White matter hyperintensities and mild behavioral impairment: Findings from the MEMENTO cohort study

Ruxin Miao a, Hung-Yu Chen a, b, Philippe Robert c, Eric E. Smith a, b, Zahinoor Ismail a, b, d, e, *, the MEMENTO Study Group

a Hotchkiss Brain Institute, University of Calgary, Calgary, Alberta, Canada
b Department of Clinical Neurosciences, University of Calgary, Calgary, Alberta, Canada
c Clinique Gériatrique du Cerveau et du Mouvement, CMRR, CHU, COBTEK lab Université Côte d’Azur, Nice France
d Department of Psychiatry, University of Calgary, Calgary, Alberta, Canada
e Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada

A R T I C L E   I N F O
Keywords:
Mild behavioral impairment
White matter hyperintensities
Neuropsychiatric symptoms
Dementia
Vascular cognitive impairment

A B S T R A C T

Background: White matter hyperintensities (WMH) contribute to cognitive decline and increase risk for dementia. Mild behavioral impairment (MBI) is a neurobehavioral syndrome characterized by the emergence and persistence of neuropsychiatric symptoms (NPS) in later life as an at-risk state for incident cognitive decline and dementia. Both WMH and MBI are common in patients with mild cognitive impairment (MCI), but few studies have established the link between these two risk markers in this population.

Methods: Participants were memory clinic patients with MCI from the French MEMENTO study. WMH volume was quantified using brain magnetic resonance imaging. Participants were categorized into MBI+ and MBI− status based on NPS persistence, and the association between MBI status and domains with WMH volume was assessed with linear regression.

Results: A total of 768 participants [mean age 72.8 (SD=8.00); 57% female] were included. MBI (i.e., persistent NPS) was present in 229 participants (29.8%). MBI+ status was significantly associated with lower MMSE score and male sex. Compared to MBI−, MBI+ status was associated with higher WMH volume (p=0.01 [95% CI 2.0% to 16.7%]). In this model, MMSE score was not associated with WMH volume. None of the MBI domains individually predicted greater WMH volume, although emotional dysregulation, impulse dyscontrol, and apathy trended towards significance.

Conclusions: In a memory clinic sample of older adults with MCI, MBI was associated with higher WMH volume. Global MBI status outperformed MMSE and individual MBI domains, supporting the utility of MBI, a multi-NPS-domain composite assessment, for predicting WMH volume.

Background

White matter hyperintensities (WMH) are abnormalities detected on magnetic resonance imaging, which reflect subclinical small vessel cerebrovascular disease [1]. WMH burden has been associated with cognitive decline [2] and incident Alzheimer’s Disease (AD) [3,4], though the pathophysiologic interaction between WMH and clinical AD has yet to be elucidated [5]. Mild cognitive impairment (MCI) is a prodromal AD state in some, and there appears to be an association between WMH and progression from MCI to dementia. While some studies found that WMH did not predict conversion from MCI to dementia [1,6], a meta-analysis showed that baseline WMH was associated with an increase in the risk of cognitive impairment [RR = 1.27 (95% CI 1.08 to 1.48)] and all-cause dementia [RR = 1.12 (95% CI 1.07 to 1.18)] [7]. Although the cognitive implications of brain white matter lesions have been studied extensively, few studies have explored the association between WMH and neuropsychiatric symptoms (NPS).

NPS are non-cognitive markers of dementia such as changes in mood,
personality, and behavior, that manifest at any point along the cognitive continuum [8]. When NPS are concurrent with MCI, the incidence of progression to dementia increases to 25% [9] from around 10–15% at baseline [10]. Mild behavioral impairment (MBI) is characterized by the later-life emergence of persistent NPS as an at-risk state for dementia and can precede or accompany MCI [11]. MBI is associated with amyloid [12,13], tau [14,15], white matter atrophy [16], neurodegeneration [17,18], AD risk genes [19,20], and incident cognitive decline and dementia [21–24]. However, while MBI has been associated with AD-related changes, its association with vascular changes has not been explored. Here we examined MBI and WMH in participants with MCI. We hypothesized that MBI+ status would be associated with greater WMH volume, compared to MBI−.

