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Subjective memory evaluated by the Forgetful Assessment Inventory in the early detection of Dementia in patients with Subjective cognitive decline, Mild cognitive impairment and Parkinson's disease.

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Diploma Thesis

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Abstract

Background: Subjective cognitive complaints (SCC) and their clinical significance were discussed controversial until now. In mild cognitive impairment (MCI) and subjective cognitive decline (SCD) the SCC are associated with progression to Alzheimer's disease (AD) or even Parkinson disease dementia (PDD). **Objectives**: To determine differences of SCC on the basis of patients' reports among subjects with SCD, MCI and Parkinson disease (PD). **Design**: Longitudinal study with one follow up examination. **Participants:** A clinical sample of dementia free subjects with SCC (n=168), aged 50 and older, who came to the memory outpatient clinic/ Department of Neurology. **Results:** MCI patients have a higher risk than the patients with SCD in developing AD (OR = 7.3 [CI 0.9 to 61.2]. The tested groups (SCD, MCI, PD) differed (p <. 001) significantly in their SCC. No significant differences between the AD patients, and the non-converted were discovered. The groups of subjects, which detoriated, remained stable and improved in their SCC differed also significantly (p <. 05). No time effect could be confirmed in all analyses. For conversion to AD we found an area under the curve (AUC) of .62 for the FAI. **Conclusion**: SCC allows no differentiation between AD and Non-AD patients based on the initial investigation.

Keywords: Subjective cognitive decline, Mild cognitive impairment, Subjective memory impairment, Subjective cognitive complaints.

Abstract (Deutsch)

Hintergrund: In der allgemeinen Bevölkerung sind subjektive kognitive Beschwerden (SCC) und deren klinische Bedeutung bis heute kontrovers diskutiert. Bei der leichten kognitiven Beeinträchtigung (MCI) und bei subjektiver Abnahme der Gedächtnisleistung (SCD) werden die subjektiven kognitiven Beschwerden (SCC) mit der Entwicklung der Diagnose Alzheimerdemenz (AD) oder der Parkinsondemenz (PDD) in Zusammenhang gebracht. **Ziele:** Ermittlung der Unterschiede von subjektiven kognitiven Beschwerden (SCC) auf der Grundlage von Patientenberichten bei Patienten mit SCD, MCI und Parkinsonerkrankung (PD). **Design:** Längsschnittuntersuchung mit einer Follow up Untersuchung. **Teilnehmer:** Eine klinische Stichprobe der Gedächtnisambulanz an der Neurologischen Universitätsklinik (n=168) von nichtdementen Patienten und Patientinnen mit SCC, im Alter von über 50 Jahren. **Ergebnisse:** Die Patienten mit MCI haben ein höheres Risiko an AD zu erkranken als die SCD (OR = 7.3 [CI 0.9 to 61.2]. Die untersuchten Diagnosegruppen (SCD, MCI, PD) unterscheiden sich hinsichtlich ihrer SCC ($p < .001$) signifikant. Keine signifikanten Unterschiede zwischen den an AD erkrankten und den Nicht-Konvertierten wurden entdeckt. Weiters unterscheiden sich die Gruppen der Verschlechterten, Gleichbleibenden und Verbesserten in ihren SCC signifikant ($p < .05$). In keiner Analyse konnte ein Zeiteffekt bestätigt werden. Die Fläche unter der Kurve (AUC) der FAI beträgt .62 für die Konversion zu AD. **Konklusion:** SCC erlauben keine Differenzierung zwischen AD und Nicht-Konvertierten basierend auf der Erstuntersuchung.

Schlüsselwörter: Subjektive kognitive Verschlechterung, Leichte kognitive Beeinträchtigung, Subjektive Gedächtnisbeeinträchtigung, Subjekitve kognitive Beschwerden.

1. Introduction

The dementia syndrome is a progressive, ordinarily chronic disease resulting in brain disorder of higher cortical functions. Clinically noticeable are in particular cognitive symptoms as well as behavioral, somatic and mental disorders (Dilling, Mombour & Schmidt, 2008). While the etiology is still unknown it has been determined that dementia is characterised with neuropathological and neurochemical alterations. The higher cortical functions impaired by the disease include memory, reasoning, orientation, comprehension, computational ability, learning capacity, language and judgment. According to Schaub and Freyberger (2005) the development of multiple cognitive deficits, particularly memory impairment, is one of the core symptoms according to the Diagnostic and Statistical Manual of Mental Disorders, Version IV (DSM-IV) (Saß, Wittchen, Zaudig & Houben, 2003). Other cognitive disorders that may occur include aphasia, apraxia, agnosia and interference of executive functions (Schaub & Freyberger, 2005; Lehrner, Bodner, Dal-Bianco & Schmidt, 2006). A detailed description of the classifications of all dementia types can be found in the International Classification of Diseases (ICD-10) (Dilling et al., 2008). Identifying individuals with increased dementia risk at the earliest opportunity represents an important aspect in the treatment of dementia. Risk factors such as increased age or genetic dispositions are discussed as causes for the development of different forms of dementia. Other risk factors are the subjective complaints about cognitive abilities. Elderly people often complain (25-50%) about subjective forgetfulness (Jonker, Geerlings & Schmand, 2000), but not all objectively cognitive impaired complain about subjective memory deficits (Lenehan, Klekociuk & Summers, 2012). Generally, the previous research results indicate a 3 stage model of the development of dementia, which begins with subjective cognitive decline (SCD) and via mild cognitive impairment (MCI) results in dementia (Jessen et al., 2010, 2014). This paper examines the differences in the subjective judgements of cognitive decline over the course of at least 12 months between the groups SCD, MCI and even Parkinson's diseases (PD) patients. Studies conducted on the topic of dementia or MCI have to be interpreted and compared with caution, taking into account different types of population, collection methods, measurements, classifications and diagnostic criteria used (Lehrner et al., 2014). A multitude of subjective cognitive complaints (SCC) screening tools exists and thereby the comparability and interpretation of the various studies is difficult and distorts conclusions.

1.1 Epidemiological development of dementing diseases

Early diagnosis of dementia is particularly important in regards to the development of the population pyramid in an aging society. Overall, a steady increase can be observed over the years. In 2010 approximately 35.6 million people worldwide suffered from dementia. This number is expected to reach up to 65.7 million in 2030 and 115.4 million in 2050 (World Alzheimer Report, 2009). One of the most significant risk factors in relation to dementia diseases is age, as older people are more prone to fall ill. Thus, the problem of an aging society is directly correlated with an increasing number of dementia patients. According to Wancata, Musalek, Alexndrowicz & Krautgartner (2003) 90.500 patients in Austria were affected by dementia in the year 2000 which is expected to reach 250.000 in 2050. In Europe, the age-specific (>65 of age) prevalence rates of dementia vary between 5.9% and 9.4% depending on country and study (Berr, Wancata & Ritchie, 2005). In Austria the incidence rates in the year 2000 were at 23.600 and they are expected to rise up to 65.500 in the midcentury, which represents a 2.8-fold increase (Wancata, Takacs, Fellinger, 2011, cited in Österreichischer Demenzbericht, 2014). This supports the significance of diagnosing and dealing with dementia symptoms as early and effectively as possible. Early recognition of the disease would make it possible for patients to take precautions and prepare for potential future consequences. And most importantly it is important to begin medical treatment as early as possible. The two types of dementia used as a proxy for the issues of the disease in this study were Alzheimer dementia (AD) and Parkinson disease dementia (PDD). AD is a steadly progressive neurodegenerative disease with unknown etiology. It is characterized through an increasing decline of neurons particularly in the hippocampus, substantia innominata, the locus coeruleus in the medial temporal lobe and the frontal cortex with accompanying neurochemical changes specifically a reduction of the enzyme choline acetyltransferase and other neurotransmitters such as acetylcholine itself (Dilling et al., 2008; Lehrner et al., 2006). Neuropathic changes caused by the disease AD include the extracellular amyloidplaques of abnormal modified Aß42-protein and the formation of abnormal Tau-protein, which is followed by the degeneration of neurofibrillary tangles (Thal & Braak, 2004, cited by Lehrner et al., 2006). PD is one of the most progressive neurodegenerative disorders in middle and older age groups, typically characterised by a core motoric symptoms tremor, bradykinesia, rigor and as a cardinal symptom the postural instability. The causes of PD are largely unknown. The neurodegenerative process is described as particularly nigrostriatal

pathway of the leading substantial degeneration of dopaminergic neurons to the deeper basal ganglia, leading to the well-known motoric symptoms (Auff & Kalteis, 2011). Frequently occurring non-motor symptoms of PD include sleeping disorders, autonomic, sensory and gastrointestinal among others. Numerous neuropsychiatric symptoms are also mentioned (Muzerengi, Contrafatto, & Chaudhuri, 2007). The risk of dementia is sixfold increased in PD compared to healthy controls (Aarsland et al. 2001). When comparing MRT scans of PDD and PD patients, Burton, McKeith, Burn, Williams, & O'Brien (2004) found that PDD patients had significantly more bilateral grey matter atrophy in the occipital lobe than patients only suffering from PD. In addition it was detected that AD patients showed more atrophy of the Gyrus temporalis inferior, including the hippocampus and parahippocampal gyrus, than PDD patients. Wancata et al. (2011, cited in Österreichischer Demenzbericht, 2014) predict 182.600 AD patients in 2050. The corresponding prevalence of PD rates is 1 - 2 percent among those over 60 years of age (Auff & Kalteis, 2011). Janvin, Larsen, Aarsland & Hugdahl, (2006) came to similar conclusions in a long - term study where 43.3% of PD patients had been diagnosed with baseline survey cognitive decline within the meaning of dementia. Janvin, Aarsland, & Larsen (2005) examined not demented PD patients within 4 years and demonstrated that 42% of them developed dementia. In the course of 10 years, 75% of surviving patients with PD developed PDD (Aarsland & Kurz, 2010). After 20 years, 83% of PD survivors suffer from dementia in addition to their motor and non-motoric symptoms (Hely, Reid, Adena, Halliday & Morris, 2008). Almost all of them no longer lived independently, half of them in nursing homes. Early diagnosis with regard to the premature onset of medical treatment with anti-dementia drugs is particularly important for maintaining of cognitive statuses.

