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SHORT REPORT

Retrosplenial hypometabolism precedes the conversion from mild cognitive impairment to 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: Not all individuals who experience mild cognitive impairment (MCI) transition through progressive stages of cognitive decline at the same rate, if at all. Previous observational studies have identified the retrosplenial cortex (RSC) as an early site of hypometabolism in MCI which seems to be predictive of later transition to Alzheimer's disease (AD).

METHODS: We examined $N = 399$ MCI subjects with baseline ^{18}F-fluorodeoxyglucose positron emission tomography. Subjects were classified based on whether their diagnosis converted from MCI to AD.

RESULTS: Whole-brain metabolism was decreased in converters (MCI-AD). This effect was more prominent at the RSC, where MCI-AD subjects showed even greater hypometabolism. Observations of RSC hypometabolism and its utility in predicting transition from MCI-AD withstood statistical analyses in a large retrospective study.

DISCUSSION: These results point to the utility of incorporating RSC hypometabolism into predictive models of AD progression risk and call for further examination of mechanisms underlying this relationship.

KEYWORDS
biomarkers, cognitive decline, FDG-PET, metabolic impairment, neurodegeneration

Highlights

- Not all individuals who develop MCI will progress to AD.
- Individuals with MCI who progress to AD show early whole-brain hypometabolism.
- Early hypometabolism is particularly prominent at the RSC.

1 | INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disorder wherein many affected individuals transition through prodromal stages of mild cognitive impairment (MCI) to progressive dementia. However, not all individuals who experience MCI transition through these stages of cognitive decline at the same rate, if at all.[1–5] In fact, some individuals do not progress, or convert from MCI to AD. To better intervene in the early stages of AD it is imperative that we understand the signs and risk factors that predict conversion between MCI and AD.

The retrosplenial cortex (RSC) (BA29/30) is a site of particular interest in the study of AD progression as recent findings have suggested that the connectivity of the RSC is an important mediator of healthy cognitive aging.[6–8] Nearly 30 years ago the RSC was observed to be one of the earliest areas of dysfunction in AD.[9–11] Here, hypometabolism has been observed during the early prodromal stages of MCI. The magnitude of RSC hypometabolism was greatest in individuals who would later progress to AD.[12–14] These early studies played critical roles highlighting the RSC as an early site of dysfunction with potential predictive power over the transition from MCI to AD.[13,15,16] However, limited sample sizes restrict the potential significance of these findings.

In the present study, we took advantage of the Alzheimer's Disease Neuroimaging Initiative (ADNI) database which contains a large cohort of standardized subject imaging to revisit the question of RSC hypometabolism as a predictor of MCI to AD conversion. To extend and validate prior findings, we compared subjects that had been classified as non-converters (MCI) or converters (MCI-AD) to assess whether RSC hypometabolism during the early stages of MCI is able to predict subsequent disease progression.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors extensively reviewed literature (eg, PubMed), meeting abstracts, and presentations. Based on the available literature, the identification of the retrosplenial cortex (RSC) as an early site of metabolic dysfunction was based on small sample sizes with limited statistical analysis. With access to large retrospective databases, these early questions can be revisited and extended. Relevant citations are appropriately cited.
2. **Interpretation**: Our findings indicate that in a large sample of MCI subjects, early brain hypometabolism is predictive of the later development of AD. Furthermore, the metabolic impairment observed in individuals who will later develop AD is even more pronounced when analyses are tuned to the RSC. This suggests that the metabolic activity of the RSC may serve as an early biomarker for the risk of cognitive decline.
3. **Future directions**: Future studies could examine potential mechanisms through which RSC hypometabolism arises within the context of early mild cognitive impairment.

2 | METHODS

2.1 | Subjects

Data used in the preparation of this manuscript were obtained from the ADNI database (https://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 magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. For up-to-date information, see http://www.adni-info.org.