Methods

MBI case ascertainment

Neuropsychiatry Inventory (NPI) [28] scores were used to determine global MBI status in accordance with a published algorithm that maps NPI items onto MBI domains [29]. The NPI, rated by a clinician after an interview with an informed caregiver, consists of 12 NPS domains, scored for frequency by severity over a 1-month reference range. MBI domains were derived from 10 select NPI domains as follows: MBI delusions/hallucinations, MBI affective flattening, MBI apathy/indifference; MBI paranoia, MBI mood disturbance; MBI anxiety, MBI agitation, MBI sleep disturbance; MBI appetite/eating, MBI sleep disturbance. Converted NPI scores were transformed into the 5 MBI domains, calculated as the product of domain frequency and severity (theoretical range of 0 to 60). The NPI neurovegetative domains of appetite/eating and sleep disturbances do not translate readily to MBI criteria and were not included in the algorithm. MBI criteria stipulate symptom persistence for ≥ 6-months, thus NPS data at baseline and 6-month visits were used to operationalize this persistence criterion. For each visit (either time 0 or time 6-months), individuals who had a transformed MBI total score ≥ 0 at that visit were classified as NPS+. Those with a transformed MBI total score of 0 were considered NPS−. Then, for each participant, the two visits were considered together to determine baseline MBI status. MBI+ status was defined as NPS at both visits, whereas MBI− status was defined as either non-persistent or no NPS (i.e., NPS+ status at either time point but not both, NPS− status at either baseline or 6-months, or NPS− status at baseline and missing 6-month data). MBI− status was assigned to a subset of participants with visit 1 NPS− and no NPS data for the 6-month visit because they would not meet the persistence criterion for MBI+ status regardless of visit 2 NPS score. MBI domain status was determined similarly to global MBI status, with the exception that rather than using MBI total score, presence, or absence of symptoms in each of the five MBI domains was used.

Sample

A detailed flowchart of sample selection is shown in Fig. 1. A total of 768 participants with MCI were included in the study, all of whom had WMH data based on magnetic resonance imaging. Based on our MBI case ascertainment criteria, participants were divided into MBI+ (n = 229) and MBI−status (n = 533). Participants with visit 1 NPS− but without NPS data for the 6-month visit were excluded from the analysis due to uncertain MBI status (n = 198, Fig. 1). The domain analysis consisted of the same participants as the primary MBI analysis.

White matter hyperintensity

All participants agreed to receive magnetic resonance imaging scanning as part of the inclusion criteria [25]. Multicentre neuroimaging was acquired and harmonised through the Center for Automated Treatment of Images (cati-neuroimagine.com) [30]. WMH volume (in cm3) was measured with White Matter Hyperintensities Automated Segmentation Algorithm software, a novel method for automatically segmenting WMH from T2-weighted fluid attenuated inversion recovery images [31], and quantitatively verified by two trained physicians.

Statistical analysis

Statistical analysis was performed using R (version 4.0.2). Basic demographic information, including age, sex, education, and MMSE score were abstracted. WMH volume and demographic variables in the MBI+ group were compared against the MBI- group using Chi-squared tests (categorical variables, reported with%) and independent t-tests (continuous variables, reported with SD).

We investigated the association between MBI status (MBI+/-) as independent variable and WMH as dependent variable, using a linear regression model adjusted for age, sex, education, MMSE score, and total intracranial volume (TICV). Since greater MBI burden has been associated with lower MMSE scores in previous studies [32], we fitted a similar model to test the association between MBI status and WMH, but without MMSE score as a covariate. Similarly, we fitted a model testing the association between MMSE and WMH without MBI status as a covariate. To reduce skewness, base-10 logarithm was used to transform WMH. MBI status was coded using dummy variables in R, corresponding to MBI+ and MBI−groups. Contrasts were set up for comparisons against the MBI−group. As secondary analyses, linear regressions were similarly fitted to assess the association between MBI domain scores and WMH volume. Emotional dysregulation, impulse dyscontrol, and apathy domains were analyzed, but social inappropriateness and abnormal thoughts/perception were low frequency domains insufficiently
endorsed to warrant analysis.

