Psychosis associated behavioral and psychological signs and symptoms in mild cognitive impairment and Alzheimer's dementia

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Abstract

Objectives: The aim of this study is to determine the prevalence of psychosis in mild cognitive impairment (MCI, Petersen's criteria) and patients with Alzheimer's dementia (AD); and to characterize the associated behavioral symptoms.

Method: A cross-sectional analysis of baseline data from a prospective, longitudinal study on behavioral symptoms was performed, including 270 MCI and 402 AD patients. Behavioral assessment was performed through Middelheim Frontality Score (MFS), Behave-AD, Cohen-Mansfield Agitation Inventory (CMAI) and Cornell Scale for Depression in Dementia (CSDD). Psychosis was considered to be clinically relevant when delusions and/or hallucinations occurred at least once in the last two weeks prior to the behavioral assessment.

Results: The prevalence of psychosis in AD (40%) was higher than in MCI (14%; $p<0.001$). AD patients with psychosis showed more severe frontal lobe, behavioral symptoms, agitation and depressive symptoms (MFS, Behave-AD, CMAI and CSDD total scores), whereas MCI patients with psychosis only showed more severe frontal lobe and physically non-aggressive agitated behavior. In addition, only in psychotic AD patients, all behavioral symptoms and types of agitation were more severe compared to non-psychotic AD patients. Comparing MCI and AD patients: MCI patients with psychosis did not show more severe frontal lobe, behavioral, depressive symptoms or agitation than AD patients without psychosis.

Conclusion: AD patients clearly display psychosis associated behavioral symptoms, whereas MCI patients only display more severe frontal lobe symptoms and physically non-aggressive agitated behavior, but also less pronounced than in AD.

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Introduction

Behavioral and psychological dementia-related problems increase caregiver burden in mild cognitive impairment (MCI) (Bruce, McQuiggan, Williams, Westervelt, & Tremont, 2008; Frank et al., 2006; Garand, Dew, Eazor, Dekosky, & Reynolds, III, 2005; Garand et al., 2007) and dementia due to Alzheimer's disease (AD) (Levy, Lanctot, Farber, Li, & Herrmann, 2012) and this might affect the quality of care for patients and the quality of life of relatives and caregivers (Hazzan, Ploeg, Shannon, Raina, & Oremus, 2013). Moreover, these neuropsychiatric manifestations, such as aggression, depression and hallucinations, are consistent predictors for institutionalization (Gaugler, Yu, Krichbaum, & Wyman, 2009; Luppa, Luck, Brahler, Konig, & Riedel-Heller, 2008).

The thorough understanding of behavior in MCI and AD is necessary, as behavioral features may represent risk factors for MCI or predictors for the progression of MCI to AD (Monastero, Mangialasche, Camarda, Ercolani, & Camarda, 2009). In addition, better behavioral understanding may be important for (non-) pharmacological behavioral research and management, aiming to reduce institutionalization and to improve quality of life for patients, relatives and caregivers.

Psychosis belongs to the behavioral and psychological signs and symptoms of dementia (Finkel, Costa e Silva, Cohen, Miller, & Sartorius, 1996), research reports a prevalence of 30 – 50% of psychosis in AD patients (Jeste & Finkel, 2000; Paulsen et al., 2000; Schneider & Dagerman, 2004) and the prevalence of psychosis in mild cognitive impairment (MCI) is up to 10% in population-based and up to 14% in hospital-based studies (Apostolova & Cummings, 2008; Monastero et al., 2009).

Three subtypes of psychosis can be differentiated in AD in their 'diagnostic criteria for psychosis of AD': psychosis of AD *with agitation*, when there is evidence of prominent agitation, with or without physical or verbal aggression; psychosis of AD *with negative symptoms*, when apathy, affective flattening, avolition or motor retardation are prominently present; and psychosis of AD *with depression*, when depressed mood, insomnia or hypersomnia, feelings of worthlessness or excessive or inappropriate guilt, or recurrent thoughts of death are prominently present (Jeste & Finkel, 2000). A psychosis syndrome in AD is repeatedly found as a principal behavioral component beside an agitation and a mood factor (Cummings, McRae, & Zhang, 2006; Frisoni et al., 1999; Hollingworth et al., 2006; Kang, Ahn, Kim, & Kim, 2010; Mirakhur, Craig, Hart, McLlroy, & Passmore, 2004; Spalletta et al., 2004; Spalletta et al., 2010; Vilalta-Franch et al., 2010). To our knowledge, the relationship, between psychosis and associated behavioral symptoms in MCI and as compared to AD, has not been investigated.

This study aims to test the hypotheses that psychotic patients display more frontal lobe, agitated, depressive and other neuropsychiatric symptoms, such as activity, sleep and affective disturbances, aggressiveness and anxiety/phobias, as compared to non-psychotic patients; and that psychotic AD patients have more associated behavioral symptoms than psychotic MCI patients, as behavioral symptoms are more present in AD (Van der Mussele et al., 2012).

Methods

Study population and diagnostic criteria

The study population consisted of MCI patients (n=270) and AD patients (n=402).

Patients were consecutively included in our memory clinic at the moment of their diagnostic work-up, consisting of a general physical and neurological examination, blood screening, structural neuroimaging, standard electroencephalogram and an extensive time-linked (±3 months) neuropsychological examination with adjustment for age and education, comprising amongst others the Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975) and the Wechsler Memory Scale III (The Psychological Corporation, 1998), Hierarchic Dementia Scale (Cole & Dastoor, 1987) and/or Repeatable Battery for the Assessment of Neuropsychological Status (Randolph, Tierney, Mohr, & Chase, 1998).