Subjects from the ADNI-1, ADNI-GO, and ADNI-2 phases were screened for the following inclusion criteria: (1) MCI diagnosis upon initial screening; (2) baseline ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) scan; (3) structural T1-weighted MRI imaging (MP-RAGE sequence) within 1 year of the FDG-PET scan; and (4) Mini-Mental State Examination (MMSE) scores from baseline to a two-year follow-up timepoint. All scans were manually inspected for quality control prior to analysis. Amyloid-beta (Aβ) positivity was not required for inclusion as, in clinical practice, many subjects living with MCI have an unknown Aβ status and Aβ positivity does not mean progression in the majority of MCI subjects.[17] However, when available, Aβ- and tau-positivity were considered during analyses using published amyloid (^{18}F-florbetapir) and tau (^{18}F-flortaucipir) PET datasets.[18] Individuals with a brain-wide standardized uptake value ratio (SUVr) of >1.0 in either of these measures were considered to be positive for their respective pathologies.

Neuroimaging data and MMSE scores were downloaded from the ADNI repository on February 13, 2024. Ethical approval was obtained by the ADNI investigators at each participating ADNI site, and all participants provided written informed consent. All analysis of human neuroimaging data was conducted with the approval of the University of Calgary Conjoint Health Research Ethics Board (REB22-0776).

2.2 | Conversion criteria

Subjects in the ADNI database are labeled as cognitively normal (CN), MCI, or AD; however, changes in diagnosis over time are also reported. In the current study, only subjects who were classified as MCI during baseline diagnostic assessments were considered. Further information on ADNI diagnostic criteria can be obtained from the ADNI website (https://adni.loni.usc.edu/methods/documents/).

Subjects whose diagnosis did not change over the course of the trial, according to ADNI guidelines, were considered to be non-converters (MCI). However, subjects whose symptoms worsened to meet AD criteria were classified as converters (MCI-AD). ADNI conversion status

was verified in the current study by comparing the stability of MMSE scores over time.

2.3 | Neuroimage preprocessing

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 pre-processed format. Scans were processed using SPM12 software (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) and the PETPVE12 toolbox (https://github.com/GGonEsc/petpve12) using previously described pipelines.[19] Briefly, structural MRI images were skull-stripped; segmented into grey matter, white matter, and cerebrospinal fluid; and normalized in Montreal Neurological Institute (MNI) space with co-registered FDG-PET scans.[20] FDG-PET scans were corrected for partial volume effects using the 3-compartmental voxel-wise Müller-Gärtner method.[21]

2.4 | Spatial normalization and quantification

Statistical parametric mapping was performed using SPM12 software. Voxel-wise *t*-test comparisons were performed between MCI and MCI-AD groups to assess relative hypometabolism from FDG-PET scans. For subsequent analyses, each scan was matched to a brain parcellation atlas using DARTEL registration.[22–24] Intensity values were normalized based on the mean voxel intensity across the cerebellum to yield an SUVr.[24,25] The SUVr obtained from bilateral regions of interest (ROIs) corresponding to the RSC was then compared between groups. The bilateral RSC seeds each measured 5 mm in diameter and were centered about MNI coordinates $x = \pm 6$, $y = -50$, $z = 10$, based on expected local activity maxima for this region.[26,27] The SUVr across the rest of the brain not included within these seeds was also assessed as a measure of brain-wide glucose metabolism.

2.5 | Statistics and data visualization

Statistical parametric mapping analyses were performed in SPM12 using MATLAB (MathWorks Inc., R2020a). From these comparisons, t-score maps were thresholded based on a family-wise error-corrected $p < 0.05$.

All other statistical analyses were performed in Prism (GraphPad Software, Version 9.4.0). FDG-PET SUVr within the RSC and across the rest of the brain was analyzed using two-way analysis of variance (ANOVA). Multiple logistic regression analyses were used to assess the extent to which RSC FDG-PET SUVr, brain-wide FDG-PET SUVr, Aβ-PET SUVr, sex, and tau-PET SUVr were predictive of conversion from MCI to AD.

Hypothesis testing was complemented by estimation statistics for each comparison using https://estimationstats.com.[28] For these estimation statistics, the effect size (Cohen's d) was calculated using a bootstrap sampling distribution with 5000 resamples along with a 95% confidence interval (CI; bias-corrected and accelerated). All plots were generated in either MATLAB or Prism and all figures were compiled in Adobe Photoshop.

