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RESEARCH ARTICLE

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Association of neighborhood disadvantage with cognitive function and cortical disorganization in an unimpaired cohort: An exploratory study

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Abstract

INTRODUCTION: Neighborhood disadvantage has been shown to impact health and cognitive outcomes, while morphological similarity network (MSN) can elucidate structural morphological patterns underlying cognitive functions. We hypothesized MSNs could provide cortical patterns linked with neighborhood disadvantage and cognitive function, explaining the potential risk of cognitive impairment in disadvantaged neighborhoods.

METHODS: For cognitively unimpaired participants from the Wisconsin Alzheimer's Disease Research Center or Wisconsin Registry for Alzheimer's Prevention ($n = 524$), and the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort ($n = 100$), neighborhood disadvantage was obtained using Area Deprivation Index (ADI) and its association with cognitive performance and MSN features was analyzed using linear regression and mediation analysis.

RESULTS: Neighborhood disadvantage was associated with worse cognitive performance on memory, executive function, processing speed, and preclinical Alzheimer's tests on both datasets. Local morphological organization of predominantly the frontal and temporal regions showed association trends with ADI.

DISCUSSION: Morphological patterns associated with ADI, in-part, may explain the risk for poor cognitive functioning in a neighborhood disadvantaged population.

KEYWORDS
Alzheimer's disease, area deprivation index, cognitive function, morphological similarity networks, neighborhood disadvantage, social determinant of health

Highlights

- Social determinants of health such as neighborhood context can be studied using ADI.
- High neighborhood disadvantage was related to worse performance on category fluency, implicit learning speed, story recall memory and pre-clinical Alzheimer's cognitive composite.
- In this exploratory study, using morphological brain networks that indicate similarity in distribution of cortical thickness between regions, we observed that centrality of predominantly frontal and temporal regions was marginally linked with neighborhood disadvantage status and also partially mediated its association with preclinical Alzheimer's composite test.
- There is a potential role for considering neighborhood status in early screening of cognitive impairment and dementia.

1 | BACKGROUND

Health authorities including the US Department of Health and Human Services and the World Health Organization have emphasized the role of social determinants of health (SDOH), including the neighborhood environment where people are born, live, learn, work, play, worship, and age, as a factor playing a role in cognitive and health outcomes.[1–3] The Area Deprivation Index (ADI) is a validated measure of neighborhood disadvantage for the United States which includes factors for the theoretical domains of income, education, employment, and housing quality measured within a discrete geographic area.[4]

SDOH focused studies have reported associations of neighborhood disadvantage with cognitive decline,[5] whole brain and hippocampal atrophy,[6,7] cortical thinning,[8] as well as Alzheimer's neuropathology,[9,10] supporting the notion of neighborhood disadvantage as a risk factor for cognitive decline and neurodegeneration in Alzheimer's disease (AD). Neuroimaging studies investigating the link between brain patterns, poor cognitive performance, and neighborhood disadvantage,[3,6–8] have been restricted to traditional region level cortical markers. Investigating advanced imaging markers which can elucidate the morphological patterns between brain regions may be especially important, given that the neural mechanisms underlying cognitive functioning are complex and typically involve an interplay of several brain regions and an interregional network pattern. Thus, in the context of examining associations of neighborhood disadvantage with neurocognitive brain patterns, there exists an opportunity to go beyond individual regional measures (e.g., volume, cortical thickness) and explore the interrelated morphological patterns in the brain associated with neighborhood disadvantage.

Recently, morphological similarity networks (MSN) have emerged as a promising alternative to study the cortical organization and inter regional morphological patterns in the brain. MSNs can elucidate the coordinated patterns or similarity in distribution of cortical thickness between brain regions, which are represented in the form of a graph.[11] Network measures computed using graph theoretical techniques can further quantify the local and global topological characteristics or organization of the network, thereby providing network level insights into complex cognitive mechanisms. Our study is based on the hypothesis that MSN may capture the potential effects of neighborhood disadvantage via ADI on inter regional cortical patterns and thereby partially explain the risk of poor cognitive functioning in later life. Our approach leverages the ADI as a geographical measure of neighborhood disadvantage to investigate its association with morphological network patterns and cognitive function. Specifically, we sought to explore the following cross-sectional investigations in a cognitively unimpaired cohort from two independent cohorts. First, we examined association of ADI category with (i) cognitive test scores and (ii) MSN measures, and subsequently, we investigated (iii) how significantly associated MSN measures mediated associations between ADI category and cognitive function.

2 | METHODS

2.1 | Study participants

The primary datasets in this study consisted of participants who were enrolled in two large longitudinal studies of AD, namely the Wisconsin Registry for Alzheimer's Prevention (WRAP)[12] study and the

Wisconsin Alzheimer's Disease Research Center (WADRC) clinical, which together amount to more than 2500 participants (henceforth referred as UW cohort). Both studies determine cognitive status after each visit using National Insititute on Aging–Alzheimer's Association (NIA-AA) criteria for mild cognitive impairment (MCI) and dementia. Inclusion criteria for these parent studies included (a) fluency in spoken English; (b) adequate visual and auditory acuity to complete study tasks; (c) absence of major psychiatric illness expected to interfere with study participation; and non-demented at cognitive baseline for WRAP participants. Among these, $n = 1529$ participants who had completed neuroimaging and were cognitively unimpaired were selected for potential inclusion in this study. Some individuals could not be included due to (missing T1-weighted magnetic resonance imaging (MRI) ($n = 86$); impairment at baseline cognitive assessment ($n = 90$); missing cognitive assessment closest to MRI ($n = 72$); difference of more than 6 months between neurocognitive assessment closest to the MRI used in this study ($n = 128$), leaving $n = 1213$ eligible for consideration. From that set, we selected only participants in the two top and two bottom deciles of ADI as explained in Section-2.2, which resulted in 537 participants for further analysis. The University of Wisconsin Institutional Review Board approved all study procedures and informed written consent was provided by all participants. Additionally, we considered another independent cohort of cognitively unimpaired participants from the ADNI dataset, to assess the reproducibility of our analysis. This secondary dataset consisted of $n = 100$ participants, containing information on ADI (state and national ranks), cognitive assessment and MRI scans within 6 months of cognitive assessment.

