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RESEARCH ARTICLE

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Neural correlates of the impulse dyscontrol domain of mild behavioral impairment

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Abstract

Objectives: 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 objective of this work was to investigate if regional micro- and macro-structural brain properties were associated with impulse dyscontrol symptoms in older adults with normal cognition, mild cognitive impairment, and Alzheimer's disease (AD).

Methods: Clinical, neuropsychiatric, and T1-weighted and diffusion-tensor magnetic resonance imaging (DTI) data from 80 individuals with and 123 individuals without impulse dyscontrol were obtained from the AD Neuroimaging Initiative. Linear mixed effect 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 (FA), and greater mean, axial, and radial diffusivity in the fornix; (2) lesser FA and greater radial diffusivity in the superior fronto-occipital fasciculus; (3) greater axial diffusivity in the cingulum; (4) greater axial and radial diffusivity in the uncinate fasciculus; (5) gray matter atrophy, specifically, lower cortical thickness 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

Abbreviations: AD, Alzheimer's disease; AxD, axial diffusivity; DTI, diffusion tensor imaging; FA, fractional anisotropy; ICV, intracranial volume; MBI, mild behavioral impairment; MBI-C, Mild Behavioral Impairment Checklist; MD, mean diffusivity; MRI, magnetic resonance imaging; NC, Normal Cognition, NPI Neuropsychiatric Inventory; NPI-Q, Neuropsychiatric Inventory Questionnaire; RD, radial diffusivity; SCD, subjective cognitive decline.

Data used in preparation of this article was obtained from the Alzheimer's disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wpcontent/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

is controlled for, and possibly in advance of dementia. Our findings support the growing evidence for impulse dyscontrol symptoms as an early manifestation of AD.

KEYWORDS
aggression, agitation, Alzheimer's disease, geriatric psychiatry, impulse dyscontrol, mild behavioral impairment

Key points

- Impulse dyscontrol is a frequently endorsed domain of mild behavioral impairment (MBI), which is an at-risk state for incident cognitive decline and dementia
- Impulse dyscontrol is common in this sample of dementia and pre-dementia participants at a frequency of 17% in normal cognition, 43% in mild cognitive impairment, and 66% in Alzheimer's disease
- Impulse dyscontrol is associated with loss of white matter integrity in the cingulum, fornix, superior fronto-occipital fasciculus, and uncinate fasciculus, as well as parahippocampal gyrus atrophy
- This MBI domain may serve as a potential treatment target, even in advance of dementia

1 | INTRODUCTION

Mild behavioral impairment (MBI) is a validated neurobehavioral syndrome that describes the later life emergence of persistent neuropsychiatric symptoms (NPSs) as an at-risk state for incident cognitive decline and dementia.[1] These NPS have been suggested to be an index manifestation of dementia.[2–10] MBI captures preclinical and prodromal disease symptoms and is associated with known dementia biomarkers including amyloid-β,[11] tau,[12,13] neurofilament light,[14] brain atrophy,[15,16] and Alzheimer's disease (AD) risk genes.[2,17] Impulse dyscontrol is one of the MBI domains and includes behavioral symptoms of agitation/aggression, irritability, and aberrant motor behavior amongst others.

The clinical manifestations of MBI impulse dyscontrol including agitation, aggression, and irritability are common in dementia and are associated with caregiver stress and poorer outcomes.[18,19] In a population-based study of older adults ranging from normal cognition (NC) to mild cognitive impairment (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.[20] A concurrent study in a cognitive neurology clinic sample assessed MBI domains in those with subjective cognitive decline (SCD) and MCI[21] and reported the frequency of impulse dyscontrol in both groups being greater than 50%.[21] 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.[22] 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).[23] 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, the right posterior cingulate, and left hippocampus.[24] Aberrant motor behavior symptoms have been associated with atrophy in the right basal nuclei and frontal cortex.[25] Furthermore, reduced fractional anisotropy (FA) in the anterior cingulum[26] 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 (Figure 1[27]). Volumetric analysis included the hippocampus, caudal and rostral anterior cingulate, amygdala, parahippocampal gyrus, and the medial orbitofrontal cortex (Figure 2[28]). We hypothesized that symptoms of impulse

