



Heterogeneity of depression across the socioeconomic spectrum

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Why is lower socioeconomic status associated with higher rates of depression? And, is the surplus of depression at lower SES just more of the same type as depression found at higher levels, or is it distinctive? We addressed these questions by examining the relations among SES, amygdala volume, and symptoms of depression in healthy young adults. Amygdala volume, a risk factor for depression, does not synergize with SES in a diathesis–stress relation, nor does it mediate the relation of SES to depression. Rather, SES and amygdala volume are independent, additive risk factors. They are also associated with different depression symptoms and, whereas perceived stress fully mediates the relation of SES to depression, it has no relation to amygdala volume. These findings suggest heterogeneity of depression across the socioeconomic spectrum, with implications for treatment selection as well as for future genetic and brain studies.

socioeconomic status | depression | amygdala | stress

Sociologists and epidemiologists have long noted that lower socioeconomic status (SES) is associated with higher rates of depression (1, 2) as well as subthreshold symptoms of depression (3). The strength of these relations is substantial. A US National Center for Health Statistics (NCHS) report (1), found that adults living at or below the poverty line (then defined as the equivalent of \$26,500/y for a family of four) were four and a half times more likely to experience depression than adults in the same size family making \$106,000/y or more.

Here, we address the nature of depression across SES: Is the surplus of depression at lower levels of SES the same as, or distinct from, depression found across the SES spectrum? If it is distinctive, there would be one form of depression that afflicts people, regardless of SES, and another form that afflicts those of lower SES and is responsible for the surplus.

Our approach to this question is to determine the relations between SES and other known risk factors in predicting depression symptoms (4). One possibility is that different factors contribute to depression vulnerability independently (e.g., ref. 5). For example, depression risk could be increased by lower SES and, independently, by some other risk factor that is not related to SES. In such a case, depression would be heterogeneous with respect to risk factors, with implications for etiology and treatment targets.

Alternatively, risk factors can synergize, as in a classic diathesis–stress model (e.g., ref. 6). For example, vulnerability to depression could be reflected by a neurobiological characteristic, and the experience of lower SES could increase the likelihood that this vulnerability becomes manifest as depression. According to this model, the surplus depression at lower levels of SES would result from depression vulnerability being triggered more often. This suggests that once the vulnerability (common to higher and lower SES) is triggered, the nature of the depression would be the same and simply more frequent at lower SES.

Or factors could stand in a mediation relation to depression (e.g., ref. 7), as when a distal factor such as SES increases depression risk by way of a more proximal risk factor. Here too, the surplus depression at lower levels of SES would simply consist of more of the same depression that afflicts all patients. The mediation hypothesis implies that depression risk at higher and lower levels of SES is similarly related to the mediating risk factor, and the only difference between SES levels is that there is simply more of that risk factor at lower levels.

Considerable research links amygdala volume to depression. Although findings are variable, they generally indicate that larger amygdala volumes are a risk factor for depression. Larger volumes have been found with first-episode depression (8) and with subclinical depression (9) which itself is a risk factor for major depression (10). Unaffected first-degree relatives of people with depression also have larger amygdalae (11). In contrast, amygdala volume is unrelated to depression in some samples, including the large, pooled sample of the ENIGMA consortium (12). Finally, some studies find depression associated with smaller amygdala volumes; this has been conjectured to result from progressive excitotoxicity in recurrent, long-lasting, or untreated depression (13, 14). Consistent with this interpretation is the finding that patients in remission have larger amygdalae compared to those who are currently depressed or never

Significance

Depression diagnoses rise sharply with decreasing socioeconomic status (SES). Here, we attempt to characterize the surplus of depression symptomatology found at lower SES. We find that the depression symptom load of lower SES individuals is distinctive in its relation to a neuroanatomical risk factor for depression (amygdala volume) and a psychological risk factor (perceived stress) and may manifest differently in terms of specific depression symptoms. No support was found for alternative hypotheses relating SES and amygdala volume to depression symptomatology, specifically diathesis–stress and mediation. The cross-sectional and observational nature of this study prevents conclusions about causality, but the finding of SES-based heterogeneity has implications for diagnosis, treatment, and future genetic and imaging research studies.