3 | RESULTS

3.1 | Subject demographics

Following the application of subject inclusion and conversion criteria, we were left with four groups: male MCI, female MCI, male MCI-AD, and female MCI-AD. These groups contained 114, 88, 121, and 76 subjects, respectively. Demographics have been outlined in Table 1.

MCI to AD conversion criteria were also assessed by comparing the stability of MMSE scores at 6-month intervals across two years (Figure 1). We observed a decrease in MMSE scores in both male and female MCI-AD groups (three-factor mixed-effects ANOVA; Time × Conversion Status Interaction: $F_{(4,1211)} = 16.01$, $p < 0.0001$). The slopes of linear regression lines fitted to these data differ significantly from zero in the MCI-AD groups (male MCI-AD: $F_{(528)} = 35.61$, $p < 0.0001$; female MCI-AD: $F_{(328)} = 49.40$, $p < 0.0001$). This was not the case with the MCI groups, where MMSE scores remained stable across this period (male MCI: $F_{(433)} = 0.5811$, $p = 0.4463$; female MCI: $F_{(329)} = 2.334$, $p = 0.1275$).

3.2 | Retrosplenial hypometabolism precedes conversion from MCI to AD

FDG-PET signals were compared between male and female MCI and MCI-AD groups upon intake into the ADNI trial. This approach allowed

TABLE 1 Subject demographics and baseline cognitive scores.

	Male MCI	Female MCI	Male MCI-AD	Female MCI-AD
N	114	88	121	76
Age (years)	75.28 ± 6.50	74.28 ± 7.56	75.46 ± 6.54	74.11 ± 6.89
Education (years)	16.57 ± 2.710	15.73 ± 2.80	16.31 ± 2.61	15.29 ± 2.83
Race (% White)	93.86%	88.64%	97.52%	96.05%
ΔMMSE (2 years)	−0.48 ± 2.337	−0.50 ± 1.88	−2.27 ± 3.30	−2.81 ± 2.85

Abbreviations: AD, Alzheimer's disease; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination.

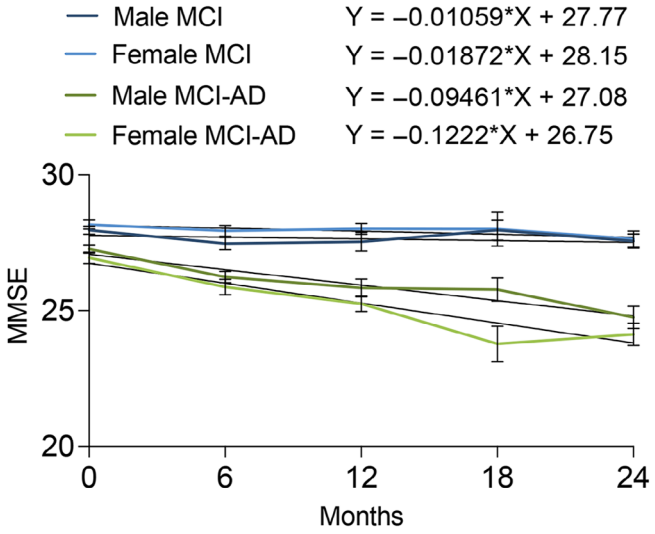

FIGURE 1 Stability of MMSE scores over time. Black lines represent linear regression lines for each group. The equations for each of these lines have been provided in the figure legend. Data are presented as mean ± SEM. AD, Alzheimer's disease; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; SEM, standard error of the mean.

us to assess whether metabolic changes can be found prior to the transition to AD. Statistical parametric mapping revealed several clusters of hypometabolism in MCI-AD groups relative to MCI groups (Figure 2A,B). Peaks of hypometabolic activity were observed at MNI coordinates considered to be part of the RSC in males (MNI: −2, −56, 26; $T = 6.72$; $p_{FWE\text{-}corr} < 0.001$) and females (MNI: −4, −64, 32; $T = 6.70$; $p_{FWE\text{-}corr} < 0.001$). Additional peaks were observed in the angular gyri in both sexes and in the left fusiform gyrus in females (Table 2).

