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# A research agenda for understanding how social inequality is linked to brain structure and function

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Consistent evidence documents powerful effects of social inequality on health, well-being and academic achievement. Yet research on whether social inequality may also be linked to brain structure and function has, until recently, been rare. Here we describe three methodological approaches that can be used to study this question—single site, single study; multi-site, single study; and spatial meta-analysis. We review empirical work that, using these approaches, has observed associations between neural outcomes and structural measures of social inequality—including structural stigma, community-level prejudice, gender inequality, neighbourhood disadvantage and the generosity of the social safety net for low-income families. We evaluate the relative strengths and limitations of these approaches, discuss ethical considerations and outline directions for future research. In doing so, we advocate for a paradigm shift in cognitive neuroscience that explicitly incorporates upstream structural and contextual factors, which we argue holds promise for uncovering the neural correlates of social inequality.

Extensive evidence from numerous disciplines, including sociology, psychology, economics and public health, demonstrates that various forms of social inequality may exert a powerful influence on human health and well-being. This work has examined the role of income inequality[1], racial residential segregation[2,3], exposure to neighbourhood violence[4,5], community-level prejudice[6–12], structural racism[13] and institutional policies that restrict the rights of immigrants[14–16] and lesbian, gay, bisexual and transgender (LGBT)[17–24] people. The link between such factors and outcomes as diverse as longevity[25,26], educational achievement[27], mental health problems[28] and physical disease prevalence[29,30] is well documented. Yet despite the weight of evidence that social inequalities are key risk factors for so many outcomes, there has been much less research on how inequalities may be linked to the structure and function of the human brain.

We believe that one of the main barriers to the study of social impacts on neural outcomes is the fact that most neuroimaging studies are conducted in a single community. In such designs, respondents are ubiquitously exposed to the same macro-social context[31], which precludes the possibility of studying the effects of differences in social context. In this Perspective, we draw on advances in population neuroscience[32,33] to present a call to action to the field of cognitive neuroscience to systematically examine associations between social inequalities and neural outcomes, as well as potential causal mechanisms. We first describe how social inequality is operationalized and make the case for why studying social inequalities matters for cognitive neuroscience. We then describe three methodological approaches that can be used to explore associations between social inequalities and neural outcomes. Finally, we highlight recent evidence that has begun to leverage these methods to identify the associations of social inequality with brain structure and function. In doing so, we advocate for a paradigm shift in cognitive neuroscience that explicitly incorporates upstream contextual factors, which we argue holds promise for uncovering the neural correlates of social inequality.

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## Conceptualizing and operationalizing social inequality

Social inequalities have been defined in various ways across disciplines but generally refer to "the unequal distribution of, and unequal access to, highly valued and desired material and nonmaterial social goods. Social inequalities imply systematic advantages and disadvantages in life chances, living conditions, opportunity structures, and life outcomes of individuals and social groups."[34] As suggested by this conceptualization, scholars have examined different dimensions and forms of social inequality—including economic inequality, health inequality and inequality related to social position (for example, based on gender, race and sexuality). Depending on the research question, a dimension of social inequality can reflect either an outcome (for example, studies examining causes of gender inequality) or a mechanism (for example, studies examining whether economic inequality causes differences in health status between white and Black Americans).

Social inequality is measured in a variety of ways. To illustrate these differing approaches to operationalization, we draw on illustrative examples from research on two sources or forms of social inequality—stigma and socioeconomic status (SES). Stigma is a social factor that has been conceptualized as existing at individual, interpersonal and structural levels[35,36]. Stigma has been measured: (1) at the individual level, in the form of perceptions and reactions, such as stereotype embodiment[37] or identity concealment[38]; (2) at the interpersonal level, as differential treatment resulting from one's social position, such as having a criminal record[39]; and (3) at the structural level, in the form of social policies that restrict opportunities, resources and well-being, such as state laws denying services to same-sex couples[21]. The literature on SES, which can similarly be measured across individual, group and structural levels, offers another instructive example. SES has been variously measured: (1) at the individual level, as personal income, occupation, educational attainment or perceptions of one's subjective social status; (2) at the group level, via household family income or the highest educational level achieved by an adult in the household; and (3) at the structural level, as the median income level of one's neighbourhood, an area-level measure of deprivation, or level of income inequality across countries[40–42]. Of course, these three levels are not independent, but rather are mutually constitutive. That is, structural forms of stigma not only shape how individuals perceive and react to stigma[43] but also influence how stigmatized individuals are treated in interpersonal contexts (for example, employment)[44]. Similarly, individuals with lower income reside in neighbourhoods with greater material deprivation, which in turn shapes individual income through institutional policies and practices, as in the case of racial covenants that restrict Black Americans from purchasing homes in neighbourhoods with more economic resources[2].

As is evident from these examples, structural measures of social inequalities are those that reflect properties of a particular spatial location at a particular moment in time that are either aggregated across the group of people who inhabit that location (for example, median household income) or that exist only at a level of aggregation above individuals (for example, city-, county-, state- or country-level policies). Consequently, the measurement approaches that are necessary to operationalize these structural constructs differ from those approaches that are used to capture the individual-level experiences (for example, income or educational attainment) more traditionally explored in the cognitive neuroscience literature (Table 1). Thus, in our Perspective, we only review articles that have used the kinds of structural measures of social inequality as reflected in Table 1.

