Early emergence of neuropsychiatric symptoms in cognitively normal subjects and mild cognitive impairment

Keiichiro Tsunoda, Toru Yamashita, Yosuke Osakada, Ryo Sasaki, Koh Tadokoro, Namiko Matsumoto, Emi Nomura, Ryuta Morihara, Yumiko Nakano,
Yoshiaki Takahashi, Noriko Hatanaka, Jingwei Shang, Kota Sato, Mami Takemoto, Nozomi Hishikawa, Yasuyuki Ohta, and Koji Abe*

Department of Neurology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 2-5-1 Shikatacho, Okayama 700-8558, Japan.

Running title: BPSD in preclinical stage of dementia

*Corresponding author: Koji Abe

Address: Department of Neurology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 2-5-1 Shikatacho, Okayama 700-8558, Japan.

E-mail: ktzz0909@gmail.com

Abstract. The world is rapidly aging and facing an increase in the number of dementia patients, so it is important to detect the preclinical stage of dementia in such countries. We examined both cognitive and affective functions among cognitively normal control (n=218), mild cognitive impairment (MCI, n=146) and Alzheimer's disease (AD, n=305) subjects using two evaluation tools for behavioral and psychological symptoms of dementia (BPSD) (Abe's BPSD score (ABS) and mild behavioral impairment (MBI)). BPSD were present in 12.4% (ABS) and 9.6% (MBI) of cognitively normal people, 34.9% and 32.2% in MCI subjects, and 66.2% and 51.1% in AD patients. Both ABS (§ $p < 0.05$) and MBI (§§ $p < 0.01$) score showed worse score with cognitive decline of the mini-mental state examination in the AD group in BPSD-positive participants. Similar correlations were found in all participants in AD group (|||| $p < 0.01$ vs ABS and MBI). Among the subscales in BPSD-positive participants, an apathy/indifference score of ABS and a decreased motivation of MBI showed significant differences in AD patients compared to the control and MCI subjects (** $p<0.01$). In addition, subscale analyses further showed a downward trend from the control to MCI and AD subjects in four ABS subscales and three MBI subscales. The present study showed the preclinical presence of BPSD in cognitively normal people, more so in MCI subjects, and ABS detected BPSD more sensitively than MBI in all three groups.

Key words: dementia, cognitive dysfunction, affective symptoms, behavioral symptoms

INTRODUCTION

The world is rapidly aging since older populations are growing both in developed and developing countries. Currently, nearly 50 million people across the globe have dementia, and this is estimated to increase to 75 million by 2030 and to 132 million by 2050 [1]. Japan is the most aged country in the world, and there are more than 4.6 million people with dementia [2].

In addition to cognitive decline, dementia causes affective dysfunctions, which are referred to as behavioral and psychological symptoms of dementia (BPSD) [3], consisting of wandering, eating/toilet problem, delusion/hallucination, offensive/abusive words, day-night reversal, excitation/agitation, apathy/indifference, depressive/gloomy mood, violent force and high irritability. Although BPSD has long been recognized as emerging after cognitive decline, a recent report suggested the earlier emergence of BPSD before cognitive decline [4].

In the present study, therefore, we examined both cognitive and affective functions among cognitive normal control, mild cognitive impairment (MCI) [5] and Alzheimer's disease (AD) subjects using two useful evaluation tools for BPSD (Abe's BPSD score, ABS [6] and mild behavioral impairment, MBI [7, 8]).

MATERIALS AND METHODS

Participants

Individuals aged ≥50 were recruited from 19 Okayama University-affiliated hospitals between May and December of 2018. The hospitals included Okayama University Hospital, Kurashiki Heisei Hospital, Okayama Kyokuto Hospital, Himeji Central Hospital, Okayama City Hospital, Chokyu Hospital, Ino Hospital, Tsuyama Chuo Hospital, Ibara City Hospital, Yubaraonsen Hospital, Ako Central Hospital, Ota Memorial Hospital, Akaiwa Medical Association Hospital, Kasaoka Daiichi Hospital, Okayama Saiseikai General Hospital, Kousei Hospital, IHI Harima

Hospital, Okayama Saidaiji Hospital, and Midori Clinic. Patients with a previous history of cerebral vascular disease, neurodegenerative disease, psychiatric disorder, and other central nervous system diseases were excluded. Finally, three groups of participants including control subjects (88 men and 130 women, mean age: 71.7 ± 8.9 years), MCI [5] (70 men and 76 women, mean age: 76.9 ± 8.2 years) and AD (101 men and 204 women, mean age: 81.1 ± 6.6 years) were established. The present study was approved by the Ethics Committee on Epidemiological Studies of Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences (Approval number #1603-031), and informed written consent was obtained from participants.

