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**Depressive symptoms in patients with subjective cognitive decline (SCD),
mild cognitive impairment (MCI) and Parkinson`s disease (PD) in detecting
conversion to dementia**

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Lisa Tejkl

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Abstract

Depressive symptoms may be the first symptoms of cognitive decline and therefore highly important for early disease detection. The research focused on appropriateness of two questionnaires for depressive symptoms, the Beck Depression Inventory Revision (BDI II) and the Geriatric Depression Scale Short Form (GDS) in detecting early signs and conversion to dementia. Sixty-nine patients with subjective cognitive decline (SCD), seventy-two patients with mild cognitive impairment (MCI) and twenty-seven patients with Parkinson's disease (PD) were included in the study ($n = 168$, mean age = 67.5 ± 9.06 years). Participants were estimated two times to establish a longitudinal view. Unexpectedly, no significant differences appeared. Result did not lend support that depressive symptoms are a risk factor for cognitive decline and dementia. Both tests failed to find an effect of depressive symptoms on cognitive decline and dementia. Thus, further investigations of depressive symptoms are indicated.

Keywords: Depressive symptoms; Mild cognitive impairment; Dementia

Zusammenfassung

Depressive Symptome gelten als die ersten Anzeichen für kognitive Beeinträchtigungen und sind daher von großer Bedeutung für die Früherkennung. Es wurde untersucht, ob das Beck Depressions Inventar Revision (BDI II) und die Geriatrische Depressionsskala Kurzform (GDS) frühe Symptome und die Konversion zur Demenz voraussagen können. Die Untersuchung wurde mit neunundsechzig Patienten mit subjektiven kognitiven Beeinträchtigungen (SCD), zweiundsiebzig Patienten mit leichter kognitiver Beeinträchtigung (MCI) und siebenundzwanzig an Parkinson erkrankten Patienten (PD) durchgeführt ($n=168$, Durchschnittsalter = 67.5 ± 9.06 Jahre). Die

Versuchspersonen wurden zweimal getestet um einen Längsschnitt zu gewährleisten. Entgegen den Erwartungen ergaben sich keine signifikanten Unterschiede. Den Ergebnissen zufolge haben depressive Symptome keinen Einfluss auf eine spätere kognitive Beeinträchtigung und Demenz. Weitere Studien sind zur genaueren Betrachtung zu empfehlen.

Schlüsselbegriffe: Depressive Symptome; Leichte kognitive Beeinträchtigung; Demenz

I. Theoretical part. Dementia is a syndrome that is characterized by cognitive deficits that affect daily functioning and can be caused by different diseases, with Alzheimer's disease (AD) as the most common cause (Krstic et al., 2012). In 2010, approximately 35.6 million individuals experienced dementia worldwide with an estimated prevalence that double every 20 years (Prince et al., 2013). Current estimates suggest that in Austria, the number of people with dementia is approaching 100,000. Since our population is growing steadily, by 2050, that number will increase to 250,000 (Gleichweit & Rossa, 2009). Diagnosis of dementia as early as possible has become more and more important and represents an enormous challenge to the medical and especially neuropsychological sector (Petersen, 2004). An early detection of dementia is a necessary prerequisite for the research and to guide therapy. In this context, within the last decade the concept of mild cognitive impairment (MCI) has emerged as a transitional stage between the expected cognitive decline of normal aging and the more severe decline of dementia

(Petersen et al., 2001). Importantly, the main factor that differentiates between MCI and dementia is that MCI does not significantly disrupt the individual's ability to carry out daily living activities (Salloway & Correia, 2009). More precisely, researchers subdivide mild cognitive impairment based on the cognitive domains affected: mild cognitive impairment that primarily affects memory is known as amnesic mild cognitive impairment (aMCI), whereas mild cognitive impairment that affects cognitive skills other than memory is known as non-amnesic mild cognitive impairment (naMCI) (Petersen et al., 1999; Petersen et al., 2001). Patients who come to a memory clinic often worry that their perceived cognitive decline could be an early sign of Alzheimer's disease. If these patients are observed over a longer period, it is found that a person with mild cognitive impairment is at an increased risk of developing Alzheimer's or another dementia, but, not all people with mild cognitive impairment get worse and some eventually get better. Previous work has shown, that people with mild cognitive impairment progressed to dementia with an annual conversion rate of 10 % - 15 % (Petersen et al., 2001; Petersen et al., 2004). In the Austrian population, the annual incidence of dementia is 1 % - 2 %, therefore, the incidence among patients with mild cognitive impairment is significantly higher (Petersen et al., 2001). Furthermore, especially amnesic mild cognitive impairment is increasing the risk of developing Alzheimer's dementia, with an estimated annual rates of progression of 10 % - 18 %, nearly 80 % converted to Alzheimer's dementia after a six year follow-up (Peterson, 2004; DeCarli, 2003). In a study from Busse et al. (2006), the progression to Alzheimer's dementia was faster in people with amnesic mild cognitive impairment than in those with non-amnesic mild cognitive impairment. As is apparent from the literature, mild cognitive impairment is a common risk factor for

the development of cognitive decline and dementia. The group of MCI patients represented the first group in our study. Pusswald et al. (2013) reported, that prevalence of cognitive deficiencies such as mild cognitive impairment vary extensively from 39.5 % - 84.3 %. These findings may be due to various factors, including the use of different neuropsychological assessment parameters. In light of this, it's important to enhance neuropsychological test assessment in terms of early disease detection and progression to dementia. We secondly included participants with Parkinson's disease. Parkinson's disease is a neurodegenerative disorder which leads to cognitive deficiencies such as memory complaints, mostly combined with the known symptoms, e.g. motor resting tremor, rigidity, slowness of movement and difficulty with walking (Cooper et al., 1991). Parkinson's disease too is increasing the risk of developing dementia: point prevalence of dementia in PD is close to 30 % (Aarsland, Zacai, & Brayne, 2005). According to Dalrymple-Alford et al. (2011), patients with Parkinson's disease nearly have a 75% - 90% increased frequency of developing dementia (PDD). Moreover, within Parkinson's disease, mild cognitive impairment is also recognized to be relatively common. It is estimated that the prevalence of mild cognitive impairment in Parkinson's disease patients is 26.7 %, ranging from 18,9 % - 38,2 % (Litvan et al., 2011). In a longitudinal study from Williams-Gray, Foltynie, Brayne, Robbins & Barker (2007), two-thirds of the PD patients experienced cognitive deficiencies after almost 3.5 years. Additionally, with PD and aMCI at baseline, patients showed even higher risk for conversion to AD than patients with PD and naMCI (Aarsland et al. 2001). Our PD group consisted of PD patients that were cognitively healthy (PD-SCD), PD patients showing memory impairments (PD-aMCI) and PD patients showing impairment in one or more cognitive domains other than memory

(PD-naMCI). It should be noted that this characterization (aMCI, naMCI, PD-aMCI, PD-naMCI, PD-SCD, SCD) was also used by Härtl (2014).

