Neural Correlates of the Impulse Dyscontrol Domain of Mild Behavioral Impairment

Sascha Gill  
University of Calgary  
https://orcid.org/0000-0001-9978-8691

Meng Wang  
University of Calgary

Pauline Mouches  
University of Calgary

Deepthi Rajashekar  
University of Calgary

Tolulope Sajobi  
University of Calgary

Frank P MacMaster  
University of Calgary

Eric E Smith  
University of Calgary

Nils D Forkert  
University of Calgary

Zahinoor Ismail  
ismailz@ucalgary.ca  
3280 Hospital Drive NW, TRW Building 1st Floor Calgary, AB T2N 4Z6, Canada  
https://orcid.org/0000-0002-5529-3731

Research

Keywords: Agitation, Aggression, Impulse Dyscontrol, Alzheimer's Disease, Geriatric Psychiatry, Mild Behavioural Impairment

DOI: https://doi.org/10.21203/rs.3.rs-96272/v1

License: ☑️ ☐ This work is licensed under a Creative Commons Attribution 4.0 International License.  Read Full License
Abstract

Background: Agitation and aggression are common in dementia and pre-dementia. The dementia risk syndrome mild behavioral impairment (MBI) includes these symptoms in the impulse dyscontrol domain. However, the neural circuitry associated with impulse dyscontrol in neurodegenerative disease is not well understood. The aim of this work is to investigate if regional micro- and macro-structural brain properties are associated with impulse dyscontrol symptoms in older adults with normal cognition, mild cognitive impairment, and Alzheimer's disease.

Methods: Clinical, neuropsychiatric, and T1-weighted and diffusion-tensor MRI (DTI) data from 80 individuals with and 123 individuals without impulse dyscontrol, were obtained from the Alzheimer's Disease Neuroimaging Initiative. Linear mixed effect (LME) models were used to assess if impulse dyscontrol was related to regional DTI and volumetric parameters.

Results: Impulse dyscontrol was present in 17% of participants with NC, 43% with MCI, and 66% with AD. Impulse dyscontrol was associated with: 1) lower fractional anisotropy, and greater mean, axial, and radial diffusivity in the fornix; 2) lesser fractional anisotropy, and greater radial diffusivity in the superior fronto-occipital fasciculus; 3) greater axial diffusivity in the cingulum; 4) grey matter atrophy, specifically, lower cortical thickness and greater surface area in the parahippocampal gyrus.

Conclusion: Our findings provide evidence that well-established atrophy patterns of AD are prominent in the presence of impulse dyscontrol, even when disease status is controlled for, and possibly in advance of dementia. Our findings support the growing evidence base for impulse dyscontrol symptoms as an early manifestation of Alzheimer's disease.

Background

Agitation, aggression, and impulsivity are common in dementia and are associated with caregiver stress and poorer outcomes (1, 2). These symptoms are clinically meaningful, often requiring intervention – both non-pharmacological and pharmacological (3). Agitation in individuals with neurocognitive disorders is associated with emotional distress and symptoms of excessive motor activity, verbal aggression, or physical aggression (4). In a recent systematic review, the prevalence of agitation/aggression in patients with Alzheimer's disease (AD) was estimated to be 40% (5). Agitation can also present in advance of dementia in those with mild cognitive impairment (MCI), subjective cognitive decline (SCD), or even normal cognition (6–9). In the population-based Mayo Clinic Study of Aging, which enrolled participants ≥ 70 years of age, prevalence of irritability was 7.6% in normal cognition (NC) and 19.4% in MCI, while prevalence of agitation was 2.8% in NC and 9.1% in MCI (5). Importantly, in a subsequent analysis, these same impulse dyscontrol symptoms when present at study baseline predicted incident MCI. Hazard ratio for incident MCI with baseline irritability was 1.84 and for agitation hazard was 3.06 relative to the absence of symptoms (10). Thus, neuropsychiatric symptoms in older adults are important features of dementia risk stratification.

Mild behavioral impairment (MBI) is a validated neurobehavioral syndrome that describes the later life emergence of persistent NPS as an at-risk state for incident cognitive decline and dementia (11). These NPS have been suggested to be an index manifestation of dementia for some(12–20). MBI captures preclinical and prodromal disease symptoms and is associated with known dementia biomarkers including amyloid-β (21), tau (22, 23), neurofilament light (24), brain atrophy (25, 26), and AD risk genes (27, 28). MBI impulse dyscontrol domain includes behavioral symptoms of agitation/aggression, irritability, and aberrant motor behavior. In a population-based study of older adults ranging from NC to MCI, cross-sectional assessment of NPS using the neuropsychiatric inventory found impulse dyscontrol symptoms to be the most common domain with frequencies of 17.2% in NC and 33.8% in MCI (29). A concurrent study in a cognitive neurology clinic sample assessed MBI domains in those with subjective cognitive decline (SCD) and MCI (8) and reported the frequency of impulse dyscontrol in both groups being greater than 50% (8). Longitudinal analysis of the National Alzheimer Coordinating Center cohort described phases of NPS emergence in advance of dementia with symptoms of irritability/lability emerging in the first wave of pre-dementia NPS, and agitation emerging in the second wave (30). Subsequent analysis of the same population demonstrated that NPS emerged in advance of cognitive symptoms in 59% of dementia participants, including 30% of those who developed AD. For impulse dyscontrol symptoms, irritability emerged before dementia in 38% of cases (21% before MCI), agitation before dementia in 26% of cases (13% before MCI), and motor disturbance before dementia in 6% of cases (3% before MCI) (31). These symptoms of impulse dyscontrol are common in preclinical and prodromal disease, are associated with greater risk of incident cognitive decline and dementia and represent clinically significant symptoms often requiring pharmacological intervention. Further exploration of impulse dyscontrol is warranted.

