Original Investigation

Neuroimaging Evidence for a Role of Neural Social Stress Processing in Ethnic Minority–Associated Environmental Risk

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IMPORTANCE Relative risk for the brain disorder schizophrenia is more than doubled in ethnic minorities, an effect that is evident across countries and linked to socially relevant cues such as skin color, making ethnic minority status a well-established social environmental risk factor. Pathoepidemiological models propose a role for chronic social stress and perceived discrimination for mental health risk in ethnic minorities, but the neurobiology is unexplored.

OBJECTIVE To study neural social stress processing, using functional magnetic resonance imaging, and associations with perceived discrimination in ethnic minority individuals.

DESIGN, SETTING, AND PARTICIPANTS Cross-sectional design in a university setting using 3 validated paradigms to challenge neural social stress processing and, to probe for specificity, emotional and cognitive brain functions. Healthy participants included those with German lineage (n = 40) and those of ethnic minority (n = 40) from different ethnic backgrounds matched for sociodemographic, psychological, and task performance characteristics. Control comparisons examined stress processing with matched ethnic background of investigators (23 Turkish vs 23 German participants) and basic emotional and cognitive tasks (24 Turkish vs 24 German participants).

MAIN OUTCOMES AND MEASURES Blood oxygenation level–dependent response, functional connectivity, and psychological and physiological measures.

RESULTS There were significant increases in heart rate ($P < .001$), subjective emotional response (self-related emotions, $P < .001$; subjective anxiety, $P = .006$), and salivary cortisol level ($P = .004$) during functional magnetic resonance imaging stress induction. Ethnic minority individuals had significantly higher perceived chronic stress levels ($P = .02$) as well as increased activation (family-wise error–corrected [FWE] $P = .005$, region of interest corrected) and increased functional connectivity ($P_{FWE} = .01$, region of interest corrected) of perigenual anterior cingulate cortex (ACC). The effects were specific to stress and not explained by a social distance effect. Ethnic minority individuals had significant correlations between perceived group discrimination and activation in perigenual ACC ($P_{FWE} = .001$, region of interest corrected) and ventral striatum ($P_{FWE} = .02$, whole brain corrected) and mediation of the relationship between perceived discrimination and perigenual ACC–dorsal ACC connectivity by chronic stress ($P < .05$).

CONCLUSIONS AND RELEVANCE Epidemiologists proposed a causal role of social-evaluative stress, but the neural processes that could mediate this susceptibility effect were unknown. Our data demonstrate the potential of investigating associations from epidemiology with neuroimaging, suggest brain effects of social marginalization, and highlight a neural system in which environmental and genetic risk factors for mental illness may converge.

Editorial

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Migrants face a complex set of physical, psychological, and social challenges that can affect their mental health.[1] Prior meta-analyses identified migration as one of the best-established environmental risk factors for schizophrenia across countries,[2-5] particularly in individuals who stand out from their social environment (eg, through skin color[3]). This adverse effect clearly persists into the second generation,[4] ie, it is similarly effective in individuals born and raised in the respective host country who have never been exposed to adverse premigratory or perimigratory events.[3,4] Consequently, current explanatory models focus on the postmigratory social milieu[6] and propose effects of chronic social stress in ethnic minority groups,[2-4,7] an established environmental risk factor for mental health[8] and a potent stimulus for the functional reorganization of neural regulatory circuits.[9-11] Accumulating evidence points to a role for social adversity linked to ethnic minority status,[12-14] a factor that seems to be particularly detrimental during development.[14] Epidemiologists highlight perceived discrimination as a psychological mechanism that may link social stress and mental health risk in ethnic minorities,[14-17] calling for clarification of the biology,[12,13] but the neural mechanisms are unexplored to date.

We aim to fill this gap by examining whether the neural processing of social stress is altered in individuals with ethnic minority status and, if so, whether perceived discrimination is a relevant psychosocial factor that relates to these changes. In doing so, we did not assume that there is a single migrant effect (ie, that the same risk-associated social cues yield the same effects across all migrant ethnicities and host countries). Instead, we proceeded on the idea that different risk-associated factors may converge, via shared psychological mechanisms (eg, perceived discrimination), on overlapping neural circuits.

