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Neuropsychiatric symptoms in MCI subtypes: the importance of executive dysfunction

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Abstract

Objective—Mild cognitive impairment (MCI) is a syndrome thought to be a prodrome of dementia for some patients. One subtype, amnestic MCI, may be specifically predispose patients to develop Alzheimer's Dementia (AD). Since dementia has been associated with a range of neuropsychiatric symptoms (NPS), we sought to examine the prevalence of NPS in MCI and its subtypes.

Methods—1779 participants in the National Alzheimer Coordinating Center (NACC) with MCI were included in this study. All participants were evaluated systematically with a thorough cognitive battery, clinical interview, and consensus diagnoses, and subtyped as: 1) amnestic (aMCI) (single- or multiple-domain) vs. non-amnestic (non-aMCI); 2) executive dysfunction-MCI (exMCI) (single- or multiple-domain) vs. no executive dysfunction-MCI (non-exMCI); 3) both aMCI and exMCI; 4) and neither aMCI nor exMCI. Additionally , aMCI vs. nonaMCI and exMCI vs. non-exMCI dichotomies were explored. NPS were assessed with the Neuropsychiatric Inventory (NPI-Q) and Geriatric Depression Scale (GDS).

Results—1379 participants (77.5%) met criteria for aMCI and 616 (34.6%) for exMCI. No differences were observed in the prevalence of NPS between aMCI vs. non-aMCI. However, exMCI was associated with greater severity of depression, anxiety, agitation, disinhibition, irritability, and sleep problems, although these differences do not persist after adjustment for several variables. .

Conclusions—While there were few associations between aMCI and NPS, the presence of executive dysfunction in MCI was associated with greater severity of symptoms and specifically with depression (evidenced by GDS score) and anxiety. These findings may have implications for MCI prognosis and need to be explored in longitudinal studies.

Keywords

Mild Cognitive Impairment; Depression; Executive Dysfunction; Neuropsychiatric symptoms

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Introduction

There is growing evidence that dementia is preceded by a prodrome in which persons at risk can be identified by clinical characteristics, especially the emergence of mild cognitive deficits (Petersen *et al*., 2001; Winblad *et al*., 2004). The syndrome "mild cognitive impairment" (MCI) has been proposed as one way to identify this prodrome and is used to describe individuals who are neither cognitively normal nor demented, but who are exhibiting cognitive impairment in the absence of functional impairment (Winblad *et al*., 2004). MCI has been subtyped by the number and characteristics of the affected cognitive domains: single- vs. multiple-domain, and amnestic (affecting episodic recall) vs. non-amnestic. (Petersen *et al*., 2001; Winblad *et al*., 2004). Persons with amnestic MCI (aMCI) are at particularly high risk of developing Alzheimer's Dementia (AD) in the near term, with annual rates of progression from aMCI to AD estimated at 10-18%; up to 80% develop AD at 6 year follow-up (Petersen, 2004; Gauthier *et al*., 2006; Tschanz *et al*., 2006). Several longitudinal studies report that persons with aMCI progress to AD faster than persons with non-aMCI (Busse *et al*., 2006; Ravaglia *et al*., 2006b; Tschanz *et al*., 2006; Fischer *et al*., 2007).

In addition to cognitive deficits, AD is characterized by neuropsychiatric symptoms (NPS) including depression, apathy, agitation, irritability, delusions, and hallucinations (Lyketsos *et al*., 2000; Lyketsos *et al*., 2001; Lyketsos *et al*., 2002b; Steinberg *et al*., 2003; Steinberg *et al*., 2007). NPS are near-universal in dementia with 97% of participants in one study experiencing at least one NPS (Steinberg *et al*., 2007). It is possible that the prodrome of dementia may have both cognitive and non-cognitive symptoms. As a prodrome of AD, NPS may be associated with increased risk for MCI progression to dementia and the prevalence of NPS in MCI would be expected to be greater than in cognitively healthy persons but less than in dementia; the latter finding has been reported in epidemiologic studies of population-based samples (Lyketsos *et al*., 2002b; Geda *et al*., 2008). A corollary is that if different MCI subtypes have different NPS profiles, these differences might be reflected in different prognoses. Differences in NPS between MCI subtypes have not been clearly established, with the Cardiovascular Health Study (CHS) reporting no difference in NPS profile between participants with amnestic single-domain MCI compared to other MCI subtypes (Lopez, Becker, Sweet, 2005) while the Mayo Clinic Study of Aging reporting differences that were small in magnitude (Geda *et al*., 2008).

