; the sample group comprises the patient group vs. healthy control group.

Table 13

Mixed Design ANCOVA for NTBV: Tests of Within-subject-effects

Variable	*F*	*p*	η_p^2
NTBV_z	0.06	.800	.001
NTBV_z * sex	1.90	.172	.026
NTBV_z * age	1.67	.200	.023
NTBV_z * education	0.63	.431	.009
NTBV_z * WST-IQ	1.10	.297	.015
NTBV_z * BDI-II	0.05	.821	.001
NTBV_z * SMC group	0.94	.337	.013
NTBV_z * sample group	1.46	.231	.020
NTBV_z * SMC group * sample group	0.15	.704	.002

Note. N = 81. Degrees of freedom = 1. NTBV = Neuropsychological Test Battery Vienna; η_p^2 = partial eta squared; WST = Wortschatztest; BDI = Beck Depression Inventory; SMC = subjective memory complaints. The SMC group comprises high SMC vs. low SMC; the sample group comprises the patient group vs. healthy control group.

Table 14

Estimated Marginal Means and Pairwise Within-group Comparisons of NTBV Between T1 and T2 for the Whole Sample Split Into the SMC and Sample Groups

			T1	T2	T2 – T1		
Group		*n*	*M* (*SE*)	*M* (*SE*)	*M* (*SE*)	*p*	95%-CI
PG	High SMC	7	0.53 (0.20)	0.56 (0.19)	0.03 (0.11)	.783	-0.18 – 0.24
	Low SMC	29	0.35 (0.10)	0.31 (0.10)	-0.04 (0.06)	.490	-0.15 – 0.07
HCG	High SMC	2	0.23 (0.36)	0.45 (0.37)	0.23 (0.20)	.266	-0.18 – 0.63
	Low SMC	43	0.27 (0.08)	0.33 (0.08)	0.07 (0.05)	.149	-0.03 – 0.16

Note. N = 81. Reported means are adjusted for covariates: sex = .37, age = 63.16, education = 13.01, Wortschatztest = 114.65, Beck Depression Inventory = 6.52. Šidak correction for multiple comparisons. NTBV (Neuropsychological Test Battery Vienna) is an age-, sex- and education-adjusted *z*-score, higher values indicate better NTBV performance. T1 = baseline; T2 = follow-up; SMC = Subjective Memory Complaints; PG = patient group; HCG = healthy control group; CI = confidence interval for the mean difference.

Table 15

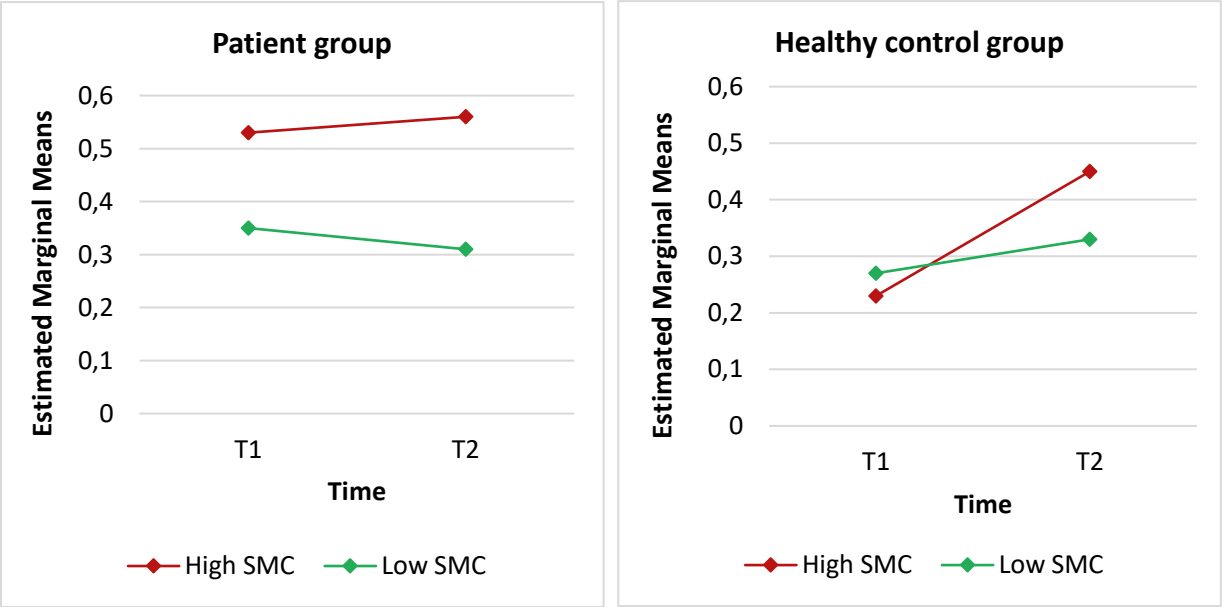
Pairwise Between-group Comparisons of NTBV at T1 and T2 for the Whole Sample Split Into the SMC and Sample Groups

