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

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ABSTRACT (147 / 150 words)

INTRODUCTION: Health disparities arise from biological-environmental interactions to differentially impact ethnoracial groups. 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 neuroimaging data.

METHODS: Structural MRI from 239 city-dwelling participants in St. Louis, MO were used to estimate brain age gap (BAG). We compared spatial distribution of participants to population-level estimates from the American Community Survey. We then used geospatial analysis to identify neighborhoods associated with patterns of altered brain structure linked with poor neurological health.

RESULTS: We present a spatially representative cohort that identified areas in St. Louis, MO that were significantly associated with high BAG. We provide the code necessary for replicating these results.

CONCLUSION: We observe a relationship between neighborhoods and brain health using neuroimaging. Future large studies could use geocoded participant information to evaluate biological-environmental interaction evaluation.

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, many 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, as well as demonstrating the exaggerated effect of aging in cohorts of HIV seropositive individuals10.

Given the sensitivity of BAG to quantify structural changes in the brain and the role environment plays in health disparities2, we will assess the spatial relationship between BAG and the urban 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, the Infectious Disease Clinic at Washington University in St. Louis (WUSTL) and the WUSTL AIDS Clinical Trial Unit16. For inclusion, participants were non-demented, provided complete mailing address indicating residence within the city limits of St. Louis, MO (Figure 1B), 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*

Utilizing ACS data to estimate full populations is imperfect17; however, it remains the best available population estimate across many scenarios. In addition to population counts, the ACS provides estimates of counts of individuals by sex, race, and education at the tract level. We extracted population and demographic information (Table 1), and produced a visualization of population counts at the tract level (Figure 1A).

*Statistical Analysis for Demographic Comparisons*

To assess the representativeness of the imaged sample, we apply typical statistical tests for a stratified demographic comparison. We perform a t test to compare the average participant age to the average median age of individuals living in St. Louis, MO (the ACS provides the median age of each tract; we calculate the average, weighted by tract density). 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 1C), 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).

*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 them18. 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 populations19. In this case, it allows us to test for differences in spatial distribution of the St. Louis population as compared to the sample population.

*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 risk20 as well as generate *p* values to assess if the observed risk ratio is consistent with a constant risk ratio18. *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.

*Comparison to Known Neighborhood Characteristics*

We conducted paired t-tests to compare the ADI for regions associated with elevated BAG and the overall city.

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. Neuroimaged participants are also more 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*).

*Spatial Results*

Kernel Density plots show a high 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). When we apply the Cramer-von Mises test, we observe that there is no statistically significant difference in spatial distribution comparing the population to the sample (*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). We then compare the ADI of these regions to the city at large, finding a statistically higher level of ADI for one of the three identified regions (Supplemental Figure 2).

DISCUSSION

Here we demonstrate a careful study of sampling distribution in a spatial context. We find that while the imaged cohort does differ demographically from the population (the imaged cohort is more heavily male and Black), it is spatially distributed in a representative manner. Although we cannot analyze race or sex by environment interactions in this cohort, we should be able to draw inference about biological – neighborhood relationships given the spatial distribution of participants.

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. While the purpose of this manuscript was to provide the reader with practical examples of how to consider geospatial information in a neuroimaging context, we do note one of the three regions has a significantly higher ADI than the city. The other two regions have non-significant higher-than-average ADI (Supplemental Figure 2). Future work will aim to disentangle the possible multidimensional impact of the environmental mechanisms on brain health.

Most importantly, 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. 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. We recommend that large cohort studies retain and share geocoded participant information as this will facilitate future public health-medical research collaborations.

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TABLES & FIGURES

Table 1. Recruited participants differ in several ways from the total St. Louis, MO Population.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **St. Louis City** | **Participants** | **p** |
| N | 308174 | 239 |  |
| Age | 37.3 (6.4) | 53.2 (11.5) | < 0.001 |
| Sex |  |  | < 0.001 |
| Female | 158999 (51.6%) | 87 (36.4%) |  |
| Male | 149175 (48.4%) | 152 (63.6%) |  |
| Race |  |  | < 0.001 |
| Black | 143018 (46.4%) | 146 (61.1%) |  |
| White | 143401 (46.5%) | 93 (38.9%) |  |
| Education |  |  | 0.206 |
| Less than High School | 26828 (8.7%) | 39 (16.3%) |  |
| High School | 52444 (17.0%) | 60 (25.1%) |  |
| Some College | 60331 (19.6%) | 58 (24.3%) |  |
| BS or Higher | 79669 (25.9%) | 82 (34.3%) |  |