## Why studying social inequalities matters for cognitive neuroscience

Although the importance of studying whether broad macro-social factors are related to brain development has repeatedly been articulated[33,45–47], studies have only recently begun to examine associations of social inequality with brain structure and function. This work has shown, for example, that greater neighbourhood-level disadvantage in early childhood is associated with elevated amygdala response to neutral faces in early adulthood[48], that exposure to state-level structural stigma is associated with smaller hippocampal volume among Black and Latinx youth[49], and that the magnitude of the association between SES and brain volume varies significantly across European countries[50].

We argue that further systematic investigation into associations between social inequalities and neural outcomes will advance research in cognitive neuroscience in several substantive ways. First, cognitive neuroscience has the potential to reveal the neural mechanisms through which social inequality relates to behaviour and school achievement as well as health disparities[51,52], particularly mediating processes that may be difficult to detect via self-report[53]. By linking macro-level factors related to social inequality with micro-level neural processes, such findings would complement research on other mechanisms underlying the negative effects of social inequality—such as health behaviours[54], access to medical care[55] and disinvestment of economic resources[2].

Second, cognitive neuroscience has provided essential insights into how social factors—such as social rejection[56], exposure to interpersonal violence[57], intergroup prejudice[58], childhood maltreatment[59] and low SES[60,61]—relate to brain structure and function. To date, however, this work has focused almost exclusively on social factors measured at the level of individual or interpersonal experiences and/or perceptions. Expanding the level of analysis to broader structural factors may shed light onto previously unexamined correlates of neural structure and function.

Third, integrating greater focus on structural factors in neuroimaging research can contribute to efforts to improve reproducibility in cognitive neuroscience by revealing meaningful explanations for replication failures[62–64]. For example, the association of SES with brain volume and cognitive ability varies significantly across European countries[50], with the association being weak in some countries and pronounced in others. Thus, depending on where the neuroimaging study is conducted, researchers may come to different conclusions about the significance and magnitude of observed associations. Rather than a failure to replicate, this may instead reflect the fact that social context is a meaningful moderator of associations frequently examined in cognitive neuroscience studies. Although the role of contextual sensitivity has been highlighted in discussions of scientific reproducibility[65], few studies have provided empirical evidence for it, particularly in cognitive neuroscience.

Finally, understanding whether social inequalities are associated with brain structure and function has not only scientific but also societal implications. Debate about the impact of decades of growing income inequality, persistent systemic racism and policies that restrict the rights of large swathes of the population (for example, on the basis of sexual orientation, gender identity or immigration status) is at the forefront of public discourse. Research into the neural correlates of social inequality may inform these debates as well as litigation efforts to address inequality, similar to the role that such evidence has played in other legal domains, including the treatment of minors in the criminal justice system[66].

We develop our arguments by first reviewing three methodological approaches that can be used to examine the relationship between social inequalities and neural outcomes. After reviewing these methods, we discuss their relative strengths and limitations (summarized in Table 2) and suggest areas for future enquiry that are necessary to advance this work.

## Methodological approaches

### Single site, single study

The most straightforward and frequently employed approach to examining associations between social inequalities and neural outcomes is

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**Table 1 | Measurement approaches for studying associations between social inequalities and neural structure and function**

| Measure | Level of aggregation | Data sources | Illustrative references[a] |
|---|---|---|---|
| **Individual-, interpersonal- and group-level social factors** | | | |
| Perceived discrimination | Individual | Everyday Discrimination Scale | Ref. 110 |
| Couple-level minority stress | Dyadic | Relationship Timeline | Ref. 111 |
| Intergroup conflict | Intergroup | Preference for in-group over out-group: for example, resource allocation, prosocial behaviours | Ref. 112 |
| **Structural-level factors** | | | |
| Attitude measures (self-reported) | County, state | Cooperative Congressional Election Survey<br>American National Election Survey | Ref. 12.<br>Ref. 113 |
| Attitude measures (non-self-reported) | County, state | Project Implicit<br>Google search terms | Ref. 114<br>Ref. 7 |
| Social policies | City, state | Movement Advancement Project<br>Historical records (for example, presence of Jim Crow laws)<br>Center for Public Health Law Research<br>National Conference of State Legislatures | Ref. 115<br>Ref. 116<br>Ref. 117<br>Ref. 15 |
| Behavioural measures | Neighbourhood, city, state | Federal Bureau of Justice Statistics (hate crimes)<br>Federal Bureau of Justice Statistics (incarceration/death row) | Ref. 22<br>Ref. 30 |
| Media market ad-buy data for exposure to negative political campaigns | Media market | Campaign Media Analysis Group (CMAG) advertising data report and ad alerts | Ref. 118 |

[a]References provide examples of studies that have used these measures of structural factors related to stigma and prejudice to examine their influence on a range of outcomes (for example, psychological distress and social behaviours), but most have not been linked specifically to neural structure and function.

**Table 2 | Advantages and limitations of different methodological approaches for studying associations between social inequalities and neural structure/function**