Abnormalities before dementia diagnosis. Neuropsychological deficits can exist long before a final AD or PDD diagnosis and also behavioral changes or the loss of everyday life skills are noticeable. MCI, as predictor for subsequent dementia is well understood due to the extensive research by Ronald C. Petersen (Petersen et al., 1999; Petersen, 2004, 2011). Comprehensive reviews of literature on MCI already exist (Portet et al., 2006). Also the relation between MCI and PD, which allows a better understanding of MCI and its subtypes in PD, has been discussed in several reviews (Litvan et al., 2011; Palavra, Naismith & Lewis, 2013; Yarnall, Rochester & Burn, 2013). SCC represented one criterion of MCI. Considering the group of MCI, this group

showed already objectified memory deficits.

1.2 Mild cognitive Impairment and its subtypes

Petersen (2004, 2011) classified MCI into two subtypes, namely amnestic MCI (aMCI) and nonamnestic MCI (naMCI). The diagnostic criteria of MCI by Petersen were considered for the present study. aMCI is characterised by significant memory impairment, whereas naMCI patients showed no memory impairment. naMCI means a decline in subtle functions such as attention, use of language, executive functions or visuospatial skills. It should be mentioned that Petersen (2011) further divided these two subtypes into a "single domain" (only one cognitive function is impaired) and a "multiple domain" (deficits in several cognitive domains). However, this was not relevant to this paper and will therefore not be explained in more detail. Approximately two thirds of patients reporting cognitive problems and seeking help in a memory outpatient clinic are diagnosed as MCI on the basis of formal neuropsychological testing with varying frequencies of MCI subtypes (Lehrner, Maly, Gleiss, Auff & Dal-Bianco, 2008). The conversion rate of persons with MCI at baseline and progression to dementia at follow up was specified with an annual rate of 10-20% in persons older than 65 years of age of those in specialty clinics (Farias, Mungas, Reed, Harvey & DeCarli, 2009; Ganguli, Chang, Snitz, Saxton, Vanderbilt & Lee, 2010; Lehrner et al., 2005). Within PD, MCI is also recognised to be common and it is the focus of research predicting progression to PDD (Aarsland and Kurz, 2010). Considering published research the conversion rate from MCI to dementia in PD is at least as high as those not suffering from PD (Janvin et al., 2006). Until now there exists a lack of consensus criteria for PD and MCI. Previous research of Movement Disorders Society (MDS) Task Force reported a wide range of prevalence rates (18.9 - 38.2%) of nondemented patients with PD having MCI (Litvan et al., 2011, Foltynie, Brayne, Robbins & Barker, 2004; Aarsland, Brønnick, Larsen, Tysnes & Alves, 2009; Aarsland et al., 2010). The study designs differed considerably and therefore the comparability of long term studies was limited. The probability of progressing to AD increases significantly, if patients show MCI during the investigation period. Increased progression to AD was common (25% - 30%) if MCI existed already at the beginning of the investigation (Tabert et al, 2006; Nordlund et al., 2010). However, even in a shorter study interval (at least 18 months), already over 21% of MCI patients converted to AD. Compared to normal elderly subjects those with MCI were 2.8 times more likely to experience development of AD (Manly at al., 2008). Also interesting are the different

progressions to AD, depending on whether only the patients' memory, or multiple domains were already affected. Thus, amnestic MCI patients, who also showed other cognitive deficits are generally more likely (50%) to convert to AD within 3 years compared to 10% of pure aMCI (Tabert et al., 2006). Monastero et al. (2011) found in comparative studies more naMCI are reported in PD patients than in neurologically healthy people (23.8 vs. 14.4%). The risk of naMCI was higher in PD patients showing MCI than for neurologically healthy controls. This is probably due to frontal-subcortical involvement, which characterises the disease. Different prevalence rates of MCI in PD are also reported in numerous studies. 25.8% of Parkinson's sufferers had MCI of which 13% showed memory impairment as defined by aMCI (Aarsland et al., 2010). The same study found that for the incident, not yet medicated community-based cohort, the proportion of MCI was lower (18.9 %). The reason for this low number is probably that it relates to patients in the earliest stage of PD. This argument is supported by the fact that already 39.4% of advanced PD patients showed MCI. A few studies compared neurologically healthy and PD patients. About 53% of PD patients showed cognitive impairment according to the diagnostic criteria in the sense of MCI (Janvin et al., 2006; Monastero et al., 2011) compared to 45% of neurologically healthy controls who showed MCI. The main result of the study from Janvin et al. (2006) is that PD-MCI patients are three times more likely (62 %) to develop dementia during the 4-year period between baseline and follow-up assessments compared to 20% of those who were cognitively intact. Pedersen, Larsen, Tysnes & Alves (2013) substantiate the different conversion rates with lower results. In longitudinal studies which demonstrated 27% of patients with MCI at diagnosis of PD developed dementia within 3 years compared with less than 1% of patients without MCI at PD diagnosis (Pedersen et al., 2013). But the patients showed during the course not only poorer cognitive performance, but also improved their cognitive performance. The reversion rates of MCI to normal or near normal cognitive function range from 4.5% to 31% according to several studies; 20% of people who converted to dementia from MCI did not show memory impairment at baseline (Nordlund et al., 2010; Koepsell & Monsell, 2012; Manly et al., 2008). Methodological differences between the studies yield different prevalence rates depending on the classification method. Prevalence rates for example show considerable differences, with a range from 58.3% to 97.5% for MCI in PD patients, and a range of 20% to just over 50% for amnestic MCI in PD patients (Lehrner et al., 2014). MCI patients have one thing in common: they have subjective cognitive

complaints in addition to other criteria (cf. 2.4 Classification procedure). Is it now possible to identify these high-risk patients for progressing dementia already to an earlier stage using their subjective ratings? If dementia was to be diagnosed at an early stage, people affected are still able to consciously take precautions. Therefore, the predictive validity of SCD for dementia is an important issue. The present work is based on the current Framework of Jessen et al. (2014). This current model proposes that subjective cognitive decline is a predictor for later cognitive decline for the course of SCD, MCI and later life dementia. Due to the fact that the term Subjective Impairment does not immediately reflect the temporal course of subjective cognitive change, a new concept of this course also taken into account was established - Subjective Cognitive Decline (Jessen et al., 2014).

1.3 Subjective cognitive decline - How informative are the estimates of subjective cognitive complaints?

Until now, studies were only partially comparable due to the lack of consistent definition and also due to methodological differences between studies. The recently published work of the Subjective Cognitive Decline Initiative (SCD-I) Working Group now offers a conceptual Framework of Common Standards referring to a common terminology (Jessen et al., 2014). Previous concepts include the subjective memory impairment (SMI), subjective memory complaints (SMC), subjective cognitive impairment (SCI) and subjective cognitive complaints (SCC). This paper however uses the concept introduced above, namely the subjective cognitive decline (SCD). Several studies were able to identify SMC as a predictor for a lower memory performance (Schmand, Jonker, Geerlings & Lindeboom, 1997, Reid & MacLullich, 2006) and therefore it should be taken seriously as a possible early sign of dementia (Jonker et al., 2000). But Reid & MacLullich (2006) detected no consistent association between subjective memory problems and current objective memory impairment. SCC sometimes had a stronger association with depressive symptoms than they do with objective cognitive performance (Reid & MacLullich, 2006; Jorm, Christensen, Korten, Jacomb & Henderson, 2001, Lehrner et al., 2014). Jonker et al. (2000) identified a negative association among SMC and cognitive performance. Considering the current state of research regarding the prognostic value of SCD in long term studies, previous research reported different results based on the prognostic value of SCC, which may be attributed to definition differences. However, subjective cognitive complaints in long-term studies seem to result in an increased conversion to independent deterioration of memory in objective test

batteries. Lenehan, Klekociuk & Summers (2012) could not find a correlation of subjective assessment of memory and objective performance and so they denied the diagnostic usefulness from the subjective assessments. In a recent study Lehrner et al. (2014) investigated the relationship between the assessment of subjective memory and the results in objective tests performance on Neuropsychological Test Battery Vienna (NTBV) (Lehrner, Maly, Gleiß, Auff & Dal-Bianco, 2007) and also Mini Mental State Examination (MMSE) (Folstein, Folstein & McHugh, 1975). Higher correlations were especially found for the subtests of the Verbal Selective Reminding Test (VSRT) delayed recall and VSRT learning performance and particulary for the PD group. Lehrner et al. (2014) discovered barely significant correlations between SCC and age or education, however, higher SCC tends to affect people of older age and lower education. Depression as measured by Beck Depression Inventory - II (BDI - II) (Hautzinger, Keller & Kühner, 2009) showed consistently significant relationships with SCC, even stronger relationships than with memory.

However, the subjective declines of cognitive abilities were also illustrated in neuroimaging techniques and biomarker abnormalities consistent with AD changes in the brain detected during SCC, which devolved several years before the onset of MCI. The presence of subjective memory impairment (SMI) was associated with decrease in hippocampal and grey matter volume and changes in the CSF were found (Stewart et al., 2011; Hafkemeijer et al., 2013). The findings suggest that SMI is a reflection of objective alterations in brain functions, which should identify the vulnerability for dementia in the best case. But no consistent findings exist on the presence of biomarkers and performance in objective neuropsychological tests (Amariglio et al., 2012; Perrotin, Mormino, Madison, Hayenga & Jagust, 2012). Those PD patients with SCD showed significant less density in the anterior cingulate gyrus grey matter in the right lower parietal lobe and also several areas with significant focal cortical thinning compared PD patients without SCD (Hong, Lee, Son & Lee, 2012). Compared with cognitively healthy (31%) CSF markers were common in subjects with SCI (52%), naMCI (68%), and aMCI (79%) and are associated with cognitive decline in patients with naMCI and aMCI (Visser et al., 2009).

