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Famous faces and lexical-geographical knowledge as low effort tasks 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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Famous faces and lexical-geographical knowledge as low effort tasks 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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Abstract **Background:** Early detection of dementia is becoming more and more important due to the increasing possibilities of pharmacologic treatment. Novel tests assessing semantic memory seem promising. Evidence for predictive value for conversion to Alzheimer's disease (AD) is pending.

Objective: Tests of face-to-name (FACE) and capital-to-country matching (CITY) were approved in detection of conversion to AD.

Design: Patients complaining about cognitive problems who came to the memory outpatient clinic for assessment of a possible cognitive disorder were included in the study. Each patient was assessed twice to establish a longitudinal view.

Participants: Sixty-nine patients subjectively complaining about memory problems (SCD), seventy-two patients meeting criteria for mild cognitive impairment (MCI), and twenty-seven patients with Parkinson's disease (PD) fulfilled inclusion criteria (n = 168, mean age: 67.5 ± 9.06 years).

Results: An area under the curve (AUC) of .72 for the CITY (.59 for the FACE) resulted for conversion to AD. The CITY showed a sensitivity of .71 and a specificity of .76 (.57 and .77 for the FACE). The CITY revealed a positive predictive value (PPV) of .14 and a negative predictive value (NPV) of .98 (.12 and .97 for the FACE). Overall accuracy (ACC) of .76 appeared for the CITY (.76 for the FACE). Both tests failed in differentiating between SCD, MCI and PD at baseline measurement after correction for confounding variables.

Conclusion: Both tests of semantic memory have potential for prediction of conversion to AD (stronger magnitude in the CITY). As in the current version, they do not measure up with tests of episodic memory owing to extensive ceiling effects and confounding. Raising item difficulties and approving them for specific objectivity by Item Response Theory may increase their predictive value.

Keywords: Semantic memory; Mild cognitive impairment; Dementia

1. Introduction. In an aging society, two questions are becoming more and more fundamental to the growing number of elderly people: *Do I already suffer from dementia? And if I don't, will I become demented?* Ferri et al. (2006) estimated that about 24.3 million people are suffering from dementia worldwide and that prevalence will double every 20 years. Dementia is known as highly conditional on age: Estimates so far indicate a rate of about 10 % of people older

than 65 years suffer from dementia (Knopman et al., 2001). Furthermore, probability of conversion to dementia increases with age: In people 55-59 years old, annual conversion rate (ACR) was found to be less than 1 %, whereas it was about 9 % in people older than 95 years (Petersen et al., 2001). Dementia, as a term, refers to a human condition in which brain damage causes sustainable cognitive decline se-

verely enough to interfere with daily functioning. Therefore, dementia describes a group of symptoms, which can be caused by different diseases. According to a 30 year retrospective study investigating the distribution of neuropathologically-defined dementia subtypes, Alzheimer's disease (AD) was the most common cause of dementia (42 %), followed by vascular diseases (23.7 %) and combined Alzheimer's and vascular pathology (21.6 %) (Brunnström, Gustafson, Passant, & Englund, 2009). The Rotterdam Study provided more differentiated results: Overall prevalence of dementia was 6.3 %. AD dementia was the main sub-diagnosis (72%). Compared to AD, the relative proportion of vascular dementia (16 %), Parkinson's disease (PD) dementia (6 %) and other forms of dementia (5 %), decreased with age. The prevalence of dementia increases exponentially with age; about one third of people older than 85 years have dementia (Ott et al., 1995). Degenerative processes in AD primarily involve degradation in posterior cortical regions reflecting in memory problems, but degradation in frontal cortical regions causing impairment of executive functioning have also come to discussion (Rozzini et al., 2007).

Morbus Parkinson, mainly affecting the extrapyramidal motor system, is also increasing the risk of final dementia: Point prevalence of dementia among PD varies from about 30 % (Aarsland, Andersen, Larsen, & Lolk, 2003; Aarsland, Tandberg, Larsen, & Cummings, 1996; Aarsland, Zaccari, & Brayne, 2005) to 43.3 % (Janvin, Larsen, Aarsland, & Hugdahl, 2006) in the literature, thus showing relatively stable rates. A six-fold increased risk for dementia development with PD as a generic illness compared to healthy controls has been reported (Aarsland et al., 2001). According to Aarsland et al. (2003), nearly 80 % of PD will finally develop dementia: In an eight-year prospective study, 26 % of PD were diagnosed with dementia at baseline. 78.2 % of PD finally developed dementia after 8 years. Patients who are diagnosed with AD or PD are definitely at a vastly increased

risk for developing dementia. Therefore, the current study takes both disease groups into account.

Detecting dementia in early stages has become a major challenge for clinicians. According to Knopman et al. (2001), no laboratory measures have yet emerged that are appropriate for routine use in the clinical evaluation of persons with suspected AD. Thus, neuropsychological assessment is playing an increasingly important role in diagnostic of early dementia. Mild cognitive impairment (MCI) has become the most prominent term in dementia early diagnosis over the last decades. Traced by neuropsychological test batteries, MCI implies impairment in one or more cognitive domains, which does not meet criteria for dementia (Petersen et al., 2001). Estimated prevalence of MCI in population-based studies ranges from 10 % to 20 % in persons older than 65 years (Busse, Hensel, Gühne, Angermeyer, & Riedel-Heller, 2006; Di Carlo et al., 2007; Lopez et al., 2003; Manly et al., 2008; Plassman et al., 2008). According to Petersen et al. (1999), about 12 % of patients with MCI convert to dementia yearly, whereas the ACR in the cognitively normal population is about 1-2 %. ACRs vary from 1 % to 25 % in the literature, dependent on sample characteristics, diagnostic criteria and measurement instruments (Dawe, Procter, & Philpot, 1992). For example, the ACR in clinical samples is estimated about 10 % to 15 %, while it is about 5 % to 10 % in population-based samples (Petersen, 2011). Compared to controls, MCI show poorer performance in both verbal and visuospatial episodic memory, semantic memory, executive functioning and praxis, processing speed and attention (de Jager, Hogervorst, Combrinck, & Budge, 2003). Furthermore, mild cognitive impairment can be divided into amnesic mild cognitive impairment (aMCI) and non-amnesic mild cognitive impairment (naMCI). The amnesic type of mild cognitive impairment means clinically significant memory impairment that does not meet criteria for dementia. It is the most common type of MCI, showing a

point prevalence of about 11.1 % within a sample of 79 to 90 year-old patients in the Mayo Clinic Study of Aging (Petersen, 2011). Lehrner et al. (2005) reported an ACR of about 20 % for patients diagnosed with aMCI. They concluded that the risk for conversion to AD with aMCI as a preceding diagnosis is about 8.6 times higher than the risk for patients without any objective memory impairment. Furthermore, there is a higher risk for patients diagnosed with aMCI for progression to AD than to other dementia forms reflecting the memory specific symptoms of early AD (Amieva et al., 2004; Mitchell & Shiri-Feshki, 2009; Petersen, 2011). Non-amnesic MCI instead is characterized by subtle decline of cognitive functions other than memory, such as attention, use of language, executive functioning or visuospatial skills (Petersen, 2011). With a point prevalence of 4.9 % in the Mayo Clinic Study of Aging, it is considered less common than aMCI. Characterized by non-memory cognitive impairment, it is supposed to be a forerunner of dementia not related to AD, such as frontotemporal lobar degeneration or dementia with lewy bodies (Petersen, 2011). But the concept of MCI is problematical. Of course, there are patients converting to AD with preceding naMCI and patients converting to less common dementia forms with preceding aMCI. Literature suggests even a reversion rate from MCI to regular cognitive states of about 25 % to 30 % (Petersen, 2011). The instability of MCI diagnosis shows that MCI is not a diagnostic entity in the same way as AD (Milwain, 2000). Additionally, prevalence of MCI and characterization of different subtypes, if varying widely, are dependent on measures used, numbers of tests, reliability of measures, quality of normative data and statistical thresholds (Puszwald et al., 2013). Equivalent and extensive prevalence variations of MCI subtypes, owing to different MCI classification modes, could also be observed in PD (Lehrner et al., 2014). Establishment of the Mayo criteria is the most promising approach to standardize and improve MCI diagnostic at present. Petersen et

al. (2001) postulated that 80 % of MCI diagnosed with explicit Mayo criteria would convert to dementia within a six-year time period. Mitchell and Shiri-Feshki (2009) found in a meta-analysis, that MCI patients diagnosed with Mayo criteria had an ACR of 10 %, compared to an ACR of 5 % in patients diagnosed with concepts not using Mayo criteria. Mayo criteria were also used for MCI classification in the current study and will be described below. According to Mitchell and Shiri-Feshki (2009), MCI is neither sufficient nor necessary for transition to dementia and may reflect a group of various diseases. Thus, the heterogeneous character of MCI gives needs to find predictors and tests, which may improve measurement of early signs of dementia (Amieva et al., 2004). Taking this intent into consideration, the current article sheds light on two semantic memory tests (assessing the remote memory), to investigate applicability of those tests for daily clinical use in detecting dementia in early phases and conversion to AD.

A patient's self-referred memory problems, known as subjective cognitive decline (SCD) in literature (Jessen et al., 2014), may both enhance validity of MCI diagnostics and be predictive for later dementia even without meeting full criteria for MCI. A risk that is two to five times higher in people complaining about memory problems for developing dementia is reported, especially when MCI criteria are met (Jonker et al., 2000). In contrast, Jessen et al. (2010) did not find predictive capacity of pure SCD for later dementia. Links to depression, gender (female), lower premorbid IQ and lower education are reported. Therefore, especially in older and higher-educated persons, SCD revealed predictive capability, while in younger and lower educated persons, it may be due to personality factors, anxiety or depression (Jonker et al., 2000). Nevertheless, with SCD at baseline and MCI following, patients showed greatest risk for conversion to AD (OR: 19.8). An even higher risk was observed with preceding SCD and aMCI following (OR 60). This

gives rise for modeling an ideal course of pathological aging ending up in dementia, with healthy aging in the beginning, followed by self-sensed memory problems (SCD) not resulting in test performance significantly under average, changing to objective memory impairment not meeting criteria for dementia (MCI) and finally ending up in dementia. SCD as an antecedent stage may improve specificity (Jessen et al., 2010).

The concepts of MCI and SCD are also common in PD. According to Lehrner et al., (2014) about 15% of PD seeking help in a movement disorder clinic reported significant self-referred memory problems (PD-SCD), with an increasing degree from cognitively healthy PD to PD with MCI (PD-MCI). In a longitudinal study, Janvin et al. (2006) found cognitive impairment not meeting dementia criteria in 52.8 % of PD at baseline and 68 % of them reported memory or other cognitive problems. After 4 years, 62 % of PD-MCI were demented, compared to 20 % of PD showing no cognitive impairment at baseline.

Although the concept of MCI is problematical, it definitely suggests, at least, where present, a higher risk for falling ill with forms of dementia and thus justifiably takes its place in clinical daily work. Revising the concept, the measurement and the applicability of MCI seems profitable. Thus, this study takes a closer look at the concept of semantic memory, which will be described below.

1.1 Episodic and semantic memory

Memory is a cardinal point in neuropsychological test batteries used for detection of dementia. Theory of memory is manifold, but Tulvings (1972) concept of episodic and semantic memory is widely accepted and applied: The episodic memory receives and stores information about temporally dated episodes, and temporal-spatial relations among those events. It is consid-

ered to hold personal experiences. Compared to semantic memory, it is more susceptible for transformation, easier to forget and has to be recorded directly into memory storage. AD patients show significant problems in encoding new material, thus impairment of episodic memory is considered as the main symptom of AD (Dudas, Clague, Thompson, Graham, & Hodges, 2005; Thompson, Graham, Patterson, Sahakian, & Hodges, 2002). Episodic memory is considered to be the domain earliest affected in approaching AD (de Jager et al., 2003) and is correlated to the structures of the medial temporal lobe including the hippocampus and transenthorinal regions (Braak & Braak, 1991; Thompson et al., 2002). This is also where maximum pathology in early AD occurs, spreading subsequently from the limbic stage to the neocortex (de Jager et al., 2003). In neuropsychological test batteries, transenthorinal damage is reflected by impaired delayed recall of recently learned episodic memory units and can be considered as the most important marker for AD (Greene & Hodges, 1996; Thompson et al., 2002).