In the human brain, the neural processing of social adversity involves evolutionarily conserved areas mediating survival-related defense functions (eg, brainstem) as well as higher-order control regions such as the anterior cingulate cortex (ACC) that integrate social cues and conceptual knowledge to complex social experiences such as social exclusion or perceived social threat.[18,19] We recently studied brain response to social-evaluative stress with functional magnetic resonance imaging (fMRI)[20] and found that the perigenual ACC (pACC), a key neural region for the regulation of negative emotion and stress,[18,21-23] was selectively associated with urban upbringing, another complex social environmental risk factor for schizophrenia.[2] Consequently, we hypothesized that we would see similar pACC functional alterations during neural social stress processing in individuals born and raised in Germany who share an ethnic minority status in German society. While epidemiological evidence is still limited, increased rates of schizophrenia diagnoses and perceived discrimination in ethnic minorities have been reported in Germany.[24-26]

Herein, we examined children of first-generation immigrant parents who were born in (and had migrated from) the same foreign country of origin. Notably, the studied offspring with ethnic minority background were born and raised in Germany because we wanted to exclude premigratory effects and the effects of environmental exposures unrelated to migrant status but differing between country of family origin and Germany. Ethnic background was defined based on the parents' country of birth. Groups were carefully matched for a broad range of sociodemographic attributes to control for personal and situational (eg, relative social, educational, or economic standing) variables[19,27] as well as many other trait and state variables (eg, intimidation by investigators; see Author Methods and Author Tables 1 and 2 at http://www.ub.uni-heidelberg.de/archiv/16088 for details).

First, we studied 40 ethnic minority individuals from different parental ethnic backgrounds (eg, parents born in Turkey, Italy, and Poland) and 40 matched individuals of German heritage (Author Table 1). Consistent with our prior work,[20] we probed the integrity of the neural stress response system by exposing participants to challenging cognitive tasks and disapproving verbal and visual feedback during fMRI (**Figure 1**A). We then tested for differences in neural stress response in ethnic minority individuals and associations with perceived dis-

Figure 1. Experimental Setup of the Social Stress Paradigm

In the social stress condition, shown here, investigators faced the participants, directed their attention to the participant's performance, and provided disapproving visual feedback after incorrect or slow responses. This was done by pressing a buzzer-shaped button device visible on live video stream, which prompted negative visual feedback on the task screen ("Error!" or "Respond faster!"). In addition, after the first of 2 runs, participants received negative verbal feedback indicating that the participant's performance was below average. In the control condition (not shown), investigators disengaged their attention from the participant and no feedback was provided. To account for the ethnic social distance of participants to the experimenters, experiments were conducted by either German (A) or Turkish (B) investigator teams.

crimination of their own ethnic group (which is of higher significance relative to perceived personal discrimination[28,29]). Next, to explore whether differences in social distance (ie, experimenter ethnicity relative to participant ethnicity) affected our findings, we compared the neural stress response of a subsample of 23 Turkish individuals (from the ethnically heterogeneous sample described earlier) examined by German investigators with that of 23 German individuals examined by Turkish investigators (Figure 1B). Finally, we probed for specificity by exposing 24 Turkish and 24 German individuals to fMRI tasks challenging emotional and cognitive circuits in the absence of stress.

Methods

Participants

We recruited healthy volunteers residing in a radius of approximately 50 km around Mannheim, Germany, by means of newspaper advertisement, information from local registration offices, posters, flyers, and the Internet. Responding individuals were screened thoroughly via telephone interview for the presence of exclusion criteria (see Author Methods for details). All participants were highly proficient in German language and provided written informed consent for a protocol approved by the University of Heidelberg Medical Faculty Mannheim Ethic Board.

We studied a total of 136 healthy, right-handed, Germany-born participants. Individuals either were of German family lineage (n = 87), including their parents and grandparents, or were born to first-generation migrant parents from the same foreign country (n = 49). Demographic characteristics and measures are reported in Author Tables 1, 2, and 3. The precise overlap of individuals with ethnic minority background between the main stress experiment and the control comparisons is given in the corresponding tables.

Social Stress Task

Neural social stress processing was studied using fMRI and a social stress task as previously described.[20] In the stress condition, participants performed tasks challenging arithmetic and mental rotation abilities under time pressure. For social-evaluative stress induction, 2 investigators in laboratory coats provided disapproving feedback and were continuously shown to the participants via live video stream (Figure 1). In the control condition, participants performed figure- and number-matching tasks in the absence of time pressure or feedback. See Author Methods for further details on the task.

fMRI Control Tasks

Neural processing of negative social emotional stimuli and working memory was studied with 2 well-established fMRI paradigms (emotional face matching task, *N*-back task) as previously described.[30-35] See Author Methods for further details on the rationale and methods.

fMRI Data Acquisition and Preprocessing

All fMRI data were acquired on a 3-T Siemens scanner using gradient-echo echo-planar imaging. Image processing followed previously published procedures[20,30-35] using Statistical Parametric Mapping 8 (http://www.fil.ion.ucl.ac.uk/spm/) standard routines. See Author Methods for further details.

fMRI Activation Analyses

For each paradigm and participant, linear contrast images of the task and control conditions were calculated and subjected to second-level random-effects analyses. To reflect our hypothesis derived from previous work,[20] significance for the stress task was defined as $P < .05$, family-wise error (FWE) corrected, over an a priori–defined mask of the rostral ACC. Outside this region, significance was defined as $P_{FWE} < .05$, whole brain corrected. The control task analyses followed the stress task procedures. To maximize sensitivity, a significance threshold of $P < .05$, uncorrected, was adopted for all regions highlighted by the stress experiments (ie, pACC, ventral striatum, frontoinsular cortex, dorsal ACC [dACC]). See Author Methods for further details.