Research attempts have become more concentrated on detecting dementia in early stages and on awareness in groups at risk for future dementia. In regard of this, the third group of participants in our study consisted of patients with subjective cognitive decline (SCD). Recently, Jessen et al. (2014) pointed out, that patients with subjective cognitive decline report of cognitive impairment, such as inattention and difficulties to word something but neuropsychological test diagnosis is normal. Memory complaints could be associated with changes of healthy aging but otherwise they could also be associated with other conditions, especially mild cognitive impairment and dementia, as well as depression (Reisberg & Gauthier, 2008). Interestingly, as proposed by Reisberg and Gauthier (2008) subjective cognitive decline could be a 'harbinger' of further cognitive decline. In 2009, Visser et al. reported, that individually experienced problems about the own cognitive functioning, without objective evidence of cognitive impairment on neuropsychological test diagnosis, could be classified as an indicator for early states of brain diseases. Furthermore, Stewart (2011) investigated, that elderly people could be more aware of underlying brain changes, so the subjective consciousness of cognitive decline could contribute subtle information for early disease detection, whereas other studies have failed to do so. Thus, the association of subjective cognitive decline with mild cognitive impairment and dementia is still not fully enlightened. Nevertheless, a model has been proposed that divide the course to dementia into three clinical stages from SCD via MCI to dementia: it begins with healthy aging, followed by subjectively reported change in memory without objective evidence on neuropsychological

assessment (SCD), further changing to objective memory impairment (MCI) and finally ending up with dementia (Jessen et al., 2010). Apparently, subjective cognitive decline is also common in patients with Parkinson's disease. In a study from Lehrner et al. (2014) it was found, that 15 % of PD patients who visit an outpatient clinic for assessment of a possible motor disorder reported about self-referred memory complaints (PD-SCD). Aside from quite a bite of evidence that mild cognitive impairment is a high-risk condition for dementia, what other risk factors for cognitive decline and dementia can be addressed? In the literature, several other factors have been associated with dementia risk such as genetics (e.g. the APOE- ϵ 4 allele), life-style (e.g. exercise, social activity), personality traits (e.g. neuroticism) and physical variables (e.g. vitamin B deficiency) (McCullagh et al, 2001; Chen et al., 2009; Daviglus et al., 2010). In addition, a factor that is thought to be a risk factor for dementia later in life, namely depressive symptoms, will be explained in more detail in the next section. Lifetime risk of depression is about 10 % - 16 % in men, whereas it's about 20 % - 26 % in women (Margraf & Schneider, 2009). Depressive symptoms were frequently detected in the older population and were associated with poor cognitive functions (Alexopoulos et al., 1992). Austin, Mitchel and Goodwin (2011) found support for the association of mood disorders and distinct pattern of cognitive impairment. For example, several clinical-based studies in elderly samples have shown that depressive symptoms are linked with cognitive functions: cognitive deficits were found on tests of memory (King, Cox, Lyness & Caine, 1995), attention (King et al., 1995) psychomotor functions (Purcell et al., 1997) and executive functions (Butters et al., 2004). According to Bhalla et al. (2009), nearly twice as many participants with depression were diagnosed with mild cognitive

impairment (48 %) or dementia (28 %) in comparison to healthy controls. Out of those one-hundred-nine depressed patients, forty-one (38 %) showed signs of mild cognitive impairment. In more detail, fifteen participants (37 %) showed signs of naMCI, whereas twenty-six patients (63 %) showed signs of aMCI. In 2004, Modrego et al. investigated, if depressive symptoms in patients with mild cognitive impairment lead to a faster cognitive decline and increase the risk of developing dementia. They examined the association between depressive symptoms that were measured through self-report assessment and longitudinal cognitive changes in older adults. Higher depressive symptoms at baseline were linked with a greater three-year decrease in cognitive performance. Additionally, they stated that in patients with mild cognitive impairment depressive symptoms double the risk of developing dementia. Therefore, they concluded that depressive symptoms predict cognitive decline and dementia in older persons. Furthermore, Penkert (2014) investigated that depressive symptoms were higher in participants with cognitive decline compared with participants without cognitive decline. Unfortunately, the relation between depressive symptoms and risk for later development of dementia is still unclear, since there are data to support different hypotheses. In 2000, Jorm proposed in his review, that depressive symptoms are likely to be a risk factor for the development of cognitive decline and dementia and offered a few hypotheses: firstly, depressive symptoms could be an early possible prodrome of dementia. Some researchers assumed that depressive symptoms as a prodrome could appear from subcortical cerebrovascular disease. Secondly, depressive symptoms could be an early reaction to cognitive decline. A possible explanation is that this reaction occurs because people in the earliest stages of dementia have an alertness of their declining

cognitive functions. Thirdly, diagnoses of dementia could occur when a threshold is reached, where people experience gradual loss of ability to carry out daily activities. Depressive symptoms concern cognitive impairment, which could cumulate with those in early dementia, leading to an earlier stage of reaching the threshold. However, depressive symptoms as a risk factor for the development of dementia later in life is still controversial (Hermida et al., 2012). Ownby et al. (2006) showed in their review, that depressive symptoms lead to subsequent development of dementia. The review has shown, that patients with dementia were more likely than non-demented patients to have a history of depressive symptoms. Additionally, Hidaka et al. (2011) mentioned in their research article concerning patients with mild cognitive impairment, that the spreading of depression (26.3 %) is significantly higher in comparison to a healthy control group (18.0 %). Depressive symptoms are also relatively common in PD patients. Depression is with a prevalence of 70 % one of the most common neuropsychiatric disorders among PD patients (Gerschlager, 2009). Apparently, the distribution of depressive symptoms is significantly higher in PD-MCI patients than in the healthy (Hulka, 2014). Starkstein, Bolduc, Mayberg, Preziosi & Robinson (1990) evaluated in their longitudinal study a cohort of patients with Parkinson's disease in terms of depression and cognitive decline. They discovered a significantly faster cognitive decline among depressed than non-depressed patients with Parkinson's disease 12 months after. In the follow-up testing the researchers investigated between both groups (depressed vs. not depressed patients with Parkinson's disease) a significant deterioration of the cognitive functions as well as in the memory tasks. Thus, they showed a greater reduction among their cognitive functions than the non-depressed patients with Parkinson's disease. A new study has

shown, that depression can occur as first symptom of Parkinson's disease, even years before the onset of the motor symptoms, e.g. motor resting tremor, rigidity, slowness of movement and difficulty with walking (Gerschlager, 2009). Recently, a study has shown, depression (65.5 %) was the most common neuropsychiatric symptom in PD-MCI patients, followed by sleep disturbances (63.3 %), anxiety (58.2 %) and apathy (50.7 %) (Monastero et al., 2013). The reported rates of depression in persons with Parkinson's disease vary from 7 % -76 % according to different measurements and different criteria using to diagnose depression (Veiga, Borges, Silva, Goulart & Ferraz, 2009).