Research has assessed neuroimaging correlates of agitation, aggression, and impulse dyscontrol in dementia but to a lesser extent in predementia groups. Agitation/aggression in MCI and AD has been associated with atrophy in fronto-limbic regions, right posterior cingulate, and left hippocampus (32). Aberrant motor behavior symptoms have been associated with atrophy in the right basal ganglia and frontal cortex(33). Furthermore, reduced fractional anisotropy (FA) in the anterior cingulum (34) has been associated with agitation and irritability. This present study focused on identifying the neuroanatomical correlates of impulse dyscontrol in older adults, outside of diagnostic and
nosological boundaries. Increasing knowledge of the neural correlates of impulse dyscontrol may improve diagnosis, aid in disease prognostication, and identify potential treatment targets. The objective of this study was to assess white matter and volumetric parameters in a priori selected brain regions in association with symptoms of impulse dyscontrol in individuals with NC, MCI, and AD. Based on our literature review, the large white matter tracts assessed include the cingulum, fornix, superior fronto-occipital fasciculus, inferior fronto-occipital fasciculus, and the uncinate fasciculus (35). Volumetric analysis included the hippocampus, caudal and rostral anterior cingulate, amygdala, parahippocampal gyrus, and the medial orbitofrontal cortex (36). We hypothesized that symptoms of impulse dyscontrol would be associated with decreased white matter integrity in the cingulum and with atrophy patterns in fronto-limbic structures.

Methods

Alzheimer’s Disease Neuroimaging Initiative (ADNI)

Data was extracted from the ADNI database (http://adni.loni.usc.edu/). ADNI is a large, multi-center longitudinal study that aims to track the progression of AD. We focused on participants within the ADNI-GO/2 cohort because they had processed diffusion tensor imaging (DTI) and volumetric magnetic resonance imaging (MRI) data were also available. Participants met the general ADNI eligibility, inclusion and exclusion criteria. ADNI grouped participants into multiple diagnostic categories based on their clinical assessments (For further detail see: http://adni.loni.usc.edu/).

Data Extraction

Demographic, clinical, and quantified structural MRI and DTI data were used for the analysis. To quantify symptoms of impulse dyscontrol, NPI questionnaire (NPI-Q) (37) scores were also extracted. All datasets were downloaded before January 25, 2019.

To evaluate both white and grey matter regions associated with impulse dyscontrol, we included all participants that had baseline quantified DTI, MRI, and NPI-Q data available. Participants were excluded for: 1) missing baseline DTI data; 2) missing NPI-Q scores (i.e. no impulse dyscontrol score); 3) quantitative MRI analysis classified as “Fail” or “Hippocampus only” by visual quality control by the UCSF core lab; or 4) missing cognitive composite scores. Figure 1 shows the step-by-step process of participants included/excluded from the analysis.

Participants

A total of 203 participants were included for the analysis: n = 70 NC; n = 95 MCI; and n = 38 AD-dementia.

Measures

Clinical variables. Age, sex, education, baseline diagnostic status, and composite scores for memory and executive function were included as clinical features to investigate the potential relationships with neural correlates associated with impulse dyscontrol scores. The diagnostic status was determined by clinical assessments at the time of visit. The cognitive composite scores were standardized scores calculated by transforming data collected through the ADNI neuropsychological battery into memory and executive functioning domains (38).

Neuropsychiatric variables. Since ADNI uses the NPI-Q to capture NPS, these data were transformed into MBI domains using a published algorithm (8). NPI-Q items were combined to form a composite MBI impulse domain score by adding NPI-Q agitation/aggression, irritability, and aberrant motor behavior scores. The reference range for the NPI-Q is 1 month, and thus the transformation algorithm generated an approximation for 1 month only. For the statistical analysis, impulse dyscontrol was classified as 0 or 1 to indicate the absence and presence of symptoms respectively.

Neuroimaging variables. Quantified neuroimaging data were downloaded from ADNI. The output from processed diffusion-tensor MRI and T1-weighted images was used in the analyses. UCLA core lab processed the DTI datasets, generating average fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AxD), and radial diffusivity (RD) values within regions of interests from the John Hopkins University DTI atlas. MD measures the molecular diffusion rate, FA measures the directional preference of water, RD and AxD measure the rate of diffusion along the transverse and main axis respectively (39). In a neurodegenerative disease, the typical pattern of DTI parameters is a decrease in FA, and an increase in MD, AxD and RD indicative of neuronal tissue damage (40). Additional information about the UCLA DTI methods are described in more detail elsewhere (41). For the T1-weighted images, UCSF core lab used FreeSurfer version 5.1 for cortical reconstruction and volumetric segmentation. Outputs included cortical thickness, surface area, and volumetric measurements within regions labelled by the 2010 Desikan-Killany and 2009 Destrieux atlas. Additional information on UCSF FreeSurfer methods is also available elsewhere (42). In order to control for intracranial volume (ICV) differences, we generated a normalization factor by averaging ICV of the whole sample and dividing it by individual ICV. This ratio was multiplied with all cortical and subcortical volume variables (43).

Statistical Analysis
Sample characteristics are reported using means, standard deviations, and frequency distributions. Chi-square tests and the Kruskal Wallis tests (or Wilcoxon-Mann-Whitney tests) were used to investigate univariate associations between categorical and continuous patient characteristics and impulse dyscontrol symptoms, respectively. For the linear mixed effect models, six a priori regions were selected for the analysis. Four models were computed for DTI and three models for the volumetric variables. White matter regions included in this analysis are the cingulum, cingulum (hippocampus), fornix, superior fronto-occipital fasciculus, inferior fronto-occipital fasciculus, and the uncinate fasciculus. In this analysis, we generated separate models for FA, MD, RD, and AxD values for the individual tracts. Regions included for the volumetric analysis were the hippocampus, caudal and rostral anterior cingulate, amygdala, parahippocampal gyrus, and the medial orbitofrontal cortex. In this analysis, we computed separate models for cortical thickness, surface area, and volume for the structures. Linear mixed effect models were used to assess if impulse dyscontrol presence was related to DTI/volumetric parameters. Fixed effects included presence of impulse dyscontrol symptoms, disease status, structure, age, gender, and education. Random effects included the hemisphere of the structure (left/right) and intercept. With the primary interest of the analyses being investigation of the region and its association with impulse dyscontrol, having laterality as a random effect in the mixed effect model allowed adjustment for variations due to differences between hemispheres. With seven different LME models in total (4 for DTI, 3 for volumetric measures), significance level was adjusted to 0.01 (instead of 0.05) to minimize inflation in type 1 error. The analyses were conducted in SAS v9.4.