Instead, the semantic memory is described as a mental thesaurus in which organized knowledge about words and other verbal symbols, their meaning and referents, relations among them, rules, as well as formulas and algorithms for symbol manipulation are organized. Unlike episodic memory, it refers to knowledge. It is less susceptible to transformation, more difficult to forget, usually assimilated into a rich structure of concepts and their relations can be recorded indirectly (Tulving, 1972). It may be difficult to grasp the full meaning of semantic memory, but Verma and Howard (2012) provide a holistic but short definition: "*Semantic knowledge relates to entities around us, and semantic memory represents neural concepts of these. Through life, these concepts are learned and built upon with experience and interaction with the world.*" (p. 1211)

The semantic memory, too, undergoes several changes during the course of AD.

Impairment is indicated by problems in naming objects and pictures, in defining objects, and by poor comprehension of oral and written language (Mårdh, Nägga, & Samuelsson, 2013). It is possible that learned and saved units belonging to the episodic memory may become semantic ones through dissociation of time and spatial relations. If a first grade child, for example, learns to write the word “dad” for the very first time, he/she surely will remember the classroom, the teacher’s movements performed on the blackboard, the special time in the class schedule or other distinctive features of class. The knowledge how to write the word “dad” and its meaning, therefore, is an episodic one. But after a while, all those times, space and movement relations will have vanished. What remains is the mere knowledge of the word “dad” and its meaning, therefore faded from episodic memory into becoming a semantic memory unit.

These processes are included and linked to brain areas in the Standard Model of Memory Acquisition (Squire, 1992): The hippocampus and related medial temporal lobe structures play a time-limited role in the storage and recovery of a memory trace, which diminishes as consolidation proceeds. Conversely, with time, long-term memory storage becomes increasingly dependent on the temporal neocortex. Through repetition and practice, episodic memory units become semantic knowledge (Cermak, 1984). Semantic memory impairment, therefore, suggests dysfunction beyond hippocampal structures and is also prevalent in AD. Dudas et al. (2005) and Amieva et al. (2004) could show a link between measurement of temporal lobe structures and progression of dementia. Because of the unclear concept of MCI and its need for improvement as well as expressing the difficulties of early dementia diagnosis, this article questions if the concept of semantic memory with its construed tests is predictive for AD and can enrich neuropsychological tests batteries designed to signal conversion to dementia. Perry and Hodges

(2000) did not find significant correlations between episodic memory and functional performance. Instead, they postulated high correlations between semantic memory and functional performance. They concluded that semantic memory together with spatial functions might be the most important domains of everyday skills known to be impaired in AD. As already pointed out, semantic memory has a strong relation to the use of language. AD show a mixture of expressive and receptive language deficits (Appell, Kertesz, & Fisman, 1982). Naming and verbal fluency deteriorate in progressing AD (Taler & Phillips, 2008). This language dysfunction appears prediagnosical: Verbal fluency, for example, is already impaired 5 years prediagnostically, with a most significant drop two years before conversion to AD (Auriacombe et al., 2006). MCI show comparable semantic memory deficits like AD (e. g. category fluency and object knowledge) with a stronger extent for aMCI (Adlam, Bozeat, Arnold, Watson, & Hodges, 2006; Lonie et al., 2009). There have been considerations about dependencies of these pathological language dysfunctions, either being dependent on overall breakdown of semantic memory, or being due to failing phonological access and retrieval problems (Bayles, Tomoeda, Kaszniak, & Trosset, 1991; Mårdh et al., 2013). Verma and Howard (2012) showed that language impairment in AD has clear dependency on semantic memory breakdown. Stronger impairment of semantic memory fluency and naming tasks than for phonological fluency in early AD, suggests general semantic breakdown to be a main reason for language impairment (Taler & Phillips, 2008). Also a steeper decline in semantic fluency (naming animals and supermarket items) than for letter fluency (phonological fluency with letters f, a and s) over time in MCI and AD compared to cognitively normal patients could be observed in a longitudinal view (Clark et al., 2009). Of course, harder semantic fluency and naming impairment over phonological impairment in approaching and current AD, does not

predestine overall semantic breakdown to be a singular reason for language dysfunction. But Mårdh et al. (2013) could show congruent impairment patterns in a longitudinal study: Word reading, word reading comprehension, as well as semantic attribute judgment tests were applied to AD patients in three test occasions within one year. Significantly more semantically related attributes were found for comprehended words by the patients. In the second and the third test occasion, mostly the same words and the same categories (out of 10 possible and easy categories like animals, fruits or vegetables) were found to be impaired by each patient. The impairment patterns, given by special configurations of deteriorated knowledge for specific categories, remained stable over all three test occasions for most of the AD patients. Varying impairment patterns would have suggested an increased influence of phonological retrieval problems. Therefore, a bulk of language problems in early and current AD seems to be due to basal semantic memory deterioration. Evidence for predictive value of semantic memory tests for conversion to AD, when compared to literature about episodic memory, is rare. The main purpose of this study is an attempt to close this gap. Quaranta et al. (2014), for example, identified different subtype patterns of MCI by cluster analysis and focused on conversion to AD within a time frame of five years. A pure amnesic cluster, defined by episodic memory impairment, showed a conversion rate of 48.3 %. Multiple domain cluster, defined by impairment in various domains, showed the highest conversion rate (68.5 %). An amnesic/semantic cluster, defined by semantic memory impairment, showed a conversion rate of 36.4 %. They concluded that episodic and semantic memory deficits without any other cognitive disturbances are associated with a slower disease progression than multiple domains of MCI.

In sum, semantic memory is affected in neurodegenerative diseases like AD and related memory problems do not seem to stem from failed phonological access. Semantic

memory deterioration is also prevalent in MCI. Evidence for predictive value of semantic memory impairment for conversion to dementia is largely pending so far and has yet to be adopted.

1.2 Famous faces

In foretelling difficulties that come with trying to define semantic memory, assessment of semantic memory can be arranged in many ways and often is accompanied by problems. The challenge is to ask for knowledge certainly learned in the past and which has already been consolidated into semantic memory. Fluency and naming tests have been widely adopted for diagnostic work (e. g. Murphy, Rich, & Troyer, 2006; Piatt, Fields, Paolo, Koller, & Tröster, 1999; Randolph, Braun, Goldberg, & Chase, 1993), but it may be difficult to assess less common, more unique and arbitrary knowledge. Application of semantic memory assessment for dementia diagnosis purposes further requires relevance to the symptoms of dementia. Loss of person-related knowledge, such as remembering names or identifying faces, might be a main symptom in AD (Werheid & Clare, 2007). It is well known that access to semantic knowledge about famous people is particularly vulnerable in patients in the early stages of AD (Ahmed, Arnold, Thompson, Graham, & Hodges, 2008; Greene & Hodges, 1996). This considerations lead to the idea of testing for knowledge about famous faces to differentiate MCI from cognitively healthy controls, which has been done in a few studies so far (Ahmed et al., 2008; Clague, Graham, Thompson, & Hodges, 2011; Greene & Hodges, 1996; Snowden, Thompson, & Neary, 2004; Thompson et al., 2002). Another attempt has already been carried out to assess knowledge about famous buildings (Ahmed et al., 2008). As mentioned earlier, two semantic memory tests are under investigation in this study: (1) The FACE test, involving celebrity face-to-name matching

and (2) the CITY test, involving country-to-capital matching. In both tests, items are answered in a multiple choice format (one out of four options; guessing probability 25 %). Basically, assessment of semantic memory goes along with two very important considerations: (I) What type of knowledge is used for assessment of semantic memory, and (II) how is it tested?

(I) First of all, it is important to consider the special topic of semantic knowledge asked for in a test. Vogel, Gade, Stokholm and Waldemar (2005) focused on impairment distributions of different semantic memory tests, including naming of famous faces among mild cases of AD and pre-demented AD: Among patients with mild AD, category fluency (67 %) and naming of famous faces (53.5 %) was proven to be mostly impaired, when compared to naming common objects (14.9 %) and phonological fluency (14.0 %). Also among predemented patients with AD, category fluency (31.8 %) and naming famous faces (22.7 %) were showed to be impaired more frequently, when compared to naming of common objects (0 %) and phonological fluency (0 %). The authors concluded that since subtle changes of semantic memory are present prior to clinical diagnosis of AD, famous faces tests may be more sensitive to the earliest phases of AD than tests in which naming of objects is required. Naming common objects appears to be much easier than retrieving the names of celebrities by looking at photos of their faces. Proper names are arbitrary and unique so it is possible that neural connectivity may be weaker than with concrete nouns, which usually refer to a whole class of objects (Werheid & Clare, 2007). Thompson et al. (2002) found that 29% of AD performed normally on graded object naming tests, while 16 % of them performed normally on a graded face-naming test. 96 % of patients with questionable dementia of Alzheimer's type (QDAT, a term related to the concept of MCI), performed normally on a graded object-naming test, whereas 64% of them showed impairment on graded face-naming tests. Retrieval

of unique exemplars, when compared to common ones, may be more difficult and therefore be more sensitive for dementia and its preceding states (Ahmed et al., 2008). Also Clague et al. (2011) found naming and semantic knowledge of famous people to be more impaired than naming and semantic knowledge of objects in patients with MCI. Furthermore, proper nouns showed accelerated deterioration in the course of AD. Hypothesizing a possible explanation, they assumed that knowledge of unique exemplars is "less robust" than more generic knowledge. Objects may rely to a much greater extent upon their sensory and functional properties and thus be more trained. Knowledge of famous people instead, may be more unique and idiosyncratic, thus leading to greater sensitivity for semantic degradation (Joubert et al., 2010). A higher degree of impairment of specific semantic knowledge compared to general semantic knowledge has been corroborated in a few studies (Clague et al., 2011; Greene & Hodges, 1996; Joubert et al., 2010; Swainson et al., 2001; Thompson et al., 2002). The idea of core concepts of semantic knowledge which are less susceptible for deterioration in approaching AD, like single words or common objects, compared to peripheral concepts like special and unique knowledge of famous persons, gives rise to the idea of famous faces tests and related attempts.