Besides, several studies did not find a statistically significant relationship between depression and dementia (Chen, Ganguli, Mulasnt, & deKosky, 1999). Additionally, depressive symptoms have been reported to be strongly associated with subjective cognitive decline (Reisberg and Gauthier, 2008). But so far, there are only a few follow-up studies of patients with subjective cognitive decline evaluating the influence of depressive symptoms. As mentioned above, depressive symptoms in patients with mild cognitive impairment and Parkinson's disease have received increasing attention recently. In contrast, previous studies have not evaluated differences in depressive symptoms in patients with mild cognitive impairment in comparison to patients with Parkinson's disease. Since the aspect of 'subjective cognitive decline' had not been covered sufficiently before, also participants with SCD patients were taken into account. Based on the literature above, the current study is a more detailed examination of depressive symptoms in patients with SCD, MCI and PD concentrated in terms of an evolving dementia. Taken together, the present study focuses on the diagnostic value of two questionnaires measuring depressive symptoms in terms of early detection and conversion to

dementia. For this purpose, a baseline- examination and one follow-up visit were carried out to establish a longitudinal view. Specifically, according to the subtypes of mild cognitive impairment (aMCI, naMCI), possible differences have still to be investigated. Hence, the following hypotheses can be derive: firstly, the present study tried to determine test differences between the main groups of SCD, MCI and PD. Group, time and interaction effects in repeated measures ANOVA are anticipated to be significant. Secondly, differences in test performance between SCD and the subtypes aMCI, naMCI, PD-aMCI, PD-naMCI and PD-SCD were examined. Once again, effects of group, time and interaction are expected to be significant in all comparisons. Thirdly, differences between participants who converted to AD and those who did not were assessed. Group and interaction effect are anticipated to be significant. The effect of time is not expected to be significant, suggesting that significant time differences are only occurring for the converted. Fourthly, differences between participants who deteriorated, improved and remained stable their initial cognitive abilities were assessed. Again, group, time and interaction effect should be significant. Clarifying these differences might improve understanding of risk factors for disease mechanisms in dementia. Finally, this study draws also attention the conversion rates.

2. Methods

2.1 Subjects and Procedure

The present study was conducted in the context of a larger-scaled project, the Vienna Conversion to Dementia Study (VCDS) of the Medical University of Vienna, administrated by the Department of Neurology. The Vienna Conversion to Dementia Study has two main objectives: (a) to determine the

prevalence of MCI subtypes and (b) to investigate the progression of the MCI subtypes to AD. The study was performed in accordance with the Helsinki Declaration and approved by the Ethical Committee of the Medical University of Vienna. Furthermore, all subjects provided written informed consent for study participation. The data we analyzed, obtained from this larger data set, included patients with SCD, MCI and PD. At this point it's important to consider that my colleague Härtl (2014) examined the same sample in his diploma thesis.

The number of valid data was $N = 168$. The sample consisted of 90 (53.6 %) female and 78 (34.2 %) male participants. The average age of the sample was 67.5 years (ranging from 50 to 88 years; $SD = 9.06$ years). Participants' mean years of formal schooling were 11.7 years ($SD = 3.6$ years). At baseline, the mean MMSE score was 28.1 ($SD = 1.6$). Importantly, at step 3, we excluded patients with PD at baseline from the total sample, leaving data of $N = 141$ for analysis, because only the conversion to AD within SCD and MCI was of interest to us. All participants were either referred by neurologists, psychiatrists or were self-referrals (especially those patients with Parkinson's disease were referred from the Neurology or Psychiatry Unit). The included area of the study was Vienna, Lower Austria and Burgenland. As already mentioned, each participant was assessed twice. The average time span between baseline and follow up assessment was 32 months ($SD = 15.8$, ranging from 12 months to 60 months). All participants received a standardized neuropsychological examination. Sociodemographic data (age, highest education and employment status) and information about participants' memory complaints, medical history and regular medication were provided, using the brief cognitive rating scale (Reisberg & Ferris, 1998). In some cases, images of the brain were obtained using magnetic resonance imaging

(MRI) and computed tomography (CT). Inclusion and exclusion criteria were similar to previous studies. The general conditions for exclusion from the study were the following:

- Evidence of stroke, as determined by neuroradiology and clinical examination;
- History of severe head injury;
- Current psychiatric diagnosis according to International Classification of Disease, tenth revision (Organization, 1993); apart from mild depressive symptoms because of the high prevalence of depressive symptoms in older patients;
- Any medical condition that leads to severe cognitive deterioration including renal, respiratory, cardiac and hepatic disease;
- Less than 50 years of age;
- An already given diagnosis of dementia according to International Classification of Disease, tenth revision (Organization, 1993).

2.2 Neuropsychological Measurement

Firstly, participants were assessed on the following cognitive screening tests: We used the Mini Mental State Examination Test by Folstein, Folstein & McHugh (1990), the Clock Drawing Test (Powlishta et al., 2002) and the Test zur Erfassung der Visuokonstruktion (Lehrner et al., 2015). Secondly, the Neuropsychological Test Battery Vienna (NTBV) was part of the assessment, which consisted of the following domains: (a) attention, (b) executive functioning – phonematic verbal fluency, (c) executive functioning – interference, (d) language, (e) memory and (f) executive functioning – planning and nonverbal fluency (Lehrner, Maly, Gleiß, Auff, & Dal-Bianco, 2007; Lehrner et al., 2005; Lehrner, Gleiß, Maly, Auff, & Dal-Bianco, 2006; Puszwald et al., 2013).

Subsequently, the subtests we used to assess domains are described. Attention was assessed with the Alter-Konzentrations-Test (Gatterer, Fischer, Simanyi, & Danielczyk, 1990), the digit symbol test of the German Wechsler Adult Intelligence Scale - Revised (Tewes, 1994), the symbol counting task from the Cerebral Insufficiency test (Lehrl & Fischer, 1997), the Trail Making Test version B (TMT B) and the score difference from the Trail Making Test A (TMT A) and the Trail Making Test B (TMT B) (Reitan, 1979). Executive functioning – phonematic verbal fluency was investigated with the phonematic verbal fluency test. This test requires participants to name as many words beginning with letter “B”, “F” and “L” as they can within one minute for each letter (Goodglass & Kaplan, 1983). Executive functioning – interference was measured with the Stroop test from the Nürnberger Alters Inventar (Oswald & Fleischmann, 1997) and the interference test from the Cerebral Insufficiency test (Lehrl & Fischer, 1997). Language was assessed using two tests. Firstly, the semantic verbal fluency test was used. In this test, participants were asked to list as many words as feasible belonging to the categories of animals, supermarket articles and tools. The time limit for every category was one minute (Goodglass & Kaplan, 1972). In order to test naming capabilities, we used the modified Boston Naming Test (Morris, Mohs, Rogers, Fillenbaum, & Heyman, 1987). Episodic memory was measured using the Verbal Selective Reminding Test (Lehrner et al., 2006) with the subtests of immediate recall, mediate recall, total recall, delayed recall and recognition. Executive functioning – planning and nonverbal fluency were tested using the Trail Making Test A (TMT A) (Reitan, 1979), the Five-Point Test (Regard, Strauss & Knapp, 1982) and the maze test from the Nürnberger Alters Inventar (Oswald & Fleischmann, 1997). In all cases, participants were