We consequently examined NPS profiles in several MCI subtypes in a large multi-center cohort from the National Alzheimer Coordinating Center (NACC) database, (Beekly *et al*., 2004; Beekly *et al*., 2007). Since depression in older adults is characterized by deficits in executive function (Alexopoulos *et al*., 1997), that persist even when depressive symptoms resolve (Murphy and Alexopoulos, 2004), we included the presence or absence of executive dysfunction as well as memory dysfunction to subtype MCI. We hypothesized that the presence of executive dysfunction (regardless of memory dysfunction) in MCI would be associated with greater severity of NPS, particularly depressive symptoms.

Methods

The National Alzheimer's Coordinating Center (NACC) is responsible for developing and maintaining a database combining the data collected at the 29 Alzheimer's Disease Centers (ADCs) funded by the National Institute of Aging (Beekly *et al*., 2004). The NACC database has been operational since 2000 and since 2002 has expanded its efforts into a fully integrated data system, the Uniform Data Set (UDS) (Beekly *et al*., 2007), which is available to investigators in the field for analytic projects. Methods for the administration of the UDS in the ADCs have been previously published (Morris *et al*., 2006).

Standard Protocol Approvals, Registrations, and Patient Consents

All participants or their legally authorized representatives signed informed consent prior to participation, and the procedures were approved by the Institutional Review Board overseeing each ADC.

MCI and dementia diagnoses

NACC participants receive a diagnosis adjudicated by an experienced clinician or an interdisciplinary team as previously described (Morris *et al*., 2006). Diagnosticians considered history and test performance in several cognitive domains (episodic recall, language, attention, executive function, and visuospatial function) as well as psychosocial functioning in making diagnoses. The UDS neuropsychological battery was used to inform the diagnostic process, but diagnoses were made clinically and not on the basis of strict cutoffs on neuropsychologic tests. The battery included Mini-Mental State Exam (Folstein, Folstein, McHugh, 1975), Wechsler Memory Scale-Revised Logical Memory IA (Wechsler and Stone, 1973), Digit Span Forward and Backward (Wechsler and Stone, 1973), Category Fluency (animals and vegetables) (Morris *et al*., 1989), Boston Naming Test (Goodglass and Kaplan, 1983), WAIS-R Digit Symbol (Wechsler, 1955), Trailmaking Test Parts A and (Armitage, 1946), and Wechsler Memory Scale (Revised) Logical Memory IIA (Wechsler and Stone, 1973). Participants were assigned diagnoses of 1) "cognitively normal" if they lacked significant cognitive or functional impairment; 2) "MCI" if they had objective or subjective evidence of cognitive impairment but no significant functional impairment to meet criteria for dementia; 3) "demented" if they had significant cognitive and functional impairment.

MCI was further subtyped into 1) aMCI if they had significant impairment in memory; 2) non-aMCI if they had normal performance in memory but impairment in another cognitive domain; 3) single-domain MCI if they had impairment in one cognitive domain only; 4) multiple-domain MCI if they had impairment in more than one cognitive domain. Thus, a participant with MCI might have been diagnosed with single- or multiple-domain aMCI, or single- or multiple-domain non-aMCI (Winblad *et al*., 2004). In addition, non-aMCI and multiple-domain aMCI were further subtyped according to the cognitive domains affected including memory, visuospatial, attention, language, and executive function. We used these clinical consensus diagnoses available in the UDS to define two dichotomies of MCI subtypes (below).

Definition of MCI subtypes

aMCI vs. non-aMCI—We first dichotomized MCI by distinguishing all amnestic subtypes (single- or multiple-domain) vs. all non-amnestic subtypes (single- or multiple-domain). We chose to combine single- and multiple-domain subtypes because a) neither of our hypotheses was affected conceptually by the distinction between single- and multiple-domain subtypes of MCI; and b) comparing two (instead of multiple) categories improves statistical power. This dichotomy is similar though not identical to the approach used in the Cardiovascular Health study (CHS) (Lopez, Becker, Sweet, 2005) and in the Olmsted County Study (Geda *et al*., 2008).In the CHS, the investigators compared single-domain aMCI vs. all other types of MCI including multiple-domain; we chose to combine multiple-domain aMCI with single-domain because the clinical presentations are similar and the prognoses not yet known.

