universität wien

MASTERARBEIT / MASTER'S THESIS

Titel der Masterarbeit / Title of the Master's Thesis

„The Predictive Validity of Subjective Memory Impairments for Future Verbal Memory Performance“

verfasst von / submitted by

Jonas Hamburger, BSc

angestrebter akademischer Grad / in partial fulfilment of the requirements for the degree of

Master of Science (MSc)

Wien, 2018 / Vienna 2018

Studienkennzahl lt. Studienblatt / degree programme code as it appears on the student record sheet:	A 066 840
Studienrichtung lt. Studienblatt / degree programme as it appears on the student record sheet:	Psychologie
Betreut von / Supervisor:	Univ.-Prof. Dr. Claus Lamm
Mitbetreut von / Co-Superviser:	

Acknowledgements

First of all, I would like to thank Prof. Dr. Lehrner for giving me the opportunity to work under his guidance in this project and Prof. Dr. Lamm for supervising the thesis. I would also like to thank Dr. Weber who reviewed my statistical analysis. I would especially like to thank every study colleague and friend who took the time and helped me with proofreading and gave me feedback on my work. Last but not least I would like to thank my parents Sigrid and Michael for supporting me through my entire academic studies and my partner Miriam for being the best support during my writing I could ask for.

Background

According to the World Health Organization, approximately 47 million people are currently affected by dementia (WHO, 2017), a syndrome that is characterized by deteriorations of cognitive functions beyond the normal effects of aging and leading to functional impairments in activities of daily life. Due to an aging global population, the steadily rising numbers of people affected by dementia (an estimated number of 75 million people in 2030 and 132 million people in 2050), its strong personal, social and economical impacts and the fact that there is currently no treatment method available, the WHO has announced specific goals for dementia. One of these goals is an „early diagnosis in order to promote early and optimal management“ (WHO, 2017). The importance of an accurate and early diagnosis is also emphasized by specific interventions that have been shown to lower the risk of disease progression and functional incapacities (Scheltens et al., 2016).

In order to accurately diagnose dementia at an early stage it is important to have a comprehensive understanding of the subtle appearances of pre-dementia stages. Recent research on the development and progression of dementia proposed a model with three conceptually different stages (Jessen et al., 2010; 2014). The model describes a slow and gradual development, beginning with subjective cognitive decline (SCD) as the first stage (Jessen et al., 2010; 2014). Mild cognitive impairment (MCI) is described as the second stage in the model and the final stage is marked by dementia (Jessen et al., 2010; 2014).

Subjective cognitive decline is characterized by individuals expressing impairments about their cognitive abilities, although their objective cognitive performance is still within the range of sociodemographic norms (Jessen et al., 2010; 2014).

Mild cognitive impairment describes individuals who already show decreased cognitive performances in neuropsychological test procedures outside the normal aging related ranges of cognitive deficits (Petersen, 1999; 2004; 2011). Yet, the assessed cognitive impairments are neither

severe enough, nor causing the necessary functional disturbances to meet the criteria for a dementia diagnosis (Gauthier et al., 2006).

The final stage of the proposed model marks dementia. Dementia is a broad term used for irreversible neurodegenerative diseases that are characterized by memory impairments, aphasia and/ or apraxia, agnosia, impairments of executive functions and significant impairments in social or occupational functioning (Dilling, H., Mombour, W., Schmidt, M. H., & World Health Organization, 1991). Alzheimer's disease (AD) is the most common type of dementia, accounting for 50 to 70 percent of all dementia cases worldwide (Winblad et al., 2016). Other common types of dementia are vascular dementia, Lewy body dementia and frontaltemporal lobe dementia (caused by a group of diseases contributing to the degeneration of the frontal lobe) (WHO, 2017).

Longitudinal deteriorations in cognitive performances caused by progressing neuro-degenerative processes are an essential hallmark symptom of MCI and AD. As a pre-dementia stage, the concept of SCD and its relation to cognitive performance have been extensively researched in the past and many studies identified SCD to be a risk factor for future cognitive decline, leading to MCI or dementia (Jessen et al., 2014; Mitchell, Beaumont, Ferguson, Yadegarfar, & Stubbs, 2014; Rabin, Smart, & Amariglio, 2017). A recent meta-analysis found annual conversion rates among individuals with SCD of 6.6% to MCI and 2.3% to dementia, compared to 1% without SCD (Mitchell et al., 2014). Long-term (over 4 years) conversion rates of individuals with SCD are 24.4% to MCI and 10.9% to dementia, compared to 4.6% in individuals without SCD (Mitchell et al., 2014). The predictive value of SCD is even stronger when combined with other highly reliable risk factors, such as biomarker positivity (Ferreira et al., 2017; Rabin et al., 2017; Winblad et al., 2016).

Cross-sectional studies investigating the relationship of subjective cognitive impairments and objective cognitive performance have yielded mixed results (Jonker, Geerlings, & Schmand,

2000; Reid & MacLullich, 2006). By definition, individuals with SCD score within normal performance ranges on neuropsychological test procedures (Jessen et al., 2014). However, neuropsychological tests only assess the cognitive performance of an individual at a single given point in time, yet subjective cognitive impairments mark a longitudinal change (Jessen, 2014). Therefore, individuals without subjective cognitive impairments who score within the average range on neuropsychological tests could perform as well as individuals with above-average cognitive performances, who have already objectively declined and subjectively experienced this decline, which may explain poor correlations in cross-sectional study designs (Jessen, 2014). On the other hand, several longitudinal studies have more reliably linked subjective cognitive impairments to future cognitive decline (Jonker et al., 2000; Mendonça et al., 2016; Mitchell et al., 2014; Reid et al., 2006). However, studies that investigated the relationship between subjective and objective cognition are marked by high heterogeneity in their designs, definitions of subjective impairments, assessment procedures and statistical methods, making valid comparisons between studies difficult and partly explaining existing inconsistent results (Rabin et al., 2015).

Existing studies frequently used assessment tools for subjective memory impairments that were not comprehensive enough. Many studies have used a single „yes“ or „no“ questionnnaire to determine whether an individual experiences subjective cognitive impairments (Mitchell et al., 2014; Rabin et al., 2015). More comprehensive measurements of subjective cognitive impairments that focus on different contexts and are rated on an interval scale have shown to result in more reliable outcomes (Crumley et al., 2014; Rabin et al., 2015; Burmester et al., 2016). For example, a recently conducted longitudinal study could show that the extent of subjective cognitive impairments (low or high) played an important role for future cognitive performance (Snitz et al., 2015). In their conceptual framework for research on SCD, Jessen et al. (2014) also suggested to focus on subjective impairments in memory, rather than in other cognitive domains, as they are

assumed to increase the likelihood of preclinical dementia. Therefore, this study focused on memory impairments.

Additionally, when investigating the relationship between subjective cognitive impairments and cognitive performance, psychological characteristics need to be included. Depressive symptoms are argued to have the highest impact on subjective cognitive impairments and cognitive decline and are a possible risk factor for dementia (Jessen et al., 2014). Research suggested that individuals with depressive symptoms experience attentional biases towards negative information (Peckham et al., 2010). Based on this assumption elderly individuals with age-related changes in cognition and depressive symptoms may have a heightened sensitivity for their cognitive failures, which in turn may result in overreports of subjective cognitive impairments (Rabin et al., 2017). Longitudinal research also suggested the relationship between depressive symptoms and subjective cognitive impairment to be reciprocal (Hill et al., 2016), with higher subjective cognitive impairments at baseline predicting more future depressive symptoms and also more baseline depressive symptoms predicting higher subjective cognitive impairments at follow-up. Additionally, depressive symptoms are argued to be a prodrome and a risk factor for future cognitive decline, leading to dementia (da Silva, Goncalves-Pereira, Xavier, & Mukaetova-Ladinska, 2013). However, studies investigating the relationship of subjective cognitive impairments and future cognitive performance are not always including depressive symptoms in their designs, making comparisons across studies difficult (Burmester et al., 2016; Mendonça et al., 2016).