Results

Impulse dyscontrol (presence of any items in the impulse dyscontrol domain) was present in 17% of the individuals with NC, 43% with MCI, and 66% with AD. Table 1 shows the demographic characteristics and cognitive test scores in individuals with or without symptoms of impulse dyscontrol. Across the two groups, there were no significant differences in age and education. There were significantly more males with impulse dyscontrol symptoms than females. Worse cognitive diagnostic status was associated with the presence of impulse dyscontrol. In normal cognition, impulse dyscontrol performed significantly better on memory tests, but there were no impulse dyscontrol differences in memory for MCI and AD. Impulse dyscontrol did not identify any groups with poorer executive function.

Linear Mixed Effect Models

DTI variables. Participants with impulse dyscontrol had lower FA in the fornix ($\beta_{FA} = -17.0 \times 10^{-6} \text{ mm}^2/\text{s}$) and lower FA in superior fronto-occipital fasciculus ($\beta_{FA} = -13.0 \times 10^{-6} \text{ mm}^2/\text{s}$) compared to those without. Significantly higher MD, AxD, and RD values were observed in the fornix ($\beta_{MD} = 117 \times 10^{-6} \text{ mm}^2/\text{s}$; $\beta_{AxD} = 165 \times 10^{-6} \text{ mm}^2/\text{s}$; $\beta_{RD} = 187 \times 10^{-6} \text{ mm}^2/\text{s}$). Higher AxD in the cingulum ($\beta_{AxD} = 3.00 \times 10^{-6} \text{ mm}^2/\text{s}$) and RD in the superior fronto-occipital ($\beta_{RD} = 12.9 \times 10^{-6} \text{ mm}^2/\text{s}$) was identified to be associated with impulse dyscontrol symptoms compared to those without ($p < 0.01$). Other structures showed no significant interaction with impulse dyscontrol scores. See Table 2 for details.

Volumetric variables. Impulse dyscontrol symptoms were associated with participants having smaller cortical thickness by 0.102 mm in the parahippocampal gyrus ($p = 0.002$). On the contrary, the surface area of the parahippocampal gyrus was greater by 20.7 mm$^2$ in participants that had impulse control symptoms compared to those who did not ($p = 0.006$). No significant differences were identified to be associated with presence of impulse dyscontrol symptoms in other structures. See Table 3 for details.

Discussion

In this study, the relationship between structural neuroimaging markers and impulse dyscontrol symptoms was explored across cognitive categories. In those with normal cognition, MCI and AD, both white and grey matter differences were identified in individuals with impulse dyscontrol emphasizing the importance of these symptoms in neurodegenerative disease and supporting the notion of behavioural sequelae of brain structural changes across the cognitive spectrum.

As shown by the altered DTI parameters, lower white matter integrity in tracts including the cingulum, fornix and superior fronto-occipital fasciculus was associated with impulse dyscontrol. To our knowledge, Tighe et al. (34) published the only DTI study to date that reported lower FA of the anterior cingulum to be associated with symptoms of agitation and irritability. While differences in the FA of the cingulum were not significant in our study, the cingulum was still implicated with greater AxD in individuals with impulse dyscontrol symptoms. The cingulum is an important tract that connects frontal, parietal, and medial temporal regions, including several limbic structures, and microstructural changes in this tract have been associated with MCI and AD (44). Furthermore, a recent study identified altered DTI parameters in the cingulum in early-stage AD (45). In another ADNI study of participants with preclinical AD (amyloid and tau positive), irritability predicted hypometabolism in the posterior cingulate cortex 2 years later, supporting the role of irritability as a preclinical AD marker (46). Our study extends the evidence base for the cingulum as a potential early neuroimaging marker, which can show changes in DTI parameters in individuals with impulse dyscontrol symptoms in advance of dementia.
With significant differences in all diffusion parameters, the fornix was another important tract that was associated with symptoms of impulse dyscontrol. The relationship of the fornix and neuropsychiatric symptoms in pre-dementia and dementia populations is largely unexplored. However, there is evidence supporting neurodegeneration in the fornix predicting degree of memory impairment and the likelihood of progression to AD (47, 48). A reduced fornix FA is one of the earliest MRI abnormalities observed in individuals at risk of AD (49) and has been explored as a treatment target using deep brain stimulation for mild AD (50). In a recent study, damaged white matter integrity of the fornix was also associated with reduced resting-state functional connectivity of the hippocampus in individuals with MCI and AD (51). Observing fornix impairment in association with impulse dyscontrol highlights neuropsychiatric symptoms as part of the early disease process. The cingulum, fornix, and fronto-occipital fasciculus tracts are all important for connections between hippocampus to the hypothalamus and connecting orbitofrontal areas to the occipital regions. These white matter differences combined with grey matter atrophy in the parahippocampal gyrus provide evidence that the well-established atrophy patterns in AD (52, 53) are also prominent in the presence of behavioral symptoms, even after adjustment for disease status.