To diagnose MCI, Petersen's diagnostic criteria (2004) were applied. Objective cognitive impairment for age and education was quantified as a performance of more than 1.5 standard deviation below the appropriate mean on the neuropsychological subtests. As all cognitive domains of subjects were tested in an extensive time-linked (±3 months) neuropsychological examination, all MCI patients were categorized as amnestic/non-amnestic, single/multiple domain. The MCI group (n=270) consisted of 53 amnestic single domain, 150 amnestic multiple domain, 29 non-amnestic single domain and 38 non-amnestic multiple domain MCI patients.

Probable AD was diagnosed according to NINCDS/ADRDA criteria (National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association) (McKhann et al., 1984), though all patients as well fulfilled the DSM-IV criteria (American Psychiatric Association, 1994). Clinical and neuropsychological follow-up of included patients and autopsy in deceased consented patients during follow-up

period, did contribute to the diagnostic accuracy of the subjects in this study. The AD group consisted of 35 definite and 367 probable AD patients.

Staging of cognitive deterioration was assessed by means of the Global Deterioration Scale (GDetS) (Reisberg, Ferris, de Leon, & Crook, 1982).

To get a cursory idea about how psychotropic drug intake might have affected our study results, we investigated the difference in behavior between treated and untreated patients with psychosis by comparing the total scores of the behavioral assessment scales. MCI and AD patients were categorized as treated when they took medication from at least one of the psychotropic drug categories mentioned in table 1.

The local ethics committee approved this study. All patients and/or patients' caregivers gave written informed consent. All patients were of Caucasian origin.

Behavioral assessment

All subjects underwent in-depth behavioral assessment at inclusion (baseline) consisting of an interview of both patient and caregiver, covering a period of two weeks prior to inclusion. In case a non-professional caregiver was lacking, the patient's main professional caregiver was contacted and interviewed. The interview was performed by the clinician or researcher who was not blinded for the subject's cognitive diagnosis. The battery of behavioral assessment scales comprised: Behavioral Pathology in Alzheimer's Disease Rating Scale (Behave-AD), Middelheim Frontality Score (MFS), Cohen-Mansfield Agitation Inventory (CMAI) and Cornell Scale for Depression in Dementia (CSDD).

The MFS is a validated clinical and behavioral assessment scale that measures frontal lobe features and reliably discriminates FTD from AD patients with a sensitivity and specificity of almost 90% and with good inter- and intra-rater reliability (Aries et al., 2010; De Deyn et al., 2005). According to the Instructions for Administration and Scoring, the MFS was obtained

by summating scores in a standardized fashion on ten items. Each item was scored either zero (absent) or one (present) yielding a total maximal score of 10. The 10 items scored are noted in figure 1. The presence of frontal lobe symptoms was considered to be clinically relevant in case of a total MFS score of ≥5 (De Deyn et al., 2005).

The CMAI assesses 29 agitated behaviors on a seven-point scale of increasing frequency/severity (1=never to 7=several times an hour) (Cohen-Mansfield, 1996). CMAI cluster scores include aggressive behavior (10 items), physically non-aggressive behavior (11 items) and verbally agitated behavior (8 items); a total score is provided as well.

Depressive symptoms were assessed by means of the CSDD, a 19-item depression scale (Alexopoulos, Abrams, Young, & Shamoian, 1988a). Item scores range from 0 (absent) to 2 (severe), with a maximum total score of 38 points. The presence of significant depressive symptoms was defined as a total CSDD score >7 (Burns A, Lawlor B, & Craig S, 2004). Studies have shown the CSDD to be valid for screening depression in non-demented patients too (Alexopoulos, Abrams, Young, & Shamoian, 1988b).

Behavioral Pathology in AD Rating Scale and Psychosis

The Behave-AD is a 25-item scale that measures behavioral symptoms in seven clusters (figure 2), scored on a four-point scale of increasing severity (Reisberg et al., 1987). The cluster paranoid/delusional ideation consists of 7 items or types of delusions: ‘people are stealing things’, ‘one’s house is not one’s home’, ‘spouse or caregiver is an imposter’, ‘delusions of abandonment’, ‘infidelity’, ‘suspiciousness/paranoia’ and ‘other delusions’ (than the specifically previously described ones). The cluster hallucinations consists of 5 items: visual, auditory, olfactory, haptic and other hallucinations. A psychosis cluster score is calculated by summating the scores of the paranoid/delusional ideation (delusions) and hallucinations clusters. Besides a total score, a global score on a four-point scale of increasing

severity is provided, reflecting how troubling to the caregiver or dangerous to the patient the behavioral symptoms are, from not troubling or dangerous (score 0) to severe (score 3). We dichotomized the severity scores to calculate prevalence percentages for Behave-AD clusters and global score. Psychosis was considered to be present when delusions and/or hallucinations occurred at least once in the last two weeks prior to the behavioral assessment.

Statistical analyses

The (behavioral) assessment scales provide semi continuous variables. Therefore, non-parametric statistics were used: Mann-Whitney U test was applied to compare (semi) continuous variables, Chi-square statistics for categorical data and Spearman Rank to correlate (semi) continuous data.

To reduce the type I error rate, probability levels of 0.01 were considered significant. Statistical analyses were carried out using SPSS Statistics 17.0.