Group		Comparison	Mean Difference (*SE*)	*p*	95%-CI
PG	T1	High SMC vs. Low SMC	-0.18 (0.21)	.383	-0.60 – 0.23
	T2	High SMC vs. Low SMC	-0.25 (0.21)	.237	-0.68 – 0.17
HCG	T1	High SMC vs. Low SMC	0.04 (0.37)	.908	-0.69 – 0.77
	T2	High SMC vs. Low SMC	-0.12 (0.37)	.753	-0.86 – 0.62
High SMC	T1	HCG vs. PG	0.30 (0.41)	.463	-0.52 – 1.13
	T2	HCG vs. PG	0.11 (0.42)	.799	-0.73 – 0.94
Low SMC	T1	HCG vs. PG	0.08 (0.14)	.581	-0.20 – 0.36
	T2	HCG vs. PG	-0.03 (0.14)	.840	-0.31 – 0.26

Note. N = 81. Comparisons are based on the Estimated Marginal Means (see Table 14). Šidak correction for multiple comparisons. NTBV = Neuropsychological Test Battery Vienna; T1 = baseline; T2 = follow-up; SMC = Subjective Memory Complaints; PG = patient group; HCG = healthy control group; CI = confidence interval for the mean difference.

Figure 2

Interaction Between NTBV, the SMC Group and the Sample Group



Note. The course of NTBV_z from baseline (T1) to follow-up (T2) separately for the SMC groups (high SMC vs. low SMC) split into the sample groups (patient group vs. healthy control group). This interaction effect is non-significant. The values are based on the estimated marginal means adjusted for covariates (see table 14). NTBV_z is an age-, sex- and education-adjusted standardized score, higher values in indicate better performance on NTBV_z. NTBV = Neuropsychological Test Battery Vienna; SMC = Subjective Memory Complaints.

variables at T1, as well as with interval, Spearman correlation coefficients were calculated for the whole sample ($N = 81$). Significant correlations could be detected for FAI_raw at T1 with FAI_raw at T2 ($r_s = -.60$, $p \leq .001$), FAI_z at T1 ($r_s = -.96$, $p \leq .001$) and T2 ($r_s = -.57$, $p \leq .001$), age ($r_s = .38$, $p \leq .001$), interval ($r_s = .29$, $p = .010$) and BDI-II ($r_s = .52$, $p \leq .001$). For FAI_z at T1, significant correlations with FAI_z at T2 ($r_s = -.56$, $p \leq .001$) FAI_raw at T1 ($r_s = -.96$, $p \leq .001$) and T2 ($r_s = -.55$, $p \leq .001$), interval ($r_s = -.22$, $p = .048$) and BDI-II ($r_s = -.44$, $p \leq .001$) could be found. The results are displayed in table 16.

Receiver Operating Characteristic Analysis

To assess if the FAI is a valid tool for discriminating converters to aMCI ($n = 5$) from the other diagnostic groups (naMCI and SCD, $n = 31$), ROC analyses were conducted for FAI_raw and FAI_z. The ROC curves are displayed in figure 3. The AUC for FAI_raw was .55 ($SE = 0.16$, 95%-CI [.23 - .84]). The chosen cut-off score was 2.21 with a sensitivity of

Table 16

Spearman Correlation Coefficients (r_s) for FAI at Baseline with Study Variables

Variables	FAI_raw		FAI_z	
	r_s	*p*	r_s	*p*
FAI_raw	1.00	-	**-.96**	**≤ .001**
FAI_z	**-.96**	**≤ .001**	1.00	-
FAI_raw T2	**.60**	**≤ .001**	**-.55**	**≤ .001**
FAI_z T2	**-.57**	**≤ .001**	**.56**	**≤ .001**
Sex	-.01	.954	.03	.779
Age	**.38**	**≤ .001**	-.17	.132
Education	-.20	.080	.08	.456
Interval [a]	**.29**	**.010**	**-.22**	**.048**
WST-IQ	-.11	.312	.11	.349
BDI-II	**.52**	**≤ .001**	**-.44**	**≤ .001**
NTBV_z	-.09	.422	.07	.522
NTBV_z T2	-.12	.334	.05	.634

Note. $N = 81$. Variables originate from the baseline examination if not otherwise stated. FAI = Forgetful Assessment Inventory; T2 = Follow-up; WST = Wortschatztest; BDI = Beck Depression Inventory; NTBV = Neuropsychological Test Battery Vienna.

[a] months between baseline and follow-up.

