

Originalie / Clinical investigation

# Neuropsychological performance and mild cognitive impairment subtypes in patients reporting cognitive problems attending a memory outpatient clinic

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## Summary

**Background:** Early detection of dementia is becoming more and more important due to new pharmacological treatment options. The objectives of this study were to characterize the neuropsychological performance of patients reporting cognitive impairment, and to establish the frequency of MCI subtypes in an outpatient memory clinic cohort. Patients who came to the memory outpatient clinic for assessment were included in the study consecutively.

**Methods:** One hundred and twenty patients were eligible for the study. The patients underwent a clinical examination and completed a battery of standard cognitive tests. The patients scored, on average, within the normal range of cognitive testing. However, up to 30 % of the patients showed impaired performance in single cognitive tests.

**Results:** Measurements of delayed recall, executive function, semantic verbal fluency and sustained attention showed the highest impairment rates. Mild Cognitive Impairment (MCI) was found in 83 of the 120 patients; 4 were classified as amnesic single-domain MCI, 26 as amnesic multiple-domain MCI, 18 as non-amnesic single-domain MCI and 35 with non-amnesic multiple-domain MCI.

**Conclusion:** Our study gives information on the neurocognitive profile and frequency of MCI subtypes in patients reporting cognitive impairment in the setting of a memory clinic.

## Key words

mild cognitive impairment subtypes – amnesic mild cognitive impairment – non-amnesic mild cognitive impairment – neuropsychological testing – memory outpatient clinic

## Zusammenfassung

**Neuropsychologisches Leistungsprofil von Gedächtnisambulanz-Patienten mit kognitiven Beschwerden:**

**Hintergrund:** Die frühzeitige Erkennung von Demenzkrankheiten wird aufgrund von neuen pharmakologischen Therapieoptionen immer wichtiger. Ziel der vorliegenden Studie war die Charakterisierung des neuropsychologischen Leistungsprofils von Patienten, die kognitive Beschwerden berichten und die Erfassung der Häufigkeit von Subtypen der Leichten kognitiven Störung (MCI) in einer Kohorte von Patienten einer Gedächtnisambulanz. In die Studie eingeschlossen wurden Patienten, die in der Gedächtnisambulanz der Neurologischen Universitätsklinik mit kognitiven Störungen vorstellig wurden.

**Methoden:** 120 Patienten wurden klinisch untersucht und unterzogen sich einer ausführlichen neuropsychologischen Untersuchung. Das kognitive Leistungsvermögen der Patienten lag im Durchschnitt innerhalb der entsprechenden Altersnorm.

**Ergebnisse:** Bis zu 30 % der Patienten zeigten in einzelnen Testverfahren unterdurchschnittliche Leistungen. Verzögerter Abruf des episodischen Gedächtnisses, exekutive Funktionen, semantische Wortflüssigkeit und geteilte Aufmerksamkeit zeigten die häufigsten Auffälligkeiten. Eine leichte kognitive Störung (MCI) wurde bei 83

von 120 Patienten gefunden; vier Patienten wurden klassifiziert als „amnestische leichte kognitive Störung single domain“, 26 als amnestische leichte kognitive Störung multiple domain, 18 als „nicht amnestische leichte kognitive Störung single domain“ und 35 als „nicht amnestische leichte kognitive Störung multiple domain“.

*Schlussfolgerung:* Die vorliegende Studie liefert Hinweise in Bezug auf das neurokognitive Profil und die Häufigkeit von MCI Subtypen bei kognitiv beeinträchtigten Patienten in einer Gedächtnisambulanz.

### Schlüsselwörter

Subtypen der leichten kognitiven Störung – amnestische leichte kognitive Störung – nicht amnestische leichte kognitive Störung – neuropsychologische Untersuchung – Gedächtnisambulanz

In recent years the advent of new pharmacological treatment options for Alzheimer's Disease (AD) has spurred the interest in diagnosing dementia as early as possible in order to provide early treatment. As a consequence, the concept of Mild Cognitive Impairment (MCI) was developed [29]. MCI applies to a group of individuals who have some cognitive impairment which is, however, not severe enough to constitute dementia, with very slight degrees of functional impairment. Initially, MCI was defined as a clinical condition with memory impairment with or without cognitive impairment in other domains (amnestic multiple-domain MCI vs. amnestic single-domain MCI) implying a pre-AD state, and most research has focused on that clinical entity [2, 27, 30]. However, in the meantime it has become apparent that several clinical subtypes of MCI exist, and the concept of MCI has been expanded to include other types of cognitive impairment beyond memory, taking into account multiple aetiologies or causes of cognitive impairment and dementia in older persons. Thus, a third clinical type of MCI is called non-amnestic multiple-domain MCI involving various degrees of impairment in multiple cognitive domains without memory impairment. A fourth type of MCI is non-amnestic single-domain MCI in which a person has an impairment in a single non-memory cognitive domain. Whereas the amnestic type would likely represent a prodromal form of AD with an annual conversion rate of 10–20 % per year [4, 18, 30], the other subtypes showing impairments in non-memory domains may have a higher likelihood of progressing to non-AD dementia such as vascular dementia, frontotemporal dementia or dementia with Lewy bodies [26, 28].

