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SHORT REPORT

SSRIs reduce plasma tau and restore dorsal raphe metabolism in Alzheimer's disease

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Data used in preparation of this article were 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/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

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Abstract

INTRODUCTION: Tau pathology impacts neurodegeneration and cognitive decline in Alzheimer's disease (AD), with the dorsal raphe nucleus (DRN) being among the brain regions showing the earliest tau pathology. As a serotonergic hub, DRN activity is altered by selective serotonin reuptake inhibitors (SSRIs), which also have variable effects on cognitive decline and pathology in AD.

METHODS: We examined $N = 191$ subjects with baseline ^{18}F-fluorodeoxyglucose positron emission tomography and plasma biomarker data to study the effects of SSRIs on tau pathology, cognitive decline, and DRN metabolism.

RESULTS: Plasma phosphorylated tau 181 (p-tau181) was lower with SSRI use. The effect of SSRIs on cognition varied by cognitive assessment. The DRN was hypometabolic in AD patients relative to healthy controls; however, SSRI use restored the metabolic activity of this region in AD patients.

DISCUSSION: Long-term SSRI use may reduce the pathological presentation of AD but has variable effects on cognitive performance.

KEYWORDS
cognitive decline, dorsal raphe nucleus, ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) metabolic impairment, neurodegeneration, selective serotonin reuptake inhibitor, tau

Highlights

- Tau pathology spreads throughout the brain during AD pathogenesis.

- The DRN is among the first regions to develop tau pathology during this process.
- SSRI use restores the metabolic activity of the DRN and reduces plasma p-tau181.

1 | INTRODUCTION

Evidence from *post mortem* histology and neuroimaging studies suggests a link between serotonin dysfunction and Alzheimer's disease (AD). Impaired serotonergic regulation has been associated with the aggregation of pathological proteins, such as tau and amyloid beta, throughout the brain, including the dorsal raphe nucleus (DRN), the brain's primary serotonin source.[1–4] Furthermore, major depressive disorder, closely linked to serotonin dysfunction, ranks among the most common comorbidities in AD.[5–8] Given the interplay between the serotonergic system and AD pathogenesis, modulating serotonin regulation could impact AD pathology. However, treatment with selective serotonin reuptake inhibitors (SSRIs) has demonstrated variable effects on cognition and pathology in AD,[9–12] underscoring the need for further nuanced investigation of this relationship.

AD is also marked by substantial impairments in brain energy metabolism, particularly glucose utilization.[13,14] ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) allows for the assessment of glucose metabolism in living patients and has identified metabolic dysfunction in several key brain regions in AD.[15,16] Under physiological conditions, SSRIs increase DRN metabolic activity,[17,18] which correlates with serotonergic activity.[19] However, the role of SSRIs in modulating glucose metabolism at the DRN remains underexplored.

While serotonin depletion and metabolic imbalances are well documented in AD, the mechanisms of how these affect tau pathologies remain largely unknown. It is unclear whether long-term SSRI use could mitigate metabolic impairments. The Alzheimer's Disease Neuroimaging Initiative (ADNI) has advanced our understanding of AD through large-scale neuroimaging data, yet limited information exists on the relationship between SSRI use and metabolic states in the progression of tau pathology, particularly in the DRN, an early site of tau deposits in AD.[2] Using ADNI neuroimaging and clinical data, this report aims to address these gaps and explore how SSRIs influence tau pathology and DRN activity in AD.

2 | METHODS

2.1 | Subjects

Data used in the preparation of this manuscript were obtained from the ADNI database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public–private partnership led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment could be combined to measure the progression of MCI and early AD. For up-to-date information, see http://www.adni-info.org.

Medical records were obtained for subjects from the ADNI-1, ADNI-GO, ADNI-2, and ADNI-3 phases, and participants were screened for the following criteria: (1) information about SSRI use upon initial screening, (2) baseline FDG-PET scan at a voxel size of 2.0 mm, and (3) T1-weighted MRI (magnetization-prepared rapid gradient echo sequence) scan. Only scans taken within 1 year of each other were considered for these analyses. When available, subjects with information about SSRI use but no FDG-PET scans were included in cognitive function analysis. All data were screened for quality assurance prior to analysis by independent reviewers.