**Results**

The final study sample included 768 MCI participants (Table 1). Mean age was 72.8 (SD 8.0) and 57.5% of participants were female. There was modest NPS burden in this sample, with a median NPS score of 6 at both baseline and 6-month visits (Supplemental Data, Table 1). MBI (i.e., persistent NPS) was present in 29.8% of participants (n = 229, Table 1). MBI+ status was significantly associated with lower MMSE score (p < 0.001) and male sex (p = 0.02), and not associated with unadjusted WMH volume (p = 0.12). In linear regression, adjusted for age, sex, education, TICV, and MMSE score, MBI+ status was associated with 9.4% higher WMH volume than MBI- status ([95% CI 2.0% to 16.7%], Table 2). As expected, greater age and TICV were significantly associated with higher WMH volume [EE = 2.4% (95% CI 2.0% to 2.8%); EE = 0.08% (95% CI 0.05% to 0.10%)]; however, MMSE score was not [EE = −0.7% (95% CI −2.3% to 0.9%)]. Adjusting for age, sex,
education, and TICV, MBI+ status was significantly associated with 10.0% higher WMH volume ([95% CI 2.8% to 17.2%]), Table 3). Adjusting for these same covariates, MMSE score was not associated with WMH [EE = −1.1% (95% CI −2.7% to 0.5%), Supplemental Data, Table III].

The association between MBI and WMH while controlling for age, sex, education, TICV, and MCI subtype was also investigated. There were 80 participants with amnestic single-domain MCI, 389 with amnestic multi-domain MCI, 167 with non-amnestic single-domain, and 132 with non-amnestic multi-domain MCI. Amnestic single-domain MCI was chosen as the reference group since it was the MCI group that appeared most like AD and had the lowest WMH coefficient. MBI+ status was associated with 8.0% higher WMH volume ([95% CI 1.0% to 15.5%), Table 4]. Amnestic multi-domain MCI was the only group associated with higher WMH volume compared to amnestic single-domain MCI [EE = 14.5%, (95% CI 3.3% to 26.9%)], whereas both non-amnestic single and multi-domain MCI were not.

While no significant associations between MBI domains and WMH were found, the direction and magnitude of effect were similar across all three domains analyzed. The analyses of emotional dysregulation, impulse dyscontrol, and apathy with WMH volume had effect estimates of 6.6% (95% CI −1.1% to 14.4%), 9.9% (95% CI −0.3% to 20.2%), and 13.1% (95% CI −1.9% to 28.2%) respectively (Table 5). Only 10 and 3

---

### Table 1

Sample characteristics.

| Characteristics               | Overall N | MBI+ n | MBI- n | p values for MBI+ vs. MBI- |
|-------------------------------|-----------|--------|--------|---------------------------|
| Age (mean, SD)                | 72.75     | 72.04  | 73.05  | 0.12                      |
| (8.00)                        | (8.37)    | (7.82) |        |                           |
| Female sex (n,%)              | 443       | 117    | 326    | 0.020                     |
| (57.48)                       | (51.09)   | (60.48)|        |                           |
| Education primary school or lower (n,%) | 104  | 39    | 65    | 0.13                      |
| (13.54)                       | (17.03)   | (12.06)|        |                           |
| Education secondary school first cycle (n,%) | 191 | 62    | 129   |                          |
| (24.87)                       | (27.07)   | (23.93)|        |                           |
| Education upper secondary school (n,%) | 225 | 44    | 129   |                          |
| (29.53)                       | (19.21)   | (23.93)|        |                           |
| Education third level or higher (n,%) | 300 | 84    | 216   |                          |
| (39.06)                       | (36.68)   | (40.07)|        |                           |
| Mini-Mental State Examination score (mean, SD) | 27.74 | 27.12 | 28.01 | <0.001                    |
| (1.98)                        | (2.32)    | (1.75)|        |                           |
| White matter hyperintensity in cm³ (mean, SD) | 10.68 | 11.96 | 10.14 | 0.12                      |
| (14.36)                       | (15.81)   | (13.68)|        |                           |

* Categorical variables were obtained via Chi-squared test and reported with %, whereas continuous variables were obtained via t-test and reported with SD.