| Methodology | Advantages | Limitations | Questions to consider when using this methodology |
|---|---|---|---|
| Single site, single study | Pragmatic (easiest). | When there is only one site, research questions are limited to 'objective' measures of social inequalities that vary within that single site, typically neighbourhood-level influences. Although neighbourhood influences are certainly important, social inequalities are often generated by institutional policies and practices that occur at broader geographic scales, including counties, states and countries, and thus will be missed with this approach. | (1) Does the measure of social inequality exist at the neighbourhood level, or at a broader geographic scale?<br>(2) Do you have adequate variation in the measure of social inequality of interest among your study sample? |
| Multi-site, single study | Provides variation in exposure to broad social contexts, such as states and countries, that vary on the dimension of interest related to social inequality. | The resources needed to conduct and coordinate these large team-based efforts are typically prohibitively expensive.<br>Some existing multi-site studies do not provide information that would enable participants to be linked to site locations. | (1) How will you address the substantial resource challenges in conducting this type of design?<br>(2) Among the study sites you have, is there sufficient variation in the measure of social inequality? |
| Multi-site, multi-study (via spatial meta-analyses) | Easier to conduct than the multi-site, single study, while still having adequate structural variation in social inequality.<br>Can examine temporal dimensions (for example, whether the associations between social inequalities and neural outcomes differ across time or across historical changes). | Data constraints in terms of where studies were conducted (that is, spatial clustering or geospatial autocorrelation), what data are available (for example, length of exposure to current environment, covariates, mechanisms) and ability to synthesize fMRI data across multiple laboratories.<br>Often individual studies included in the meta-analysis provide inexact data on where the study occurred. | (1) Are the measures you need (for example, for confounders and outcome) available across all studies?<br>(2) Where were the studies in the meta-analysis conducted, and do they vary along the dimensions of social inequality of interest? |

the single-site, single-study approach. In these studies, structural measures of social inequality are typically assessed at the neighbourhood level, because this is the only contextual unit of analysis with variability within a single site (that is, a metropolitan area and/or its surrounding regions). Most commonly, these studies measure neighbourhood-level socioeconomic disadvantage[48,67–71], frequently operationalized via composite scales, such as the Area Deprivation Index, which includes area-level factors such as income, education, housing quality and employment. As with all measures, the Area Deprivation Index has strengths and limitations, including a potential over-emphasis on home values in some regions[72]. We refer readers to an excellent scoping review of different area-based socioeconomic deprivation indices[73] to guide their selection of the appropriate measurement approach.

An example of this single-site, single-study approach[48] was a study that examined the association of neighbourhood-level socioeconomic disadvantage—operationalized with a composite measure that included factors such as the proportion of families below the poverty line or households on public assistance[74,75]—with neural responses to ambiguous (that is, neutral) faces among participants sampled from the Pittsburgh area. Greater neighbourhood disadvantage in early childhood was associated with elevated amygdala response to neutral faces in early adulthood, after adjusting for family-level SES and other

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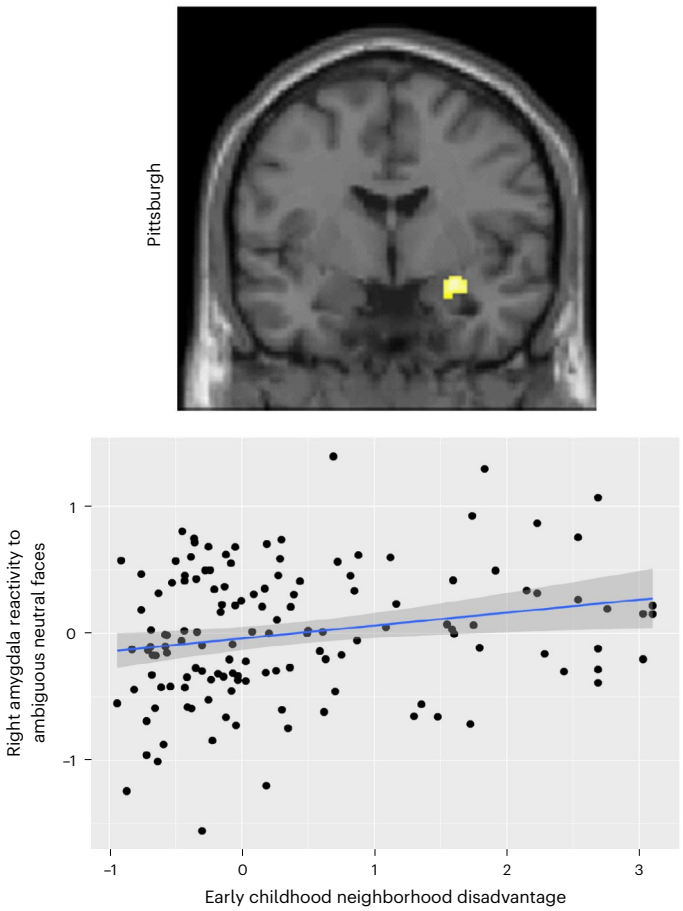


**Fig. 1 | Childhood neighbourhood disadvantage is associated with greater amygdala reactivity.** Greater neighbourhood disadvantage in early childhood was associated with elevated amygdala response to neutral faces in early adulthood ($n = 167$), after adjusting for family-level SES and other forms of adversity, including maternal depression and harsh parenting. Figure adapted with permission from ref. 48, Wiley.

forms of adversity including maternal depression and harsh parenting[48] (Fig. 1). These results suggest that neighbourhood-level socioeconomic disadvantage is associated with neural response to ambiguous social cues over and above individual and family-level factors known to be associated with these responses.

**Strengths and limitations.** The primary advantage of the single-site, single-study approach is pragmatic—it is easier to obtain neuroimaging data on sample individuals living within a smaller geographic region (that is, neighbourhoods) and on a single scanner. But this advantage also represents the principal limitation of this approach: it is constrained in its ability to examine social inequalities beyond neighbourhood-level characteristics. This is an important limitation, given that social inequalities are often generated by norms, attitudes, and institutional policies and practices that occur at broader geographic scales, including counties, states and countries. Researchers interested in evaluating these broader sources of social inequalities must use one of the two other methods, to which we now turn.