Cognitive and affective functions

Cognitive function was assessed using the clinical dementia rating (CDR) [9, 10] scale and mini-mental state examination (MMSE) [11]. To assess affective function, ABS [6] and MBI [8] checklists were used. The participants were evaluated based on the AD neuroimaging initiative (ADNI) [12] criteria and diagnosed mainly by cognitive and affective symptoms, neurological examination and head magnetic resonance imaging (MRI). Control subjects had a MMSE score of ≥24 and a CDR of 0, a non-MCI status and no symptoms of dementia. MCI subjects had a MMSE score of ≥24, memory complaints, a CDR of 0.5, the absence of significant impairment in other cognitive domains, essentially preserved activities of daily living (ADLs) and the absence of dementia. AD subjects had a MMSE score of ≤26 and a CDR of ≥0.5.

ABS is a new, simple and quick score that assesses BPSD of mild to moderate AD and other types of dementia, ranging between 0 and 44 from no BPSD (score = 0) to full BPSD (score = 44). ABS consists of only 10 items (wandering, eating/toilet problem, delusion/hallucination, offensive/abuse words, day-night reversal, excitation/agitation, apathy/indifference, depressive/gloomy mood, violent force and high irritability) and a grading score for each BPSD

item based on its frequency and severity. ABS shows a good correlation with the neuropsychiatric inventory (NPI) [13] score in AD patients [6]. MBI consists of a total of 34 items organized into five main domains: (1) decreased motivation, (2) emotional dysregulation, (3) impulse dyscontrol, (4) social inappropriateness, (5) abnormal perception or thought content. For each item, a 'yes' or 'no' question is followed by a severity rating scale of 1 (mild), 2 (moderate), and 3 (severe) [8].

Statistical analysis

We carried out statistical analysis using SPSS 22.0.0.0 software (IBM Corporation, Armonk, NY, USA). The data was not normally distributed, therefore statistical significance was assessed using nonparametric tests. We performed the Mann-Whitney U test with a Bonferroni correction to compare cognitive and affective functions between the three groups, a chi-square test to examine the relationship between gender and cognitive function. Furthermore, BPSD-positive subjects were extracted and we performed a Spearman's rank correlation coefficient test to examine the relationship between MMSE and affective function, and the Kruskal-Wallis test to examine subscale analyses of ABS and MBI. Trend analysis using the Jonckheere-Terpstra test was conducted to examine the relationship between cognitive function and subscales of the affective test. Statistical significance was assessed at $p < 0.05$.

RESULTS

The baseline demographic data of participants is shown in Table 1. We analyzed the participants dividing into three groups according to their baseline cognitive status. Participants consisted of 218 control subjects (88 men and 130 women), 146 MCI subjects (70 men and 76 women) and 305 AD patients (101 men and 204 women). The 218 control subjects consisted of 99 asymptomatic subjects who were interested in their own cognitive function, 35 with subjective

cognitive impairment and 84 non-cognitive patients with symptoms such as headaches, dizziness and cervical dystonia. A chi-square test showed a significant difference in the gender ratio among the three groups (¶¶ $p < 0.01$). Statistical analysis showed significant differences among the three groups in terms of age (control 71.7 ± 8.9 years, MCI 76.9 ± 8.2 years (†† $p < 0.01$ vs control) and AD 81.1 ± 6.6 years (†† $p < 0.01$ vs control and ‡‡ $p < 0.01$ vs MCI)) and CDR (control 0, MCI 0.5 (†† $p < 0.01$ vs control) and AD 0.9 ± 0.6 (†† $p < 0.01$ vs control and ‡‡ $p < 0.01$ vs MCI)).