Male and female subjects were classified as cognitively normal (CN) or AD based on physician assessments during initial screening and ADNI diagnostic criteria. CN subjects required a Mini-Mental State Examination (MMSE) score of 24 to 30 (inclusive), a Clinical Dementia Rating (CDR) score of 0, and no signs of dementia or mild cognitive impairment (MCI). AD subjects required MMSE scores of 20 to 26 (inclusive), a CDR score of 0.5 or 1.0, and fulfillment of National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association criteria for probable AD. Cognitive testing data, including MMSE, Montreal Cognitive Assessment (MoCA), and CDR scores, were collected at trial intake and a 24-month follow-up when available. Details on ADNI diagnostic criteria are accessible on the ADNI website (https://adni.loni.usc.edu/methods/documents/). Subjects were further categorized by SSRI use. SSRI type, dosage, frequency, and duration were not considered during subsequent analyses to maintain adequate group sizes for statistical analysis. Participants in the no-SSRI group were excluded if they had ever used SSRIs or other antidepressants. Subjects with MCI but no signs of dementia were excluded due to insufficient power in MCI SSRI groups. Subject demographics for each experiment are summarized in Table 1.

Specific details about the imaging protocols employed across ADNI sites can be found on the ADNI website (http://adni.loni.usc.edu/methods/). All images were retrieved from the ADNI database in their most preprocessed format. Neuroimaging data were downloaded from the ADNI repository on August 9, 2024. Ethical approval was obtained by the ADNI investigators at each participating ADNI site, and all participants provided written informed consent. All analyses of human neuroimaging data were conducted with the approval of the University of Calgary Conjoint Health Research Ethics Board (REB22-0776).

2.2 | Plasma phosphorylated tau assessment

Plasma phosphorylated tau 181 (p-tau181) concentration was obtained from published datasets using previously described methods.[20,21] Briefly, the authors of this dataset collected, processed, stored, and analyzed blood samples collected upon intake into

RESEARCH IN CONTEXT

1. **Systematic review**: The authors extensively reviewed literature (eg, PubMed), meeting abstracts, and presentations. The available literature revealed a lack of information on the impact of SSRI on the metabolic activity of the DRN in AD. With access to a large neuroimaging database and clinical records, this question can be addressed. Relevant citations are appropriately cited.
2. **Interpretation**: SSRI use decreased systemic p-tau concentration and restored metabolic activity of the DRN in AD. Results from cognitive batteries were variable across tests in individuals with prior SSRI use. Together, SSRI use may reduce the pathological presentation of AD but has variable effects on cognitive performance.
3. **Future directions**: With the current dataset, we are unable to discern individuals who began SSRI treatment prior to developing AD symptomology. Future studies could examine the direct impact of the timing and duration of SSRI use relative to disease stage during AD pathogenesis.

the trial, as previously described.[22] Plasma p-tau181 concentration was then measured using a Simoa HD-X Automated Immunoassay Analyzer (Quanterix, Billerica, MA, USA), and quality control samples were used to assess within-run coefficients of variation, between-run coefficients of variation, and internal calibration.[21] The samples used in the present study all surpassed the lower limit of quantification determined by the authors of the original dataset (1.0 pg/mL).

2.3 | PET analyses

Preprocessing and statistical parametric mapping were performed on these scans using SPM12 software (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) and previously described pipelines.[23] Briefly, all scans were imported to SPM12, where they were co-registered to skull-stripped structural MRI scans. These co-registered scans were then spatially normalized to the standard Montreal Neurological Institute 152 (MNI) reference space. From here, voxel-wise *t*-test comparisons allowed for the generation of *t*-score maps for each set of statistical comparisons. These *t*-score maps were used to assess local differences at a DRN seed (15 mm radius sphere, MNI coordinates: $x = 0$, $y = -30$, $z = -8$). The coordinates of the DRN seed were selected based on expected local maxima for activity in this region.[24]

2.4 | Statistics and data visualization

All statistical parametric mapping analyses were performed in SPM12 using MATLAB (MathWorks, R2020a). For these comparisons, *t*-score maps were thresholded based on a p value of $<.05$.