## Multi-site, single study

The second methodological approach involves a single study that includes multiple data collection sites that have harmonized the collection of neuroimaging data. By including multiple sites that provide variation in social inequalities across different geographic scales (for example, states and countries), this approach overcomes one of the key limitations of the single-site, single-study design. Although multi-site studies have examined sources of social inequality across smaller geographic scales such as neighbourhoods—including racial residential segregation[76] and socioeconomic disadvantage[77]—we focus in this section on studies that have investigated social inequality at broader units of analysis.

Recently, two studies leveraged the contextual variability from a multi-site study—the Adolescent Brain and Cognitive Development (ABCD) Study, which was conducted at 21 sites across the USA—to examine whether social inequalities, measured at the state level, were associated with neural outcomes among youth. One study[49] operationalized the level of structural stigma related to gender, race and ethnicity in each state, which was measured separately for each stigmatized group using state-level indicators of social policies (for example, whether immigrants were granted access to health services) and aggregated prejudicial attitudes (for example, endorsement of racial stereotypes). Black youth residing in environments characterized by higher structural racism had smaller hippocampal volume than Black youth residing in environments with lower levels of structural racism, controlling for demographics and family SES; the same pattern was observed for Latinx youth residing in contexts involving high structural stigma related to Latinx ethnicity compared with Latinx youth in low-stigma contexts. Further, perceived discrimination was unrelated to hippocampal volume among Black and Latinx youth, suggesting that an objective measure of stigma at the contextual level (that is, structural stigma) may be more strongly associated with neurodevelopment than subjective perceptions of stigma measured at the individual level[49].

Another study[78] examined whether cost of living and the generosity of the social safety net for low-income families moderated the well-replicated association between family income and hippocampal volume in children[61,75,79,80] across 21 sites in the ABCD Study. Three policies aimed at providing support for low-income families that vary meaningfully across states were examined: (1) the amount of monthly benefits provided by the Temporary Assistance for Needy Families (that is, welfare, a federal programme that operates through state block grants; the generosity of the benefit therefore varies between US states); (2) the amount of the state-level earned income tax credit; and (3) whether the state enacted the expansion of Medicaid benefits made available by the Affordable Care Act, which expanded access to free health insurance through Medicaid to all US citizens with income up to 138% of the federal poverty line, although not all states adopted these expanded benefits. The association between family income and hippocampal volume varied significantly across states, such that the association was stronger in states with higher cost of living. Critically, however, the magnitude of this association also varied as a function of the generosity of state-level policies designed to help low-income families. Among states with high cost of living, more generous cash benefits for families with lower SES reduced the association between SES and hippocampal volume by 34% (Fig. 2).

**Strengths and limitations.** The primary advantage of the multi-site, single-study approach is that it provides variation in exposure to broad social contexts, such as states and countries, that vary on the dimension of interest related to social inequality. In Table 3, we provide details of several multi-site neuroimaging studies that have sufficient variability in social contexts beyond the neighbourhood level to examine associations between social inequality and neural outcomes. We also refer interested readers to the linked external data source provided by the ABCD Study, which includes residential, census and state-level variables that provide new opportunities for examining how social inequalities relate to neural outcomes[81].

One limitation of this approach is that some multi-site studies do not provide information about the site where each participant was scanned, precluding the ability to link the dataset to structural measures of social inequality. An additional limitation is that the resources

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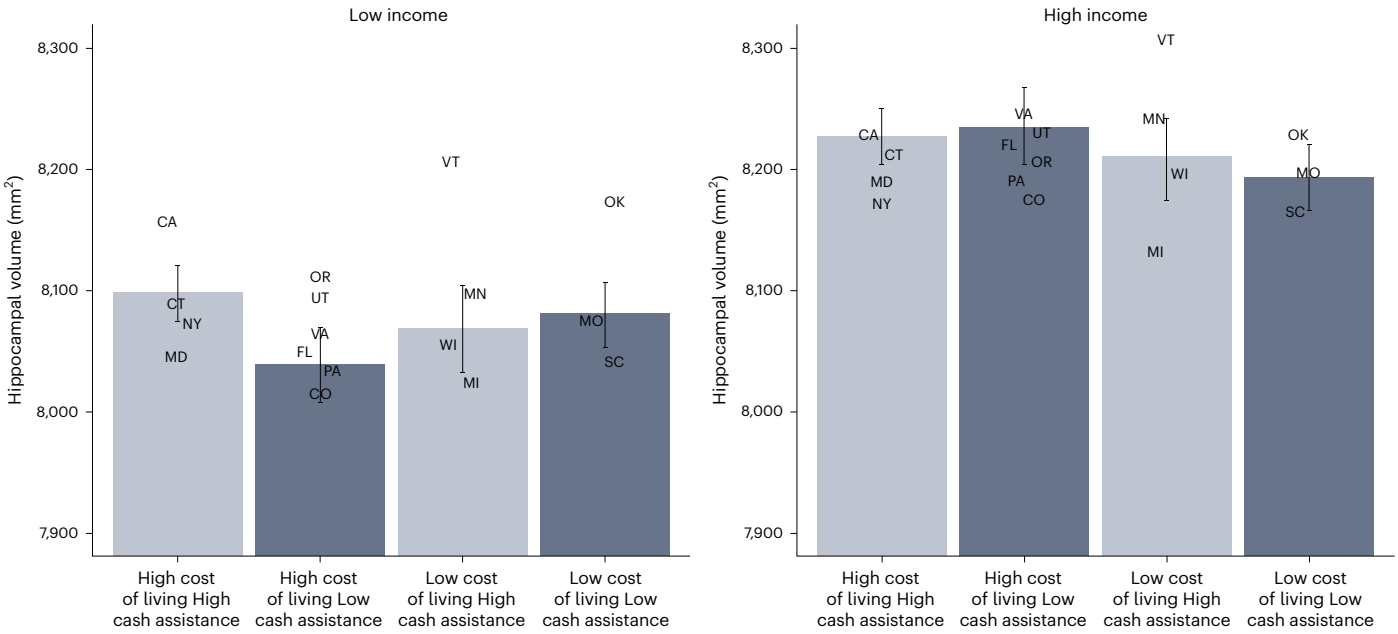