### Table 2

The association between Mild Behavioral Impairment (MBI) and the log of white matter hyperintensity, controlling for age, sex, education, total intracranial volume, and Mini-Mental State Examination (MMSE) score.

| Estimate | Unstandardized Coefficients | p value |
|----------|-------------------------------|---------|
| Age      | 2.37 × 10⁻²                   | 2.4%    | 2.0% to 2.8%   | <0.001        |
| Sex      | −6.17 × 10⁻²                  | −5.7%   | −13.1% to 1.7% | 0.13          |
| Education | −5.69 × 10⁻²                 | −5.0%   | −14.7% to 4.6% | 0.27          |
| Upper secondary school versus primary school or lower | 3.76 × 10⁻² | 4.4% | −6.6% to 15.4% | 0.48          |
| Third-level or higher versus primary school or lower | −2.44 × 10⁻² | −1.9% | −11.6% to 7.7% | 0.63          |
| Total intracranial volume | 7.72 × 10⁻³ | 0.8% | 0.05% to 2.0% | <0.001        |
| MMSE     | −7.20 × 10⁻³                  | −0.7%   | −2.3% to 9.9%  | 0.38          |
| MBI+ vs MBI- | 8.74 × 10⁻³ | 9.4% | 2.0% to 16.7% | 0.01          |

### Table 3

The association between Mild Behavioral Impairment (MBI) and the log of white matter hyperintensity, controlling for age, sex, education, total intracranial volume, and mild cognitive impairment (MCI) subtype.

| Estimate | Unstandardized Coefficients | p value |
|----------|-------------------------------|---------|
| Age      | 2.41 × 10⁻²                   | 2.4%    | 2.1% to 2.8%   | <0.001        |
| Sex      | −6.10 × 10⁻²                  | −5.9%   | −13.1% to 1.8% | 0.144         |
| Education | −5.43 × 10⁻²                 | −5.3%   | −14.4% to 4.8% | 0.235         |
| Upper secondary school versus primary school or lower | 4.54 × 10⁻³ | 4.6% | −5.8% to 16.2% | 0.562         |
| Third-level or higher versus primary school or lower | −1.81 × 10⁻³ | −1.8% | −11.0% to 8.4% | 0.719         |
| Total intracranial volume | 7.44 × 10⁻³ | 0.07% | 0.05% to 15.5% | <0.001        |
| MBI+ vs MBI- | 7.71 × 10⁻² | 8.0% | 1.0% to 15.5% | 0.025         |

### Table 4

The association between Mild Behavioral Impairment (MBI) and the log of white matter hyperintensity, controlling for age, sex, education, total intracranial volume, and mild cognitive impairment (MCI) subtype.

| Estimate | Unstandardized Coefficients | p value |
|----------|-------------------------------|---------|
| Multi-domain amnestic MCI | 1.35 x 10⁻¹ | 14.5% | 3.3% to 26.9% | 0.010         |
| Multi-domain non-amnestic MCI | 1.66 x 10⁻² | 1.6% | −9.7% to 14.4% | 0.784         |
| Single-domain non-amnestic MCI | 7.24 x 10⁻³ | 7.5% | −4.0% to 20.4% | 0.209         |
patients had persistent symptoms of social inappropriateness and abnormal thoughts/perceptions respectively. Thus, separate analyses of these domains were not pursued.

Discussion

In a sample of 768 participants with MCI, MBI+ status was associated with 9.4% greater WMH volume in adjusted analysis. The association of MBI with WMH was stronger than the association of cognition with WMH, as measured by the MMSE, recognizing the limited sensitivity of the MMSE for executive dysfunction. Of MCI subtypes, amnestic multi-domain MCI was significantly associated with WMH relative to amnestic single-domain MCI, while non-amnestic single and multi-domain MCI were not. Individual MBI domains were not associated with greater WMH volume, but effects trended towards significance; direction of effect was consistently positive with similar confidence internals for emotional dysregulation, impulse dyscontrol, and apathy. To our knowledge, this is the first study to demonstrate the relationship between MBI and WMH.