Only few long-term-studies examined the diagnostic value of SCD in PD and whether their prediction for a later MCI or even dementia in patients with PD was useful. There is only a small amount of follow-up studies about the subtypes of MCI, naMCI and aMCI and even less about SCD patients. SCI in patients with PD may reflect an early manifestation of

underlying PD-related pathological changes. Compared to the previous cognitive performance, 68% of the cognitively impaired PD patients reported subjective decline in cognitive performance (Janvin et al., 2006) and approximately 25 % of de novo patients with PD complained about SMI (Erro et al., 2014). Those with subjective complaints were more likely to develop MCI at follow-up and may represent an early sign of a neurodegenerative disease, subsequently PDD. Therefore, SCC should be taken seriously as possible early signs of incident dementia. Hong et al. (2014) investigated, whether in patients with PD, SCD was predictive for future cognitive decline. They demonstrated that SCD is an independent risk factor for future cognitive decline in cognitively healthy patients with PD. Those, who converted to MCI status outnumbered those without SCD (44% vs. 9.5 %). The newly published findings of Luck et al. (2015) indicated that incident SMC in individuals aged > 75 years were associated with a significantly increased risk of progression to dementia and a significantly shorter dementia- free survival. Reisberg, Shulman, Torossian, Leng & Zhu (2010) indicated that people showing SCI across 7 years had 4.5 times higher risk (even with a high Mini Mental Status Examination (MMSE) score >29) to progress to MCI or dementia (54%) than people free of these symptoms (15%). Silva et al. (2014) determined that within two years 36.6% of non-demented patients with SMC converted to dementia of which 80% have been diagnosed as AD. But these numbers were not uniformly found in literature. Wang et al., (2004) showed in a long term study over 5 years, that 15% of persons with baseline subjective memory deterioration developed dementia. However, there were no significant differences at the baseline assessment in the total SMC score between Non-Converters and Converters and it was also found that self-reported memory deficits are not useful. Lehrner et al., (2005) found an annual conversion rate of 6.5% for clinical sample reporting memory decline.

The results of the German Study on Ageing, Cognition and Dementia in primary care patients (AgeCoDe), a longitudinal cohort study with two follow-up examinations after baseline, showed that cognitively healthy subjects older than 80 years have a threefold increased risk of developing AD within 3 years (Jessen, et al., 2010). Additional findings of AgeCoDe (Jessen, et al., 2010) showed greater risk for conversion to any dementia for subjects which showed SMI at baseline and MCI at follow up. Furthermore the number of subjects developing AD was much higher among subjects with SMI at baseline and with amnestic MCI at follow-up than among those without SMI at baseline investigation. One reason for the numerous different results for the prognostic value of SCD may be the form

of data collection of SCC. Regarding the extraction of subjective memory, there are different methods. One common method used a single question (Jessen et al., 2010; Mol, Boxtel, Willems & Jolles, 2006), a detailed assessment of memory with several questions (Silva et al., 2014) or even with multilevel response format in form of a likert scale (Reisberg et al., 2010, Lehrner et al., 2014).

Zlatar, Moore, Palmer, Thompson & Jeste, (2014) indicated that modifiable risk factors such as depression or less education for AD are also associated with SMI. Relationships between age and SCC were also well studied and do not lead to uniform results (Jorm et al. 2001). The association between the level of education and the SMC seemed inverse; high level of education implied less SMC´s (Jonker et al., 2000). And even SCC´s are more likely linked to symptoms of depression rather than existing objective cognitive impairment.

1.4 Aim of the study

The importance of SCD and its potential role as prodromal stage of MCI and dementia in neurologically healthy people as well as in people with PD was object of this longitudinal study with a baseline and one follow up examination. The purpose of this study was to identify the differences in SCC using structured questionnaires (Forgetful Assessment Inventory, see 2.3) in terms of early detection of AD or even PDD. No investigation is known to us where the groups SCD, MCI and PD patients' differences of FAI scores have been tested. The focus of all steps was to detect the diagnostic and clinical value of SCC. Investigation was carried out in 4 steps. In step 1, the diagnostic groups SCD, MCI and PD were tested for differences in FAI-scores. Step 2 included the split diagnostic subgroups SCD, naMCI and aMCI and in addition the same groups in PD patients. Again differences in the FAI-score in the examined course were tested in both steps. In both steps different SCC ratings and also time effects were expected to be statistically significant in the groups. Furthermore, differences of converted patients to extent AD according ICD-10 (Dilling et al., 2008) with the Non-Converters were assessed in Step 3. Anticipating statistically significant group differences, time effect was not expected to be different assuming only the converters show significant time differences. A detailed analysis of the predictive value of the FAI for conversion to AD and VSRT - subtests were analyzed by applying Receiver Operator Characteristics (ROC) was carried out. Since not all participants deteriorated over time in their cognitive performance, a fourth step was essential to perform. In step 4 subjects were divided into 3 groups: those who improved, those who deteriorated and those who remained stable

in their objective cognitive performance. Again, statistically significant group and time differences in FAI ratings were expected. The conversion rates of SCD and also MCI within subtypes equally in PD patients were determined. Additionally, the correlation of the SCC and various variables of interest as reported in previous studies (e.g. depressive symptoms, years of age, IQ and the years of education) was investigated. Furthermore, the correlation between the FAI-scores and objective test performance was collected, whereas here MMSE score and the subtests of VSRT, delayed recall, was used. A modest association was expected between subjective cognitive complaints and objective cognitive performance.

2. Methods

2.1 Ethics statement and study background

The present study was based on data collected in an ongoing research project called „The Vienna Conversion to Dementia Study" (VCDS). The entire study was approved by the Ethics Committee of the Medical University of Vienna and the study complied with the ethical principles of Helsinki´s Declaration. From all participants of this study a signed informed consent was obtained. The data of this quasi-experimental longitudinal study was presented at the Department of Neurology/ Medical University of Vienna. The ultimate ambition of this prospective clinical cohort study was detecting differences in SCC over time in different groups and determining the rates of progression from SCD to MCI or to dementia.

2.2 Subjects

The clinical sample consisted of patients, who consulted the neurological outpatient clinic of the Medical University of Vienna due to memory problems. These patients with SCC looked for clarification by themselves or were referred by the Department of Neurology for further investigation of suspected memory deficits or they were invited to follow up investigation. The included area of the VCDS was Vienna and eastern Austria. Similar to other studies the following exclusion criteria were collected in the anamnesis: 1. Neurological disorders like the evidence of a cortical stroke, traumatic brain injuries in the past, determined by neuroradiologic and clinical examination. 2. Medical condition, that could interfere with normal cognitive abilities including renal, respiratory, cardiac and hepatic disease. 3. Current major psychiatric disorder according to ICD-10 (Dilling et al., 2008). 4. Significant auditory, visual, language or motor deficits. 5. The presence of dementia according to DSM-IV at baseline (Saß et al., 2003). 6. Age less than 50 years. It was assumed that the above-mentioned diseases and deficits lead to cognitive deterioration and affect the

cognitive performance of subjects and therefore interfere with the conduction of the investigation (Stephan, Brayne, Savva & Matthews, 2011). As part of the initial examination both neuro-imaging and clinical patients' features were used. All patients received a complete neurological examination, standard laboratory blood tests, and psychometric tests. Additionally, in most cases a magnetic resonance imaging (MRI) scan or a computer tomography (CT) scan of the brain was obtained.

2.3 Assessment procedures

All participants were assessed by semistructured interviews, using the brief cognitive rating scale (Reisberg, Ferris, De Leon & Crook, 1988). Screening tools applied in the study included in addition the Mini Mental Status Examination (MMSE) (Folstein et al., 1975) to identify cognitive deficits. The established method is mainly used for the staging of dementia. Participants achieving a MMSE score < 24 from 30 points were excluded. The "Wortschatztest" (WST; Schmidt and Metzler, 1992), a standardized vocabulary test, was used to estimate the verbal intelligence levels and provided an estimate of premorbid IQ. In order to collect the ratings of depression, the BDI - II (Hautzinger et al., 2009) and the Bayers Activities of Daily Living Scale (BADL) (Hindmarch, Lehfeld, de Jongh, & Erzigkeit, 1998) were applied.

Objective memory performance - Neuropsychological Measurements

All participants were subjected to the comprehensive Neuropsychological Test Battery Vienna (NTBV) (Lehrner et al., 2007). The standardized, validated and normed NTBV was specifically designed to detect dementia in a clinical setting and it evaluates multiple cognitive domains: attention, executive functioning, language and memory domains with corresponding domain z-scores and a computed total z-score across all tests. (Lehrner et al., 2007; Pusswald, Moser, Gleiß, Janzek-Hawlat, Auff, Dal-Bianco & Lehrner, 2013). Regarding the total population, a Cronbach alpha with values ranging from 0.83 to 0.93 was determined for the total NTBV-z-score which represents a high internal consistency. Even high internal consistency has been achieved for the patients group suffering from dementia, with a Cronbach alpha ranging from 0.87 - 0.89. Overall test-retest reliability of corresponding total NTBV – z-scores was also substantial for total population, with correlation coefficients ranges from r = 86 – 94. In the patients group suffering from dementia correlation coefficients ranging from r = .69 – .90. The NTBV successfully differentiated AD patients from healthy controls (Lehrner et al., 2007; Macher, 2013).

The implementation of neuropsychological testing based on the NTBV took about 45 - 60 minutes.

Attention performance was assessed by using the Alters-Konzentrations-Test (AKT) (Gatterer, 2008), the Symbol Counting task from the inventory of cerebral insufficiency (C.I.) for the early diagnosis of dementia (Lehrl & Fischer, 1997), the second part of the Trail Making Test, Part B (TMTB) and the score difference oft the Trail Making Test A and B (Reitan, 1979). The digit-symbol-subtest of the german WAIS-R (Tewes, 1994) were further applied for detecting attention. Executive functions were investigated using the Trail Making Test A (TMTA) (Reitan, 1979), the Five-Point Test (Regard, Strauss & Knapp, 1982), the Maze test and the Stroop test of the Nürnberger Aging Inventory (NAI) (Oswald & Fleischmann, 1997). Additionally, the Interference subtest from the C.I. (Lehrl & Fischer, 1997) was used to detect the executive performance. The lexical verbal fluency was investigated by naming as many words beginning with the letters b, f and l and was assessed by using the Phonematic verbal fluency test (Goodglass & Kaplan, 1983). For detecting verbal fluency and confrontation naming task, the modified Boston Naming Test (BNT) (Morris et al., 1989) and the Semantic Verbal Fluency test (Goodglass & Kaplan, 1983) were applied. Memory performance, especially episodic memory, was tested by using the Verbal Selective Reminding Test (VSRT) (Lehrner et al., 2007) with several subtests (immediate recall, total recall, delayed recall and recognition of presented foods before).