**Fig. 2 | Association between family income and hippocampal volume is stronger in US states with higher costs of living, but weaker in US states with more generous anti-poverty policies.** Three-way interactions between state-level cost of living, generosity of anti-poverty programmes and individual family income-to-needs ratio (log transformed). Cash assistance was based on both monthly Temporary Assistance for Needy Families benefits in that state and the average monthly Earned Income Tax Credit in that state. Higher cost of living was associated with smaller hippocampal volume among low-income participants, but this was attenuated when states also offered more generous cash benefits. Postal abbreviations for the 17 states in the ABCD Study (CA, California; CO, Colorado; CT, Connecticut; FL, Florida; MD, Maryland; MI, Michigan; MN, Minnesota; MO, Missouri; NY, New York; OK, Oklahoma; OR, Oregon; PA, Pennsylvania; SC, South Carolina; UT, Utah; VT, Vermont; VA, Virginia; and WI, Wisconsin) are placed along the *x*-axis in the location that corresponds most closely to their cost of living and cash assistance relative to other states. Hippocampal volume estimates are equivalent to the random intercept of the relation between income and hippocampal volume for that state when family income is 1 s.d. above (high income) or below (low income) the mean. Figure adapted with from ref. 78 under a Creative Commons licence CC BY 4.0.

needed to conduct and coordinate large team-based efforts are often prohibitive, which means that researchers must almost always rely on existing multi-site studies, such as the ABCD Study, where the data have already been collected. Consequently, researchers are constrained by the measures and tasks that were previously collected, which may not always align with the research question and may not include the measures that are needed to improve inferences (for example, key confounders, plausible alternative explanations and candidate mechanisms). Given these challenges, researchers may need to consider alternative approaches to study whether social inequalities are related to neural outcomes, such as the one we consider next.

## Multi-site, multi-study

Despite the important insights that the methodological approaches reviewed above have produced, they are limited in that single-site studies can only examine variation across neighbourhoods, and multi-site studies require massive funding investments and coordination across institutions and researchers. As such, a third approach—a multi-site, multi-study approach known as 'spatial meta-analysis'—circumvents the challenges associated with single- and multi-site, single-study designs. This approach retains many aspects of a traditional meta-analysis, with the added step that studies are geo-located, allowing researchers to characterize each included study in terms of the social context in which it was conducted[82]. Spatial meta-analyses therefore leverage the contextual variability that naturally exists across neuroimaging studies to examine associations between contextual variables and neural outcomes. This approach allows researchers to utilize data that are already published and generate new insights by linking those results to structural measures of inequality after the fact.

Although meta-analyses of functional magnetic resonance imaging (fMRI) data are commonplace in cognitive neuroscience, only two recent studies, to our knowledge, have used spatial meta-analyses to examine contextual variation across studies. The first re-analysed a comprehensive set of studies examining white participants' neural responses to Black (versus white) faces within the USA to determine whether community-level racial prejudice was associated with the degree of neural activation to Black (versus white) faces in primarily white participants[83]. A substantial body of work in social neuroscience has examined the neural underpinnings of racial prejudice[58]. Initial work on this topic centred on the role of threat-related responses in the amygdala to out-group members as a potential neural mechanism underlying racial prejudice[58]. Despite decades of research, however, evidence for a stronger amygdala response to racial out-group compared with in-group members has been mixed[58]. A spatial meta-analysis was used to examine[83] whether these inconsistencies may be due, in part, to contextual factors typically ignored in cognitive neuroscience, such that observed associations are more (or less) pronounced depending on the structural context in which participants are embedded—specifically, to the varying levels of racial prejudice in these communities. To test this hypothesis, the authors aggregated racial attitudes, obtained from over 10,000 respondents from Project Implicit, to the 17 counties in which each study was conducted. Multi-level kernel density analysis demonstrated that significant differences in neural activation to Black (versus white) faces in two key nodes of the salience network (right amygdala and dorsal anterior cingulate cortex) were detected more often in communities with higher (versus lower) levels of explicit racial prejudice. Sensitivity analyses revealed that this pattern of activation was unrelated to three alternative variables that may serve as common causes or consequences of racial prejudice (that is, income inequality, community-level racial composition and community-level education), providing further evidence for specificity of the results to community-level racial prejudice[83].

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**Table 3 | Examples of multi-site neuroimaging studies**

| Study name | Sample size (*n*) | Sites |
|---|---|---|
| National Institutes of Health (NIH) Magnetic Resonance Imaging (MRI) Study of Normal Brain Development | 505 | Massachusetts, Ohio, Texas, California, Pennsylvania, Missouri |
| Adolescent Brain and Cognitive Development Study | 11,878 | California, Colorado, Connecticut, Florida, Maryland, Michigan, Minnesota, Missouri, New York, Oklahoma, Oregon, Pennsylvania, South Carolina, Utah, Virginia, Vermont, Wisconsin |
| Human Connectome Project | 1,350 | Massachusetts, California, Minnesota, Missouri |
| Lifespan Human Connectome Project | 1,200 | Massachusetts, California, Minnesota, Missouri |
| Lifebrain consortium | 5,140 | Spain, Germany, Sweden, Norway, Great Britain, Denmark, Netherlands, Switzerland |
| IMAGEN Study | 2,000 | Great Britain, Ireland, Germany, France |
| UK Biobank (neuroimaging subsample) | 46,924 (as of February 2023) ~100,00 (planned) | Counties in the UK |