Psychological Assessments

Psychometric assessments included the quantification of self-esteem,[36] chronic stress,[37] personality,[38] social support,[39] social network size, perceived social status in German society,[19,40] urbanization level of the environment,[20] fear of negative evaluation,[41] and self-monitoring.[42,43] To control for potential preexisting differences in the handling of performance situations, self-ratings for sensitivity to criticism, susceptibility to intimidation and dominant behavior, aggressiveness in competitive situations, fear of failure and negative evaluation, and achievement motivation were assessed. In migrants, perceived discrimination of the own person and that of the own ethnic group in German society were assessed using an adapted version of the perceived discrimination measure by Ruggiero and Taylor[44] (see Author Methods for further details).

Assessment of Stress Task–Related Psychological and Hormonal Variables

Stress task–related psychometric assessments included a scale for subjective emotional responses to acute stress[45] and items quantifying the individuals' degree of effort, achievement motivation, error monitoring, and intimidation by the investigators during the stress task. For quantification of cortisol response, a total of 8 salivary samples per participant were acquired throughout the stress experiment. See Author Methods for further details.

Analysis of Demographic, Psychometric, and Physiological Variables

Data analysis was performed using SPSS Predictive Analytics Software (SPSS version 20 statistical software; IBM Corp). See Author Methods for further details.

fMRI Connectivity Analyses

Based on the observed stress-related pACC activation differences, supplementary functional connectivity analyses were conducted following previously published procedures[20,22,32,34,46] using individual pACC time series as seeds. The same procedures were also applied to the control tasks to probe the specificity of findings. See Author Methods for further details.

Post Hoc Mediation Analysis

The potential causal contributions of perceived discrimination to the observed association of perceived chronic social stress and altered pACC-dACC functional connectivity during social stress processing were explored with statistical mediation analysis. See Author Methods for details.

Results

Effects of Stress Induction and Correlations With Cortisol Increase

Stress induction resulted in robust increases in heart rate (all $F \geq 73.814$; $P < .001$ for comparison groups 1 and 2 [Author Tables 1 and 2]), subjective emotional responses (Subjective-Emotional Response Scale [SERS] self-related emotions; all $F \geq 33.7$; $P < .001$ for both comparison groups), and salivary cortisol level (all $F \geq 9.0$; $P = .004$ for comparison group 1 [Author Table 1] and $P = .002$ for comparison group 2 [Author Table 2]). Moreover, a further stress-related acceleration of the overall heart rate in the stress blocks after the negative verbal feedback was seen (run 2 − run 1; $P = .01$). No significant main effects of group or task condition by group interaction effects were detected (all $P > .31$). This indicates that while our stress manipulation per se was successful, no differences in the peripheral stress response were seen between German and ethnic minority individuals in any part of the fMRI experiment. In the brain, stress induction engaged a distributed network including pACC ($P_{FWE} < .001$, whole brain corrected), ventral striatum ($P_{FWE} < .001$, whole brain corrected), frontoinsular cortex ($P_{FWE} < .001$, whole brain corrected), hippocampus ($P_{FWE} < .001$, whole brain corrected), and amygdala ($P_{FWE} < .04$, whole brain corrected) (eFigure 1 in Supplement). Moreover, a significant association of pACC activation estimates and delta cortisol values was observed (Montreal Neurological Institute [MNI] coordinates: x = 6, y = 47, z = −3; $t = 3.68$; $P_{FWE} = .02$ corrected for the pACC region of interest [ROI]) (eFigure 2 in Supplement). While this effect did not differ significantly between groups (group by cortisol interaction analysis: MNI coordinates: x = 9, y = 23, z = −9; $t_{maximum} = 2.44$; $P_{minimum} = .009$, uncorrected), it was mainly driven by German individuals (German group: MNI coordinates: x = 6, y = 26, z = 15; $t = 3.41$; $P_{FWE} = .045$; ethnic minority group: MNI coordinates: x = −15, y = 35, z = 24; $t_{maximum} = 2.75$; $P_{FWE} = .23$). Consistent with this, a significant positive association was detected between pACC response and relative acceleration of stress-related heart rate after verbal feedback (MNI coordinates: x = 3, y = 29, z = −3; $t = 3.82$; $P_{FWE} = .02$), including a similar tendency for a group-dependent dissociation (German group: MNI coordinates: x = 3, y = 32, z = 0; $t = 4.16$; $P_{FWE} = .03$; ethnic minority group: MNI coordinates: x = 0, y = 26, z = −3; $t_{maximum} = 2.68$; $P_{FWE} = .27$).