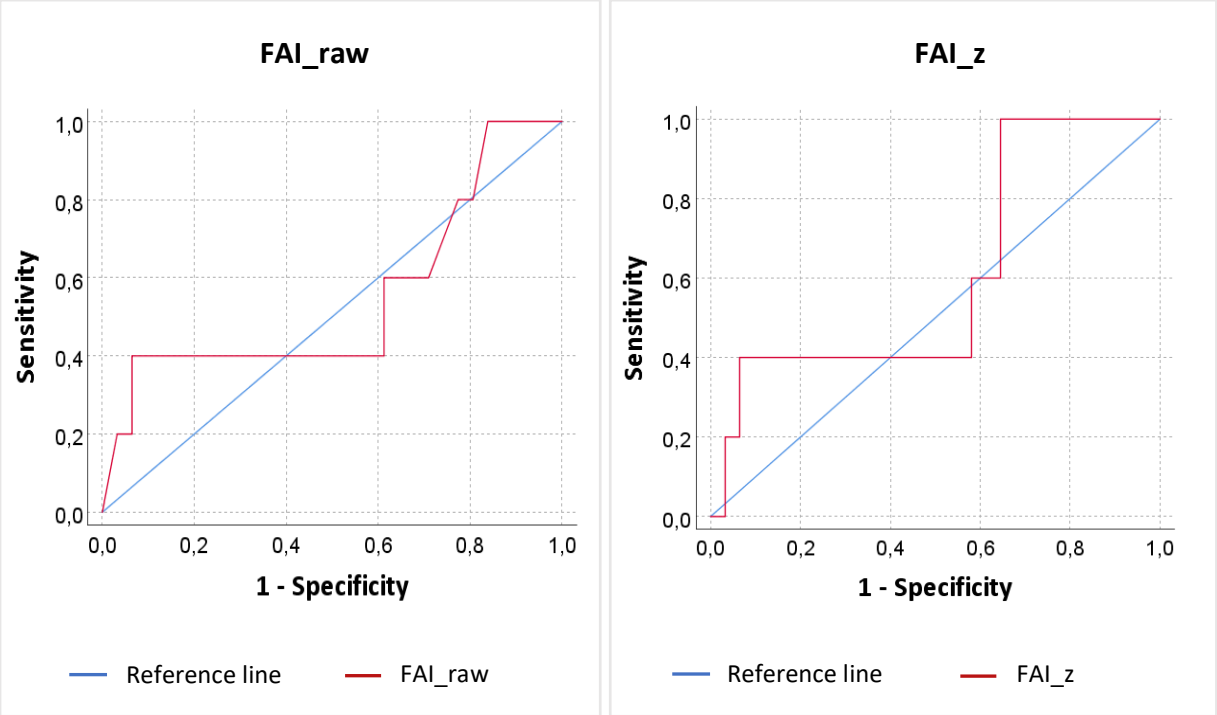
.40 and a specificity of .94. The PPV was .50 and the NPV was .91. The LR+ was 6.15 and LR- was 0.64. The ROC analysis for FAI_z revealed similar results. The AUC was .61 (*SE* = 0.14, 95%-CI [.33 - .84]). The chosen cut-off score was 0.37. Sensitivity, specificity, PPV, NPV, LR+ and LR- were the same as for FAI_raw.

Reliable Change Analysis

Following the aim to compare different methods for assessing if a change of ratings on FAI (FAI_raw and FAI_z) between the two testing points was reliable due to actual change in SMC, RC scores were calculated following the methods by Chelune et al. (1993), McSweeny et al. (1993) and Maassen et al. (2006). The results regarding FAI_raw are reported first. Higher FAI_raw scores indicate higher rated and therefore more severe SMC. The mean (*SD*) of the 45 healthy controls was 2.27 (0.66) at T1 and 2.15 (0.61) at T2, with a test-retest

Figure 3

Receiver Operating Characteristic Curves for FAI



Note. $N = 36$. Converters to aMCI ($n = 5$) was set as the positive condition as compared to non-converters to aMCI (including SCD and naMCI, $n = 31$).

reliability of .42. A reliable increase of FAI_raw scores indicating a significant deterioration could be detected for 0% - 27.3% of the non-converters/SCD, for 0% of the converters to naMCI and for 0% - 20% of the converters to aMCI. A reliable decrease of FAI_raw scores indicating a significant improvement could be detected for 0% of the non-converters/SCD, for 11.1% of converters to naMCI and for 0% of the converters to aMCI. Furthermore, 72.7% - 100% of the non-converters/SCD, 88.9% of the converters to naMCI, and 80% - 100% of the converters to aMCI did not show reliable change. The results illustrating the directions of reliable change of FAI_raw for the three aforesaid methods are displayed in table 17.