Whereas this spatial meta-analysis measured structural sources of inequality (that is, area-level prejudice) at the local level (US counties), a second spatial meta-analysis assessed gender inequality at the level of 29 countries, using nation-level data derived from two widely utilized indicators of gender inequality[84,85]. The authors then examined associations of gender inequality with sex differences in cortical thickness and surface area in adult men and women. The study found thinner cortices among women (versus men) in countries with greater gender inequality—especially in neural regions involved in salience processing (that is, right caudal anterior cingulate and right medial orbitofrontal) and in left lateral occipital cortex[86] (Fig. 3). By contrast, there were no sex differences in these neural regions between men and women in countries with less gender inequality. Analyses remained robust after controlling for other country-level economic characteristics (that is, per capita gross domestic product).

Collectively, these two sets of findings confirm the feasibility of using spatial meta-analysis to link structural measures of social inequality to neural outcomes, highlight the novel insights it can generate regarding how social inequality relates to brain structure and function, and underscore the utility of this method for reconciling conflicting results in the cognitive neuroscience literature.

**Strengths and limitations.** Spatial meta-analysis capitalizes on the substantial heterogeneity in exposure to various forms of social inequality that occurs across individual neuroimaging studies. This represents its greatest advantage: the ability to leverage geographic and temporal variation in existing neuroimaging studies to examine relationships between social inequalities and neural outcomes.

This approach also has limitations. One relates to data constraints in terms of where studies are conducted, as the social contexts have already been selected based on where the individual studies happened. This may not be an issue if these studies are spatially distributed; however, if studies are conducted in a few communities, this could introduce issues related to spatial clustering (for example, geospatial autocorrelation) or to restricted ranges in the measures of social inequality. A second set of limitations concerns the ability to synthesize fMRI data across multiple laboratories. These issues include differences in pre-processing, thresholding of whole-brain effects, reporting of parameter estimates and regions of interest used to extract effects. That said, researchers have developed analytic techniques to overcome these challenges, including in meta-analyses, with notable successes in identifying, for example, the brain bases of emotion and memory[87–93]. A third limitation involves the availability of data on the location of the individual studies. Often, this information is not provided, is inexact or must be inferred based on the institution of the first or senior author. This limitation means that it is often necessary to contact individual researchers to request specific details on study location. One recommendation of our analysis, which others have also called for[82], is to require this type of geographic information to be more systematically reported in neuroimaging studies.

## Steps for research linking social inequality and neural outcomes

In this section, we offer several strategies and considerations to guide programmatic research on the links between social inequality and neural outcomes, and we discuss ethical issues in conducting this work.

### Identify form of social inequality to be evaluated

The first step is to identify the form of social inequality that will be the focus of the investigation. We suggest three specific questions to help to inform the selection of this variable. (1) What theoretical support exists for this factor? (2) What is the empirical evidence for this factor influencing cognitive, affective and behavioural processes, and are these processes plausibly related to brain structure and function? (3) How strong is this evidence and has it been established across multiple methods (for example, observational and quasi-experimental) and measures? In answering these questions, we encourage researchers to consider literature outside of cognitive neuroscience, given that the topic of social inequality is an inherently interdisciplinary field. For example, scholarship from sociology[35], psychology[36], anthropology[94] and public health[2] has revealed that stigma and discrimination are structural causes of population-level inequalities[95]. Interdisciplinary collaborations with colleagues from these allied disciplines ensure that cognitive neuroscientists are well-versed in the sources of social inequality that may be most relevant to their question of interest.

### Identify appropriate structural measures of social inequality across relevant levels of analysis

A second step is to identify reliable and valid measures of the social inequality variable of interest. Structural measures, including social attitudes, have been collected by survey research firms or other agencies (for example, the National Opinion Research Center). However, it is often necessary to apply for restricted access to obtain these measures at certain geographic scales (for example, states and counties). In other instances, structural measures must be assembled by researchers themselves. In these cases, it is advisable to include collaborators on the research team who possess the necessary expertise in the collection of these data, as in the case of social policies. Scholars have also noted the importance of incorporating the perspectives of communities with lived experience in the development of measures of structural inequality (for example, structural racism), through methods such as community-based participatory research[96]. Doing so ensures that measurement approaches are also ecologically valid.

Another important measurement consideration is the geographic level(s) most relevant for the research question. In the context of social attitudes, it is probably important to obtain them at levels that are most proximate to the respondent (for example, county)[97]. By contrast, for other measures, such as laws, states or countries may be the most relevant unit of analysis.