Stress-Related Differences in pACC Activation in Ethnic Minority Individuals

Participants with an ethnic minority status showed a significant increase in pACC activation relative to the German group (MNI coordinates: x = 6, y = 44, z = 0 ; $t = 4.18$; $P_{FWE} = .005$, ROI corrected) (**Figure 2**A and B). According to Cohen,[47] the corresponding r^2 of 0.2 indicates a medium to large effect size of the detected group difference. Furthermore, individuals with ethnic minority status reported significantly higher perceived chronic stress levels (Chronic Stress Screening Scale, $t = 2.472$; $P = .02$ for comparison group 1 [Author Table 1] and $P = .003$ for comparison group 2 [Author Table 2]). Secondary analyses showed that the group-dependent activation in pACC did not relate to chronic stress ($P = .34$).

Association of pACC Activation With Perceived Group Discrimination

Consistent with the literature,[28,29] we observed higher levels of perceived group discrimination relative to perceived personal discrimination in ethnic minority individuals (dependent *t* test: $t = 7.55$; $P < .001$)[28,29] and a highly significant positive correlation of perceived discrimination of the own ethnic group with brain activation measures in pACC (MNI coordinates: x = −12, y = 50, z = 9; $t = 5.33$; $P_{FWE} = .001$, ROI corrected; $r = 0.48$) and ventral striatum (MNI coordinates: x = −9, y = 5, z = −9; $t = 5.65$; $P_{FWE} = .02$, whole brain corrected; $r = 0.50$) (Figure 2C and D). No significant correlations between perceived group discrimination and any performance ($P = .94$), physiological (heart rate [$P = .44$], cortisol level [$P = .92$]), or state (SERS self-related emotions [$P = .77$], SERS tense arousal [$P = .61$], and SERS anxiety [$P = .89$]) variables were detected.

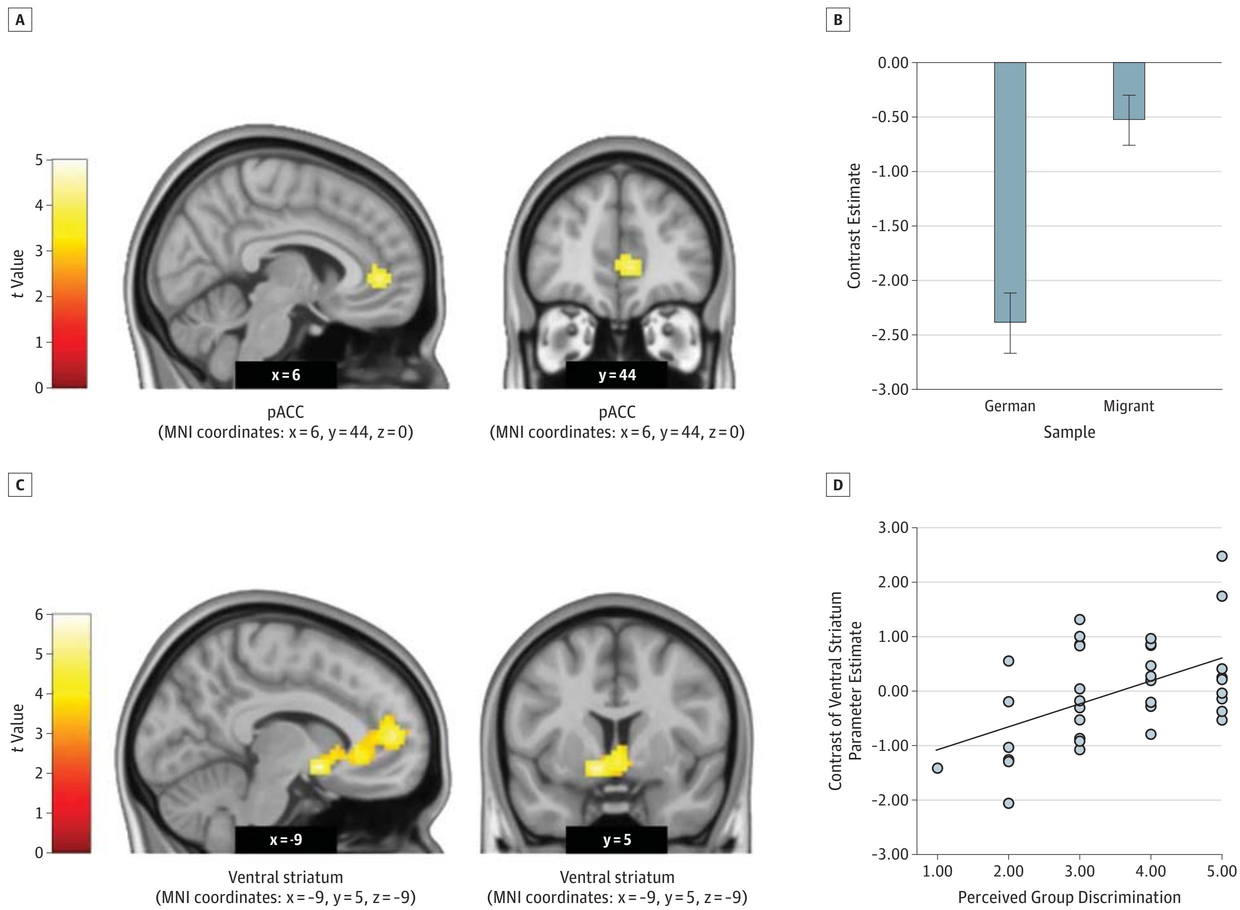
Stress-Related Group Differences in pACC Functional Connectivity