The assessments of cognitive impairment revealed a mean MMSE score of 28.3 ± 1.8 in the control, 27.2 ± 2.0 in the MCI subjects (†† $p < 0.01$ vs control) and 19.7 ± 4.4 in the AD patients (†† $p < 0.01$ vs control and ‡‡ $p < 0.01$ vs MCI). The assessment of affective impairment revealed a mean ABS score of 0.4 ± 1.3 in the control, 1.5 ± 3.2 in MCI subjects (†† $p < 0.01$ vs control) and 4.2 ± 5.3 in AD patients (†† $p < 0.01$ vs control and ‡‡ $p < 0.01$ vs MCI). Furthermore, the mean MBI scores displayed a similar pattern (2.9 ± 4.5 in the control, 7.5 ± 8.1 in MCI subjects (†† $p < 0.01$ vs control) and 12.9 ± 12.9 in AD patients (†† $p < 0.01$ vs control and ‡‡ $p < 0.01$ vs MCI)) to the ABS scores.

Fig. 1 represents the prevalence of BPSD expressed in ABS or MBI (ABS >0.5 or MBI >8.5) in each group. Cut-off points of ABS were set at 0.5 and of MBI at 8.5 in accordance with previous reports [14, 15]. BPSD were found in 12.4% (ABS) and 9.6% (MBI) of the cognitively normal control group. In contrast, MCI subjects showed BPSD in 34.9% (ABS) and 32.2% (MBI), and AD patients showed BPSD in 66.2% (ABS) and 51.1% (MBI).

Fig. 2 shows the relationship between MMSE and ABS (Fig. 2a) or MBI (Fig. 2b) in BPSD-positive participants (plain columns, net gray area of Fig. 1) and all participants (shaded columns) in each group. In BPSD-positive participants, although ABS and MBI did not show a significant correlation with MMSE in control and MCI groups ($p > 0.05$ vs ABS and MBI with a correlation coefficient of 0.049 and -0.137, respectively in control group, $p > 0.05$ vs ABS and MBI with a

correlation coefficient of 0.058 and 0.126, respectively in MCI group, dotted black lines), both ABS and MBI scores presented an inverse correlation with MMSE in the AD group (§ $p < 0.05$ vs ABS, §§ $p < 0.01$ vs MBI, dotted black lines) with a correlation coefficient of -0.477 and -0.579, respectively. Similarly, ABS and MBI scores presented weak inverse correlation with MMSE in only AD group in full sample analysis (|||| $p < 0.01$ vs ABS and MBI, dotted gray lines) with correlation coefficient of -0.277 and -0.294, respectively.

Fig. 3 shows subscale analyses of ABS (Fig. 3a) and MBI (Fig. 3b) in BPSD-positive participants (plain columns, net gray area of Fig. 1) and all participants in each group (shaded columns). In BPSD-positive participants, subscales of both ABS and MBI showed worse scores from the control to MCI and AD except for high irritability of ABS. Among the subscales, the apathy/indifference score in ABS was significantly worse in AD patients (36.5 ± 41.3%) compared to the control (9.5 ± 27.3%; ** $p < 0.01$) and MCI subjects (20.5 ± 31.6%; * $p < 0.05$). A similar result was found in the subscales of MBI for decreased motivation (control 29.4 ± 18.0%, MCI 34.1 ± 18.5%, AD 45.1 ± 22.6%; ** $p < 0.01$ vs control, ** $p < 0.01$ vs MCI), and abnormal perception or thought content (MCI 3.7 ± 7.9%, AD 9.4 ± 17.1%; * $p < 0.05$). In addition, subscale analyses showed a downward tendency in four ABS subscales (wandering, eating/toilet problems, delusion/hallucination, apathy/indifference, Jonckheere-Terpstra test, # $p < 0.05$, ## $p < 0.01$), and three MBI subscales (decreased motivation, social inappropriateness and abnormal perception or thought content, Jonckheere-Terpstra test, # $p < 0.05$, ## $p < 0.01$). Subscale analysis using full sample revealed significant difference between the three groups, especially between control and AD group, and MCI and AD group, other than violent force and high irritability in ABS (shown by gray characters). Significant differences between control and MCI were observed in offensive/abusive words in ABS and decreased motivation, emotional dysregulation, impulse dyscontrol, and social inappropriateness in MBI (** $p < 0.01$).

DISCUSSION

In the present study, we examined the cognitive and affective functions of cognitively normal participants and those who had MCI and AD. This is the first study to assess BPSD both with ABS and MBI, finding that approximately 10% of BPSD existed in cognitively normal participants, that the prevalence of BPSD was different significantly depending on cognitive function among normal, MCI and AD subjects, and that ABS showed a higher prevalence of BPSD than MBI among these three groups (Fig. 1). ABS and MBI showed a similar relationship with MMSE and presented an inverse correlation with MMSE in only the AD group (Fig. 2).