TABLE 1 Subject demographics by experiment. Data presented as mean ± SD.

	MALE		FEMALE					
	CN		AD		CN		AD	
	No SSRI	SSRI	No SSRI	SSRI	No SSRI	SSRI	No SSRI	SSRI
Plasma p-tau181 analyses								
N	20	5	16	16	22	8	18	15
Age (years)	74.52 ± 4.20	75.98 ± 6.27	75.20 ± 7.17	75.20 ± 7.17	74.75 ± 5.84	72.44 ± 5.63	74.44 ± 5.15	73.39 ± 7.07
Education (years)	17.50 ± 2.24	16.60 ± 3.51	16.94 ± 2.65	16.56 ± 2.28	15.86 ± 2.36	17.38 ± 1.60	15.50 ± 2.60	15.00 ± 2.93
GDS	0.70 ± 1.17	1.20 ± 1.10	2.00 ± 1.83	2.00 ± 1.27	0.36 ± 0.80	1.63 ± 1.19	0.89 ± 1.02	2.20 ± 2.11
Cognitive testing								
N			30	16			30	15
Age (years)			75.12 ± 5.51	75.20 ± 7.17			75.65 ± 4.97	73.39 ± 7.07
Education (years)			16.80 ± 2.64	16.56 ± 2.28			15.03 ± 2.47	15.00 ± 2.93
GDS			2.00 ± 1.89	2.00 ± 1.27			0.93 ± 1.08	2.20 ± 2.11
FDG-PET analyses								
N	13	12	30	14	16	27	28	13
Age (years)	74.96 ± 5.21	76.03 ± 6.55	75.12 ± 5.51	74.06 ± 6.86	75.90 ± 5.30	73.11 ± 4.69	75.83 ± 5.07	72.98 ± 7.46
Education (years)	16.62 ± 2.22	17.00 ± 2.56	16.80 ± 2.64	16.50 ± 2.44	15.13 ± 2.09	15.77 ± 2.36	14.89 ± 2.36	15.00 ± 3.14
GDS	0.77 ± 1.17	1.08 ± 1.51	2.00 ± 1.89	2.29 ± 1.07	0.38 ± 0.62	1.44 ± 1.34	0.86 ± 1.04	2.15 ± 2.03

Abbreviations: AD, Alzheimer's disease; CN, cognitively normal; FDG-PET, ^{18}F- fluorodeoxyglucose positron emission tomography; GDS, geriatric depression scale; SSRI, selective serotonin reuptake inhibitor.

All other statistical analyses were performed in Prism (GraphPad Software, Version 10.2.3). Plasma p-tau181 concentration was analyzed using two-way ANOVA.

Hypothesis testing was complemented by estimation statistics using https://estimationstats.com. For these estimation stats, the Cohen's *d* effect size was calculated using a bootstrap sampling distribution with 5000 resamples and a 95% confidence interval (bias-corrected and accelerated).

All plots were generated in either Prism or MATLAB, and all figures were compiled in Adobe Photoshop.

3 | RESULTS

3.1 | SSRI treatment decreased plasma p-tau181 in AD

In plasma, the concentration of tau protein phosphorylated at threonine 181 (p-tau181) has been associated with AD disease severity and pathological development, with elevated plasma p-tau181 being indicative of elevated tau pathology in the brain.[25] The concentration of p-tau181 recorded in plasma was compared by sex and SSRI use. There were no differences in plasma p-tau181 levels in CN subjects, regardless of sex or SSRI use in this cross-sectional analysis (Figure 1A). In AD, while no significant effect of sex was observed, individuals using SSRIs had a lower concentration of plasma p-tau181 (Figure 1B; two-way ANOVA; $F_{61} = 4.099$; $p = 0.0473$).