The results regarding FAI_z are reported next. Higher FAI_z scores indicate lower rated and therefore less severe SMC. The mean (*SD*) of the 45 healthy controls was 0.02 (1.05) at T1 and 0.32 (1.01) at T2, with a test-retest reliability of .45. A reliable increase of FAI_z scores indicating a significant improvement could be detected for 0% of the non-converters/SCD, for 11.1% of the converters to naMCI and for 0% for the converters to aMCI. A reliable decrease of FAI_z scores indicating a significant deterioration could be detected for 0% - 18.2% of the non-converters/SCD, for 0% of the converters to naMCI and

Table 17

Directions of Reliable Change of FAI_raw for the Patient Group Split Into the Diagnostic Groups

RCI method	SCD (n = 22)			aMCI (n = 5)			naMCI (n = 9)		
	→	↑	↓	→	↑	↓	→	↑	↓
Chelune et al.	22 (100)	0 (0)	0 (0)	5 (100)	0 (0)	0 (0)	8 (88.9)	0 (0)	1 (11.1)
McSweeny et al.	16 (72.7)	6 (27.3)	0 (0)	4 (80)	1 (20)	0 (0)	8 (88.9)	0 (0)	1 (11.1)
Maassen et al.	21 (95.5)	1 (4.5)	0 (0)	5 (100)	0 (0)	0 (0)	8 (88.9)	0 (0)	1 (11.1)

Note. n (percentage). „→“ = no change group, „↑“ = gain group (significant higher FAI_raw score after follow-up, indicating a deterioration), „↓“ = loss group (significant smaller FAI_raw score after follow-up, indicating an improvement). RCI = Reliable Change Index; SCD = subjective cognitive decline; aMCI = anmestic mild cognitive impairment; naMCI = nonamnsestic mild cognitive impairment. RCI methods by Chelune et al. (1993), McSweeny et al. (1993) and Maassen et al. (2006).

for 0% - 20% of the converters to aMCI. Additionally, 81.8% – 100% of the non-converters/SCD, 88.9% of the converters to naMCI and 80% - 100% of the converters to aMCI did not show reliable change. The results illustrating the directions of reliable change of FAI_z for the three aforesaid methods are displayed in table 18.

Regarding the responsiveness of the different methods to detect reliable change, the analysis for FAI_raw and FAI_z showed very similar results and are reported simultaneously. All methods responded equally to positive change (improvement by reporting less SMC). However, the three methods differed in responsiveness to negative change (deterioration by reporting more SMC). Referring to this, the method by McSweeny and colleagues was most responsive, followed by the method of Maassen and colleagues. In contrast, the method by Chelune and colleagues failed to detect negative change in any of the patients.

Discussion

In recent years, SMC gained attention as a very early predictor for future objective cognitive decline. However, there is rather mixed evidence regarding the prognostic utility of

Table 18

Directions of Reliable Change of FAI_z for the Patient Group Split Into the Diagnostic Groups

RCI method	SCD (n = 22)			aMCI (n = 5)			naMCI (n = 9)		
	→	↑	↓	→	↑	↓	→	↑	↓
Chelune et al.	22 (100)	0 (0)	0 (0)	5 (100)	0 (0)	0 (0)	8 (88.9)	1 (11.1)	0 (0)
McSweeny et al.	18 (81.8)	0 (0)	4 (18.2)	4 (80)	0 (0)	1 (20)	8 (88.9)	1 (11.1)	0 (0)
Maassen et al.	21 (95.5)	0 (0)	1 (4.5)	5 (100)	0 (0)	0 (0)	8 (88.9)	1 (11.1)	0 (0)

Note. n (percentage). „→“ = no change group, „↑“ = gain group (significant higher FAI_z score after follow-up, indicating an improvement), „↓“ = loss group (significant smaller FAI_raw score after follow-up, indicating a deterioration). RCI = Reliable Change Index; SCD = subjective cognitive decline; aMCI = anmestic mild cognitive impairment; naMCI = nonamnsestic mild cognitive impairment. RC methods by Chelune et al. (1993), McSweeny et al. (1993) and Maassen et al. (2006).

SMC for early diagnosis of AD dementia. Most previous studies have investigated SMC cross-sectionally by using a variety of differing assessment methods (Reid & MacLullich, 2006). This has resulted in mixed findings and impedes clear conclusions. Hence, the present study aimed to provide further findings about the predictive value of SMC by performing repeated assessments and using the Forgetful Assessment Inventory as a self-report questionnaire regarding memory complaints. In order to help determine if individuals with SCD are at the preclinical stage of the AD continuum and could therefore benefit from early intervention, SMC have been investigated in a clinical sample of elderly seeking help for subjective complaints about memory decline.

Summary and Interpretation of Findings

Statistical analysis revealed that the amount of SMC could not predict conversion to MCI in elderly with SCD. The regression model was non-significant for both the raw and the *z*-score of SMC predicting the diagnostic group. Therefore, hypotheses 1 and 2 have to be rejected. Furthermore, when looking at the trajectories of SMC across both measurement

points for the different diagnostic groups separately, they showed differing courses regarding both the raw score and the *z*-score of SMC. Therefore, hypotheses 3 and 4 can be accepted. Lastly, when dividing the sample into elderly reporting a significant amount of SMC (FAI_z values ≤ -1.5 *SD*) and elderly reporting medium or low levels of SMC (FAI_z values > -1.5 *SD*), these groups did not show differing courses of objective cognitive performance over time. Therefore, hypothesis 5 has to be rejected. In the following, the results are discussed in more detail.