Existing research on subjective cognitive impairments was also heterogenous concerning the inclusion of confounding variables into their design, with studies partly or completely omitting variables known to have an effect and subjective cognitive impairments (Burmester et al., 2016; Mendonça et al., 2016). Research suggested to consider certain confounding variables that have shown to be related to subjective cognitive impairments in order to identify individuals who are at

risk for future cognitive decline (Rabin et al., 2017; Slavin et al., 2010). Sociodemographic characteristics like age, gender and education are argued to have an impact on the association between subjective cognitive impairments and cognitive decline. The effect was found to be stronger with proceeding age (Crumley et al., 2014; Jonker et al., 2000) and the likelihood for progression to MCI or AD was higher (Jessen et al., 2014). Regarding gender, females expressing subjective cognitive impairments were associated with a higher risk for the development of future dementia (Pérès et al., 2011). Furthermore, higher educated individuals with SCD showed greater risks for prospective cognitive decline (Aghjayan et al., 2017; Jonker et al., 2000; Mendonça et al., 2016). It is suggested that higher educated individuals are more likely to report subjective cognitive impairments due to a higher level of self-awareness and thus a higher sensitivity to subtle changes in their cognitive functions (Rabin et al., 2017).

Research question

Considering previous mentioned research attempts and results regarding subjective cognitive impairments and objective cognitive decline, the following research question was proposed: Are subjective memory impairments a valid predictor for future verbal memory performance?

The research question was addressed using longitudinal data of patients from a memory outpatient clinic. As suggested by Rabin et al. (2017) the data was analyzed using advanced statistical methods (structural equation modeling) in order to produce robust results. Subjective memory impairments were measured using a comprehensive questionnaire. Also, depressive symptoms were added to the design as a third variable of interest. Furthermore, confounding effects of age, gender and education were statistically controlled within the design.

Hypotheses

The study was aiming to replicate and validate the findings of Jorm, Christensen, Korten, Jacomb & Henderson (2001), who conducted a study using structural equation modeling techniques and a cross-lagged-panel-design with three waves to examine the relationship of subjective memory complaints, verbal memory and also negative affect. Results suggested the relationship between memory performance and memory complaints to be reciprocal, with baseline memory performance negatively affecting future memory complaints and vice versa (Jorm et al., 2001). Based on these results, our first two hypotheses of interest were:

H1: Baseline subjective memory impairments negatively affect follow-up verbal memory performance.

H2: Baseline verbal memory performance negatively affect follow-up subjective memory impairments.

Furthermore results of the study could show that negative affect was cross-sectionally correlated with memory complaints (Jorm et al., 2001). However the authors either removed pathways due to model modification indices or did not include pathways to other cross-sectional or follow-up variables in the first place (Jorm et al., 2001). Due to other more recent and reliable research outcomes (Hill et al., 2016), the hypotheses of interest for the relationship of subjective memory impairments with depressive symptoms were:

H3: Baseline subjective memory impairments positively affect follow-up depressive symptoms.

H4: Baseline depressive symptoms positively affect follow-up subjective memory impairments.

Furthermore, the study of Jorm et al. (2001) also had limitations concerning the assessment of variables of interest. The authors noted that subjective memory complaints and verbal memory performance might not have been assessed comprehensively enough and possible confounding variables were not considered, which both could have affected the results (Jorm et al., 2001). This study attempted to address these methodological issues, by using more thorough assessment methods.

The goal of this study was to overcome methodological issues of past research attempts and contribute to the growing body of literature regarding the predictive value of subjective cognitive impairments for future cognitive decline and progression to MCI or dementia in elderly individuals.

Methods

Sample

The used dataset is part of the Vienna Conversion to Dementia Study (VCD-Study), a larger research project with a broad scope. The VCD is an ongoing cohort study that consecutively encompasses community-dwelling patients who are concerned about their cognitive abilities and examined at a memory outpatient clinic for possible cognitive disorders.

All patients received a complete neurological examination, standard laboratory blood tests and psychometric testing. In most cases, a magnetic resonance imaging (MRI) scan of the brain was obtained. In determining significant cerebrovascular diseases, both neuroimaging and clinical patient features were used. All participants were subjected to the Neuropsychological Test Battery Vienna (NTBV) that includes attention, executive functioning, language, and memory domains

(Lehrner et al., 2007). Furthermore patients were offered to participate in follow-up assessments in order to determine the course of their cognitive abilities. These follow-up assessments were voluntary. A written informed consent was attained from each patient in order to use their data within the study.

Data was collected from January 2008 until March 2018. In total n = 1280 patients received a baseline assessment, n = 503 of which also received a follow-up assessment. Patients were excluded from the study if the follow-up assessment interval was outside of 12 to 48 months, if they had a dementia diagnosis at baseline or if their MMSE score was below 24 at baseline or follow-up. The reason for the last criteria is that subjects with high cognitive deteriorations would possibly not have had the necessary cognitive resources to complete the applied test- and questionnaire battery. Also, possible effect biases due to anosognosia were avoided by excluding subjects with an MMSE score below 24. Anosognosia is a phenomenon occuring in the course of dementia. It is defined as a deficit in self-awareness in one's own cognitive abilities (Cosentino, Metcalfe, Butterfield, & Stern, 2007). Individuals with anosognosia frequently neglect their cognitive deficits and overestimate their abilities, which adds to the complexity of the predictive value of subjective cognitive impairments, as with more cognitive decline and progression towards dementia, individuals are becoming less self-aware of their cognitive abilities and express less subjective impairments (Jessen et al., 2014; Mitchell et al., 2014). Researchers suggested there might be a time point at which subjective impairments have the highest predictive value for future cognitive decline (Mitchell et al., 2014), yet it is not entirely clear at what stage of the disease anosognosia occurs (Jessen et al., 2014). Some researchers proposed intact self-awareness for individuals with MCI (Kalbe et al., 2005), while others do not (Galeone, Pappalardo, Chieffi, Iavarone, & Carlomagno, 2010; Lehrner et al., 2015). Furthermore, a subsample of n = 103

healthy controls was also included in the sample, since healthy individuals are underlying normal age related cognitive deteriorations as well (Deary et al., 2009). After applying these criteria, the sample consisted of *n* = 307 subjects. The mean age of the sample was 66.69 years (SD = 8.07), 58% were male, 42% were female. The participants had a mean of 12.28 years (SD = 4.18) of education. The mean interval between baseline and follow-up assessment was 28.22 months (SD = 11.54). At baseline assessment, *n* = 34 subjects had a SCD diagnosis, *n* = 170 subjects had a MCI diagnosis and *n* = 103 subjects were healthy controls. Figure 1 displays conversion rates of diagnostic groups from baseline to follow-up assessment.