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depressed (15). Both right- and left-sided amygdala volumes have been associated with depression, including the early and/or trait vulnerability findings cited here (left-sided relation only in (9); bilateral in refs. 8 and 11).

How might SES and amygdala volume jointly predict depression risk? Given that SES is associated with amygdala volume, the amygdala is a plausible mediator between SES and depression. For example, in a study examining SES, amygdala volume, and internalizing symptoms in children and youth from families with a wide range of SES, Merz, Tottenham, and Noble (16) modeled the relations among these and other variables. The pattern of results was consistent with the hypothesis that “differences in amygdala development may partially explain the higher levels of depressive symptoms often found among children from disadvantaged families” (p. 320). However, a formal mediation analysis was not reported, and interpretation was complicated by an age effect on the relation of SES to amygdala volume (cf. ref. 17).

The amygdala has been singled out as a likely mediator between SES and affective disorders by other authors as well. For example, Palacios-Barrios and Hanson [(18), p.59] suggest that “alterations in the amygdala have been linked to major depression, anxiety, post-traumatic stress disorder, and aggression, with higher functional reactivity and smaller volumes often relating to psychopathology ... These associations between neurobiology and psychopathology are particularly important given that these same brain regions are impacted by poverty.” Similar proposals concerning SES, amygdala, and affective disorders have been put forth by Kim et al. (19), McEwen and Gianaros (20), Nusslock and Miller (21), and Smith and Pollak (22).

A direct test of these hypotheses requires information about SES, amygdala volume, and depression to be analyzed in the same participants and has not, to our knowledge, been reported. We therefore carried out such an analysis of levels of depression symptomatology in a sample of healthy young adults.

Results

Descriptive Statistics on Main Variables of Interest. The Table 1 shows the means and SDs of key variables of interest, indicating their raw values in relevant units of measurement, before adjustment for covariates. Distributions of each measure are shown in *SI Appendix, Fig. S1*.

Table 1. Descriptive statistics of key variables of interest

Variable	Measurement	Mean (SD)
Income (for SES composite)	Income band* 1 to 7	5.267 (2.09)
Educational attainment (for SES composite)	Years* 11 to 17	14.97 (1.85)
Amygdala volume (left)	mm ³	1555 (205.84)
Amygdala volume (right)	mm ³	1637 (218.71)
Current depression symptom load	Sum of 14 items (response 0, 1, or 2)	4.10/28 (3.39)
Past depression experience	Sum of 9 items (response 0 or 1)	1.29/9 (2.57)
Perceived stress	T-score of sum of 10 items (responses 1 to 5)	47.96/87 (9.07)

The coding of income and education (*) is described in *SI Appendix*.

Table 2. Results of regressions relating SES, amygdala volume, and current depression symptom load, controlling for gender, age, and race

Each risk factor individually (with covariates)	Beta (S.E.)	P-value
SES predicting depression	−0.14 (0.04) ***	0.000
Amygdala predicting depression	0.11 (0.04) **	0.007
SES predicting amygdala	0.11 (0.03) ***	0.000
Both risk factors together (with covariates)	Beta (S.E.)	p-value
SES predicting depression (amygdala volume in model)	−0.16 (0.04) ***	0.000
Amygdala predicting depression (SES in model)	0.14 (0.04) **	0.001
SES and amygdala interaction predicting depression	0.02 (0.03)	0.494
Indirect path from SES to depression via amygdala (note different sign from SES to depression)	0.02 (0.01) 95% CI = 0.005 to 0.030	

Notation: *** $P < 0.001$, ** $P < 0.01$, * $P < 0.05$, † $P < 0.1$

Three Hypotheses about SES, Amygdala Volume, and Depression.

The first hypothesis, of a diathesis–stress relation between amygdala volume and SES, predicts that lower SES would synergize with amygdala volume leading to an interaction between these risk factors. As shown in Table 2, the interaction is not significant. In addition, it does not differ by gender, age, or race ($P > 0.1$ in all cases). Thus, we find no evidence of a diathesis–stress relation.