Results

The AD group comprised a higher percentage of women than the MCI group. MCI patients were younger at inclusion and disease onset and their disease duration was shorter. In AD patients, GDetS scores were higher and MMSE scores were lower as compared to the MCI group. Table 1 shows that there is no difference in gender, age, disease duration, GDetS, MMSE and psychotropic drug intake between MCI patients with and without psychosis. In contrast, psychotic AD patients had higher GDetS scores and used more antipsychotics than non-psychotic AD patients.

The prevalence of psychosis in AD patients (40%) was higher than the prevalence of psychosis in MCI patients (14%; $p<0.001$).

The prevalence of delusions, as measured by the Behave-AD, was 37% in AD patients and 12% in MCI patients ($p<0.001$) and the prevalence of hallucinations was 15% in AD patients and 6% in MCI patients ($p<0.001$).

MCI patients with psychosis suffered most from auditory hallucinations (23%) and AD patients with psychosis mainly from visual hallucinations (30%). However there was no difference in prevalence of auditory hallucinations ($p=0.017$) and visual hallucinations ($p=0.142$) between MCI and AD patients with psychosis.

In MCI patients, neither a difference in prevalence of psychosis was found among the four subtypes of MCI ($p=0.616$), nor a difference in prevalence of delusions ($p=0.466$) or hallucinations ($p=0.530$). Furthermore in MCI patients, neither the severity of psychosis correlated with the MMSE ($r_s=-0.031$; $p=0.613$) or the GDetS ($r_s=0.101$; $p=0.099$) scores, nor the severity of delusions (MMSE: $r_s=-0.021$, $p=0.737$; GDetS: $r_s=0.073$, $p=0.233$) or hallucinations (MMSE: $r_s=0.010$, $p=0.873$; GDetS: $r_s=0.070$, $p=0.252$) did so.

In AD patients, the severity of psychosis correlated positively with the GDetS scores (r_s=0.152; p=0.002), but did not correlate with the MMSE scores (r_s=-0.098; p=0.049). However, the severity of hallucinations correlated negatively with the MMSE (r_s=-0.146; p=0.003) and positively with the GDetS (r_s=0.203; p<0.001). On the other hand, the severity of delusions did not correlate with the MMSE (r_s=-0.087; p=0.082) or GDetS (r_s=0.126; p=0.012).

The prevalence of MFS items and MFS total scores in MCI patients with and without psychosis are displayed in figure 1 and table 2. Frontal lobe symptoms were present in 13% of the MCI patients with psychosis and in 5% of the MCI patients without psychosis (p=0.043). Frontal lobe symptoms were present in 37% of the AD patients with psychosis and in 19% of the AD patients without psychosis (p<0.001). AD patients with psychosis had higher MFS total scores as compared to MCI patients with psychosis (figure 3).

The prevalence of Behave-AD clusters and the severity of Behave-AD clusters, total and global scores in MCI and AD patients with and without psychosis are displayed in figure 2 and table 2. MCI patients with psychosis had a comparable prevalence and severity of individual behavioral symptoms (Behave-AD items) as compared to MCI patients without psychosis. Behave-AD total scores were higher in MCI patients with psychosis. However, after removing the cluster scores delusions and hallucinations from the Behave-AD total score, there was no difference anymore in Behave-AD total scores between patients with or without psychosis (p=0.066). In addition to the prevalence and severity of behavioral symptoms, Behave-AD global scores, indicating how troubling to the caregiver and/or dangerous to the patient the behavioral symptoms are, were higher in MCI patients with

psychosis. From the MCI patients with psychosis, 63% was rated as at least mildly troubling or dangerous, as compared to 29% in MCI patients without psychosis ($p<0.001$).

In AD patients with psychosis, all behavioral symptoms were more severe and more prevalent. Behave-AD total scores remained statistically significant higher ($p<0.001$) in patients with psychosis, even after removing the cluster scores delusions and hallucinations from the Behave-AD total score. Behave-AD global scores were higher in AD patients with psychosis. From the AD patients with psychosis, 93% was rated as at least mildly troubling or dangerous, as compared to 59% in AD patients without psychosis ($p<0.001$).

AD patients with psychosis displayed more severe behavioral symptoms as compared to MCI patients with psychosis (figure 3). The higher Behave-AD total scores remained statistically significant ($p<0.001$) even after removing the cluster scores delusions and hallucinations from the total score. Furthermore, MCI patients with psychosis showed more severe behavioral symptoms than AD patients without psychosis (figure 3). However, this finding did not remain statistically significant ($p=0.562$) after removing the cluster scores delusions and hallucinations from the Behave-AD total score.

The frequency of physically non-aggressive behavior was higher in MCI patients with psychosis (table 2). The frequency of aggressive behavior, physically non-aggressive behavior and verbally agitated behavior were higher in AD patients with psychosis compared to the AD patients without psychosis (table 2). AD patients with psychosis displayed more agitated behavior as compared to MCI patients with psychosis (figure 3).

There was neither a difference in the severity of depressive symptoms (table 2), nor a difference in the prevalence of significant depressive symptoms between MCI patients with psychosis (23%) and patients without psychosis (14%; $p=0.161$).

AD patients with psychosis displayed more depressive symptoms than patients without psychosis (table 2). The prevalence of significant depressive symptoms in AD patients with psychosis (35%) was higher than the prevalence of depressive symptoms in patients without psychosis (18%; $p<0.001$).

MCI patients with psychosis showed obviously, but not significantly more depressive symptoms than AD patients without psychosis (figure 3).