tested individually. The cognitive assessment took approximately forty-five to sixty minutes and was carried out in one part. Due to that, in some cases, participants complained about fatigue and lack of motivation. All of the subtests of the NTBIV have been used in several other studies. The neuropsychological measurement described above is equivalent to the measurement explained in earlier work (Härtl, 2014; Hulka, 2014; Okonnek, 2014; Penkert, 2014). After cognitive testing with the NTBIV, participants were subjected to the Beck Depression Inventory Revision (BDI II) (Hautzinger, Keller, & Kühner, 2009) and the Geriatric Depression Scale Short Form (GDS) (Bach, Nikolaus, Oster, & Schlierf, 1994).

2.3 Measurement of Depressive Symptoms

Over the years, the Beck Depression Inventory has undergone various revisions. For this study, the second edition of the Beck Depression Inventory (BDI II) was used in which four items (weight loss, body image, hypochondria and difficulty working) were replaced so that the measurement was consistent with the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria. It consists of a total of 21 groups, which represents the respective symptoms of depression: (1) sadness (2) pessimism (3) sense of failure (4) loss of pleasure (5) guilty feelings (6) punishment feelings (7) self-dislike (8) self-criticalness (9) suicidal thoughts (10) crying (11) agitation (12) loss of interest (13) indecisiveness (14) worthlessness (15) loss of energy (16) changes in sleeping pattern (17) irritability (18) changes in appetite (19) concentration difficulty (20) tiredness of fatigue and (21) loss of interest in sex. Most of these groups assess depressive symptoms on a four-point Likert scale, with options from 0 (not at all) to 3 (extreme form of each symptom). Two exceptions to this are group 16 and 18. The scale in

these two items consists of 0, 1a, 1b, 2a, 2b, 3a & 3c. Patients were instructed to carefully read each group of statements and then mark the one statement in each group that best describes the participants condition in the last two weeks (e.g. group “sadness:” (0) I do not feel sad. (1) I feel sad. (2) I feel sad at any time. (3) I feel sad and unhappy that I can’t sustain it). Patients were instructed to choose the highest number for a group whenever more than one statement seems to apply well. The total score is the sum of all responses, the cut-off value is at nine points, a maximum of 63 points and a minimum of 0 points could be achieved. A higher score indicates more severe depressive symptoms. Correspondingly, the internal consistency (Cronbach’s alpha) is around 0.9 and retest reliability range from 0.73 to 0.96. The Geriatric Depression Scale Short Form (GDS) was developed to reduce the possibility of test fatigue in the elderly (Sheikh & Yesavage, 1986). It consists of 15 questions and participants are supposed to record a response in reference to how they felt over the past week. Possible answers are yes and no. The following item is an exemplary one: “Are you afraid that something bad is going to happen to you?” The sum of all bolded responses represents the total score, the cut-off score is at five points, a maximum of 15 points and a minimum of 0 points could be achieved, with a higher score meaning higher depressive symptoms. The internal consistency (Cronbach’s alpha) is 0.79. In 2007, Sansoni et al. concluded that the GDS is a valid measure to determine depressive symptoms. Both tests are paper and pencil self-report measures and the administration for both tests took approximately 15 - 20 minutes. No time limit was imposed for either of the tests. Great care was taken with participants who showed higher BDI II and GDS scores. They received particular attention.

2.4 Classification Methods

For MCI categorization, a z-score was estimated for each subtest of the Neuropsychological Test Battery Vienna, demonstrating the extent of cognitive impairment from cognitively healthy control patients. According to Pusswald et al. (2013), impairment was defined by z-scores lower than -1.5 standard deviations. In accordance with the so-called minimum mode of MCI classification, a domain was obtained to be impaired when at least one subtest that measures a domain was showing a z-score lower than -1.5 standard deviations below the age- and education-matched norms for healthy controls (Pusswald et al., 2013). Furthermore, MCI participants were then subdivided into two groups: (a) an amnesic MCI subtype (aMCI), in which impairment of the memory domain was common and (b) a non-amnesic MCI subtype (naMCI), in which one or more of the other domains showed impairment. Additionally, diagnosis of MCI was determined according to the following objective Mayo criteria for MCI classification, which can be viewed as widespread, published by Petersen (2004): participants with MCI have (a) subjective memory complaints (b) objective memory impairment for age (c) intact general cognitive function (as measured by a MMSE score of 24 or higher) (d) normal activities of daily living and (e) no dementia. If a participant perceived memory problems but however, scored normal throughout cognitive assessment with the NTB (no z-score beneath -1.5 standard deviations) the patient was assigned to SCD. Diagnosis of Parkinson’s disease and Alzheimer’s dementia was determined by neurologists, psychiatrists and psychologists. PD patients were divided into three subgroups: PD patients who reported memory problems without measurable cognitive impairment in any of the subtests of the NTB were assigned to the Parkinson’s disease subjective cognitive decline

group (PD-SCD). Secondly, PD patients were attached as amnesic mild cognitive impairment (PD-aMCI) when a z-score lower than -1.5 standard deviations in the subtest of the NTBv that measures the domain memory was found. Thirdly, PD patients who showed a z-score lower than -1.5 standard deviations in one or more cognitive domains other than memory were assigned to the Parkinson's disease non-amnesic mild cognitive impairment group (PD-naMCI). Recently, this classification of MCI subtypes according to Pusswald et al. (2013) was also used in several other unpublished studies (Härtl, 2014; Hulka, 2014; Okonnek, 2014; Penkert, 2014).

2.5 Statistical Analyses

Descriptive statistics were used to characterize the study sample. The assumptions of normal distribution, linearity and homoscedasticity were fulfilled. Product moment correlation was built to check for possible confounding variables of BDI II and GDS. Covariates were age, sex, education, baseline WST-score and baseline MMSE-score. As mentioned before, a basic assessment and one follow-up assessment were used to establish a longitudinal view, providing data of two test occasions. Thereby, test score difference as a new variable was built by subtracting scores of basic assessment from follow up scores. Specifically, a positive value indicates an increase in the BDI II and GDS score. It was chosen to set the level of statistical significance in all statistical procedures to 0.05. All computations were performed using Statistical Package for the Social Sciences for Windows (SPSS, 2004). Prior to the main data analysis, one focus was set to the prevalence of conversion and distribution of converted among the groups. The conversion rates were presented in percentages. Then, the main data analysis was conducted in four subsequent steps, which are

explained in more detail below. The first, second and third step are similar to those steps discussed more precisely in previous work (Kogler, 2013). Because of repeated measurements, Bonferroni post hoc tests were performed as well.