These findings also suggest that white matter damage is more prominent than grey matter atrophy, which is in line with past literature, which has determined that microstructural white matter changes precede grey matter atrophy (54). With the goal to identify the neural correlates associated with the MBI impulse dyscontrol domain, the results suggest that the fronto-striatal network plays a key role in regulating these behaviors. Rosenberg et al. (55) identified that the agitation circuit consists of the frontal cortex, anterior cingulate cortex, orbitofrontal cortex, amygdala, hippocampus, and insula. Since these regions associated with agitation mapped onto the salience network, the authors proposed that increased connectivity within this network could explain agitation in individuals. Similarly, we observed the cingulum, fronto-occipital tracts, fornix, and parahippocampal gyrus as key regions associated with impulse dyscontrol. Some of the regions from this study also overlap with the agitation circuits previously identified (55) providing evidence of brain changes similar to core AD pathology, which can precede cognitive symptoms or dementia.

There are several strengths of this study. This is the first study to explore neural correlates of the MBI impulse dyscontrol domain in a majority of predementia participants. Being a relatively new syndrome, understanding the biological changes associated with MBI domains can help clinicians and researchers appreciate the neural underpinnings of later life behavioral changes, and link these to dementia risk. Additionally, our sample primarily consisted of individuals in the preclinical and prodromal stages of AD-dementia - identifying patterns of micro/macro-structural changes at earlier stages could support future prediction models and enable early patient identification.

There are some limitations of this study. MBI case detection was approximated using transformations of the NPI-Q. Since NPI-Q measures symptoms within 1-month range, it is possible that we captured transient symptoms that may have resolved, thus decreasing diagnostic specificity. Studies have shown inflated MBI prevalence using transformed scores (8, 9) in comparison to the use of the MBI checklist (MBI-C), which is the validated a priori case ascertainment instrument developed for MBI(56). The MBI-C has demonstrated ability to serve as a proxy marker for older adults with subtle cognitive changes or early neurodegenerative disease (13, 57). Thus, diagnostic sensitivity of this approach may also be a limitation, as the whole breadth of MBI impulse dyscontrol, validated by network meta-analysis (58) is not captured by the NPI-Q. Future studies that use MBI-C should further investigate the neural correlates associated with MBI impulse dyscontrol and other domains to verify our results. Additionally, ADNI excludes patients with psychiatric illness (some of which may actually be prodromal dementia symptoms) (20) or those with severe NPS. Thus, the sample included in this study might underappreciate the extent of NPS in the preclinical and prodromal population. Other datasets should be explored for further validation of our results.

**Conclusions**

To our knowledge, this is one of the first few studies that explores the neural correlates of impulse dyscontrol in predementia participants. We demonstrate typical AD structural changes in the brain associated with these behavioral symptoms, even in advance of dementia or cognitive decline, emphasizing the utility of assessing behaviour. Understanding the neuropsychiatric manifestations of the neurodegenerative disease can help clinicians in predicting the progression of the disease.

**List Of Abbreviations**
Declarations

Ethics approval and consent:

the ADNI study was approved by all the Institutional Ethical Review Boards of all participating centers. All participants signed written informed consent.

Consent for publication:

Not applicable

Availability of data and materials:

the datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests:

Dr. Ismail reports consultation fees and honoraria from Janssen, Lundbeck, and Otsuka, outside the submitted work; Dr. Smith reports personal fees from Alnylman Pharmaceuticals and Biogen, outside the submitted work; no other authors have financial interests with commercial interests.

Funding:

Alzheimer Society of Calgary via the Hotchkiss Brain Institute – University of Calgary.

Authors’ contributions:

SG analyzed and interpreted the data and contributed to writing the manuscript. PM, MW, DR, and TS were involved in the statistical analyses. FPM, EES, and NDF critically analyzed the results and made intellectual contributions and manuscript revisions. ZI contributed to study design, data interpretation, and manuscript writing. All authors read and approved the final manuscript.

Acknowledgements:

Data collection and sharing for this project was funded by the Alzheimer’s Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer’s Association; Alzheimer’s Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpire, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; Eurolimmon; F. Hoffmann-La Roche Ltd and its
affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; Mesoscale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California.