MBI was present in 29.8% of participants with MCI. There were significant sex differences in the prevalence of MBI, in that males were more frequently MBI+. This finding is corroborated by an earlier MBI prevalence study, which found significant sex differences driven by the apathy and impulse dyscontrol domains [29]. Previous prevalence estimates of MBI in MCI populations vary due to differences in patient settings and case ascertainment. In MCI, MBI prevalence ranged from 14.2% in primary care [33] using the MBI Checklist [34], to 48.9% in a community-based population study [29] using the NPI, to 85.3% in a memory clinic sample [35] using the NPI Questionnaire [36]. Importantly, the studies using the NPI/NPI-Q approximated MBI over a one-month period prevalence instead of ≥6-months with the MBI Checklist, potentially inflating estimates. Nonetheless, despite the high prevalence of MBI in MCI populations, the existing literature on non-affective NPS in cerebral small vessel disease and WMH is somewhat limited. A meta-analysis found associations between greater WMH severity and apathy [OR = 1.41 (95% CI 1.05 to 1.89)]; unfortunately, the studies on anxiety, emotional lability, and psychosis were too varied or sparse for analysis [37]. An extensive meta-analysis on WMH and late-life depression found that WMH were associated with cross-sectional depression [OR = 1.29 (95% CI 1.19 to 1.39)] as well as incident depression over a mean follow-up period of 3.7 years [OR = 1.18 (95% CI 1.08 to 1.28)]. These associations remained significant after controlling for vascular risk factors [38].

WMH are common, with frequencies ranging from 11 to 20% in the late-middle aged to over 90% in octogenarians [39]. Although WMH increase significantly with age, the numerous associations with poorer cognitive outcomes cannot be accounted for by age alone [39,40]. Some suggest that WMH and classic AD pathology, like amyloid and tau, contribute synergistically to the development of cognitive decline [5], particularly in early AD. In a multi-cognitive-domain meta-analysis, the negative associations between WMH and overall cognition were stronger in MCI (r = −0.25, 95% CI −0.36 to −0.14) than in AD (r = −0.11, 95% CI −0.14 to −0.08) [41]. White matter lesions are also associated with impairments in executive function [42], a cognitive domain often linked to cerebrovascular damage. In domain-specific analyses of both MCI and AD populations, the largest effect sizes were found for the negative associations between WMH and attention and executive function as well as processing speed, though this association was also present with memory to a lesser degree [41]. We found that MMSE score was not associated with WMH volume; this lack of an association is not surprising, given that the MMSE is a global cognition screen based mostly on memory and orientation. Furthermore, screening tools such as the Montreal Cognitive Assessment are more sensitive to white matter lesions than the MMSE in MCI populations [43]. While the cognitive profile of WMH has been established in the literature, more needs to be done to determine the neurobehavioral associations.

In this study, global MBI status was associated with greater WMH volume, but individual MBI domains were not. The lack of MBI domain-specific relationships between MBI and WMH supports the use of a composite, multi-NPS-domain MBI score in predicting WMH in MCI, which outperforms individual domains. The lack of a statistically significant association between individual MBI domains and WMH may have been explained in part by small sample size (Supplemental Data, Tables IV-VI). Further research is needed to clarify the relationship between NPS domains and WMH.

Since the association between MBI+ status and WMH was present both with and without MMSE score as a covariate, MBI may be more sensitive to changes in WMH volume than a global cognitive composite measured this way. By including MMSE score as a covariate, the estimated effect of the association between MBI+ status and WMH decreased from 10.0% (Table 3) to 9.4% (Table 2). This suggests that though MMSE score accounts for a small percentage of the variance, MBI may be used as a predictor of WMH regardless of cognitive test score in MCI participants. It is interesting to note how MCI subtypes associate differently with WMH. Using single-domain amnestic MCI as the reference group, only multi-domain amnestic MCI was significantly associated with greater WMH burden, despite the lack of association between MMSE and WMH. This could be explained in part by the methods for determining amnestic MCI in this cohort. Although performance on the Free and Cued Selective Reminding Test has been found to have significant correlations with total MMSE score [44], Delayed Matching-to-Sample 48 was not associated with total MMSE score [45]. Overall, there may be unique drivers differentially affecting cognition within this MCI population which are not captured in the association between MBI+ status and WMH.

