A PRACTITIONER’S GUIDE TO GEOSPATIAL ANALYSIS IN A NEUROIMAGING CONTEXT

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ADRD Special Edition

Short Report: 1657/1500 words, 149/150 word abstract, 22/20 References, 2/2 tables/figures, 2 Supplemental Files

**Conflict of Interest and Disclosure Statement**

JKW reports no disclosures

GMB reports no disclosures

KP reports no disclosures

PM reports no disclosures

ES reports no disclosures

SS reports no disclosures

AHB reports no disclosures

SF reports no disclosures

SK reports no disclosures

BAG receives research support from Eli Lilly and Avid Radiopharmaceuticals.

Neither JCM nor his family owns stock or has equity interest (outside of mutual funds or other externally directed accounts) in any pharmaceutical or biotechnology company.

BMA reports no disclosures.

**Funding**

This work was funded by the National Institute of Health (NIH) grants R01NR012907 (BA), R01NR012657 (BA), R01NR014449 (BA), R01DA054009 (BA), R01MH118031 (BA), K01 AG053474 (BG), F32MH129151 (KJP), P30 AG066444 (JCM), P01AG003991 (JCM), P01AG026276 (JCM), U19 AG032438 (JCM), and U19 AG024904 (JCM). This work was also supported by the generous support of the Barnes-Jewish Hospital; the Washington University Institute of Clinical and Translational Sciences Foundation (UL1 TR000448); the Hope Center for Neurological Disorders; the Paula and Rodger O. Riney Fund; the Daniel J Brennan MD Fund; the Fred Simmons Olga Mohan Fund; the Bright Focus Foundation A2022014F (PRM); and the Chuck Zuckerberg Initiative (CZI).

ABSTRACT (149 / 150 words)

INTRODUCTION: Health disparities arise from biological-environmental interactions. Neuroimaging cohorts are reaching sufficiently large sample sizes such that analyses could evaluate how the environment affects the brain. We present a practical guide for applying geospatial methods to a neuroimaging cohort.

METHODS: We estimated brain age gap (BAG) from structural MRI from 239 city-dwelling participants in St. Louis, MO. We compared these participants to population-level estimates from the American Community Survey (ACS). We used geospatial analysis to identify neighborhoods associated with patterns of altered brain structure. We also evaluated the relationship between Area Deprivation Index (ADI) and BAG.

RESULTS: We present a spatially representative cohort that identified areas in St. Louis, MO that were significantly associated with higher BAG. We provide replication code.

CONCLUSION: We observe a relationship between neighborhoods and brain health, but not ADI and brain health. Future studies could use geocoded participant information to evaluate biological-environmental interaction.

INTRODUCTION

Health disparities are established pathways responsible for differential onset of symptomatic Alzheimer disease (AD)1. The National Institute on Aging Health Disparities Research Framework (NIA – HDRF) both acknowledges the presence of health disparities across racial and ethnic bounds, and highlights biological-environmental interactions as the source of these inequities2. Area Deprivation Index (ADI) is one summary measure of socioeconomic disadvantage applied in this context3 Structural and social determinants of health studies frequently identify significant effects of risk modifiers external to the participant and quantify the level of contribution of the environment to overall health, including brain health (e.g. 4–7). These studies are often performed at the population level relying on centralized healthcare data7, surveys, or neuropsychological exams4–6. While useful, these methods of data collection are often limited by recall bias and lack of direct measurement of biological phenomena.

Neuroimaging data isn’t included *a priori* in epidemiological studies due to cost and participant burden; however, existing studies can address this limitation if proper methodological approaches from epidemiological studies are adapted. Many research centers have cohorts numbering in the thousands with participants concentrated in a single geographic area, providing a unique opportunity to investigate the interaction between environment and health without increasing participant burden. Brain Age Gap (BAG), which assesses discrepancies between the brain’s chronological age and biological age, can be viewed as a summary measure of brain health8. This technique has demonstrated success at distinguishing between AD, mild cognitive impairment and healthy controls9.

Given the sensitivity of BAG to quantify structural changes in the brain and the role environment plays in health disparities2, we will assess the association between BAG and the environment in St. Louis, MO. Now is the opportune time to link spatial analysis approaches from public health applications with richly characterized neuroimaging phenotypes11. To support other researchers, we present an analytical approach to evaluating sample, as well as a brief introduction to point pattern analysis. Complete example code is available at <https://github.com/jwisch/PractitionersGuideSpatAnalysis> or in the supplemental materials.