RESEARCH IN CONTEXT

1. **Systematic review**: Our literature search involved neuroimaging studies on neighborhood disadvantage defined using Area Deprivation Index (ADI) using PubMed and Google Scholar. Previous neuroimaging studies demonstrated association of ADI with longitudinal cognitive decline and regional structural brain markers. However, no prior study has evaluated the cross-sectional whole brain morphological network markers associated with cognitive functioning by neighborhood disadvantage context, using multiple cohorts.
2. **Interpretation**: Our findings indicate high neighborhood disadvantage status are linked with worse cognitive functioning and show a trend towards disrupted morphological patterns of predominantly frontal and temporal regions. Results demonstrate potential role of neighborhood status in early screening and risk assessment for dementia.
3. **Future directions**: Future hypothesis driven studies investigating the impact of duration and timing of exposure to neighborhood disadvantage, along with longitudinal whole brain network markers, could provide additional potential evidence for causal association between neighborhood disadvantage, neurodegeneration, and cognitive decline.

2.2 | Neighborhood disadvantage

Neighborhood disadvantage was measured by the ADI which is curated, distributed, and validated at the Census block group level by University of Wisconsin Center for Health Disparities Research via the Neighborhood Atlas.[4, 13] ADI is constructed using 17 area-level indicators of poverty, employment, education, and housing quality from the 2015 American Community Survey.[14] The ADI scores were determined for individual census block group areas and based on statewide distributions were ranked into relative deciles. Individuals were geocoded to their respective census block group and assigned an ADI score using the most recently reported residential address. The complete list of ADI indicators and detailed method on determination of ADI for WADRC and WRAP cohorts for the current study cohort has been previously described.[8] A higher ADI indicates greater statewide neighborhood disadvantage, whereas lower ADI indicates lower neighborhood disadvantage statewide. Among the ADI state ranks distributed in deciles from 1 to 10, for the UW cohort we considered individuals from the two lowest (1,2) and two highest (9,10) deciles, based on findings from previous studies which show strongest adverse health effects of neighborhood level factors at the highest level of disadvantage.[6, 8–10] ADI national ranks indicating neighborhood disadvantage at nationwide level are represented as percentiles ranging from 1 to 100, with 100 indicating highest level of disadvantage. With the UW cohort, we evaluated the impact of neighborhood disadvantage on cognition and brain morphology using the above-mentioned deciles for ADI state rank as well as the complete percentile spectrum for national rank, of which the latter ensured the entire cohort could be utilized. The histogram plots of state and national ADI ranks are shown in Figure S1 of supplementary materials. For ADNI dataset, we considered the ADI national rank, as it comprises a multisite cohort with a nationwide population distribution.

2.3 | Cognitive assessment

At each visit, participants in the WRAP study completed a comprehensive cognitive battery including six tests in total that evaluated memory, executive function, processing spend, and language ability. Likewise, Wisconsin Alzheimer's Disease Research Center (ADRC participants completed the comprehensive National Alzheimer's Coordinating Center's Uniform Data Set (UDS) battery.[15] Leveraging tests that overlap in the two cohorts along with published crosswalks mapping same-domain tests to each other,[16] we have made use of several individual cognitive tests and composite scores created from those tests. Individual cognitive test scores for this cross-sectional study included the Rey Auditory Verbal Learning Test learning trials 1–5 score (RAVLT-L), Category fluency (CF) test (animal names) score, time

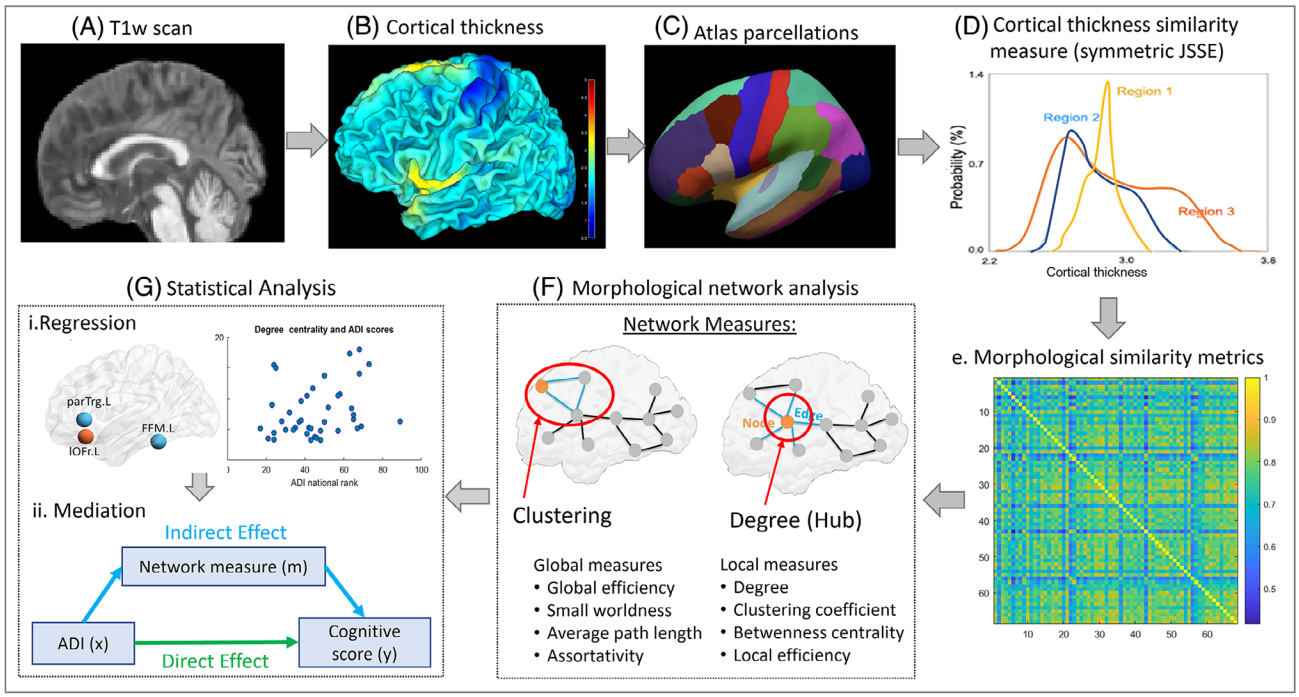

FIGURE 1 Methodical pipeline framework for investigating the associations between neighborhood disadvantage measured using ADI, features from MSNs and cognitive performance. Using (A) preprocessed T1w scans, (B) cortical thickness was computed for 68 cortical brain parcellations from the (C) Desikan–Killiany atlas. (D) JSSE was applied between distributions of cortical thickness values of parcellated brain region, in a pairwise manner to construct the (E) MSN graph metrics, followed by computation of (F) local and global network features using graph theoretical techniques. (G) Statistical analysis using linear regression was performed to obtain association of ADI with cognitive scores and MSN features, along with an assessment of the mediating role of MSN features. ADI, Area Deprivation Index; JSSE, Jenson Shannon similarity estimate; MSNs, morphological similarity networks.

