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

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ABSTRACT (147 / 150 words)

INTRODUCTION: Health disparities arise from biological-environmental interactions to differentially impact minoritized populations. Neuroimaging cohorts are reaching sufficiently large sample sizes such that analyses could be deployed to understand how the environment affects the brain. We present a practical guide for applying spatial 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 detrimental effects on brain structure and health.

RESULTS: We present a representatively spatially sampled cohort and identify areas in St. Louis, MO that significantly associate with high BAG and provide all necessary code for replication.

CONCLUSION: We observe a relationship between neighborhoods and brain health. Future large studies should share geocoded participant information to facilitate biological-environmental interaction evaluation.

RESEARCH IN CONTEXT (119 / 150 words)

SYSTEMATIC REVIEW The authors reviewed the literature concerning the relationships between place and aging, methods for spatial analysis, and neuroimaging literature concerning brain age gap (BAG). Health disparities have been associated with levels of neighborhood deprivation. BAG is a means to quantify structural changes in the brain and associates with development of symptomatic Alzheimer Disease (AD).

INTERPRETATION The significant relationship between BAG and neighborhood suggests that where you live affects your brain health. This indicates that place-based interventions to improve brain health are possible.

FUTURE DIRECTIONS Large cohort studies should share geocoded participant information to facilitate further study across more cities. In depth characterization of neighborhood dynamics and characteristics is necessary to develop targeted policies to improve brain health.

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. Structural and social determinants of health (SSDOH) 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. 3–6). These studies are often performed at the population level relying on centralized healthcare data6, surveys or neuropsychological exams3–5.While useful, these methods of data collection are often limited by recall bias and ecological fallacies.

Neuroimaging data addresses typical limitations, but is more burdensome for study participants. Many research centers now 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 adding to participant burden. Many neuroimaging techniques exist, but here we will evaluate Brain Age Gap (BAG), which assesses discrepancies between the brain’s chronological age and structural age. This technique has demonstrated success at distinguishing between AD, mild cognitive impairment and healthy controls7.

Given the sensitivity of BAG to identify early cognitive changes in the progression of AD and the role environment likely plays in AD incidence, we will assess the spatial relationship between BAG and the urban environment in St. Louis, MO. Beyond this specific application, we believe that this is the opportune time to link spatial analysis approaches from public health applications with richly characterized neuroimaging phenotypes9. To support other researchers, we present an analytical approach to evaluating sample representativeness in this context, as well as a brief introduction to point pattern analysis. Complete example code is available at github.com/jwisch/XXX.

METHODS

*Participant Recruitment*

Inference about a population is based on the available sample10. Non-representative samples pose a particular challenge to many neuroimaging cohorts11,12 and thus, careful consideration is required. The 2019 5-year American Community Survey (ACS) allows for both (1) determining accurate demographic sample representation and (2) assessing environment and social conditional exposure based on geography, regardless of membership. US based researchers can assess if their sample is representative by comparing the demographic and spatial characteristics of their cohort to published ACS data13.

*WUSTL Participant Recruitment*

We present a combined cohort, containing individuals recruited from the Knight Alzheimer Disease Research Center14 and individuals recruited from the Infectious Disease Clinic at Washington University in St. Louis (WUSTL) and the WUSTL AIDS Clinical Trial Unit15. For inclusion, participants provided demographic information, complete mailing address indicating residence within the city limits of St. Louis, MO (locations shown in 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 imperfect. Undercounting of minoritized populations and increased spatial uncertainty, particularly in urban contexts, exist16. Although users should be aware of these pitfalls, 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.

The R package tidycensus facilitates work with ACS datasets. Extraction of population and demographic information is outlined in the posted example (github.com/jwisch/XXX), as well as the corresponding 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. 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 segmented using FreeSurfer 5.3 (Martinos Center for Biomedical Imaging, Charlestown, Massachusetts, USA), using the Desikan-Killiany atlas. Brain Age Gap (BAG) was then estimated using DeepBrainNet8 (Figure 1C). Participants were classified as having a “high BAG” if their BAG was at least 1.5 standard deviations 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 them17. Here we will assess the spatial representativeness of our sample (e.g. Are we recruiting 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 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 populations18. 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” (that is, individuals with high BAG) 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 ratio17. Complete examples are available on github.

RESULTS

*Sample vs. Population*

We identify several key differences in cohort demographics (Table 1). Enrolled participants are significantly older (µAge = 53.2 vs. µAge = 37.3, *p < 0.001*) than the median age of St. Louis residents. Neuroimaged participants are also substantially 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 across St. Louis. We identify a large region in North St. Louis and a smaller region in South St. Louis where individuals are significantly more likely to have a high BAG. The probability of having a high BAG across the city is shown with contour lines on Figure 1F, with regions of statistical significance outlined in black..