Of note, the present data reveals that BPSD exists even in 9.6-12.4% of cognitively normal people (Fig. 1). A previous study [16] reported that the prevalence of BPSD was 76.5% in subjects with subjective cognitive decline and 85.3% in their MCI group. Mortby et al. reported that the prevalence of BPSD was 27.6% in the cognitively normal group, 43.1% in cognitively normal, but-at-risk group and 48.9% in their MCI group [17]. In these previous studies, BPSD was evaluated with the neuropsychiatric inventory questionnaire (NPI-Q) [18]. The prevalence of BPSD in these papers is higher than the present study in the cognitively normal or MCI group, probably because NPI-Q has a reference range of one month whereas MBI requires six months of new-onset symptoms. On the other hand, our previous report [19], which was a population based study, showed that the prevalence of BPSD detected by ABS was 6.6% in cognitively normal subjects, 17.7% in MCI and 33.3% in subjects with apparent cognitive decline. A higher prevalence of BPSD in ABS than MBI in the present study may be due to differences in the study design between this patients-based study and the previous population-based study.

The present study shows that ABS appears to be compatible with MBI, or even more sensitive than MBI to detect BPSD in all normal, MCI and AD subjects (Fig. 1 and 2). MBI may be useful

to evaluate BPSD for all causes of dementia because it covers a wide range of BPSD. However, compared with ABS, MBI has too many and complicated queries that require a considerable amount of time to fill in all queries. This may result in some questions being skipped, or inadequate answers. In contrast, ABS is a simple and quick test, and requires about only one minute [6], so it was designed for busy daily neurological/psychiatric practices or even general medicine. Furthermore, ABS is also useful to discriminate MCI from normal subjects [14]. Concordantly, the ABS score showed a significant difference among the three groups (normal control 0.1 ± 0.4, MCI 0.9 ± 1.5 and AD 6.0 ± 7.5) in the present study (Table 1). In addition, ABS has been already used in several studies that compared BPSD between AD and Parkinson's disease [20] or between Parkinson's disease with dementia and dementia with Lewy bodies [21]. On the other hand, MBI is a newly proposed BPSD score and its usefulness will be evaluated in the future. Although MBI may be a useful clinical battery to detect BPSD in each stage of cognitive decline, ABS could be equal or even better than MBI to assess BPSD even in cognitively normal subjects.

BPSD can be a risk of MCI for the cognitive normal group and a risk of dementia for the MCI group [22, 23]. Forrester et al. suggested that individuals with BPSD without cognitive deficits appear to be at risk of dementia [24]. The present study compared two newly established BPSD scores among three groups with different cognitive function revealed features and differences concerning BPSD among each group as above. It is limitation of this study that this is cross-sectional study without longitudinal cognitive or affective data of the subjects. However, based on the previous papers [4, 22-24], it may be possible to assess BPSD in preclinical stage of dementia by ABS and MBI. It should be proved by the further study.

ACKNOWLEDGEMENTS

This work was partly supported by Grants-in-Aid for Scientific Research (B) 17H0419619, (C) 15K0931607, 17H0419619, and 17K1082709, and by Grants-in-Aid from the Research Committees (Kaji R, Toba K, and Tsuji S) from the Japan Agency for Medical Research and Development (AMED).

CONFLICT OF INTEREST

The authors disclose no conflicts of interest.

REFERENCES

[1] Prince M, Wimo A, Guerchet M, Ali G, Wu Y, Prina M (2015) World Alzheimer Report 2015–The Global Impact of Dementia, an analysis of prevalence, incidence, cost and trends Alzheimer's Disease International. **17**, 2016.

[2] Sado M, Ninomiya A, Shikimoto R, Ikeda B, Baba T, Yoshimura K, Mimura M (2018) The estimated cost of dementia in Japan, the most aged society in the world. *PLoS One* **13**, e0206508.

[3] Finkel SI, Costa e Silva J, Cohen G, Miller S, Sartorius N (1996) Behavioral and psychological signs and symptoms of dementia: a consensus statement on current knowledge and implications for research and treatment. *Int Psychogeriatr* **8 Suppl 3**, 497-500.

[4] Mortby M, Anstey K (2015) Mental health and aging. *Encyclopedia of Geropsychology*, 1-6.