to completion on Trail-Making Test, (TMTt, part B), WAIS-R Digit symbol test (WAIS-DS) and Story Memory Delayed Recall (SM-DR) score consisting of a cross-walked score between the Wechsler Memory Scale–Revised Logical Memory delayed recall and Craft Story delayed recall.[17] We also calculated a modified Preclinical Alzheimer's Cognitive Composite (mPACC) using the following three tests: RAVLT-L, TMTt, and LMIIA.[16] This composite was designed to resemble the PACC described by Donohue et al.[18] Composite scores may demonstrate less intraindividual variation in performance compared to individual tests, providing higher sensitivity in detecting exceedingly early cognitive changes related to AD.[14, 19]

In the ADNI dataset, cognitive assessment of participants was also done using the UDS battery. We considered the cognitive tests scores common in both the UW and ADNI dataset, which included- 1–5 score RAVLT-L, CF test (animal names) score, time to completion on TMTt, part B, SM-DR, MMSE, and the mPACC composite score was constructed as per ADNI guidelines using normalized scores from TMTt, SM-DR and MMSE.

2.4 | MRI acquisition and processing

UW cohort: High-resolution T1-weighted MRI scans were acquired on 3.0T GE MR750 Scanners using an 8 or 32 channel head coil and a spoiled gradient echo scanning sequence with repetition time = 6.68–8.16 ms, echo time = 2.94–3.18 ms, inversion time = 400–450 ms, flip angle 11-12°, and slice thickness of 1×1×1 mm. All structural T1w images underwent surface-based analysis using Computation Anatomy Toolbox 12 (CAT12, http://www.neuro.uni-jena.de/cat/) based on Statistical Parametric Mapping 12, which employs a projection-based thickness approach to compute cortical thickness.[20] The complete analysis pipeline for this study is illustrated in Figure 1. Initially, all T1w images were preprocessed as per the standard preprocessing pipeline of CAT12, involving correction of bias field inhomogeneities, segmentation of gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF), and normalization to the Montreal Neurological Institute (MNI) template. A fully automated projection approach was implemented for the reconstruction of central surface and computation of cortical thickness, which was measured as the distance between the inner surface (GM/WM boundary) and outer surface (GM/CSF boundary/pial surface) of the GM.[21] Cortical thickness maps were smoothed using a Gaussian kernel with 12-mm full width at half maximum. Images that produced erroneous cortical reconstructions and surface estimates in CAT12 were excluded from further analysis (n = 13). Thus, the total no. of participants containing complete and good quality of imaging, cognitive, and ADI data for the UW cohort comprised of (n = 524, gender = 343 (66%) female, 181 (34%) male; age = 62.96 ± 8.37), which were considered for further

TABLE 1 Detailed demographic characteristics of the total population included for analysis in this study from UW and ADNI cohorts, with UW cohort comprising of population living in least (ADI state rank decile-1,2) and highest (ADI state rank decile-9,10) disadvantaged neighborhoods.

Variables	UW cohort	UW: Samples with low_ADI	UW: Samples with high_ADI	ADNI cohort
Sample size	524	450 (85.9%)	74 (14.1)	100
Female, N (%)	343 (65%)	287 (63.7%)	56 (75.7%)*	59 (59%)
Age (years: mean ± SD)	62.96 ± 8.37	62.97 ± 8.26	62.93 ± 9.11	72.71 ± 9,69
Education (years: mean ± SD)	16.45 ± 2.43	16.63 ± 2.38	15.33 ± 2.45*	16.78 ± 2.22
APOE e4 positive	37.8%	38%	37.8%	48%
Parental dementia history	32%	29.7%	46%**	54%
Primary race (% within each sample) (White / Black or African American / Hispanic /Asian)	88 / 11 / 1.3 / 0.0	91 / 7.5 / 1.5 / 0.0	69 / 31 / 0 / 0 *	59/ 26 / 14 / 8
Cognitive score (mPACC)	0.04 ± 1.12	0.11 ± 1.06	−0.43 ± 1.35*	0.05 ± 1.95
Number of exposures to cognitive tests (practice effect): (median (min-max))	0 (0–7)	0 (0–7)	1 (0–6)	7 (0–19)
Absolute time between MRI scan and cognitive test(months)	2.0 ± 1.7	2.1 ± 1.7	1.6 ± 1.5	1.1 ± 4.1

Note: ADNI cohort comprise of total population with entire percentile spectrum of the ADI national rank. Difference in characteristics between least and highest neighborhood disadvantaged population was tested using Student's t-test and chi-squared test for gender.
Abbreviation: ADI, Area Deprivation Index; ADNI, Alzheimer's Disease Neuroimaging Initiative; APOE, apolipoprotein E; mPACC, modified Preclinical Alzheimer's Cognitive Composite; UW, Wisconsin Registry for Alzheimer's Prevention study and the Wisconsin Alzheimer's Disease Research Center cohorts.
*$p < 0.005$.
**$p < 0.001$.

statistical analysis. Table 1 indicates their detailed demographic information containing sociodemographic characteristics, including age, sex, race/ethnicity, parental dementia history, and educational level of the selected participants.

ADNI cohort: T1-weighted MRI scans of participants (n = 100, (age = 72.71 ± 9.69, gender (M:F) = 40:60) acquired within 6–8 months of their cognitive assessment were considered for analysis. Acquisition details for this ADNI cohort are provided on previous publication of ADNI study.[22] Detailed demographic information of this cohort is given in Table 1. Data were preprocessed, and cortical thickness was computed in the same manner as given above, and subsequently morphological networks were constructed for both UW and ADNI as mentioned in the next section.