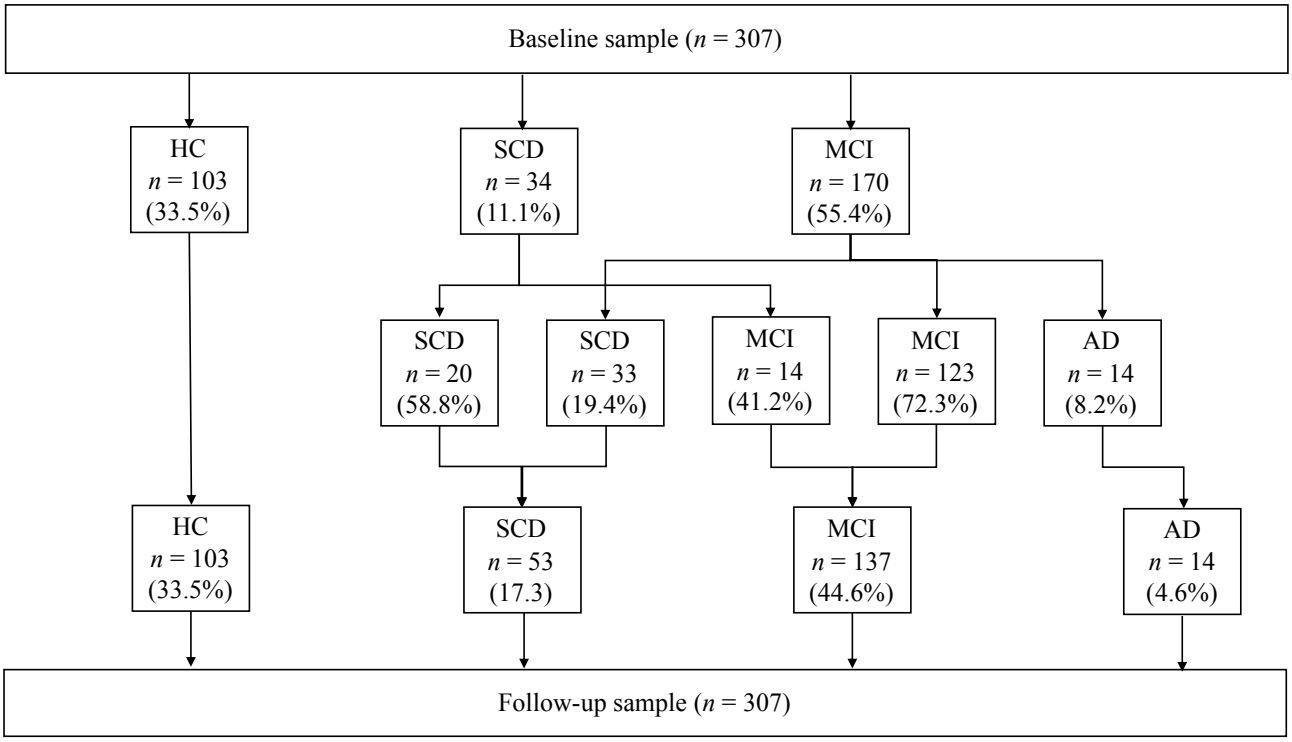

Figure 1. Conversion rates of diagnostic groups from baseline to follow-up assessment; HC = Healthy Controls, SCD = Subjective cognitive decline, MCI = Mild cognitive impairment, AD = Alzheimer's disease.

Assignment to the diagnostic groups (SCD and MCI):

SCD was defined by individuals having subjective impairments in memory and an objective cognitive performance with an age-, sex- and education-adjusted mean z-score of each cognitive domain greater than -1.5 standard deviations on the NTBV. MCI criteria were set out as follows (Petersen, 2011): (a) patients or/and their families report subjective memory impairments, (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., 1996).

Assessment of subjective memory impairments

Subjective memory impairments were assessed using the Forgetfulness Assessment Inventory (FAI) (Lehrner, et al., 2014). The FAI is a self-report questionnaire, consisting of sixteen items measuring the subjects perception of change in the past four weeks in specific memory related domains of everyday life. Items are scored on a 5-point-likert-scale ranging from 1 (never) to 5 (very often). For the statistical analysis an average score of all 16 items was used with higher scores indicating more self-reported cognitive impairments. The FAI showed good internal consistency with $\alpha = .93$ (Lehrner et al., 2014).

Assessment of depressive symptoms

Depressive Symptoms were assessed using the Beck Depression Inventory (BDI-II; Beck, Steer, Brown, 1996) and the Geriatric Depression Scale (GDS; Sheikh, & Yesavage, 1986). The BDI-II is a 21-item questionnaire detecting depressive symptoms in adults. It asks about how often subjects felt certain ways within the past two weeks, rated on a four-point scale. The total score takes values from 0 to 63, with higher scores indicating more depressive symptoms. The internal

consistency ranges from α = .89 to α = .93. The test-retest reliability was reported to be *r* = .78 (Hautzinger et al., 2006).

The GDS is a 15-item self-report questionnaire aimed at assessing depressive symptomatology specifically in elderly people. Subjects respond to questions regarding depressive symptoms in a „yes or no“ format. Out of the 15 items, 10 indicate the presence of depression when answered positively while the other five are indicative of depression when answered negatively. The total score ranges from 0 to 15 with higher scores being indicative for more depressive symptoms. A meta-analysis reported a mean internal consistency coefficient of α = .85 and a test-retest reliability of *r* = .83 (Kieffer & Reese, 2002).

Assessment of verbal memory performance

Verbal memory performance was measured using the immediate (IR) and delayed recall (DR) task of the Verbal Selective Reminding Test (VSRT; Lehrner et al., 2006). Subjects are instructed to recall a grocery list including 15 items immediately and 20 minutes after a learning phase. The two subscales range from 0 to 15, the score equals the total words remembered. The test-retest reliability with a 1 year interval was reported to be *r* = .67 for the immediate recall task and *r* = .67 for the delayed recall task (Lehrner et al., 2006).

Statistical analysis

The statistical analysis of the data was conducted using SPSS 24 and SPSS AMOS 24. The maximum likelihood method was used to estimate the model parameters. The adequacy of the model fit was assessed using the root mean-square error of approximation (RMSEA), the comparative fit index (CFI) and the Tucker-Lewis index (TLI). Acceptable model fit is indicated by

RMSEA < 0.08 and CFI and TLI > .90 (Hu & Bentler, 1999). Path coefficients with *p*-values < .05 were considered to be statistically significant.

The proposed model shown in figure 2 is a two-wave-three-variable cross-lagged-panel-design. Shown on the left side are the main variables of interest at baseline assessment, on the right side at follow-up assessment. The covariances between error terms at baseline and follow-up were cross-sectional correlations. Longitudinal pathways of the same variable from baseline to follow-up (i.e. Depressive Symptoms T1 to Depressive Symptoms T2) were indicating the stability of the variables of interest respectively. Longitudinal pathways of one variable at baseline to another variable at follow-up (i.e. Depressive Symptoms T1 to Subjective Memory Impairments T2 or Verbal Memory Performance T2) were direct effects. If any direct effects reached significance, they were considered to indicate possible causality. Furthermore, depressive symptoms and verbal memory were treated as latent variables. BDI and GDS total scores were used as manifest indicator variables for depressive symptoms at both measurements points. The scores of the immediate and delayed recall task were used to indicate verbal memory performance at both time points. This approach allowed to account for measurement errors. Subjective memory impairments were treated as a manifest variable, as only total scores and not single items were available for the analysis.