MCI with executive dysfunction (exMCI) vs. MCI without executive dysfunction (non-exMCI)—we similarly dichotomized MCI according to the presence or absence of executive dysfunction as defined by the clinician or interdisciplinary team at each ADC,

combining together single/multiple-domain and aMCI/non-aMCI subtypes. We examined differences in NPS between the setwo dichotomies.

Since the categories of aMCI and exMCI were not mutually exclusive, we additionally subtyped MCI into four mutually exclusive categories:

- **a.** neither aMCI nor exMCI
- **b.** aMCI only
- **c.** exMCI only
- **d.** both aMCI and exMCI

Outcomes

Clinical Dementia Rating (CDR) (Morris, 1993)—The CDR is the most widely used rating of global function in dementia and MCI. The CDR is performed via a semi-structured interview and it has been demonstrated to have excellent reliability and validity. The CDR uses a 4 to 5-point ordinal scale to characterize six domains of cognitive and functional performance: memory, orientation, judgment, community, hobbies, and personal care. Each domain is rated (0=no impairment, 0.5=questionable impairment, 1=mild impairment, 2=moderate impairment, 3=severe impairment), with the exception of personal care which omits the questionable impairment category. A global score (CDR-composite) is created using a predefined algorithm. The CDR-Sum of Boxes (CDR-Sum) score is the sum of individual ratings in each of the six domains, with a range of 0 (no impairment) to 30 (maximum impairment in all domains). Both CDR-composite and CDR-Sum scores were examined as outcome measures in this study. The CDR-Sum score has demonstrated sensitivity in changes within MCI and AD as demonstrated by epidemiological (Pavlik *et al*., 2006) and functional magnetic resonance imaging studies (Dickerson *et al*., 2004).

Neuropsychiatric Inventory Questionnaire (NPI-Q) (Cummings *et al*., 1994; Kaufer *et al*., 2000)—The NPI is the most widely used measure of NPS in dementia research that assesses the type and severity of behavioral disturbances in dementia. It evaluates 12 domains: agitation, delusions, hallucinations, depression, euphoria, aberrant motor behavior, apathy, irritability, disinhibition, anxiety, sleep, and eating. The NPI is administered as a structured interview with a knowledgeable informant who can report the patient's NPS. The NPI-Q is a simplified clinical form of the NPI, with two scores reported for each domain: a) presence of symptoms; and b) severity on a 0-3 scale (0= none, 1=mild, 2=moderate, 3=severe). We report severity for each individual NPI domain, and further calculated the sum (NPI-total, range 0-36). The frequency of symptoms is not assessed on NPI-Q,(Kaufer *et al*., 2000) unlike the NPI(Cummings *et al*., 1994).

Geriatric Depression Scale (GDS), short-form (Yesavage *et al*., 1982)—The GDS(short-form) is a 15-item scale in which each item is endorsed "yes" or "no" by the participant. The GDS is widely used in the geriatric population and its reliability and validity compared to other depression measures are well established (Lichtenberg *et al*., 1992). The GDS (short-form) has also been validated in cognitively impaired persons (Burke, Roccaforte, Wengel, 1991).

Hachinski Ischemia Scale (Hachinski, 1975)—The Hachinski Ischemia Scale was devised to differentiate vascular dementia from degenerative dementia (largely AD). The scale rates eight items associated with vascular dementia including abrupt onset, stepwise progression, emotional incontinence, history of stroke or hypertension, and focal neurologic signs and symptoms. The range is 0-12; scores of 4 or less are consistent with primary

degenerative dementias, scores of >=7 with vascular dementias, while scores of 5-6 are considered equivocal (Swanwick *et al*., 1996).

Analyses

Two approaches to dichotomizing the MCI group were examined: aMCI vs. non-aMCI and exMCI vs. non-exMCI. These dichotomies constituted the independent variables. The dependent variables were CDR-Sum, NPI-Q total severity scores and individual NPS scores (score> 0 or frequency X severity), and GDS total and item scores. The occurrence of categorical variables (choosing the "depressed" response to a GDS item) was compared between diagnoses using the χ^2(df=1) statistic. For dichotomous comparisons (aMCI vs. nonaMCI, and exMCI vs. nonexMCI) the statistic used was χ^2 (df=1). For comparison of continuous variables (including CDR Sum of Boxes, NPI-Q sum of frequency X severity for all domains, and NPI-Q scores (prevalence and frequency X severity) for individual domains), multivariate analysis of variance (ANOVA) was performed, with Tukey's HSD used to correct for multiple comparisons where appropriate. We also assessed the prevalence of vascular conditions causing atherosclerotic disease (myocardial infarction, atrial fibrillation, stroke, hypertension, hypercholesterolemia, diabetes, and congestive heart failure), since they have been reported as impacting the incidence of both AD and non-AD dementias (Forti *et al*., 2006; Ravaglia *et al*., 2006a). P<.05 was used as the cutoff for statistical significance, and Holms' procedure (Aickin and Gensler, 1996) was used to adjust for multiple comparisons. The unadjusted p values are presented in each table, with significance after adjustment marked with *. Analyses were run using Stata, version 10 (Statacorp, College TX, 2009).