Within ACC, the dorsal-caudal aspects (dACC) have been highlighted as a region that forms specific structural connections with pACC,[48] serves as a control area of pACC during emotion and stress,[22,49,50] and is crucial for processing complex social experiences such as social support,[27] social exclusion,[51] and race attitudes.[52] Guided by these data, we conducted a supplementary connectivity analysis examining whether ethnic minority individuals show differences in the functional coupling of pACC and higher-order dACC (see Author Methods for details). Relative to the German group, we detected a significant increase in pACC-dACC functional connectivity in our ethnic minority sample (MNI coordinates: x = 6, y = 14, z = 25; $t = 3.70$; $P_{FWE} = .01$, ROI corrected) (**Figure 3**). According to Cohen,[47] the corresponding r^2 of 0.16 indicates a medium to large effect size of the detected group difference. Secondary analyses demonstrated a significant association of pACC-dACC connectivity with chronic stress (Chronic Stress Screening Scale, $t = 2.415$; $P = .02$) but not acute stress (delta cortisol, $t = 0.91$; $P = .37$). No significant correlations with any other trait-, state-, or performance-related variables were detected (heart rate, $P = .77$; performance, $P = .49$; cortisol level, $P = .58$; SERS self-related emotions, $P = .71$; SERS tense arousal, $P = .77$; SERS anxiety, $P = .77$; self-esteem, $P = .16$; fear of negative evaluation, $P = .61$).

Group Comparisons With Matched Ethnic Background of Investigators

Previous studies have shown that brain processing of social information is modulated by social distance that is higher when interacting individuals belong to different social (including eth-

Figure 2. Altered Neural Stress Processing in Perigenual Anterior Cingulate Cortex in Ethnic Minority Individuals and Relationship to Perceived Group Discrimination



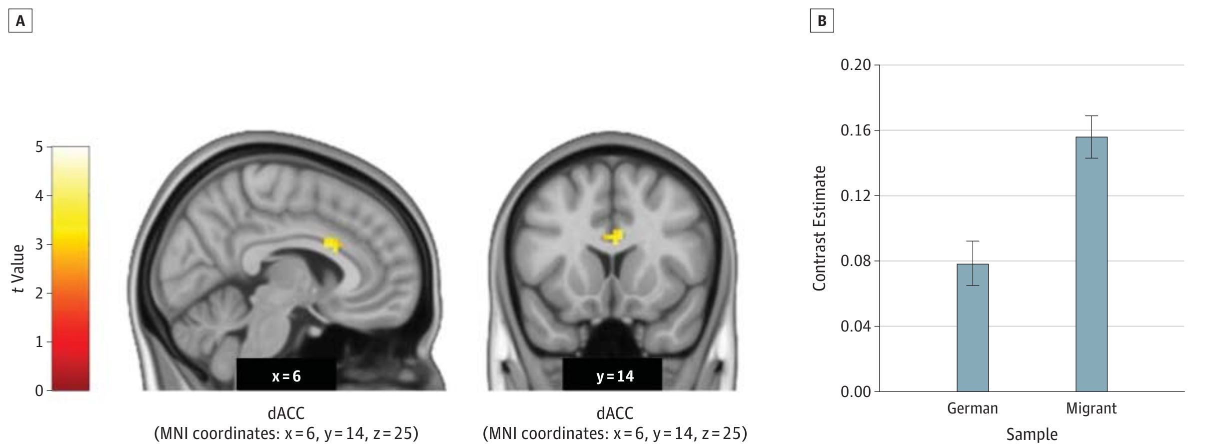
A, Significant increase in perigenual anterior cingulate cortex (pACC) activation in an ethnic minority sample compared with a German sample during stress processing (t = 4.18; family-wise error–corrected [FWE] P = .005, region of interest corrected) displayed on sagittal (left) and coronal (right) sections of a structural-template magnetic resonance image. Functional maps are thresholded at P = .001, uncorrected, for presentation purposes. MNI indicates Montreal Neurological Institute. B, Mean contrast estimates extracted from the peak voxel of the analysis. The MNI coordinates are x = 6, y = 44, z = 0. Error bars indicate standard error of the mean. C, Significant correlation of ventral striatum (t = 5.65; P_{FWE} = .02, whole brain corrected) and pACC activation (t = 5.33; P_{FWE} = .001, region of interest corrected) with perceived group discrimination in ethnic minority individuals. Functional maps are thresholded at P = .001, uncorrected, for presentation purposes and are displayed on sagittal (left) and coronal (right) sections of a structural-template magnetic resonance image. D, Scatterplot of the correlation of ventral striatum parameter estimates extracted from the peak voxel (MNI coordinates are x = −9, y = 5, z = −9) and perceived discrimination scores.