(II) Second, embodiment of assessment of semantic knowledge is highly decisive. Simplified, there are three ways of retrieving information about famous faces or equivalent knowledge: (i) Asking for free reproduction of a memory unit without any hint, from now on referred to as "confrontation naming task" (e. g. "What is the name of this person?"), (ii) Requiring proof of acknowledgment about a stimulus by asking for specific information, from now on referred to as "identification task" (e. g. "What do you know about this person?"), and (iii) requiring recognition of a name or a related attribute for a special stimulus by multiple choice task (e. g. word-to-picture

matching), from now on referred to as “recognition task” (e. g. “Which one of the four names given belongs to the face on the picture?”). As Werheid and Clare (2007) pointed out, naming tasks appeared to be the most difficult in cases already impaired by very early forms of neurodegenerative processes like MCI. According to Burke, MacKay, Worthley and Wade (1991), names are purely referential so they need a level of proper one-to-one connections to be activated. Impairment of identification tasks, instead, tolerating higher levels of degradation of knowledge by giving a wider scope of possibilities to resolve an item, should be absent in milder states of memory degeneration. Finally, recognition tasks required little effort and, thus, are easy to solve and should only show impairment in advanced forms of memory degeneration. Thereby, the possibility to draw conclusions about disease severity arises. As Thompson et al. (2002) could show, AD are impaired in naming, knowledge (identification) and recognition of famous faces. Patients with questionable dementia of Alzheimer type (QDAT) also performed under average in the naming tasks, but only showed a non-significant trend of impairment in identification tasks. The results of impairment in person-naming tasks of MCI and AD could be replicated (Dudas et al., 2005). Greene and Hodges (1996) found further evidence for this suggested framework: In a total of 63 subjects, AD also showed impairment in face naming, identification and recognition tasks. Furthermore, AD identified a smaller proportion (68 %) of faces they recognized, than controls (91 %). AD also named a smaller proportion (42 %) of faces they identified, than controls (79 %). These percentages show how embodiment of assessment influences difficulty of the tasks and, hence, test performance of patients. In contrast, Clague et al. (2011) found impairment of MCI in naming, identification, verbal and nonverbal associatives and sorting tasks, as well as matching names to faces (recognition) relatively to controls. But as with the findings of Greene and Hodges (1996),

identification tasks were easier than naming for both groups. There is evidence that MCI cannot be separated from controls on the basis of knowledge (identification) and familiarity (recognition) of famous people (Juncos-Rabadán, Rodríguez, Facal, Cuba, & Pereiro, 2011). But it also may be crucial to identify the subtype of MCI in question. For example, impairment of naming and knowledge of famous people was found for aMCI (Joubert et al., 2010). All of these suggestions can be fitted into a model, namely, the Sequential Model of Face Recognition (Bruce & Young, 1986). It declares face recognition and face naming as a successive sequential mode, in which preceding levels are presupposed for subsequent levels. Three levels are important to this model: (1) Structural representation: Distinguishing the specific facial configuration of a person [Face matching]; (2) Face recognition units: Familiarity judgment [Yes or No decisions]; (3) Person identity nodes: a) access to semantic information; b) name access and generation (phonological). According to this model, AD affects level 3 with progression to level 2 and finally level 1. That means that in MCI, access to semantic knowledge (identification) and free recall of person names (naming) should be impaired. With progression of the disease and its conversion to dementia, recognition of a special face should also become problematical. The dependency of famous faces tests on disease severity as measured by MMSE has been rarely proved yet. Greene and Hodges (1996) found only weak correlations between naming, identification and recognition of famous faces and dementia severity measured by MMSE. Giannakopoulos et al. (2000) found, instead, that the grade of impairment of faces tasks is associated with disease severity evidenced by autopsy in density of neurofibrillary tangles in the prefrontal and anterior cingulate cortex.

In short, stimuli content and embodiment of the task is crucial to test performance within semantic memory assessment. Tests asking for unique and arbitrary

knowledge may be more sensitive to early AD than tasks asking for common knowledge. Additionally, task effort of resolved items may be an indicator of disease severity. If these suggestions can be held true, construction of semantic memory tests designed to predict conversion to dementia has to consider this framework. This study also tries to investigate the latter-made suggestions in an exploratory manner.

General semantic memory tests requiring verbal abilities (e. g. semantic or phonological fluency tests) do not show high correlations with person-specific semantic knowledge. Tests of general semantic knowledge explained only 20 % of variance in person-specific tasks, suggesting independence for person specific semantic knowledge (Thompson et al., 2002). However, person-specific knowledge accessed by names or face-naming, appeared to be stronger correlated with general semantic memory tests than identification and recognition of famous faces (Greene & Hodges, 1996; Snowden et al., 2004).

Indeed, famous faces tasks do show value for clinical diagnostic work. A positive prediction value (PPV) of .60 and a negative prediction value (NPV) of .94, with sensitivity of 87 % and a specificity of 81 % were found for dementia conversion in a graded face-naming test (Thompson et al., 2002). An attempt of assessing knowledge about famous buildings in a comparable manner was likewise promising: Graded building tests showed the highest correlation with dementia diagnosis ($r = .60$), followed by graded face tests ($r = .47$), while the graded naming tests using pictures of objects showed weakest correlation ($r = .16$). Graded face tests and graded building tests also separated MCI from controls better than graded object-naming tests. Accuracies for graded building tests and graded face tests were equivalent (Ahmed et al., 2008). However, episodic memory tests seem to outrank famous face tests in detecting conversion to dementia. The Hopkins Verbal Learning Test (Brandt, 1991) for example, an episodic memory test, showed

sensitivity higher than 90 % for conversion to dementia. On the other hand, there is also evidence for weaknesses for episodic memory tests. The Rivermead Paragraph Recall Test (Wilson, Cockburn, & Baddeley, 1985) for example, failed to distinguish MCI from controls (de Jager et al., 2003). The question of what test predicts dementia best cannot be clearly answered and is due to multiple factors, including the subtype of dementia, duration of progress and disease severity. As Semenza, Mondini, Borgo, Pasini and Sgaramella (2003) pointed out, tests of person knowledge are sensitive to early phases of AD. As already suggested, literature about the predictive value of semantic memory impairment for dementia conversion is rare. This is also true for deteriorated person knowledge. However, it seems possible that person knowledge impairments may provide some marker of disease severity and possibly predict conversion to AD. The severity sensitivity of semantic tests might serve as an indicator of conversion to dementia (Clague et al., 2011). Blackwell et al. (2004), for example, found a test composite consisting of a graded naming test and a visuospatial learning test with 100 % accuracy for detecting cognitive dysfunction characteristics of pre-clinical AD. Finally, and also in an explanatory manner, this study compares both semantic memory tests under investigation with other tests and further tries to elicit a most predictive test composite for MMSE.

In brief, this study tries to investigate applicability of two semantic memory tests with a low effort task embodiment for detecting early signs and conversion to dementia. Therefore, a longitudinal view with two assessment sessions was established. Both tests are reviewed for confounding variables. (1) The first goal of the study was to determine test differences between the groups of SCD, MCI and PD. Due to low effort task embodiment achieved by multiple choice response format, no group, time or interaction effects in repeated measures ANOVA are expected. (2) As a second goal, figuring out differences in test performance

between various subtypes of MCI, PD-MCI and SCD was aspired. Again, due to low task effort, no group, time or interaction effects are anticipated. (3) Third goal was to determine if these tests could predict conversion to AD. For patients on the verge of conversion to dementia, a weaker test performance and thus lower test score in both tests is anticipated. Additionally, decline of test performance for converters should be visible over time. A significant group effect and a significant interaction effect should result, showing a steeper decline of test scores for converters. Detailed investigation of the predictive value of the FACE and the CITY for conversion to AD by applying Receiver Operator Characteristics (ROC) is carried out. Additionally, some explorative questions are pursued: (4) To draw further conclusions about the influence of stimuli content and task embodiment, both tests in question, as well as other tests of semantic memory, are related to disease severity measured by MMSE. If suggestions about task demands and stimuli content are realistic, this should reflect in predictive power for disease severity measured by MMSE. (5) Finally, score of FACE and CITY is linked to disease severity measured by MMSE while tests of memory, attention, planning and non-verbal fluency are controlled. This last target should elicit a more predictive composite for MMSE and provide better insight in relations of both tests under investigation to MMSE if other cognitive domains are taken into account. References for improvement of FACE and CITY are recommended. Additionally, conversion rates are presented.

2. Methods

2.1 Subjects and procedure

The data used for this study are part of a larger research project known as the Vienna Conversion to Dementia Study. For projects using subsets of this main data set, methods,

test instruments and test procedures are similar to previous studies (Lehrner et al., 2014; Pusswald et al., 2013). The Vienna Conversion to Dementia study is a prospective cohort study of the Medical University of Vienna, administrated by the Department of Neurology. As approved by the Ethical Committee of the Medical University of Vienna, the study protocol was in accordance with the Helsinki Declaration. Encompassing consecutive, community-dwelling patients complaining about cognitive problems who come to the memory outpatient clinic for assessment of possible cognitive disorder, focus in this larger project is primarily on the determination of prevalence of four MCI subtypes. Examining conversion rates to AD using these four MCI subtypes is of further research interest. The current data, deriving from this larger data set, consists of SCD, MCI, and PD. Patients ($n = 168$) varying from 50 to 88 years in age with a mean of 67.5 ± 9.06 years. Seventy eight (46.4 %) of them were male and ninety (53.6 %) of them were female. Mean years of formal education were 11.7 ± 3.6 years. An MMSE mean of 28.1 ± 1.6 was observed overall. For Step 3 analysis, PD were excluded from the total sample providing a smaller subset ($n = 141$), because conversion to AD was only possible within SCD and MCI. All patients involved in the study fulfilled inclusion criteria. Patients were either referred by physicians or were self-referrals. Catchment area of the Department of Neurology and thus for current subjects in this study is Vienna and its surrounding area. Every subject in the sample was assessed twice. Time intervals between assessments are varying from 12 to 60 months (mean = 33 months; SD = 15.8 months). A u-shaped distribution was found for the interval variable and Shapiro-Wilk tests did not suggest normal curve distribution ($w = .90$; $p < .0001$).

A complete neuropsychological assessment was conducted with every subject. Further information about health status and behavioral disease characteristics of pa-

tients was gathered from relatives/caregivers using standardized questionnaires. A computed tomography scan or magnetic resonance imaging scan of the brain was obtained in most cases.

Exclusion criteria were in line with similar other studies. Patients were excluded if any of the following conditions applied: (a) evidence of stroke, as determined by neuro-radiologic and clinical examination; (b) history of severe head injury; (c) current psychiatric diagnosis according to International Classification of Disease, tenth revision (Organization, 1993); because of high prevalence of (sub)depressive symptoms in the elderly, patients with (sub)depressive symptoms were included; (d) any medical condition that led to severe cognitive deterioration, including renal, respiratory, cardiac, and hepatic disease; and (e) diagnosis of dementia according to Diagnostic and Statistical Manual of Mental Disorders, fourth edition (Association, 2000).

2.2 Neuropsychological assessment

Patients were subjected to a screening at the beginning of every investigation. The mini mental state examination (Folstein, Folstein, & McHugh, 1975), the clock drawing test (Sunderland et al., 1989) and the brief cognitive rating scale (Reisberg & Ferris, 1988) were applied. After completed screening, every patient was subjected to the Neuropsychological Test Battery Vienna (NTBV), which includes six domains as indicated by cluster analysis: (1) attention, (2) executive functioning – phonematic, (3) executive functioning – interference, (4) language, (5) memory and (6) executive functioning – planning and nonverbal fluency (Lehrner, Maly, Gleiß, Auff, & Dal-Bianco, 2007; Lehrner et al., 2005; Lehrner, Gleiß, Maly, Auff, & Dal-Bianco, 2006; Lezak, 2004; Pusswald et al., 2013). The following subtests were applied to assess domains: For assessment of attention, a geriatric cancellation test, the *Alters – Kon-*

zentrationen – Test (Gatterer, Fischer, Simanyi, & Danielczyk, 1989) was used, as well as the Trail Making Test version B (TMTB) and the score difference between Trail Making Test A (TMTA) and TMTB (Reitan, 1979), the digit symbol test of the German Wechsler Adult Intelligence Scale – Revised (Tewes, 1994) and the symbol counting task from the Cerebral Insufficiency Test (Lehrl, 1997). Assessment of language function was accomplished with a confrontation-naming test: the Boston Naming Test (Morris, Mohs, Rogers, Fillenbaum, & Heyman, 1987). To test semantic verbal fluency, patients were asked to name as many words as possible in the categories of animals, supermarket items, and tools within one minute for each category (Goodglass & Kaplan, 1972). Executive functioning – phonematic verbal fluency was assessed with a phonematic word fluency test (Goodglass & Kaplan, 1972). Patients were asked to name as many words as possible within one minute with beginning letters b, f, and l. Executive functioning – Interference was assessed with the Stroop test from the Nürnberger Alters Inventar (Oswald & Fleischmann, 1997) and the interference test from the Cerebral Insufficiency Test (Lehrl, 1997). Executive functioning – planning and nonverbal fluency was assessed with the planning maze test from the Nürnberger Alters Inventar (Oswald & Fleischmann, 1997), the Five-Point Test (Regard, Strauss, & Knapp, 1982) and the Trail Making Test version A (Reitan, 1979). Episodic memory was tested with the Verbal Selective Reminding Test (Lehrner et al., 2006) with the subtests of immediate recall, total recall, delayed recall, and recognition. Both the total recall and the recognition task were applied 20 minutes after the patients learned the words. Cognitive testing lasted approximately 45 minutes and was performed within one session for each patient. The NTBV showed very good ability in detecting AD in patients with an area under the curve reaching from .79 (Boston Naming Test) to .99 (Verbal Selective Reminding Test – delayed recall) as suggested

by the receiver operating characteristics curve analysis in previous studies (Lehrner et al., 2007). Questionnaires like the Becks Depression Inventory German version (Hautzinger, Bailer, Worall, & Keller, 1995), the Geriatric Depression Scale German version (Bach, Nikolaus, Oster, & Schlierf, 1994) and the Bayers Activities of Daily Living Scale (Hindmarch, Lehfeld, de Jongh, & Erzigkeit, 1998) were applied after cognitive testing. The FACE and the CITY test were also submitted within this consecutive test phase after the NTBV.