References

1. Lanctôt KL, Amatniek J, Ancoli-Israel S, Arnold SE, Ballard C, Cohen-Mansfield J, et al. Neuropsychiatric signs and symptoms of Alzheimer's disease: New treatment paradigms. Alzheimer's & Dementia: Translational Research & Clinical Interventions. 2017;3:440-9.
2. Fischer CE, Ismail Z, Schweizer TA. Impact of neuropsychiatric symptoms on caregiver burden in patients with Alzheimer's disease. Neurodegener Dis Manag. 2012;2(3):269-77.
3. Ismail Z, Goodarzi Z. Neuropsychiatric Aspects of Alzheimer's Disease Clinically significant neuropsychiatric symptoms need evidence-based treatment. Practical Neurology. 2019;June:78-83.
4. Cummings J, Mintzer J, Brodaty H, Sano M, Banerjee S, Devanand DP, et al. Agitation in cognitive disorders: International Psychogeriatric Association provisional consensus clinical and research definition. Int Psychogeriatr. 2015;27:7-17.
5. Zhao Q-F, Tan L, Wang H-F, Jiang T, Tan M-S, Tan L, et al. The prevalence of neuropsychiatric symptoms in Alzheimer's disease: Systematic review and meta-analysis. Journal of Affective Disorders. 2016;190:264-71.
6. Geda YE, Roberts RO, Knopman DS, Petersen RC, Christanson TJ, Pankratz VS, et al. Prevalence of neuropsychiatric symptoms in mild cognitive impairment and normal cognitive aging: population-based study. Arch Gen Psychiatry. 2008;65(10):1193-8.
7. Monastero R, Mangialasche F, Camarda C, Ercolani S, Camarda R. A systematic review of neuropsychiatric symptoms in mild cognitive impairment. Journal of Alzheimer's Disease. 2009;18:11-30.
8. Sheikh F, Ismail Z, Morby ME, Barber P, Cieslak A, Fischer K, et al. Prevalence of mild behavioral impairment in mild cognitive impairment and subjective cognitive decline, and its association with caregiver burden. International Psychogeriatrics. 2018;30:233-44.
9. Morby ME, Ismail Z, Anstey KJ. Prevalence estimates of mild behavioral impairment in a population-based sample of pre-dementia states and cognitively healthy older adults. Int Psychogeriatr. 2018;30(2):221-32.
10. Geda YE, Roberts RO, Mielke MM, Knopman DS, Christanson TJ, Pankratz VS, et al. Baseline neuropsychiatric symptoms and the risk of incident mild cognitive impairment: a population-based study. Am J Psychiatry. 2014;171(5):572-81.
11. Ismail Z, Smith EE, Geda Y, Sultzer D, Brodaty H, Smith G, et al. Neuropsychiatric symptoms as early manifestations of emergent dementia: provisional diagnostic criteria for mild behavioral impairment. Alzheimers Dement. 2016;12(2):195-202.
12. Creese B, Griffiths A, Brooker H, Corbett A, Aarsland D, Ballard C, et al. Profile of mild behavioral impairment and factor structure of the mild behavioral impairment checklist in cognitively normal older adults. International psychogeriatrics. 2020;32(6):705-17.
13. Creese B, Brooker H, Ismail Z, Wesnes KA, Hampshire A, Khan Z, et al. Mild behavioral impairment as a marker of cognitive decline in cognitively normal older adults. The American Journal of Geriatric Psychiatry. 2019;27(8):823-34.
14. Mallo SC, Ismail Z, Pereiro AX, Facal D, Lojo-Seoane C, Campos-Magdaleno M, et al. Assessing mild behavioral impairment with the mild behavioral impairment-checklist in people with mild cognitive impairment. Journal of Alzheimer's Disease. 2018;66(1):83-95.
15. Mallo SC, Ismail Z, Pereiro AX, Facal D, Lojo-Seoane C, Campos-Magdaleno M, et al. Assessing mild behavioral impairment with the mild behavioral impairment checklist in people with subjective cognitive decline. International psychogeriatrics. 2018:1-9.
16. Matsuoka T, Ismail Z, Narumoto J. Prevalence of mild behavioral impairment and risk of dementia in a psychiatric outpatient clinic. Journal of Alzheimer's Disease. 2019;70(2):505-13.
17. Taragano FE, Allegri RF, Heisecke SL, Martelli MI, Feldman ML, Sánchez V, et al. Risk of conversion to dementia in a mild behavioral impairment group compared to a psychiatric group and to a mild cognitive impairment group. Journal of Alzheimer's Disease. 2018;62(1):227-38.
18. Gosselin PA, Ismail Z, Faris PD, Benkoczi CL, Fraser TL, Cherry SW, et al. Effect of Hearing Ability and Mild Behavioural Impairment on MoCA and Memory Index Scores. Canadian Geriatrics Journal. 2019;22(3):165.
19. Ismail Z, McGirr A, Gill S, Hu S, Forkert ND, Smith EE. Mild Behavioral Impairment and Subjective Cognitive Decline predict Mild Cognitive Impairment. medRxiv. 2020.
20. Gill S, Mouches P, Hu S, Rajashekar D, MacMaster FP, Smith EE, et al. Using Machine Learning to Predict Dementia from Neuropsychiatric Symptom and Neuroimaging Data. Journal of Alzheimer's Disease. 2020(Preprint):1-12.

21. Lussier FZ, Pascoalo TA, Chamoun M, Therriault J, Tissot C, Savard M, et al. Mild behavioral impairment is associated with β-amyloid but not tau or neurodegeneration in cognitively intact elderly individuals. Alzheimers Dement. 2020;16:192-9.

22. Johansson M, Smith R, Stromud E, Johansson P, Janelidze S, van Westen D, et al., editors. Mild behavioral impairment is predictive of tau deposition in the earliest stages of Alzheimer’s disease. 2020 Alzheimer's Association International Conference; 2020:32.

23. Lussier F, Pascoalo T, Therriault J, Chamoun M, Tissot C, Savard M, et al., editors. Mild behavioral impairment is associated with beta-amyloid and tau across the Alzheimer’s disease spectrum. JOURNAL OF CEREBRAL BLOOD FLOW AND METABOLISM; 2019: SAGE PUBLICATIONS INC 2455 TELLER RD, THOUSAND OAKS, CA 91320 USA.

24. Naude J, Gill S, Hu S, Mcgirr A, Forkert N, Monchi O, et al. Plasma Neurofilament Light: a marker of cognitive decline in Mild Behavioural Impairment. J Alzheimes Dis. 2020;76(3):1017-27.

25. Matuskova V, Ismail Z, Nikolai T, Markova H, Cechova K, Laczó J, et al., editors. Mild behavioral impairment is associated with atrophy in Alzheimer’s disease-related regions in non-demented older adults. 2020 Alzheimer's Association International Conference; 2020: ALZ.

26. Yoon E, Ismail Z, Hangaru A, Kibreab M, Hammer T, Cheetham J, et al. Mild Behavioral Impairment is linked to worse cognition and brain atrophy in Parkinson's disease. Neurology. 2019;93(8):e766-e77.

27. Creese B, Brooker H, Aarsland D, Corbett A, Ballard C, Ismail Z. Genetic risk for Alzheimer disease, cognition and Mild Behavioral Impairment in healthy older adults. medRxiv. 2020:2020.05.13.20100800.

28. Andrews SJ, Ismail Z, Anstey KJ, Mortby M. Association of Alzheimer's genetic loci with mild behavioral impairment. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics. 2018;177(8):727-35.

29. Mortby ME, Ismail Z, Anstey KJ. Prevalence estimates of mild behavioral impairment in a population-based sample of pre-dementia states and cognitively healthy older adults. International Psychogeriatrics. 2018;30:221-32.