Limitations and future directions

To our knowledge, this study is the first to establish a relationship between MBI and WMH in an MCI population. However, potential sources of bias include recruitment from urban memory clinics and a predominantly White participant sample, which may limit generalizability to MCI populations in community and other racial groups. MENTO cohort data on executive function testing or vascular risk factors were not available to us. Future studies with WMH volume should incorporate these features into analytical models. Finally, it is unclear the degree to which white and gray matter atrophy mediate the relationship between WMH and MBI. Here, we have controlled for TICV, recognizing that brain atrophy likely plays a more complex role in the development of NPS than our models have allowed. However, mediation analyses are outside the scope of the current study and should be pursued in future work.

An important consideration is that causality between WMH and MBI development cannot be determined in this study. Practically, however, MBI+ status can serve as a proxy marker to identify a group with greater WMH volume. We approximated MBI+ status using the NPI, which captures point estimates of NPS over a 1-month period. To account for this relatively short reference period, we used 2 consecutive visits to determine symptom persistence consistent with the MBI criteria. Nonetheless, the current MBI case ascertainment method may not be representative of true persistent and emergent NPS, as we excluded participants with unclear MBI status. Further, not all aspects of MBI are

Table 5

| Predictor                  | Estimate (percent) | 95% CI          | p value |
|----------------------------|--------------------|-----------------|---------|
| Emotional Dysregulation    | 6.6%               | −1.1% to +14.4% | 0.10    |
| Impulse Dyscontrol         | 9.9%               | −0.3% to +20.2% | 0.06    |
| Apathy                     | 13.1%              | −1.9% to +28.2% | 0.09    |

Cerebral Circulation - Cognition and Behavior 2 (2021) 100028
represented in the NPI, potentially limiting the sensitivity of this approach. These measurement issues could have been addressed by incorporating the MBI Checklist. The MBI Checklist[34] is the instrument developed to measure MBI in accordance with the International Society to Advance Alzheimer’s Research and Treatment – Alzheimer’s Association MBI criteria[11]. The MBI Checklist has been validated in community[21,46], primary care[33,47], and memory clinic populations[48,49], for in-person, online, and telephone administration, and could be explored in future work to examine the relationship between NPS and vascular pathology.

Conclusions

In a memory clinic sample of older adults with MCI, MBI was associated with greater WMH volume. A composite multi-NPS-domain assessment, as defined by MBI+ status, may be more effective at predicting WMH than MMSE or individual MBI domains. Incorporating simple, informant-rated measures of behavior such as MBI is a scalable clinical approach to capture those with greater WMH and potentially greater risk for incident dementia.

Declaration of Conflicting Interests

Dr. Smith reports consulting fees from Bayer, Biogen, and Cyclerion. Dr. Ismail reports consulting fees from Lundbeck and Otsuka, outside the submitted work. Other authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Acknowledgments

The MEMENTO cohort was funded through research grants from the Fondation Plan Alzheimer (Alzheimer Plan 2008–2012), the French Ministry of Higher education, and Research and Innovation (Pal-Marie 2014–2019).

Funding

Dr. Ismail is supported by the Canadian Institutes of Health Research. This work was also supported by CIC1401-EC, Bordeaux University Hospital (CHU Bordeaux, sponsor of the cohort), Inserm, and the University of Bordeaux.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jccb.2021.100028.