2.3 Semantic memory assessment

Semantic memory was assessed with the FACE and the CITY test. Both tests include 16 items. For the FACE test, patients were provided with 16 cards (8 cm x 7 cm), each of them showing the face of a former or current celebrity. The portrait photo shots on the cards represent common figures of celebrities. Faces depicted on the cards belong to actors or musicians who produced songs or films in the last century. Every card was numbered on its reverse side with a number from one to 16. The cards were sorted and stacked in such a way that patients faced the back of the first card (with the number one on its reverse side) when cards were put on the desk in front of them. Patients only had to flip this first card to see the black and white face on its front, whereas the second card appeared beneath the first one in a similar way. Patients could pick up and flip the cards from the first one on the top (card number one) to the last card at the bottom (card number 16). Thus, patients had no problem to sort or arrange the cards during test performance. Additionally, a sheet of paper (ISO A4) was provided with 16 rows on it, representing the numbers one to 16 with four celebrity names on each. Every row showed the true celebrity name for the corresponding picture (row one corresponding to face on card one and so on). The other three names in a single row were neither true for the corresponding card nor for one

of the other cards (e. g. 'picture' – John Wayne; Tony Curtis; James Stewart; Clint Eastwood). This meant that guessing probability was .25 for each item. Position of the true name among the four possibilities was randomized. Patients were instructed to mark the written celebrity name on the paper by encircling the name they thought to be correct. They were supposed to also follow the line suggested by the card numbers on the reverse side of the card, but could take a look at already discarded ones and correct their marks on the paper. For the CITY test, patients were provided with another sheet of paper (ISO A4) on which 16 capital names were arranged in 16 rows. For every single capital name in a row, four country names were optional. Patients were instructed to choose the country of which they thought the given city was the capital and circle it. Again, one single country name was correct for the capital in each row, whereas the other three did not correctly match any given city (e .g. *Tunis* – Kuba; Libyen; Sri Lanka; Tunesien). Guessing probability also was .25 for each item. Position of the correct country name among the four options given was randomized. Patients were allowed to review and correct already discarded items whenever they wanted during the test procedure. The FACE test preceded the CITY test in most cases. Test duration for both tests was 5-10 minutes. There was no time limit for either test. Patients were instructed to choose one of the four possibilities by guessing whenever they did not know the correct answer in either test. So sixteen valid responses for each were available at the end of assessment. Every correct answer was scored with one point in both tests. A maximum of 16 points and a minimum of 0 points could be achieved. In previous unpublished work (Doblinger, 2013), test criteria of FACE and CITY were analyzed by using a sample of 970 patients (231 cognitively healthy controls (HCs), 281 SCD, 321 MCI, 41 AD, 115 PD) with a mean age of 67 ± 9.5 and mean years of education of 11.8 ± 3.8 (42.6 % male; 57 % female). Catchment area of

the sample was Vienna and surrounding area. Participants in this study were also patients who came to the memory outpatient clinic for assessment of possible cognitive disorder. Doblinger (2013) found a ceiling effect for both tests, but with a stronger magnitude in the FACE. Median of the FACE ranged from 11 (AD) to 15 (HC, SCD, MCI) among subgroups. Median of the CITY ranged from 10 (AD) to 14 (SCD) among the subgroups. The FACE showed a mode of 16 in all subgroups implying that most of the patients recognized all of the prominent faces on the cards correctly. Mode of the CITY varied from 12 (AD) to 16 (SCD, PD). In sum, descriptive analysis showed that both tests (but especially the FACE) were very easy to solve. Cronbach's α of the FACE was .86 (.80 for the CITY) for the total sample, thus showing acceptable reliability. Retest reliability after 4 years was .77 for the FACE (.82 for the CITY). Adequate sensitivities for detecting AD were found in both tests (.85 for the FACE; .82 for the CITY) but very poor specificities (.37 for the FACE; .52 for the CITY).

2.4 Classification procedures

For MCI classification, a z-score was calculated for each subtest of the NTBIV indicating the relative degree of impairment from cognitively healthy patients in SD units. Age, gender and education showed to be influential on cognitive variables (Chandler et al., 2005), so z-scores were estimated depending on these demographic variables based on the cognitively healthy control sample (Pusswald et al., 2013). Impairment was indicated by z-scores lower than -1.5 SD. The minimum mode of MCI classification was used, i.e. a domain was considered to be impaired if at least one subtest showed a z-score lower than -1.5 SD (Pusswald et al., 2013). Depending on the specific domain which appeared to be impaired, patients were classified into two MCI subtypes: (1) Amnesic MCI subtype (aMCI), if

the memory domain appeared to be impaired (either with or without impairment in other domains) and (2) non-amnesic MCI (naMCI), if one or more of the non-memory domains showed impairment. Additionally, patients had to be in line with objective Mayo criteria for MCI classification suggested by Petersen (2004): (i) memory complaint, preferably corroborated by an informant, (ii) objective memory impairment for age, (iii) relatively well-preserved general cognition for age, (iv) essentially intact activities of daily living, and (v) not demented. If a patient reported memory problems but no z-scores beneath -1.5 SDs resulted from cognitive assessment with the NTBIV, the patient was allocated to SCD. Qualified physicians made the diagnosis of Parkinson's disease and Alzheimer's dementia. PD patients who complained about memory deficits but did not perform significantly under average in any test of the NTBIV were allocated to the Parkinson's disease subjective memory impairment group (PD-SCD). PD with a z-score beneath -1.5 SD in the memory domain of the NTBIV were allocated to the Parkinson's disease amnesic mild cognitive impairment group (PD-aMCI), independent of whether other domains revealed impaired. PD with one or more z-scores lower -1.5 SD in domains other than memory were allocated to the Parkinson's disease non-amnesic mild cognitive impairment group (PD-naMCI).

2.5 Statistical methods

The Spearman correlation matrix was built to check for possible confounding variables of FACE and CITY. Confounding variables were taken into account throughout data analysis by defining them as covariates in extra ANOVA analysis. Conversion rates are presented in percentages. Odds ratios (OR) with 95 % CIs of MCI, aMCI and naMCI for conversion to AD when compared to SCD were conducted with univariate and multivariate logistic regression model ($\alpha = .05$). To investigate the

three main goals, data analysis was conducted in three Steps.

(*Step 1*) For the first Step to determine test score differences between SCD, MCI and PD in FACE and CITY, two repeated measures ANOVA (3 x 2) were applied. FACE and CITY as dependent variables and diagnosis group as independent variable. However, because of the extensively left-skewed distribution of FACE and CITY, assumption of normal distribution was violated. In respect of this constriction, non-parametric analysis (Kruskall-Wallis test) was applied as well. If results of parametric and non-parametric analysis are alike, it is legitimate to interpret the parametric values (Kothgassner & Stetina, 2011). However, because KW test does not provide opportunity to include repeated measurement design, mean rank differences between diagnosis-groups are tested for both test occasions. Additionally, a test score difference was built. This procedure provided additional values, allowing adjustment of ANOVA results: Mean rank difference between groups at baseline assessment ($\chi^2_{\text{base}}/p_{\text{base}}$) and mean rank differences between groups at follow up assessment ($\chi^2_{\text{fu}}/p_{\text{fu}}$). To generate a single value representing both assessment occasions, the test score difference (follow up score – baseline score) was created and applied to Kruskal-Wallis test ($\chi^2_{\text{diff}}/p_{\text{diff}}$). Thus, a negative difference score represents a decline in test performance and a positive difference score represents an improvement in test performance over time. These additional values were used for adjustment of ANOVA results by non-parametric analysis: Significant p-values (< .05) in the group factor (Diagnosis) of an ANOVA were adjusted by p_{base} and p_{fu} , both lower than .05. Significant p-values in the time factor would have been adjusted by a significant p_{diff} -value, however, forestalling results, there was no significant time effect (there were no significant interaction effects as well). If non-parametric analysis did not confirm significant ANOVA results, the effect that was found was not completely ruled out. But in case of

failed adjustment, results were interpreted cautiously and attention was shifted to effect-size and statistical power.

(*Step 2*) Step two analysis involved checking for test score differences between SCD, aMCI, naMCI, PD-SCD, PD-aMCI and PD-naMCI in FACE and CITY score and was conducted in a way similar to Step 1 analysis. Again, a repeated measure ANOVA (6 x 2) with non-parametric adjustment was applied. Step 1 and Step 2 analysis both have more than two groups in the group factor. Thus, for significant results in the group factor, Bonferroni (due to multiple comparison), Hochberg and Games-Howell (because of unequal group sizes) post-hoc tests were applied. Unfortunately, n-sizes were too low to establish sufficient power. Therefore, ANOVA α -adjustment was disclaimed.

(*Step 3*) For the third Step, determining differences between converters to AD and non-converters in test score of FACE and CITY, repeated measures ANOVA with non-parametric adjustment were used as well. Diagnosis groups in the first two Steps are built upon baseline assessment. In order to evaluate predictive value of FACE and CITY, receiver operator characteristics analysis (ROC) was conducted. Positive prediction value (PPV), negative prediction value (NPV), sensitivity and specificity, as well as area under the curve (AUC) values are presented. The AUC was used to measure accuracy (ACC) of discrimination between converters to AD and non-converters. AUC allows determination of discriminative ability of FACE and CITY between converters to AD and non-converters over the entire range of cut off points. An area of 1 is perfect, while an area of .5 is non-informative. The cut-off point facilitating the least distance between sensitivity and specificity was chosen. Since PPV and NPV are undependable if prevalence varies within different populations, positive likelihood ratios (LR+) and negative likelihood ratios (LR-) are given. With a LR+ of 10 or more, this signals that a positive test will be very good at including the disorder. A LR- of .10

or lower signals that a negative test result will be very good at excluding the disorder. A LR, which is at 1 or is close to 1 indicates no remarkable changes in probability of having a disorder (Fischer, Bachmann, & Jaeschke, 2003). As a rule of thumb, LRs from .33 to 3 rarely alter clinical decisions (Jaeschke et al., 1994). Because of varying time intervals between baseline and follow up assessment, converters and non-converters groups are examined for mean rank differences in the time interval by U-test for independent groups. Other conversion groups than conversion to AD (e. g. from SMI to MCI) were tested for significant differences in test performance when compared to their responding non-converters. Anticipating the results, there were no significant group differences in ANOVA or KW tests in this attempt, regardless which conversion groups were compared. So, conversion to AD is the only conversion group, which provided interesting results in this study.