[5] Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E (1999) Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol* **56**, 303-308.

[6] Abe K, Yamashita T, Hishikawa N, Ohta Y, Deguchi K, Sato K, Matsuzono K, Nakano Y, Ikeda Y, Wakutani Y, Takao Y (2015) A new simple score (ABS) for assessing behavioral and psychological symptoms of dementia. *J Neurol Sci* **350**, 14-17.

[7] Taragano FE, Allegri RF, Lyketsos C (2008) Mild behavioral impairment: A prodromal stage of dementia. *Dement Neuropsychol* **2**, 256-260.

[8] Ismail Z, Aguera-Ortiz L, Brodaty H, Cieslak A, Cummings J, Fischer CE, Gauthier S, Geda YE, Herrmann N, Kanji J, Lanctot KL, Miller DS, Mortby ME, Onyike CU, Rosenberg PB, Smith EE, Smith GS, Sultzer DL, Lyketsos C (2017) The Mild Behavioral Impairment Checklist (MBI-C): A Rating Scale for Neuropsychiatric Symptoms in Pre-Dementia Populations. *J Alzheimers Dis* **56**, 929-938.

[9] Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL (1982) A new clinical scale for the staging of dementia. *Br J Psychiatry* **140**, 566-572.

[10] Morris JC (1993) The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology* **43**, 2412-2414.

[11] Folstein MF, Folstein SE, McHugh PR (1975) "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* **12**, 189-198.

[12] Mueller SG, Weiner MW, Thal LJ, Petersen RC, Jack CR, Jagust W, Trojanowski JQ, Toga AW, Beckett L (2005) Ways toward an early diagnosis in Alzheimer's disease: the Alzheimer's Disease Neuroimaging Initiative (ADNI). *Alzheimers Dement* **1**, 55-66.

[13] Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J (1994) The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in

dementia. *Neurology* **44**, 2308-2314.

[14] Fukui Y, Yamashita T, Hishikawa N, Kurata T, Sato K, Omote Y, Kono S, Yunoki T, Kawahara Y, Hatanaka N, Tokuchi R, Deguchi K, Abe K (2015) Computerized touch-panel screening tests for detecting mild cognitive impairment and Alzheimer's disease. *Intern Med* **54**, 895-902.

[15] Mallo SC, Ismail Z, Pereiro AX, Facal D, Lojo-Seoane C, Campos-Magdaleno M, Juncos-Rabadan O (2018) Assessing Mild Behavioral Impairment with the Mild Behavioral Impairment-Checklist in People with Mild Cognitive Impairment. *J Alzheimers Dis* **66**, 83-95.

[16] Sheikh F, Ismail Z, Mortby ME, Barber P, Cieslak A, Fischer K, Granger R, Hogan DB, Mackie A, Maxwell CJ, Menon B, Mueller P, Patry D, Pearson D, Quickfall J, Sajobi T, Tse E, Wang M, Smith EE (2018) Prevalence of mild behavioral impairment in mild cognitive impairment and subjective cognitive decline, and its association with caregiver burden. *Int Psychogeriatr* **30**, 233-244.

[17] Mortby ME, Ismail Z, Anstey KJ (2018) Prevalence estimates of mild behavioral impairment in a population-based sample of pre-dementia states and cognitively healthy older adults. *Int Psychogeriatr* **30**, 221-232.

[18] Kaufer DI, Cummings JL, Ketchel P, Smith V, MacMillan A, Shelley T, Lopez OL, DeKosky ST (2000) Validation of the NPI-Q, a brief clinical form of the Neuropsychiatric Inventory. *J Neuropsychiatry Clin Neurosci* **12**, 233-239.

[19] Hishikawa N, Fukui Y, Sato K, Yamashita T, Ohta Y, Abe K (2017) Clinical features of incidental mild cognitive impairment and dementia in a population-based study. *Geriatr Gerontol Int* **17**, 722-729.

[20] Tokuchi R, Hishikawa N, Sato K, Hatanaka N, Fukui Y, Takemoto M, Ohta Y, Yamashita T, Abe K (2016) Age-dependent cognitive and affective differences in Alzheimer's and Parkinson's diseases in relation to MRI findings. *J Neurol Sci* **365**, 3-8.

[21] Takemoto M, Sato K, Hatanaka N, Yamashita T, Ohta Y, Hishikawa N, Abe K (2016) Different Clinical and Neuroimaging Characteristics in Early Stage Parkinson's Disease with Dementia and Dementia with Lewy Bodies. *J Alzheimers Dis* **52**, 205-211.