In MCI, there was no difference ($p=0.744$) in prevalence of psychosis between the patients treated with psychotropic medication (n=123) and the untreated (n=131) patients with respectively 14% and 15%. Treated (n=17) and untreated (n=20) MCI patients with psychosis did neither differ regarding MFS total scores ($p=0.539$), depressive symptoms (CSDD total score: $p=0.020$) and agitated behavior (CMAI total score: $p=0.987$), nor with regard to being troubling to the caregiver and/or dangerous to themselves (Behave-AD global score: $p=0.089$). Treated MCI patients with psychosis displayed more behavioral symptoms as compared to untreated patients with psychosis (Behave-AD total score: $p=0.004$). However, this finding did not remain statistically significant ($p=0.036$) after removing the cluster scores delusions and hallucinations from the Behave-AD total score.

In AD, there was no difference ($p=0.886$) in prevalence of psychosis between the treated (n=333) and untreated (n=68) patients with respectively 40% and 41%. Treated (n=134) and untreated (n=28) AD patients with psychosis did neither differ regarding MFS total scores ($p=0.421$), behavioral symptoms (Behave-AD total score: $p=0.991$) and agitated behavior (CMAI total score: $p=0.795$), nor with regard to being troubling to the caregiver and/or dangerous to themselves (Behave-AD global score: $p=0.854$). However, treated AD patients with psychosis displayed more depressive symptoms as compared to untreated patients with psychosis (CSDD total score: $p=0.009$).

Discussion

Our findings on the prevalence of psychosis in MCI (14%) and AD (40%) are in line with previous research, stating 30-50% of AD patients are suffering from psychosis (Jeste & Finkel, 2000; Paulsen et al., 2000; Schneider & Dagerman, 2004) and 14% of MCI patients, according to hospital based studies (Apostolova & Cummings, 2008; Monastero et al., 2009). Our findings on associated behavioral symptoms of psychosis support the three described subtypes of psychosis in AD (Jeste & Finkel, 2000), but also ruled out the existence of these subtypes in our MCI subgroup with psychosis. Psychosis of AD was associated by higher CMAI total scores (*agitation*), CSDD total scores (*depression*) and a higher prevalence of emotional bluntness (*negative symptoms*). However, emotional bluntness might have been overestimated as it is part of the MFS item 'impaired control of emotions – euphoria – emotional bluntness'. In contrast, none of these three behaviors are associated with psychosis in MCI.

The prevalence of delusions and hallucinations differs greatly within the AD (37% and 15%) and MCI (12% and 6%) diagnoses. These results in AD are in line with the review findings of Ropacki and Jeste (2005) who calculated a psychosis prevalence of 41%, a delusions prevalence of 36% and a hallucinations prevalence of 18% in AD. So, psychosis is prominent in AD and in determining brain-behavior correlates, neuroimaging literature has largely studied psychosis as a whole entity. However, compelling evidence supports the need to study delusions separate from hallucinations or psychosis and that delusions should also be subtyped into persecutory or misidentification for further study (Ismail et al., 2011). Our findings acknowledge the domination of delusions within psychosis in AD, as delusions are more prevalent than hallucinations. According to the majority of studies, delusions appear to

be associated with a breakdown in the function and connectivity of frontal and temporal networks, predominantly on the right side (Ismail, Nguyen, Fischer, Schweizer, & Mulsant, 2012). This breakdown in function and connectivity could be linked to the AD brain pathology. Furthermore, in a general neuropsychological model of delusion, Braun and Suffren (2011) have pointed to the importance of the left hemisphere overactivity secondary to the right hemisphere impairment in the DSM-IV delusional disorder. As the left hemisphere is an activator and the right hemisphere an inhibitor of mentation and behavior, the two hemispheres compete and cooperate to maintain balance. As a consequence, left-frontal predominance and release caused by right-sided deficits appear to be a more primary origin of delusional disorder.

The clinical implications of this study are that in MCI patients with psychosis, behavioral management should primarily address the psychotic symptoms; and in AD, the management of psychosis might decrease associated behavioral symptoms, as well as the opposite approach, that the treatment of associated behavioral symptoms might reduce psychotic symptoms in AD patients. The quality of care for patients with cognitive deterioration could be increased by the implementation of a systematic behavioral screening policy in the geriatric in- and outpatient services. Specific tools and training could support the implementation of this behavioral screening policy.

Further research would assist in understanding the underlying pathophysiology of associated behavioral symptoms in agitation and in the understanding the possible inter-relation of behavioral symptoms, the epidemiology of MCI and the diagnostic and prognostic value of behavioral symptoms and syndromes. Follow-up of the included MCI patients is ongoing to test the hypothesis that behavioral disturbances in MCI predict progression to dementia. The occurrence of psychosis in MCI might be of prognostic value for progression to AD.

To our knowledge, this study is the first to investigate associated behavioral symptoms in and between psychotic AD and MCI patients.

This study has additional strengths. First, the study included large and well-characterized MCI and AD patient groups that have been diagnosed following strict application of clinical diagnostic criteria. Second, as the data came from a prospective, longitudinal study, the follow-up of included subjects and AD autopsy confirmation (n=35) contributed to increased AD diagnostic certainty. Third, all patients were diagnosed by clinicians in the same centre in order to preserve homogeneity in the diagnostic groups.