Results

MCI participants grouped by mutually exclusive subtypes

We initially subtyped MCI by the presence or absence of amnestic and executive function, categorizing all participants into mutually exclusive subtypes: 1) neither amnestic nor executive dysfunction; 2) amnestic only; 3) executive dysfunction only; or 4) both amnestic and executive dysfunction. Of the 1779 NACC participants with MCI, 1379 (77.5%) met criteria for aMCI and 400 (22.5%) for non-aMCI. Of the aMCI participants, 783 were impaired only in memory (i.e., aMCI single-domain) and 596 in multiple cognitive domains. 1163 (64.4%) met criteria for non-exMCI and 616 (34.6%) for exMCI. Demographic variables and vascular conditions in these groups are in Table 1. Participants with executive dysfunction tended to be younger; aMCI participants were less likely to be African-American or Hispanic. Of the vascular conditions, only stroke varied by subtype such that persons with both amnestic and executive dysfunction had the highest prevalence of stroke.

Functional impairment and neuropsychiatric severity scores are presented in table 2. The presence of executive dysfunction (with or without amnestic deficits) was associated with lower MMSE and higher Hachinski scores. A trend toward greater GDS scores in persons with executive dysfunction was no longer significant after adjustment for multiple comparisons. Amnestic and "both" participants were more functionally impaired on the CDR-Global, while executive dysfunction and "both" participants had greater total severity on the NPI-Q compared to those with "neither" or with amnestic deficits only.

The prevalence of NPI-Q symptoms by domain is presented in table 3A and the severity of NPI-Q symptoms by domain in table 3B. The severity of anxiety varied by MCI subtype such that participants with both amnestic and executive dysfunction had higher anxiety scores compared to those with neither. Executive dysfunction was associated with greater prevalence and severity of agitation, disinhibition, and irritability as well as greater severity

of sleep problems, but these associations were no longer significant after adjustment for multiple comparisons.

MCI subtyped dichotomously (amnestic vs. nonamnestic, executive dysfunction vs. no executive dysfunction)

The association of executive dysfunction with greater severity of neuropsychiatric symptoms led us to examine two dichotomies for MCI subtyping: amnestic vs. nonamnestic and executive dysfunction vs. no executive dysfunction.

Functional impairment and neuropsychiatric severity scores are presented in table 4. Amnestic deficits were associated with greater functional impairment on CDR-Global and with lower Hachinski scores. Executive dysfunction was associated with lower MMSE scores and with greater NPI-Q total severity, GDS, and Hachinski scores.

The prevalence of NPI-Q symptoms by domain is presented in table 5A and the severity of NPI-Q symptoms by domain in table 5B. Amnestic deficits were associated with greater prevalence and severity of aberrant motor behavior and greater severity of hallucinations, while executive deficits were associated with greater prevalence and severity of agitation, anxiety, disinhibition, irritability, and sleep problems. However, none of the associations in table 6 were statistically significant after adjustment for multiple comparisons.

Discussion

We present data comparing NPS in several subtypes of MCI. The prevalence of NPS in the overall cohort was similar to other published reports. For example, using the NPI-Q we report a depression prevalence of 27.3% compared to the CHS, which reported a prevalence of 20% (Lyketsos *et al*., 2002a). Comparable figures for apathy are 16% in this cohort and 15% in the CHS; for irritability, the prevalence here (25%) was higher than in the CHS (15%).

The overall severity of NPS was not high (table 2), nor were prevalences and severities in individual NPI domains (table 3). Nonetheless we were able to observe associations between MCI subtypes and NPS: executive dysfunction (with or without associated amnestic deficits) was associated with greater NPI-Q total severity and GDS, and with worse anxiety specifically. Thus our hypoe=thesis waqs supported by these data. Although the associations were not significant after adjustment for multiple comparisons, executive dysfunction was associated with several other NPI domains including agitation, disinhibition, irritability, and sleep problems. While these associations may be due to chance, it is notable that for each of these domains the presence of executive dysfunction predicted greater severity and/or prevalence of certain NPS, suggesting a characteristic pattern of NPS associated with executive dysfunction in MCI.