Because no commonly accepted specific test battery is available, a recent review of MCI which was recently published with recommendations for future research advocated additional research to develop appropriate and sensitive neuropsychological methods [22]. Another recent consensus suggested the development and use of tests capable of detecting dysexecutive syndrome in the preclinical stage of dementia [34].

The objectives of the study were to study the neuropsychological profile of patients attending a memory outpa-

tient clinic but having no diagnosis of dementia using a comprehensive neurocognitive test battery. Additionally, we applied the suggested criteria of MCI subtypes and determined the frequency of the four subtypes in our cohort by using the predetermined specific domains.

## METHODS

### Subjects

We included 584 elderly participants, classified into two groups: patients with mild cognitive impairment (MCI) and elderly controls (EC). The study protocol was in accordance with the Declaration of Helsinki.

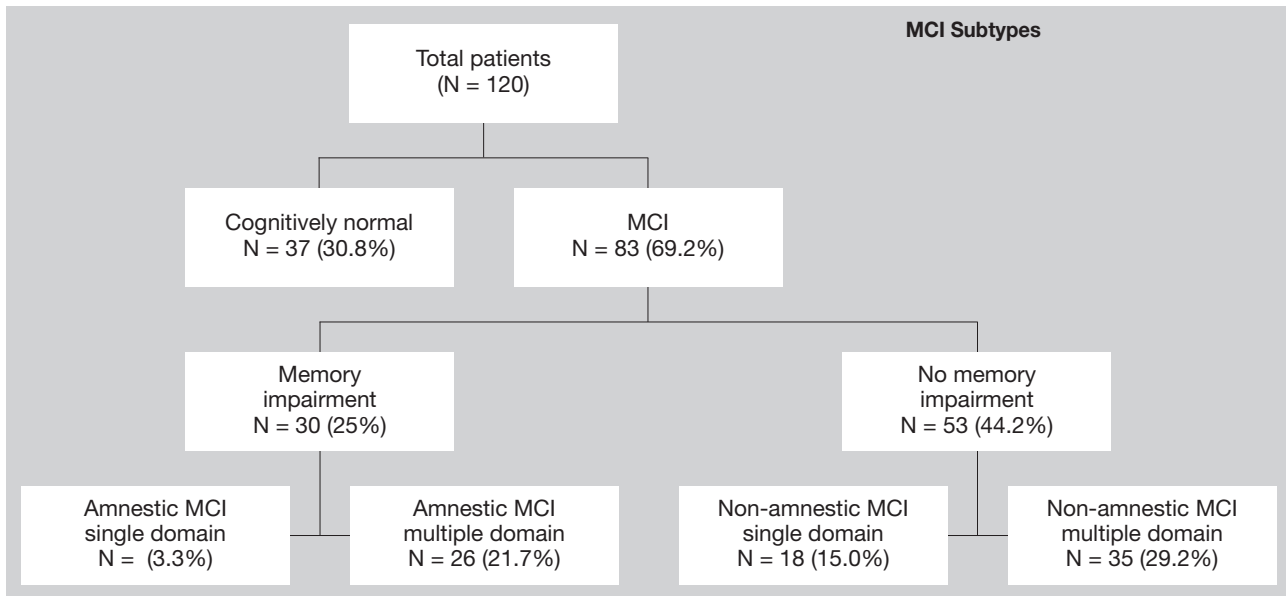
All participants received a complete neurological examination, standard laboratory blood tests and psychometric testing. In most cases a computer tomography (CT) scan or magnetic resonance imaging (MRI) scan of the brain was obtained. Electroencephalogram and single-photon emission computed tomography (SPECT) scans were performed on some patients. In determining significant cerebrovascular disease, both neuroimaging and clinical patient features were used.

The inclusion and exclusion criteria were similar to other studies. Patients were excluded from the study if any of the following conditions applied:

- evidence of stroke as determined by neuroradiologic and clinical examination,
- history of severe head injury,
- current psychiatric diagnosis according to ICD-10 [7] (patients with (sub)-depressive symptoms were, however, included because (sub)-depressive symptoms often occur in elderly patients),
- any medical condition that leads to severe cognitive deterioration including renal, respiratory, cardiac and hepatic disease,
- diagnosis of dementia according to DSM IV [35].

### MCI patients

Patients complaining of cognitive problems who came to the memory outpatient clinic between the beginning of 2005 and the end of 2005 for assessment of their cogni-



**Fig. 1: Flow chart of mild cognitive impairment (MCI) subtypes.**

tive disorder were included in the study consecutively. One hundred and fifty-five patients fulfilled the inclusion criteria. Patients were either referred by physicians or were self-referrals. The area of the study was Vienna.