Assessment of subjective cognitive complaints

SCC´s were assessed using "The Forgetful Assessment Inventory" scale (FAI) (Lehrner et al., 2014). The self-report questionnaire included 16 specific items assessing perception of change in the past 4 weeks on specific memory related areas based on everyday life scored on the basis of a likert scale (1 = never, 2 = rarely, 3 = sometimes, 4 = often, 5 = very often). Participants were required to answer describing situations relevant to everyday life: „How often did you have problems in daily life during the past 4 weeks remembering 1) names of people, 2) telephone numbers, 3) faces, 4) birthdays, 5) poems, 6) book titles, 7) content of TV broadcasts, 8) shopping lists, 9) directions, 10) discussion topics 11) content of radio broadcasts or 12) news broadcasts, 13) arrangements, 14) prices of bread or milk, 15) numbers, 16) lyrics". For statistical analyses the average score (range 1.00 – 5.00) across all 16 items was used with higher scores indicating more self-reported cognitive failures. In addition, the FAI proven itself due to its ease of use, short implementation and evaluation time. The FAI was assessed in terms of quality criteria and showed internal consistency with an evaluated Cronbach alpha of 0.85 (Lehrner et al., 2014).

Follow-up investigation was done at least 12 months after the baseline investigation by using the same test procedure.

2.4 Classification procedure

For the proposed study-design a multi-group design approach was chosen. The patients were classified based on their neuropsychological test results into the diagnostic groups SCD´s, the MCI´s and patients with PD disorder. The MCI criteria (Petersen, 2004, 2011) included two subtypes: naMCI and aMCI. Similarly, participants with PD were split in the same diagnosticgroups: PD-SCD and PD-MCI and these similarily divided into the mentioned subgroups PD-naMCI and PD-aMCI. The diagnosis was set in consensus with neuropsychologists, neurologists and other study personal involved in the evaluation of the cognitive status of subjects. In previous work influencing demographic variables of cognitive variables were detected (Chandler et al., 2005). For the evaluation and comparison of achieved individual performance in each test the raw scores of the various tests were transformed into z-values. The standard value describes the relative position of the test performance with respect to the corresponding reference population adequately. Depending on age, education and gender reported effects of cognitive variables these demographic variables based on the cognitive healthy control sample z-scores for each neuropsychological variable were estimated. For this purpose, the flexible generalized additive models for location scale and shape (GAMLSS) model class was used (Pusswald et al., 2013, Stasinopoulus & Rigby, 2007).

Subjective Cognitive Decline

The current study is based on the recently published framework for research on subjective cognitive decline in the context of preclinical AD by SCD-I (Jessen et al., 2014). SCD was defined by subjective decline in memory or non-memory domain specific concerns associated with SCD and an objective performance with an age, sex - and education-adjusted mean z-score of each domain greater than 1.5 standard deviation (SD) on NTBV. PD patients with normal range in all domains are equally allocated to the diagnostic group PD-SCD.

Mild Cognitive Impairment

The following criteria (Petersen, 2011) were set out as follows: (a) patients or/and their families report subjective memory complaints, (b) functional activities are not significantly impaired, (c) decline in cognition in at least one cognitive domain by – 1.5 SD below age related norm, (d) clinician has determined no dementia according to the Diagnostic and Statistical Manual of Mental Disorders, version IV (DSM-IV) (Saß et al., 2003). According to the current guidelines (Petersen, 2004, 2011) MCI, classified to amnestic MCI and naMCI, was defined by -1.5 SD

performance below age- and education-adjusted normal ranges in at least one domain in the NTBV. The aMCI was diagnosed by a z-score below -1.5 SD in memory domain. The naMCI is characterized by a subtle decline in not related memory functions such as executive functions, attention, language use and visuopatial skills (Petersen, 2011) defined by -1.5 SD performance below age- and education-adjusted normal ranges in at least one mentioned domain. The memory is not affected in naMCI. PD patients were allocated equally into the groups in this manner (PD-aMCI & PD-naMCI). Criteria in this paper for PD are also along the lines of Petersen (2011).

Dementia

Dementia was diagnosed according to the criteria set of DSM-IV at follow up investigation in a consensus conference with neurologists (Saß et al., 2003) and ICD-10 (Dilling et al., 2008).

2.5 Statistical Analysis

Statistical analyses of the clinical data were conducted using SPSS (version 20) for Windows. Descriptive statistics were used to characterize the study groups. Demographic variables and neuropsychological data are described by means and standard deviations. Crosstabulations were created to report the number of conversionrates. FAI scores represented the dependent variable. Two-factor GLM repeated measures ANOVAs were performed, with group as a between factor, time as a within factor since all necessary conditions were met (Field, 2009; Bortz & Döring, 2006). Post hoc pairwise comparisons were adjusted using Bonferroni method or Hochberg´s GT2 was used (Field, 2009). The continuous variables with skewed distributions were compared using Kruskal-Wallis test. In Step 2 the violation of the conditions for parametric approach existed, additionally Kruskal-Wallis test was conducted. Spearman r correlations were calculated to discover correlates of SCC and interested variables. Correlationscoefficients (r_s) and effect sizes of partial eta-square ($\eta^2_{p)}$ were calculated as well. According to Cohen (1988) $r_s < .10$ and $\eta^2_p < .05$ represents a small effect size, $r_s > .10$ and η^2_p approximately .10 represents a medium effect size and a $r_s > .50$ and $\eta^2_p > .20$ represents a large effect size. Receiver Operator Characteristic (ROC) curves were calculated checking the prognostic value of the FAI to obtain the optimal cut-off scores for testing sensitivity and specificity using the Youden index. The evaluation of the ROC in terms of prognostic significance of the FAI was based on the "area under the curve" (AUC) (Bortz & Döring, 2006). Positive predicted value (PPV) and negative predicted value (NPV), positive likelihood ratio (LR+) and negative likelihood ratio (LR-) were calculated (Weiß, 2013), where a LR+ > 10 enclosed a sought AD and a LR <0.1 can reliably

excluded an AD. A LR+ between 1 - 2 and a LR- 0.5 - 1 hardly change the pretest probability in a clinically relevant extent. A LR+ between 5 to 10 and a LR- between .1 to .2 are hardly clinically relevant (Glenck, Pewsner & Bucher, 2001). A analysis of VSRT - subtests was carried out by determining the mentioned values.

3. Results

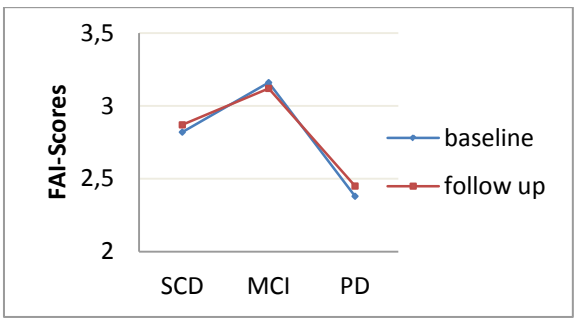
A total of 168 adults, complaining about cognitive deficits, which came to the memory outpatient clinic to clarify whether they were suffering from a cognitive disorder, participated in this study. The sample consisted of 78 men (46.4%) and 90 women (53.6%) between 50 and 88 years of age (M = 67.5, SD = 9.1). Mean years of formal education were 11.7 ± 3.6. All participants reached a higher MMSE score than 23 at baseline (M = 28.1, SD = 1.6). Mean premorbid WST-IQ was 109.7 (SD = 12.3) and the mean duration of follow-up investigation was nearly 33 months (SD = 15.8), showing a U-shaped distribution (p <.001). 158 participants completed assessments of the FAI at both measuring dates and this FAI score represented the dependent variable. Table 1. shows baseline characteristics of the total sample. Of the 168 subjects included in this study, 27 (16.1%) suffered from Parkinson and 69 subjects (41.1%) had SCD, of which 39 (56,5%) subjects remained at SCD at follow up. 72 (42.9%) subjects showed MCI at baseline and of these, 54 subjects (75%) remained at MCI at follow up. See table 2 for conversion rates in split diagnostic groups (Step 2). No one of the subjects suffering from PD developed PDD. This corresponds to 4.8% of the total non-demented clinical sample converted to AD. Seven (9.7%) patients from the 141 subjects with MCI and only one subject (1.4%) with SCD progressed to AD in the investigation period, which corresponds to an OR of 7.3 [CI 0.9 to 61.2]. More precisely, 5 of aMCI and 2 of naMCI converted to AD, indicating an OR of 2.0 [CI 0.4 to 11.2] for aMCI vs. naMCI. For Step 1 and 2 baseline diagnose were used as the focus of the entire investigation is to detect early differences in the SCC in progression to AD. The investigation of the differences in SCC was performed in 4 steps:

Step 1

In the first step, the difference in FAI-scores between the diagnostic groups SCD, MCI and PD was examined. SCD subjects showed a significant (p <. 01) higher IQ than MCI subjects and a significant (p < .05) higher IQ than PD subjects. MMSE scores were significant (p < .01) lower in MCI subjects. A 3x2 repeated measures ANOVA showed a significant main effect of diagnostic groups ($F(2, 155) = 11.79$, $p < .001$, $\eta^2_p = .132$). The main effects can be interpreted without any restriction since the interaction effect and also main effect for time was not

statistically significant. ANOVA results are summarised in table 3. Post hoc Bonferroni analysis showed, that the MCI subjects esteemed their subjective cognition worse than only SCD subjects ($p < .05$) and the PD patients ($p < .01$) (see Fig. 1.).

Fig. 1. FAI–Scores at baseline and follow up investigation across Step 1



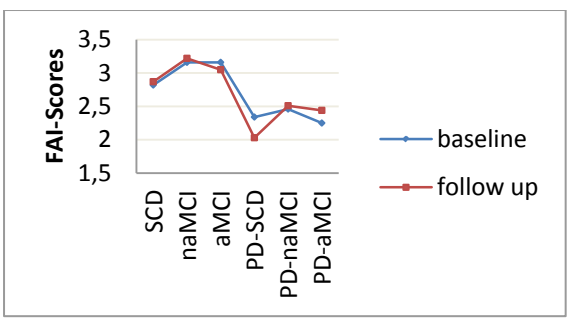
Note: FAI-Scores, Forgetful Assessment Inventory-Scores; SCD, Subjective cognitive decline; MCI, Mild cognitive impairment; PD, Parkinsondisease.