We observed relatively minor differences in NPS between participants with amnestic vs. non-amnestic MCI, similar to reports from CHS (Lopez, Becker, Sweet, 2005) and the Mayo Clinic Study of Aging (Geda *et al*., 2008). These symptoms are similar to those recently proposed as characteristic of MCI (Geda *et al*., 2008), of “Depression of AD” (Lyketsos *et al*., 2001; Lyketsos and Olin, 2002; Olin *et al*., 2002a; Olin *et al*., 2002b; Rosenberg *et al*., 2005; Appleby *et al*., 2007) and the syndrome of late life depression with executive dysfunction (Alexopoulos, 2002).

These data suggest that the pattern of NPS in exMCI is similar to depression in AD and to the late life depression executive dysfunction syndrome. It is possible that this NPS profile is prodromal to a similar profile in AD, and its presence may signal a greater likelihood of

dementia development in MCI participants. If borne out in longitudinal studies this finding would be important since NPS and particularly depression add significantly to the burden of AD for both patients and caregivers (Teri, 1997). Identifying these symptoms at an earlier stage of disease such as MCI offers opportunities for earlier intervention. While the overall severity of symptoms is relatively low and well within the range of "subsyndromal" symptoms, it is possible that this relatively mild degree of symptom severity will predict prognosis of cognitive, functional, and neuropsychiatric symptoms. These results shed new light on the nosology and subtyping of MCI. It is possible that executive dysfunction and a characteristic NPS profile are associated with prodromal AD, and conceivably this profile might constitute a subtype of prodromal AD with implications for prognosis and treatment.

The study has several limitations including 1) limited number of neuropsychiatric measures; 2) cross-sectional design, preventing prognostic inferences; 3) and study of a referral population which may skew these results towards a more "ill" population. However, the prevalence of NPS we report is close to that found in the CHS which is a population-based sample (Lopez, Becker, Sweet, 2005); 4) low levels of symptom severity limit generalizability of these findings, which may not be applicable to persons suffering from a primary diagnosis of major depression with co-morbid cognitive deficits. The study has several strengths including 1) very large multi-center cohort of MCI participants characterized with standardized methods; 2) clinical diagnoses of MCI and its subtypes by experienced interdisciplinary teams and current consensus-criteria.

In conclusion, we report that in a large well-characterized MCI cohort, executive dysfunction is associated with greater severity of NPS, specifically depression, anxiety, agitation, apathy, disinhibition, irritability, and sleep disturbance. These results may have implications for the treatment of MCI and its nosology, and merit follow-up longitudinal studies.

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Key Points

- Few differences in neuropsychiatric symptoms were found between participants with amnestic and those with non-amnestic MCI.

-Participants with MCI and executive dysfunction had more neuropsychiatric symptoms and depression, including a symptom constellation similar to depression of Alzheimer's disease, including depression, agitation, anxiety, apathy, disinhibition, irritability, appetite and sleep disturbances.

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Table 1

Demographic variables and prevalence of vascular conditions stratified by mutually exclusive MCI subtypes

Demographics and prevalence of vascular risk factors for NACC participants with MCI, stratified by mutually exclusive MCI subtypes. Categorical variables reported as %, with statistical test Pearson's $\chi^2(3)$. Continuous variables reported as mean(SD), using analysis of variance with calculated using ($F_{3,1775}$) statistic. Post-hoc comparisons were performed using Tukey's HSD using $p<.05$ for threshold of statistic significance.