nic) groups.[51-53] To examine whether ethnic social distance from the experimenters may have affected our findings, we compared the neural response of 23 ethnic minority individuals with a Turkish parental background (derived from the ethnic minority sample described earlier) with that of 23 matched German participants where social-evaluative stress was induced by a trained Turkish investigator team (Figure 1B and Author Table 2). The group comparison confirmed a significant pACC activation increase in ethnic minority individuals with a Turkish background (MNI coordinates: x = 3, y = 41, z = 12; t = 4.62; P_{FWE} = .004, ROI corrected) and provided additional evidence for increased activity in medial prefrontal cortex (t = 5.64; P_{FWE} = .02, whole brain corrected) and frontoinsular cortex (t = 5.32; P_{FWE} = .04, whole brain corrected) (eFigure 3A and B in Supplement). Functional connectivity analysis further confirmed a significantly higher pACC-dACC coupling in ethnic minority individuals with a Turkish background (MNI coordinates: x = 0, y = 23, z = 19; t = 3.91; P_{FWE} = .01, ROI corrected) (eFigure 3C and D in Supplement).

Post Hoc Mediation Analysis

To explore the potential causal contributions of perceived discrimination to the relationship between chronic social stress and pACC-dACC connectivity, mediation analysis[54] was performed in 37 ethnic minority individuals with all available variables (see Author Methods for details). Guided by the literature, we included chronic stress as proposed mediator,[14-17] perceived group discrimination[17,28] as proposed causal variable, and individual contrast estimates for pACC-dACC functional connectivity as dependent variable, thereby controlling for age, sex, education, and other plausible influencing social factors that have been discussed as risk and resilience

Figure 3. Altered Perigenual Anterior Cingulate Cortex–Dorsal Anterior Cingulate Cortex Functional Connectivity in Ethnic Minority Individuals



A, Significant increase in perigenual anterior cingulate cortex–dorsal anterior cingulate cortex (dACC) functional connectivity during social stress in ethnic minority individuals compared with German comparison participants during stress processing (t = 3.70; family-wise error–corrected P = .01, region of interest corrected) displayed on sagittal (left) and coronal (right) sections of a structural-template magnetic resonance image. Functional maps are thresholded at P = .005, uncorrected, for presentation purposes. MNI indicates Montreal Neurological Institute. B, Mean contrast estimates extracted from the peak voxel (MNI coordinates are x = 6, y = 14, z = 25). Error bars indicate standard error of the mean.

factors for mental health and may affect neural stress circuits (ie, social network size,[27,55,56] migrant density in the neighborhood,[12,57] perceived social status,[19,58] and urban upbringing[20,59]). Path analysis showed that chronic stress significantly mediated the relationship between perceived discrimination and pACC-dACC coupling (standardized indirect effect = 0.165; P < .05; standardized bootstrap confidence interval, 0.0045-0.4065) (eFigure 4 in Supplement). Following the procedures suggested by Kenny,[60] the product of the partial correlation coefficients of the a path (r_a = 0.43) and b path (r_b = 0.35) of the model resulted in $r_a \times r_b$ = 0.15, corresponding to a medium effect size[47] of the indirect effect.

fMRI Control Experiments

In our fMRI control experiments, we detected no differential activations in ethnic minority individuals relative to German participants in any of the regions found to be significant in our stress experiments (eFigure 5 in Supplement). Also, no differences in pACC-dACC functional connectivity or associations with perceived group discrimination were found (for N-back paradigm: pACC, P = .08, uncorrected; ventral striatum, P = .06, uncorrected; for faces paradigm: pACC, P = .25, uncorrected; ventral striatum, P = .16, uncorrected; for pACC-dACC connectivity: N-back, P = .05, uncorrected; faces, P = .06, uncorrected).

Discussion

We aimed to provide neurobiological evidence for a prominent pathoepidemiological concept in psychiatry, namely that the processing of social stress is altered in individuals with ethnic minority status and modulated by an adverse social environmental factor linked to their minority status, perceived discrimination.[13,14,17] Consistent with this, we detected increased pACC activation during social-evaluative stress processing in our ethnic minority sample and increased functional coupling of this region to higher-order dACC. The results were not explained by a social distance effect, were correlated with perceived discrimination or affected by perceived discrimination by means of mediation through chronic stress, and were present during social stress but not during basic emotional or cognitive processing.