[22] Peters ME, Rosenberg PB, Steinberg M, Norton MC, Welsh-Bohmer KA, Hayden KM, Breitner J, Tschanz JT, Lyketsos CG (2013) Neuropsychiatric symptoms as risk factors for progression from CIND to dementia: the Cache County Study. *Am J Geriatr Psychiatry* **21**, 1116-1124.

[23] Geda YE, Roberts RO, Mielke MM, Knopman DS, Christianson TJ, Pankratz VS, Boeve BF, Sochor O, Tangalos EG, Petersen RC, Rocca WA (2014) Baseline neuropsychiatric symptoms and the risk of incident mild cognitive impairment: a population-based study.

Am J Psychiatry **171**, 572-581.

[24] Forrester SN, Gallo JJ, Smith GS, Leoutsakos JM (2016) Patterns of Neuropsychiatric Symptoms in Mild Cognitive Impairment and Risk of Dementia. *Am J Geriatr Psychiatry* **24**, 117-125.

Table 1

Demographic data of the 669 participants divided into three groups of normal control, mild cognitive impairment (MCI) and Alzheimer's disease (AD).

	Control	MCI	AD
n	218	146	305
Age (years)	71.7 ± 8.9	76.9 ± 8.2 ††	81.1 ± 6.6 †† ‡‡
Male:female	88 : 130 ¶¶	70 : 76 ¶¶	101 : 204 ¶¶
CDR	0	0.5 ††	0.9 ± 0.6 †† ‡‡
MMSE	28.3 ± 1.8	27.2 ± 2.0 ††	19.7 ± 4.4 †† ‡‡
Abe's BPSD score (ABS)	0.4 ± 1.3	1.5 ± 3.2 ††	4.2 ± 5.3 †† ‡‡
MBI	2.9 ± 4.5	7.5 ± 8.1 ††	12.9 ± 12.9 †† ‡‡

†† $p < 0.01$ vs control, ‡‡ $p < 0.01$ vs MCI, ¶¶ $p < 0.01$

FIGURE LEGENDS

Fig. 1. Prevalence of BPSD expressed in ABS and MBI (positive as ABS >0.5 and MBI >8.5) in the three groups. Net gray area shows a BPSD-positive rate.

Fig. 2. Relationship between MMSE and ABS (a) or MBI (b) in the BPSD-positive participants (plain columns) and all participants (shaded columns) in each group: control (white columns), mild cognitive impairment (MCI; gray columns) and Alzheimer disease (AD; black columns). Both ABS and MBI scores in the BPSD-positive participants show an inverse correlation with MMSE only in the AD group (§ $p < 0.05$ vs ABS, §§ $p < 0.01$ vs MBI, dotted black lines) with a correlation coefficient of -0.477 and -0.579, respectively. Numbers above columns show number of BPSD-positive participants. Similarly, ABS and MBI scores presented weak inverse correlation with MMSE in only AD group in full sample analysis (|||| $p < 0.01$ vs ABS and MBI, dotted gray lines) with correlation coefficient of -0.277 and -0.294, respectively Numbers in columns show number of the participants.

Fig. 3. Subscale analyses of ABS (a) and MBI (b) in BPSD-positive participants (plain columns) and all participants in each group (shaded columns) among the three groups: control (white columns), mild cognitive impairment (MCI; gray columns) and Alzheimer's disease (AD; black columns). BPSD-positive participants showed a significant difference of subscales in the AD group than in the control and MCI groups for wandering, eating/toilet problems, delusion/hallucination, apathy/indifference in ABS and decreased motivation, social inappropriateness and abnormal perception or thought content in MBI (* $p<0.05$, ** $p<0.01$, # $p<0.05$ for trend and ## $p< 0.01$ for trend, shown by black characters). Full sample analysis showing a significant difference in the AD group than in the control and MCI groups in eight out

of ten subscales (wandering, eating/toilet problem, delusion/hallucination, offensive/abusive words, day-night reversal, excitation/agitation, apathy/indifference and depressive/gloomy mood) in ABS and all five subscales (decreased motivation, emotional dysregulation, impulse dyscontrol, social inappropriateness and abnormal perception or thought content) in MBI (shown by gray characters). The results are expressed as mean percentages of full scores.