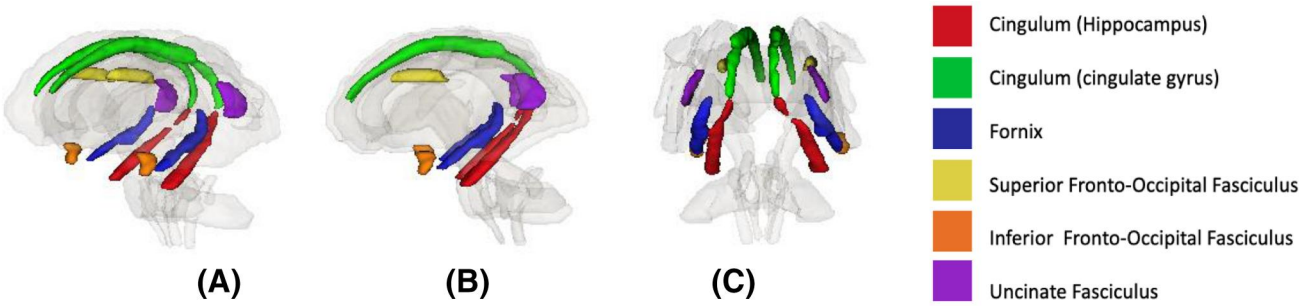

FIGURE 1 Visual representation of diffusion tensor imaging regions analyzed in association with impulse dyscontrol symptoms (A) profile view, (B) sagittal view, (C) coronal view [Colour figure can be viewed at wileyonlinelibrary.com]

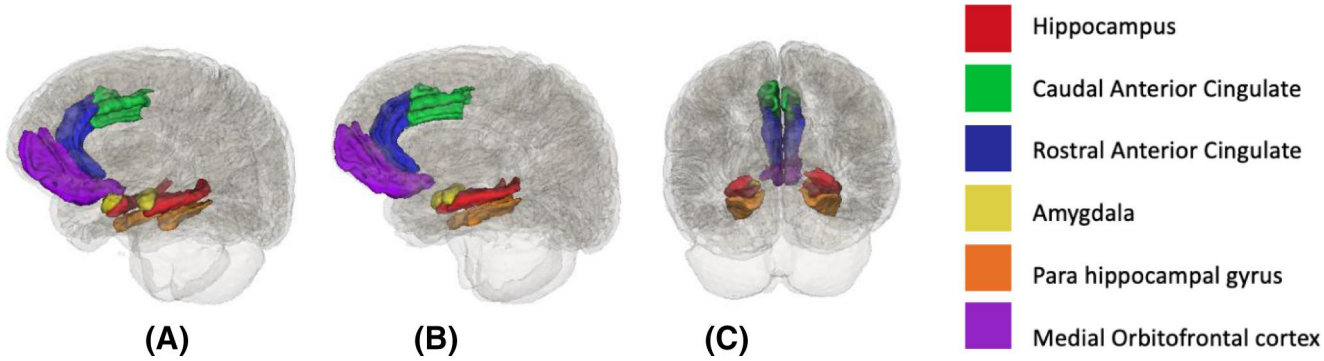

FIGURE 2 Visual representation of volumetric regions analyzed in association with impulse dyscontrol symptoms (A) profile view, (B) sagittal view, (C) coronal view [Colour figure can be viewed at wileyonlinelibrary.com]

dyscontrol would be associated with decreased white matter integrity in the cingulum and with atrophy patterns in fronto-limbic structures.

2 | METHODS

2.1 | Alzheimer's Disease Neuroimaging Initiative

Data was extracted from the Alzheimer's Disease Neuroimaging Initiative (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 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/).

2.2 | 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)[29] scores were also extracted. All datasets were downloaded before January 25, 2019.

To evaluate both white and gray 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.