Variable	All MCI	Neither aMCI nor exMCI	aMCI only	exMCI only	Both aMCI and exMCI	Statistic	p	Post-hoc comparisons
Age (years)	75.4 (9.6)	75.1(8.3)	76.2(9.6)	72.9(9.8)	75.1(9.5)	$F_{3,1775} = 8.38$	<.001	Neither, aMCI, both>exMCI
Education (years)	15.2 (7.8)	15.2 (7.7)	15.6 (7.8)	15.0 (8.6)	14.4 (7.2)	$F_{3,1775} = 2.04$	.10	
Female (%)	52.3	59.5	51.1	56.2	51.6	$\chi^2(3) = 5.3$	.15	
African-American (%)	15.4	20.3	10.6	21.5	22.2	$\chi^2(3) = 63.6$	<.001	
Hispanic (%)	7.4	6.3	5.4	11.2	11.0	$\chi^2(3) = 42.0$	<.001	
Myocardial infarction (%)	7.8	5.1	8.6	7.9	7.0	$\chi^2(3) = 6.1$	.73	
Atrial fibrillation (%)	8.0	6.3	7.6	9.5	9.1	$\chi^2(3) = 2.9$	.97	
Stroke (%)	6.24	3.17	5.2	7.0	9.6	$\chi^2(3) = 20.1$	.017	
Hypertension(%)	54.7	54.4	52.8	57.9	58.0	$\chi^2(3) = 9.4$	.40	
Hypercholesterolemia (%)	51.9	53.8	51.0	48.8	55.6	$\chi^2(3) = 13.5$	.14	
Diabetes (%)	12.9	12.7	11.5	14.9	15.5	$\chi^2(3) = 8.4$	.49	
Congestive heart failure (%)	4.0	3.2	3.9	7.0	2.6	$\chi^2(3) = 12.7$	.17	

Table 2

Functional and neuropsychiatric summary scores stratified by mutually exclusive MCI subtypes

Mean (standard deviation) presented for CDR-Global, CDR-Sum, NPI-Q Total Severity (sum of severity for all NPI-Q domains), GDS total, and Hachinski Ischemia Scale scores, stratified by mutually exclusive MCI subtypes. Covariates include MCI subtype, age, education, and sex. The statistic used was ANOVA with post-hoc Tukey's HSD adjustment for 4-way comparison within each ANOVA. P-values <.05 after adjustment for multiple comparisons within 12 NPI domains using Holms' procedure are marked with *.

Variable [Mean(SD)]	All MCI (N=1779)	Neither aMCI nor exMCI (N=158)	aMCI only (N=1005)	exMCI only (N=242)	Both aMCI and exMCI (N=374)	$F_{3,1772}$	p (unadjusted)	Post-hoc comparisons
MMSE	27.8 (7.5)	28.8 (9.8)	28.1 (8.6)	27.2 (3.2)	26.5 (4.7)	5.84	.0006*	aMCI, neither>both aMCI>exMCI
CDR-Global	.46 (.59)	.30 (.28)	.50 (.69)	.38 (.24)	.49 (.52)	7.52	.0001*	aMCI, Both>neither
CDR-Sum	1.6 (5.8)	.72 (1.01)	1.72 (7.0)	1.26 (1.3)	1.86 (5.2)	1.95	.12	
NPI-Q (total severity)	2.0 (2.9)	1.5 (2.6)	1.8 (2.8)	2.4 (3.2)	2.4 (3.1)	5.29	.0002*	Both, exMCI>neither
GDS Total	2.5 (3.9)	2.1 (2.3)	2.3 (2.6)	3.0 (6.2)	2.8 (5.3)	2.97	.03	exMCI>neither
Hachinski Ischemic Scale	1.1 (1.5)	1.1 (1.5)	.92 (1.2)	1.5 (1.8)	1.4 (1.8)	19.19	<.0001*	Both, exMCI>neither, aMCI

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Table 3

Prevalence and severity of NPI-Q domains stratified by mutually exclusive MCI subtypes

The prevalence (3A) and severity (3B) of individual NPI-Q domains are presented stratified by mutually exclusive MCI subtypes.. Prevalence (%) was reported according to NPI-Q responses ("present" or "absent"). The statistic used was χ^2 (df=3). Severity mean (SD) scores ranged from 1 (mild) to 3 (severe). The statistic used was ANOVA with post-hoc Tukey's HSD adjustment for 4-way comparison within each ANOVA. Covariates include MCI subtype, age, education, sex, and MMSE. P-values <.05 after adjustment for multiple comparisons within 12 NPI domains using Holms' procedure are marked with *.