30. Masters MC, Morris JC, Roe CM. "Noncognitive" symptoms of early Alzheimer disease A longitudinal analysis. Neurology. 2015;84:1-6.

31. Wise EA, Rosenberg PB, Lyketsos CG, Leoutsakos J-M. Time course of neuropsychiatric symptoms and cognitive diagnosis in National Alzheimer's Coordinating Centers volunteers. Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring. 2019;11:333-9.

32. Trzepacz PT, Yu P, Bhamidipati PK, Willis B, Forrester T, Tabas L, et al. Frontolimbic atrophy is associated with agitation and aggression in mild cognitive impairment and Alzheimer's disease. Alzheimers Dement. 2013;9(5 Suppl):S95-S104.e1.

33. Hu X, Mcberth D, Newport B, Jessen F. Anatomical correlates of the neuropsychiatric symptoms in Alzheimer's disease. Current Alzheimer Research. 2015;12(3):266-77.

34. Tighe SK, Oishi K, Mori S, Smith GS, Albert M, Lyketsos CG, et al. Diffusion tensor imaging of neuropsychiatric symptoms in mild cognitive impairment and Alzheimer's dementia. J Neuropsychiatry Clin Neurosci. 2012;24(4):484-8.

35. Pievani M, Agosta F, Pagani E, Canu E, Sala S, Absinta M, et al. Assessment of white matter tract damage in mild cognitive impairment and Alzheimer's disease. Human brain mapping. 2010;31(12):1862-75.

36. Bateman DR, Gill S, Hu S, Foster ED, Ruthirakuhan MT, Sellek AF, et al. Agitation and impulsivity in mid and late life as possible risk markers for incident dementia. Alzheimer's & Dementia: Translational Research & Clinical Interventions. 2020;6(1):e12016.

37. Kaufer DI, Cummings JL, Ketchel P, Smith V, MacMillan A, Shelley T, et al. Validation of the NPI-Q, a brief clinical form of the Neuropsychiatric Inventory. J Neuropsychiatry Clin Neurosci. 2000;12(2):233-9.

38. Gibbons LE, Carle AC, Mackin RS, Mukherjee S, Insel P, Curtis SM, et al. Composite measures of executive function and memory: ADNI_EF and ADNI_Mem. Alzheimer's Disease Neuroimaging Initiative. 2012.

39. Soares J, Marques P, Alves V, Sousa N. A hitchhiker's guide to diffusion tensor imaging. Frontiers in neuroscience. 2013;7:31.

40. Talai AS, Sedlacik J, Boelmans K, Forkert ND. Widespread diffusion changes differentiate Parkinson's disease and progressive supranuclear palsy. NeuroImage Clinical. 2018;20:1037-43.

41. Nir TM, Jahanshad N, Villalon-Reina JE, Toga AW, Jack CR, Weiner MW, et al. Effectiveness of regional DTI measures in distinguishing Alzheimer's disease, MCI, and normal aging. NeuroImage Clinical. 2013;3:180-95.

42. Hartig M, Truran-Sacrey D, Rapantsetsang S, Simonson A, Mezher A, Schuff N, et al. UCSF FreeSurfer Methods. 2014.

43. Talai AS, Ismail Z, Sedlacik J, Boelmans K, Forkert ND. Improved Automatic Morphology-Based Classification of Parkinson's Disease and Progressive Supranuclear Palsy. Clinical Neuroradiology. 2018:1-10.

44. Bubb EJ, Metzler-Baddeley C, Aggleton JP. The cingulum bundle: Anatomy, function, and dysfunction. Neuroscience and biobehavioral reviews. 2018;92:104-27.

45. Wen Q, Mustafi SM, Li J, Risacher SL, Tallman E, Brown SA, et al. White matter alterations in early-stage Alzheimer's disease: A tract-specific study. Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring. 2019;11:576-87.
46. Ng KP, Pascoaal TA, Mathotaarachchi S, Chung C-O, Benedet AL, Shin M, et al. Neuropsychiatric symptoms predict hypometabolism in preclinical Alzheimer disease. Neurology. 2017;88:1814-21.

47. Oishi K, Lyketsos CG. Alzheimer’s disease and the fornix. Frontiers in aging neuroscience. 2014;6:241.

48. Mielke MM, Okonkwo OC, Oishi K, Mori S, Tighe S, Miller MI, et al. Fornix integrity and hippocampal volume predict memory decline and progression to Alzheimer’s disease. Alzheimer’s & Dementia. 2012;8(2):105-13.

49. Kantarcı K. Fractional anisotropy of the fornix and hippocampal atrophy in Alzheimer’s disease. Frontiers in aging neuroscience. 2014;6:316.

50. Leoutsakos J-MS, Yan H, Anderson WS, Asaad WF, Baltuch G, Burke A, et al. Deep brain stimulation targeting the fornix for mild Alzheimer dementia (the ADvance trial): a two year follow-up including results of delayed activation. Journal of Alzheimer’s Disease. 2018;64(2):597-606.

51. Wang P, Zhou B, Yao H, Xie S, Feng F, Zhang Z, et al. Aberrant Hippocampal Functional Connectivity Is Associated with Fornix White Matter Integrity in Alzheimer’s Disease and Mild Cognitive Impairment. Journal of Alzheimer’s Disease. 2020(Preprint):1-16.

52. Ewers M, Sperling RA, Klunk WE, Weiner MW, Hampel H. Neuroimaging markers for the prediction and early diagnosis of Alzheimer’s disease dementia. 2011.

53. Mak E, Gabel S, Mirette H, Su L, Williams GB, Waldman A, et al. Structural neuroimaging in preclinical dementia: From microstructural deficits and grey matter atrophy to macroscale connectomic changes. Ageing Research Reviews. 2017;35:250-64.