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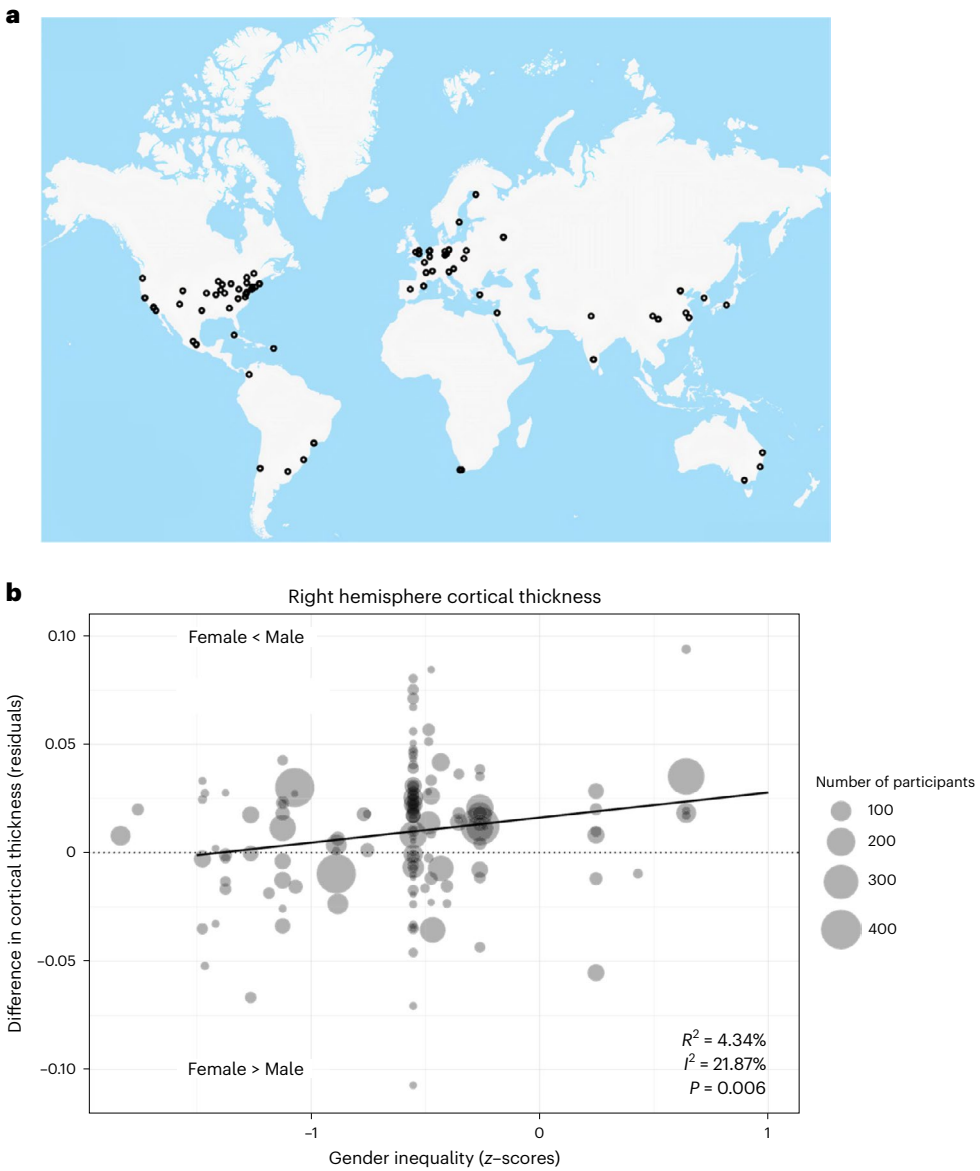


**Fig. 3 | Spatial meta-analysis of the association between gender inequality in 29 countries and cortical structure. a**, In total, ref. 86 identified 139 studies across 29 countries. **b**, Association between gender inequality and sex differences in cortical thickness and surface area using nation-level data from the United Nations and the World Economic Forum. In studies conducted in countries with greater gender inequality, men tended to have greater right hemisphere cortical thickness. Associations between gender inequality and sex differences in cortical thickness in specific neural regions were also observed. Figure adapted with from ref. 86 under a Creative Commons licence CC BY 4.0.

## Identify the sample

Once researchers have selected the structural measure(s) of social inequality, they must make decisions regarding the study sample(s). Typically, research on the consequences of social inequality is focused on marginalized groups. As other commentators have noted, sample sizes for minoritized individuals are typically quite small in neuroscience research[98], and stratified estimates are frequently not reported for key sociodemographic characteristics (for example, race)[99]. To these important points we add that social inequality may influence who is ultimately recruited and retained in research samples, including in neuroscience studies. Although such selection factors are often treated as nuisance variables, sociologists have urged scholars to conceptualize selection instead as a social process that is worthy of study in its own right[100].

These observations have important implications for identifying the samples in studies that employ the methodological approaches outlined in this Perspective. For single-site, single-study approaches, in which researchers are typically collecting their own data, a priori power analysis should be used to determine sufficient sample sizes of marginalized groups. For multi-site studies (whether single- or multi-study), cognitive neuroscientists must rely on previously collected data, and thus should be cognizant that selection processes could operate such that marginalized individuals who are most vulnerable to the consequences of social inequality are the least likely to be included in these neuroimaging studies. Critically, this selection bias most probably leads to an underestimate of the association between social inequality and neural outcomes, a point that is important to consider in evaluating findings across studies.

## Identify appropriate research design

The next step is the identification of the appropriate research design. Table 2 provides a list of questions across each of the three methodological approaches to help to guide the selection of study design for a particular research question.

### Analysis and addressing issues of causal inference

In many respects, after the first four steps have been completed, the final step in terms of analysis proceeds according to most other research studies. Cognitive neuroscientists are already intimately acquainted with the error of reverse inference in neuroimaging data[101]. We highlight two additional issues that deserve particular attention when examining social inequalities as predictor variables. The first is the importance of using mixed-effects models (also known as multi-level models) to appropriately account for clustering, given that individuals will be nested within context. In addition, in multi-site, single-study approaches, it is often necessary to include random effects for site.

The second issue concerns causal inference. In experimental studies, individuals are randomly assigned to condition; researchers can therefore be reasonably confident that the independent (manipulated) variable caused the dependent variable (outcome), thereby ruling out alternative explanations. It is neither ethical nor feasible to randomly assign individuals to different social contexts. As such, researchers must rely on observational and quasi-experimental designs, which necessitate the use of different strategies for addressing alternative explanations for the observed association between social inequality and neural outcomes. Here, we briefly highlight two such strategies that have been used in extant studies.