1. Step

On the first level of analysis, test score differences between patients with SCD, MCI and PD in BDI II and GDS were investigated. In order to test this, 3x2-repeated-measures ANOVA's were performed, with diagnosis group as the between subject factor and time as the within subject factor. In each single step, BDI II and GDS acted as dependent variables while diagnosis group acted as independent variable.

2. Step

Second step analysis is similar to first step analysis. To test whether test score differences existed between SCD, aMCI, naMCI, PD-SCD, PD-aMCI and PD-naMCI in BDI and GDS, 6x2-repeated-measures ANOVA's were conducted again. Unfortunately, on this level of analysis, the group sizes were very low. Due to this, no significant result could be expected.

3. Step

In the third step, participants were grouped into those who showed transition to AD over time and those who did not. Differences in BDI II and GDS score between converters and non-converters were examined. Therefore, 2x2-repeated measures ANOVA's were used again. As considered earlier, this third level of analysis was only performed with SCD and MCI patients, because conversion to AD was only possible within SCD and MCI, so valid data was based on $N = 141$. For step 1 and step 2 analysis levels, diagnosis group was built upon baseline examination. In this third step it's the other

way, diagnosis group was built upon follow-up assessment.

4. Step

In an additional analysis, participants were grouped into those who deteriorated in their cognitive abilities over the course of the study, improved in their cognitive functions and those who remained cognitively stable. In this fourth step, differences between those three groups in test score of BDI and GDS were explored. Again, 3x2-repeated-measures ANOVA's were conducted. Similar to step 3 analyses, diagnosis group was made upon follow up examination. The present study was originally not created to explicitly investigate this step.

3. Results

3.1 Conversion Rates

As can be seen in table 1, eight participants (5.7 %) met the criteria for AD over the course of the study. In more detail, we investigated that out of sixty-nine SCD patients at baseline, one patient (1.4 %) converted to AD. Twenty-nine SCD patients (42 %) converted to MCI, while out of those twenty-nine SCD patients, eighteen converted to naMCI (26.1 %) and eleven converted to aMCI (15.9 %). Thirty-nine SCD patients' cognitive state didn't change (56.6 %). In the MCI group, out of seventy-two patients at baseline, seven participants (9.7 %) converted to AD. In more detail, two of the thirty-one naMCI patients (1.8 %) and five of the forty-one aMCI patients (12.2 %) converted to AD. Fourteen out of the thirty-one naMCI patients (45.2 %) converted to aMCI. Out of forty-one aMCI patients at baseline, thirteen (34.2 %) converted to naMCI. Out of the seventy-two MCI patients, eleven (15.3 %) returned to cognitive

normal state as assessed with the Neuropsychological Test Battery Vienna. Finally, it should be made clear that the same conversion rates have already been presented in an earlier study (Härtl, 2014).

3.2 Depressive Symptoms

For BDI II analysis, one SCD patient ($n = 68$), three MCI patients ($n = 68$) and two PD patients ($n = 25$) were excluded ($N = 162$) because full data was missing. For the GDS analysis, three SCD patients ($n = 66$), three MCI patients ($n = 69$) and three PD patients ($n = 24$) with missing values were excluded ($N = 159$). Pearson's product moment correlation admitted significant relations between BDI II and GDS ($r = .313, p < .001$). No significant differences were found when age was used to exclude confounding effects. Nevertheless, because there was a tendency in terms of education ($p = .066$), Fisher's LSD post-hoc comparisons were conducted, which revealed significant differences ($p = .028$) in the SCD group. WST-score ($p = .001$) as well as MMSE-score ($p = .008$) were significant in the SCD group. Participants with higher scores in BDI II and GDS at baseline also had high scores at the follow-up. Respectively, participants with lower scores in BDI II and GDS at baseline also showed lower scores at the follow up ($r = .774, R^2 = 59.9 \%, p < .001$).

1. Step

In a first step, differences between the three main groups SCD, MCI and PD in BDI II and GDS were examined. In table 2, means and standard deviations for demographic variables as well as for dependent variables are listed. In the SCD group, there were significantly more female than male subjects participating (SCD = 66.7 %, MCI = 47.2 %, PD = 37.0 %, $p < 0.01$).

We found a higher median in BDI and GDS for MCI than for SCD and PD. Slightly lower BDI II and GDS means were obvious for PD patients than for SCD and MCI. ANOVA results are shown in table 6. Briefly, no significant differences were obvious for the three main groups in BDI II and GDS. The main effect of diagnosis was not significant for both tests. Further, the within factor time did not show significance. Also no significant interaction effect was found. The ANOVA results are in contrast to the expectations stated earlier.

2. Step

For the second level of analysis, test score in BDI II and GDS between the subgroups of MCI and PD (SCD, aMCI, naMCI, PD-SCD, PD-aMCI and PD-naMCI) were examined. A description of the means and standard deviations of demographic and dependent variables for subtypes are shown in table 3. Higher BDI II means were found for the aMCI and PD-aMCI than for the naMCI, PD-SCD and PD-naMCI group. Unfortunately, on this level of analysis, the group sizes were slightly different (SCD = 69, aMCI = 41, naMCI = 31, PD-SCD = 2, PD-aMCI = 6, PD-naMCI = 16). Due to this, no significant result could be expected. The highest MMSE-scores were obvious in PD-naMCI patients. Table 6 summarizes the ANOVA analysis results. Similarly to the results described above, ANOVA did not reveal a significant group difference for BDI II and GDS score between subgroups. Once again, the main effect of diagnosis as well as the within factor time did not show significance. No significant interaction effect was found.

3. Step

In the third step, group differences in BDI II and GDS score between converters to AD and non-converters were investigated. Table 4 shows means and standard deviations for demographic variables

as well as for dependent variables of converters and non-converters. It's graphically depicted in figure A and B that both tests showed higher means in the converter group. As can be seen in table 6, main effect of group was not significant, those who convert did not show more severe depressive symptoms. Additionally, the within factor time did not show significance and no interaction effect was investigated.

4. Step

The fourth goal was to investigate group differences in BDI and GDS score between participants who deteriorated, improved or had no change in their cognitive abilities. Means and standard deviations of demographic and dependent variables are summarised in table 5. In this analysis, a higher median was found for the Improvement group than for the other Deterioration and No change group. Table 6 shows that all ANOVA results were non-significant. Again, in step 4, no main effect, no time effect and no interaction effect were found.