2.5 | Construction of MSNs

Networks are graph structures, composed of nodes and edges. We constructed MSNs for each subject individually, where nodes denote brain regions, whiles edges indicate the interregional similarity in cortical thickness. Nodes of the MSN were defined using the parcellations from the Desikan–Killiany surface atlas,[23] which consisted of 68 left and right hemispheric regions of interest (ROIs) of the cerebral cortex.

Edges indicating morphological similarity between ROIs were estimated using Jensen–Shannon divergence similarity estimate (JSSE).[24] Firstly, the vertex wise cortical thickness values were extracted for each ROI, followed by a kernel density estimation to obtain the probability density function. Using this resultant probability density function, a probability distribution function (PDF) was obtained for each ROI. Given two PDFs P and Q for a pair of ROIs, JSSE is computed as the average of Kulback–Leibler Divergence (KLD) between P and M, where M is the average of P and Q. The formulation for KLD based JSSE is given as follows:

$$JS(P \parallel Q) = 0.5\,(KLD(P \parallel M) + KLD(Q \parallel M)); M(i) = 0.5(P(i) + Q(i)$$

Where, KLD between two probability distributions P and Q is calculated as -

$$KLD(P \parallel Q) = \sum_i P(i) \log \frac{P(i)}{Q(i)}$$

In this study, JSSE was used in the following manner, as a similarity measure-

$$JSSE = 1 - \sqrt{JS(P \parallel Q)}$$

Unlike the asymmetric KLD measure, JSSE is a symmetric metric, with values in the range of 0 to 1, making it a more reliable measure to characterize the morphological similarity between ROIs.[25] Higher JSSE value indicates that the cortical thickness distribution of two ROIs are closer and signifies higher similarity. Thus, the morphological network based on JSSE between 68 brain regions resulted into a 68 × 68 symmetric JSSE graph metric for each participant.

2.6 | Network measures

Graph theoretical techniques to characterize the local and global topology of the MSN were implemented on each participant's symmetric JSSE graph metric using the GRETNA toolbox.[26] To avoid the threshold selection bias, a sparsity-based threshold selection technique was employed, where sparsity was defined as the ratio of the number of actual edges divided by the maximum possible number of edges in a graph. A set of binary adjacency matrices were obtained in the sparsity range from 0.05 to 0.5 at an interval of 0.05. This sparsity range was selected as networks tend to be more fragmented and not fully connected at lower sparsity thresholds, while at higher thresholds they are less random and more likely to maintain small world architecture.[27, 28] The local and global network measures were calculated at each sparsity level and were integrated by calculating their area under the curve for further statistical analysis.

For each subject, using graph theoretical measures four local and four global features were computed, which characterized network integration and segregation respectively. Local features such as clustering coefficient (CC), degree centrality (DC), betweenness centrality (BC) and local efficiency (LE) were computed for each of the 68 nodes of the Desikan–Killiany atlas. Global features such as small worldness (SW), global efficiency (GE), assortativity (AST) and characteristic path length (CPL) were computed for the entire graph. To determine whether the MSNs were non randomly organized, all global measures were independently normalized by the corresponding mean of 100 randomly generated networks.[26] The detail description of global and local MSN features is provided in Table S1 of supplementary materials.

2.7 | Statistical analysis

Statistical analyses were performed using the R software (version 4.1.3) and the PROCESS macro library in Python[29] was used for mediation analysis. The sample characteristics for both UW and ADNI cohort were evaluated using a student's *t*-test as shown in Table 1. Linear regression models were fit to understand the association of neighborhood disadvantage separately with cognitive scores and MSN features as illustrated in Figure 1(G). For ADI state rank in UW cohort, ADI deciles were coded into two level categorical variables (0 as decile 1,2 and 1 as decile 9,10), while ADI national ranks were considered as continuous variables for UW and ADNI cohort. For each of the six cognitive outcomes of interest, we examined the linear regression models (at significance level $p < 0.005$) as: (i) Cognitive outcome ~ ADI + covariates; where ADI was the independent variable of interest and covariates included age, gender, years of education and practice (i.e., number of prior completions for that outcome). In addition, for each of the global and local network measures, we examined models of network measure with bootstrapped statistics (iterations $n = 10{,}000$, significance level of $p < 0.005$) as: (ii.a) $MSN_{global(n=4)} \sim$ ADI + covariates, (ii.b) $MSN_{local(n=4x68)} \sim$ ADI + covariates; where covariates included age, gender (Female-0, Male-1) and years of education. We also evaluated the association of average cortical thickness of 68 regions with ADI and aforementioned covariates using similar regression model. For (i) and (ii), we report the coefficients, *p*-value and confidence intervals (CIs) obtained from the bootstrap statistics to assess the direction and significance of associations, Lastly, (iii) Mediation analysis was conducted to evaluate a hypothesized causal pathway between neighborhood disadvantage and cognitive function via morphological organization which was ascertained through MSN features. For mediation analysis, we considered MSN features that were statistically significant in regression models (iia,b). We obtained the regression parameter estimates for pathways of mediation model and quantified the indirect effect of MSN features on relationship between ADI and cognitive function using product of coefficients method.[29] To assess statistical significance of the indirect mediating effect, a non-parametric bootstrapping (iterations = 10,000) approach was implemented, and 95% CIs along with beta coefficients, were considered at significance level of $p < 0.05$.

3 | RESULTS

3.1 | Participant demographics

The detailed demographic characteristics of total study population of UW cohort, and by state level of neighborhood disadvantage (Low_ADI and High_ADI), as well as for the entire ADNI cohort are provided in Table 1. The total study population comprised of 65% females with average years of education as 16.45 ± 2.43. Of the total sample size, 450 participants (85.9%) lived in least disadvantaged (ADI decile = 1,2) neighborhoods, whereas 74 participants (14%) lived in a highly disadvantaged (ADI decile = 9,10) neighborhood, relative to their state of residence, with the low neighborhood disadvantage group showing significantly higher education level and cognition. The majority of total as well as ADI based sub samples of the study cohort consisted of white individuals, with the high neighborhood disadvantaged sample containing relatively more African American individuals compared to other sub samples as depicted in Table 1. On average, the time between cognitive examination and MRI scanning for all participants was less than 3 months, and the participants from least and highest disadvantaged neighborhood did not significantly differ on practice effect (number of attempts) during cognitive examination. The ADNI cohort had similar distribution as UW cohort on gender, years of education and primary race, had showed higher percentage on apolipoprotein E (APOE) positivity, parental dementia history and exposures to cognitive tests. The detailed demographic information on UW cohort considered for ADI national rank analysis is provided in Table S2 of the supplementary materials.