Conversion From SCD to MCI

Conversion rates from SCD to MCI were calculated, revealing 39% converters to MCI and almost 61% non-converters who remained at the stage of SCD. This is partly in line with previous research. The meta-analysis by Mitchell et al. (2014) found a smaller conversion rate of almost 27% for elderly converting from SCD to MCI over a period of 4 years. Furthermore, the present study found a similar conversion rate for non-converters as the study conducted by Lehrner et al. (2016), which found about 57% non-converters who remained at the sage of SCD. When looking at conversion from SCD to naMCI and aMCI separately within the present study, more individuals converted to naMCI (25%) than to aMCI (nearly 14%). This contradicts the findings of Petersen et al. (2010), who found higher prevalence rates of aMCI than naMCI. However, Petersen and colleagues have assessed within a community sample. When examining a clinical sample of elderly seeking help for SMC (Lehrner et al., 2014), more elderly were classified as having naMCI than aMCI, therefore supporting the findings of the present study. It should be noted that the naMCI group showed a considerable higher retest interval in the present study, appearing for follow-up examination on average 10 months later than the aMCI group. It may be possible that more individuals would have further converted from SCD to aMCI after a longer retest interval.

Prognostic Utility of SMC for Future Objective Cognitive Impairment

When trying to predict whether patients will convert to aMCI or naMCI after follow-up based on the FAI scores of the initial examination, the amount of subjective memory complaints could not predict conversion. Albeit non-significantly, higher SMC predicted conversion to naMCI or SCD rather than conversion to aMCI. The diagnostic groups did not differ in baseline SMC, which is in line with previous research. For example, Lehrner et al. (2016) also did not find differences in baseline SMC between converters and non-converters within a clinical sample of 141 elderly showing SCD or MCI. Although the groups did not differ significantly in SMC at both testing points within the present study, the naMCI group

showed the highest amount of baseline SMC, followed by SCD and aMCI. In contrast, after the follow-up examination, the naMCI group showed the lowest amount of SMC, followed by aMCI and SCD. Contrarily, a cross-sectional study conducted by Lehrner et al. (2014) examined a clinical sample consisting of 581 elderly in the patient group having either SCD or MCI. Lehrner and colleagues found a statistically significant difference in SMC between all diagnostic groups (SCD group, naMCI group and aMCI group), except for the SCD group and the naMCI group which showed no significant difference in SMC. The aMCI group reported the highest amount of SMC, followed by SCD and naMCI (Lehrner et al., 2014). The differing results may be due to the small sample sizes in the present study.

When dividing the whole sample into groups with high and low SMC after baseline examination, nine individuals were classified as the high SMC group, out of which seven individuals originate from the PG. This is in line with previous research which found 7% of the healthy controls and 36% of the patient group having reported elevated SMC (Lehrner et al., 2014), as compared to 4% and 25% respectively in the present study. After controlling for the covariates, mean scores of objective cognitive performances over both testing points did not depend on expressing high vs. low SMC. Only verbal IQ turned out to have a significant moderate effect on objective performance, with a higher verbal IQ meaning better performance. This effect is present only at the follow-up examination. An explanation could be that individuals with a higher verbal IQ may take more benefit out of practice effects resulting from neuropsychological reassessments. When looking at the trajectories of objective cognitive performance across both testing points, none of the variables had a significant effect. This indicates that reporting high or low SMC at baseline had little prognostic utility for future objective cognitive decline.

SMC Trajectories

Looking at the SMC trajectories within the groups revealed a strong overall interaction effect between SMC and the diagnostic group ($p = .010$, $\eta^2 = .278$ and $p = .010$, $\eta^2 = .280$ for FAI_raw and FAI_z respectively), indicating that the diagnostic groups showed different SMC trajectories over time. When examining this interaction effect more closely, the naMCI group reported significantly less SMC at follow-up as compared to baseline with a strong effect size ($p = .003$, $f = .61$ and $p = .002$, $f = .64$ for FAI_raw and FAI_z respectively). The SCD group and aMCI group reported slightly and non-significantly more SMC after follow-up as compared to baseline. These two groups showed very similar SMC trajectories, with the

SCD group reporting slightly and non-significantly more SMC than the aMCI group at both testing points.