4. Discussion

4.1 Summary of Results

This diploma thesis investigated, if measures of depressive symptoms are valuable for detecting onset and conversion to dementia in a large sample of elderly participants with different statuses of disease severity. For this purpose, a longitudinal study, including one baseline examination and one follow-up visit was carried out by using different diagnostic methods based on data from the Vienna Conversion to Dementia Study. In order to test this, differences in BDI II and GDS between "harbingers" of dementia (SCD, MCI and PD) and their subtypes (aMCI, naMCI, PD-SCD, PD-aMCI,

PD-naMCI), as well as differences in BDI and GDS between converters to AD and non-converters were examined. To further assess predictive value of BDI II and GDS differences between participants who deteriorated, improved or remained stable in their initial cognitive abilities over the course of the study were investigated. Thereby, it offered an easy interpretation of the results. In PD patients depressive symptoms measured through BDI II have been described to differ significantly in comparison to cognitively healthy controls (Hulka, 2014) but our data did not support this. In our study, lower scores in BDI II and GDS were found for PD patients than for MCI and SCD. In Step 2 analysis, patients with aMCI and PD-aMCI showed higher scores in BDI II and GDS than patients with naMCI, PD-SCD and PD-naMCI. These findings are consistent with previous work (Hulka, 2014; Shahnawaz et al., 2012) that found higher BDI II scores in aMCI patients than in naMCI patients. As has been shown in the results section above, ANOVAs indicated no significant group differences (all the values were bigger than .05) in BDI II and GDS, regardless which groups were compared. Participants did not significantly differentiate in their depressive symptoms over time. Those with subjectively cognitive decline without measurable cognitive deficiencies appeared to be distinct from those with mild cognitive impairment as well as from those with dementia. Both BDI II and GDS did not differentiate participants who were free of cognitive impairment from those with impaired functions. The present study did not replicate prior findings by Modrego et al. (2007), who found an influence of depressive symptoms on cognitive decline. Findings of Ellison et al. (2008), who found that depressive symptoms were a predictor for future cognitive decline and dementia, have not been replicated either. Thus, BDI II and GDS are not able to identify early signs of dementia. Although analyses did not reveal

significant differences, converters to AD showed higher mean scores in BDI II and GDS than non-converters. Summarizing, BDI II and GDS are not able to identify early signs of dementia. The results are not even conforming partially to the hypothesis. This was especially surprising for the converter group because previous work has shown that patients who indicated dementia over time differentiated significantly in their depressive symptoms from those patients who did not indicate dementia (Ownby et al., 2006). Both BDI II and GDS did not distinguish groups of converters to AD from non-converters. Surprisingly, our data showed that in Step 4 analysis scores of BDI II and GDS were slightly higher in the Improvement group than in the Deterioration group and the group with No change. Thus, depressive symptoms at baseline could not be considered as a predictor of future cognitive decline. In the GDS, although participant scores ranged from 0-14, overall mean scores were below 5.3, indicating relatively low levels of depressive symptoms. However, in the SCD group, women were significantly overrepresented as compared with the other study groups. We can only speculate that women came earlier than men to the memory clinic for evaluation and therefore. Additionally, we take a closer look at the results of the conversion rates. In the SCD group, 42 % converted to MCI and 1.4 % converted to AD. These findings are consistent with those reported by Jonker et al (2000), who suggested a 2 to 5 time increased risk for the development of cognitive decline in SCD patients. In the MCI group, a total of 9.4 % converted to AD. In our study, the characterization of MCI subtype analysis showed that two of the thirty-one naMCI patients (1.8 %) and five of the forty-one aMCI patients (12.2 %) converted to AD. Fourteen out of the thirty-one naMCI patients (45.2 %) converted to aMCI. Out of the forty-one MCI patients, thirteen (34.2 %) converted to naMCI. Based on today's literature,

there is a consistent view on MCI's influence on the development of AD. In 1999, Petersen et al. reported a conversion rate of 12 % from MCI to AD over the course of 12 months, in a clinical population, while Amieva (2004) found a 32 % conversion rate over a 2-year period. While our study confirms Petersen's and Amieva's findings, our conversion rate of 9.7 % over the course of the average 32 months was far below their findings. Our findings therefore weaken Petersen's and Amieva's claim. As opposed to the preceding analysis, which focused on rates of conversion in cognitive abilities, the next part of the study highlighted the prevalence of SMI and MCI in PD patients. In current literature, Janvin (2006) investigated that 52 % of PD patients were cognitively impaired. Additionally, Janvin (2006) stated that 44.7 % of cognitively impaired PD patients showed signs of naMCI. Prevalence of baseline MCI in PD was much bigger than suggested in literature. In the present study, out of twenty-seven PD patients at baseline, twenty-five patients (92.6 %) showed signs of MCI. More precisely, 16 patients (59.3 %) were diagnosed with naMCI, while 9 patients (33.3 %) were diagnosed with aMCI at baseline. Therefore, our study's outcome support Janvin's claim.

4.2 Strengths and Limitations

As every study, there are some strengths and limitations that need to be considered. An essential strength of the study is the inclusion of the SCD group. Thus, a contribution to a yet neglected field was aspired. Secondly, the present study is the first study that inspected the possible differences in depressive symptoms between patients with SCD, MCI and PD longitudinally. Therefore, it's an addition to the present state of research in the field of AD. Another strength is the current study's

appropriate and good design. Participants received a comprehensive neuropsychological examination. The Neuropsychological Test Battery Vienna was found to have a good discrimination power in detecting AD. The items of the BDI II were clear and the BDI II allowed participants to easily comprehend the questions and respond appropriately. Despite the strengths described above, this study possesses also some limitations that concerned to be acknowledged. Firstly, sample sizes were not regarded as appropriate. For example, subgroups of PD patients were relatively small. At the follow up, only eight out of one-hundred-forty-one participants were diagnosed with AD. In light of this, no significant ANOVA results could be expected. Results did not support the findings of earlier studies, with larger cohorts and longer observation periods. Future studies should choose a more appropriate sample to eliminate the possibility that significant results were absent due to group sizes that were too small. Secondly, a wide range of the time interval was found. Thus, it may have an impact on conversion rates and may have obscured the results as well. Thirdly, there was no information available regarding the behaviour or measurements experienced by the participants between the two assessments. No data was gathered in terms of cognitive training or therapeutic measures experienced by the participants individually. Fourthly, our study represented a clinical sample and was therefore very specific. That means, that most of the patients had subjective cognitive decline. Hence, a generalization of the results to the general population is not possible, because those who visit a memory outpatient clinic for assessment of possible cognitive disorder only represent a part of the affected ones. Those who don't recognize limitations in their cognitive performance are underrepresented in this sample. Another limitation concerns the use of the GDS as a screening instrument for depressive symptoms.

On the one hand, the GDS is a short structured interview, it's user-friendly and older participants may have an easier time providing it. But on the other hand, participants could only respond with yes or no. This certainly allows less assurance about the justification of depressive symptoms. In future studies, a more detailed interview should be conducted. Future follow up studies should assess depressive symptoms more extensively. Additionally, BDI II and GDS scores can be easily minimized or exaggerated by the person completing them. This is a general problem of self-report questionnaires and illustrates a common limitation researchers are confronted with. Finally, it has to be noted that procedures with older participants whose cognitive functions are impaired has to be applied with care due to ethical considerations. Due to fatigue and in some cases compromised concentration and motivation, not every patient performed each test. In conclusion, depressive symptoms in patients with SCD, MCI and PD didn't predict a faster deterioration and didn't increase the risk of developing dementia later in life. In the end, it should be noted that participants with depressive symptoms and SCD, MCI and PD deserve more attention and should be observed more closely.