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, it is spatially distributed in a similar manner. Given the differences we observe between sample and the population, we feel confident in drawing inference about the spatial influences of the neighborhood environment on brain health in St. Louis, MO. However, we note that these observations are drawn from a sample that is more heavily male and Black than the mean population.

We observe a significant relationship between neighborhood and brain health. Two 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 spatial information in a neuroimaging context, we do note that the neighborhoods associated with high BAG are known for high vacancy and crime rates and high rates of environmental toxin exposure 21. These results support the potential for observing a deleterious impact of the environment on brain health, aligning with established studies on overall health and racial disparities in St. Louis (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 progression7, 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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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%) |  |

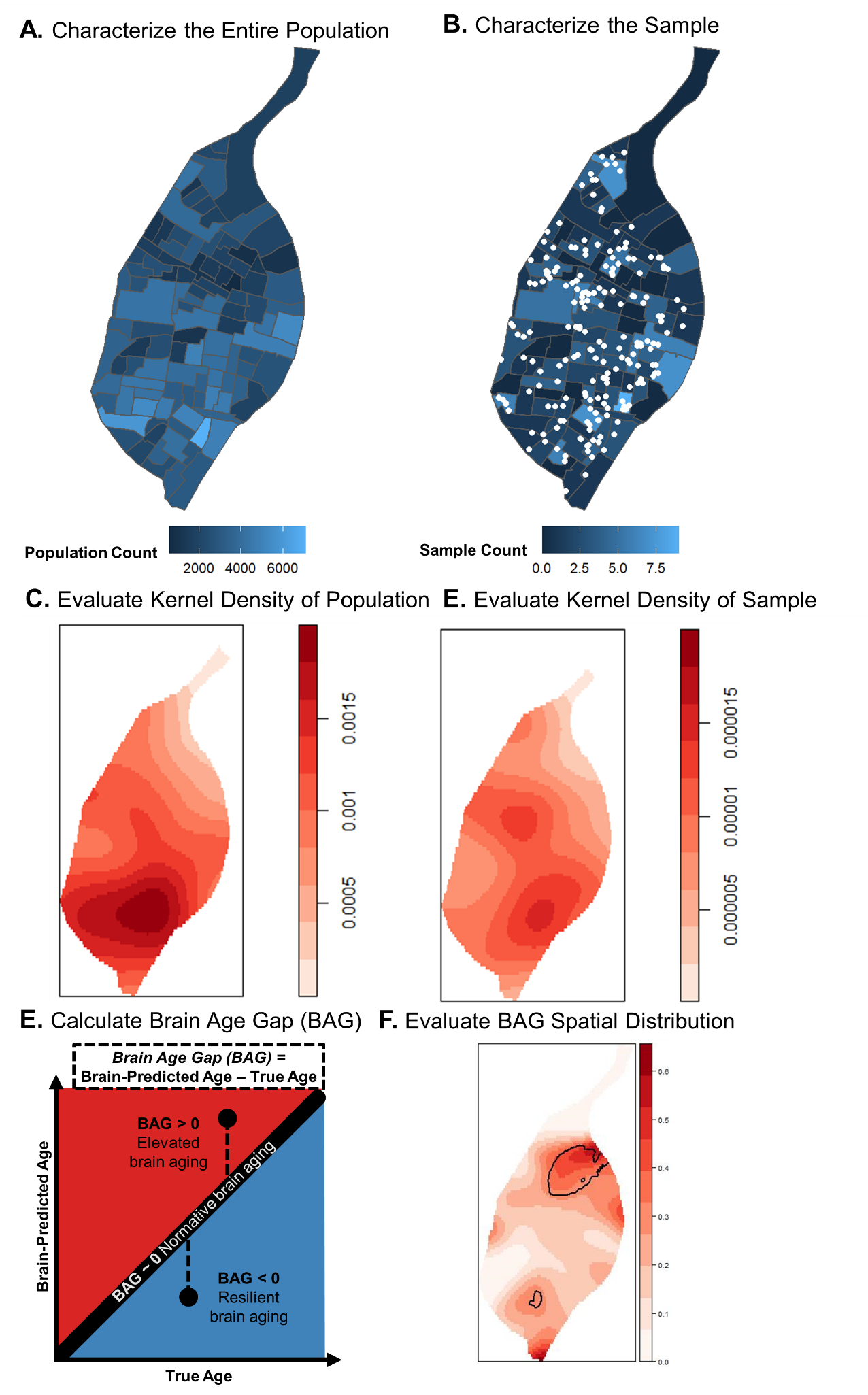
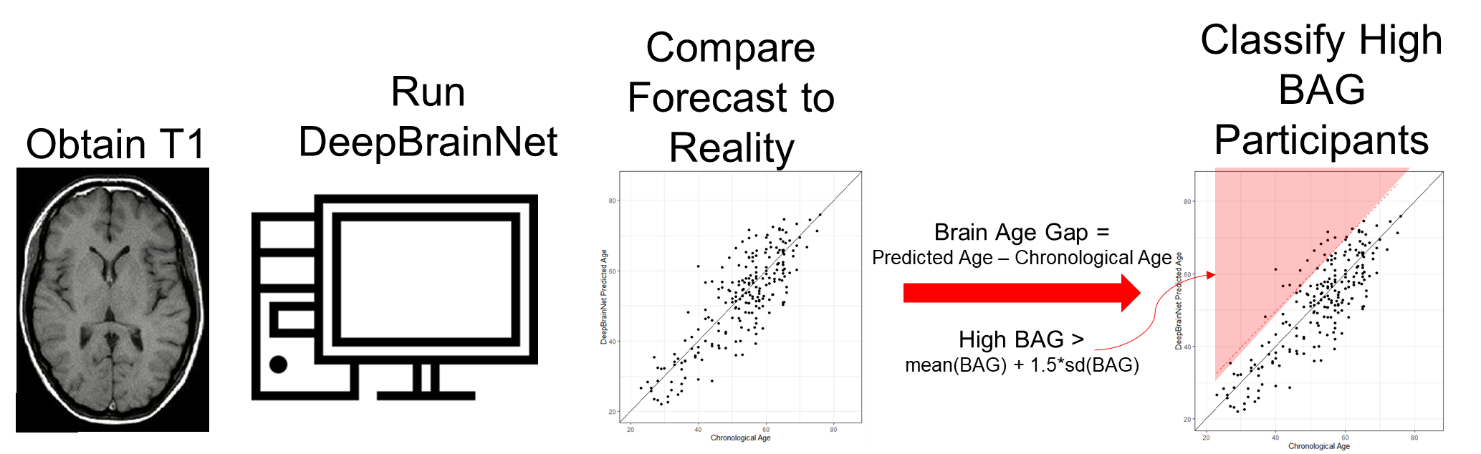
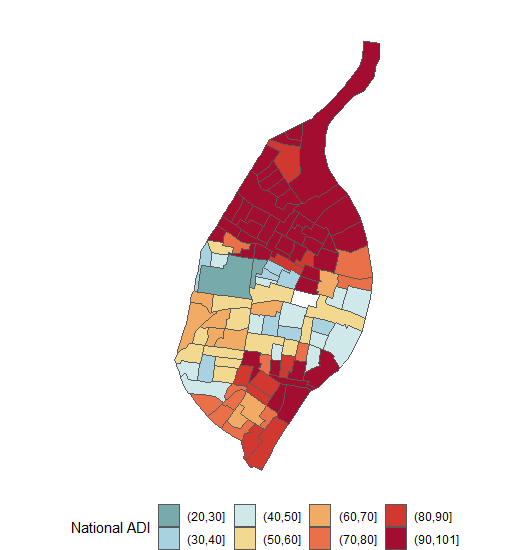