2.3 | Participants

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

2.4 | Measures

Clinical variables. Age, sex, education, baseline diagnostic status, psychotropic medication use, 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. Psychotropic medications included

antidepressants, benzodiazepines, and z-drugs. 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.[30]

Neuropsychiatric variables. Since ADNI uses the NPI-Q to capture NPS, these data were transformed into MBI domains using a published algorithm.[21] 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. University of California Los Angeles (UCLA) core lab processed the DTI datasets, computing average 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.[31] 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.[32] Additional information about the UCLA DTI methods are described in more detail elsewhere.[33] 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 labeled by the 2010 Desikan-Killany and 2009 Destrieux atlas. Additional information on UCSF FreeSurfer methods is also available elsewhere.[34] In order to control for intracranial volume (ICV) differences, we computed 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.[35]

Figures 1 and 2 show the a priori selected brain regions in association with symptoms of impulse dyscontrol. The regions were labeled on the JHU atlas Desikan-Killany atlas respectively. For details on the atlas see: https://neurovault.org/images/1401/; https://dataverse.harvard.edu/dataset.xhtml?persistentId=doi:10.7910/DVN/XCCE9Q).

2.5 | Statistical analysis

Sample characteristics are reported using means, standard deviations, and frequency distributions. Wilcoxon-Mann-Whitney tests were used to investigate univariate associations between patient characteristics and impulse dyscontrol symptoms. Linear mixed effect (LME) models were used to assess if impulse dyscontrol was associated with DTI parameters. White matter regions included in this analysis were the cingulum, cingulum (hippocampus), fornix, superior fronto-occipital fasciculus, inferior fronto-occipital fasciculus, and the uncinate fasciculus. Fixed effects included impulse dyscontrol, regions, impulse dyscontrol by regions, disease status, age, sex, psychotropic drug use, and education. Random effects included the hemisphere of the structure (left/right) and subjects. In the LME models, our primary predictors of interest were impulse dyscontrol, white matter regions, and impulse dyscontrol by regions. Similar analyses were conducted to test if impulse dyscontrol presence was related to volumetric measures, where regions included the hippocampus, caudal and rostral anterior cingulate, amygdala, parahippocampal gyrus, and the medial orbitofrontal cortex. Simple effect of MBI on the ROIs after LME modeling are reported. 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.

3 | 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 impulse dyscontrol groups, there were no significant differences with the exception of diagnostic status ($p < 0.01$), wherein worse cognitive diagnostic status was associated with the presence of impulse dyscontrol. Notably, there were more males with impulse dyscontrol symptoms than females. Additionally, there were more individuals with impulse dyscontrol symptoms that were using psychotropic medications.

3.1 | Linear mixed effect models

DTI variables: After controlling for age, sex, education, disease status, and psychotropic drug use, participants with impulse dyscontrol had lower FA in the fornix ($\beta FA = -0.02$ $SE = 5.1 \times 10^{-3}$ $p = 0.001$) and lower FA in superior fronto-occipital fasciculus ($\beta FA = -0.01$; $SE = 4.7 \times 10^{-3}$; $p = 0.007$) compared to those without. Significantly higher MD, AxD, and RD values were observed in the fornix ($\beta MD = 0.18 \times 10^{-3}$ $SE = 0.04 \times 10^{-3}$ $p < 0.0001$; $\beta AxD = 0.16 \times 10^{-3}$ $SE = 0.03 \times 10^{-3}$ $p < 0.0001$; $\beta RD = 0.19 \times 10^{-3}$ $SE = 0.04 \times 10^{-3}$ $p < 0.0001$, respectively), and superior fronto-occipital fasciculus ($\beta MD = 0.11 \times$ 10-3 $SE = 0.03 \times 10^{-3}$ $p = 0003$; $\beta AxD = 0.12 \times 10^{-3}$ $SE = 0.03 \times 10^{-3}$ $p < 0.0001$; $\beta RD = 0.13 \times 10^{-3}$ $SE = 0.03 \times 10^{-3}$ $p < 0.0001$, respectively) for patients with impulse dyscontrol. See Table 2 for details.