References

[1] E.E. Smith, S. Egorova, D. Blacker, R.J. Killiany, A. Muzikansky, B.C. Dickerson, R. DeCarli, D. Mungas, D. Harvey, B. Reed, M. Weiner, H. Chui, W. Jagust, Memory impairment, but not cerebrovascular disease, predicts progression of MCI to dementia, Neurology 63 (4) (2004) 220–227, https://doi.org/10.1212/01. WNL.000013051.90205.EF.
[2] H.Y. Hu, Y.N. Ou, X.N. Shen, Y. Qu, Y.H. Ma, Z.T. Wang, Q. Dong, L. Tan, J.T. Yu, White matter hyperintensities and risks of cognitive impairment and dementia: a systematic review and meta-analysis of 36 prospective studies, Neurosci. Biobehav. Rev. 120 (2021) 16–27, https://doi.org/10.1016/j.neubiorev.2020.11.007.
[3] E.A. Wise, P.B. Rosenberg, C.G. Lyketsos, J.M. Outtsaks, Time course of neuropsychiatric symptoms and cognitive diagnosis in National Alzheimer’s Coordinating Center volunteers. Alzheimer’s Disease, Diagnosis, Assess. Dis. Monit. 11 (2019) 333–339, https://doi.org/10.1016/j.ndadis.2019.02.006.
[4] P.B. Rosenberg, M.M. Millec, B.S. Appleby, E.S. Oh, Y.E. Geda, C.G. Lyketsos, The association of neuropsychiatric symptoms in MCI with incident dementia and Alzheimer disease, Am. J. Geriatr. Psychiatry 21 (7) (2013) 685–695, https://doi.org/10.1016/j.jager.2013.01.006.
[5] Y.E. Geda, R.O. Roberts, M.M. Millec, D.S. Knopman, T.J.H. Christianson, V.S. Parks, J.K. Katz, B.F. Boeve, R.C. Sohmer, E.G. Tison, et al., Baseline neuropsychiatric symptoms and the risk of incident mild cognitive impairment: a population-based study, Am. J. Psychiatry 171 (5) (2014) 572–581, https://doi.org/10.1176/appi.ajp.2013.13060821.
[6] Z. Ismail, E.E. Smith, Y. Geda, D. Sults, H. Brodaty, G. Smith, L. Agüera-Oria, R. Sweet, D. Miller, C.G. Lyketsos, Neuropsychiatric symptoms as early manifestations of emergent dementia: provisional diagnostic criteria for mild behavioral impairment, Alzheimer’s Disease 12 (2) (2016) 195–202, https://doi.org/10.1089/adi.2015.05.017.
[7] F.Z. Lussier, T.A. Pascoal, M. Chamoun, J. Thérriault, C. Tissot, M. Savidar, M. S. Kang, S. Mathotaraachchi, A.L. Benedet, M. Parsons, et al., Mild behavioral impairment is associated with β-amyloid but not tau or neurodegeneration in cognitively intact elderly individuals. Alzheimer’s Disease. 16 (1) (2020) 192–199, https://doi.org/10.1002/12007.
[8] R. Miao, H.Y. Chen, S. Gill, J. Naude, E.E. Smith, Z. Ismail, Plasma β-amyloid in mild behavioural impairment – neuropsychiatric symptoms on the Alzheimer’s continuum, J. Geriatr. Psychiatry Neurol. (May 26, 2021), https://doi.org/10.1097/JGP.0000130531.90205.EF. Published online.
[9] M. Johansson, E. Stomrud, P.S. Insel, A. Leuzy, P.M. Johansson, R. Smith, Z. Ismail, S. Janezdze, L. Palmqvist, D. van Westen, et al., Mild behavioral impairment and its relation to tau pathology in predementia Alzheimer’s disease, Transl. Psychiatry 11 (1) (2021) 76, https://doi.org/10.1038/s41398-021-01206-z.
[10] F.Z. Lussier, T.A. Pascoal, J. Thérriault, M. Chamoun, C. Tissot, M. Savidar, S. Mathotaraachchi, Z. Ismail, P. Rosa-Neto, S. Gauthier, Mild behavioral impairment is associated with beta-amyloid and tau across the Alzheimer’s disease spectrum, J. Cereb. Blood Flow Metabol. 39 (2019) 158–159. SAGE PUBLICATIONS INC.