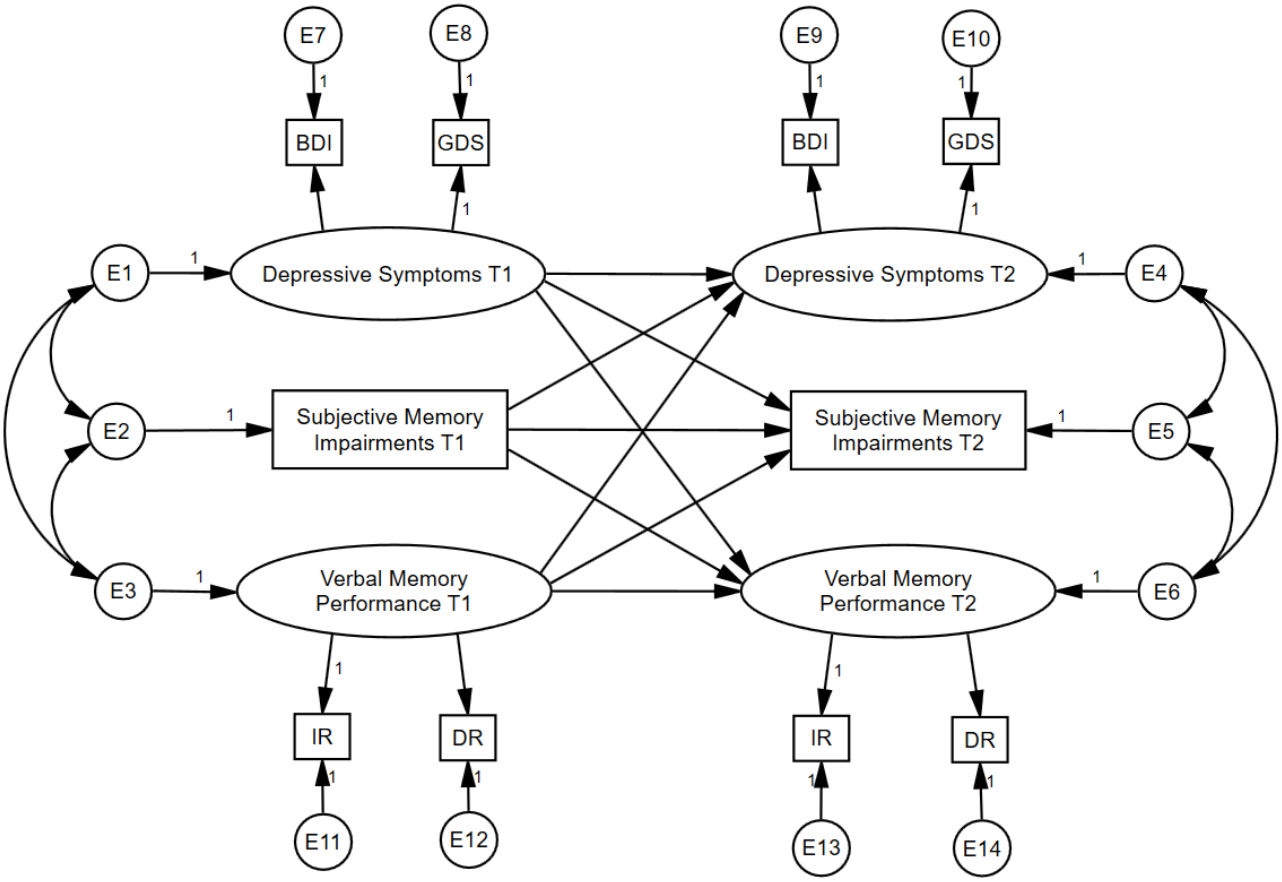

Figure 2. Conceptual structural equation model; T1 = Baseline; T2 = Follow-up; BDI = Beck Depression Inventory, GDS = Geriatric Depression Scale, IR = Immediate Recall, DR = Delayed Recall.

The model shown in figure 2 is a conceptual model, the actual statistical model used for the parameter estimates can be found in the appendix (figure 4). The statistical model also incorporated the statistical control for effects of confounding variables.

Results

Table 1 shows the results for relevant psychometric measurements and questionnaires at baseline and follow up.

Table 1

Mean, standard deviation and number of observations for relevant psychometric tests and questionnaires at baseline and follow-up assessment

	Baseline			Follow-up		
	Mean	***SD***	***n****	**Mean**	***SD***	***n****
FAI	2.76	0.74	302	2.72	0.73	290
BDI	8.92	7.60	302	8.69	7.24	307
GDS	2.90	3.11	305	2.84	3.09	306
VSRT Immediate Recall	8.05	2.05	307	7.40	2.24	307
VSRT Delayed Recall	10.11	3.07	307	9.68	3.79	307

Note. *Variables with missing values were excluded for the calculation of means and standard deviations.

The chi-square-test of the model reached significance ($\chi 2 = 98.762$, $df = 43$, $p < .001$). However, the model was not modified based on this fit index, since chi-square is sensitive to sample size. Other fit indices reached the prescribed standards for an acceptable model fit (RMSEA = .065, CFI = .968, TLI = .932), indicating the model fitted the data. Figure 3 displays the model with significant pathways, standardized regression weights and factor loadings. Pathways that did not reach significance were excluded for a clearer representation of the model. Missing values were estimated using full information maximum likelihood methods (FIML), since they were assumed to be missing at random (MAR).

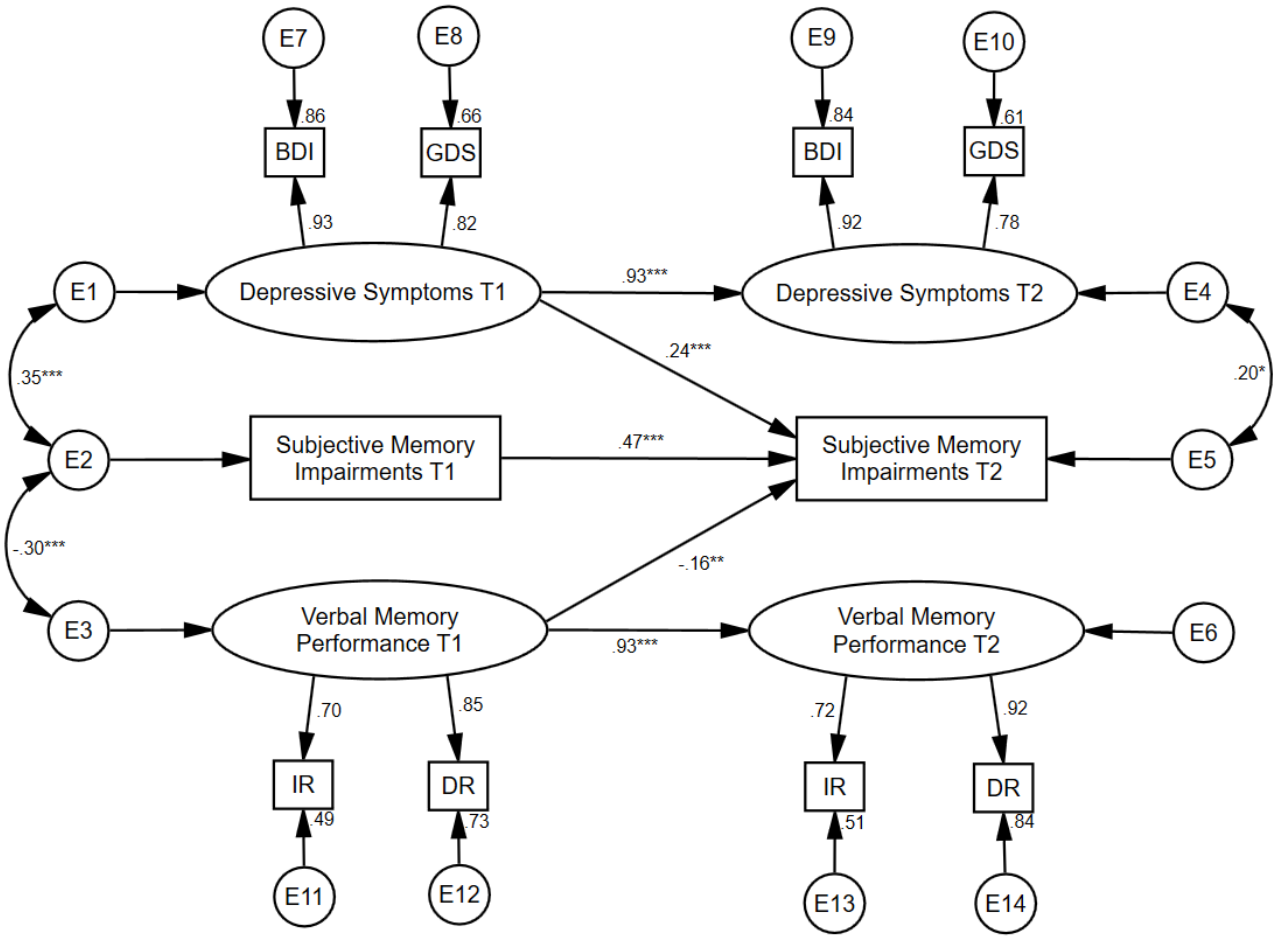

Figure 3. Structural equation model with estimated standardized regression weights of statistically significant pathways and regression weights of latent variables; T1 = Baseline; T2 = Follow-up; BDI = Beck Depression Inventory, GDS = Geriatric Depression Scale, IR = Immediate recall, DR = Delayed recall.

The factor loadings for depressive symptoms at baseline and follow-up as well as for verbal memory performance at baseline and follow-up were all acceptably high with rates of .70 to .93.

Subjective memory impairments were significantly correlated with depressive symptoms (r = .35, p < .001) and verbal memory performance (r = -.30, p < .001) at baseline. At follow-up only depressive symptoms were significantly correlated with subjective memory impairments (r = .20,

p = .040). Depressive symptoms and verbal memory performance showed high stability over time respectively (β = .93, p < .001 for both variables). Subjective memory impairments were not as stable as the other two variables (β = .47, p < .001).