The memory outpatient clinic of the University Clinic of Neurology of the Medical University of Vienna is a well-known research center for memory disorders in Vienna. The clinic serves patients from the Vienna area and most of the patients were referred by physicians. A minority of the patients were self-referrals. The clinic is government-funded and is accessible free of charge for patients within the Austrian health insurance system. Representatives of the memory outpatient clinic regularly inform physicians and the public about scientific programs within the clinic.

For the purpose of this study we excluded MCI patients with invalid measurements due to missing values in cognitive performance tests ( $n = 35$ ), leaving 120 MCI patients for analysis. The mean age of the MCI patients was  $67.7 \pm 9.0$  years. 39.2 % of the patients were male and 60.8 % of the patients were female. The mean number of years of formal schooling was  $11.4 \pm 3.9$ . The median MMSE performance of the patients was 28 (range 24–30).

### Elderly controls

Adequate normative data of cognitively normal elderly subjects ( $n$  ranging from 122 to 434 for single tests) from the neuropsychological measurements are available and a detailed description of the standardization procedures, norms and validation is published elsewhere [19]. Cognitively normal elderly control subjects of the normative sample were taken from the General Hospital of Vienna inclu-

ding the Department of Neurology. The elderly control subjects underwent a standard medical evaluation and were assessed as being in good health. Criteria for normal function were identified as being similar to those in the Mayo research studies [14, 26]:

- no active neurological or psychiatric disease,
- no psychotropic medication, and
- the subjects may have medical disorders but neither they nor their treatment compromises cognitive function. They were required to have an MMSE score greater than or equal to 27 and a memory score greater than -1.5 standard deviations on the face recognition memory test of the Memory Assessment Clinics (MAC) test battery [6].

The mean age of the elderly controls was  $62.0 \pm 12.3$  years. 32.8 % of the elderly controls were male and 67.2 % of the elderly controls were female. The mean number of years of formal schooling was  $12.4 \pm 3.9$ . The median MMSE performance of the elderly controls was 29 (range 27–30).

### Neuropsychological measurements

All participants were subjected to the Vienna Neuropsychological Test Battery (VNTB) that included psychomotor speed, concentration/attention, language, memory and executive functioning domains [17, 18, 19, 20]. Psychomotor speed was assessed using the symbol-counting exercise from the cerebral insufficiency test (C.I.) [16] and the Trail Making Test A [32]. The Alters-Konzentrations-Test (AKT) [9], a geriatric cancellation test, the digit symbol subtest of the German WAIS-R [38], the Stroop Test from the NAI Test Battery [25] and the interference

test from the C.I. [16] were applied to assess attention. In order to test language functions, we used verbal fluency exercises and a confrontation naming task [11]. Naming as many animals, supermarket items and tools that came to mind within one minute for each exercise was used to tap semantic verbal fluency. Naming as many words beginning with the letters b, f and l that came to mind within one minute for each exercise was used to tap lexical verbal fluency. The modified Boston Naming Test (mBNT) [24] was used for assessing naming capabilities. Episodic memory was tested using the Verbal Selective Reminding Test (VSRT) [17] which is the Austrian paper-pencil version [36] of the Memory Assessment Clinics (MAC) Grocery List Selective Reminding Test with the subtests of immediate recall, total recall and delayed recall [6, 40]. Executive functions were investigated using the Trail Making Test B and the score difference of the Trail Making Tests A and B [32], the Five-Point Test [31] and the Maze Test from the NAI Test Battery [25]. In addition, participants completed the Geriatric Depression Scale (GDS) and the Beck Depression Inventory (BDI) in order to assess depressive symptoms. Data of depressive symptoms will be presented in a forthcoming publication.

For this study the whole VNTB was used. Cognitive testing for each patient lasted approximately 45 minutes. Testing was performed within one test session. In some cases patients reported fatigue and lack of motivation. As some patients forgot their eyeglasses, cognitive testing could not be performed completely. Both circumstances resulted in missing values. Cognitive function tests were selected to assess a broad range of cognitive abilities commonly affected by AD and other types of dementia. The ability of the VNTB subtests to detect dementia was established in a prior study and we recently published results for sensitivity, specificity, positive and negative predicted value, and found very good discrimination power for the neuropsychological test battery in detecting Alzheimer's disease dementia. Specifically, comparing the predictive accuracy using results from receiver operating characteristics analyses (area under the curve; AUC), we found very good discriminative power for single tests with an area under the curve ranging from 0.79 for the mBNT to 0.99 for the VSRT delayed recall [19].

**Procedure**

Neurological examination, standard laboratory blood tests and radiological evaluation were performed approximately two weeks prior to neuropsychological testing. After the completion of the evaluation, a consensus committee meeting was held involving the neurologists, neuropsychologists and other study personnel who had evaluated the patients in order to determine the cognitive status of the par-

ticipants. The cognitive status of MCI subtypes was determined according to the Peterson criteria, and the cutoff score used was 1.5 standard deviations below the age and education-corrected norms for the elderly controls [26, 28].