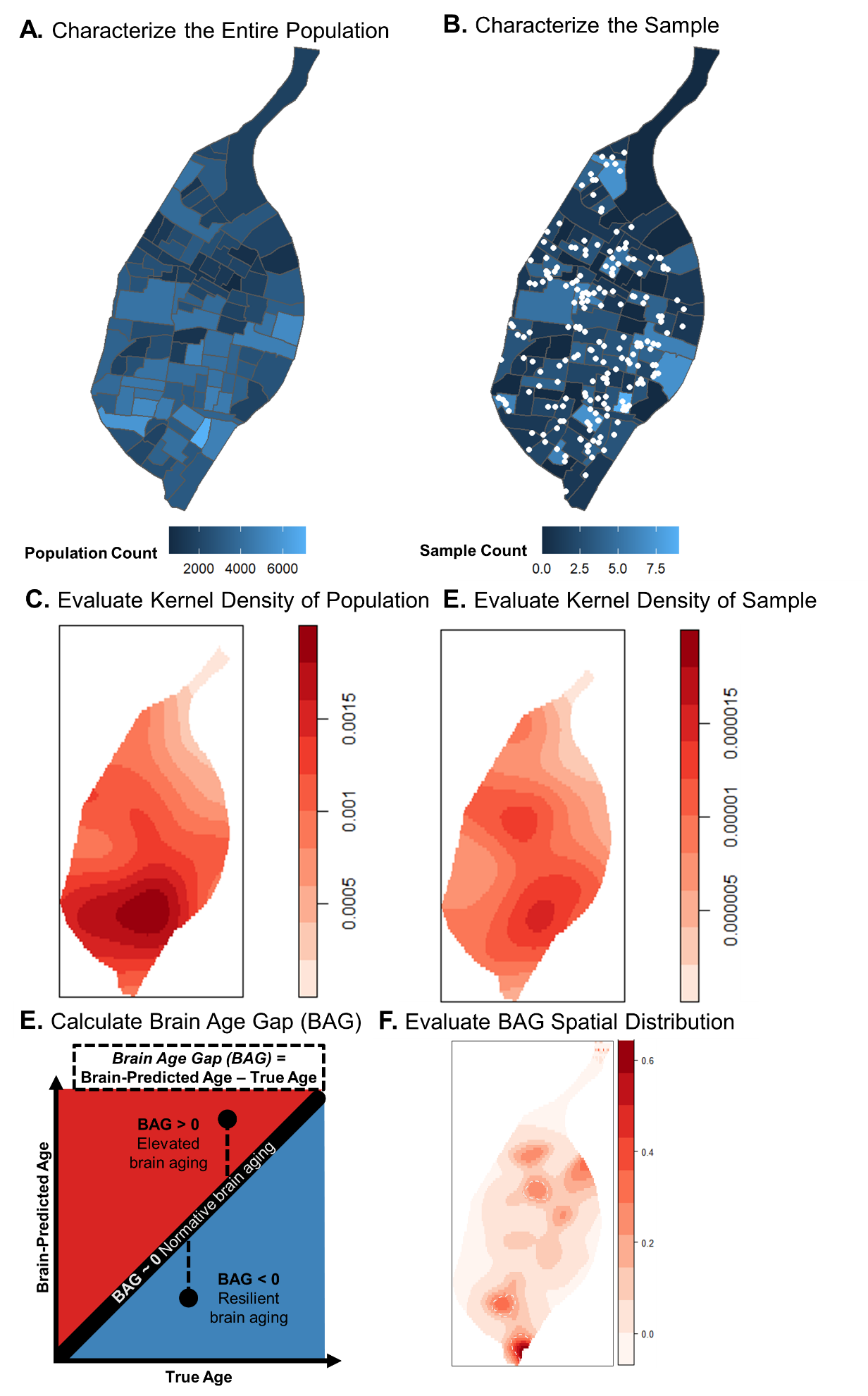


Figure 1. (A) St. Louis City Population estimates are obtained from the American Community Survey (ACS) and visualized by census tract. (B) Individual participants are displayed in white with total tract counts of participants shown in a gradient corresponding with that displayed in Fig. 1A. (C & D) 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.