Regarding longitudinal cross pathways, baseline depressive symptoms positively predicted subjective memory impairments at follow-up (β = .24, p < .001) and baseline verbal memory performance negatively predicted subjective memory impairments at follow up (β = -.16, p < .001). Baseline subjective memory impairments had no significant cross-lagged effect on follow-up depressive symptoms or verbal memory performance.

Concerning direct effects of confounding variables on baseline variables, age had a significant positive effect on subjective memory impairments at baseline (β = .05, p = .005) and a negative effect on verbal memory performance (β = -.46, p < .001). Gender significantly affected depressive symptoms (β = .17, p = .003) and verbal memory (β = .16, p = .004). At last, education had no significant influence on any baseline variable. An overview of the regression weights, correlations and significance levels of the model can be found in the appendix (see: Table 2).

Discussion

Cross-lagged-panel designs can be used as a method to test causal relationships between two or more variables (Kearney, 2017). Although some researchers suggest that two waves might not be sufficient for causal claims (Singer & Willett, 2003), they can be used to make first careful assumptions about the causal order of the examined variables (Kenny, 2005). In this study, the significant longitudinal pathways are also used to indicate the effective direction for the significant cross-sectional correlations. The results support the hypothesis that subjective memory impairments are influenced by present and also past depressive symptoms, meaning that participants with more depressive symptoms also express more subjective memory impairments. This result is consistent

with existing literature (Hill et al., 2016; Jorm et al., 2001) and research suggests there could be an attentional bias towards negative information in individuals with depressive symptoms (Peckham et al., 2017), leading to higher reports of subjective memory impairments (Rabin et al., 2017).

Furthermore, the results support the hypothesis that subjective memory impairments reflect present and also past verbal memory performance, showing that subjects had some degree of insight into their own memory functions and abilities (Burmester et al., 2016; Jorm et al., 2001; Snitz et al., 2015). It is important to note that the correlation between verbal memory performance and subjective memory impairments was only significant at baseline (r = -.30, p < .001) and not follow-up (r = -.21, p = .058). Although it was only barely not significant at follow-up, the missing correlation in our model might be explained by patients losing insight into their cognitive abilities over the course of time. This phenomenon known as anosognosia frequently occurs in patients with age-related cognitive deteriorations and need to be considered when researching subjective insights to cognitive performances (Cosentino et al., 2007; Jessen et al., 2014; Lehrner et al., 2015; Rabin et al., 2017).

Baseline subjective memory impairments were not predictive for future verbal memory performance nor depressive symptoms. This result is inconsistent with existing literature findings that have reliably linked these two variables in longitudinal study settings, with more subjective impairments predicting future objective impairments (Jonker et al., 2000; Jorm et al., 2001; Mendonça et al., 2016; Mitchell et al., 2014; Reid et al., 2006; Snitz et al., 2015). One possible explanation for the missing relationship could be the statistical control for confounding variables within the model which revokes the effect of subjective memory impairments on verbal memory performance. However, this would imply that the effect would not be existing. Given the amount of longitudinal studies that have already linked subjective memory impairments and verbal memory performance, this tends to be somewhat unlikely. Another possible explanation might lie

within the study's design and the methods used. The comprehensiveness and robustness of measurement tools and the advanced statistical analysis might have caused the effect not to be significant. A third and most likely explanation is, that our sample was biased due to the selection of participants. On the one hand, participants dropped out because the second examination was voluntary. Therefore, participants with greater cognitive deteriorations might not have attended the second examination because they possibly felt unable to complete the assessment. On the other hand, participants were excluded from the study if their MMSE score was below 24. This implies that participants with high cognitive deteriorations and possibly also with high subjective memory impairments were excluded from the study by default. Although the exclusion of participants with high cognitive deteriorations was due to profound reasons, such as feasibility, ethical considerations and loss of insight, this is a strong limitation to this study.

Conclusively and to answer our proposed research question, statements on subjective memory did not seem to be a valid predictor for future verbal memory performance and seemed to be more likely based on individuals present and past verbal memory performance and depressive symptoms.

The study had several limitations that must be acknowledged. Besides the selection bias, the design did not control for possible time effects of different measurement intervals. It is likely that time plays an important role between the relationships of subjective and objective cognition, since age is one of the greatest risk factors for cognitive deteriorations (WHO, 2017). Hence it is possible that subjects observed after 12 months have different outcomes in the observed variables than subjects observed after 48 months. However, significant effects might be considered as especially robust when they are demonstrable despite time intervals of varying length (Oud, 2002). A differentiation between the diagnostic groups (HC, SCD, MCI) was not possible, since the individual group sample sizes of n = 103 (HC), n = 34 (SCD) and n = 170 (MCI) were too small

and too unequal to calculate separate models for group comparisons. Lastly, the study was conducted in a clinical setting and participants were patients who were either concerned with their cognitive abilities or referred by a doctor. Hence, it is not clear to what extent the results can be transferred from clinical to community settings. Furthermore, the study only focused on subjective impairments and objective performance in memory and not on other domains on cognition, whereas the diagnostic criteria for SCD is not restricted to memory and also symptoms of dementia are not limited to decline in memory (Jessen et al., 2014). In the case of this study memory was chosen, as research offers the most evidence for an association with preclinical AD (Jessen et al., 2014). However, further research using other domains of cognition should be considered, as it would offer additional information on SCD and future cognitive decline. In summary the results of this study might not be generalized and should be interpreted with caution.

Despite the limitations, our study also had several strengths. First, verbal memory performance, subjective memory impairments and depressive symptoms were very thoroughly and comprehensively assessed, using standardized, reliable and validated questionnaires and measurement tools. Furthermore, we used robust structural equation modeling techniques within a longitudinal research design that offered possible causal relationships for the observed variables. Moreover we included and statistically controlled effects of confounding variables.

Future research should consider the limitations of this study while aiming to replicate its findings with similar methods. The aforementioned selection bias of the study could have had a great effect on the results, since patients with an MMSE score below 24 were excluded. Future research should focus on finding a solution to longitudinally examine elderly subjects who show greater cognitive deteriorations over the course of time, while simultaneously excluding patients with anosognosia. This could be done by comparing self and informant evaluations about patients general cognitive or memory abilities for example. Standardized tests are already available to

examine the extent of anosognosia for language impairments (VATA-L; Cocchini, Gregg, Beschin, Dean, & Sala, 2010) or motor impairments (MOTOR-M; Sala, Cocchini, Beschin, & Cameron, 2009), however a standardized test for anosognosia in general cognition or only memory domains has not been developed to the author's knowledge. Since we did not control for possible effects of different time intervals from baseline to follow-up assessment, future research should take this into consideration and evaluate differences between the results. Future research should also consider using different memory tasks. Episodic memory tasks, as used in this study, are dependent on a number of different factors that can confound the results, such as attention, executive functions and motivational variables (Lehrner et al., 2017). Furthermore, episodic memory tasks can be more frustrating for participants to complete, since low performance is immediately noticed and understood as a deficiency to acquire new information (Lehrner et al., 2017). Semantic memory tasks on the other hand, have proven to be a successful predictor for dementia, have less confounding variables and participants may attribute low performances on semantic memory tasks, indicating cognitive deteriorations and possible dementia, to a feeling of „unknowing" (i.e. something the participant has never learned) and are therefore less frustrated after completion (Lehrner et al., 2017). Furthermore, a larger sample with more subjects in different diagnostic domains is needed to compare effects of different diagnoses. Additionally, since the data of this research was taken from a larger study with a broader scope many different test procedures and questionnaires, future research should try to minimize the subjects effort by reducing the measurements to a minimum that is needed to answer their research questions. Concerning effects of third variables, there are additional confounding variables that were not taken into account in our study. For example research suggested neuroticism to have an effect on subjective memory impairments, as people with high neuroticism tend to be overly concerned with their cognitive abilities (Rabin et al., 2017). Furthermore, two waves are argued not to be sufficient enough for

causal statements (Singer & Willett, 2003) and studies with three or more waves can offer more information about causal relationships. Lastly, research should consider examining SCD in the context of other domains of cognition rather than in memory. In general, additional research is needed to clarify and validate the results of this study.