54. Zhuang L, Sachdev PS, Trollor JN, Reppermund S, Kochan NA, Brodaty H, et al. Microstructural White Matter Changes, Not Hippocampal Atrophy, Detect Early Amnestic Mild Cognitive Impairment. PLoS ONE. 2013;8:e58887.

55. Rosenberg PB, Nowranghi MA, Lyketsos CG. Neuropsychiatric symptoms in Alzheimer’s disease: What might be associated brain circuits? Molecular Aspects of Medicine. 2015;43-44:25-37.

56. Ismail Z, Aguera-Ortiz L, Brodaty H, Cieslak A, Cummings J, Fischer CE, et al. The Mild Behavioral Impairment Checklist (MBI-C): A Rating Scale for Neuropsychiatric Symptoms in Pre-Dementia Populations. J Alzheimers Dis. 2017;56(3):929-38.

57. Kassam F, Chen H-Y, Nosheny RL, Williams T, Mackin RS, Weiner MW, et al., editors. Cognitive profile of mild behavioral impairment (MBI) in Brain Health Registry participants. 2020 Alzheimer’s Association International Conference; 2020: ALZ.

58. Saari T, Smith EE, Ismail Z. Network analysis of impulse dyscontrol in mild cognitive impairment and subjective cognitive decline. 2020.

### Tables

**Table 1**

| Demographic characteristics and cognitive test scores across groups. |
|---------------------------------------------------------------|
| Total Sample (n = 203) | Impulse Dyscontrol Symptoms Absent (n = 123) | Impulse Dyscontrol Symptoms Present (n = 80) | p-value |
|------------------------|-----------------------------------------------|---------------------------------------------|---------|
| **Age (M, SD)**        | 73.30 (6.67)                                  | 73.30 (6.66)                                | 0.59    |
| **Education (M, SD)**  | 16.10 (2.71)                                  | 16.10 (2.82)                                | 0.74    |
| **Female (n, %)**      | 92 (45.32)                                    | 64 (69.60)                                  | 0.021   |
| **Diagnostic Status (n, %)** |                                    |                                              | <.001   |
| NC                     | 70 (34.48)                                    | 58 (82.86)                                  |        |
| MCI                    | 95 (46.80)                                    | 52 (54.74)                                  |        |
| AD                     | 38 (18.72)                                    | 13 (34.21)                                  |        |
| **ADNI_MEM (M, SD)**   |                                              |                                              | 0.04    |
| NC                     | 1.09 (0.62)                                   | 1.03 (0.63)                                 |        |
| MCI                    | 0.22 (0.59)                                   | 0.21 (0.57)                                 |        |
| AD                     | -0.82 (0.48)                                  | -0.86 (0.47)                                |        |
| **ADNI_EF (M, SD)**    |                                              |                                              | 0.42    |
| NC                     | 0.87 (0.74)                                   | 0.83 (0.77)                                 |        |
| MCI                    | 0.17 (0.79)                                   | 0.15 (0.74)                                 |        |
| AD                     | -0.87 (0.93)                                  | -1.04 (1.05)                                |        |

Notes: MBI = mild behavioral impairment; M= mean; SD=standard deviation; NC= normal cognition; MCI = mild cognitive impairment; AD= AD-dementia; ADNI_MEM=memory composite score; ADNI_EF= executive functioning composite score. All group comparisons at significance level of $p<0.05$ (two-sided).
Table 2
Summary of linear mixed effect models for DTI parameters within regions of interest in association with impulse dyscontrol scores.

| Parameters                              | FA Estimate x10^-3 (SE) | p     | MD Estimate x10^-3 (SE) | p     | AxD Estimate x10^-3 (SE) | p     | RD Estimate x10^-3 (SE) | p     |
|-----------------------------------------|-------------------------|-------|-------------------------|-------|--------------------------|-------|-------------------------|-------|
| Intercept                               | 322(19.87)              | < .001| 0.600(0.052)            | < .001| 0.870(0.047)             | < .001| 0.556(0.060)            | < .001|
| Impulse dyscontrol present vs. absent   | 1.96(4.65)              | 0.674 | 0.037(0.015)            | 0.015 | 0.049(0.017)             | 0.003 | 0.041(0.016)            | 0.009 |
| Diagnosis (MCI vs. NC)                  | -4.37(3.23)             | 0.177 | 0.027(0.007)            | < .001| 0.030(0.007)             | < .001| 0.025(0.008)            | 0.002 |
| Diagnosis (AD vs. NC)                   | -15.5(4.31)             | < .001| 0.064(0.009)            | < .001| 0.059(0.010)             | < .001| 0.062(0.011)            | < .001|
| Age                                     | -1.28(0.206)            | < .001| 0.004(0.001)            | < .001| 0.003(0.004)             | < .001| 0.004(0.001)            | < .001|
| Sex (M vs. F)                           | 2.77(2.86)              | 0.557 | 0.006(0.006)            | 0.319 | 0.009(0.006)             | 0.158 | 0.008(0.007)            | 0.283 |
| Education                               | -0.306(0.522)           |       | 0.002(0.001)            | 0.058 | 0.002(0.001)             | 0.056 | 0.001(0.001)            | 0.605 |
| CGC                                     | 50.2(13.8)              | 0.011 | -0.122(0.049)           | 0.048 | -0.095(0.035)            | 0.037 | -0.143(0.059)           | 0.053 |
| CGH                                     | 26.6(13.8)              | 0.101 | -0.032(0.050)           | 0.543 | 0.0002(0.036)            | 0.996 | -0.050(0.060)           | 0.434 |
| FX                                      | -15.3(14.0)             | 0.316 | 1.31(0.054)             | < .001| 1.61(0.040)              | < .001| 1.17(0.063)             | < .001|
| IFO                                     | 84.9(13.8)              | < .001| -0.071(0.049)           | 0.200 | 0.026(0.036)             | 0.486 | -0.013(0.059)           | 0.076 |
| SFO                                     | 18.8(13.9)              | 0.225 | 0.062(0.052)            | 0.280 | 0.101(0.040)             | 0.044 | 0.038(0.062)            | 0.558 |
| UNC                                     | 0 (ref)                 |       | 0 (ref)                 |       | 0 (ref)                 |       | 0 (ref)                 |       |
| MBI*CGC                                 | -3.22(4.22)             | 0.445 | -0.033(0.014)           | 0.020 | -0.046(0.016)            | 0.004 | -0.034(0.015)           | 0.021 |
| MBI*CGH                                 | -2.56(4.29)             | 0.552 | -0.013(0.016)           | 0.405 | -0.018(0.018)            | 0.306 | -0.017(0.016)           | 0.301 |
| MBI*FX                                  | -19.0(5.63)             | < .001| 0.140(0.037)            | < .001| 0.116(0.035)             | < .001| 0.146(0.038)            | < .001|
| MBI*IFO                                 | -3.12(4.33)             | 0.472 | -0.032(0.015)           | 0.034 | -0.041(0.017)            | 0.014 | -0.030(0.015)           | 0.046 |
| MBI*SFO                                 | -15.3(5.31)             | 0.004 | 0.075(0.031)            | 0.015 | 0.075(0.033)             | 0.023 | 0.088(0.031)            | 0.004 |
| MBI*UNC                                 | 0 (ref)                 |       | 0 (ref)                 |       | 0 (ref)                 |       | 0 (ref)                 |       |