Within the present study, the reports of subjective complaints remained largely stable over time within the SCD and the aMCI group. Whereas cognitive performance objectively deteriorated within the aMCI group, cognitive performance remained stable within the SCD group. Following the suggestions by Jessen and colleagues (2020), the SCD group fulfilled criteria for stable/non-reversible SCD (non-remitting SCD but no objective decline to a level of impairment), therefore linking the subjective complaints to the normal ageing process. However, objective performance of the SCD group may still decline to a level of impairment in the future. This may be the case if the SCD group is actually on the AD continuum, but at a much earlier stage. Therefore, performance of the SCD group may have objectively declined after a higher retest interval or within additional follow-up measures. In contrast, the aMCI group showed stable SMC with a subsequent progressive cognitive decline to a level of impairment, linking the SMC in the aMCI group to neurodegenerative diseases like AD dementia (Jessen et al., 2020, Roehr et al., 2016). Additionally, previous longitudinal research investigating SCD trajectories in 5661 healthy elderly suggested that individuals reporting stable and persistent subjective complaints are at higher risk of MCI as well as dementia than individuals reporting intermittent or no SCD across time (Liew, 2020). Additionally, in the aMCI group within the present study, the subjective complaints increase slightly over time but much less in relation to the deteriorating cognitive abilities. This may be explained by the sinking awareness of cognitive deficits which accompanies actual objective deterioration (Lehrner et al., 2015).

The naMCI group showed unstable patterns of SMC over time (significantly less SMC after follow-up), with a concurrent objective cognitive decline in domains other than memory. This finding is hard to interpret. At baseline, the naMCI group may subjectively perceive actual (non-memory) cognitive deterioration too small to reach the threshold of impairment. As the memory domain may be the best-known cognitive domain affected by deficits within the general population, the non-memory cognitive deficits might be wrongly attributed to memory dysfunction by the patient. After elucidation by the clinician about unimpaired memory function at baseline, the cognitive deficits may be correctly attributed by the patient to dysfunction in the respective (non-memory) domain. Hence, this could explain the declined subjective complaints in the naMCI group within the present study, as the FAI only captures subjective complaints within the memory domain. However, although reporting less SMC after follow-up, the naMCI group still reported some SMC in absence of actual objective

memory impairment, which may be caused by the general tendency to overestimate memory dysfunction found in elderly with naMCI (Lehrner et al., 2015) or simply due to the normal ageing process.

Associations with SMC

The first exploratory aim of the present study was to find associations between SMC and other variables. The correlation analysis revealed an almost perfect correlation between the raw score and the age-, sex- and education-adjusted *z*-score of SMC (r = -.96, $p \leq .001$). This was an expected outcome, as the *z*-score was derived from the raw score. In addition, the raw score of SMC correlated moderately positive with age (r = .38, $p \leq .001$), which is in line with most previous research (Jonker et al., 2000). This association was expected because cognitive functions decline with age, even if simply due to the normal ageing process. Again as expected, this association disappeared in the present study after adjusting the SMC raw score (r = -.17, p = .132). Furthermore, higher raw SMC were found to moderately correlate with a higher retest interval (r = .29, p = .010). This association may be mediated by age, as a higher interval indicates a higher age at follow-up. However, the moderate association between SMC and interval remains stable after adjusting the SMC raw score (r = -.22, p = .048). Next, a strong association between raw SMC and depressive symptoms was found (r = .52, $p \leq .001$). This association was still moderate for the adjusted SMC score (r = -.44, $p \leq .001$). Most previous research could also find associations between SMC and depressive symptoms (Reid & MacLullich, 2006). Within the present study, the link between subjective and objective impairment turned out to be small and non-significant. This is again in line with previous research which found that associations of SMC with depressive symptoms were stronger than with actual objective memory impairment (Lehrner et al., 2014).

Validity of the FAI for Identifying Converters to aMCI

Another objective of the present study was to investigate if the FAI serves as a valid tool for discriminating between converters to aMCI and non-converters to aMCI, as the aMCI group is the one of most interest within AD dementia research (Peterson et al., 2004). The resulted AUC of .55 indicates that if the patients would have been classified as having aMCI or not after follow-up based on the scores of the FAI, the classifications would have been made randomly. The prognostic validity of the adjusted *z*-score of SMC was slightly better (AUC = .60), but still poor. The analysis further revealed a sensitivity of .40 and a specificity of .94 with a cut-off raw score of 2.21 and *z*-score of 0.37. This indicates that the FAI is a better tool for identifying elderly not converting to aMCI. This may be more useful for early

diagnosis of other neurodegenerative diseases than AD. However, for distinguishing between converters to aMCI and non-converters to aMCI within elderly with SCD, the FAI shows poor diagnostic utility, as it classifies only 40% of the converters correctly. In accordance to this, the analysis revealed a PPV of .50, NPV of .91, LH+ of 6.13 and LR- of 0.64, which indicates weak diagnostic evidence. The results of the ROC-analysis overall indicate that the FAI is not a valid diagnostic tool to discriminate between elderly which will convert to aMCI and elderly which will not. This is in line with previous research, as the study by Lehrner et al. (2016) also revealed weak diagnostic evidence of the FAI for predicting objective memory decline in a clinical sample of 141 patients expressing SMC.