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Table 1.*Rates of Conversion in SCD, naMCI, aMCI and SCD and MCI in PD (N=168)*

		Follow-up							Total
		SCD	naMCI	aMCI	PD-SCD	PD-naMCI	PD-aMCI	AD	
Baseline	SCD	39 (56.6 %)	18 (26.1 %)	11 (15.9 %)	-	-	-	1 (1.4 %)	69
	naMCI	5 (16.1 %)	10 (32.3 %)	14 (45.2 %)	-	-	-	2 (1.8 %)	31
	aMCI	6 (14.6 %)	13 (31.7 %)	17 (41.5 %)	-	-	-	5 (12.2 %)	41
	PD-SCD	-	-	-	-	1 (50 %)	1 (50 %)	-	2
	PD-naMCI	-	-	-	2 (12.5 %)	10 (62.5 %)	4 (25 %)	-	16
	PD-aMCI	-	-	-	-	2 (22.2 %)	7 (77.8 %)	-	9
Total		50	41	42	2	13	12	8	168

Table 2.*Sample Characteristics and Dependent Variables for Step 1 (N=168)*

	SCD (N=69)	MCI (N=72)	PD (N=27)
Age	66.1 ± 9.5	68.9 ± 9.1	67.3 ± 7.2
Education	12.5 ± 3.7	11.2 ± 3.5	11.3 ± 3.3
WST - IQ	113.9 ± 10.9	106.8 ± 12.3	106.6 ± 12.7
Female	66.7 %	47.2 %	37.0 %
MMSE	28.5 ± 1.3	27.7 ± 1.6	27.9 ± 2
BDI II	10.23 ± 7.3	11.24 ± 7.5	9.4 ± 5.5
GDS	3.3 ± 3.0	4.1 ± 3.4	2.9 ± 2.0

Note: Age and education in years.

Table 3.*Demographic characteristics of the sample and Dependent Variables for Step 2 (N=99)*

	aMCI (N=41)	naMCI (N=31)	PD-SCD (N=2)	PD-aMCI (N=9)	PD-naMCI (N=16)
Age	68.2 ± 9.2	69.7 ± 9.2	70.5 ± 2.1	65.2 ± 7.8	68.1 ± 7.2
Education	11.7 ± 3.8	10.5 ± 2.8	15.5 ± 3.5	9.1 ± 2.0	11.9 ± 3.1
WST - IQ	108.7 ± 12.3	104.2 ± 11.9	116.5 ± 17.7	98.4 ± 12.8	109.4 ± 10.6
Female	46.3 %	48.4 %	0.0 %	44.4 %	37.5 %
MMSE	27.9 ± 1.4	27.4 ± 1.8	28.5 ± 0.7	26.4 ± 2.4	28.6 ± 1.3
BDI II	12.4 ± 1.1	9.6 ± 1.3	8.0 ± 5.0	12.2 ± 3.0	8.4 ± 1.8
GDS	4.3 ± 0.5	3.9 ± 0.6	4.0 ± 2.8	3.8 ± 1.3	2.3 ± 0.8

Note: Age and education in years.**Table 4.***Demographic characteristics of the sample and Dependent Variables for Step 3 (N=141)*

	Converters (N=8)		Non-Converters (N=133)	
	(Baseline)	(Follow-up)	(Baseline)	(Follow-up)
Age	69.1 ± 9.6	71.1 ± 9.5	67.4 ± 9.4	70.4 ± 9.2
Education	10.5 ± 3.8	-	11.9 ± 3.6	-
WST-IQ	107.4 ± 14.2	103.3 ± 11.3	110.5 ± 12.0	108.2 ± 18.2
Female	37.5 %	-	57.9 %	-
MMSE	25.9 ± 2.2	25.0 ± 1.6	28.2 ± 1.3	28.0 ± 1.4
BDI II	11.1 ± 7.4	11.4 ± 8.6	10.7 ± 7.4	10.7 ± 7.2
GDS	4.9 ± 4.9	5.3 ± 3.4	3.7 ± 3.1	3.4 ± 3.3

Note: Age and education in years.

Table 5.*Demographic characteristics of the sample and Dependent Variables for Step 4 (N=168)*

	Improvement (N=28)		Deterioration (N=57)		No Change (N=83)	
	(Baseline)	(Follow-up)	(Baseline)	(Follow-up)	(Baseline)	(Follow-up)
Age	67.3 ± 8.5	69.9 ± 8.2	69.0 ± 9.3	72.0 ± 9.0	66.5 ± 9.0	69.2 ± 9.1
Education	11.1 ± 3.7	-	12.0 ± 3.5	-	11.8 ± 3.6	-
WST-IQ	106.8 ± 12.1	105.9 ± 11.6	111.9 ± 12.0	109.2 ± 18.9	109.2 ± 12.3	106.5 ± 17.4
Female	20.0 %	-	28.9 %	-	51.1 %	-
Male	12.8 %	-	39.7 %	-	47.4 %	-
MMSE	28.0 ± 1.6	27.6 ± 1.2	27.6 ± 1.8	27.7 ± 1.8	28.4 ± 1.3	27.9 ± 1.5
BDI II	12.6 ± 7.7	11.3 ± 7.5	10.2 ± 6.7	10.6 ± 7.0	10.2 ± 7.2	10.0 ± 7.3
GDS	4.3 ± 3.1	3.8 ± 3.0	3.6 ± 3.1	3.3 ± 3.0	3.4 ± 3.0	3.4 ± 3.6

Note: Age and education in years.