Note: FA = fractional anisotropy; MD = mean diffusivity; AxD = axial diffusivity; RD = radial diffusivity; SE = standard error; NC = normal cognition; MCI = mild cognitive impairment; AD = AD-dementia; M = male; F = female; CGC = cingulum, CGH = cingulum (hippocampus); FX = fornix; IFO = inferior fronto-occipital fasciculus; SFO = superior fronto-occipital fasciculus; UNC = uncinate fasciculus; MBI = presence of impulse dyscontrol symptoms. The significant interaction terms show the influence of impulse dyscontrol is structure dependent and the effect size can be calculated by adding the beta-coefficients for MBI impulse dyscontrol and MBI *structure interaction term (p < 0.01).
Table 3

Summary of linear mixed effect models for cortical thickness, surface area, and volume within regions of interest in association with impulse dyscontrol scores.

| Parameters                        | Cortical Thickness (mm) | Surface Area (mm²) | Volume (mm³) |
|-----------------------------------|-------------------------|--------------------|--------------|
|                                   | Estimate (SE)           | p                  | Estimate (SE) | p              | Estimate (SE) | p               |
| Intercept                         | 3.04(0.119)             | < .001             | 741(74.9)     | < .001        | 3466 (180)    | < .001          |
| Impulse dyscontrol present vs. absent | 0.027(0.030)           | 0.374              | -16.4(15.0)   | 0.265         | 1.59(47.9)    | 0.974           |
| Diagnosis (MCI vs. NC)            | -0.004(0.022)           | 0.858              | -4.50(11.8)   | 0.703         | -97.5(29.1)   | < .001          |
| Diagnosis (AD vs. NC)             | -0.104(0.030)           | 0.004              | -24.0(15.7)   | 0.126         | -319(38.7)    | < .001          |
| Age                               | -0.002(0.001)           | 0.221              | -1.07(0.748)  | 0.151         | -12.8(1.85)   | < .001          |
| Sex (M vs. F)                     | -0.023(0.020)           | 0.249              | 73.3(10.4)    | < .001        | -21.2(25.7)   | 0.410           |
| Education                         | -0.001(0.003)           | 0.706              | 0.201(1.90)   | 0.916         | -8.59(4.69)   | 0.067           |
| Caudal Anterior Cingulate         | -0.259(0.028)           | < .001             | -38.4(57.6)   | 0.542         | -432(129)     | 0.015           |
| Medial Orbitofrontal             | -0.537(0.021)           | < .001             | 1094(58.4)    | < .001        | 2483(130)     | < .001          |
| Parahippocampal Gyrus             | -0.156(0.028)           | 0.005              | -62.6(57.5)   | 0.337         | -244(127)     | 0.103           |
| Amygdala                          | -                       | -                  | -             | -             | -901(126)     | < .001          |
| Hippocampus                       | -                       | -                  | -             | -             | 1258(129)     | < .001          |
| Rostral Anterior Cingulate        | 0 (ref)                 | .                  | 0 (ref)       | .             | 0 (ref)       | .               |
| MBI* Caudal Anterior Cingulate    | 0.016(0.041)            | 0.705              | 8.10(14.9)    | 0.587         | 30.0(60.6)    | 0.621           |
| MBI* Medial Orbitofrontal        | 0.015(0.028)            | 0.585              | 31.0(21.4)    | 0.146         | 83.4(65.4)    | 0.203           |
| MBI* Parahippocampal              | -0.129(0.040)           | 0.002              | 37.1(13.6)    | 0.006         | 42.9(49.9)    | 0.389           |
| MBI* Amygdala                     | -                       | -                  | -             | -             | -7.66(44.0)   | 0.862           |
| MBI* Hippocampus                  | -                       | -                  | -             | -             | -127(62.1)    | 0.041           |
| MBI* Rostral Anterior Cingulate   | 0 (ref)                 | .                  | 0 (ref)       | .             | 0 (ref)       | .               |

Note: SE = standard error; NC = normal cognition; MCI = mild cognitive impairment; AD = AD-dementia; M = male; F = female; MBI = presence of MBI impulse dyscontrol symptoms. The significant interaction terms show the influence of impulse dyscontrol is structure dependent and the effect size can be calculated by adding the beta-coefficients for MBI impulse dyscontrol and MBI *structure interaction term (p <0.01).