3.2 | Neighborhood disadvantage and association with cognitive performance

In UW cohort, neighborhood level disadvantage was negatively associated with five of six cognitive test scores. Participants from highly disadvantaged neighborhoods tended to have lower average scores

TABLE 2 Results of regression models for (A) UW and (B) ADNI cohorts assessing association of neighborhood disadvantage (for ADI = high) with cognitive test scores, using age, gender (coded as male-1, female-0), education(years), and practice effect on cognitive test as covariates.

(A) UW cohort					
Test	**ADI**	**Age**	**Gender**	**Education**	**Practice**
mPACC	−0.47 (0.13)[d]	−0.05 (0.005)[d]	−0.49 (0.09)[d]	0.12 (0.02)[d]	0.10 (0.02)[d]
TMTt	18.47 (4.38)[d]	1.70 (0.19)[d]	1.46 (3.13)[ns]	−2.98 (0.63)[d]	−2.97 (0.78)[d]
SM-DR	−1.66 (0.51)[c]	−0.07 (0.02)[c]	−0.79 (0.38)[a]	0.34 (0.07)[d]	0.01 (0.09)[ns]
RAVLT	−1.83 (1.09)[ns]	−0.40 (0.05)[d]	−6.10 (0.81)[d]	0.85 (0.16)[d]	1.20 (0.19)[d]
CF	−1.58(0.69)[a]	−0.16 (0.03)[d]	0.41 (0.51)[ns]	0.37 (0.10)[d]	0.25 (0.13)[a]
WAIS-DS	−3.63 (1.35)[b]	−0.62 (0.06)[d]	−2.95 (0.96)[c]	0.55 (0.20)[c]	0.47 (0.23)[a]
(B) ADNI cohort					
Test	**ADI**	**Age**	**Gender**	**Education**	**Practice**
mPACC	−0.009 (0.007)[ns]	−0.06 (0.02)[a]	−0.46 (0.38)[ns]	0.27 (0.08)[b]	0.10 (0.05)[a]
TMTt	0.33 (0.15)[d]	1.16 (0.53)[d]	−2.26 (7.59)[ns]	−2.80 (1.69)[d]	−0.84 (1.04)[d]
SM-DR	−0.003 (0.01)[ns]	−0.07 (0.05)[ns]	−2.00 (0.76)[a]	0.50 (0.16)[b]	0.27 (0.10)[b]
RAVLT	0.006 (0.04)[ns]	−0.23 (0.17)[ns]	−6.80 (2.46)[a]	1.69 (0.54)[b]	0.07 (0.33)[b]
CF	−0.008 (0.02)[ns]	−0.04 (0.07)[ns]	0.28 (1.11)[ns]	0.32 (0.24)[ns]	0.01 (0.15)[ns]
MMSE	0.0003 (0.005)[ns]	−0.01 (0.02)[ns]	0.10 (0.28)[ns]	0.10 (0.06)[ns]	0.006 (0.03)[ns]

Note: Results represented as β-coefficients (Standard Error).
Abbreviations: ADI, Area Deprivation Index; ADNI, Alzheimer's Disease Neuroimaging Initiative; CF, category fluency, MMSE, Mini-Mental State Examination; mPACC, modified Preclinical Alzheimer's Cognitive Composite, RAVLT, Rey Auditory Verbal Learning Test; SM-DR, Story Memory Delayed Recall; TMTt, time to completion on Trail-Making Test; WAIS-DS, Wechsler Adult Intelligence Scale-Digit Symbol.
[a] $p < 0.05$.
[b] $p < 0.01$.
[c] $p < 0.005$.
[d] $p < 0.001$.

across all cognitive tests. Of the six cognitive test scores, ADI showed significant association with five tests: mPACC ($\beta = -0.47, p < 0.001$), CF ($\beta = -1.58, p = 0.023$), TMTt ($\beta = 18.47, p < 0.001$), WAIS-DS ($\beta = -3.68, p = 0.007$), and SM-DR ($\beta = -1.66, p < 0.005$) after controlling for age, sex, education, and practice as shown in Table 2. On TMTt and SM-DR scores, neighborhood disadvantage had a more robust relationship as indicated through the large magnitude of their effect sizes (β coefficient) as well as p-value < 0.001. The distribution of all cognitive scores across the low and high ADI deciles for the UW cohort are shown in supplementary material (Figure S2).The ADI national rank also showed similar association with cognitive performance particularly for RAVLT ($\beta = -0.032, p = 0.022$), TMTt ($\beta = 0.162, p = 0.005$), SM-DR ($\beta = -0.020$, $p = 0.002$), and the mPACC tests ($\beta = -0.006, p = 0.001$), as shown in Table S3 of supplementary material. In the ADNI dataset, high ADI national rank showed significant ($p < 0.05$) association only with poor reaction time on TMTt tests ($\beta = 0.336, p = 0.028$), as shown in Table 2.

3.3 | Neighborhood disadvantage and association with cortical MSN features

In the UW cohort, among the 68 cortical regions, centrality of left fusiform ($\beta = -3.75$, $p = 0.002$), and right supramarginal region ($\beta = -1.32, p = 0.002$) was negatively related with ADI state rank, while centrality of left bankssts ($\beta = 1.33, p = 0.003$), CC ($\beta = 0.02, p = 0.002$) and LE ($\beta = 0.02, p = 0.005$) of right parstriangularis showed a positive association with ADI, as shown in Table 3 and Figure 2A. Neighborhood disadvantage (at state and national level) showed common association trends for regions of the frontal, temporal and parietal region, as shown in Table S4 and Figure S3 of supplementary material. The above-mentioned brain regions that showed significant association of their MSN features with ADI did not show any significant ($p < 0.005$) association with ADI with respect to their average cortical thickness, as shown in Tables S5 of supplementary material.