3.2 | Effect of SSRI treatment on cognitive function in AD varied by means of cognitive assessment

Cognitive performance in AD patients typically declines over time, with measurable changes occurring within as little as 2 years.[26] In this study, cognitive decline was assessed by comparing cognitive test scores at trial intake and a 2-year follow-up. MMSE scores decreased over time in the AD groups (Figure 1C; three-factor ANOVA; $F_{174} = 26.24$; $p < 0.0001$); however, the rate of decline did not differ between those taking SSRIs and those not taking them. MoCA scores were significantly higher in individuals using SSRIs, indicating improved performance compared to those not taking SSRIs (Figure 1D; three-factor ANOVA; $F_{164} = 3.97$; $p = 0.0480$).

Interestingly, MMSE and MoCA scores were highly correlated with one another in participants who were not being treated with SSRIs during intake (males: Pearson's $r = 0.458$; $p = 0.02118$; females: Pearson's $r = 0.775$; $p < 0.00001$) and follow-up (males: Pearson's $r = 0.766$; $p = 0.00001$; females: Pearson's $r = 0.756$; $p = 0.00001$) tests. However, with SSRI treatment, MMSE and MoCA scores were no longer correlated during either the intake (males: Pearson's $r = -0.113$; $p = 0.68781$; females: Pearson's $r = 0.221$; $p = 0.44869$) or 24-month follow-up (males: Pearson's $r = 0.201$; $p = 0.47154$; females: Pearson's $r = 0.454$; $p = 0.10316$) sessions.

When considering dementia presentation, the CDR sum of boxes analysis revealed significant main effects of both SSRI use (three-factor ANOVA; $F_{172} = 5.650$; $p = 0.0186$) and time (three-factor ANOVA; $F_{172} = 31.74$; $p < 0.0001$). These results suggest increased dementia symptomology in AD subjects with both time and SSRI use (Figure 1E).

3.3 | SSRI treatment restores metabolic activity of DRN in AD

SSRI use significantly affects the activity of the DRN, a serotonergic hub and an early site of tau pathology.[2,3] To investigate this relationship, we assessed DRN metabolic activity in untreated or SSRI-treated CN and AD subjects using FDG-PET. Statistical parametric mapping was applied to these scans to identify clusters of altered metabolic activity within a spherical region of interest (ROI) in the DRN. Activity peaks identified through SPM were manually cross-referenced by independent reviewers to ensure analysis was confined to the DRN. Within this ROI, peaks of hypometabolic activity were observed in both male and female AD no-SSRI groups relative to CN no-SSRI groups (Figure 2A and Table 2).

With SSRI treatment, the hypoactivity observed in the DRN of AD patients was reversed, with peaks of hypermetabolic activity being observed within this ROI in male and female AD SSRI groups relative to AD no-SSRI groups (Figure 2B and Table 2). Interestingly, SSRI use did not drive any hypermetabolic peaks in the FDG-PET scans of CN individuals relative to no-SSRI control groups (Figure 2C).

4 | DISCUSSION

The cerebral accumulation of intraneuronal neurofibrillary tau tangles in AD is highly correlated with the degree of cognitive impairment observed in patients.[27,28] In the current study, plasma p-tau181 – a peripheral biomarker – was decreased with SSRI use. While a direct analysis of regional tau accumulation would be preferable, the limited availability of tau (^{18}F-flortaucipir)-PET scans in AD patients with a history of SSRI use in the ADNI database prevented such analyses. However, numerous studies have demonstrated that plasma p-tau181 concentration correlates with tau accumulation in the brain[29,30] and that this metric performs equally as well as tau-PET in identifying AD pathology.[31] While these results suggest a link between SSRI use and brain tau pathology, peripheral biomarkers such as plasma p-tau181 do not indicate the brain regions involved. Additionally, although animal studies show SSRIs can reduce tau hyperphosphorylation,[32,33] the cross-sectional design of this study cannot determine whether SSRIs directly lower plasma p-tau181 or if underlying conditions prompting SSRI use influence tau pathology susceptibility.