The identified brain regions are closely connected and relevant for stress processing. Specifically, pACC is a key region of the limbic stress regulatory system,[9,61,62] exhibits high glucocorticoid receptor expression,[63] modulates hypothalamic-pituitary-adrenal axis activation,[21] covaries with cardiovascular stress markers,[18,23] and relates to social stressors and mental health risks such as urban upbringing,[20] low socioeconomic status,[19] unstable social hierarchies,[58] and urban violence.[64] We further confirm prior data by showing that individuals with an ethnic minority status report increased chronic stress and perceived group discrimination.[17,28,29] Interestingly, while perceived discrimination correlated with pACC response, which in turn was associated with cortisol level, we detected no corresponding group differences in the peripheral stress response. Instead, we observed a pattern of partial decoupling in the ethnic minority group, suggestive of reduced neural control of (or feedback from) the periphery. While speculative, these findings are consistent with the idea that pACC responses to social stress are less limited in healthy individuals with an ethnic minority status but also that full derailment of the system to the point of a disinhibited peripheral stress response is prevented, possibly by a higher-order neural compensatory control mechanism.

A plausible candidate region for such a top-down effect on pACC is dACC, a higher-order regulatory area involved in the detection and resolution of conflict, error, negative emotion, and stress[22,49,50] that may arise from various sources, including socially salient stimuli.[51,52] We observed increased functional connectivity of pACC and dACC in migrants, a direct association between pACC-dACC coupling and chronic stress, and an indirect influence of perceived discrimination on pACC-dACC coupling through chronic stress. These data suggest that social stressors converge on pACC,[19,20,58,64] thereby increasing emotional, neuroendocrine, and autonomic defense functions and health risks,[18] while compensatory and/or resilience factors may involve higher-order areas such as dACC,[27,52,65] which may attenuate the adverse emotional, physiological, and health-related effects of social stress. The highlighted brain regions may further be relevant for schizophrenia risk. Specifically, pACC is among the best-supported regions where structural and functional changes are evident at disease onset,[66] and downstream areas such as ventral striatum and insular cortex have been closely linked to emergence of psychotic symptoms.[67,68] Of note, several genome-wide-supported psychosis risk variants affect ACC,[69-73] suggesting that this region and the areas linked to it may be a crucial point of convergence for genetic and environmental risk factors for the illness.[74]

Our study design does not allow for a causal interpretation of the observed effects. However, cumulative evidence from rodent,[75,76] primate,[77] and human[19,20,64,78,79] research suggests that neuronal remodeling of ACC is a consequence of social environmental stress, particularly when it coincides with neurodevelopment. We therefore speculate that chronic social stress may causally contribute to the observed neural alterations during social stress processing in ethnic minorities, especially because chronic stress mediated the effects of perceived discrimination on pACC coupling, and pACC was also highlighted in our previous work on another complex social stressor operating in early life, urban upbringing.[20]

The confounding of social neural stress processing with other dispositional or task-related behaviors may have affected the interpretation of the detected functional differences. Specifically, because we examined socially successful individuals of ethnic minority background, an important question to discuss is whether the observed effects in dACC may relate to systematic differences in the handling of the stress task. We deem this interpretation unlikely because our basic cognitive and emotional control experiments yielded a null finding and the groups were balanced for many dispositional and task-related variables including task performance, self-monitoring, competitiveness, fear of negative evaluation, sensitivity to criticism, intimidation by the investigators, error monitoring, and achievement motivation. For the same reason, we examined a highly educated subsample of ethnic minority individuals fluent in German to avoid the confounding of our measures with language and/or cognitive capability, although the examination of a representative sample may have yielded even greater differences in the neural stress response.

Our study has several limitations. First, many socioeconomic and psychological variables may be linked to migrant or ethnic minority status.[3] We therefore focused on a specific a priori hypothesis suggested by prior epidemiological data, examined individuals born to first-generation migrant parents in Germany to exclude premigratory effects, balanced our groups for a broad range of demographic, social, psychological, and task-related characteristics, and canvassed those variables that were most discussed in the literature. Nevertheless, we cannot exclude that our findings were influenced by confounds that we may have missed such as other disregarded factors or complex interactions of the variables used for matching the groups. Second, while we examined an a priori hypothesis based on epidemiological research, the myriad of common exclusion criteria of fMRI (eg, implants, tattoos) and related neurobiological considerations (eg, regarding left-handedness, scanning of individuals aged ≥55 years) prevented us from following a strictly population-based recruitment strategy. Third, while our prior work on urbanicity[20] suggested a relative specific increase of cortisol levels in response to the stress manipulation and nearly all of our individuals were accustomed to fMRI, we cannot fully exclude that our cortisol measures were partially influenced by the discomforts of the scanning environment. Fourth, as we examined healthy volunteers, our data do not prove any immediate pathophysiological conclusions. We studied healthy at-risk individuals to minimize the neural effects of disease-related confounds and have yielded findings consistent with a large body of evidence from psychiatric epidemiology and biological psychiatry. Even so, the processes that tie ethnic minority status to psychosis are manifold and complex, and the relevance of our findings to pathophysiology needs to be substantiated in future work. Lastly, because individuals with ethnic minority status are relatively rare in rural areas and we matched our groups for the effects of urban exposure, the examined samples were largely urban and we could not study potential interactions or additive effects of urbanization and migration.