METHODS

*Participant Recruitment*

Non-representative samples pose a particular challenge to many neuroimaging cohorts12,13 and thus, careful consideration is required. US based researchers can assess if their sample is representative by comparing the demographic and spatial characteristics of their cohort to published American Community Survey (ACS) data14.

*WUSTL Participant Recruitment*

We present a combined cohort, containing individuals recruited from the Knight Alzheimer Disease Research Center15 (Knight ADRC), the Infectious Disease Clinic at Washington University in St. Louis (WUSTL) and the WUSTL AIDS Clinical Trial Unit16. For inclusion, participants were non-demented as assessed by CDR17 (Knight ADRC recruited participants) or Global Deficit Score18 (all other participants), provided complete mailing address indicating residence within the city limits of St. Louis, MO, and completed a structural MRI. All participants (ages 23 - 89) completed informed consent. This study was approved by the WUSTL Institutional Review Board. Due to data sharing restrictions, synthetic data is provided on github, rather than actual participant data.

*Population Estimate Extraction from ACS*

ACS estimates have a relatively high level of uncertainty in urban areas19, and users should remain cognizant when taking advantage of this freely available estimate of population/demographics. The best way to reduce uncertainty when using ACS estimates is to reduce the granularity of the data19. We extracted population and demographic information, aggregated to the city level, and produced a visualization of population counts at the tract level (Methods Supplement, *Sample and Population Comparisons*).

*Statistical Analysis for Demographic Comparisons*

To assess the representativeness of the imaged sample, we applied typical statistical tests for a stratified demographic comparison. In all comparisons, we limited the St. Louis population to individuals aged 20 – 84 years. We performed a t-test to compare the average participant age to the average age of individuals living in St. Louis, MO. We performed chi-square tests to compare the categorical demographic variables assessed (race, sex, education).

*MRI Collection and Brain Age Gap Calculation*

MRI images were obtained on 3T Siemens scanners. T1-weighted scans were skull-stripped and affine-registered to the Montreal Neurological Institute atlas (MNI152). Brain Age Gap (BAG) was then estimated using DeepBrainNet8 (Figure 1E), with no correction for age applied. Participants were classified as having a “high BAG” if their BAG was at least 1.5 standard deviations (SD) greater than the mean (Supplemental Figure 1). A sensitivity study was performed with age-corrected BAG values and was found to have no effect on the spatial or traditional statistical analyses.

*Spatial Analysis*

The purpose of point pattern analysis is twofold: 1. To understand the distribution of events in space and 2. To understand possible interactions between them20. Here we will assess recruitment bias (e.g. Are we including participants from all parts of the city, consistent with the distribution of the overall population?) as well as inspect the relationships between neighborhood characteristics and brain health (e.g. what, if any, neighborhoods demonstrate an increased probability of high BAG classification?).

*Cramer-von Mises Test for Differences in Distribution of Spatial Values*

The two-sample Cramer-von Mises test assesses differences between the spatial distributions of two populations21. In this case, it allows us to test for differences in spatial distribution of the St. Louis population as compared to the sample population. This permutation-based test is available in the R package ecespa and its implementation is shown in the Methods Supplement *(Spatial Analysis)*.

*Kernel Density & Probability Map Generation*

To assess the interaction between neighborhood and brain health we calculate the spatial intensity of “cases” (individuals with BAG > 1.5 SD from the mean) and “controls” (other scanned individuals). The ratio of spatial intensity is called the risk ratio. From here one can map the kernel ratio function to assess the spatial variation in risk22 as well as generate *p* values to assess if the observed risk ratio is consistent with a constant risk ratio20. *P* values are calculated via Monte Carlo simulation. Smoothing can be completed using a manually selected bandwidth value or one generated by a variety of cross-validated bandwidth selection algorithms. We used 1000, which was the approximate mean of the cross-validated bandwidth recommendations derived from the Diggle and Cronie & van Lieshout’s Criterion. The R package spatstat contains the tools required for this portion of the analysis, and its usage is demonstrated in the Methods Supplement (*Spatial Analysis)*.

*Area Deprivation Index*

We present ADI for readers who are not familiar with St. Louis, MO. This summary measure of socioeconomic status can be extracted from The Neighborhood Atlas 3 (Methods Supplement, *Area Deprivation Index*). After identification of neighborhoods associated with a significantly elevated risk of having high BAG, we extract the ADI from these neighborhoods and compare them to the total city ADI using the Wilcoxon test.