The PD patients had significantly lower scores in the FAI than the group of SCD ($p < .05$).

Step 2

In the second analysis, we examined the differences in their FAI-scores between the split diagnostic groups SCD, naMCI, aMCI, PD-SCD, PD-naMCI, PD-aMCI. A description of the means and standard deviations of baseline characteristics and dependent variables for split diagnostic groups are shown additionaly to total sample in table 1. Differences in split diagnostic groups were detected in years of education ($p < .05$), MMSE-scores ($p < .01$) and IQ ($p < .01$). The Box´s test showed higher significant differences in covariance ($p = .002$) than suggested cut off score ($p < .001$) and higher variance of smaller sample size group existed (Field, 2009). So we used parametric and non-parametric calculation additionally. An 6x2 repeated measures ANOVA revealed a significant main effect of subgroups on SCC ratings ($F(5, 152) = 4.863$, $p < .001$, $\eta^2_p = .138$), no main effect of time and also no significant interaction was detected (see Table 3). Pairwise post hoc comparisons using Hochberg´s GT2 analysis showed, that the group of aMCI patients had significantly higher SCC in the FAI than the group of PD-naMCI ($p <.05$) (Fig.2.). The naMCI subjects perceived their subjective cognition more declined than PD-naMCI ($p < .05$) and PD-aMCI ($p < .05$). Due to the small size of the group, the PD patients (N=27) were tested separately for differences with non-parametric method; Kruskal-Wallis test was applied (Field, 2009).

Fig.2. FAI–scores at baseline and follow up investigation across Step 2



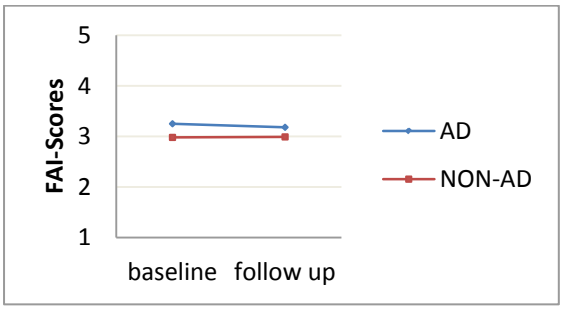
Note: FAI, Forgetful Assessment Inventory – Scores; SCD, Subjective cognitive decline ; naMCI, nonamnestic Mild cognitive impairment; aMCI, amnestic Mild cognitive Impairment; Park SCD, Parkinson disease Subjective cognitive decline; Park naMCI, Parkinson disease nonamnestic Mild cognitiveimpairment; Park aMCI, Parkinson disease amnestic Mild cognitive impairment.

PD patients did not reveal a significant group difference for FAI – scores at baseline, ($H(2) = 0.27$, $p = .87$) and no significant differences for follow up FAI – scores were detected with $H(2) = 0.74$, $p = .69$. The newly builded differences in FAI - scores did not revealed a significant group difference ($H(2) = 1.53$, $p = .47$). Additionally 3x2 ANOVA with repeted measure revealed a significant main effect of split groups (SCD, naMCI and aMCI) on FAI – scores was detected with $F(2, 130) = 4.037$, $p < .05$, $\eta^2_p = .058$, no main effect of time ($F(1, 130) = .006$, $p = .94$) and also no significant interaction effect ($F(2, 130) = 0.408$, $p = .67$) was detected. For this calculation PD patients were excluded (N = 141). Post hoc Bonferroni analysis showed, that the naMCI subjects esteemed their subjective cognition worsen than only SCD subjects ($p < .05$).

Step 3

In the third analyses furthermore differences in SCC among Converters and Non-Converters were examined with 2x2 repeated measures ANOVA. Of the PD patients, no one developed PDD in the studied period. For this calculation PD patients were excluded so the sample size was smaller than calculated steps before (N= 141). A description of the means and standard deviations of baseline and follow up demographic characteristics for Converters and Non-Converters are shown in table 4. Eight patients (5.7 %) out of 141 converted to AD. MMSE-scores differed statistically significant with lower baseline MMSE scores in Converters ($p < .05$). Subjects with AD at follow-up had a shorter follow up interval ($p < .05$). Average FAI scores are shown in Figure 3.

Fig.3. FAI–Scores at baseline and follow up investigation across the Step 3



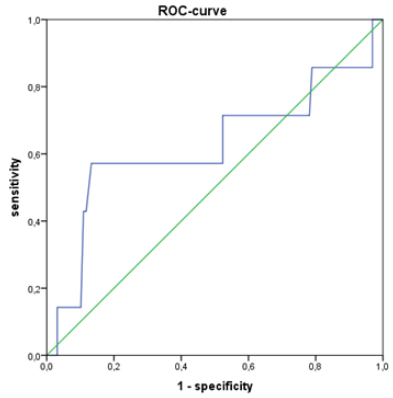
Note: FAI-Scores, Forgetful Assessment Inventory – Scores. AD, Alzheimerdementia; NON_AD, not converted to Alzheimerdementia

No statistically significant main effect between groups, even no main effect for time and also no interaction effect between group and time were detected (see Table 3).

ROC –Analyses

A receiver operating characteristic curve (ROC) analysis was conducted to establish a cut-off score which revealed the highest rates of sensitivity and specificity for the diagnosis of AD. The area under the ROC curve (AUC) for FAI shown in Fig. 4. was .622, 95% CI [0.36 to .89] and its standard error was .03 ($p = .28$).

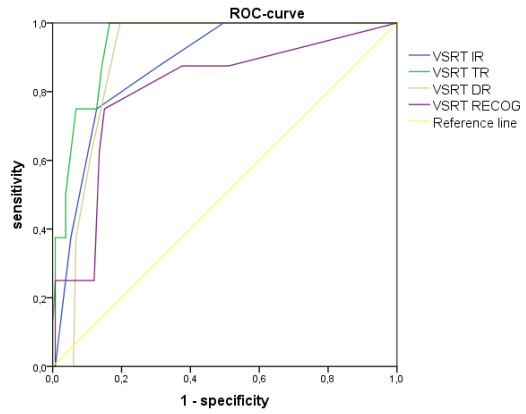
Fig.4. ROC – curve analyses depicting FAI



Note: FAI, Forgetful Assessment Inventory

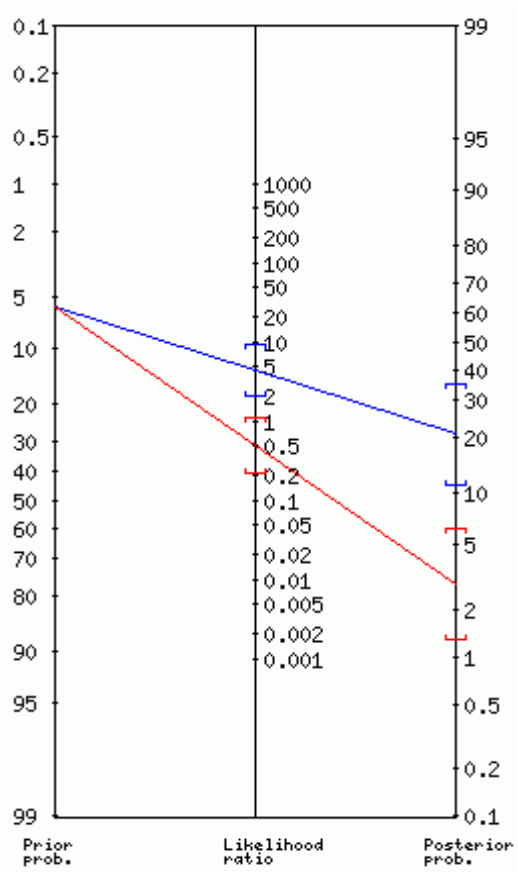
The optimal FAI cut-off score with 3.72 was calculated using the highest Youden - Index of 0.43. A list of sensitivity and specificity pairs as different FAI - scores are shown in excerpts in Table 5. A sensitivity of .57 and specificity of .87 was attained. For the cut-off of 3.72, a PPV of .21, 64% CI [.11 to .35] and a NPV of .97, 95% CI [.94 to 1] was found. A LR+ with 4.30 and a LR- with 0.49 was found for FAI (see. Fig. 5). The area under the ROC curve (AUC) for VSRT – subtests are shown in Fig. 6.

Fig.6. ROC – curve analyses depicting and VSRT – subtests



Note: VSRT, Verbal selctive reminding test; IR, immediate recall; TR, total recall; DR, delayed recall; RECOG, recognition;

Fig.5. Nomogram for interpreting diagnostic test results (LR) of FAI



The results of VSRT subtests (immediate recall, total recall, delayed recall; recognition) are summarized in table 6.

The ROC analyses for all VSRT subtests were significant with an area under the curve (AUC) between .805 (p < .05) to .945 (p < .000).

Step 4

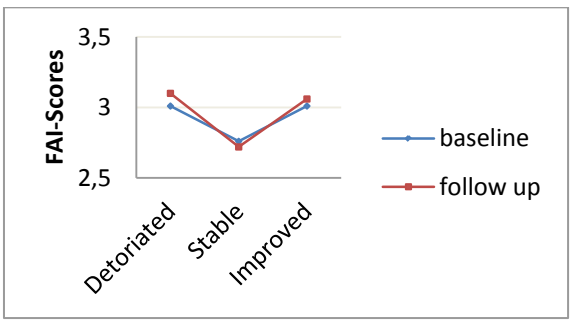
To further explore the outcome of the subgroups, we compared the FAI-scores of those, who improved in their objective memory performance (n=29), those who remained stable (n=75) and those who deteriorated in their objective cognitive performance (n=54) in the suggested course SCD – naMCI - aMCI - Dementia (Jessen et al., 2010). A description of the means and standard deviations of baseline

and follow up demographic characteristics are shown in table 7. A 3x2 repeated measures ANOVA was conducted. The change of diagnoses was considered significant with $F(2,155) = 4.463$, $p < .05$, $\eta^2_p = .054$ whereas the main effect of time was not and also no interaction was detected. (see Table 3). See Fig. 7 for FAI scores of detoriated or improved in their objective cognitive performance and those remained stable. Pairwise post hoc Bonferrioni analyses showed significant differences in the ratings of the deteriorated, which estimate higher SCC than those who remained stable ($p < .05$).