In ADNI cohort, ADI national rank showed significant negative association trend ($p \leq 0.005$) with centrality of right lateral orbitofrontal ($\beta = -0.16$, $p = 0.003$), entorhinal ($\beta = -0.16$, $p = 0.005$), and left pars opercularis region ($\beta = -0.14$, $p = 0.002$), positive association was seen with centrality of left rostral anterior cingulate region ($\beta = 0.05$, $p = 0.005$), as shown in Figure 2B. In the ADNI cohort neighborhood disadvantage was prominently associated with morphological patterns of the frontal regions, and the association trend for one temporal region was similar to that seen in the UW cohort. Global network features did not yield significant association with state or national ADI, in both UW and ADNI cohort.

3.4 | Mediating effect of MSN on neighborhood disadvantage and cognitive function

We evaluated mediation models, specifically for the local MSN features that showed an association with neighborhood disadvantage,

TABLE 3 Results of regression models on bootstrap analysis on (A) UW and (B) ADNI cohorts, providing associations between neighborhood disadvantage (ADI state and national) and local MSN features, with age, gender (coded as male-1, female-0), education (years) as covariates.

(A) UW cohort				
	ADI	Age	Gender	Education
MSN features	Coefficient (CI low, CI high)	Coefficient (CI low, CI high)	Coefficient (CI low, CI high)	Coefficient (CI low, CI high)
BC_l_fusiform	−3.75[c] (−5.97, −1.45)	0.18[c] (0.05, 0.31)	2.89[b] (0.65, 5.17)	−0.2[ns] (−0.70, 0.26)
DC_r_supramarginal	−1.32[c] (−2.17, −0.47)	−3.54E−03[ns] (−0.04, 0.03)	0.45[ns] (−0.10, 0.97)	−0.06[ns] (−0.16, 0.04)
DC_l_bankssts	1.33[c] (0.44, 2.17)	0.02[ns] (−0.02, 0.05)	−0.37[ns] (−1.06, 0.30)	−0.05[ns] (−0.18, 0.08)
CC_r_parstriangularis	0.02[c] (0.01, 0.03)	−1.86E−04[ns] (0.00, 0.00)	8.69E−04[ns] (−0.01, 0.01)	−7.12E−04[ns] (0.00, 0.00)
LE_r_parstriangularis	0.02[c] (0.01, 0.03)	−4.30E−04[ns] (0.00, 0.00)	2.83E−03[ns] (−0.01, 0.01)	−5.31E−04[ns] (0.00, 0.00)
(B) ADNI cohort				
MSN features	ADI	Age	Gender	Education
BC_l_parsopercularis	−0.14[c] (−0.24, −0.05)	−0.01 [ns] (−0.23, 0.24)	−2.23 [ns] (−6.93, 2.95)	−0.5 [ns] (−1.50, 0.52)
BC_r_lateralorbitofrontal	−0.16[c] (−0.29, −0.05)	−0.03 [ns] (−0.27, 0.22)	−0.82 [ns] (−7.44, 5.47)	−0.16 [ns] (−2.56, 1.65)
BC_r_entorhinal	−0.16[c] (−0.27, −0.05)	−0.12 [ns] (−0.58, 0.29)	−0.64 [ns] (−7.62, 6.67)	0.49 [ns] (−1.06, 2.37)
DC_l_ rostralanteriorcingulate	0.05[c] (0.01, 0.08)	0.04 [ns] (−0.06, 0.13)	−0.78 [ns] (−2.66, 1.12)	−0.08 [ns] (−0.51, 0.34)

Note: Results represented as β-coefficients (Standard Error) for each MSN feature.
Abbreviations: ADI, Area Deprivation Index; ADNI, Alzheimer's Disease Neuroimaging Initiative; CI, confidence interval; MSNs, morphological similarity networks; UW, Wisconsin Registry for Alzheimer's Prevention study and the Wisconsin Alzheimer's Disease Research Center cohorts.
[ns]non-significant.
[a]$p < 0.05$.
[b]$p < 0.01$.
[c]$p < 0.005$.
[d]$p < 0.001$.

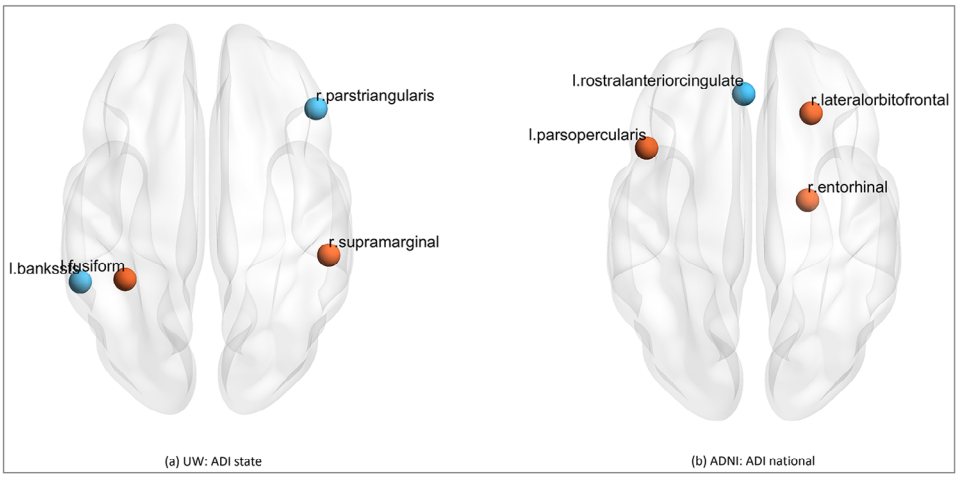

FIGURE 2 Illustration of cortical brain regions whose local network features showed significant association with neighborhood disadvantage after controlling for age, gender, and education (years) as covariates using (A) UW and (B) ADNI cohort. ADI, Area Deprivation Index; ADNI, Alzheimer's Disease Neuroimaging Initiative; UW, Wisconsin Registry for Alzheimer's Prevention study and the Wisconsin Alzheimer's Disease Research Center cohorts.

to assess their involvement in cognitive functions. In the UW cohort, for the ADI state rank-based assessment, centrality of left bankssts showed a marginal partially mediating effect with the mPACC test score. Figure 3 represents the complete parameter estimates for the mediation effect, indicating that neighborhood disadvantage had a partial mediating effect through increased centrality of left bankssts region on the mPACC test score, which can capture early signs of AD dementia. For ADI national rank-based assessment, no significant mediation effect was found by any of the local MSN features, in both UW and ADNI cohort.