To follow up on these results with a targeted analysis of the RSC, the FDG-PET SUVr of this region was compared between male and female MCI and MCI-AD groups (Figure 2C). A significant decline in RSC FDG-PET SUVr was observed; wherein the MCI-AD group showed hypometabolism prior to conversion to AD (two-factor ANOVA; main effect of conversion status: $F_{(391)} = 30.97$, $p < 0.0001$).

To ensure that the effects observed in the RSC were region-specific and not the product of global hypometabolism, the global SUVr from across the entire brain, excluding the RSC seeds, was analyzed. Decreased brain-wide FDG-PET SUVr was observed in the MCI-AD groups (Figure 2D; two-factor ANOVA; main effect of conversion status: $F_{(394)} = 8.258$, $p = 0.0043$). However, the effect size of global hypometabolism was marginal in male MCI-AD converters (Cohen's d = −0.183). The difference in brain-wide FDG-PET SUVr between MCI and MCI-AD was more prominent in female MCI-AD converters (Cohen's d = −0.497). However, the effect size was greatest and much more balanced between sexes when analyses were targeted to the RSC (males: Cohen's d = −0.475; females: Cohen's d = −0.659). These results suggest that RSC-targeted analyses of glucose metabolism may improve our ability to predict the conversion from MCI to AD, particularly in male subjects.

3.3 | Retrosplenial hypometabolism improves the ability to predict conversion from MCI to AD in individuals without Aβ or tau pathology

Using global Aβ- and tau-PET SUVr, subjects were classified as positive or negative for AD pathology. Decreased FDG-PET SUVr was observed in pathology-positive subjects who would later convert from MCI to AD at both the level of RSC (Figure 2E; two-factor ANOVA; main effect of conversion status: $F_{(243)} = 19.17$, $p < 0.0001$) and across the rest of the brain (Figure 2F; two-factor ANOVA; main effect of conversion status: $F_{(244)} = 9.780$, $p = 0.0020$). Examining individuals who were negative for both Aβ and tau pathology, decreased FDG-PET SUVr was only observed in the RSC of MCI-AD subjects (Figure 2G; two-factor ANOVA; main effect of conversion status: $F_{(44)} = 4.727$, $p = 0.0351$) and not on a brain-wide level (Figure 2H). Furthermore, using multiple logistic regression with sex, Aβ-PET SUVr, tau-PET SUVr, and either RSC FDG-PET SUVr or brain-wide FDG-PET SUVr, it was determined that RSC FDG-PET SUVr is a significant predictor of transition from MCI to AD ($|Z| = 3.181$, $p = 0.0015$) while the FDG-PET SUVr is not ($|Z| = 1.390$, $p = 0.1645$).

4 | DISCUSSION

In the present study, we utilized the extensive collection of FDG-PET scans in the ADNI database to compare the metabolic activity of the RSC in MCI subjects who later converted to AD to those MCI subjects who did not convert. We identified peaks in hypometabolic activity in the converters compared to the non-converters corresponding to the RSC in males and females and the left and right angular gyri, albeit to a lesser extent in males than females. Thus, the hypometabolism of the RSC seems to be the best predictor region when considering both males and females. In addition, the morphology and connectivity of the angular gyrus is known to be highly variable across individuals.[29] Therefore, subsequent analyses focused on the metabolic activity of the RSC compared to the rest of the brain. We identified that while brain-wide metabolic activity is decreased in subjects who later transition to AD, this effect was more pronounced when the scope of the analyses was restricted to the RSC. Importantly, the metabolic activity of the RSC was decreased in individuals who converted from MCI to AD regardless of whether they expressed measurable Aβ or tau pathology. Conversely, brain-wide hypometabolism was predictive of conversion to AD only in Aβ and tau-positive individuals. These results support the utility of the RSC as an early site of metabolic impairment and a predictor of later transition from MCI to AD.