Three limitations to the study are known to the authors. First, our study population was recruited in a memory clinic, which might have introduced a selection bias as behavioral symptoms might have contributed to referral. Second, behavioral assessment raters were not blinded for the subjects' clinical MCI or AD diagnosis. On the other hand, due to strict application of clinical diagnostic criteria, which do not include behavioral changes, behavior did not impact the clinical diagnosis. Third, included subjects were not free of psychotropic medication at the moment of their behavioral observation. However, there is no difference in prevalence of psychosis between the treated and untreated MCI or AD patients and intra-diagnostic group analysis did not reveal important differences in behavior between treated and untreated patients. We did not assess in detail the effects of psychotropic drugs on behavior, as this is not a pharmacological study. Furthermore, psychotropic drug intake rates vary among countries and Belgium is known to have a high prevalence of psychotropic drug utilization in community-dwelling elderly and nursing home residents (Azermai, Elseviers, Petrovic, Van Bortel, & Vander Stichele, 2011). This also partially explains the high prevalence of psychotropic drug intake in MCI and AD patients in this study.

In conclusion, the prevalence of psychosis in AD patients is higher than in MCI patients, respectively 40% and 14%. AD patients with clinical relevant psychosis display more severe frontal lobe, behavioral and depressive symptoms and agitated behavior as compared to AD patients without psychosis. In AD patients, higher MFS total scores reflect also in a higher prevalence of frontal lobe symptoms (MFS total score ≥5). In contrast, MCI patients with psychosis only display more physically non-aggressive agitated behavior and have higher MFS total scores, but not resulting in a higher prevalence of frontal lobe symptoms. In addition, in AD with psychosis three MFS items and all behavioral symptoms are more prevalent, whereas with exception of one MFS item there are no individual associated behavioral symptoms more prevalent in the MCI subgroup with psychosis. Comparing MCI and AD patients: psychosis in AD is accompanied with higher MFS total scores and more severe behavioral symptoms and agitated behavior, but not depressive symptoms, than in MCI patients with psychosis. Consequently, only for the AD patients we can confirm our hypothesis that psychotic patients display more frontal lobe, agitated, depressive and other neuropsychiatric symptoms, as compared to non-psychotic patients. However, for the intra-diagnostic comparison of MCI patients with or without psychosis, we could not find sufficient evidence to support this hypothesis. Furthermore, we can also confirm the hypothesis that psychotic AD patients have more associated behavioral symptoms than psychotic MCI patients, as behavioral symptoms are more present in AD.

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Table 1 Demographic, clinical and neuropsychological data

	MCI			AD		
	Total	Psychosis		Total	Psychosis	
	n=270	No n=231	Yes n=39	n=402	No n=240	Yes n=162
%		85.6%	14.4%		59.7%	40.3%
Male / Female	120/150	105/126	15/24	132/270 *	81/159	51/111
Age at inclusion (yrs)	75.5 ± 8.1 (50-94)	75.2 ± 8.2 (50-94)	77.3 ± 6.6 (63-92)	80.1 ± 7.6 (51-97) **	79.9 ± 7.5 (51-97)	80.3 ± 7.6 (55-97)
Age at onset (yrs)	73.2 ± 8.3 (48-90)	72.9 ± 8.5 (48-90)	74.8 ± 6.9 (60-89)	76.8 ± 8.4 (48-96) **	76.8 ± 8.1 (48-96)	76.7 ± 8.9 (51-95)
Disease duration (yrs)	2.2 ± 1.7 (0-11)	2.2 ± 1.7 (0-11)	2.4 ± 1.9 (0-7)	3.3 ± 2.5 (0-16) **	3.0 ± 2.2 (0-13)	3.7 ± 2.9 (0-16)
Global Deterioration Scale (1-7)	3.0 ± 0.7 (1-5)	3.0 ± 0.7 (1-5)	3.2 ± 0.8 (2-5)	5.1 ± 1.0 (2-7) **	5.0 ± 1.0 (2-7)	5.3 ± 0.9 (3-7) *
MMSE score (/30)	25.6 ± 2.9 (16-30)	25.7 ± 2.9 (16-30)	25.5 ± 2.8 (19-30)	15.2 ± 6.3 (0-30) **	15.6 ± 6.5 (0-30)	14.6 ± 5.9 (0-28)
Free of psychotropic medication (%)	51.6	51.2	54.1	17.0 **	16.7	17.3
Antidepressants (%)	25.1	26.0	19.4	38.8 **	39.2	38.3
Antipsychotics (%)	5.0	4.9	5.4	45.2 **	39.9	53.1 *
Hypnotics, sedatives, anxiolytics (%)	29.1	29.0	29.7	23.6	21.2	27.2
Cholinesterase inhibitors (%)	3.4	4.0	0.0	36.8 **	39.7	32.7
Antiparkinsonian agents (%)	2.7	2.2	5.3	1.5	1.7	1.2
Antiepileptics (%)	2.3	2.7	0.0	1.5	1.7	1.2

Data are given as ratio, percentage or mean ± SD with ranges represented between brackets.
Significant differences comparing the MCI group with the AD group; and the groups with and without psychosis within the MCI group and within the AD group are mentioned as follows: * = $p<0.01$, ** = $p<0.001$.
Psychosis was considered to be present (Yes) when delusions and/or hallucinations occurred at least once in the last two weeks.
For comparison of male-female ratios and percentages, Chi-square statistics were used.
For other comparisons, Mann-Witney U test was applied.
The level of significance was set at $p<0.01$.
Abbreviations: MCI = mild cognitive impairment; AD = dementia due to Alzheimer's disease