Correlations between FAI and variables of interest

The investigation on correlations between the SCC and the variables of interest was carried out in the diagnostic groups and subgroups, further in the Converted and Non-Converted and also the changes over time were examined.

Fig.7. FAI–Scores at baseline and follow up investigation across the Step 4



For the correlation calculation between diagnostic groups and also split diagnostic groups scores of the baseline survey were used as the focus of the entire investigation is to detect early differences in the SCC in AD. Subjects with higher SCC at baseline showed higher SCC at the follow up investigation ($r = .57$, $p < .001$). Consider the total sample, subjective memory was significantly related to estamination of functional activities of daily living (BADL), $r_s = .33$, $p < .05$. Depressive status on BDI - II revealed a moderate correlation. All Spearman Correlations (r_s) between FAI-Scores and variables of interest are listed in Table 8. PD-SCD has been included in the calculation but could not be interpreted meaningfully due to the small sample size (Field, 2009).

As in step 1 the subjects diagnosed with SCD showed, that SCC was significantly related to how well subjects did in the MMSE, $r_s = –.27$, $p < .05$. Consider the split diagnose groups as in step 2 the subjects diagnosed with naMCI showed significantly relationship between SCC and values on depression rated on BDI - II, $r_s = .55$, $p < .01$. SCC in naMCI group was also related to how well subjects rated their ADL´s on BADL, $r_s = .58$, $p < .01$. Those subjects, who did not convert to AD over investigation period, the level of SCC was moderatly related to how depressed people evaluate themselves on BDI - II, $r_s = 13$. The Non-Converters showed significantly relationship between SCC and BADL, $r_s = .36$, $p < .01$. Those, who were deteriorating in the investigation period in their objective cognition showed a significant relationship between the level of SCC and the BADL's, $r_s = .42$, $p < .01$;

and also those who remained stable in their objective memory performance, showed relationships in the SCC and functional ADL, $r_s = .33$, $p < .01$.

4. Discussion

This quasi-experimental longitudinal study was performed in a clinical setting. The major objective of the study was to determine differences in subjective assessment of memory among patients with SCD, MCI or PD in the investigated course. Also differences between the MCI subtypes aMCI and naMCI, even in diagnosed PD were considered. The main focus was to detect differences in the SCC among Converters and Non-Converters and additionally the differences in objective cognitive changes were investigated for differences in their SCC. The evaluation of the objective cognitive status was assessed by using the Neuropsychological Test Battery Vienna, NTBV (Lehrner et al., 2007). To assess the subjective memory performance, a questionnaire consisting of 16 items was used (Forgetful Assessment of memory, FAI) (Lehrner et al., 2014). In summary, this study described a clinical cohort of patients seeking help in an outpatient clinic with varying degrees of SCC ranging from subjective symptoms to those with objectified symptoms, based on neuropsychological testing within the meaning of MCI. In this clinical study the conversion rate of a total sample to AD in the investigated period was 4.8%. Higher risk to convert to AD (OR 7.3) was detected in MCI compared to SCD. None of the PD patients deteriorated in this period to PDD. In our clinical sample 1.4% of those with SCD, 6.5% of those with naMCI and 12.5% of those with aMCI at baseline converted to AD. This shows the trend along the continuum SCD, naMCI, aMCI and AD (Jessen et al., 2010). In our clinical sample a total of 18.7% of MCI converted in the investigation time to dementia and thus indicating a lower annual rate (Farias, Mungas, Reed, Harvey & DeCarli, 2009; Ganguli, Chang, Snitz, Saxton, Vanderbilt & Lee, 2010). More specifically, those who converted from aMCI to dementia, explicitly 12%, the numbers were comparable to other studies (Tabert et al., 2006). Considerably in this clinical sample fewer subjects were suffering from AD in the studied time period compared to other studies. Further comparisons with other studies also showed, that fewer people of the sample with MCI at baseline converted to AD (Tabert et al., 2006; Nordlund, 2010). These differing results can partly be explained by methodological differences. If patients are only asked whether they experience SCC, they are more likley to answer this question with yes because of its suggestive character.

Comparing the numbers in this study with Petersen (2003; cited in Petersen 2004) these high rates of progression could

not even be found in the present study. In this study, a rather U-shaped distribution displayed and no normal distribution in the time interval could be assumed. Thus, the follow-up examination was performed rather shorter after the baseline examination (median = 29) and may have had a straining impact of conversion rates. Subjects with AD showed shorter time interval than Non-Converters. Individuals with SMC at baseline showed in a recently published longitudinal study (Silva et al., 2014; Luck et al., 2015) higher progression to dementia, than in this clinical sample (36.6% -18.5% vs. 1.4%). It is also important to mention, that the investigation periods in the mentioned study were longer (2 – 8 years) than in our study (nearly 3 years). In our sample over 56.5% of SCD at baseline remained stable and 43.5% deteriorated during the time frame. Progression rates to MCI showed the trend, that subjects at first were affected in the nonamnestic domains. Comparable to other studies 7.8% of MCI subjects improved their objective cognitive performance to only SCD in the investigated course. Higher reversionrates were reported in the study by Manly et al., (2008) in which 31% of subjects with MCI reverted to normal. 47% of MCI patients in the same study remained unchanged whereas 38% of MCI patients remained stable in our clinical sample.

The low progression to dementia in PD does not reflect published results (Janvin et al., 2006). None of the PD patients developed to PDD and these findings do not correspond with previous research. However, it should be mentioned that the PD sample consisted only of a small group (n = 27) compared to the neurologically healthy individuals (n = 141) in our sample. As initial visit to the clinic in order to clarify SCC, 25 patients diagnosed with PD showed objectified cognitive impairment in the sense of MCI. Only two subjects showed SCD at baseline.

An important goal of the current study was to investigate the differences of FAI-Scores across all 4 steps. It has never been investigated before, how SCD, MCI and PD patients compare in their SCC ratings within a longitudinal course. Differences in SCC ratings between groups were detected whereas the group of PD assessed their memory less affected than the SCD and MCI. This was also confirmed by ANOVA. One reason why PD patients showed less SCC might be, that PD diagnoses may be also related to a cognitive decline and therefore the memory is judged less affected in terms of reactants of behavior. The assumed time effects were not confirmed. Even in second analyses assumed group differences were confirmed. Subjects with PD showed fewer SCC also in split dignostic groups. Looking at the mean values of the FAI scores in the split diagnostic groups at least tend to the proposed course of Jessen et al.

(2010) was noticed; patients with aMCI indicated a higher subjective complaint level as patients with naMCI and these indicated in turn less SCC than the patients with SCD. PD and neurological healthy patients were testet seperatly because of the unequal group size

PD patients showed no different estimation of SCC at baseline and follow up investigation. PD–SCD, PD-naMCI and PD-aMCI do not differed when differences of the FAI score were studied over time. naMCI subjects esteemed their SCC worsen than only SCD subjects. But no differences were detected between aMCI and SCD, whereas impaired awarenesslevel might be a reason for this results. Our assumed time effects were also not confirmed. The main aim of this study was whether those Converters differ between Non-Converters in their SCC based on the basic examination. The subjective assessment of memory allowed no differentiation between AD and Non-Converters. The Converters and Non-Converters in this clinical sample did not differ in their FAI-Scores and even both groups had identical estimation at baseline and follow up investigation similar to Wang (2004). This could be due to the small sample size in the group of AD (n=8) and differences with a larger study sample might be statistically significant. One reason for the nearly identical assessment of SCC at both measure dates might be the increase of anosognosia for cognitive performance in early stages of AD and this may cause an underestimation of cognitive dysfunctions (Kalbe et al., 2005). However, not only in patients with AD, even in those with aMCI an impaired awareness for memory deficits was detected (Lehrner et al., 2014). It is therefore, conceivable that some subjects reported no alteration but were well aware of their cognitive problems. Summarised the proposed hypothesis could not be confirmed and SCC was not able to distinguish between Converters and Non-Converters. In Step 4 significant group differences were detected in the SCC between those who deteriorated in their cognitive status in the investigated course and those who remained stable with nearly identical estimation at baseline and follow up investigation. So time effect, contrary to our assumption, was not significant. Therefore SCC could distinguish between those who deteriorated in their objective cognitive performance and those who remained stable. This prognostic value must be discarded again, because those who improved, estimated SCC as bad as the deteriorated patients. Considering the low effect size of $\eta^2_p = .05$ little variance was explained by these differences in the SCC. Observed statistical power ranged between .05 and .13 in detected significant group differences (Step 1, Step 2 and Step 4) which represented a small to medium effect. In future, a balanced group size should be aimed to minimize the likelihood

of type II error and to guarantee the statistical power. We studied a clinical sample and therefore there was no randomization and no control over the size of the investigated groups.

Additional research is required to study the causes and consequences of SCD steadiness over time. In our sample the SCC was completely stable in all investigated steps. Furthermore, it is important to carry out from which date the SCC decreased although the objective cognitive performance begins to decline. Another option for future research would be focusing on a longitudinal design, whereas in addition to SCC the estimation of subjective memory of the members as defined in an external evaluation should be extended.

Another part of the study was carrying out correlations with variables of interest in the course. The focus was on the patient who deteriorated (Step 3 and Step 4). But what may be concluded? Subjects who developed AD during the course, showed a low correlation between higher age and lower SCC at the baseline examination and the subjects with higher education correlated with higher subjective complaint levels. Considering age and years of education (cf. Jorm et al. 2001, Jonker et al., 2000) the total sample showed no consistent correlations with the SCC. Low correlations were found in MMSE, where the negative correlation value indicated that higher SCC were associated with lower values in the MMSE (carried out in 7 of 14 calculations). Considering the changes over time and the converted to AD, in particular no consistent logical direction was detected in this clinical sample in objective memory performance. The AD subjects, who have obtained lower scores in the MMSE at baseline, reported also lower SCC (r_s = 73). However, the relationship between SCC and the VSRT delayed recall, which is sensitive for early detection of cognitive decline in AD, the Converters and also the Non-Converters showed similar correlates (r_s = -.16, r_s = -.11). Depressive symptoms were often associated with SCC. As seen in Lehrner et al. (2014), large positive correlations between depressive status and SCC were found in naMCI and so they were in this clinical sample group. The Converters showed a low correlation with the SCC and depressed values in turn compared to Non-Converters. For detecting depression, no consistent correlations between the SCC and depressive status were found. In summary, the highest correlations at all investigation steps were discovered between SCC and ADL (r_s = .33 - .58), and they showed moderate effects according to Cohen (1988). Even these correlations were also higher than those of objective memory performance with SCC. The PD-naMCI showed that older subjects had lower SCC, while the neurologically healthy MCI subjects do not show this correlation. Subjects with higher SCC

reported fewer items at the NTBV subtest VSRT-delayed recall while functional ADL significant correlations of medium strength were detected in the group of naMCI. SCD actually is still in fact subjective estimation. The clinical value of SCD and its relationship to objective cognitive performance or future cognitive disorders like AD pathology still remained disagreement in positions. The results in our sample allow no conclusion, confirming the clinical value of the SCC in detecting AD.