These results point to the metabolic activity of the RSC as a potential biomarker to aid in identifying those MCI subjects who are most at risk for further cognitive decline to AD. The identification of strongly predictive biomarkers is particularly important when considering that approximately 10% to 15% of individuals living with MCI progress to further stages of AD each year. Currently, very few of the already identified biomarkers currently being used to assist in predicting the transition from MCI to AD show exceptional predictive power on their

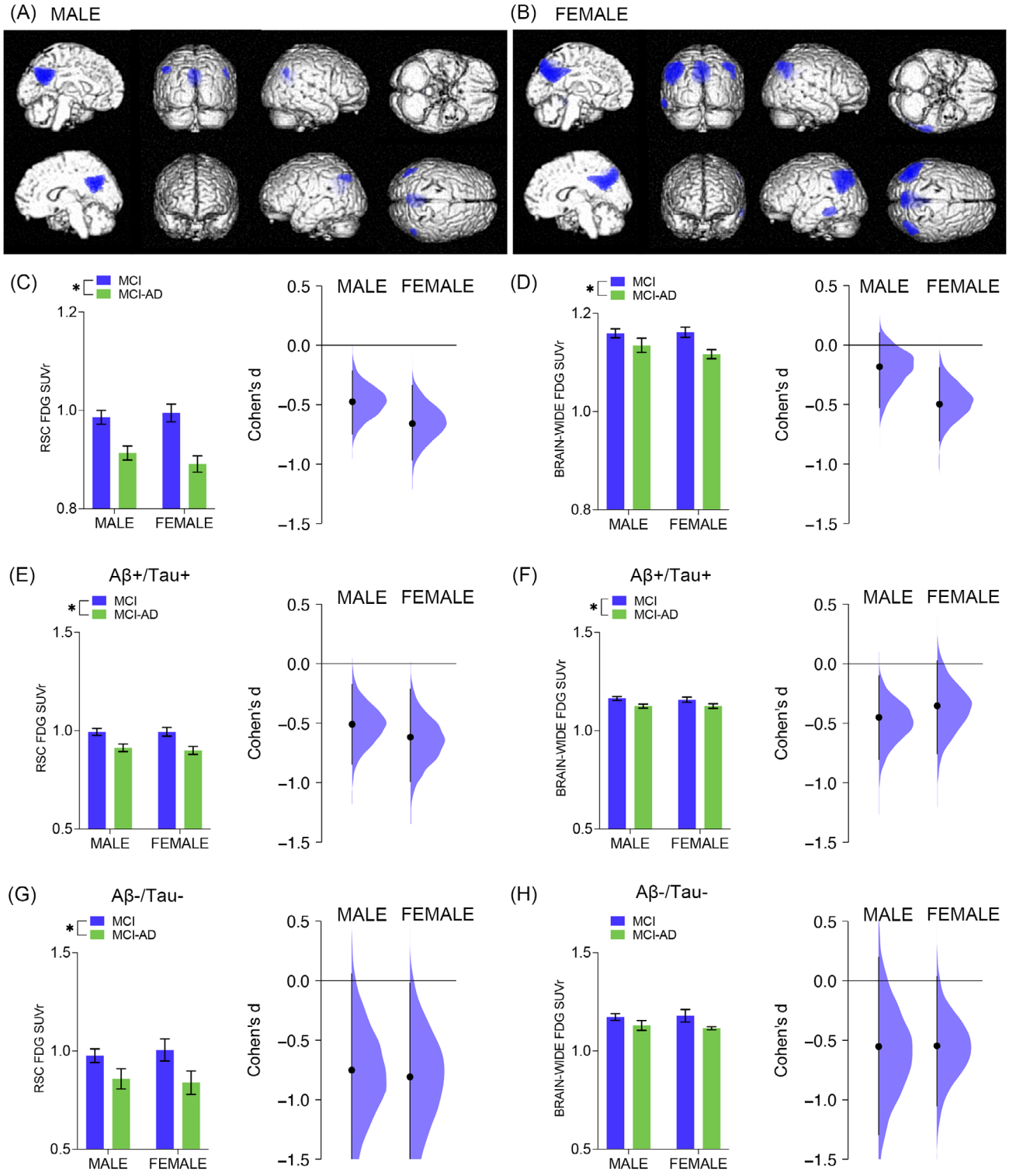

FIGURE 2 (A,B) Differences in brain metabolism between subjects with MCI who do and do not transition to AD. Statistical parametric mapping highlighting peaks of hypometabolism in male (A) and female (B) subjects who transition from MCI to AD relative to FDG-PET activity in subjects who do not transition from MCI. (C) Bar plot (left) showing FDG-PET SUVr at the RSC. Cumming estimation plot (right) showing the effect size of the difference in metabolic activity between MCI and MCI-AD in male and female groups. (D) Bar plot (left) showing FDG-PET SUVr across the rest of the brain. Cumming estimation plot (right) showing the effect size of the difference in metabolic activity between MCI and MCI-AD in male and female groups. (E,F) Bar plots (left) showing FDG-PET SUVr at the RSC (E) or across the rest of the brain (F) of individuals with positive Aβ and/or tau status. Cumming estimation plots (right) showing the effect size of the difference in metabolic activity between MCI and MCI-AD in male and female groups. (G,H) Bar plots (left) showing FDG-PET SUVr at the RSC (G) or across the rest of the brain (H) of individuals with negative Aβ and/or tau status. Cumming estimation plots (right) showing the effect size of the difference in metabolic activity between MCI and MCI-AD in male and female groups. Aβ, amyloid beta; AD, Alzheimer's disease; MCI, mild cognitive impairment; FDG-PET, ^{18}F-fluorodeoxyglucose positron emission tomography; RSC, retrosplenial cortex; SUVr, standardized uptake value ratios.

TABLE 2 Statistical parametric mapping of hypometabolic activity between subjects who transition from MCI to AD and subjects who do not.

MALE											
Set		Cluster-level			Peak-level				MNI coordinates		
p	c	p_{FWE}	k_E	p_{uncorr}	p_{FWE}	T	(Z_E)	p_{uncorr}	X	Y	Z