In a first step, the domain structure of the VNTB was investigated empirically in the elderly control sample by means of cluster analysis. Because age, education and gender effects on cognitive variables have been reported in the literature [5], regression-based z-scores using the elderly control sample were calculated for each neuropsychological variable (after appropriate normalizing transformations if necessary, using a multiple linear regression formula with age, education and gender as regressors) [3, 19]. In a subsample of 107 elderly controls, for which results of all sixteen tests were available for the variable clustering procedure, the z-scores of the cognitive variables were clustered into cognitive domains.

The mean age of the elderly control subsample was 61.0 ± 12.5 years. 42.1 % of the elderly control subsample were

Cluster	R <sup>2</sup> with own cluster	R <sup>2</sup> with next closest
<b>Attention</b>		
AKT	0.49	0.12
Digit-Symbol -Test (WAIS-R)	0.57	0.13
TMTA	0.46	0.20
Stroop (NAI)	0.58	0.18
Symbol counting (C.I.)	0.60	0.22
Interference Test (C.I.)	0.64	0.22
<b>Memory</b>		
Verbal memory immediate recall (VSRT)	0.68	0.03
Verbal memory total recall (VSRT)	0.90	0.10
Verbal memory delayed recall (VSRT)	0.74	0.04
<b>Executive Function shifting capability</b>		
TMTB	0.95	0.32
Difference score TMTB-TMTA	0.95	0.13
<b>Executive Function planning and non-verbal fluency</b>		
Planning (Maze Test -NAI)	0.59	0.04
Non-verbal Fluency (Five Point Test)	0.59	0.06
<b>Language</b>		
Semantic verbal fluency	0.66	0.22
Lexical verbal fluency	0.39	0.07
Boston Naming Test (mBNT)	0.38	0.10
Abbreviations: AKT = Alters-Konzentrations-Test; WAIS-R = Wechsler Adult Intelligence Scale - Revised; TMTA = Trail Making Test Version A; TMTB = Trail Making Test Version B; NAI = Nürnberger Alters Inventar; C.I. = Cerebral Insufficiency Test; VSRT = Verbal Selective Reminding Test; mBNT = modified Boston Naming Test		

**Table 1: A variable clustering procedure with 107 healthy controls resulted in a 5-cluster solution.**

male and 57.9 % of the elderly control subsample were female. The mean number of years of formal schooling was  $12.3 \pm 4.3$ . The median MMSE performance of the elderly controls was 29 (range 27–30).

The clustering into domains reflects the correlation structure of the z-scores as implemented in “proc varclus” of the software package SAS. The variable clustering procedure revealed a 5-cluster solution for the 16 cognitive variables. Allowing for more than five clusters would result in two single-variable clusters while leaving the other clusters unchanged. See *Table 1* for the 5 clusters with corresponding cognitive variables.

In order to characterize the neuropsychological profile of MCI patients, a z-score for each variable was calculated which indicates the relative degree of impairment from normal in SD units, thereby allowing direct comparison across different cognitive tests. MCI patients were then divided into five groups of patients based on cognitive features: cognitively normal patients: z-scores of each of the 5 domains were greater than -1.5 SD, amnesic MCI single-domain patients: the z score of at least one memory test was below -1.5 SD, all other z scores were greater than -1.5 SD, amnesic MCI multiple domain: the z-score of at least one memory test was below -1.5 SD and at least one

other z-score of the remaining tests was below -1.5 SD, non-amnesic MCI single-domain patients: there is exactly one domain other than the memory domain where the minimum of the z-scores within this domain was below -1.5 SD, non-amnesic MCI multiple-domain patients: at least two tests from different domains other than memory tests below -1.5 SD, respectively.

**Statistical methods**

Demographic variables are described by means and standard deviations except MMSE scores, which are given as median and range due to the skewed distribution of this variable.

Since the raw values for the majority of the neuropsychological variables are not normally distributed, median and quartiles are given for all of them in order to give a consistent presentation. Z-scores of the neuropsychological test variables are described by mean and standard deviation.

In order to compare the MMSE score and the raw values of each neuropsychological variable between MCI subtypes, Kruskal-Wallis tests were performed, while for comparing demographic variables (age, years of education) and z-scores of neuropsychological variables one-way AN-