As suggested in goal four, performance in tests with distinctive task demands (recognition, identification, naming) and distinctive stimuli content (e. g. naming general object vs. naming concrete faces), might be determined by the status of neurodegeneration and thus could reflect disease severity. This study was not designed to explicitly test this hypothesis, but because of this framework relevance for semantic memory assessment, suggestions shall be under exploratory investigation. For this attempt, the total sample is divided into two sub-samples: MMSE low-scorer (< 27 ; $n = 22$) and MMSE high-scorer (≥ 27 ; $n = 146$). This cut-off score of 27 has been chosen, because it represents the middle of MMSE score range (23-30) in the total sample. Since BNT, CITY, FACE, SWT and PWT are related to semantic memory, they were included in the analysis. If suggestions that had been made earlier about task demands were realistic, the relationship between this test and the MMSE low scorer group, should be clearly different to the relationship between these tests and MMSE in the

high scorer group. Therefore, two multiple regressions (enter method) were applied to the high- and the low-scorer group as dependent variables with BNT, CITY, FACE, SWT and PWT as independent variables. In the high scorer group, no significant β -values for BNT (because of general stimuli content), CITY and FACE (because of recognition task) were expected to occur, whereas in the low scorer group, they were expected to occur.

Goal number five is to link FACE and CITY to overall MMSE while memory and other cognitive tests are controlled. Therefore, another multiple regression (backwards) was applied with MMSE as dependent variable and BNT, CITY, FACE, SWT, PWT, AKT, TMTA, TMTB and VSRT (immediate recall, total recall, delayed recall, recognition) as predictors. Regression with backwards method Stepwise excludes independent variables with non-significant β -values. Entry significance threshold into the model for tests was set to .05, while for exclusion in subsequent steps, the p-value had to be higher than .10. In each single step, every predictor was corrected for influence of the (at that point) remaining other predictors. Finally, a most predictive composite for MMSE, consisting of most predictive cognitive tests, remains. This allows further interpretation about dependence of semantic memory on attention, premorbid IQ, planning and non-verbal fluency and episodic memory in a clinical sample with different statuses of disease severity as measured by MMSE.

An entire data analysis was conducted with the R 3.0.2 software. The following software packages were used: 'pROC' (Robin et al., 2011), 'car' (Fox et al., 2009), 'ROCR' (Sing, Sander, Beerenwinkel, & Lengauer, 2005), 'ggplot2' (Wickham, 2009), 'Hmisc' (Harrell Jr & Dupont, 2012), 'caret' (Kuhn, 2008), 'stats' (Solé, Guinó, Valls, Iniesta, & Moreno, 2006) and 'Aod' (Lesnoff & Lancelot, 2012).

Table 1

Means and Standard Deviations of Demographic and Dependent Variables for Step 1 Analysis Patient Groups (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 _a *	11.2 ± 3.5 _b	11.3 ± 3.3
WST – IQ	113.9 ± 10.9 _a **	106.8 ± 12.3 _b	106.6 ± 12.7 _b
Female	66.7 % _a *	47.2 %	37.0 % _b
MMSE (range)	28.5 ± 1.3 (24-30) _a **	27.7 ± 1.6 (23-30) _b	27.9 ± 2 (23-30)
FACE (median)	14.20 ± 2.56 (15) _a *	13.24 ± 3.27 (14)	12.72 ± 3.94 (14) _b
CITY (median)	13.19 ± 2.95 (14) _a *	11.78 ± 3.13 (12) _b	11.81 ± 3.61 (13)

Note. Means with differing subscripts within rows are significantly different based on Fisher’s LSD post-hoc paired comparisons. Age and education in years. * p ≤ .05. ** p ≤ .01.

Table 3

Means and Standard Deviations of Demographic and Dependent Variables for Step 2 Analysis Patient Groups (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 _c *	10.5 ± 2.8 _b	15.5 ± 3.5 _a **	9.1 ± 2.0 _{b d}	11.9 ± 3.1
WST-IQ	108.7 ± 12.3 _e *	104.2 ± 11.9	116.5 ± 17.7 _a *	98.4 ± 12.8 _{b d f}	109.4 ± 10.6 _c *
Female	46.3 %	48.4 %	0.0 %	44.4 %	37.5 %
MMSE	27.9 ± 1.4 _c **	27.4 ± 1.8 _b	28.5 ± 0.7	26.4 ± 2.4 _{b d}	28.6 ± 1.3 _a **
FACE	13.5 ± 3.2	12.9 ± 3.4	12.5 ± 3.5	12.8 ± 5.0	12.7 ± 3.6
CITY	12.0 ± 3.0	11.5 ± 3.3	15.0 ± 0.0	10.6 ± 4.3	12.1 ± 3.2

Note. Age and education in years. Means with differing subscripts (a vs. b; c vs. d; e vs. f) within rows are significantly different based on Fisher’s LSD post-hoc paired comparisons. * p ≤ .05. ** p ≤ .01.

Table 2

Diagnose x Time for Step 1 (3 x 2), Step 2 (6 x 2) and Step 3 (2 x 2) Factorial ANOVA with Repeated Measurement for FACE and CITY Score adjusted by Kruskal-Wallis Test ($N_{Step 1,2} = 168$, $N_{Step 3} = 141$)

Source	Dependent Variable	Analysis Level	df	F (χ^2_{base} ; χ^2_{fu} ; χ^2_{diff})	η^2_p	p (p_{base} ; p_{fu} ; p_{diff})
Diagnose	FACE	Step 1	2	3.11 (4.93; 5.51; 0.64)	.038	.047 (.085; .064; .725) b
		Step 2	5	1.50	.047	.191
		Step 3 (Conversion)	1	6.18 (0.65; 2.01; 1.07)	.045	.014 (.420; .157; .302) b c
	CITY	Step 1	2	4.93 (8.55; 11.8; 2.60)	.060	.008 (.014; .003; .273) a
		Step 2	5	2.47 (7.41; 9.66; 6.05)	.075	.035 (.033; .011; .159) a
		Step 3 (Conversion)	1	7.89 (3.90; 4.59; 1.24)	.057	.006 (.048; .032; .266) a c
Time	FACE	Step 1	1	0.12	.001	.732
		Step 2	1	0.14	.001	.711
		Step 3 (Conversion)	1	0.67	.005	.414
	CITY	Step 1	1	0.13	.001	.719
		Step 2	1	0.22	.001	.638
		Step 3 (Conversion)	1	1.73	.013	.191
Diagnose x Time	FACE	Step 1	2	1.63	.020	.200
		Step 2	5	2.04	.077	.062
		Step 3 (Conversion)	1	0.20	.002	.655
	CITY	Step 1	2	1.25	.016	.290
		Step 2	5	3.06	.039	.299
		Step 3 (Conversion)	1	0.94	.007	.335
Error	FACE	Step 1	156			
		Step 2	153			
		Step 3 (Conversion)	132			
	CITY	Step 1	155			
		Step 2	152			
		Step 3 (Conversion)	130			

Note: Table shows the main and interaction effects of Step 1 (SCD, MCI, PD), Step 2 (SCD, aMCI, naMCI, PD-SCD, PD-aMCI, PD-naMCI) and Step 3 (Converters to AD, Non-Converters to AD) analysis levels. Baseline Diagnosis are used for Step 1 and Step 2 analysis. Significant ANOVA p-values (uncorrected) are adjusted by non-parametric analysis due to violation of assumptions (depending χ^2 and p – values in parenthesis: χ^2_{base}/p_{base} = values of baseline measurement; χ^2_{fu}/p_{fu} = values of follow up measurement; χ^2_{diff}/p_{diff} = values of 'follow up – baseline' difference). Partial η^2_p is presented. Subscripts: a = non – parametric analysis adjustment is confirming ANOVA results; b = non – parametric adjustment is indicating influence of assumption violation; c = significant after correction for multiplicity.

Table 4

Means and Standard Deviations of Demographic and Dependent Variables for Converters to AD vs. Non-Converters to AD (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***
FACE	11.7 ± 5.1 (12)	10.4 ± 5.9 (11.5)	13.8 ± 2.8 (15)	13.6 ± 3.3 (15)
CITY	9.7 ± 4.0 (9)	8.7 ± 4.5 (8)	12.6 ± 3.0 (13) *	12.6 ± 4.1 (13) *

Note. Median for CITY and FACE in parenthesis. Age and education in years. * $p \leq .05$. *** $p \leq .001$.

3.0. Results

3.1. Conversion rates

Eight patients out of one hundred and forty-one (5.7 %) converted to AD overall. Seven out of seventy-two MCI (9.7 %) converted to AD, denoting an OR of 7.3 (CI 1.3 to 138.9) for conversion to AD with baseline MCI vs. SCD. After adjustment for sex, age and education, the OR for developing AD of MCI vs. SCD decreased to 5.8 (CI 0.9 to 113.5). Five of the forty-one aMCI (12.2 %) converted to AD, denoting an OR of 9.4 (CI 1.5 to 184.6) for aMCI vs. SCD. When corrected for age, sex and education, the OR of aMCI vs. SCD decreased to 7.0 (CI 1.0 to 140.6). Two out of thirty-one (6.5 %) naMCI converted to AD, denoting an OR of 4.7 (CI 0.4 to 103.3) for naMCI vs. SCD. When corrected for age, sex and education, the OR of naMCI vs. SCD decreased to 4.1 (CI 0.3 to 97.7). One patient out of sixty-nine SCD (1.4 %) converted to AD. Twenty-nine out of sixty-nine SCD converted to MCI (42.0 %). Eighteen of the SCD converted to naMCI (26.1 %) and

eleven to aMCI (15.9 %). Fourteen out of thirty-one naMCI (45.2 %) converted to aMCI. Thirteen of the forty-one aMCI (34.2 %) converted to naMCI. Eleven out of the seventy-two MCI (15.3 %) went back to cognitive normal state as assessed with the NTBIV.

3.2 Semantic memory

Due to missing data, two PD (n = 25) and seven MCI (n = 65) were excluded (N = 159) for FACE analysis. For CITY analysis, seven MCI (n = 65), two SCD (n = 67) and one PD (n = 26) did not provide full data and had to be excluded (N = 158). Spearman correlations revealed significant relations between FACE and age ($r = -.31, < .0001$). Age will be defined as a covariate in an additional ANOVA. Significant relations between CITY and education ($r = .41, < .0001$) and CITY and premorbid IQ as measured by WST ($r = .57; < .0001$) were found. Premorbid IQ and years of formal education were controlled throughout CITY

analysis. FACE and CITY were significantly related ($r = .30, < .0001$). No significant correlations were found between CITY/FACE and measures of episodic memory.

Step 1

The purpose of the first goal was to determine mean differences between SCD, MCI and PD in FACE and CITY scores. Table 1 shows means (standard deviations) of demographic and dependent variables for analysis groups.

A lower mean (median) for MCI than for SCD and PD was observed. Table 2 shows full ANOVA results. ANOVA indicated significant group differences between SCD, MCI and PD in the FACE. But the Bonferroni post-hoc test did not reveal any significant group difference. Only tendencies of significance between SCD and MCI based on Bonferroni ($p = .063$), Hochberg ($p = .061$) and Games-Howell ($p = .054$) were found. Additionally, the KW test did not confirm these results by indicating non-significant rank mean differences at baseline measurement and follow up measurement. The ANOVA result is in contrast to the expectations described earlier. But as indicated by non-significant post-hoc tests, evidence for significant group differences is scarce. Additionally, due to failed non-parametric adjustment, Step 1 group differences for the FACE have to be interpreted carefully. The group effect disappeared ($F_{(2, 155)} = 2.07, p = .129$) when age was entered as a covariate into the ANOVA. After correction, this finding was expected. A significant Step 1 group difference was found for the CITY. This was also confirmed by non-parametric analysis with KW test. The Bonferroni post-hoc test revealed a significant group difference between SCD and MCI ($p < .01$). However, the effect disappeared ($F_{(2, 151)} = 1.06, p = .348$) when CITY score was corrected for education and WST-IQ. ANOVA results after correction are in accordance with the hypothesis.