RESULTS

*Sample vs. Population*

We identify several differences in cohort demographics (Table 1). Enrolled participants are older (µAge = 53.2 vs. µAge = 37.3, *p < 0.001*) than the median age of St. Louis residents. Participants who had neuroimaging are more often male (64% vs. 48%, *p < 0.001*) and contain a higher proportion of Black individuals (61% vs 46%, *p < 0.001*) than the City of St. Louis. There is no difference in years of education between cohorts (*p = 0.206*). In a sensitivity study we repeated all spatial analyses within a limited cohort (N = 182, Supplemental Table 2) that was matched on sex (*p = 1.00*), race (*p = 0.368*), and education (*p = 0.347*)

*Spatial Results*

The areas of greatest deprivation in St. Louis are found across the northern and southeastern portions of the city (Figure 1A), while participants come from all parts of the city (Figure 1B). Kernel density plots show the highest concentration of the overall population in South St. Louis (Figure 1C), and a pair of areas of high concentration of samples: one in South St. Louis, similar to the population, and one in Central St. Louis, proximate to the facility where imaging was completed (Figure 1D). There is no significant difference in spatial distribution comparing the population to the sample (Cramer-von Mises test: *ѱ = 0.138, p = 0.214*).

Having established a reasonable sampling spatial distribution across the city, we now look for differences in brain health. We identify three regions where individuals are significantly more likely to have a high BAG. The probability of having a high BAG is shown with contour lines (Figure 1F). In the sensitivity study with the smaller, demographically matched, cohort, we identified the same three regions and two additional smaller regions (Supplemental Figure 2). We compared the ADI of the previously identified regions to the city at large, finding a statistically higher level of ADI for one of the three identified regions (Supplemental Figure 3).

DISCUSSION

We observe a significant relationship between neighborhood and brain health. Three regions display a high concentration of individuals in the bottom 20% of brain health, as assessed by BAG. This finding was supported by a sub-study from a smaller but more demographically representative cohort. Although the areas of greatest deprivation in St. Louis are found across the northern and southeastern portions of the city, not all neighborhoods associated with high BAG lie in these regions. This suggests that the underlying relationship between environment and brain health is more complex than simply what is encompassed in ADI. Future work will aim to disentangle the possible multidimensional impact of the environmental mechanisms on brain health. We hope this study draws attention to the ways in which geocoded participant information can be employed to draw insights on the influence of neighborhood on neuroimaging datasets. We recommend that large cohort studies retain and share geocoded participant information as this will facilitate future public health-medical research collaborations. Future studies should track participant location longitudinally. We did not have this information and all inferences drawn here reflect only most recent address. This represents a major limitation of the study. BAG has already been established as an important biomarker for AD progression9, and the finding that differences in BAG occur by location suggests that neighborhood-based interventions could be targeted.

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TABLES & FIGURES

Table 1. Recruited participants differ on the basis of age, sex and race from the adult population of St. Louis City, MO.

Figure 1. (A) Area Deprivation Index (ADI) across the city of St. Louis is shown. Areas of high deprivation (low socioeconomic status) are observed across the northern portion of St. Louis as well as southeastern St. Louis. (B) St. Louis City Population estimates are obtained from the American Community Survey (ACS) and visualized by census tract. Individual participant locations shown in white. (C & D) Here we ask, “Are we recruiting participants from all parts of the city, consistent with the distribution of the overall population?” We compare the population density of the total city population (C) to the sample (D), finding similar concentrations of population in South St. Louis and lower concentration in North St. Louis. We observe a greater concentration of recruited participants in the central region of the city as compared to the overall population, however analytical methods demonstrate that this difference is not statistically significant. (E) Brain Age Gap (BAG) is calculated by subtracting an individual’s true age from the Brain-Predicted Age, which is generated via structural MRI and the DeepBrainNet algorithm8. An elevated BAG may indicate worse brain health compared to normative training data. (F) Here we ask, “What neighborhoods demonstrate an increased probability of high BAG classification?” We apply spatial analysis to identify “hot spots” where individuals have an increased probability of having a high BAG (as indicated by increasing color intensity). The white line outlines an area in North St. Louis and two areas in South St. Louis where individuals are significantly more likely (p < 0.05) to have an elevated BAG.