Responsiveness of RC Methods

The last exploratory research question aimed to calculate reliable change scores and to compare their responsiveness following the three different methods by Chelune et al. (1993), McSweeny et al. (1993) and Maassen et al. (2006). The analysis of the raw score and the adjusted *z*-score of SMC showed similar results. All methods responded equally to positive change, as all methods classified only one patient of the naMCI group as reliably reporting less SMC and therefore having improved after follow-up. With regard to negative change, the McSweeny model classified six SCD patients and one aMCI patient as reliably reporting higher levels of raw SMC after follow-up and having deteriorated over time (regarding the adjusted *z*-score of SMC, this pattern appeared in four of the SCD and one of the aMCI patients). In contrast, the method by Maassen and colleagues detected reliable change in solely one of the SCD patients, whereas the method by Chelune and colleagues failed to detect negative change at all. Overall, the McSweeny model was the most responsive one, which is in line with previous research (Duff, 2014). Again in line with previous research, the McSweeny model responded more sensitively to negative change and less to positive change (Levine et al., 2007).

Present Limitations and Suggestions for Future Research

Several limitations ought to be considered when interpreting the results. First of all, the sample sizes of the patient group after being split into the diagnostic groups were rather small and unequal. Under these circumstances, the possibility to detect significance had been reduced while the likelihood of type-II errors increased. Future research should seek for larger and equal sample sizes.

Secondly, the overall generalizability of the present findings is limited as neither a probabilistic sampling procedure nor randomization took place. The patient group comprised

a clinical sample of elderly being either referred by a clinician or self-referred to a memory clinic. Additionally, the control group was recruited via advertisements. The samples had to be pre-selected in order to meet inclusion criteria, resulting in increased selection bias.

Furthermore, within the present study, solely one reassessment took place with intervals between 1 to 4 years. Therefore, it was not possible to determine if the non-converters were still going to convert in the future. As compared to the converters, they may have simply been at an even earlier stage of the AD continuum by then. However, the preclinical stage starts several years to decades before cognitive functions objectively decline to a level of impairment (Jack, 2018). Future research should consider applying multiple reassessments and following the patients over a longer overall time period as this may provide further knowledge of early diagnosis of AD dementia. In addition, more measurement points with shorter retest intervals may help finding short-term fluctuations in the course of SMC, which were not considered in the present study. This may reveal characteristic and differing SMC trajectories between SCD patients not converting and SCD patients converting to aMCI. In general, current mood or other intraindividual fluctuations were left out of consideration within the present study and should be controlled for in future research.

Lastly, some limitations are due to the testing procedure. After having completed the anamnesis and prescreening, neuropsychological assessment took approximately an additional hour and patients may have fatigued during this testing procedure. The self-report questionnaires were applied at the end. Self-ratings demand a certain amount of concentration and motivation which might have decreased by then. All these limitations might have affected measurement outcomes of the participants. Moreover, as the FAI was applied after the NTBV, perceived objective performance by the elderly could have influenced subjective ratings of memory complaints. Future research should consider evaluating the subjective ratings of cognitive decline prior to assessing the objective performance.

Conclusions and Prospects

In short, SMC had scarce prognostic validity for early diagnosis of AD dementia in the present study. The diagnostic groups did not differ in SMC at both testing points. Non-converters and converters to aMCI showed similar SMC trajectories with a stable course over time. Hence, the SMC trajectories did not provide added information to help to determine if elderly expressing SMC will proceed to aMCI and further to AD dementia. However, the naMCI group showed a different and unstable course, reporting significantly less SMC after follow-up. As the naMCI group will more likely precede other neurodegenerative diseases

apart from AD (Peterson et al., 2004), this characteristic course of SMC in elderly converting from SCD to naMCI may have more prognostic utility for early diagnosis of other forms of dementias not caused by AD.

For early diagnosis of AD dementia, an individually tailored diagnostic process should be considered. The subjective complaints should always be evaluated in addition to objective neuropsychological performance, as there seems to be no link between subjective and objective impairment in SCD patients. Possible underlying causes of SMC have to be excluded within anamnesis. The patient should be advised by the clinician to attend multiple retesting. Objective neuropsychological testing should be applied as early as possible to detect subliminal cognitive decline too small to reach the threshold of impairment within the individual patient. Thereby, small intraindividual differences in cognitive abilities can be detected to account for the subjective complaints.

The stable course of SMC in elderly converting from SCD to aMCI albeit deteriorating cognitive abilities may be due to anosognosia (Lehrner et al., 2015; Sánchez-Benavides et al., 2018). If objective neuropsychological assessment is not possible, caregiver-ratings should be considered to evaluate the amount of awareness of memory dysfunction. Hence, the sole reports of subjective memory complaints of the patients may have more prognostic validity for early diagnosis of AD dementia if accompanied by caregiver-ratings.