<0.001	3	<0.001	1536	<0.001	<0.001	7.07	6.72	<0.001	−2	−56	26
									Retrosplenial cortex		
		0.006	184	0.124	0.005	4.85	4.73	<0.001	−44	−74	42
									Left angular gyrus		
		0.010	127	0.195	0.017	4.53	4.43	<0.001	50	−62	38
									Right angular gyrus		
FEMALE											
Set		Cluster-level			Peak-level				MNI coordinates		
p	c	p_{FWE}	k_E	p_{uncorr}	p_{FWE}	T	(Z_E)	p_{uncorr}	X	Y	Z
<0.001	4	<0.001	2135	<0.001	<0.001	7.05	6.58	<0.001	−48	−60	−28
									Left angular gyrus		
		<0.001	2558	<0.001	<0.001	6.70	6.28	<0.001	−4	−64	32
									Retrosplenial cortex		
		<0.001	682	0.006	<0.001	5.60	5.34	<0.001	42	−72	48
									Right angular gyrus		
		0.002	297	0.044	0.002	5.11	4.92	<0.001	−60	−40	−14
									Left fusiform gyrus		

Note: MNI coordinates are presented in mm.
Abbreviations: AD, Alzheimer's disease; MCI, mild cognitive impairment; MNI, Montreal Neurological Institute.

own.[30] However, the inclusion of multiple classifiers in predictive models of AD progression has proven to be very powerful at predicting not only the overall risk of conversion but also the rate.[5,30–33] Therefore, the inclusion of RSC hypometabolism, another early biomarker, may help to strengthen overall prediction models.

In providing further support for the RSC as an early site of dysfunction in subjects who are at risk of developing AD, these results invite targeted analyses of mechanisms underlying the relationship between RSC hypometabolism and cognitive decline.

5 | CONCLUSIONS

The present study demonstrates that hypometabolic activity can be observed in the RSC during the early prodromal stages of MCI. We show here that the magnitude of this RSC hypometabolism is further decreased in subjects who will later transition from MCI to AD. Furthermore, the effect size of the metabolic impairments observed between individuals who do and do not progress to AD is greater at the RSC than it is on a brain-wide level. Ultimately, these results point to the RSC as a region of interest in the study and diagnosis of AD progression.

AUTHOR CONTRIBUTIONS

Dylan J. Terstege: Study design, PET analyses, statistical analyses, 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.

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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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