Cluster / neuropsychological variable	Raw score Median (25 <sup>th</sup> Pctl; 75 <sup>th</sup> Pctl)	Z-Score $\pm$ SD	number of impaired patients	percentage of impaired patients
<b>Attention</b>				
AKT	32.0 (27.0; 42.0)	-0.30 $\pm$ 1.21	19	15.8
Digit-Symbol Test (WAIS-R)	39.5 (30.0; 47.0)	-0.21 $\pm$ 1.18	22	18.3
TMTA	41.0 (32.5; 54.0)	-0.41 $\pm$ 1.06	24	20.0
Stroop (NAI)	52.0 (43.0; 67.0)	-0.58 $\pm$ 1.09	25	21.1
Symbol counting (C.I.)	18.0 (15.0; 21.0)	-0.15 $\pm$ 1.12	12	10.1
Interference Test (C.I.)	25.0 (21.0; 31.0)	-0.54 $\pm$ 1.05	25	21.0
<b>Memory</b>				
Verbal memory immediate recall (VSRT)	7.5 (6.0; 9.0)	-0.02 $\pm$ 1.06	11	9.2
Verbal memory total recall (VSRT)	46.0 (38.0; 53.0)	-0.34 $\pm$ 0.97	16	13.3
Verbal memory delayed recall (VSRT)	9.0 (7.0; 12.0)	-0.66 $\pm$ 1.27	25	20.8
<b>Executive Function shifting capability</b>				
TMTB	107.0 (78.0; 143.5)	-0.78 $\pm$ 1.27	34	28.3
Difference score TMTB-TMTA	61.0 (35.0; 95.0)	-0.60 $\pm$ 1.33	36	30.3
<b>Executive Function planning and non-verbal fluency</b>				
Planning (Maze Test -NAI)	36.5 (29.0; 45.0)	-0.32 $\pm$ 1.11	9	7.6
Non-verbal Fluency (Five Point Test)	24.5 (18.5; 34.0)	-0.37 $\pm$ 1.25	25	20.8
<b>Language</b>				
Semantic verbal fluency	52.0 (44.0; 61.0)	-0.69 $\pm$ 1.29	28	23.3
Lexical verbal fluency	29.0 (22.0; 37.5)	-0.48 $\pm$ 1.07	20	16.7
Boston Naming Test (mBNT)	14.0 (13.0; 15.0)	-0.18 $\pm$ 1.15	13	10.8
Abbreviations: Pctl = Percentile; AKT = Alters-Konzentrations-Test; WAIS-R = Wechsler Adult Intelligence Scale - Revised; TMTA = Trail Making Test Version A; TMTB = Trail Making Test Version B; NAI = Nürnberger Alters Inventar; C.I. = Cerebral Insufficiency Test; VSRT = Verbal Selective Reminding Test; mBNT = modified Boston Naming Test				

**Table 2: Raw scores with quartiles and z-scores with standard deviations for each neuropsychological variable and corresponding frequency of patients showing performance below -1.5 SD in total MCI patients sample.**

	CN	a-SD MCI	a-MD MCI	non-a-SD MCI	non-a-MD MCI
Age	64.3 ± 7.8	63.0 ± 10.2	68.2 ± 10.7	69.4 ± 7.4	70.7 ± 8.6
Male/female (percentage)	35.1/64.9	25.0/75.0	53.9/46.1	38.9/61.1	34.3/65.7
Years of formal schooling	12.2 ± 4.2	13.3 ± 5.7	11.8 ± 3.4	10.7 ± 4.6	10.4 ± 3.0
MMSE Score: median (range)	29 (25 - 30)	28 (28 - 30)	27 (24 - 29)	28 (26 - 30)	27 (24 - 30)
Abbreviations: CN = Cognitively normal; a-SD MCI = amnesic single-domain MCI; a-MD MCI = amnesic multiple-domain MCI; non-a-MCI SD = non-amnesic single-domain MCI; non-a- MD MCI = non-amnesic multiple-domain MCI					

**Table 3: Demographic and clinical details of MCI subtypes.**

OVA's were computed. In both cases, uncorrected p-values are given and, for raw values and z-scores, significance after Bonferroni-Holm correction (for 16 neuropsychological variables) is indicated. For the comparison of z-scores

(between MCI subtypes) pairwise post-hoc comparisons were performed and corrected for multiplicity using the Tukey-Kramer method, where for each of the 16 neuropsychological variables the overall significance level was set