[11] S. Gill, M. Wang, P. Mousches, D. Rajahokar, T. Sajobi, F.P. MacMaster, E.E. Smith, N.D. Forkert, Z. Ismail, Neural correlates of the impulse control disorder symptom of mild behavioral impairment, Int. J. Geriatr. Psychiatry 36 (9) (2021) 1398–1406, https://doi.org/10.1002/GPS.5540.1.
[12] J.P. Naude, S. Gill, S. Hu, A. McGirr, N.D. Forkert, O. Monchi, P.K. Stys, E.E. Smith, Z. Ismail, Plasma neurotransmitter light: a marker of neurodegeneration in mild behavioral impairment, J. Alzheimer’s Dis. 76 (3) (2020) 1017–1027, https://doi.org/10.3233/JAD-200011.
[13] V. Matsukova, Z. Ismail, T. Nikolai, H. Markova, K. Cechova, Z. Nedelska, J. Laczo, M. Wang, J. Hott, M. Vyhnanek, Mild behavioral impairment is associated with atrophy of entorhinal cortex and hippocampus in a memory clinic cohort, Front. Aging Neurosci. 13 (2021) 236, https://doi.org/10.3389/FNAGL.2021.642721.
[14] S.J. Andrews, Z. Ismail, K.J. Audsey, M. Morby, Association of Alzheimer’s disease with mild behavioural impairment in healthy older adults. Alzheimer’s Dementia. Diagnosis, Assess. Dis. Monit. 13 (1) (2021) https://doi.org/10.1016/j.dad.2021.121614.
[15] B. Creese, E. Brooker, H. Brooker, D. Aarseth, A. Corbett, L. Aarsland, Z. Ismail, Genetic risk for Alzheimer’s disease, cognition, and mild behavioral impairment in healthy older adults. Alzheimer’s Dementia. Diagnosis, Assess. Dis. Monit. 13 (1) (2021) https://doi.org/10.1016/j.dad.2021.121614.
[16] B. Creese, H. Brooker, Z. Ismail, R.A. Wennes, A. Hampshire, Z. Khan, M. Megalogeni, A. Corbett, D. Aarsland, C. Ballard, Mild behavioral impairment as a marker of cognitive decline in cognitively normal older adults, Am. J. Geriatr. Psychiatry 27 (8) (2019) 823–834, https://doi.org/10.1016/j.jagp.2019.01.215.
[17] T. Matsuoaka, Z. Ismail, J. Narumoto, Prevalence of mild behavioral impairment and risk of dementia in a psychiatric outpatient clinic. J. Alzheimer’s Dis. 70 (2) (2019) 503–511, https://doi.org/10.3233/JAD-190278.
[18] F.E. Taragano, R.F. Allegri, S.L. Heisecke, M.L. Martelli, M.L. Feldman, V. Sánchez, V.A. García, G. Tufro, D.M. Castro, P.P. Leguizamón, Risk of conversion to dementia in a mild behavioral impairment group compared to a psychiatric group and to a mild cognitive impairment group, J. Alzheimer’s Dis. 62 (1) (2018) 227–238, https://doi.org/10.3233/JAD-170632.
[19] Z. Ismail, A. McGirr, S. Gill, S. Hu, N.D. Forkert, E.E. Smith, Mild behavioral impairment and subjective cognitive decline predict cognitive and functional decline, J. Alzheimer’s Dis. 80 (1) (2021) 459–469, https://doi.org/10.3233/JAD-201184.
[20] D. Dubois, B. Dubois, B. Vellas, F. Pasquier, F. Blanc, J. Hugon, O. Hanson, J. F. Dartigues, S. Harston, A. Gabbett, et al., Cognitive and imaging markers in non-demented subjects attending a memory clinic: study design and baseline findings of the MEMENTO cohort. Alzheimer’s Res. Ther. 9 (1) (2017) https://doi.org/10.1186/s13195-017-0119-9.
[21] J.C. Morris, Clinical Dementia Rating: A Reliable and Valid Diagnostic and Staging Measure for Dementia of the Alzheimer Type (1997).