Table 2 Severity of behavioral symptoms

	MCI (n=268)		**AD** (n=393)	
	Psychosis		Psychosis	
	No n=231	Yes n=39	No n=240	Yes n=162
MFS (0-10) Total score	1.9 ± 1.5 (0-7)	2.8 ± 1.7 (0-8) *	2.9 ± 1.7 (0-8)	4.0 ± 1.8 (0-9) **
Behave-AD (0-21) Delusions	0.0 ± 0.0 (0-0)	1.6 ± 1.7 (0-9) **	0.0 ± 0.0 (0-0)	3.2 ± 3.1 (0-20) **
Behave-AD (0-15) Hallucinations	0.0 ± 0.0 (0-0)	1.1 ± 1.7 (0-6) **	0.0 ± 0.0 (0-0)	0.9 ± 1.4 (0-7) **
Behave-AD (0-36) Psychosis (delusions + hallucinations)	0.0 ± 0.0 (0-0)	2.7 ± 3.0 (1-15) **	0.0 ± 0.0 (0-0)	4.1 ± 3.5 (1-26) **
Behave-AD (0-9) Activity	0.2 ± 0.6 (0-4)	0.4 ± 0.9 (0-3)	1.2 ± 1.7 (0-8)	2.2 ± 2.2 (0-9) **
Behave-AD (0-9) Aggressiveness	1.2 ± 1.7 (0-7)	1.6 ± 2.1 (0-9)	1.5 ± 2.2 (0-9)	3.3 ± 2.8 (0-9) **
Behave-AD (0-3) Diurnal rhythm	0.4 ± 0.7 (0-3)	0.4 ± 0.7 (0-3)	0.4 ± 0.7 (0-3)	0.6 ± 0.9 (0-3) *
Behave-AD (0-6) Affective	0.9 ± 1.2 (0-5)	0.8 ± 1.0 (0-3)	0.7 ± 1.2 (0-6)	1.1 ± 1.4 (0-5) *
Behave-AD (0-12) Anxiety/Phobias	0.7 ± 1.1 (0-8)	1.1 ± 1.3 (0-4)	0.4 ± 0.9 (0-5)	0.7 ± 1.1 (0-5) *
Behave-AD (0-9) Total score	3.3 ± 3.2 (0-17)	7.0 ± 4.4 (1-20) **	4.1 ± 4.0 (0-17)	12.0 ± 6.9 (1-47) **
Behave-AD (0-3) Global score	0.4 ± 0.7 (0-3)	0.9 ± 0.8 (0-2) **	0.8 ± 0.8 (0-3)	1.6 ± 0.8 (0-3) **
CMAI (10-70) Aggressive	10.0 ± 0.3 (10-13)	10.2 ± 1.1 (10-16)	10.7 ± 2.7 (10-34)	12.8 ± 6.7 (10-50) **
CMAI (11-77) Physically non-aggressive	12.0 ± 2.3 (11-14)	13.3 ± 3.5 (11-24) *	15.2 ± 5.8 (11-48)	19.5 ± 7.8 (11-42) **
CMAI (8-56) Verbally agitated	10.9 ± 4.1 (8-36)	11.8 ± 5.5 (8-27)	11.3 ± 4.6 (8-31)	15.3 ± 7.1 (8-40) **
CMAI (29-203) Total score	33.0 ± 5.4 (29-69)	35.4 ± 8.8 (29-66)	37.2 ± 9.5 (29-77)	47.6 ± 16.0 (29-105) **
Cornell Scale for Depression (0-38) Total score	4.3 ± 4.2 (0-31)	5.8 ± 4.8 (0-22)	4.2 ± 3.7 (0-20)	6.6 ± 4.4 (0-25) **

Psychosis was considered to be present (Yes) when delusions and/or hallucinations occurred at least once in the last two weeks.

Data are given as ratio, percentage or mean ± SD with ranges represented between brackets.

Significant differences comparing the groups with and without psychosis within the MCI group and within the AD group are mentioned as follows: * = $p<0.01$, ** = $p<0.001$.

For all comparisons, Mann-Witney U test was applied and the level of significance was set at $p<0.01$.

Abbreviations: MCI = mild cognitive impairment; AD = dementia due to Alzheimer's disease; MFS = Middelheim Frontality Score; Behave-AD = Behavioural Pathology in Alzheimer's Disease rating scale; CMAI = Cohen-Manfield Agitation Inventory; CSDD = Cornell Scale for Depression in Dementia

Figures legends

Figure 1 Prevalence (%) of frontal lobe symptoms in MCI and AD patients

Psychosis was considered to be present (Yes) when delusions and/or hallucinations occurred at least once in the last two weeks.
Chi-square statistics were used, comparing the groups with and without psychosis within the MCI and AD groups. Significant differences are mentioned as follows: * = $p<0.01$, ** = $p<0.001$. The level of significance was set at $p<0.01$.
Abbreviations: MFS = Middelheim Frontality Score; MCI = mild cognitive impairment; AD = dementia due to Alzheimer's disease