Volumetric variables: After controlling for age, sex, education, disease status, and psychotropic drug use, impulse dyscontrol symptoms were associated with participants having smaller cortical thickness in the parahippocampal gyrus ($\beta = -0.1$ $SE = 0.04$ $p = 0.008$). None of the other a priori selected regions were associated with impulse dyscontrol. See Table 3 for details.

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)	73.30 (6.75)	0.59
Education (*M*, SD)	16.10 (2.71)	16.10 (2.82)	16.00 (2.56)	0.74
Female (n, %)	92 (45.32)	64 (69.60)	28 (30.40)	0.021
Diagnostic status (*n*, %)				
NC	70 (34.48)	58 (82.86)	12 (17.14)	<001
MCI	95 (46.80)	52 (54.74)	43 (45.26)	
AD	38 (18.72)	13 (34.21)	25 (65.79)	
ADNI_MEM (*M*, SD)				
NC	1.09 (0.62)	1.03 (0.63)	1.39 (0.45)	0.04
MCI	0.22 (0.59)	0.21 (0.57)	0.24 (0.62)	0.97
AD	−0.82 (0.48)	−0.86 (0.47)	−0.80 (0.49)	0.63
ADNI_EF (*M*, SD)				
NC	0.87 (0.74)	0.83 (0.77)	1.04 (0.58)	0.42
MCI	0.17 (0.79)	0.15 (0.74)	0.18 (0.86)	0.82
AD	−0.87 (0.93)	−1.04 (1.05)	−0.79 (0.87)	0.44
Psychotropic medication use (n, %)	52 (25.62)	25 (20.33)	27 (33.75)	0.03

Abbreviations: AD, AD-dementia; ADNI_EF, executive functioning composite score; ADNI_MEM, memory composite score; *M*, mean; MBI, mild behavioral impairment; MCI, mild cognitive impairment; NC, normal cognition; SD, standard deviation.

TABLE 2 Simple effect of MBI on regions of interest for DTI parameters from linear mixed-effects regression analysis controlling for age, sex, education, psychotropic medication use, and disease diagnosis (MCI, AD, or NC)

	FA		MD		AxD		RD	
	Estimate (SE)$\times 10^{-3}$	*p*	Estimate (SE) $\times$ 10^{-3}	*p*	Estimate (SE) $\times$ 10^{-3}	*p*	Estimate (SE) $\times 10^{-3}$	*p*
CGC MBI + versus MBI -	−0.75 (3.45)	0.83	<0.01 (0.01)	0.887	<0.01 (0.01)	0.854	0.01 (0.02)	0.609
CGH MBI + versus MBI -	−0.09 (3.54)	0.98	0.02 (0.02)	0.178	0.03 (0.02)	0.067	0.03 (0.02)	0.153
FX MBI + versus MBI -	−16.48 (5.08)	**0.001**	0.18 (0.04)	**<0.0001**	0.16 (0.03)	**<0.0001**	0.19 (0.04)	**<0.0001**
IFO MBI + versus MBI -	−0.64 (3.59)	0.86	<0.01 (0.02)	0.794	0.01 (0.02)	0.609	0.01 (0.02)	0.480
SFO MBI + versus MBI -	−12.88 (4.73)	**0.007**	0.11 (0.03)	**0.0003**	0.12 (0.03)	**<0.0001**	0.13 (0.03)	**<0.0001**
UNC MBI + versus MBI -	2.48 (4.66)	0.60	0.04 (0.02)	0.068	0.05 (0.02)	0.018	0.04 (0.02)	0.043

Abbreviations: AD, AD-dementia; AxD, axial diffusivity; CGC, cingulum; CGH, cingulum (hippocampus); F, female; FA, fractional anisotropy; FX, fornix; IFO, inferior fronto-occipital fasciculus; M, male; MCI, mild cognitive impairment; MD, mean diffusivity; MBI+, presence of impulse dyscontrol symptoms; NC, normal cognition; RD, radial diffusivity; SFO, superior fronto-occipital fasciculus; SE, standard error; UNC, uncinate fasciculus.

Additional results from the modeling are available in Table S1 to S4.