The second hypothesis, whereby the SES effect on depression is statistically mediated by amygdala volume, was tested by first analyzing the pairwise relations among SES, amygdala volume, and depression (Table 2). Testing SES and amygdala volume individually, we find that current depression symptom load is higher for individuals with lower SES and for those with bigger amygdalae. These results confirm the expected relation of SES to depression symptom load and are consistent with past findings of amygdala volume in individuals with subthreshold depression. Also, consistent with the trend across previous findings (23), lower SES is found to be associated with smaller amygdala volume. All of the reported results are invariant over gender, age, and race ($P > 0.1$ in all cases).

The results of the mediation analysis are surprising. The indirect effect of SES on depression via amygdala volume is significantly positive in sign (i.e., higher SES, higher depression), which is opposite in sign to the direct effect (Table 2). Thus, not only does amygdala volume mediate the effect of SES on depression, but it also significantly suppresses it (24), definitively disconfirming the mediation hypothesis for the young adult participants of the HCP.

This constitutes evidence for the third hypothesis of independent, additive risk factors for depression. Had the mediation analysis failed to find significant mediation of the SES depression relation by amygdala volume, one might wonder whether this null result was attributable to insufficient power. By finding significant suppression (also known as inconsistent mediation), the possibility of a small and undetectable mediation effect is ruled out. SES and amygdala volume do not account for common variance in depression symptom load.

*Suppression is sometimes introduced with the following intuitive example: Workers with higher IQs make fewer errors, workers with higher IQs are more prone to boredom on the job, and bored workers make more errors. Thus, the negative relation of IQ to error rate gets stronger when boredom is added as a mediator [Mackinnon et al., (24)].

This addresses the main question of this study, in that depression concentrated at lower levels of SES differs from depression found more widely distributed across SES. Past depression experience shows the same independent relation as depression symptom load, with a small suppression effect; neither the diathesis–stress model, nor standard mediation was supported (*SI Appendix, Table S1*).

In the analyses just presented, amygdala volume consists of the left and right amygdalae combined. We chose to analyze total amygdala volume given the absence of compelling reasons to focus just on one side or the other. However, we also assess possible asymmetries and report them in *SI Appendix, section 4 (SI Appendix, Table S2 and Fig. S2)*. They can be summarized thus: The left amygdala showed highly significant effects of SES, depression symptom load, and past depression experience, while the right showed significant effects of SES but only nonsignificant trends for the depression measures.

Converging Evidence of Heterogeneity: Symptom Analysis. We conclude from the above analyses that the surplus of depression in lower SES is different from depression that is associated with larger amygdalae at all levels of SES. This raises the question of whether these two forms of depression differ qualitatively, in their typical symptoms. Using the original 0, 1, or 2 ratings for each symptom, we examined the relation between each symptom's ratings and the risk factors of SES and amygdala volume together in a single model. Similar results were obtained when testing one risk factor at a time, as shown in *SI Appendix, Table S3*.

Lower SES people in the present sample are more likely than higher to report crying, trouble making decisions, sleeping more, trouble sleeping, and feeling they cannot succeed. In contrast, those with bigger amygdalae report feeling guilty, not eating well, and trouble sleeping, only significant if the model also incorporated SES. The symptom-level findings suggest that the surplus of depression at lower levels of SES may be different in kind from depression associated with amygdala volume.

In a further exploration of the association of specific symptoms with SES using a simple machine learning classifier, participants could be classified as higher or lower SES with modest but significant accuracy on the basis of their depression symptoms (*SI Appendix, section 6*).