Step 2

Purpose of the second goal was to examine differences in test performance among the subtypes of MCI and PD. Table 3 shows means (standard deviations) of demographic and dependent variables for subtypes of MCI and PD.

Again, lower CITY means (medians) were obvious for MCI subtypes than for SCD and PD-SCD. ANOVA showed significant group mean differences for the CITY. Bonferroni post-hoc test revealed a significant difference between SCD and naMCI ($p < .05$). This was also adjusted by the KW test. Once more, this result was not expected. But the effect vanished ($F_{(5, 148)} = 1.0, p = .42$), when WST-IQ and education were controlled. After correction, this result was in line with the hypothesis. No significant results were found for FACE test in Step 2, which is also in line with the hypothesis.

Step 3

The third goal was to check for group mean differences in FACE and CITY score between converters to AD and non-converters. Table 4 shows means (standard deviations) for demographic and dependent variables of converters vs. non-converters. Converters had a significant shorter time interval (median = 19) between baseline and follow up assessment than non-converters (median = 35), which was confirmed by U-test ($w = 307, < .05$).

Both tests showed lower means (medians) in the converter group (Figure A and B). ANOVA revealed a significant group difference for FACE score between converters to AD and non-converters. Adjustment by KW test did not confirm ANOVA results. ANOVA results are in line with the expectations. When FACE score was corrected for age, the effect slightly decreased ($F_{(1, 131)} = 5.12, p < .05, \eta^2_p = .038$). A significant group mean difference was found for the CITY, which could also be adjusted

with the KW test. These results are in agreement with the hypothesis. After correction for WST-IQ and education, the effect even increased ($F_{(1, 127)} = 11.16, p < .01, \eta^2_p = .081$). No significant time effects were found for both tests, which was expected. No interaction effects were found either, which contrasts expectations. Table 5 shows sensitivities, specificities, PPVs, NPVs, ACCs and AUCs of FACE and CITY for conversion to AD. A LR+ of 2.48 and a LR- of .56 equated for the FACE. A LR+ of 2.96 and a LR- of .38 was found for the CITY.

3.3 Task demands and stimuli content

As suggested earlier, influence of task demands and stimuli content within semantic memory tests seems possible. Tests with low effort task demand should not be predictive for milder states of neuro-degenerative diseases. This should also be apparent for tests with common and general stimuli content. The exploratory aim of the following analysis was to link tests with low effort embodiment (FACE and CITY) and tests with general stimuli content (BNT) to two groups with either lower disease severity ($MMSE < 27$) or higher disease severity ($MMSE \geq 27$) by multiple regression modeling (enter method). PWT and SWT, both asking for very common knowledge, were also included into analysis. MMSE should not be predicted by these tests in the high scorer group. In the low scorer group instead, those tests should be predictive. Table 6 shows multiple regression results for low scorers and high scorers. Figure C and D show scatterplots of MMSE low and high scorers vs. test score in BNT, FACE and CITY with linear model estimation.

Figure A

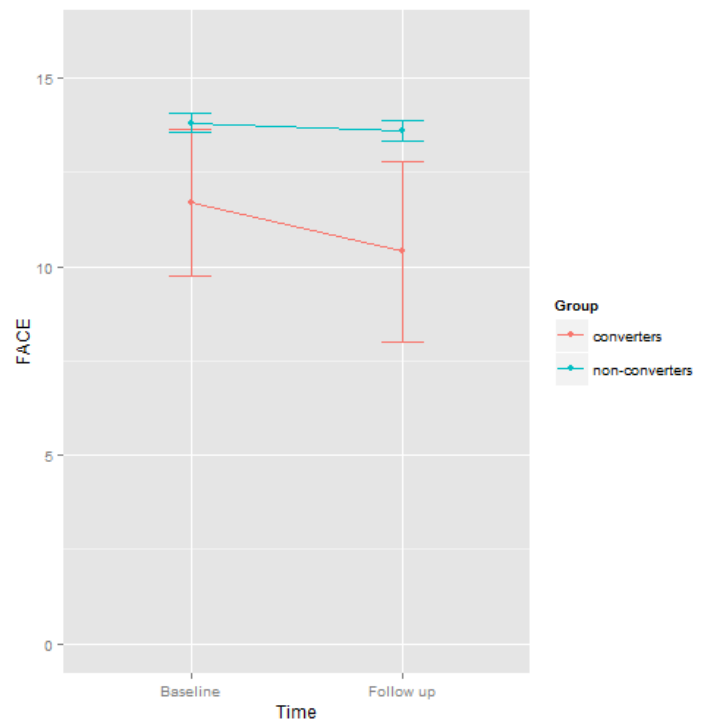


Fig. A. Lines show FACE means for converters and non – converters to AD for baseline and follow up assessment. Bars show standard errors.

Figure B

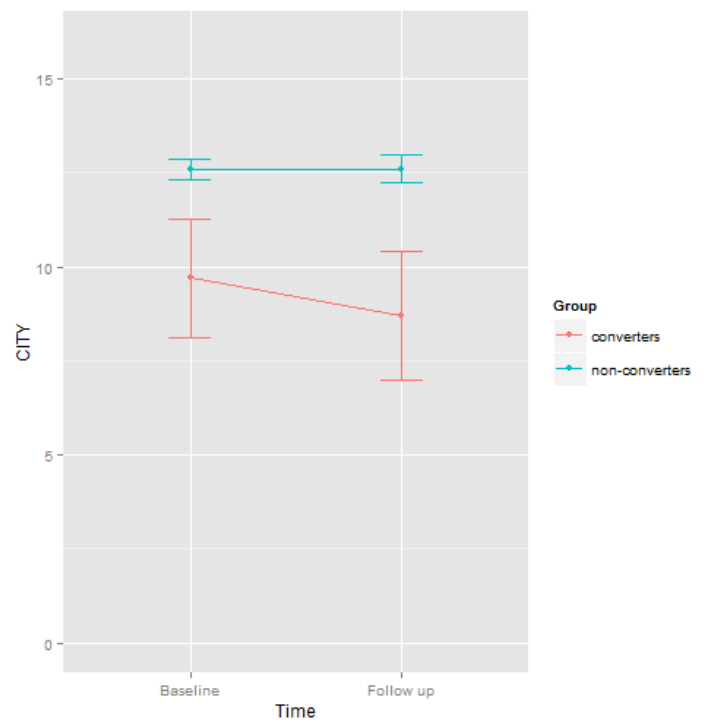


Fig. B. Lines show CITY means for converters and non – converters to AD for baseline and follow up assessment. Bars show standard errors.

Table 5

Results of Analyses of Sensitivity, Specificity, Positive (PPV) and Negative Predicted Values (NPV), Percent Correctly Predicted (ACC) at the Chosen Cut-Off Value, and Receiver Operating Characteristics (AUC) with 95% Confidence Intervals

Predictor	Cut-Off	Sensitivity	Specificity	PPV	NPV	ACC	AUC
FACE	13	.57 (.14 - .86)	.77 (.69 - .84)	.12 (.03 - .27)	.97 (.92 - .99)	.76 (.68 - .83)	.59 (.32 - .86)
CITY	11	.71 (.43 - 1)	.76 (.68 - .83)	.14 (.05 - .29)	.98 (.93 - 1)	.76 (.67 - .83)	.72 (.49 - .95)

Note. 95 % Confidence Intervals in parenthesis. FACE: $N_{\text{converters}} = 7$, $N_{\text{non-converters}} = 130$. CITY: $N_{\text{converters}} = 7$, $N_{\text{non-converters}} = 121$.

Table 6

Summary of Simple Regression Analyses (Enter) for Variables Predicting MMSE Score of 'MMSE Low Scorers (< 27)' and 'MMSE High Scorers (≥ 27)' (N = 159)

Variable	Low Scorer (n = 21)			High Scorer (n = 138)		
	B	SE B	β	B	SE B	β
BNT	.409	.201	.383 [†]	.048	.074	.059
FACE	.160	.062	.555*	-.015	.031	-.046
CITY	-.124	.056	-.432*	-.022	.033	-.062
PWT	.048	.022	.499*	.010	.010	.106
SWT	.001	.020	.010	.010	.008	.124
R^2		.581			.045	
F		4.154			1.241	

Note. [†] $\leq .10$. * $\leq .05$.

Figure C

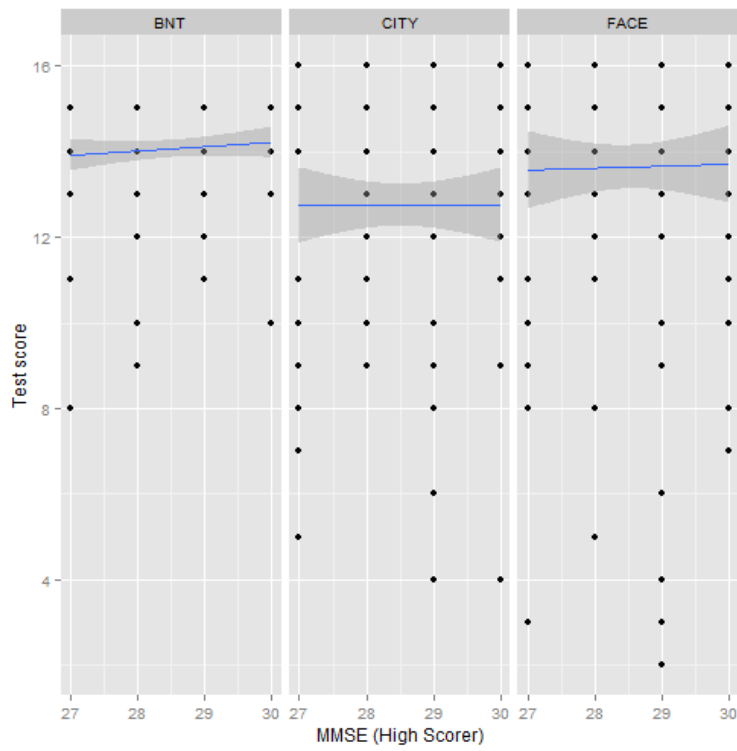


Figure C. Scatterplots for $MMSE \geq 27$ vs. test score of BNT, CITY and FACE with linear model estimation.

Figure D

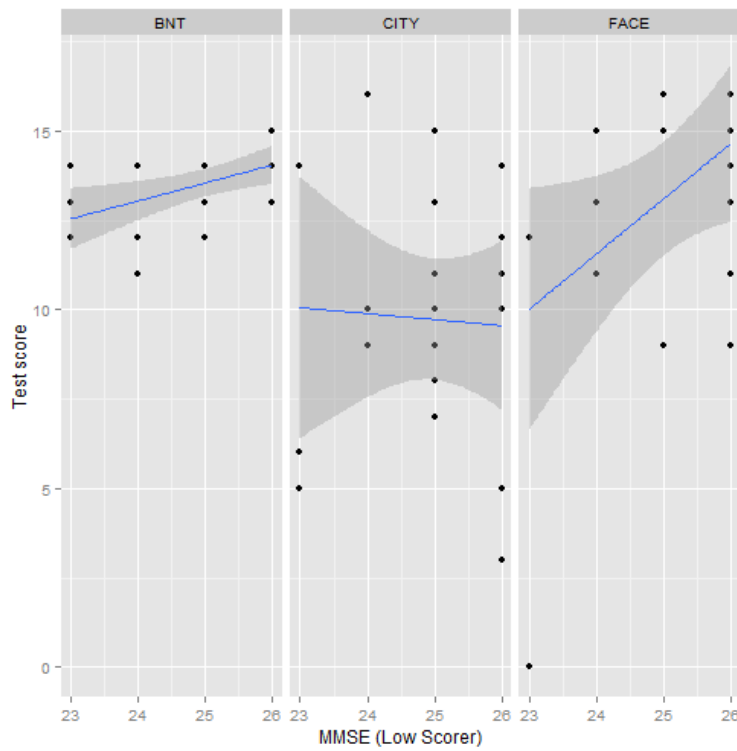


Figure D. Scatterplots for $MMSE < 27$ vs. test score of BNT, CITY and FACE with linear model estimation.