Keypoints

- Evaluation of the objective neuropsychological performance and SCC in non-demented patients.
- SCC´s were assessed using the self-report questionnaire FAI including 16 specific items on the basis of a likert scale.
- Nearly identical estimate of SCC at baseline and follow up investigation was considered.
- SCC allowed no differentiation between Converters and Non-Converters at baseline.
- FAI should be used under reserve as an indicator for risk.

The current longitudinal study has certain strengths. We used the latest definition of SCD according to Jessen et al. (2014) for the classification of SCC and the previously well-established MCI - criteria according to Petersen (2004, 2011). Furthermore, patients were subjected to a comprehensive neuropsychological testing on NTBV with respectable discrimination power in discovering AD. The SCC consultation of patient reports was not charged with a single, suggestive influencing question, whether subjective complaints are noticed or not. The survey was conducted with FAI on the basis of everyday life-related issues, which has to be answered in the form of likert scale.

When 3.72 was used as a FAI cut-off, 57.1% of patients with AD were correctly classified in our clinical sample and 86.7% of the Non - Converters were classified correctly as not affected. Accordingly, the false positive rate was 42.9% and the false negative rate was 13.3%. The FAI score represents in this case a quite applicable method. With a score higher than 3.72 even half of AD patients were correctly recognized. Moreover with this FAI - score of 3.72, two of ten people, who will be developing an AD (PPV = .21), became apparent. The residual risk to develop AD is high, even if the result in FAI is below the choosen limit. Slightly more than half of the people, who show a lower FAI score than 3.72, are proven not affected by the disease. The result of FAI just should be used under reserve as an indicator for risk. The FAI slightly differs according the prognostic value between pathological yet and normal cognitive status. Nevertheless important changes in brain in early stages of declined

cognition can be displayed by using the FAI. The score in the subtests of VSRT total recall and VSRT delayed recall is the most useful value to exclude an AD. Similar sensitivities in VSTR subtests for conversion to AD > .90 were also reported by Lehrner et al. (2007). The LR- in FAI and the subtests of VSRT immidiate recall and VSRT recognition indicate small, but important changes. The level of LR+ ensures the results. All of the VSRT-subtests indicate moderate changes. On the contrary, the LR + of the FAI has only weak impact on the security of the diagnosis of AD.

A number of study limitations must be considered. Generalization to the general population is limited due to the clinical sample. The current mood of the samples was not taken into consideration and should be also collected in future studies since the current mood at the time of testing was associated with cognitive performance (Marino et al., 2009; Caracciolo, Bäckman, Monastero, Winblad & Fratiglioni, (2011). Furthermore, anxiety was not collected in this study which again may affect the SCC and should be additionally collected in future investigations. In future analyses on this matter a complete medication evaluation between follow up investigation is necessary, since medication treatment can influence cognition (Nagaraja & Jayashre, 2001, Carrière et al., 2009). Dopaminergic medications as used in the treatment of PD influence cognitive performance or delay the progression from MCI to dementia in PD and may have been a potential confound to our results. Furthermore conducted physical activity and cognitive training as possible impact on cognitive performance are mentioned (Sinforiani, Banchieri, Zucchella, Pacchetti & Sandrini, 2004, Miller, Taler, Davidson & Messier, 2012). In our study cognitive rehabilitation and therapy among both two measure intervals were not documented and should be taken into account in further investigation.

Summarized, the Converters and the Non-Converters differed not in their SCC in baseline investigation. Our present results do not support the use of the SCC in AD and no prognostic benefit of SCC was confirmed in this sample. Providing evidence that SCC are especially prognostic for AD and further cognitive impairment additional longitudinal studies in conduction of detecting incident SCC are required.

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Table 1. Baseline characteristics for split diagnostic groups (N = 168)

	Total (N=168)	SCD (n=69)	naMCI (n=31)	aMCI (n=41)	PD-SCD (n=2)	PD-naMCI (n=16)	PD-aMCI (n=9)
Female (n/%)	90/ 53.6	46/ 27.4	15 / 8.9	19/ 11.3	0/ 0 .0	6/ 3.6	4/ 2.4
Age (years)	67.5/ 9.1	66.1/ 9.5	69.7/ 9.2	68.2/ 9.2	70.5/ 2.1	68.1/ 7.2	65.2/ 7.8
Intervall (months)	33.0/ 15.8	37.2/ 15.4	35.0/ 16.9	29.9/ 16.6	29.5/ 6.4	21.4/ 4.9	29.0/ 14.0
Education (years)	11.8/ 3.6	12.5/ 3.7	10.5/ 2.8	11.7/ 3.8	15.5/ 3.5	11.9/ 3.1	9.1/ 2.0
MMSE	28.1/ 1.6	28.5/ 1.3	27.4/ 1.8	27.9/ 1.4	28.5/ 0 .7	28.6/ 1.3	26.5/ 2.4
VSRT-IR	7.6/ 2.0	8.5/ 2.0	6.3/2.1	7.0/ 1.5	7.5/ .7	8.3/ 1.5	6.8/1.1
VSRT-TR	45.9/ 9.8	51.9/8.4	39.4/ 9.5	41.4/ 7.6	45.0/ 2.8	48.8/ 6.9	38.6/ 6.0
VSRT-DR	9.4/ 2.9	11.0/ 2.4	7.6/ 3.0	8.3/ 2.0	8.5/ 2.1	9.9/ 2.5	7.0/ 2.9
VSRT-RECOG	14.0/ 1.7	14.5/ 0.8	13.4/ 2.4	13.7/ 2.1	13.8/ 1.1	14.7/ 0.5	12.7/ 1.8
WST	109.7/ 12.3[1]	113.9/ 10.9	104.2/ 12.0[2]	108.7/ 12.3	116.5/ 17.7	109.4/ 10.6	98.4/ 12.8[3]
FAI	2.9/ 0 .8[4]	2.8/ 0.7[5]	3.2/ 0 .7[6]	3.2/ 0 .7[7]	2.3/ 0.0	2.5/ 0.8	2.3/ 0.6
BDI - II	10.5/ 7.1[8]	10.2/ 7.3	9.6/ 6.7[9]	12.4/ 7.9	8.0/1.4	8.38/5.9	11.8/ 6.8[10]

Note: variables are presented as mean & standard deviation; SCD, subjective cognitive decline; naMCI, nonamnestic mild cognitive impairment; aMCI, amnestic mild cognitive impairment; PD - SCD, Parkinson disease – subjective cognitive decline; PD - naMCI, Parkinson disease – nonamnestic mild cognitive impairment; PD - aMCI, Parkinson disease – amnestic mild cognitive impairment; M, mean; SD, standard deviation; MMSE, Mini Mental State Examination; VSRT, Verbal selctive reminding test; VSRT-IR, VSRT- immediate recall; VSRT-TR, VSRT- total recall; VSRT-DR, VSRT- delayed recall; VSRT-RECOG, VSRT- recognition; WST, Wortschatztest; FAI, Forgetful Assessment Inventory; BDI - II, Beck Depression Scale - II; WST [1]n=166 [2]n=30, [3]n=8; FAI [4]n=162 [5]n=68 [6]n=30 [7]n=37; BDI - II[8]n=165, [9]n=29, [10]n=8.

Table 2. Conversion rates in the diagnostic subgroups at baseline and follow up (N= 168)

			Follow up investigation								
			SCD	naMCI	aMCI	AD	Park SCD	Park naMCI	Park aMCI	PDD	total
Baseline	SCD	n (%)	39 (56.5)	18 (26.1)	11 (15.9)	1 (1.4)	-	-	-	-	69 (41.1)
	naMCI	n (%)	5 (16.1)	10 (32.3)	14 (45.2)	2 (6.5)	-	-	-	-	31 (18.5)
	aMCI	n (%)	6 (14.6)	13 (31.7)	17 (41.5)	5 (12.2)	-	-	-	-	41 (24.4)
	Park SCD	n (%)	-	-	-	-	0 (0.0)	1 (50.0)	1 (50.0)	0 (0.0)	2 (1.2)
	Park naMCI	n (%)	-	-	-	-	2 (12.5)	4 (25)	10 (62.5)	0 (0.0)	16 (9.5)
	Park aMCI	n (%)	-	-	-	-	0 (0.0)	2 (22.2)	7 (77.8)	0 (0.0)	9 (5.4)
	total	n (%)	50 (29.8)	41 (24.4	42 (25.0)	8 (4.8)	2 (1.2)	13 (7.7)	12 (7.1)	0 (0.0)	168 (100)

Note: SCD, subjective cognitive decline; naMCI, nonamnestic mild cognitive impairment; aMCI, amnestic mild cognitive impairment; AD, Alzheimer dementia; PD- SCD, Parkinson disease- subjective cognitive decline; PD- naMCI, Parkinson disease- nonamnestic mild cognitive impairment; PD- aMCI, Parkinson disease- amnestic mild cognitive impairment; PDD, Parkinson disease dementia.

Table 3. GLM Anova with repeated measurements Step 1 – 4

source		df_1, df_2	F	η_p^2	p^1
diagnose	Step 1	2, 155	11.79	.132	< .001
	Step 2	5, 152	4.86	.138	< .001
	Step 3	1, 131	1.415	.011	.236
	Step 4	2, 155	4.463	.054	< .05
time	Step 1	1, 155	0.18	.000	.895
	Step 2	1, 152	0.13	.001	.719
	Step 3	1, 131	0.007	.000	.934
	Step 4	1, 155	0.216	.001	.643
diagnose X time	Step 1	2, 155	0.20	.003	.816
	Step 2	5, 152	0.28	.020	.922
	Step 3	1, 131	0.00	.000	.983
	Step 4	2, 155	0.929	.12	.397

Note: main and interactioneffect are presented in Step 1 (n = 168) and Step 2 (n = 168) using baseline diagnostic group; Step 3 (n=141) and Step 4 (n=168) follow up diagnoses were used. p^1, uncorrected *p*.