References

Aghjayan, S. L., Buckley, R. F., Vannini, P., Rentz, D. M., Jackson, J. D., Sperling, R. A., … Amariglio, R. E. (2017). The influence of demographic factors on subjective cognitive concerns and beta-amyloid. *International Psychogeriatrics, 29*(4), 645–652. https://doi.org/10.1017/S1041610216001502

Beck, A.T., Steer, R.A., & Brown, G.K. (1996). *Manual for the Beck Depression Inventory-II*. San Antonio, TX: Psychological Corporation

Burmester, B., Leathem, J., & Merrick, P. (2016). Subjective cognitive complaints and objective cognitive function in aging: a systematic review and meta-analysis of recent cross-sectional findings. *Neuropsychology Review, 26*(4), 376–393. https://doi.org/10.1007/s11065-016-9332-2

Crumley, J. J., Stetler, C. A., & Horhota, M. (2014). Examining the relationship between subjective and objective memory performance in older adults: A meta-analysis. *Psychology and Aging, 29*(2), 250–263. https://doi.org/10.1037/a0035908

Cocchini, G., Gregg, N., Beschin, N., Dean, M., & Sala, S. D. (2010). Vata-L: Visual-Analogue Test Assessing Anosognosia for Language Impairment. *The Clinical Neuropsychologist, 24*(8), 1379–1399. https://doi.org/10.1080/13854046.2010.524167

Cosentino, S., Metcalfe, J., Butterfield, B., & Stern, Y. (2007). Objective metamemory testing captures awareness of deficit in alzheimer's disease. *Cortex, 43*(7), 1004–1019. https://doi.org/10.1016/S0010-9452(08)70697-X

da Silva, J., Goncalves-Pereira, M., Xavier, M., & Mukaetova-Ladinska, E. B. (2013). Affective disorders and risk of developing dementia: systematic review. *The British Journal of Psychiatry, 202*(3), 177–186. https://doi.org/10.1192/bjp.bp.111.101931

Deary, I. J., Corley, J., Gow, A. J., Harris, S. E., Houlihan, L. M., Marioni, R. E., … Starr, J. M. (2009). Age-associated cognitive decline. *British Medical Bulletin, 92*(1), 135–152. https://doi.org/10.1093/bmb/ldp033

Dilling, H., Mombour, W., Schmidt, M. H., & World Health Organization. (1991). *Internationale Klassifikation psychischer Störungen: ICD-10, Kapitel V (F, klinisch-diagnostische Leitlinien.)*

Ferreira, D., Falahati, F., Linden, C., Buckley, R. F., Ellis, K. A., Savage, G., … Westman, E. (2017). A "disease severity index" to identify individuals with subjective memory decline who will progress to mild cognitive impairment or dementia. *Scientific Reports, 7.* https://doi.org/10.1038/srep44368

Galeone, F., Pappalardo, S., Chieffi, S., Iavarone, A., & Carlomagno, S. (2010). Anosognosia for memory deficit in amnestic mild cognitive impairment and Alzheimer's disease. *International Journal of Geriatric Psychiatry*, *26*(7), 695–701. https://doi.org/10.1002/gps.2583

Gauthier, S., Reisberg, B., Zaudig, M., Petersen, R. C., Ritchie, K., Broich, K., … Winblad, B. (2006). Mild cognitive impairment. *The Lancet, 367*(9518), 1262–1270. https://doi.org/10.1016/S0140-6736(06)68542-5

Hautzinger, M., Keller, F., & Kühner, C. (2006). *Beck Depressions-Inventar (BDI-II)*. Frankfurt: Harcourt.

Hill, N. L., Mogle, J., Wion, R., Munoz, E., DePasquale, N., Yevchak, A. M., & Parisi, J. M. (2016). Subjective cognitive impairment and affective symptoms: a systematic review. *The Gerontologist, 56*(6), e109–e127. https://doi.org/10.1093/geront/gnw091

Hu, L. T., & Bentler, P. M. (1999). Cutoff criteria for fit indexes in covariance structure analysis: Conventional criteria versus new alternatives. *Structural equation modeling: a multidisciplinary journal, 6*(1), 1-55.

Jessen, F. (2014). Subjective and objective cognitive decline at the pre-dementia stage of alzheimer's disease. *European Archives of Psychiatry and Clinical Neuroscience, 264*(1), 3–7. https://doi.org/10.1007/s00406-014-0539-z

Jessen, F., Amariglio, R. E., van Boxtel, M., Breteler, M., Ceccaldi, M., Chételat, G., … Wagner, M (2014). A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association, 10*(6), 844–852. https://doi.org/10.1016/j.jalz.2014.01.001

Jessen, F., Wiese, B., Bachmann, C., Eifflaender-Gorfer, S., Haller, F., Kölsch, H., … Bickel, H. (2010). Prediction of dementia by subjective memory impairment: effects of severity and temporal association with cognitive impairment. *Archives of General Psychiatry, 67*(4), 414–422. https://doi.org/10.1001/archgenpsychiatry.2010.30

Jonker, C., Geerlings, M. I., & Schmand, B. (2000). Are memory complaints predictive for dementia? A review of clinical and population-based studies. I*nternational Journal of Geriatric Psychiatry, 15*(11), 983–991.

Jorm, A., Christensen, H., Korten, A., Jacomb, P., & Henderson, A. (2001). Memory complaints as a precursor of memory impairment in older people: A longitudinal analysis over 7-8 years. *Psychological Medicine, 31*(3), 441–449.

Kalbe, E., Salmon, E., Perani, D., Holthoff, V., Sorbi, S., Elsner, A., … Herholz, K. (2005). Anosognosia in very mild Alzheimer's disease but not in mild cognitive impairment. *Dementia and Geriatric Cognitive Disorders*, *19*(5–6), 349–356. https://doi.org/10.1159/000084704

Kearney, M. W. (2017). Cross Lagged Panel Analysis. In M. R. Allen (Ed.), *The SAGE Encyclopedia of Communication Research Methods*. Thousand Oaks, CA: Sage.

Kenny, D. A. (2005). Cross-Lagged Panel Design. In *Encyclopedia of Statistics in Behavioral Science*. American Cancer Society. https://doi.org/10.1002/0470013192.bsa156

Kieffer, K.M., & Reese, R.J. (2002) A reliability generalization study of the Geriatric Depression Scale. *Educational and Psychological Measurement, 62*(6), 969–994.

Lehrner, J., Coutinho, G., Mattos, P., Moser, D., Pflüger, M., Gleiss, A., … Stögmann, E. (2017). Semantic memory and depressive symptoms in patients with subjective cognitive decline, mild cognitive impairment, and Alzheimer's disease. *International Psychogeriatrics, 29*(7), 1123–1135. https://doi.org/10.1017/S1041610217000394

Lehrner, J., Gleiß, A., Maly, J., Auff, E., & Dal-Bianco, P. (2006). Der Verbale Selektive Reminding Test (VSRT). Ein Verfahren zur Überprüfung verbaler Gedächtnisfunktionen. *Neuropsychiatrie, 20*, 204–214

Lehrner, J., Kogler, S., Lamm, C., Moser, D., Klug, S., Pusswald, G., … Auff, E. (2015). Awareness of memory deficits in subjective cognitive decline, mild cognitive impairment, Alzheimer's disease and Parkinson's disease. *International Psychogeriatrics*, 27(03), 357–366. https://doi.org/10.1017/S1041610214002245

Lehrner, J., Maly, J., Gleiß, A., Auff, E., & Dal-Bianco, P. (2007). The Vienna Neuropsychological Test Battery (VNTB) for detecting dementia – standardization, norms, and validation. *Psychologie in Österreich, 4 & 5*, 358–365.