3.4. Most predictive composite

To further investigate the relationship between MMSE and tests related to semantic memory, a most predictive composite score of cognitive tests was created by multiple regression modeling (backwards). The following tests were entered as predictors: BNT, FACE, CITY, SWT, PWT, AKT, TMTA, TMTB, interference TMTB-TMTA and VSRT (immediate recall, total recall, delayed recall, recognition). A R^2 of .199 was found for the remaining model after seven steps of exclusion. A composite of CITY ($B = .085$, $SE = .036$, $\beta = .172$, $< .05$), VSRT delayed recall ($B = .084$, $SE = .044$; $\beta = .155$, $< .10$), VSRT recognition ($B = .147$, $SE = .073$, $\beta = .159$, $< .05$) and TMTA ($B = -.023$, $SE = .008$, $\beta = -.222$, $< .05$) showed best prediction for MMSE.

4.0 Discussion

The main purpose of this study was to investigate the predictive value of the FACE test (face-to-name matching) and the CITY test (country-to-capital matching) for conversion to AD. Therefore, differences in test performance between converters and non-converters to AD, as well as differences between groups of forerunners of dementia (SCD, MCI and PD) and their subtypes (aMCI, naMCI, PD-SCD, PD-aMCI, PD-naMCI) were assessed. In short, the CITY test seems more promising in detection of early signs of dementia than the FACE test. Both tests failed in differentiating MCI and PD from SCD properly. But they differentiated converters to AD from non-converters. Because both tests asked for recognition of names (this is easier than a free recall of a name), impairment only was expected in patients with an advanced neurodegenerative status, indicated by conversion to AD. The results were in line with the hypothesis. A closer look at the results in detail follows below.

Neither FACE nor CITY test could properly distinguish between SCD, MCI

and PD after correction for confounding variables. SCD were 2.8 years younger on average than MCI, which indeed was a non-significant difference, but contributed to the significant group effect in the FACE score between SCD and MCI in the uncorrected model. FACE score and age in years were negatively correlated ($r = -.31$), so older patients tended to achieve a lower score. Clark et al. (2009) also postulated a decline of semantic fluency in both pathological and healthy aging. Perhaps semantic degradation is common in the process of aging, which could be reflected in the relationship between age and the FACE. To further complicate matters, KW tests did not confirm results of the uncorrected ANOVA.

CITY score showed strong correlations with years of formal education ($r = .41$) and premorbid IQ measured by the WST ($r = .57$). Lower years of formal education (1.3 years in average), as well as a lower WST-IQ (7.1 in average) were found for MCI, when compared to SCD. These non-significant trends contributed to the uncorrected ANOVA group effect in CITY score between SCD and MCI.

Concerning the findings in Step 1 analysis, it cannot be assumed that FACE and CITY can distinguish between SCD, MCI and PD in our data. This is in contrast to the study of Clague et al. (2011), which found differences between MCI and cognitively healthy controls in face-to-name matching. But there is contrary evidence that face to name matching is at low task effort and hence can be spared in forerunners of AD like MCI (Thompson et al., 2002). Our study corroborates the latter finding. Equally, FACE and CITY did not differentiate properly between subgroups of PD, subgroups of MCI and SCD. In Step 2, no effects were found for the FACE. The CITY effect in Step 2, which was found in the uncorrected ANOVA model, again vanished after correction for education and WST-IQ. Subgroup of naMCI (9.7 lower in average) and PD-aMCI (15.5 lower in average) had a significant lower WST-IQ than SCD. Again, it is very likely that education and

premorbid IQ measured by WST generated the effect in the uncorrected model within the CITY score. It cannot be assumed that FACE and CITY are able to differentiate between subtypes of MCI, PD and SCD. Our findings harden the evidence of maintained ability to match names to faces in MCI, already shown by Thompson et al. (2002). No reliable effects were found in Step 1 and Step 2 analysis, which acknowledges the hypothesis.

Groups of converters and non-converters could be differentiated by both tests. This was also true for corrected ANOVA models. The group effect even increased for the CITY after correction. A η^2_p of .081 was found after correction for the CITY, which is a moderate effect. This means that 8.1 % of CITY variance (without effect-variance of time, interaction or confounders) was explained by the group factor (converts vs. non-converters). For the FACE, a η^2_p of .038 was found after correction, which is also a moderate, but smaller effect. The CITY test seems more promising in diagnosing early signs of dementia than the FACE test. Ahmed et al. (2008) found a higher correlation ($r = .60$) between a famous building naming test and AD diagnosis than for a graded famous face naming test and AD diagnosis ($r = .47$). Current data supports the idea of non-person semantic information, based on proper names, is measuring up or exceeding predictive value of famous face tests for AD. Further unsettling the FACE results, KW tests did not confirm ANOVA results of the FACE. The CITY results matched the foregoing hypothesis of a significant Step 3 group effect. This seems also likely for the FACE test, but due to the strongly skewed distribution of the FACE indicating a definite ceiling effect, data does not provide sufficient evidence. Also the missing time effect in both tests has been expected. No interaction effects were found as well, which was not in line with our assumptions. A significantly steeper decline for converters than for non-converters in test score was anticipated. Figures A and B show a trend towards an interaction effect,

accounting for a faster degeneration of test score over time for converters to AD. The time intervals between both test occasions ranged from 12 to 60 months among subjects. For converters, an even significantly smaller time interval median of 19 months was found than for non-converters (35 months). Seven of the eight converters had fewer than 30 months between baseline and follow up assessment. This might mean that the CITY (and maybe also the FACE), after revision and improvement, can predict conversion to AD about one and a half years earlier since converters were already impaired at baseline assessment. Our study supports the evidence that tests of semantic knowledge can be used for early diagnosis of AD (Clague et al., 2011; Dudas et al., 2005; Greene & Hodges, 1996; Joubert et al., 2010; Semenza et al., 2003; Thompson et al., 2002). To further assess predictive value of the FACE and the CITY, a receiver operating characteristics analysis was conducted. With an AUC of .72, the CITY test, as in the current version, is very much on the limit of practicability for early dementia diagnosis purposes. This means that a patient on the verge of converting to AD would approximately have a more abnormal test result in the CITY than 72 % of cognitively healthy controls. With an AUC of .52, the FACE test is uninformative for early dementia diagnostic. Lehrner et al. (2005) found an AUC of .94 for a delayed recall test and an AUC of .99 of the VSRT delayed recall was denoted (Lehrner et al., 2007). Sensitivities for conversion to AD of greater .90 were also reported for an episodic memory test (de Jager et al., 2003), which is also exceeding sensitivity of the CITY (.71) and the FACE (.57). The sensitivity of a test reflects the probability that the screening will be positive among those who are diseased. Thus, out of ten patients truly falling ill with AD within a short time, the CITY would screen seven as positive. This seems fairly usable for clinical purposes although there is, of course, need for improvement.

Thompson et al. (2002) reported a PPV of .60, a NPV of .90, a sensitivity of .87 and

specificity of .81 for a graded face-naming test. The PPV estimates the probability that a patient with a positive screening truly has the disease. With a PPV of the CITY (.14) and the FACE (.12), about one out of ten patients would most likely convert to AD after he/she had been screened positively by the FACE or the CITY (equal prevalence in populations preconditioned). A LR+ of 2.96 and a LR- of .38 indicates poor clinical practicability for the CITY. For the FACE, a LR+ of 2.48 and a LR- of .56 signals an even poorer practicability. For clinical purposes, predictive power in both tests is too low by far. But for screening purposes, FACE and CITY, when combined with other tests (especially those with high sensitivity), can serve as an assurance for ruling out approaching AD, as it was shown by relatively high NPVs (.98 and .97). A negative test result, meaning a score higher than 11 in the CITY and a score higher than 13 in the FACE, will suggest non-pathological aging, especially when the patient is relatively young and highly educated (this only applies if prevalence is equal to this in the study sample!). Doubtlessly, both the CITY and the FACE are under development, and these results, combined with the work of Doblinger (2013), constitute the very first steps of further development. References about possibilities to advance both tests on further are reported at the end.

Some exploratory aims were pursued concerning the idea of crucial influence of task demands and stimuli content. Literature has shown evidence that it is easier to retrieve well-trained and common knowledge (like object names) than unique and arbitrary knowledge (like person names). The latter may be less trained and thus have weaker connectivity within the semantic network. Patients in very early stages of a neurodegenerative disease, capable of most of their cognitive functions, may resolve items requiring general and common semantic knowledge with ease. Disproportionate impairment of less general and unique knowledge (e. g. famous faces),

more delicate for very early phases of cognitive impairment than general and common knowledge (e. g. objects), has already been shown (Ahmed et al., 2008; Clague et al., 2011; Greene & Hodges, 1996; Joubert et al., 2010; Swainson et al., 2001; Thompson et al., 2002). Besides stimuli content, it seems to be of crucial interest how semantic knowledge is tested. There is some reference in literature that recognition tasks demand less effort than naming (free recall) or identification (providing related information) tasks and hence, are less impaired or even spared very mild states of neurodegeneration (Greene & Hodges, 1996; Mårdh et al., 2013; Thompson et al., 2002; Werheid & Clare, 2007). If recognition tasks, or tests asking for very common knowledge do not show impairment in the very first phases of a neurodegenerative disease, this should reflect in disease severity measured by MMSE. The BNT (general knowledge) and the FACE (recognition task) were positively related to MMSE in patients with a MMSE lower than 27. In patients with MMSE higher or equal to 27, this relationship was missing. This can be interpreted as a hint that recognition tasks or general stimuli content are sensitive to cognitive decline only if impairment is severe enough. This also fits the results of Step 1 and Step 2 where FACE and CITY could not surely differentiate between MCI and SCD. The PWT (naming as many words as possible with initials b, f and l within one minute) also asks for general knowledge. However, when free recall (naming) is demanded, significant relation to MMSE only occurred for the low scorer group. One could now speculate that stimuli content is the primary influence of task difficulty and that embodiment of items resulting in task demands is the fine-tuning of a semantic memory test. The negative relationship between CITY and MMSE in the low-scorer group does not fit into this theory since it also is a recognition task. Because of unequal group size in analysis of goal 4 and a small size of the low scorer group ($n = 22$), with some dropouts due to missing data, the

analysis has low statistical power and such suggestions are highly speculative.

To draw further conclusions about the relationship between MMSE and semantic memory tests in goal 5, it was necessary to create a more predictive composite for overall MMSE. Two measures of episodic memory (VSRT recognition, VSRT delayed recall), one measure of planning and non-verbal fluency (TMTA) and one semantic memory test (CITY) remained after seven steps of exclusion in a model generated by multiple regression (backwards). This corroborates the findings of Greene and Hodges (1996) who postulated weak correlations between MMSE and naming, identifying and recognizing famous faces. Thompson et al. (2002) reported instead that a graded face-naming and identification test predicted 64 % of MMSE score in a stepwise regression model. When tests of episodic memory were entered, the episodic memory measures only predicted 34 %. They concluded that there was a reasonable association between severity of dementia and the extent of semantic memory impairment as assessed by a graded face test. The positive relation between MMSE and the CITY in goal 5 analyses suggests that the negative relation with MMSE (low scorer) in goal 4 analysis may have occurred accidentally.