Table 3A Prevalence (%)

Variable	All MCI (N=1648)	Neither aMCI nor exMCI (N=144)	aMCI only (N=922)	exMCI only (N=227)	Both aMCI and exMCI (N=355)	$\chi^2(3)$	p (unadjusted)
Delusions	4.25	2.08	4.23	3.52	5.63	3.63	.30
Hallucinations	1.82	2.08	1.30	3.08	2.25	3.84	.28
Agitation	15.8	13.2	14.5	15.9	20.3	7.19	.06
Depression	27.3	22.9	27.1	29.1	28.2	1.91	.59
Anxiety	18.5	15.3	16.8	17.6	24.5	11.3	.01
Elation	1.64	.69	1.63	1.32	2.25	1.77	.62
Apathy	16.1	11.1	15.5	18.1	18.6	5.16	.16
Disinhibition	7.65	4.17	6.83	12.3	8.17	10.53	.015
Irritability	24.9	14.6	24.4	26.9	29.0	12.0	.007
Aberrant motor	5.46	6.25	4.66	8.81	5.07	6.35	.096
Sleep	18.8	18.1	17.1	22.5	21.1	4.98	.17
Appetite	10.7	9.03	9.98	11.0	12.2	3.32	.34

Table 3B Severity (range 0-3)

Variable [Mean(SD)]	All MCI (N=1779)	Neither aMCI nor exMCI (N=158)	aMCI only (N=1005)	exMCI only (N=242)	Both aMCI and exMCI (N=374)	$F_{3,1771}$	p (unadjusted)	Post-hoc comparisons
Delusions	.056 (.31)	.019 (.14)	.058 (.32)	.041 (.24)	.075 (.35)	1.24	.14	
Hallucinations	.022 (.19)	.044 (.35)	.014 (.15)	.037 (.23)	.021 (.14)	1.84	.14	
Agitation	.19 (.52)	.15 (.42)	.18 (.50)	.18 (.46)	.27 (.62)	5.82	.04	Both > neither
Depression	.34 (.65)	.30 (.63)	.32 (.61)	.42 (.77)	.37 (.65)	1.20	.31	
Anxiety	.25 (.61)	.19 (.51)	.22 (.56)	.28 (.71)	.33 (.68)	4.16	.0002*	Both > neither
Elation	.020 (.18)	.0063 (.080)	.018 (.15)	.012 (.11)	.037 (.28)	1.70	.16	

Table 3B Severity (range 0-3)

Variable [Mean(SD)]	All MCI (N=1779)	Neither aMCI nor exMCI (N=158)	aMCI only (N=1005)	exMCI only (N=242)	Both aMCI and exMCI (N=374)	$F_{3,1771}$	p (unadjusted)	Post-hoc comparisons
Apathy	.21 (.54)	.13 (.44)	.19 (.52)	.26 (.60)	.24 (.58)	1.76	.15	exMCI>neither
Disinhibition	.091 (.36)	.044 (.24)	.82 (.35)	.14 (.42)	.099 (.37)	2.74	.04	exMCI>neither
Irritability	.31 (.64)	.19 (.53)	.30 (.62)	.37 (.70)	.37 (.68)	3.02	.03	Both, exMCI>neither
Aberrant motor behavior	.064 (.30)	.088 (.40)	.054 (.28)	.099 (.35)	.053 (.25)	1.81	.14	
Sleep	.26 (.64)	.23 (.56)	.23 (.60)	.37 (.78)	.30 (.67)	2.75	.04	exMCI>aMCI, neither
Appetite	.15 (.50)	.13 (.48)	.13 (.46)	.15 (.48)	.20 (.60)	1.53	.20	

Table 4

Functional and neuropsychiatric summary scores stratified by amnestic and executive dysfunction

Mean (standard deviation) presented for CDR-Global, CDR-Sum, NPI-Q Total Severity (sum of severity for all NPI-Q domains), GDS total, and Hachinski Ischemia Scale scores, stratified by the presence or absence of amnestic and executive dysfunction. Covariates include presence or absence of amnestic or executive dysfunction, age, education, and sex. The statistical method was ANOVA. P-values <.05 after adjustment for multiple comparisons using Holms' procedure are marked with *.

Variable [Mean(SD)]	aMCI (N=1379)	Non-aMCI (N=400)	$F_{1,1771}$	p	exMCI (N=616)	Non-exMCI (N=1163)	$F_{1,1771}$	p (unadjusted)
MMSE	27.7 (7.8)	27.9 (6.7)	.05	.82	26.8 (4.19)	28.3 (8.77)	15.5	.0001*
CDR-Global	.50 (.65)	.25 (.26)	20.92	<.0001*	.45 (.44)	.47 (.66)	.60	.44
CDR-Sum	1.76 (6.60)	1.04 (1.21)	5.00	.026	1.62	4.15	.00	.96
NPI-Q (total severity)	1.95 (2.91)	2.02 (2.98)	.07	.80	2.37 (3.15)	1.75 (2.78)	14.6	.0001*
GDS Total	2.41 (3.55)	2.63 (5.03)	.37	.54	2.87 (5.65)	2.25 (2.58)	7.95	.005*
Hachinski Ischemic Scale	1.05 (1.40)	1.33 (1.72)	14.6	.0001*	1.44 (1.80)	.94 (1.24)	47.55	<.0001*