Figure 1. (A) St. Louis City Population estimates are obtained from the American Community Survey (ACS) and visualized by census tract. (B) Individual participants are displayed in white with total tract counts of participants shown in a gradient corresponding with that displayed in Fig. 1A. (C & D) 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 algorithm. An elevated BAG indicates worse brain health than the typical individual. (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). Areas of statistically significant (p < 0.05) increased intensity of elevated BAG cases are outlined with a black line, revealing a large area in North St. Louis and a small area in South St. Louis where individuals are significantly more likely to have an elevated BAG.

SUPPLEMENT



Supplemental Figure 1. Brain Age Gap (BAG) is calculated by comparing the output of the DeepBrainNet algorithm8 to an individual’s chronological age. Individuals classified as having a high BAG have a BAG, based on T1 scan, that is at least 1.5 standard deviations above the mean. This represents approximately 20% of a normally distributed cohort of BAGs.



Supplemental Figure 2. The Area Deprivation Index (ADI) was developed to quantify socioeconomic disadvantage at the census block level21. These scores contain an aggregation of many domains including income, education, employment and housing quality. Areas of high ADI indicate greater levels of deprivation. When compared to the neighborhoods identified as having significantly increased BAG, we observe that the large region identified in North St. Louis entirely associates with tracts of the very highest ADI. The small region in South St. Louis associates with tracts of ADI 70 – 90. These results suggest a relationship between ADI and BAG within this spatially analyzed cohort.