The relationship between SSRI use and cognitive decline in AD is complex, with studies reporting SSRIs as protective,[34,35] having no effect,[36] or being detrimental.[12] This study examined SSRI impact on cognitive decline across three cognitive tests and found differing conclusions, despite all tests sampling the same cohort of participants during the same session. Generally, MMSE and MoCA scores correlate,[37–39] supported by significant correlations in participants

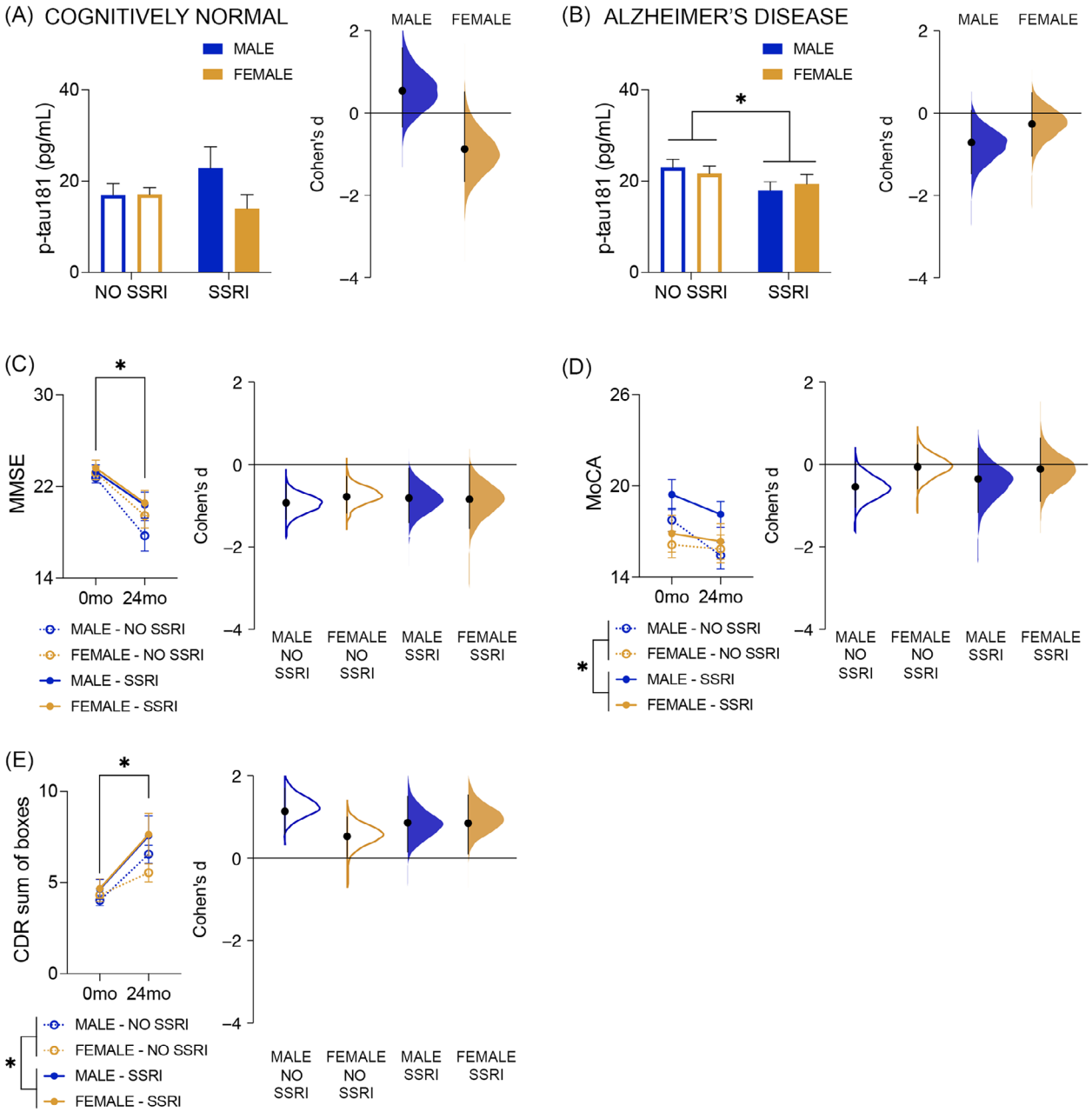

FIGURE 1 Impact of SSRI use on plasma p-tau181 concentration and cognitive function in AD. (A) In CN subjects, plasma p-tau181 concentration was comparable between sexes and did not differ with SSRI use ($N = 20$ no-SSRI males, 22 no-SSRI females, 5 SSRI males, 8 no-SSRI females). (B) In AD, SSRI use was associated with lower concentration of plasma p-tau181 ($N = 16$ no-SSRI males, 18 no-SSRI females, 16 SSRI males, 15 no-SSRI females). Cumming estimation plots show Cohen's *d* effect size of difference in plasma p-tau181 concentration with SSRI use. Under these same conditions, (C) MMSE scores decreased over a 2-year period, regardless of SSRI use ($N = 30$ no-SSRI males, 30 no-SSRI females, 16 SSRI males, 15 SSRI females). (D) MoCA scores did not decrease over a 2-year period but were higher with SSRI use ($N = 27$ no SSRI males, 27 no-SSRI females, 15 SSRI males, 14 SSRI females). (E) CDR sum of boxes scores increased with both time and SSRI use ($N = 30$ no-SSRI males, 29 no-SSRI females, 16 SSRI males, 15 SSRI females). Cumming estimation plots show Cohen's *d* effect size of difference in cognitive scores between testing upon intake and retesting 24 months later. Data are presented as mean ± SEM. AD, Alzheimer's disease; CDR, Clinical Dementia Rating; CN, cognitively normal; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; SSRI, selective serotonin reuptake inhibitor.

without SSRI use. However, limited data exist on how these tests correlate in individuals using SSRIs, as most studies examined only one test. Our findings suggest SSRI use alters the correlation between MMSE and MoCA, potentially explaining the variability in SSRIs and cognitive function in AD.

The altered relationship between MMSE and MoCA scores with SSRI use is intriguing and warrants further investigation, even beyond the scope of AD. Although both tests assess multiple cognitive domains with some overlap, such as language and delayed recognition memory, they differ in their evaluation of other cognitive and memory aspects.