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Table 5

Prevalence and severity of NPI-Q domains stratified by amnestic and executive dysfunction

The prevalence (6A) and severity (6B) of individual NPI-Q domains are presented, stratified by presence or absence of amnestic or executive dysfunction. Prevalence (%) was reported according to NPI-Q responses ("present" or "absent"). The statistic used was χ^2 (df=1). Severity mean (SD) scores ranged from 1 (mild) to 3 (severe). The statistic used was ANOVA with post-hoc Tukey's HSD adjustment for 4-way comparisons within each ANOVA. Covariates included presence of amnestic or executive dysfunction, age, education, sex, and MMSE. P-values <.05 after adjustment for multiple comparisons within 12 NPI domains using Holms' procedure are marked with *.

Table 5A Prevalence (%)

Variable	aMCI (N=1379)	Non-aMCI (N=400)	$\chi^2(1)$	p	exMCI (N=616)	Non-exMCI (N=1163)	$\chi^2(1)$	p (unadjusted)
Delusions	4.62	2.96	1.94	.16	4.81	3.94	.70	.40
Hallucinations	1.57	2.70	2.05	.15	2.58	1.41	2.99	.089
Agitation	16.1	14.8	.37	.54	18.6	14.4	4.99	.03
Depression	27.4	26.7	.076	.78	28.5	26.6	.74	.39
Anxiety	19.0	16.7	.96	.33	21.8	16.6	6.81	.009
Elation	1.80	1.08	.93	.33	1.89	1.50	.35	.55
Apathy	16.4	15.4	.21	.64	18.4	14.9	3.35	.067
Disinhibition	7.20	9.16	1.56	.21	9.79	6.57	5.88	.015
Irritability	25.7	22.1	1.97	.16	28.2	23.1	5.24	.022
Aberrant motor behavior	4.78	7.82	5.15	.02	6.53	4.88	1.99	.16
Sleep	18.3	20.8	1.18	.28	21.7	17.3	4.75	.029
Appetite	10.9	10.2	.12	.73	12.4	9.85	2.50	.11

Table 5B Severity (range 0-3)

Variable [Mean(SD)]	aMCI (N=1379)	Non-aMCI (N=400)	$F_{1,1773}$	p	exMCI (N=616)	Non-exMCI (N=1163)	$F_{1,1773}$	p (unadjusted)
Delusions	.062 (.33)	.033 (.20)	2.81	.094	.061 (.31)	.052 (.30)	.17	.67
Hallucinations	.016 (.15)	.04 (.28)	5.17	.023	.028 (.18)	.019 (.019)	.62	.43
Agitation	.20 (.54)	.17 (.45)	1.22	.27	.24 (.57)	.17 (.49)	4.35	.037
Depression	.33 (.63)	.37 (.72)	.45	.50	.39 (.33)	.32 (.61)	2.88	.090
Anxiety	.25 (.60)	.25 (.64)	.20	.65	.31 (.69)	.21 (.55)	7.73	.0055
Elation	.023 (.20)	.01 (.10)	2.57	.11	.027 (.23)	.016 (.15)	.80	.37

Table 5B Severity (range 0-3)

Variable [Mean(SD)]	aMCI (N=1379)	Non-aMCI (N=400)	$F_{1,1773}$	p	exMCI (N=616)	Non-exMCI (N=1163)	$F_{1,1773}$	p (unadjusted)
Apathy	.21 (.54)	.21 (.55)	.00	.98	.25 (.59)	.18 (.51)	3.62	.057
Disinhibition	.086 (.35)	.11 (.37)	.85	.36	.12 (.39)	.077 (.33)	4.45	.035
Irritability	.32 (.64)	.3 (.65)	.26	.61	.37 (.69)	.28 (.61)	5.86	.016
Aberrant motor behavior	.054 (.27)	.095 (.37)	5.28	.022	.071 (.29)	.059 (.30)	.20	.65
Sleep	.25 (.62)	.32 (.71)	2.76	.097	.33 (.72)	.23 (.59)	6.27	.012
Appetite	.15 (.50)	.14 (.48)	.11	.74	.18 (.56)	.13 (.46)	3.12	.077