One strategy is addressing alternative explanations through statistical controls. Because other features of the social context co-occur with structural forms of inequality, researchers must examine whether their measure of inequality remains associated with the neural outcome(s) over and above other area-level covariates. For instance, a previous study[78] found that state-level policies expanding or restricting the social safety net for low-income families moderated the relationship between family SES and hippocampal volume. In supplementary analyses, the authors showed that these findings were robust to controls for a wide range of state-level social, economic and political characteristics (for example, state preschool enrolment and unemployment). Of course, as with all observational designs, this method cannot rule out the possibility of unmeasured confounding variables, and thus results in such studies can suggest—but not definitively confirm—a causal link.

A second strategy for addressing plausible alternative explanations is the strategic selection of control groups (also known as negative control analyses)[102] in which researchers examine whether there is an association in a group where it would not be expected to occur. One study[49] using this strategy showed that structural forms of stigma (for example, aggregated social attitudes and social policies) were associated with smaller hippocampal volume among Latinx and Black youth. By contrast, structural stigma was unrelated to hippocampal volume in non-stigmatized youth. This evidence for result specificity supports the hypothesis that results are due to structural stigma itself and not to other macrosocial factors associated with it (for example, area-level SES), which should theoretically affect both stigmatized and non-stigmatized youth in similar ways.

There are many other methodological and analytical strategies for marshalling evidence for causality with observational data—including instrumental variables and regression discontinuity designs. Researchers interested in testing neuroscience models using structural data on social inequality should consider collaborating with scholars from economics, sociology and social epidemiology who have expertise in these various approaches to causal inference.

### Ethical considerations

There is a long, ignominious history of the (mis)use of scientific data with populations who have borne the brunt of the consequences of social inequality. In light of this history, researchers must be especially attentive to how their study might further contribute to the marginalization of certain social groups—especially in the context of public misunderstandings of neuroscience results, such as biological reductionism[45]. Ethical considerations require thoughtful engagement at each step of the research process outlined above—from exploring why researchers are posing their specific questions, to the specific measures they select, to the analytical approaches they employ, to how their results are communicated to the scientific community and broader public. Although the harms of historical and contemporary neuroscience practices to marginalized communities have been reviewed recently elsewhere[103], there are potential benefits as well. Indeed, providing evidence that structural sources of inequality predict neural outcomes locates any group difference in brain structure or function within aspects of the broader social context rather than within individuals; such findings may therefore be less likely to be used to perpetuate stereotypes or to justify discrimination. We refer readers to helpful recommendations for how cognitive neuroscience datasets can be used to advance health equity and to minimize harm[104].

## Recommendations for future research

Existing studies that we have reviewed in this Perspective all use observational data, which cannot establish causality. Future research would therefore benefit from utilizing methods from other fields (for example, econometrics, sociology and epidemiology) to strengthen causal inferences regarding the relationship between social inequalities and neural outcomes in order to ensure a more robust evidence base. These methods might include quasi-experimental designs that leverage short-term changes in social inequality (for example, social policies that differentially target marginalized groups for social exclusion)[105], or divergent mobility patterns that naturally occur in longitudinal studies (for example, movement of respondents to different social contexts, such as moves from higher to lower poverty neighbourhoods, or higher to lower stigmatizing climates). Both types of designs have been effectively used to study biopsychosocial consequences of social inequality, and thus hold promise for cognitive neuroscience (see reviews in the area of stigma and prejudice[36,106]; and an example of mobility studies in economics[107]).

Several research questions also remain unanswered regarding whether, how, and for whom social inequalities are related to neural outcomes. For instance, our Perspective examined structural measures of social inequality that have received the most empirical attention in the cognitive neuroscience literature—including structural stigma, community-level prejudice, gender inequality, neighbourhood disadvantage, and the generosity of the social safety net for low-income families. Future studies are needed to examine linkages between additional forms of social inequality and neural outcomes, employing the methods that we have outlined in this Perspective. Examples might include air pollution[108] and access to green spaces[109], both of which are socially patterned[108]. This research will provide important information regarding potential boundary conditions of the consequences of social inequality for brain structure and function.

In addition, existing studies have focused on direct associations of social inequalities with measures of neural structure and function. Less attention has been paid to identifying the factors that may influence the direction and magnitude of these relationships (that is, moderators). The identification of moderators at multiple levels of influence—material resources, social, psychological, biological—therefore represents an important area of enquiry. Additional questions for future enquiry include the following: are the associations between social inequalities and neural outcomes similar across different geographic units of analysis—for example, city and state—or are these associations stronger at more proximal levels? Do these different units interact to explain variation in neural structure and function, as has been found for various psychological phenomenon, such as identity concealment?[43] Are associations between social inequalities and neural outcomes sensitive to particular developmental periods?

## Conclusions

We present a call to action for the field of cognitive neuroscience to begin to grapple with the role that social inequality may play in shaping neural outcomes and highlight emerging findings suggesting that structural approaches may yield new insights into whether and how various dimensions of social inequality relate to neural structure and function. We present three methodological approaches that have recently been utilized to study associations between structural measures of social inequalities and neural outcomes. We hope our Perspective invigorates new research in cognitive neuroscience that explicitly incorporates upstream contextual factors, which holds potential promise for contributing to public discourse on some of the most meaningful social-, health- and policy-related questions of our time.

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## Competing interests
The authors declare no competing interests.

## Additional information
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