Converging Evidence of Heterogeneity: Role of Perceived Stress. SES is a fairly abstract construct, which presumably affects mental health through more proximal factors. One candidate proximal factor is psychosocial stress. Stress has a known relation to SES, with higher stress at lower levels of SES (25). It is also associated with depression, with higher stress in depression (26). Stress is measured in many ways, from tallies of recent stressful life events or cortisol measurements (which can both be viewed as “objective” measures) to self-reports of how stressful life seems (a more subjective measure). The stress measure available in the HCP is the Perceived Stress Scale, which is a subjective measure. It has been correlated with stressful life events but is intended to measure directly the respondent's appraisal of how stressful their life is, which is an even more proximal measure of SES-related causes of depression (27)

The Table 3 shows that all three pairwise relations among SES, perceived stress, and depression are significant, but perceived stress is not related to amygdala volume. These effects are invariant over gender, race, and age ($P > 0.1$ in all cases). The lack of perceived stress–SES relation disconfirms possibility that SES is a diathesis that is triggered by perceived stress. Instead, the mediation analysis shows that perceived stress fully mediates the SES–depression relation. Although not a test of the causal role of perceived stress,

Table 3. Results of regressions relating SES, perceived stress, and current depression symptom load, controlling for gender, age, and race

Each risk factor individually (with covariates)	Beta (S.E.)	<i>P</i> -value
SES predicting depression	−0.14 (0.04) ***	0.000
Stress predicting depression	0.51 (0.03) ***	0.000
SES predicting perceived stress	−0.16 (0.03) ***	0.000
Amygdala predicting stress	0.03 (0.04)	0.437
Both risk factors together (with covariates)	Beta (S.E.)	<i>P</i> -value
SES predicting depression (stress in model)	−0.04 (0.03)	0.182
Perceived stress predicting depression (SES in model)	0.51 (0.03) ***	0.000
SES and perceived stress interaction predicting depression	0.03 (0.03)	0.263
Indirect path from SES to depression via perceived stress	−0.10 (0.02) 95% CI = −0.133 to −0.061	

Notation: *** $P < 0.001$, ** $P < 0.01$, * $P < 0.05$, † $P < 0.1$

the analysis confirms that when perceived stress is added to the model relating SES and depression symptom load, the direct SES–depression effect becomes nonsignificant. The same mediation pattern of mediation by perceived stress is found for past depression experience (*SI Appendix, Table S4*). Thus, perceived stress, or some factor associated with it, statistically accounts for the lower SES surplus of depression.

Interrelations among SES, Stress, Amygdala Volume, and Depression: A Path Analysis. When we consider mediation of the SES–depression relation by perceived stress and amygdala volume together, the relations studied individually remain significant in the complete model (Fig. 1). The significant difference between these paths indicates that they account for distinct covariance of SES–depression relation. Similar results are seen in past depression experience (*SI Appendix, Fig. S3*).

Sensitivity analyses show similar results when participants without a personal or parental history of depression are analyzed. The relatively small groups with personal or parental history show few significant effects (*SI Appendix, Table S5*). Specificity test shows that SES relation to depression through amygdala path remains significant with other brain regions (lateral prefrontal cortex and hippocampus) as parallel mediators, while SES relation to depression through these other brain regions shows nonsignificant effects (*SI Appendix, section 9*).

Discussion

The excess depression at lower levels of SES is different in nature from depression at higher levels of SES. By testing whether SES differences in amygdala structure account for the SES gradient in depressive symptoms, we found that amygdala volume is predictive of depression at all levels of SES but actually comes into play more in depression at higher levels of SES. A distinct and stronger

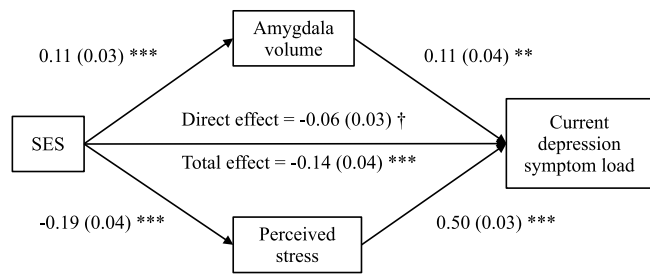


Fig. 1. Path diagram of amygdala volume and perceived stress in the association of SES and current depression symptom load, controlled for gender, age, and race. Indirect path of amygdala volume: $b = 0.01$, $S.E. = 0.01$, 95% $CI = 0.003$ to 0.024 . Indirect path of perceived stress: $b = -0.10$, $S.E. = 0.02$, 95% $CI = -0.132$ to -0.060 . Contrast of the indirect paths, $b = -0.11$, $S.E. = 0.02$, 95% $CI = -0.146$ to -0.071 . Standard coefficients on paths and SE in parentheses. Notation: *** $P < 0.001$, ** $P < 0.01$, * $P < 0.05$, † $P < 0.1$.

effect, outweighing the predictive power of amygdala volume for depression, is the effect of SES.