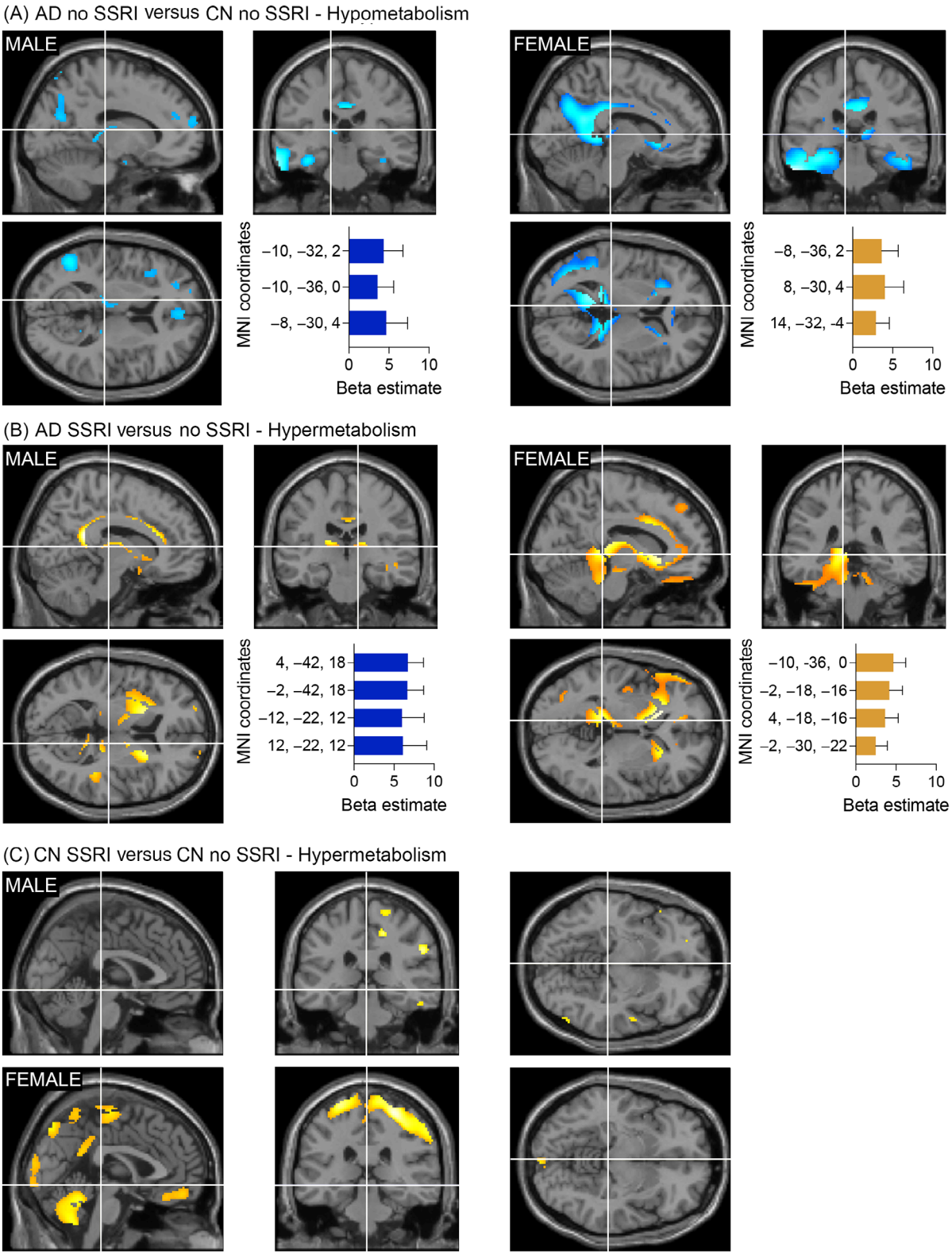

FIGURE 2 SSRI use restores AD-induced hypometabolism of DRN. (A) Statistical parametric mapping highlights peaks of hypometabolism in male (left) and female (right) AD subjects, relative to FDG-PET activity in CN subjects without prior SSRI use ($N = 13$ CN no-SSRI males, 30 AD no-SSRI males, 16 CN no-SSRI females, 28 AD no-SSRI females). Beta estimates demonstrate the magnitude of hypometabolic peaks within a DRN ROI. (B) Statistical parametric mapping highlights peaks of hypermetabolism in male (left) and female (right) AD subjects with prior SSRI use, relative to FDG-PET activity in AD subjects without prior history of SSRI use ($N = 14$ AD SSRI males, 30 AD no-SSRI males, 13 AD SSRI females, 28 AD no-SSRI females). Beta estimates demonstrating magnitude of hypermetabolic peaks within a DRN ROI. (C) Statistical parametric mapping did not reveal any peaks of altered metabolic activity within the DRN in CN groups of male (top) or female (bottom) subjects using SSRIs, relative to FDG-PET activity in CN subjects without prior history of SSRI use ($N = 13$ CN no-SSRI males, 12 CN SSRI males, 