4 | DISCUSSION

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

In interpreting DTI parameters, reduced FA and increased MD, AxD, and RD are associated with impaired white matter integrity as an outcome of several factors including cell death and altered myelination, amongst others.[31,36] In this study, as shown by the altered DTI parameters, lower white matter integrity in tracts including the

TABLE 3 Simple effect of MBI on regions of interest for cortical thickness, surface area, and volume from linear mixed-effects regression analysis controlling for age, sex, education, psychotropic medication use, and disease diagnosis (MCI, AD, or NC)

	Cortical Thickness (mm)		Surface Area (mm^2)		Volume (mm^3)	
	Estimate (SE)	*p*	Estimate (SE)	*p*	Estimate (SE)	*p*
Caudal anterior Cingulate MBI + versus MBI−	0.05 (0.04)	0.206	−6.97 (13.90)	0.616	30.92 (50.78)	0.543
Medial Orbitofrontal MBI + versus MBI−	0.05 (0.02)	0.031	15.96 (20.66)	0.440	84.27 (56.39)	0.135
Parahippocampal gyrus MBI + versus MBI−	−0.10 (0.04)	**0.008**	21.98 (12.42)	0.077	43.86 (37.28)	0.240
Amygdala MBI + versus MBI−	-		-		−6.74 (28.97)	0.816
Hippocampus MBI + versus MBI−	-		-		−125.81 (52.53)	0.017
Rostral anterior cingulate MBI + versus MBI−	0.03 (0.03)	0.309	−15.08 (14.74)	0.306	0.91 (47.97)	0.985

Abbreviations: MBI+, presence of MBI impulse dyscontrol symptoms; SE, standard error.

cingulum, fornix, superior fronto-occipital fasciculus, and uncinate fasciculus was associated with impulse dyscontrol. To our knowledge, Tighe et al.[26] 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.[37] Furthermore, a recent study identified altered DTI parameters in the cingulum in early-stage AD.[38] 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.[39] 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 NPSs in predementia 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.[40,41] A reduced fornix FA is one of the earliest MRI abnormalities observed in individuals at risk of AD[42] and has been explored as a treatment target using deep brain stimulation for mild AD.[43] 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.[44] Observing fornix impairment in association with impulse dyscontrol highlights NPSs 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 gray matter atrophy in the parahippocampal gyrus provide evidence that the well-established atrophy patterns in AD[45,46] 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 gray matter atrophy, in line with past literature, which has determined that microstructural white matter changes precede gray matter atrophy.[47] 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.[48] 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, uncinate fasciculus, 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[48] providing evidence of brain changes similar to core AD pathology, which can precede cognitive symptoms or dementia.

Beyond differences in neural correlates, we also observed group differences in the sex of the participants in our study. More men had symptoms of impulse dyscontrol present. There is some evidence that suggests males have greater impulse control behaviors,[49] however, other studies have identified NPS such as, disinhibition, verbal aggression, and irritability to be more common in females.[50–52] These differences across studies could be an outcome of variations based on recruitment strategy, study design, sample analyzed, diagnostic criteria, and the instruments used to measure NPS. The higher proportion of males with impulse dyscontrol symptoms adds to the evidence base. However, further research is required explore sex differences in association with NPS.

There are several strengths of this study. For example, this is one of the first studies 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[21,53] in comparison to the use of the MBI checklist (MBI-C), which is the validated a priori case ascertainment instrument developed for MBI.[54] The MBI-C has demonstrated ability to serve as a proxy marker for older adults with subtle cognitive changes or early neurodegenerative disease.[3,55] Thus, diagnostic sensitivity of this approach may also be a limitation, as the whole breadth of MBI impulse dyscontrol, validated by network meta-analysis[56] 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)[10] 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.

5 | 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 behavior. Understanding the neuropsychiatric manifestations of the neurodegenerative disease can help clinicians in predicting the progression of the disease.

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CONFLICT OF INTEREST

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.

ETHICS STATEMENT

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

AUTHORS' CONTRIBUTIONS

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

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available through the open access ADNI database.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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