SES and amygdala volume are associated with different sets of depression symptoms in this study, further supporting the idea that the surplus of depression in lower SES is distinctive. A third way in which the depression of lower SES individuals is distinctive is its relation to perceived stress, as measured by the Perceived Stress Scale. SES and amygdala volume stand in starkly different relations to perceived stress; the latter is related to SES and statistically fully mediates the SES–depression relation. In contrast, perceived stress is unrelated to amygdala volume in this sample.

These findings may have clinical and scientific implications. Clinically, distinguishing between SES-linked depression and other forms may enable better matching of patients to treatments. On average, lower SES patients experience poorer treatment outcomes both in psychotherapeutic (28, 29) and pharmacological interventions (30, 31).

Scientifically, parsing depression into different phenotypes related to SES may increase the power of research by accounting for unrecognized heterogeneity (32, 33). The ability to discover the genetic, physiological, anatomical, and developmental bases of depression will depend crucially on well-characterized phenotypes.

Limitations of the present study include the rudimentary measures of our key variables: depression symptoms, SES, and stress. A fuller sampling of depression symptoms would have allowed a better understanding of how and whether different forms of depression are associated with higher and lower SES. Fuller information on SES, including childhood SES and subjective SES, could have refined our understanding of the SES–depression relation. The role of stress would have been further clarified by measures of objective stress in addition to perceived stress.

The initial question motivating our analyses was to test existing hypotheses about the SES–depression relation, according to which the amygdala plays a role in this relation. While much current research on depression and the brain takes a network perspective rather than focusing on specific structures (34, 35), for the present research, we used the differential predictive power of amygdala volume as a means of parsing the heterogeneity of depression. We look forward to continued progress in the network neuroscience of SES and depression, and the insights that may come as these two bodies of knowledge are combined.

The cross-sectional and observational nature of our data limits its usefulness for addressing causal questions about the etiology of depression across levels of SES. Longitudinal assessments would, at least, have offered insight into the natural history of the forms of depression provisionally identified here. With regard to causal

inferences, it bears repeating that our tests of mediation address only statistical mediation rather than causal mediation. Although causality was not the focus of this study, a longitudinal study would be valuable in the future to constrain directions of causality. Addressing these limitations in the future with samples of different ages, races, and depression severities, and including additional biological measures and risk factors associated with SES, will further clarify the different possible etiologies of depression.

A final caution concerns the possible misinterpretation of psychological and biological explanations of hardships related to socioeconomic status. Although the present study focuses on individual minds and brains, this does not diminish the importance of the wider social context. Using neuroscience to better understand elevated rates of depression in lower SES is no more “blaming the victim” than other results concerning risk factors within the person. There is an important role for nonneural differences, including differences in access to material and social resources, which differ greatly by SES. The challenge of understanding socioeconomic disparities in depression will require us to integrate knowledge across societal and individual levels of description.

Methods

Participants. Participants were drawn from the Human Connectome Project (HCP) young adult sample (22 to 35 yo) (36, 37). We selected only participants with information about educational attainment and income, mental health, and T1 MRI scans, who were not currently working toward a degree. The final sample had 881 (females 493 or 56.96%) and broadly reflected the ethnic and racial composition of the US population (White 75.94%, Black 15.21%, Asian 4.54%, and others 4.31%). HCP procedures were conducted according to a protocol in accordance with the Declaration of Helsinki and approved by the Washington University Institutional Review Board (IRB #201204036; title: “Mapping the Human Connectome: Structure, Function and Heritability”). Our use of these data was determined to be exempt from further human subjects’ review by the Penn IRB (# 826538; title “Secondary Analysis of the Human Connectome Project”).