Although in the present study, SMC showed no predictive validity for future objective decline in a clinical sample of help-seeking elderly fulfilling criteria for SCD, previous studies have reported a clear and consistent increased risk for MCI and AD dementia in individuals with SMC as compared to individuals without SMC (Mitchell et al., 2014). Hence, SMC should not be left out of consideration during the diagnostic process. However, more research is needed in regard to clarifying the utility of SMC within the clinical context.

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Appendix

Abstract

Background: Subjective memory complaints (SMC) have gained attention as an early predictor for Alzheimer´s Disease (AD). However, the prognostic utility of SMC in the clinical context is still under question.

Objectives: To provide additional findings for facilitating early diagnosis of AD dementia by (1) investigating SMC as a valid predictor for conversion from subjective cognitive decline (SCD) to amnestic and nonamnestic mild cognitive impairment (aMCI, naMCI), and by (2) investigating trajectories of SMC longitudinally.

Method: A sample of 36 SCD patients and 45 healthy controls underwent comprehensive neuropsychological testing at baseline and follow-up (1 to 4 years later). The patients were classified into (0) non-converters and converters to (1) naMCI or (2) aMCI after follow-up. SMC were assessed via the 16-item Forgetful Assessment Inventory.

Results: Conversion rates were 14% for converters to aMCI and 25% for converters to naMCI, leaving 61% non-converters. Baseline SMC did not predict conversion to MCI. The non-converters and converters did not differ in SMC at any time. Non-converters and converters to aMCI showed similar SMC trajectories with stable SMC ratings. The converters to naMCI showed an unstable course with significant less reports of SMC at follow-up.

Conclusions: SMC had scarce predictive validity for conversion to MCI in elderly with SCD. The SMC trajectories did not provide added information to help to distinguish between non-converters and converters to aMCI. However, the SMC trajectories turned out to be more useful for differentiating non-converters from converters to naMCI. More research is needed.

Keywords: subjective memory complaints, subjective cognitive decline, mild cognitive impairment, longitudinal, Alzheimer´s Disease

Abstract in German / Abstract in Deutsch

Hintergrund: Subjektive Gedächtnisbeschwerden (SMC) haben als früher Prädiktor der Alzheimer Krankheit Beachtung gefunden. Der prognostische Nutzen von SMC im klinischen Kontext ist jedoch noch fraglich.
Ziele: Bereitstellung weiterer Erkenntnisse zur Unterstützung der Früherkennung der Alzheimer Krankheit durch (1) die Untersuchung von SMC als validen Prädiktor für die Konversion von *subjective cognitive decline* (SCD) zu amnestischer oder nicht-amnestischer leichter kognitiver Beeinträchtigung (aMCI, naMCI) und durch (2) die längsschnittliche Untersuchung der SMC Entwicklungsverläufe.
Methode: 36 SCD Patient:innen und 45 gesunde Kontrollen wurden zu zwei Testzeitpunkten (T1 und T2, Intervall von 1 bis 4 Jahren) einer umfassenden neuropsychologischen Testung unterzogen. Basierend auf den Ergebnissen zu T2 wurden die Patient:innen in die Gruppen (0) Nicht-Konvertierte und Konvertierte zu (1) naMCI oder (2) aMCI eingeteilt. SMC wurden mittels des *Forgetful Assessment Inventory* erhoben, bestehend aus 16 Items.
Ergebnisse: Die Konversionsraten betrugen 25% für naMCI und 14% für aMCI. 61% der Patient:innen konvertierten nicht. SMC zu T1 sagten die Konversion zu MCI nicht vorher. Die Nicht-Konvertierten und Konvertierten unterschieden sich zu keinem Zeitpunkt in SMC. Die Nicht-Konvertierten und Konvertierten zu aMCI zeigten ähnliche und stabile SMC Entwicklungsverläufe. Die Konvertierten zu naMCI zeigten einen instabilen Verlauf mit signifikant weniger SMC zu T2.
Konklusion: SMC zeigten kaum prognostische Nützlichkeit zur Vorhersage der Konversion zu MCI in älteren Personen mit SCD. Die SMC Entwicklungsverläufe konnten keine weiteren Erkenntnisse liefern, um zwischen Nicht-Konvertierten und Konvertierten zu aMCI zu unterscheiden. Jedoch zeigten sich die Entwicklungsverläufe nützlicher um zwischen Nicht-Konvertierten und Konvertierten zu naMCI zu unterscheiden. Weitere Forschung ist notwendig.

Schlüsselwörter: Subjektive Gedächtnisbeschwerden, subjective cognitive decline, mild cognitive impairment, längsschnittlich, Alzheimer Krankheit