Lehrner, J., Moser, D., Klug, S., Gleiß, A., Auff, E., Dal-Bianco, P., & Pusswald, G. (2014). Subjective memory complaints, depressive symptoms and cognition in patients attending memory outpatient clinic. *International Psychogeriatrics, 26*(3), 463–473. https://doi.org/10.1017/S1041610213002263

Mendonça, M. D., Alves, L., & Bugalho, P. (2016). From subjective cognitive complaints to dementia: who is at risk?: a systematic review. *American Journal of Alzheimer's Disease & Other Dementias, 31*(2), 105–114. https://doi.org/10.1177/1533317515592331

Mitchell, A. J., Beaumont, H., Ferguson, D., Yadegarfar, M., & Stubbs, B. (2014). Risk of dementia and mild cognitive impairment in older people with subjective memory complaints: meta-analysis. *Acta Psychiatrica Scandinavica, 130*(6), 439–451. https://doi.org/10.1111/acps.12336

Oud, J. H. L. (2002): Continuous time modeling of the cross-lagged-panel-design. In: Kwantitatieve Methoden, 69, S. 1-26.

Pérès, K., Helmer, C., Amieva, H., Matharan, F., Carcaillon, L., Jacqmin-Gadda, H., … Dartigues, J.-F. (2011). Gender differences in the prodromal signs of dementia: memory complaint and IADL-restriction: a prospective population-based cohort. *Journal of Alzheimer's Disease, 27*(1), 39–47. https://doi.org/10.3233/JAD-2011-110428

Petersen, R. C. (2004). Mild cognitive impairment as a diagnostic entity. *Journal of Internal Medicine, 256*(3), 183–194. https://doi.org/10.1111/j.1365-2796.2004.01388.x

Petersen, R. C. (2011). Mild cognitive impairment. *The New England Journal of Medicine*, *364*, 2227 – 2234.

Petersen, R. C., Smith, G. E., Waring, S. C., Ivnik, R. J., Tangalos, E. G., & Kokmen, E. (1999). Mild cognitive impairment: clinical characterization and outcome. *Archives of Neurology, 56*(3), 303–308. https://doi.org/10.1001/archneur.56.3.303

Rabin, L. A., Smart, C. M., & Amariglio, R. E. (2017). Subjective cognitive decline in preclinical alzheimer's disease. *Annual Review of Clinical Psychology, 13*(1), 369–396. https://doi.org/10.1146/annurev-clinpsy-032816-045136

Rabin, L. A., Smart, C. M., Crane, P. K., Amariglio, R. E., Berman, L. M., Boada, M., … Sikkes, S. A. M. (2015). Subjective cognitive decline in older adults: an overview of self-report measures used across 19 international research studies. *Journal of Alzheimer's Disease: JAD, 48*(0 1), 63–86. https://doi.org/10.3233/JAD-150154

Reid, L. M., & MacLullich, A. M. J. (2006). Subjective memory complaints and cognitive impairment in older people. *Dementia and Geriatric Cognitive Disorders, 22*(5–6), 471–485. https://doi.org/10.1159/000096295

Sala, S. D., Cocchini, G., Beschin, N., & Cameron, A. (2009). VATA-M: Visual analogue test assessing anosognosia for motor impairment. *The Clinical Neuropsychologist, 23*(3), 406–427. https://doi.org/10.1080/13854040802251393

Saß, H., Wittchen, H. U., & Zaudig, M. (1996). *Diagnostisches und statistisches Manual psychischer Störungen-DSM-IV.* Deutsche Bearbeitung u. Einleitung von H. Sass, H.-U. Wittchen, M. Zaudig.

Scheltens, P., Blennow, K., Breteler, M. M. B., de Strooper, B., Frisoni, G. B., Salloway, S., & Van der Flier, W. M. (2016). Alzheimer's disease. *The Lancet, 388*(10043), 505–517. https://doi.org/10.1016/S0140-6736(15)01124-1

Sheikh, J. I., & Yesavage, J. A. (1986). Geriatric Depression Scale (GDS): Recent evidence and development of a shorter version. Clinical Gerontologist, 5, 165-173.

Singer, J. D. & Willett, J. B. (2003). *Applied Longitudinal Data Analysis: Modeling Change and Event Occurrence*. Oxford University Press: New York.

Slavin, M. J., Brodaty, H., Kochan, N. A., Crawford, J. D., Trollor, J. N., Draper, B., & Sachdev, P. S. (2010). Prevalence and predictors of "subjective cognitive complaints" in the sydney memory and ageing Study. *The American Journal of Geriatric Psychiatry*, *18*(8), 701–10.

Snitz, B. E., Small, B. J., Wang, T., Chang, C.-C. H., Hughes, T. F., & Ganguli, M. (2015). Do Subjective memory complaints lead or follow objective cognitive change? A five-year population study of temporal influence. *Journal of the International Neuropsychological Society, 21*(9), 732–742. https://doi.org/10.1017/S1355617715000922

Winblad, B., Amouyel, P., Andrieu, S., Ballard, C., Brayne, C., Brodaty, H., … Zetterberg, H. (2016). Defeating alzheimer's disease and other dementias: a priority for european science and society. *The Lancet Neurology, 15*(5), 455–532. https://doi.org/10.1016/S1474-4422(16)00062-4

World Health Organization (2017). *Dementia*. [online] Available at: http://www.who.int/mediacentre/factsheets/fs362/en/ [Accessed 24 Sep. 2017].

List of Tables

List of Figures

List of Abbreviations

AD	Alzheimer's disease
BDI	Beck Depression Inventory
CFI	Comparative fit index
DR	Delayed recall task of the Verbal Selective Reminding Test
FAI	Forgetfulness Assessment Inventory
FIML	Full information maximum likelihood
GDS	Geriatric Depression Scale
HC	Healthy controls
IR	Immediate recall task of the Verbal Selective Reminding Test

MAR	Missing at random
MCI	Mild cognitive impairment
MMSE	Mini Mental State Examination
MRI	Magnetic resonance imaging
NTBV	Neuropsychological Test Battery Vienna
RMSEA	Root mean square error of approximation
SCD	Subjective cognitive decline
SD	Standard deviation
T1	Timepoint 1 (Baseline)
T2	Timepoint 2 (Follow-up)
TLI	Tucker-Lewis index
VSRT	Verbal Selective Reminding Test
VCD	Vienna Conversion to Dementia Study

Appendix

Abstract

Background: Subjective cognitive decline is suggested to be the first stage of dementia and associated with future cognitive decline. Research also identified depressive symptoms to have an affect on this relationship. However, past research on this association is marked by high heterogeneity within the studies definitions of constructs, designs and methods. **Objectives:** The present study tries to overcome past methodological issues by using a longitudinal two-wave cross-lagged model and reliable measurements to examine if subjective memory impairments are a valid predictor for future verbal memory performance. **Methods:** Data of a sample of patients of a memory outpatient clinic was used for the study. Subjective memory impairments, verbal memory performance and depressive symptoms were assessed at a time interval between 12 and 48 months. 307 participants had data on relevant variables. The data was analyzed using structural equation modeling techniques. **Results:** Significant paths were found from baseline memory performance and baseline depressive symptoms to future subjective cognitive decline, supporting hypotheses 2 and 4. Subjective memory impairments were not associated with future verbal memory performance or depressive symptoms. Baseline subjective memory impairments were negatively correlated with baseline verbal memory performance and positively correlated with baseline depressive symptoms. Follow-up subjective memory impairments were positively correlated with depressive symptoms only. **Conclusion:** The results indicate that statements on subjective memory did not seem to be a valid predictor for future verbal memory performance and were more likely based on individuals present and past verbal memory performance and depressive symptoms. However, the study had limitations that reduce the generalizability of these findings.