Cluster / neuro-psychological variable	CN	a-SD MCI	a-MD MCI	non-a-SD MCI	non-a-MD MCI	
<b>Attention</b>						
AKT*	28.0 (23.0; 31.0)	29.0 (21.5;35.5)	39.0 (30.0;45.0)	35.0 (29.0;42.0)	38.0 (30.0;56.0)	<0.001
Digit-Symbol Test (WAIS-R)*	52.0 (41.0;58.0)	47.5 (36.5;60.5)	30.0 (27.0;43.0)	38.5 (32.0;47.0)	33.0 (25.0;38.0)	<0.001
TMTA*	34.0 (27.0;37.0)	34.0 (20.0;45.0)	43.5 (35.0;55.0)	46.5 (40.0;58.0)	51.0 (41.0;64.0)	<0.001
Stroop (NAI)*	43.0 (36.0;51.0)	49.5 (36.5;53.5)	67.0 (50.0;74.0)	49.0 (42.0;60.0)	59.5 (48.0;78.0)	<0.001
Symbol counting (C.I.)*	15.0 (13.0;18.0)	17.0 (12.5;19.5)	18.0 (17.0;21.0)	17.5 (16.0;19.0)	20.0 (17.0;26.0)	<0.001
Interference Test (C.I.)*	21.0(17.0;24.0)	24.0 (17.5;27.5)	29.5 (22.0;34.0)	25.0 (23.0;27.0)	30.5 (26.0;35.0)	<0.001
<b>Memory</b>						
Verbal memory immediate recall (VSRT)*	8.0 (7.0;10.0)	5.5 (5.0;9.0)	5.0 (4.0;6.0)	8.5 (8.0;9.0)	8.0 (7.0;10.0)	<0.001
Verbal memory total recall (VSRT)*	52.0 (46.0;57.0)	43.0 (35.0;46.5)	32.0 (28.0;38.0)	48.5 (44.0;53.0)	47.0 (39.0;52.0)	<0.001
Verbal memory delayed recall (VSRT)*	11.0 (9.0;13.0)	7.0 (5.0;10.0)	5.0 (4.0;7.0)	10.0 (9.0;13.0)	10.0 (8.0;11.0)	<0.001
<b>Executive Function shifting capability</b>						
TMTB*	69.0(57.0;91.0)	94.5(65.0;124.5)	128.5(107.0;145.0)	90.0 (75.0;109.0)	160.0 (117.0;187.5)	<0.001
<b>Difference score</b>						
TMTB-TMTA*	37.0 (27.0;54.0)	34.0 (22.0;57.5)	81.5 (63.0;101.0)	39.0 (34.0;44.0)	103.0 (66.0;130.0)	<0.001
<b>Executive Function planning and non-verbal fluency</b>						
Planning (Maze Test-NAI)*	30.0 (25.0;38.0)	30.0 (25.5;47.5)	36.0 (30.0;43.0)	40.0 (29.0;49.0)	43.5 (36.0;63.0)	<0.001
Non-verbal Fluency (Five Point Test)*	31.0 (25.0;37.0)	33.0 (29.0;41.5)	18.5 (15.0;28.0)	31.0 (22.0;36.0)	20.0 (15.0;25.0)	<0.001
<b>Language</b>						
Semant. verb. fluency*	59.0 (54.0;68.0)	52.5 (48.0;67.5)	45.5 (34.0;52.0)	56.5 (54.0;61.0)	45.0 (37.0;52.0)	<0.001
Lexical verb. fluency*	34.0 (29.0;43.0)	33.0 (29.5;341.5)	25.0 (20.0;37.0)	33.0 (20.0;41.0)	24.0 (17.0;29.5)	<0.001
Boston Naming Test (mBNT)	14.0 (14.0;15.0)	14.5 (14.0;15.0)	14.0 (14.0;15.0)	14.0 (13.0;15.0)	14.0 (12.0;14.0)	0.022
Abbreviations: Pctl, Percentile; AKT, Alters-Konzentrations-Test; WAIS-R, Wechsler Adult Intelligence Scale - Revised; TMTA, Trail Making Test Version A; TMTB, Trail Making Test Version B; NAI, Nürnberger Alters Inventar; C.I., Cerebral Insufficiency Test; VSRT, Verbal Selective Reminding Test; mBNT, modified Boston Naming Test; CN = Cognitively normal; a-SD MCI = amnesic single-domain MCI; a-MD MCI = amnesic multiple-domain MCI; non-a-SD MCI = non-amnesic single-domain MCI; non-a-MD MCI = non-amnesic multiple-domain MCI; * indicates significance of the overall five-group comparison after Bonferroni-Holm correction. Abbreviations: CN = Cognitively normal; a-SD MCI = amnesic single-domain MCI; a- MD MCI = amnesic multiple-domain MCI; non-a-MCI SD = non-amnesic single-domain MCI; non-a- MD MCI = non-amnesic multiple-domain MCI						

**Table 4: Raw scores with medians and quartiles for each neuropsychological variable across MCI subtypes.**

to 0.05/16 = 0.003125. Thus, the global significance level (for all 16 variables and all pairwise comparisons) is restricted to 0.05. Mean z-score differences that are significant after this kind of correction are indicated. Categorical group differences (male vs. female) were investigated using the Chi<sup>2</sup> test. All computations were performed using SAS software Version 9.1 (SAS Institute Inc., Cary, NC, USA, 2001).

RESULTS

Raw scores of the cognitive variables are presented as median and quartiles, and the z-score values of the cognitive variables are presented as mean and standard deviation in Table 2 for the total MCI patient sample. For each cognitive variable the frequency of patients showing impaired performance as defined as a performance of 1.5 SD below healthy controls are also reported in Table 2.

Categorizing MCI patients into MCI subtypes revealed the following results. Thirty-seven patients (30.8 %) were categorized as cognitively normal, whereas 83 patients (69.2 %) met the criteria for MCI. MCI patients were subtyped as amnesic single-domain MCI (4 patients), amnesic multiple-domain MCI (26 patients), non-amnesic single-domain MCI (18 patients) and non-amnesic multiple-domain MCI (35 patients), respectively. (See Fig. 1 for details.)