16 CN no-SSRI females, 27 CN SSRI females). AD, Alzheimer's disease; CN, cognitively normal; DRN, dorsal raphe nucleus; FDG-PET, ^{18}F-fluorodeoxyglucose PET; ROI, region of interest; SSRI, selective serotonin reuptake inhibitor.

TABLE 2 Statistical parametric mapping of metabolic activity peaks within the DRN.

MNI coordinates			Peaks		
X	Y	Z	*T*	(Z_E)	*p*
MALE – Hypometabolism – AD no SSRI versus CN no SSRI					
−10	−32	2	1.82	1.78	0.038
−10	−36	0	1.77	1.74	0.041
−8	−30	4	1.75	1.72	0.043
FEMALE – Hypometabolism – AD no SSRI versus CN no SSRI					
−8	−36	2	3.22	3.03	0.001
8	−30	4	2.40	2.40	0.008
14	−32	−4	1.78	1.74	0.041
MALE – Hypermetabolism – AD SSRI versus AD no SSRI					
4	−42	18	3.43	3.20	0.001
−2	−42	18	3.29	3.09	0.001
−12	−22	12	2.17	2.10	0.018
12	−22	12	2.06	2.01	0.022
FEMALE – Hypermetabolism – AD SSRI versus AD no SSRI					
−10	−36	0	3.04	2.87	0.002
−2	−18	−16	2.54	2.43	0.008
4	−18	−16	2.20	2.13	0.017
−2	−30	−22	1.70	1.67	0.047

Note: MNI coordinates presented in mm.
Abbreviations: AD, Alzheimer's disease; CN, cognitively normal; MNI, Montreal Neurological Institute 152; SSRI, selective serotonin reuptake inhibitor.