Keywords: Subjective cognitive decline, Subjective memory impairments, Mild cognitive impairment, Alzheimer's disease, dementia, Structural equation modeling, depressive symptoms, verbal memory

Zusammenfassung

Hintergrund: Subjektive kognitive Einschränkungen werden als frühes Stadium der Demenz angesehen und sind mit zukünftigen objektiven kognitiven Einschränkungen assoziiert. Darüber hinaus konnten bisherige Studien zeigen, dass depressive Symptome einen Einfluss auf diesen Zusammenhang haben. Bisherige Forschungsarbeiten zu diesen Zusammenhängen sind jedoch durch eine hohe Heterogenität in ihren Methoden gekennzeichnet. **Ziele:** Um die methodologischen Limitationen vergangener Studien zu berücksichtigen, verwendete die vorliegenden Studie ein längsschnittliches Studiendesign (Cross-Lagged-Panel-Design) und reliable Messmethoden für die jeweiligen Variablen. Es wurde die Forschungsfrage untersucht, ob subjektive Gedächtnisstörungen ein valider Prädiktor für die zukünftige verbale Gedächtnisleistung sind. **Methoden:** Die Daten entstammen einer großen Stichprobe von PatientInnen einer Gedächtnisambulanz. Subjektive Gedächtnisstörungen, verbale Gedächtnisleistung und depressive Symptome der TeilnehmerInnen wurden in einem Zeitintervall zwischen 12 und 48 Monaten erhoben. Insgesamt hatten 307 StudienteilnehmerInnen Daten zu relevanten Variablen, welche mittels Strukturgleichungsmodell analysiert wurden. **Ergebnisse:** Die verbale Gedächtnisleistung bei Baseline war ein signifikant negativer Prädiktor für zukünftige subjektive Gedächtnisstörungen. Depressive Symptome bei Baseline waren ein signifikant positiver Prädiktor für zukünftige subjektive Gedächtnisstörungen. Subjektive Gedächtnisstörungen bei Baseline hatten keinen signifikanten Einfluss auf zukünftige depressive Symptome oder die verbale Gedächtnisleistung. Die subjektiven Gedächtnisstörungen bei Baseline korrelierten signifikant positiv mit depressiven Symptomen und signifikant negativ mit

verbaler Gedächtnisleistung. Die subjektiven Gedächtnisstörungen bei der Folgeuntersuchungen war lediglich signifikant negativ mit depressiven Symptomen korreliert und nicht mit der verbalen Gedächtnisleistung. **Schlussfolgerung:** Die Ergebnisse weisen darauf hin, dass Aussagen zum subjektiven Gedächtnis kein gültiger Prädiktor für die zukünftige verbale Gedächtnisleistung zu sein scheinen und diese eher auf der gegenwärtigen und früheren verbalen Gedächtnisleistung und Ausprägung der depressiven Symptome beruht. Die Studie hatte nennenswerte Einschränkungen, die die Generalisierbarkeit der Befunde reduzieren.

Schlüsselwörter: Subjektive kognitive Einschränkungen, Subjektive Gedächtnisstörung, leichte kognitive Störung, Alzheimer Krankheit, Demenz, Strukturgleichungsmodell, depressive Symptome, verbales Gedächtnis

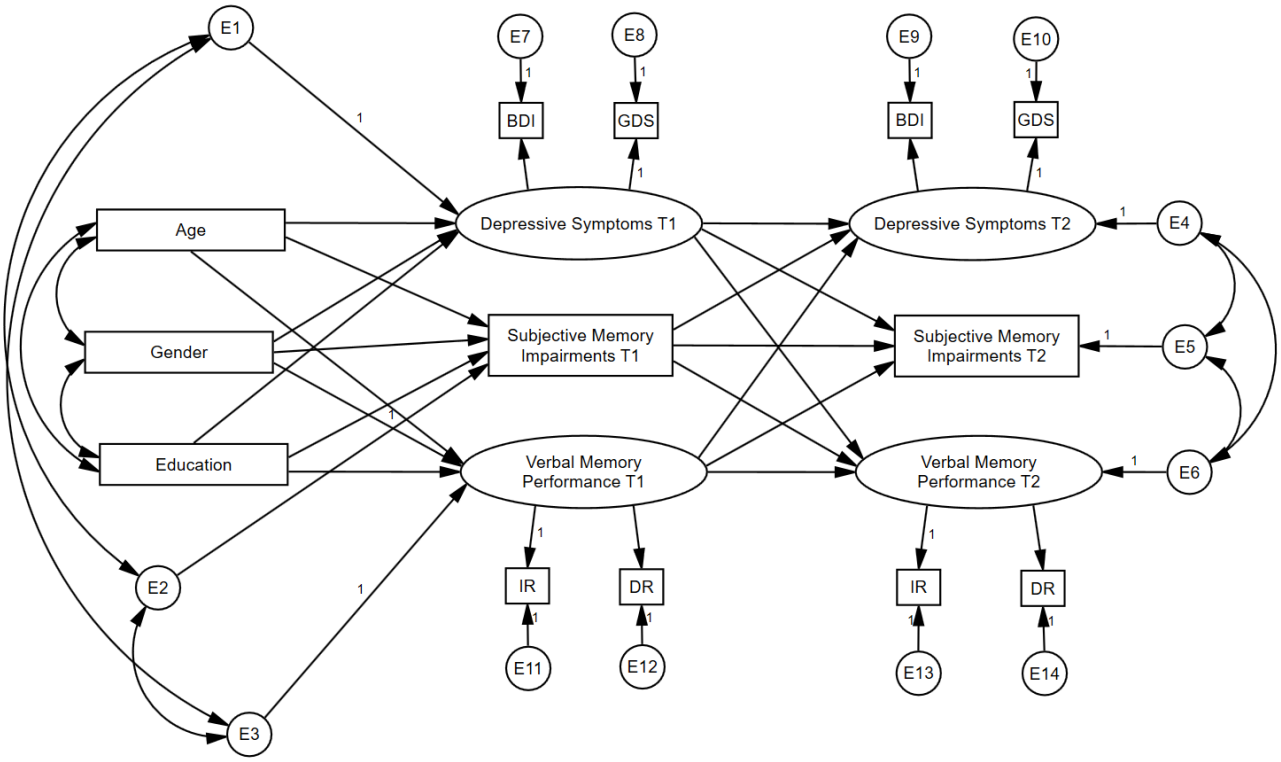

Figure 4. Statistical model including all variables and pathways of interest and further controlling for covariances of sociodemographic variables; T1 = time point 1, T2 = time point 2, BDI = Beck Depression Inventory, GDS = Geriatric Depression Scale, IR = Immediate Recall, DR = Delayed Recall.

Table 2

Parameter estimates and significance levels for the proposed statistical model (n = 307)

Parameter Estimate	**Standardized**	***p***
Gender → Depressive Symptoms T1	**.173**	.003
Gender → Subjective Memory Impairments T1	.054	.219
Gender → Verbal Memory Performance T1	**.161**	.004
Age → Depressive Symptoms T1	.074	.219
Age → Subjective Memory Impairments T1	**.164**	.005
Age → Verbal Memory Performance T1	**-.459**	.001
Education → Depressive Symptoms T1	-.117	.052
Education → Subjective Memory Impairments T1	-.036	.539
Education → Verbal Memory Performance T1	.083	.139
Depressive Symptoms T1 → Depressive Symptoms T2	**.928**	.001
Depressive Symptoms T1 → Subjective Memory Impairments T2	**.235**	.001
Depressive Symptoms T1 → Verbal Memory Performance T2	-.070	.158
Subjective Memory T1 → Depressive Symptoms T2	-.071	.103
Subjective Memory T1 → Subjective Memory Impairments T2	**.472**	.001
Subjective Memory T1 → Verbal Memory Performance T2	.067	.185
Verbal Memory Performance T1 → Depressive Symptoms T2	-.082	.065
Verbal Memory Performance T1 → Subjective Memory Impairments T2	**-.163**	.003
Verbal Memory Performance T1 → Verbal Memory Performance T2	**.928**	.001
Gender ↔ Education	-.074	.197
Gender ↔ Age	-.035	.537
Age ↔ Education	**-.224**	.001
E1 ↔ E2	**.352**	.001
E1 ↔ E3	-.102	.151
E2 ↔ E3	**-.295**	.001
E4 ↔ E5	**.201**	.040
E4 ↔ E6	-.213	.210
E5 ↔ E6	-.214	.058

Note. → illustrate regression weights of direct pathways; ↔ illustrate correlations; significant results are in boldface