The mean age was significantly different among the MCI subgroups (p = 0.023). The median education was not different among the MCI subgroups (p = 0.224). The percentage of males/females was not different among the MCI subgroups (p = 0.510). However, as expected, a Kruskal-Wallis Test revealed a significant group difference for the MMSE score (p = 0.003). (See Table 3 for demographic details of MCI subtypes.)

Cluster / neuro-psychological variable	CN	a-SD MCI	a-MD MCI	non-a-SD MCI	non-a-MD MCI	
<b>Attention</b>						
AKT <sup>a</sup>	0.36 ± 0.85	0.14 ± 0.83	-0.67 ± 1.26	-0.30 ± 0.79	-0.77 ± 1.43	<0.001
Digit-Symbol Test (WAIS-R) <sup>a,c</sup>	0.52 ± 0.82	0.15 ± 0.79	-0.85 ± 1.32	0.07 ± 1.05	-0.71 ± 1.06	<0.001
TMTA <sup>a</sup>	0.23 ± 0.88	0.33 ± 1.35	-0.60 ± 0.90	-0.71 ± 0.92	-0.91 ± 1.03	<0.001
Stroop (NAI) <sup>a,c</sup>	0.06 ± 0.86	-0.04 ± .91	-1.25 ± 1.03	-0.22 ± 0.84	-1.03 ± 1.05	<0.001
Symbol counting (C.I.) <sup>a</sup>	0.48 ± 0.91	0.35 ± 1.00	-0.37 ± 0.83	0.03 ± 1.00	-0.82 ± 1.22	<0.001
Interference Test (C.I.) <sup>a,c</sup>	0.22 ± 0.76	-0.14 ± 0.99	-0.99 ± 1.12	-0.42 ± 0.80	-1.13 ± 0.86	<0.001
<b>Memory</b>						
Verbal memory immediate recall (VSRT) <sup>c,f,h</sup>	0.14 ± 0.73	-0.64 ± 1.24	-1.12 ± 1.00	0.48 ± 0.74	0.44 ± 0.92	<0.001
Verbal memory total recall (VSRT) <sup>c,d,f,h,i</sup>	0.10 ± 0.71	-1.39 ± 0.48	-1.50 ± 0.85	0.16 ± 0.58	-0.08 ± 0.66	<0.001
Verbal memory delayed recall (VSRT) <sup>c,d,f,h,i</sup>	-0.01 ± 0.86	-1.77 ± 0.99	-2.30 ± 1.10	0.03 ± 0.82	-0.36 ± 0.72	<0.001
<b>Executive Function shifting capability</b>						
TMTB <sup>a,c,e,h</sup>	0.30 ± 0.96	-0.41 ± 1.09	-1.40 ± 0.99	-0.23 ± 0.71	-1.79 ± 0.92	<0.001
Difference score TMTB-TMTA <sup>a,c,e,h</sup>	0.26 ± 1.11	0.40 ± 1.47	-1.25 ± 1.08	0.18 ± 0.95	-1.58 ± 0.94	<0.001
<b>Executive Function planning and non-verbal fluency</b>						
Planning (Maze Test-NAI) <sup>a</sup>	0.15 ± 0.71	-0.22 ± 0.82	-0.15 ± 0.83	-0.15 ± 0.76	-1.05 ± 1.45	<0.001
Non-verbal Fluency (Five Point Test) <sup>a,c,e,h</sup>	0.31 ± 1.03	0.52 ± 0.49	-1.11 ± 1.26	0.21 ± 0.88	-0.96 ± 1.11	<0.001
<b>Language</b>						
Semantic verbal fluency <sup>a,c,e,h</sup>	0.06 ± 0.80	-0.36 ± 0.86	-1.40 ± 1.25	-0.10 ± 0.85	-1.31 ± 1.41	<0.001
Lexical verbal fluency <sup>a,c</sup>	0.14 ± 0.77	0.00 ± 0.55	-0.76 ± 1.00	-0.29 ± 1.20	-1.09 ± 0.98	<0.001
Boston Naming Test (mBNT)	0.10 ± 0.83	0.42 ± 0.82	-0.02 ± 1.16	-0.27 ± 1.11	-0.63 ± 1.37	0.051

Abbreviations: Pctl = Percentile; AKT = Alters-Konzentrations-Test; WAIS-R = Wechsler Adult Intelligence Scale - Revised; TMTA = Trail Making Test Version A; TMTB = Trail Making Test Version B; NAI = Nürnberger Alters Inventar; C.I. = Cerebral Insufficiency Test; VSRT = Verbal Selective Reminding Test; mBNT = modified Boston Naming Test; CN = Cognitively normal; a-SD MCI = amnesic single-domain MCI; a-MD MCI = amnesic multiple-domain MCI; non-a-SD MCI = non-amnesic single-domain MCI; non-a-MD MCI = non-amnesic multiple-domain MCI; \* indicates significance of the overall five-group comparison after Bonferroni-Holm correction. Abbreviations: CN = Cognitively normal; a-SD MCI = amnesic single-domain MCI; a-MD MCI = amnesic multiple-domain MCI; non-a-MCI SD = non-amnesic single-domain MCI; non-a- MD MCI = non-amnesic multiple-domain MCI

Table 5: Z-scores with means and standard deviations for each neuropsychological variable across MCI subtypes.