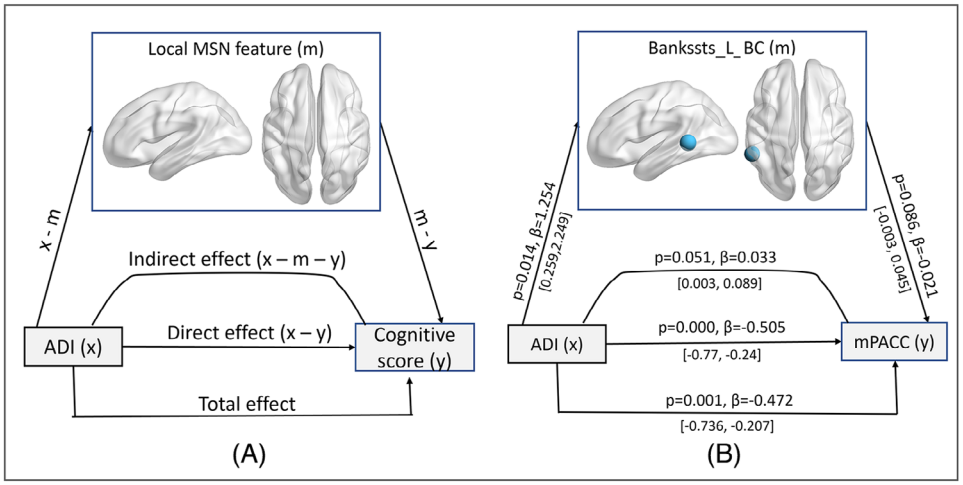

FIGURE 3 (A) Hypothetical model for mediation on the effect of neighborhood level disadvantage on cognitive function via morphological network patterns. (B) Result of mediation model illustrating the indirect effect of centrality of left banksts region on the association between ADI and performance on mPACC scores. 95% confidence interval constructed using nonparametric bootstrapping are indicated as [low, high]. ADI, Area Deprivation Index; mPACC, modified Preclinical Alzheimer's Cognitive Composite.

4 | DISCUSSION

In this exploratory study, we conducted a cross-sectional analysis on neuroimaging data derived from two extensive cohorts from Wisconsin's ADRD research and the ADNI dataset in order to investigate the associations of neighborhood disadvantage status with cognitive performance and MSNs. We observed that living in a highly disadvantaged neighborhood was associated with worse cognitive function and also showed marginal cortical disorganization of the brain indicated through the local MSN features. Specifically, morphological patterns predominantly of the frontal and temporal region played a major role in driving this association, with temporal morphology depicting a marginal, partial mediating link between heightened neighborhood disadvantage and lower performance on the mPACC test.

High neighborhood disadvantage assessed using either ADI state or national rank was associated with worse scores on TMTt, CF, WAIS-DS, RAVLT tests, and on the mPACC composite score, which also is sensitive to cognitive dysfunction in early AD. TMTt, RAVLT, and WAIS-DS tests evaluate executive function, attention and processing speed, which are shown to diminish in the initial stages of both biomarker-defined AD and cerebral small vessel disease.[30] On the other hand, CF and SM-DR tests assess semantic and episodic memory function respectively, which are found to be impaired in early AD and MCI.[31,32] Across both UW and ADNI cohorts, the high reaction time on TMTt test was found to be commonly associated with both ADI state and national rank, providing a consistent evidence of poor processing speed to be linked with high neighborhood disadvantage status. The lower performance in these cognitive domains may signal risk for possible progression to dementia-AD or vascular dementia, but additional study, including longitudinal follow-up is needed. The cognitive outcomes observed in this study align most closely with previous research[33–36] examining health outcomes with neighborhood disadvantage, which have also shown more robust associations when considering categorical indicators of neighborhood disadvantage.

Existing neuroimaging studies on SDOH have shown neighborhood disadvantage to be associated with brain atrophy[6,7] and longitudinal cortical thinning[8] upon analysis of specific AD related regions. However, they do not report evidence for any significant association with cortical thickness at a cross-sectional level. In our analysis, with the primary UW dataset frontal, temporal and supramarginal region yielded an associational trend with respect to their morphological patterns, but not in terms of their average cortical thickness as shown in Table S5 in supplementary material. This could probably imply that an advanced signature of cortical thinning is probably more sensitive to risk factors such as ADI, when assessed in a longitudinal manner, while at a cross-sectional level, cortical patterns may resonate higher with ADI related risk of cognitive impairment. Building up on this finding, our investigation of morphological networks was based on the rationale that complex cognitive mechanisms typically involve an interplay of different brain regions, rather than a singular regional dominance, which can be effectively ascertained through network analysis. Hence, we choose MSN over other conventional methods as it captures the interrelated morphological patterns and its disruption that may precede the gross effect of regional cortical thinning and provide deeper insights into the neurobiological impact of clinical cognitive impairment arising from SDOH based risk factors. Even though MSN is a sparsely explored method in the literature, studies[37,38] have indicated its potential as an early marker of cognitive impairment, showing morphological disruption linked with brain functionality and similar to the alterations of white matter connectomes. Moreover, in concordance to our findings, recent studies have also reported a variable trend in cortical disorganization, at global as well as local level in mild cognitive impairment and AD, using morphological networks.[39,40]

In our analysis of the UW cohort, assessment of neighborhood disadvantage using both ADI state and national rank demonstrated

a common associational trend with inferior frontal regions which are typically involved in language, motor, and executive function[41,42] and with supramarginal gyrus involved in phonological and emotional processing,[43,44] whereas temporal involvement was seen in fusiform, bankssts, and superior temporal region, both of which are related to facial perception and recognition.[45] These frontal, temporal and parietal regions showed variable associational trend with ADI, possibly indicating their compensatory involvement, adjusting to the cortical disorganization related to neighborhood disadvantaged status. These regions are often implicated in mild cognitive impairment[46] and stages of dementia, implying that their morphological alterations may possibly impact the risk of cognitive impairment in neighborhood disadvantaged population. Among the significant morphological patterns that were associated with ADI state rank in UW cohort, only the centrality of left bankssts region showed a marginal, partial mediating effect in the association of high neighborhood disadvantage with the mPACC scores. Presence of AD pathology in bankssts region has been shown in early stages of the disease impacting memory and executive functioning.[47] The marginal mediating effect might indicate that early signs of AD associated with disadvantaged neighborhood may be partially influenced by morphological patterns or cortical disorganization of bankssts region. However, further controlled studies are needed to effectively evaluate and add more confidence to the directionality of these associations.