Table 4. *Demographic and sample characteristics of the Converters and Non-Converters (N=141)*

	Converters (n= 8)		Non-Converters (n= 133)	
	baseline	follow up	baseline	follow up
Female (n/%)	3/ 2.1	-	77/ 54.6	-
Age	69.1/ 9.6	71.1/ 9.5	67.4/ 9.4	70.4/ 9.3
Intervall	-	23.3/ 15.4	-	35.3/ 16.1
Education	10.5/ 3.8	-	11.9/ 3.6	-
MMSE	25.9/ 2.2	25.0/ 1.6	28.2/ 1.4	28.0/ 1.5
VSRT-IR	5.0/ 1.1	4.6/ 1.4	7.7/ 2.0	7.1/ 2.2
VSRT-TR	29.9/ 4.9	28.6/ 4.0	47.1/ 9.5	45.1/ 10.8
VSRT-DR	6.0/ 0.9	4.0/ 2.5	9.7/ 2.8	8.7/ 4.0
VSRT-RECOG	11.8/ 3.5	9.7/ 4.6	14.2/ 1.5	13.8/ 2.2
WST	107.4/ 14.2	103.3/ 11.3[1]	110.5/ 12.0[2]	108.0/ 18.2[3]
FAI	3.3/ 1.0[4]	3.2/ 0.8	3.0/ 0.7[5]	3.0/ 0.7[6]
BDI - II	11.1/ 7.4	11.4/ 8.6	10.7/ 7.4[7]	10.7/ 7.2[7]

Note: all variables are presented as mean & standard deviation; MMSE, Mini Mental State Examination; VSRT, Verbal selctive reminding test; VSRT-IR, VSRT- immediate recall; VSRT-TR, VSRT- total recall; VSRT-DR, VSRT- delayed recall; VSRT-RECOG, VSRT- recognition; WST, Wortschatztest; FAI, Forgetful Assessment Inventory; BDI - II, Beck Depression Scale - II; WST[1]n=6 [2]n=132 [3]n=128; FAI[4]n=7 [5]n=128 [6]n=130 ; BDI - II[7]n=131.

Table 5. Cut-off points and diagnostic validity of FAI

Cut off point	Sensitivity	Specivicity	Youden Index
2.62	.714	.289	0.003
2.63	.714	.297	0.011
2.64	.714	.313	0.027
2.66	.714	.320	0.035
2.68	.714	.328	0.042
2.71	.714	.336	0.050
2.74	.714	.352	0.066
2.78	.714	.398	0.113
2.84	.714	.422	0.136
2.88	.714	.430	0.144
2.91	.714	.461	0.175
2.94	.714	.477	0.191
2.97	.571	.477	0.048
3.01	.571	.516	0.087
3.04	.571	.523	0.095
3.07	.571	.578	0.150
3.10	.571	.586	0.157
3.13	.571	.602	0.173
3.16	.571	.617	0.189
3.20	.571	.641	0.212
3.23	.571	.648	0.220
3.28	.571	.680	0.251
3.31	.571	.688	0.259
3.32	.571	.711	0.282
3.34	.571	.719	0.290
3.36	.571	.727	0.298
3.37	.571	.734	0.306
3.38	.571	.750	0.321
3.39	.571	.758	0.329
3.42	.571	.766	0.337
3.50	.571	.789	0.360
3.57	.571	.828	0.400
3.59	.571	.836	0.407
3.61	.571	.844	0.415
3.65	.571	.852	0.423
3.72	**.571**	**.867**	**0.439**
3.78	.429	.883	0.311
3.81	.429	.891	0.319
3.84	.143	.898	0.041
3.88	.143	.906	0.049
3.98	.143	.914	0.057
4.09	.143	.930	0.073
4.15	.143	.938	0.080

Table 6. ROC Analyses with AUC [95 % Confidence Intervals] at optimal Cut off using highest Youden Index of FAI and VSRT – Subtests (N = 141)

	Cut off	AUC [95% CI]	SE [95% CI]	SP [95% CI]	PPV [95% CI]	NPV [95% CI]	LR+	LR-
FAI	3.72	.62 [.36 - .89]	.57 [.49 to .65]	.87 [.80 to .92]	.21 [.14 to .28]	.97 [.94 to 1]	4.30	.49
VSRT-IR	5.50	.88 [.78 - .97]	.75 [.68 to .82]	.87 [.81 to .93]	.27 [.19 to .35]	.98 [.96 to 1]	5.77	.29
VSRT-TR	36.50	.95 [.90 - .99]	1,00 [-]	.84 [.78 to .90]	.27 [.19 to .35]	1 [-]	6.25	.00
VSRT-DR	7.50	.90 [.84 – 95]	1,00 [-]	.81 [.75 to .88]	.24 [17 to .30]	1 [-]	5.26	.00
VSRT-RECOG	13.50	.81 [.64 - .97]	.75 [.68 to .82]	.85 [.79 to .91]	.23 [.15 to .35]	.98 [.96 to .1]	5.00	.29

Note: FAI, Forgetful Assessment Inventory; VSRT, Verbal selctive reminding test; VSRT - IR, VSRT- immediate recall; VSRT - TR, VSRT- total recall; VSRT-DR, VSRT - delayed recall; VSRT - RECOG, VSRT – recognition; FAI, Forgetful Assessment Inventory; AUC, Area under curve; SE, Sensitivity, SP, Specificity; PPV, Positive Predicted Value; NPV, Negative Predicted Value; LR+, Positive likelihood ratio; LR-, Negative likelihood ratio.

Table 7. Demographic and sample characteristics of the Sample - improved, detoriate and stable over time (N= 168)

	Improved (n=29)		Stable (n=83)		Detoriated (n=56)	
	Baseline	Follow up	Baseline	Follow up	Baseline	Follow up
Female (n/%)	18/ 10.7	-	46/ 27.4	-	26/ 15.5	-
Age	67.8/ 8.8	70.5/ 8.7	66.5/ 9.1	69.2/ 9.1	68.8/ 9.2	71.7/ 8.9
Intervall	-	31.6/ 16.6	-	31.9/ 15.0	-	35.3/ 16.5
Education	11.2/ 3.7	-	11.8/ 3.6	-	12.0/ 3.5	-
MMSE	27.9/ 1.6	27.7/ 1.3	28.4/ 1.3	27.9/ 1.5	27.6/ 1.8	27.7/ 1.8
VSRT-IR	7.5/ 1.6	7.5/ 2.0	8.0/ 2.1	7.2/ 2.2	7.0/ 2.0	6.4/ 2.1
VSRT-TR	44.7/ 7.3	46.8/ 9.6	48.8/ 9.7	46.2/ 10.0	42.3/ 9.8	39.7/ 11.5
VSRT-DR	9.0/ 2.1	9.1/ 3.7	10.2/ 2.9	9.7/ 3.3	8.4/ 3.0	6.4/ 4.2
VSRT-RECOG	13.8/ 1.8	14.2/ 1.4	14.3/ 1.1	14.1/ 1.4	13.8/ 2.2	12.5/ 3.3
WST	107.9/ 13.3	107.1/ 13.0[1]	109.2/ 12.3[2]	106,5/ 17.4[3]	111.4/ 11.6	108.7/ 18.7[4]
FAI	3.0/ 0.8	3.1/ 0.6	2.8/ 0.8[5]	2.7/ 0.7[6]	3.0/ 0.7[7]	3.1/ 0.8
BDI - II	12.6/ 8.8	11.2/ 7.4	10.1/ 7.2[8]	10.1/ 7.3[8]	10.1/ 6.7[9]	10.8/ 7.1[9]

Note: M, mean; SD, standard deviation; MMSE, Mini Mental State Examination; VSRT, Verbal selctive reminding test; VSRT-IR, VSRT- immediate recall; VSRT-TR, VSRT- total recall; VSRT-DR, VSRT- delayed recall; VSRT-RECOG, VSRT- recognition**;** WST, Wortschatztest; FAI, Forgetful Assessment Inventory; BDI - II, Beck Depression Scale - II; WST [1]n=28 [2]n =81 [3]n=77 [4]n=54; FAI[5]n=79 [6]n=78 [7]n=54; BDI - II[8]n=81 [9]n=55.

Table 8. Spearman Correlations (r_s) between FAI-Scores and cognitive variables and moderator varables

	age	N	education	N	VSRT-DR	N	MMSE	N	WST	N	BDI - II	N	BADL	N
SCD	.053	68	-.006	68	.018	68	-.269*	68	.027	68	.025	68	.229	68
MCI	-.009	67	.054	67	-.086	67	.071	67	.189	66	.216	65	.396**	66
PD	-.017	27	-.244	27	-118	27	-.019	27	-.223	26	.068	26	.363	26
naMCI	.154	30	.033	30	-.110	30	-.010	30	.085	29	.546**	28	.577**	29
aMCI	-.092	37	.157	37	-.005	37	.088	37	.290	37	.006	37	.240	37
PD SCD[1]	1**	2	1**	2	1**	2	1**	2	1**	2	1**	2	1**	2
PD naMCI	-.116	16	-.609	16	-269	16	.025	16	-.336	16	.062	16	.680	15
PD aMCI	.050	9	.199	9	-.252	9	-.230	9	-.108	8	.048	8	.183	9
AD	-.108	7	.388	7	-.162	7	.729	7	.382	7	.027	7	.090	7
Non-AD	.068	128	-.015	128	-.106	128	-.145	128	.024	127	.129	126	.355**	127
Improved	.059	29	.038	29	220	29	.103	29	-.024	29	.092	29	.208	29
Stable	.093	79	-.017	79	-.159	79	-.191	79	.076	77	.095	77	.331**	78
Detoriated	-.033	54	-.132	54	-.081	54	.004	54	-.017	54	.181	53	.419**	53
total	.053	162	-.028	162	-.122	162	-.097	162	.050	160	.136	159	.331*	160

Note:[1]sample size only 2 subjects; interpreted with caution; .20= small -, .50 =moderate -, .80= large effect size $^{*}p < .05$. $^{**}p < .01$. (uncorrected p).

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