Their broad design, intended to evaluate diverse cognitive abilities within a short period of time, limits the depth of assessment within each domain. This makes it unclear whether SSRI use affects specific cognitive domains or if differences stem from the sensitivity and specificity of the tests within shared domains. Future studies could address this by incorporating domain-specific assessments, such as the Delayed Word Recall test,[40] to provide in-depth analysis of the cognitive abilities underlying these evaluations.

As the serotonergic hub of the brain, the activity of the DRN is influenced by long-term SSRI use.[41] Furthermore, animal studies have shown that the overexpression of p-tau in the DRN is sufficient to induce both depression- and AD-like changes in behavior.[42,43] In addition to cognitive function, the current study leveraged FDG-PET scans collected by the ADNI to examine the influence of AD and SSRI use on the metabolic activity of the DRN. Our analyses revealed hypometabolic activity within the DRN of AD patients without prior SSRI use, relative to CN individuals. Hypometabolic activity in the DRN can have considerable consequences, disrupting the brain's primary source of serotonin. This dysfunction can be linked to depressive symptoms,[44] commonly observed in AD.[8] However, with SSRI treatment, DRN metabolic activity increased in a disease-state-specific manner, wherein individuals with AD showed a recovery of DRN glucose metabolism, potentially improving serotonin regulation across the brain. This effect occurred in both sexes, with overlapping activity peaks along the dorsal edge of the DRN. Interestingly, this increase was limited to AD subjects, as CN individuals showed no changes in DRN metabolism with SSRI treatment. This lack of change in CN may reflect autoregulation of the serotonergic system, where serotonin 1A autoreceptors inhibit DRN activity when serotonin levels are high.[45,46] Notably, AD is associated with impaired serotonin 1A receptor binding and density,[47–49] which may contribute to these differences in hypermetabolic response to SSRI treatment; however, further studies are needed to directly associate these factors.

Our data reveal differences in plasma p-tau181 concentration, cognitive assessments, and DRN glucose metabolism in AD patients using SSRIs. However, this study has limitations that could be addressed in future studies. Stratification by SSRI type, dosage, frequency, and duration was not feasible due to the impact on statistical power, and other confounding factors, such as concurrent medications, underlying depression, or other comorbid conditions were not accounted for. Additionally, the lack of sufficient FDG-PET and SSRI data from MCI groups prevented their inclusion. The cross-sectional design also precluded longitudinal analysis of sustained SSRI use on plasma p-tau181, cognitive function, and DRN metabolic activity. Our findings provide a foundation for future studies employing tailored trials to address these variables more specifically.

5 | CONCLUSIONS

This study demonstrates that while SSRIs can reduce systemic p-tau181 and restore DRN metabolic activity, the impact on cognition in AD is complex. Long-term SSRI use alters the coherence between MMSE and MoCA scores, with significant implications for assessing cognitive decline in AD. These findings suggest that while long-term SSRI use may help reduce AD pathology, its effects on cognitive performance remain variable.

AUTHOR CONTRIBUTIONS

Dylan J. Terstege: study design, PET analyses, statistical analyses, writing original draft, reviewing, and editing. Shaista Jabeen: writing the original draft, reviewing, and editing. Liisa A. M. Galea: study design, reviewing, and editing. Jonathan R. Epp: funding acquisition, supervision, study design, statistical analyses, writing the original draft, reviewing, and editing. Derya Sargin: funding acquisition, supervision, study design, statistical analyses, writing the original draft, reviewing, and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Author disclosures are available in the Supporting Information.

CONSENT STATEMENT

The ADNI was approved by medical ethics committees of all participating institutions. Written informed consent was obtained from all participants.

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SUPPORTING INFORMATION

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

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