Measures. SES was a composite of continuous measures of income and education ($r = 0.39$), after z-transforming each to place them on a common scale (see *SI Appendix, section 1* for details). Current symptoms of depression were obtained from the DSM-oriented depression scale from the Achenbach System of Empirically Based Assessment (ASEBA) Adult Self-Report questionnaire and consisted of 14 items encompassing cognitive, mood, and vegetative symptoms (38). Participants rated each of the 14 symptoms as not true – 0, somewhat or sometimes true – 1, or very true or often true – 2. The sum of these 14 ratings was the current depression symptom load. Past depression experience was based on nine symptoms from the Semi-Structured Assessment for the Genetics of Alcoholism [SSAGA (39)], which were rated present – 1 or absent – 0. Given the variable temporal separation between the past depression experience scores and the current risk measures, and in anticipation of relatively few elevated SSAGA scores, we relegated this measure to secondary analyses. The SSAGA also included information about personal and parental histories of depression. Finally, the Perceived Stress Scale (27) was administered.

Images were collected on a 3T Siemens Skyra scanner (Siemens AG) with a 32-channel head coil. T1-weighted structural images were acquired with a resolution of 0.7 mm3 isotropic (FOV = 224 × 240, matrix = 320 × 320, 256 sagittal slices; TR = 2,400 ms and TE = 2.14 ms). Left and right amygdala volumes were calculated by the HCP using FreeSurfer pipeline (version 5.2).

Analyses. Given the expected right skew of the depression symptom load measure, scores were square root transformed. For past depression symptoms, for which few participants were expected to endorse any items, logistic rather than linear regression would be used. Distributions will be graphed and presented in *SI Appendix, Fig. S1*.

In overview, analyses consisted of multiple regression analyses to adjudicate among diathesis–stress, mediation, and additive models of risk factors and their relations to depression measures, followed by sensitivity analyses. Beginning with the diathesis–stress hypothesis, we tested whether an SES-by-amygdala volume interaction predicted current depression symptom load. We then examined the

mediation hypothesis, estimating indirect pathways with 95% bias-corrected CIs based on bootstrapping with 50,000 samples with the PROCESS macro in SPSS (40). We also predicted current depression symptom load by risk factors such as amygdala volume and SES, each of them in a linear regression model without the other as well as combined. All the above analyses initially included higher-order interactions of main variables with covariates (i.e., gender, age, and race), with the plan of dropping these terms from the models unless they account for significant variance. The same analyses were repeated with past depression experience. Next, motivated by the results to be reported, additional analyses were carried out with perceived stress added as an additional predictor variable using the same approach just described. We conducted analyses separately on left and right amygdala and showed the results in *SI Appendix*. In the main text, we presented the results based on the averaged amygdalae volume.

Complementary item-based analyses were then undertaken to see whether SES and amygdala volume differed in the depression symptoms with which they were associated. Using logistic regression with SES and amygdala volume as predictor variables and the same covariates as before, we tested their relation to each of the 14 individual depression symptoms, using false discovery rate correction for multiple comparisons. The analysis of individual symptoms was carried out with both SES and amygdala volume together in the model, as well as with each separately.

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To further gauge the strength of the relation between SES and symptoms, we carried out an additional analysis, reported in *SI Appendix*. A simple classifier was trained to determine higher or lower SES group on the basis of symptoms. Further details and results may be found in *SI Appendix*.

Finally, sensitivity and specificity analyses were carried out. To test the sensitivity of the findings to personal or family depression history, we repeated the analyses with groups of participants who were negative or positive for personal or parental history of depression. To test the specificity of the findings regarding amygdala volume, we assessed the suppression effect with amygdala, hippocampus, and lateral prefrontal volumes as possible mediators, and also assessed the relations of individual symptoms to hippocampus and lateral prefrontal volumes. The analyses code can be accessed at <https://osf.io/rx9p8/> (41).

Data, Materials, and Software Availability. Code data have been deposited in [OSF] (<https://osf.io/rx9p8/>) (41). Some study data available (The data we analyzed are from human connectome project, which requires applying for access: <https://www.humanconnectome.org/>) (37).

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