Table 6. Factorial ANOVA with Repeated Measurement for Step 1 (3x2), Step 2 (6x2), Step 3 (2x2) and Step 4 (3x2) for BDI and GDS Score ($N_{Step\ 1,2,4} = 168$, $N_{Step\ 3} = 141$)

Source	Dependent Variable	Analysis Level	df_1, df_2	F	η^2_p	p
Diagnose	BDI II	Step 1	2, 160	0.84	.010	.436
		Step 2	5, 157	0.92	.028	.471
		Step 3	1, 130	0.07	.001	.798
		Step 4	1, 160	1.12	.014	.329
	GDS	Step 1	2, 156	1.86	.549	.159
		Step 2	5, 153	1.01	.032	.414
		Step 3	1, 130	2.12	.016	.148
		Step 4	2, 156	0.55	.006	.580
Time	BDI II	Step 1	1, 160	0.27	.002	.601
		Step 2	1, 157	0.01	.001	.981
		Step 3	1, 130	0.01	.001	.943
		Step 4	1, 160	0.92	.006	.338
	GDS	Step 1	1, 156	0.01	.001	.934
		Step 2	1, 153	0.04	.001	.841
		Step 3	1, 130	0.01	.001	.967
		Step 4	1, 156	0.90	.006	.344
Diagnose x Time	BDI II	Step 1	2, 160	0.03	.002	.971
		Step 2	5, 157	0.37	.012	.869
		Step 3	1, 130	0.04	.000	.838
		Step 4	2, 160	1.12	.014	.329
	GDS	Step 1	2, 156	0.70	.009	.497
		Step 2	5, 153	0.64	.020	.670
		Step 3	1, 130	0.44	.003	.509
		Step 4	2, 156	0.51	.006	.602

Note: The table shows the main interaction effects of Step 1 (SCD, MCI, PD), Step 2 (SCD, aMCI, naMCI, PD-SCD, PD-aMCI, PD-naMCI), Step 3 (Converters to AD, Non-Converters to AD) and Step 4 (Deterioration, Improvement, No Change) analysis levels. Baseline Diagnoses are used for Step 1 and Step 2 analysis. Follow up Diagnoses are used for Step 3 and Step 4 analysis.

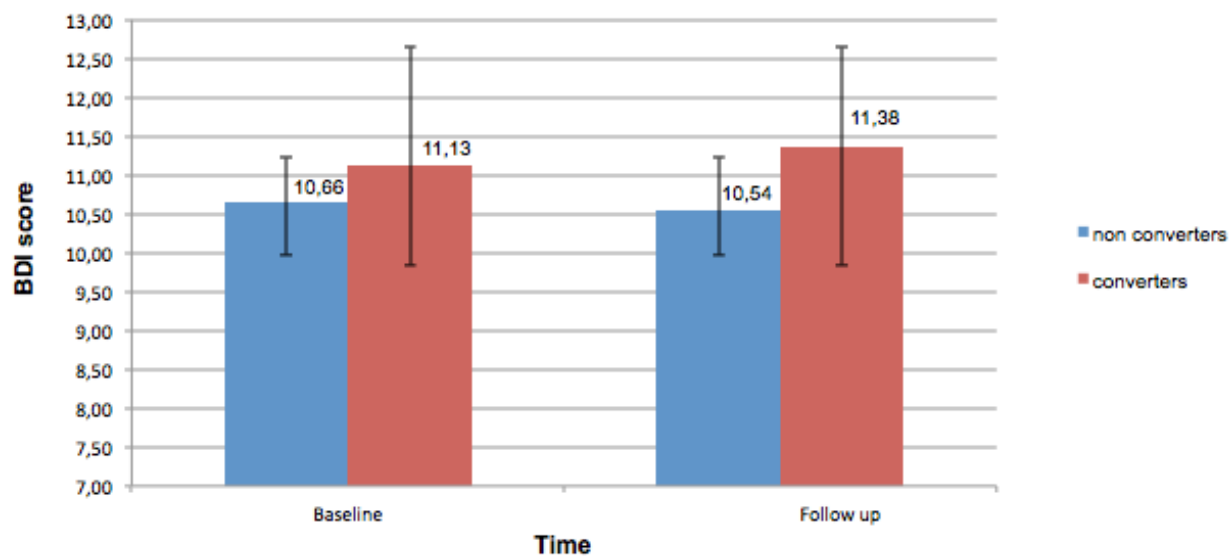
Figure A

Fig. A. Means of BDI II for converters and non-converters to AD for baseline and follow up assessment. Bars show standard errors.

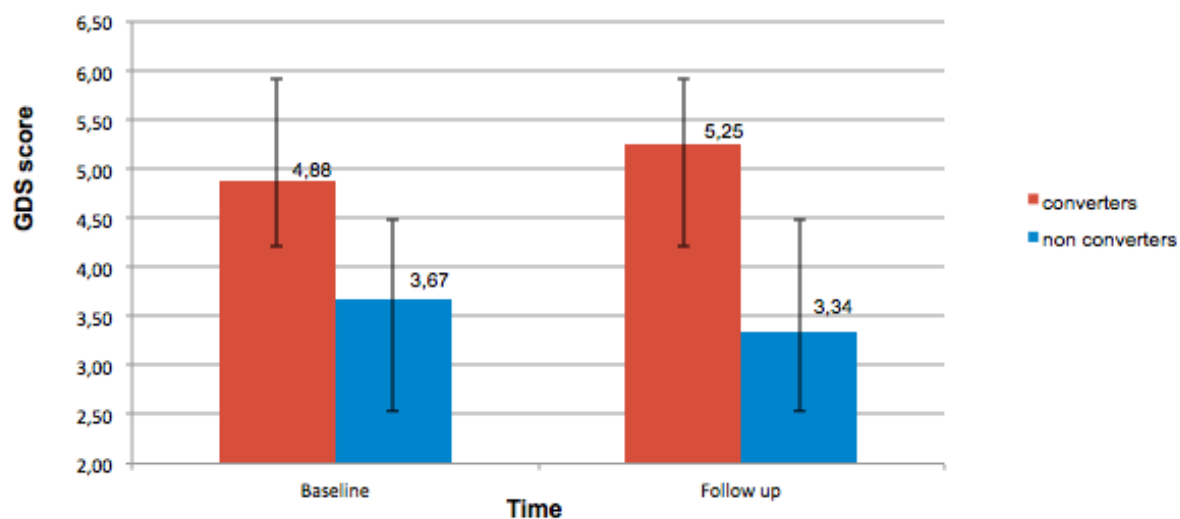
Figure B

Fig. B. Means of GDS for converters and non-converters to AD for baseline and follow up assessment. Bars show standard errors.

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Curriculum Vitae

Personal Data

Name: Lisa Tejkl
 Date of birth: March 14th, 1988
 Nationality: Austria

Education

04/2007 – 06/2015 **Diplomstudium Psychology**
 University of Vienna

10/2006 – 01/2007 Studium der Sprachwissenschaften
 University of Vienna

09/2000 – 06/2006 Gymnasium Ort der Kreuzschwestern, Gmunden

Work Experience and Activities

09/2013 – 04/2014 Student apprentice at the memory outpatient clinic, Department of
 Neurology, Medical University of Vienna

02/2013 – 04/2013 Trainee at pro mente Reha Sonnenpark, Bad Hall

10/2011 – 01/2012 Student advisor, University of Vienna

07/2007 – 08/2007 Childcare at Kindergarten Marienbrücke, Gmunden

Student Work Experience

08/2012 – 09/2013 Shop assistant at Eisgreissler, Vienna

09/2011 – 12/2014 Employee at Stadthalle Events, Vienna

11/2010 – 12/2014 Assistant at Unicef Sales, Vienna

Additional Qualifications

Foreign Languages

English: fluent
 French: basic knowledge

Computer Knowledge

Microsoft Office: Word, Excel, Power Point
 Statistical and analytical software: SPSS