Because of the CITY test remaining in the final model for prediction of overall MMSE score, it can be claimed that semantic memory tests might be functional in drawing conclusions about dementia severity. According to this finding, it seems very likely that semantic memory impairment is widely independent of episodic memory impairment as has already been suggested in literature (Dudas et al., 2005). Furthermore, missing correlations between CITY/FACE and measures of episodic memory clearly underline this suggestion. So, semantic memory tests may not only fortify episodic memory measures, they also may provide novel opportunities for clinical test assessment.

So, based on the results, what should be

done to improve the FACE and the CITY? First of all, both tests showed strong ceiling effects. Combined with a low effort recognition task, item difficulties are just too low. An easy way to correct this problem, according to results in goal 4, might be embodiment of the items as identification or a naming task. Of course this would lead to a more complex test procedure since a clinician would have to apply the test. Regrettably, explorative analysis could not definitely prove these suggestions. But it seems very likely that raising task demands will push future data into normal distribution shape and might help patients with milder cognitive damage to take on harder challenges. This could possibly also generate sufficient sensitivity for MCI and heighten sensitivity for imminent conversion to AD.

It remains unclear if a format with a lower guessing probability (e. g. one out of six or 16 %) would make both tests more difficult. This has to be a focus in future studies. Additionally, analysis should also be done on an item response level, thereby, allowing for insight in item difficulty. Items with assured distinctiveness in difficulty allow graduation of the items and hence, can cover a wider scope of cognitive breakdown. It is also very likely, as shown by confounding variables, that single items do not measure objectively. This reflects one big problem of semantic memory tests. There is no assurance that a single type of knowledge is of more, or less, "equal familiarity" for every patient. A cinema enthusiast, for example, will have little trouble with the FACE and a globetrotter will probably resolve CITY items with ease. Checking items of both tests for Rasch homogeneity allows determination of independence from the sample and can guarantee more specific objectivity. Therefore, a bigger pool of items is needed. Of course, there are other domains of semantic knowledge, which can provide opportunities for construction of semantic memory tests. At best, different types of semantic knowledge, each of them of distinguishable conversancy in the population at risk, can be, for example, combined

with different task demands, each in a graded way. If item response theory can affirm graded difficulty primarily achieved by different common knowledge domains and sub-graduated by task demands, there is a good chance to generate a semantic memory test covering a wide range of disease severity from very mild to severe semantic memory impairment. Perhaps by following this route, the full capacity for early detection of dementia, which is concealed in measurement of semantic memory, can be more easily revealed.

Lastly, limitations of this study should be mentioned. It is very difficult to assess patients whose cognitive or motoric abilities are reduced or impaired. Especially when cognitive decline reached AD status, length and number of tests have to be cut back due to ethical considerations. As a result, the number of converts assessed with the entire NTBIV is relatively low, which might be a reason for comparatively low ORs in this study. Patients had to reach the tests at the end of assessment to provide the necessary data required in this study. After about 45 minutes of NTBIV assessment, some patients, especially those with more pronounced cognitive decline, were not able to continue. This led to a lack of converts to AD in the study.

Since subjects for this study were taken from a clinical population, external validity may be high. In return, a quasi-experimental design does not allow for randomization and control of group size. For a relatively complex design like a 3 x 2 repeated measures ANOVA, which was applied for Step 1 analysis, the sample size should be big enough and about equally distributed between groups to achieve enough power to falsify an H_0 , when in reality H_1 is true. Observed power ranged between .23 and .42 in Step 1 and Step 2 analysis of corrected models. A chance of 23 % to 42 % to spot a true H_1 is unsatisfying. Thus, the missing effects in corrected ANOVA Step 1 and Step 2 analysis have to be questioned. Observed power of Step 3 analysis for the FACE also was too low (.61 in the corrected model).

For the CITY, power of Step 3 analysis was good (.91). So, Step 3 CITY results, as it was also suggested by non-parametric adjustment, may stand their ground. The results of FACE and CITY analysis differed remarkably. Effects in FACE analysis were not equal to effects in CITY analysis. There is evidence that face perception is processed in a specialized brain area (fusiform face area) (Kanwisher, McDermott, & Chun, 1997). Memory of faces may also take place in a special process, which seems to be a topic of high complexity. To investigate this phenomenon, studies with a special focus are needed. This study did not come up with requests of the diversified topic of face memory in particular. It is up to future studies to research the semantic memory in MCI and AD with a special account to face perception, storage of face images and the meaning of the emotional component expressed in mimics for retrieval of face knowledge. Additionally, there is evidence that lateralization of brain atrophy makes a difference in which type of semantic knowledge is about to diminish. Decline of face-knowledge occurs mostly when major pathology strikes the right brain hemisphere (Snowden, 2004). This is an absolutely crucial point but, unfortunately, could not be controlled in this study. Behavior of patients between the two test occasions, like cognitive training, sports or enrichment of social interactions, may have influenced the magnitude of cognitive degradation (wouldn't such things have improved cognitive abilities?). Unfortunately, data did not provide an opportunity to take into account such intervention.

It could be shown, however, that tests of semantic knowledge, based on proper names by one-to-one connections, do hold opportunities for early detection of AD, perhaps more than one and a half years earlier. An advanced predictive value for country-to-capital matching was found when compared to face-to-name matching. Both tests under research have to be expanded. Perhaps this could be done by raising their task

demands and/or lowering guessing probability. Furthermore, confounding impact of other variables in both tests showed that there is need for advanced item analysis under the light of Item Response Theory. A bigger item pool, as well as complementary knowledge domains would help. Combination of different semantic knowledge domains with different complexities of task demands may provide opportunities to draw detailed conclusions about disease severity. Item Response Theory should also approve of this idea.

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Abstract in Deutsch

Hintergrund: Aufgrund der zunehmenden Möglichkeiten von pharmakologischer Behandlung ist die Früherkennung von Demenz von großer Wichtigkeit. Die Überprüfung des semantischen Gedächtnisses mittels psychologischer Testverfahren scheint allem Anschein nach dafür geeignet zu sein.

Ziele: Der Vorhersagegehalt zweier semantischer Gedächtnistests (Namen zu Gesichtern zuordnen: FACE und Hauptstädte zu Ländern zuordnen: CITY) für die Konversion zur Alzheimer Demenz wurde geprüft.

Design: Patienten, welche über kognitive Verschlechterung klagten und zur Abklärung von möglichen kognitiven Störungen in die Gedächtnisambulanz kamen, wurden in die Studie inkludiert. Um einen Längsschnitteinblick zu erhalten, wurde jede/r PatientIn zweimal getestet.

Teilnehmer: 69 PatientInnen die über kognitive Beschwerden klagten (**Subjective Cognitive Decline**), 72 PatientInnen welche die Kriterien einer leichten kognitiven Störung erfüllten (**Mild Cognitive Impairment**) und 27 PatientInnen mit Morbus Parkinson (**PD**), waren für die Teilnahme an der Studie geeignet.

Ergebnisse: Der CITY ergab eine Fläche unter Kurve (**Area Under the Curve**) von .72 (.59 im FACE). Der CITY zeigte eine Sensitivität für die Konversion zur Alzheimer Demenz von .71 (.57 für den FACE) und eine Spezifität von .76 (.77 für den FACE). Der Positive-Vorhersage-Wert (**Positive Prediction Value**) für den CITY war .14 (.12 für den FACE). Der Negative-Vorhersage-Wert (**Negative Prediction Value**) für den CITY war .98 (.97 für den FACE). Insgesamt konnte der CITY .76 der Patienten richtig zuteilen (**Overall ACCuracy**). Der FACE erreichte eine ACC von .76. Beide Tests konnten, nach der Korrektur von konfundierenden Variablen, nicht hinreichend zwischen SCD, MCI und PD, sowie deren Subtypen, differenzieren.

Konklusion: Beide Tests zeigen Potential für die Vorhersage der Alzheimer Demenz (der CITY jedoch in höherem Ausmaß). In der derzeitigen Version können sie jedoch mit Tests, welche das episodische Gedächtnis erheben, nicht mithalten. Dies liegt am Deckeneffekt in der Verteilung und dem Einfluss anderer Variablen auf die Testleistung. Um die Vorhersagekraft zu erhöhen, sollten die Itemschwierigkeiten gesteigert werden. Die spezifische Objektivität einzelner Items sollte mittels der „*Item Response Theory*“ geprüft werden.

VITA

Personal Information

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Nationality:	German
DOB:	24 May, 1984
Gender:	Male
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EDUCATION

Oct 2008 – present, University of Vienna, AT

- Candidate for Diploma (Master) in Psychology
- Major academic course highlights: Pedagogical Psychology (Self-regulation, Emotional-regulation, Positive Psychology, Creativity); Clinical Psychology (Cyberpsychology and assistance in a memory outpatient clinic), Gender Medicine (basics) and Psychiatry (explorations with case examples)

Sep 2004 – Jun 2007, Secondary School Passau, GER

- University Entrance Qualifying Exams (*Abitur*)

Sep 2002 – Jun 2004, Child Care Training College Vilshofen, GER

- Certified Pediatric Childcare Worker

Sep 2001 – May 2002, Donner + Partner Deggendorf, GER

- External secondary modern school qualification graduation

Sep 1997 – Jul 2000, Landgraf – Leuchtenberg – Middle School, Osterhofen, GER

Sep 1995 – Jul 1997, St. Gotthard – Gymnasium (Academic Secondary School) Niederalteich, GER

Sep 1990 – Jul 1995, Abt – Joscio – Elementary School Niederalteich, GER

Professional Work Experience

Sep 2013 – present, Addiction Aid Corporation, Vienna, AT

- Psychosocial consultation for substance users
- Courses in motivational interviewing

Jul 2013 – present, Day-care Center Vienna South, AT

- Caretaking of disabled people with severe cognitive constraints
- Courses in augmentative and alternative communication

Jul 2011 – Sep 2011, Children's Psychology Office Dr. Pohl, Garmisch, GER

- Psychological Diagnostic (e. g. HAWIK-IV, WPPSI-III, WISC-IV, CFT-20)
- Extensive practice in applied behavior analysis

Sep 2007 – May 2008, Pediatric Clinic „Dritter Orden“, Passau, GER

- Community service in the psychosomatic unit

Sep 2002 – Jun 2004, Children's Day-care Center, Vilshofen and Niederalteich, GER

- Learning- and homework-support for elementary pupils

Student Work Experience

Oct 2012 – Nov 2012, “VIENNALE Filmfestival Vienna, AT

- Was in charge of the bar area
- Reception of guests
- Selling snacks and beverages
- Replenishment of barrels, bottles and grocery in the bar repository

Jul 2012 – Aug 2012, “Kino wie noch nie“ (Open-air cinema), AT

- Cashier in the restaurant area
- Mixing and selling drinks

Apr 2009 – Aug 2010, “Wohlmütstüberl“ Vienna (Restaurant) & “Mise en place“ Vienna (Catering Service), AT

- Courses in sophisticated gastronomy service
- Table waiter at events (e. g. golf tournaments and weddings at “ Schönbrunn Palace”)

Sep 2002 – Jun 2004, Private Music School „Viktor Brester“ Vilshofen, GER

- Teacher for concert flute and guitar

Skills

- Fluent in German and English
- SPSS, R-Software, Excel, PowerPoint, Endnote, Zotero, Citavi
- Piano, guitar and concert flute
- Communication and Interviewing
- Presentations

Interests

- Karate, Basketball, Music, Mountain-Climbing, Cooking