The statistical analyses for the raw scores of all neuropsychological variables revealed significant group differences after Bonferroni-Holm correction (all corrected p-values <0.05) except for the mBNT. (See *Table 4* for details.) Furthermore, statistical analyses for the z-scores of all neuropsychological variables revealed significant group differences after Bonferroni-Holm correction (all corrected p-values < 0.05) except for the mBNT. (See *Table 5* for details.)

#### DISCUSSION

The present study investigated the neurocognitive profile of patients reporting cognitive problems attending a memory outpatient clinic. After assessing the neuropsychological profile by using single tests, we explored the optimal number and content of cognitive domains characterizing the VNTB. Furthermore, we sought to establish the frequency of different MCI subtypes in our cohort.

As in other studies dealing with patients reporting cognitive impairment that was not sufficient for the diagnosis of dementia, our study population also showed a wide variety of neurocognitive impairment patterns [13]. Our patients performed, on average, between -0.02 SD and -0.78 SD below normal on cognitive measures included in the neuropsychological battery. This indicates that there is a wide overlapping with healthy controls. Psychometric testing revealed that up to 30 % of patients showed impaired performance in single neuropsychological tests. High rates of impairment were found for tests tapping executive function (shifting capability – TMTB), language function (semantic verbal fluency), memory (delayed recall – VSRT) and attention (selective attention – Stroop test). Far less impairment was detected by tests tapping immediate verbal memory (immediate recall – VSRT), pure psychomotor speed (symbol counting – C.I.) and naming capabilities (confrontation naming – mBNT).

Delayed verbal memory impairment is an early indicator of AD. Retrospective studies have shown that subtle episodic memory impairments and verbal fluency problems can be detected as early as twenty years before diagnosis [23, 39]. In a prior study of our group, we were able to demonstrate that the measurement of delayed verbal memory, as used in this study, accurately predicted future dementia within two years [18]. Measures of executive functions have been identified as good predictors for future vascular dementia. In particular, shifting capability as measured by the TMT-B has been reportedly documented to predict future vascular dementia [41]. Thus, the pattern of impairment in our patients probably reflects early stages on the way towards dementia [1], but it needs to be established in future longitudinal research.

A large part of our patient sample was outside the normal limits of cognitive testing when a cutoff score of 1.5

standard deviations below elderly controls was used. One important finding of the present study is that roughly more than two-thirds of the patients attending a memory clinic and having no dementia at the time of clinical examination have an abnormal cognitive status. The prevalence of MCI in population-based epidemiological studies was found to range from 3 % to 19 % in the general elderly population, depending on cohort characteristics and the criteria used to define MCI [12, 15, 21, 33]. The much higher prevalence found in our memory clinic cohort can, in all probability, be explained by the fact that patients referred to memory clinics are unlike the general population in that they are seeking medical help for a perceived disorder.

As in the case of most clinical studies, the current study has also some limitations that should be addressed. Due to fatigue, compromised motivation and in some cases patients having forgotten their eyeglasses, not every patient performed each test. The resulting informative missing values may lead to an underestimation (in absolute values) of the corresponding mean z-score and potentially also of its standard deviation. Furthermore, in this study we took the minimum of the specific z-scores within a domain as the summary z-score for this domain, since it is obviously usual to do so (see, e.g. [37]). However, it has to be noted that this procedure has to be applied with care, since adding an additional cognitive test to a domain can thus only decrease (at least cannot increase) a patient's summary score for this domain.

The definition of high-risk populations is of utmost importance. Incidence rates of dementia are highly elevated among cases with mild cognitive impairment compared with the general population, confirming that mild cognitive impairment compromises a high-risk population [10]. The characterization of MCI subtypes is very important because they can help understand the natural progression of patients perceiving problems. MCI subtype analysis in our cohort showed that approximately 3 % of the patients were subtyped as amnesic single-domain MCI, approximately 22 % amnesic multiple-domain MCI, approximately 15 % non-amnesic single-domain MCI and 29 % non-amnesic multiple-domain MCI, respectively. Similar results were obtained in a population-based study [15] indicating that a selective memory impairment is rather rare. Selective non-memory impairments are also found in the elderly population [8] and are much more often encountered in patients reporting cognitive problems in the setting of a memory clinic [10]. The identification of specific MCI subtypes has important practical implications. Because amnesic MCI patients show increased risk of converting to AD this MCI subtype needs to receive close clinical monitoring.

In conclusion, patients reporting cognitive problems and seeking help in a memory outpatient clinic, albeit having no clinical dementia, show a wide range of cognitive impairments. Roughly more than two-thirds of them are diagnosed as MCI on the basis of formal neuropsychological testing with varying frequencies of MCI subtypes. Together with clinical information, this classification will aid the clinician to choose the best treatment option.

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