The findings from our secondary ADNI cohort varied in terms of regional morphological associations with ADI, with a dominant frontal involvement, along with that of the entorhinal region, which is known to be involved in memory formation and retrieval and shows early impairment in AD.[48] ADNI cohort showed association of ADI with parsopercularis of the inferior frontal gyrus, which was also seen in UW cohort, that is, involved in language processing, while the additional regions- rostral anterior cingulate and lateral orbitofrontal region are found to be involved in impulse control, social conduct and decision-making.[49] Both UW and ADNI cohort demonstrated a negative association of ADI with morphological patterns of temporal regions, while a variability was seen for frontal associations, which may have arisen due to imbalanced distribution of ADI in ADNI cohort or due to the inherently variable functional role of these regions and their interactive patterns, which are captured through network level analysis. Such variability reported in MCI and AD related studies on morphological networks,[39,40] possibly portray the progressive and dynamic nature of brain morphology linked with different stages of cognitive impairment. Our finding of an association trend of ADI with brain regions that are specifically involved in cognitive impairment encourages future studies to further reproduce these associations and their directional trends on cohorts with more balanced ADI distribution.

Our study did have a few limitations that must be acknowledged when interpreting the outcomes of this study. Notably, the study cohort comprised predominantly of white individuals with high levels of education and relatively lower disadvantaged status, raising the need for acquiring and curating a well distributed ADI cohort for this research as shown in Table 1. A follow-on study is needed in more demographically and socioeconomically diverse cohorts. In interpreting the role of neighborhood disadvantage on cognitive functioning, it is essential to consider the temporal nature of extended exposure to neighborhood disadvantage and the onset of neurodegeneration and cognitive decline. Although our analysis was based on the assessment of neighborhood disadvantage at participant's most recent residential address, ongoing efforts aim to construct residential histories and explore the effects of duration and timing of exposure. It is also important to investigate specific structure inequities that underlie high ADI neighborhoods, including discriminatory zoning policies like redlining, to further understand the root causes of the associations noted herein and to better identify potential interventions towards improved population brain health. Additionally, a hypothesis driven approach pertaining to limited brain regions may be warranted in evaluating the impact of SDOH factors like neighborhood disadvantage on brain health in unimpaired individuals. This approach could provide statistical robustness to the associations and better interpretability, while our exploratory analysis could have introduced larger statistical comparisons, impacting the significance level of our findings. Nevertheless, we report the trend level associations of ADI with MSN features observed at moderately high effect size, encompassing the frontal and temporal regions, which are known to be associated with cognitive functioning. Lastly, in our empirical assessment of impact of ADI on brain morphology, even though the UW cohort demonstrated a reasonable overlap in association of both the national and state ADI with MSN features, its findings varied in comparison to the ADNI cohort. This could possibly be due to the different sample sizes and distribution of ADI across both cohorts. Hence, it raises the need for constructing datasets with more balanced ADI distribution as well as a standardized approach for performing multisite assessments of ADI, which could facilitate future studies in attaining reproducible findings towards neurobiological mechanisms linked with SDOH and to enhance its utility in predictive models of clinical cognitive impairment.

Expanding upon existing literature, this exploratory study advances our understanding of the assessment of neighborhood disadvantage and its association with cortical organization and cognitive function in several ways: (1) presenting preliminary evidence of a marginal association between neighborhood-level disadvantage and cortical networks related to cognitive function, on two independent cohorts; (2) highlighting network level signatures indicating the patterns of morphological alterations in frontal and temporal regions linked with highly disadvantaged neighborhood; (3) utilizing a validated and comprehensive multidimensional construct of neighborhood disadvantage, and explored the association on both state and national ADI, rather than a single construct measure, and lastly (4) the geographic tools employed in this study have been extensively utilized to determine the relative ADI decile of every Census block group across the United States including Puerto Rico and are publicly accessible through the neighborhood atlas, facilitating interdisciplinary research in this domain. A potential future scope of the study involving investigating the impact of duration and timing of exposure to neighborhood disadvantage across the life-course, along with longitudinal assessment of ADI with imaging and cognitive markers, could provide stronger evidence for a potential directional association between neighborhood disadvantage,

neurodegeneration, and cognitive decline. Moreover, policy initiatives aimed at enhancing community infrastructure may offer valuable opportunities to directly examine causal pathways between neighborhood disadvantage, neurodegeneration, and cognitive decline in middle- to older-age cohorts.

In conclusion, this cross-sectional exploratory study highlights the potential role of SDOH such as neighborhood disadvantage by ADI in later life cognitive impairment as well as the morphology of frontal and temporal regions of the brain. The morphological trends indicative of cortical disorganization and the poor cognitive performance observed among individuals residing in the most disadvantaged neighborhoods suggest the need for heightened clinical awareness, potentially also including regular screening within this vulnerable population for early signs of MCI or dementia. By delving deeper into the biological pathways of neighborhood disadvantage and cognitive impairment, clinicians, researchers, and policymakers stand to gain valuable insights for early screening of MCI and targeted strategies for prevention of ADRD.

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CONFLICT OF INTEREST STATEMENT

Dr. Pallavi Tiwari is an equity holder in LivAI Inc. and serves as a scientific consultant for Johnson & Johnson. Dr. Barbara Bendlin has received precursors and tracers from AVID Radiopharmaceuticals including PET precursor for AV1451 which was used in the current study. She has also received honorariums from UC-Irvine, the University of Pittsburgh, the University of Illinois, and the Karolinska Institute for lectureships. Dr. Bendlin has received payment from New Amsterdam Inc. for consulting fees and from the Alzheimer's Association for attendance at their event. She serves as the chair of the ADRC research education national committee, the CLSA-Healthy Brains Healthy Aging/Weston Advisory Committee, and Rush's ADRC external advisory board committee. Dr. Sterling Johnson has served on advisory boards for ALZPath and Enigma Biosciences. Dr. Amy Kind reported receiving multiple grants from Alzheimer's Association and National Institute of Health. The remaining authors have no disclosures. Author disclosures are available in the Supporting Information.

CONSENT STATEMENT

The University of Wisconsin Health Sciences Institutional Review Board approved all study procedures and all participants provided written informed consent.

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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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