Figure 2 Prevalence (%) of behavioral symptoms in MCI and AD patients

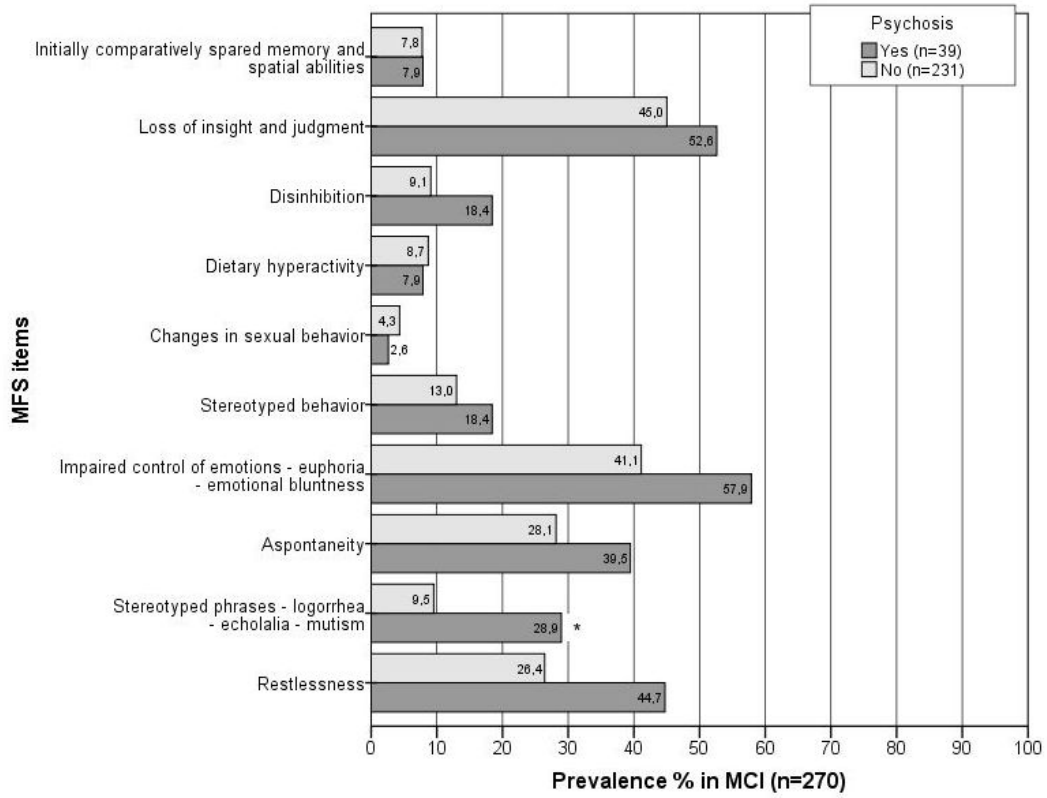
Psychosis was considered to be present (Yes) when delusions and/or hallucinations occurred at least once in the last two weeks.
Chi-square statistics were used, comparing the groups with and without psychosis within the MCI and AD groups. Significant differences are mentioned as follows: * = $p<0.01$, ** = $p<0.001$. The level of significance was set at $p<0.01$.
Abbreviations: MCI = mild cognitive impairment; AD = dementia due to Alzheimer's disease

Figure 3 Severity of frontal lobe, behavioral and depressive symptoms in MCI and AD

Psychosis was considered to be present (Yes) when delusions and/or hallucinations occurred at least once in the last two weeks.
For all comparisons, Mann-Witney U test was applied. The level of significance was set at $p<0.01$.
Abbreviations: MCI = mild cognitive impairment; AD = dementia due to Alzheimer's disease; MFS = Middelheim Frontality Score; Behave-AD = Behavioural Pathology in Alzheimer's Disease rating scale; CSDD = Cornell Scale for Depression in Dementia
a: MCI patients without psychosis; b: MCI patients with psychosis;
c: AD patients without psychosis; and d: AD patients with psychosis

Figures

Figure 1 Prevalence (%) of frontal lobe symptoms in MCI and AD patients



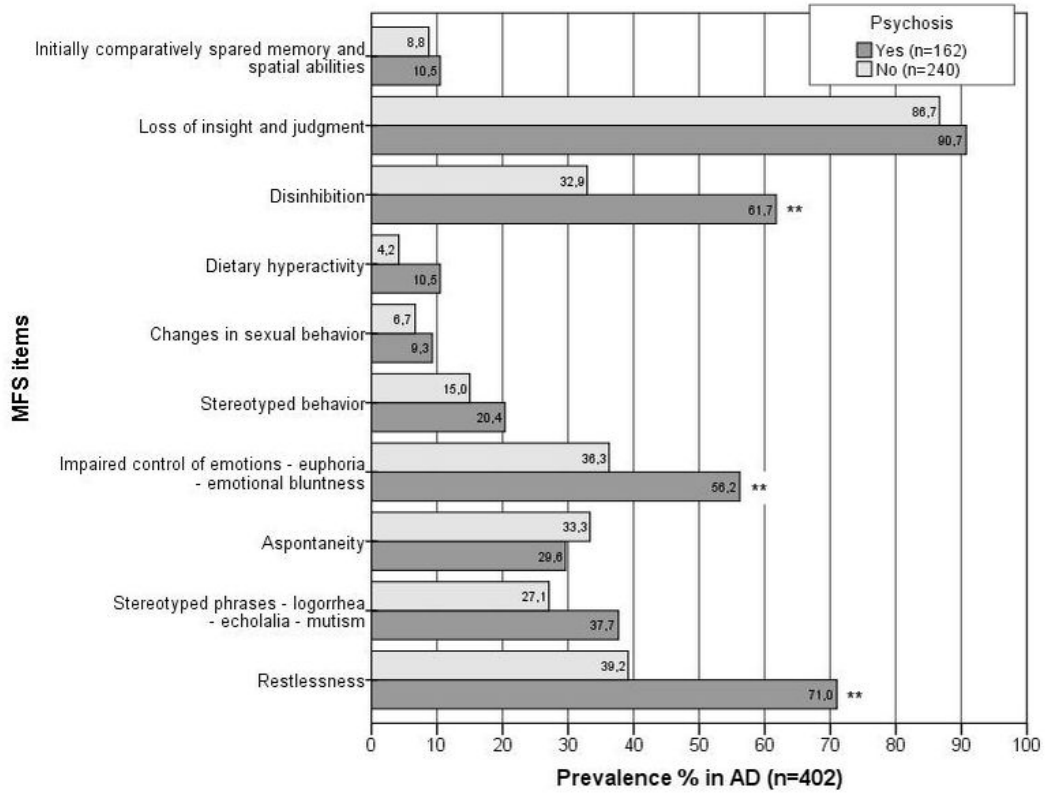
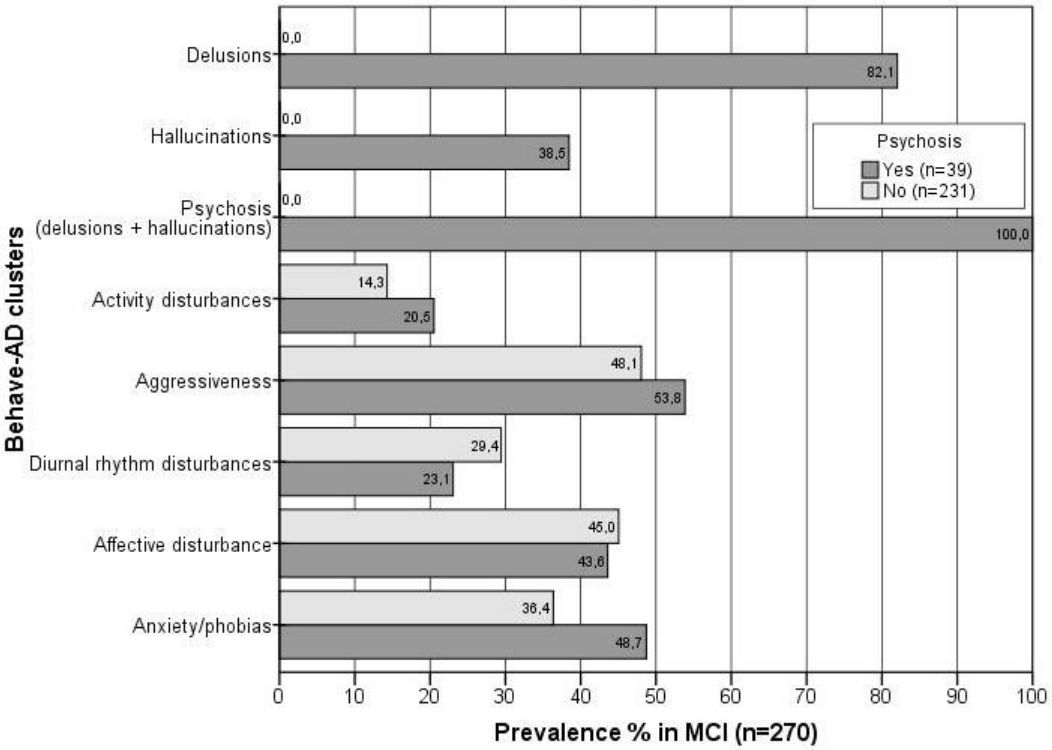


Figure 2 Prevalence (%) of behavioral symptoms in MCI and AD patients



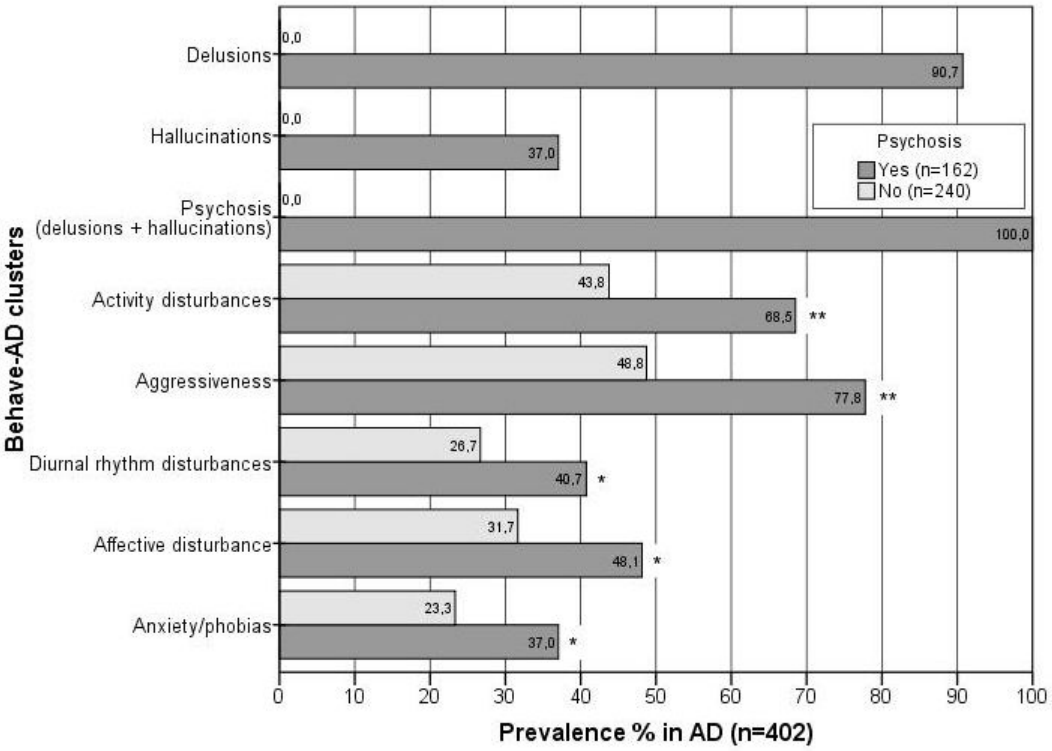


Figure 3 Severity of frontal lobe, behavioral and depressive symptoms in MCI and AD