Conclusions

Our study provides biological evidence for a long-standing hypothesis in the field by showing that neural processing of social-evaluative stress is altered in individuals with ethnic minority status and associated with a plausible facet of perceived social adversity related to this status, perceived discrimination. The results highlight the importance of a neural system for the regulation of negative emotion and stress, raise awareness of the somatic implications of social adversity in ethnic minorities, demonstrate the potential of investigating associations from psychiatric epidemiology using neuroimaging, and encourage future research on the neural convergence mechanisms of genetic and environmental risk factors in this circuitry. Optimally, these efforts would include multiple large and ethnically homogeneous samples of different heritage.

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Study supervision: Tost, Rietschel, Kirsch, Meyer-Lindenberg.

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REFERENCES

1. International Organization for Migration. *World Migration Report 2010: The Future of Migration: Building Capacities for Change.* Geneva, Switzerland: International Organization for Migration; 2010.

2. van Os J, Kenis G, Rutten BP. The environment and schizophrenia. *Nature*. 2010;468(7321):203-212.

3. Cantor-Graae E, Selten JP. Schizophrenia and migration: a meta-analysis and review. *Am J Psychiatry*. 2005;162(1):12-24.

4. Bourque F, van der Ven E, Malla A. A meta-analysis of the risk for psychotic disorders among first- and second-generation immigrants. *Psychol Med*. 2011;41(5):897-910.

5. Cantor-Graae E, Pedersen CB. Full spectrum of psychiatric disorders related to foreign migration: a Danish population-based cohort study. *JAMA Psychiatry*. 2013;70(4):427-435.

6. Coid JW, Kirkbride JB, Barker D, et al. Raised incidence rates of all psychoses among migrant groups: findings from the East London First Episode Psychosis study. *Arch Gen Psychiatry*. 2008;65(11):1250-1258.

7. Selten JP, Cantor-Graae E. Social defeat: risk factor for schizophrenia? *Br J Psychiatry*. 2005;187:101-102.

8. Heinrichs M, Gaab J. Neuroendocrine mechanisms of stress and social interaction: implications for mental disorders. *Curr Opin Psychiatry*. 2007;20(2):158-162.

9. Davidson RJ, McEwen BS. Social influences on neuroplasticity: stress and interventions to promote well-being. *Nat Neurosci*. 2012;15(5):689-695.

10. Niwa M, Jaaro-Peled H, Tankou S, et al. Adolescent stress-induced epigenetic control of dopaminergic neurons via glucocorticoids. *Science*. 2013;339(6117):335-339.

11. Burghy CA, Stodola DE, Ruttle PL, et al. Developmental pathways to amygdala-prefrontal function and internalizing symptoms in adolescence. *Nat Neurosci*. 2012;15(12):1736-1741.

12. Veling W. Ethnic minority position and risk for psychotic disorders. *Curr Opin Psychiatry*. 2013;26(2):166-171.

13. Morgan C, Charalambides M, Hutchinson G, Murray RM. Migration, ethnicity, and psychosis: toward a sociodevelopmental model. *Schizophr Bull*. 2010;36(4):655-664.

14. Veling W, Susser E. Migration and psychotic disorders. *Expert Rev Neurother*. 2011;11(1):65-76.

15. Cooper C, Morgan C, Byrne M, et al. Perceptions of disadvantage, ethnicity and psychosis. *Br J Psychiatry*. 2008;192(3):185-190.

16. Gilvarry CM, Walsh E, Samele C, et al. Life events, ethnicity and perceptions of discrimination in patients with severe mental illness. *Soc Psychiatry Psychiatr Epidemiol*. 1999;34(11):600-608.

17. Veling W, Selten JP, Susser E, Laan W, Mackenbach JP, Hoek HW. Discrimination and the incidence of psychotic disorders among ethnic minorities in the Netherlands. *Int J Epidemiol*. 2007;36(4):761-768.

18. Wager TD, Waugh CE, Lindquist M, Noll DC, Fredrickson BL, Taylor SF. Brain mediators of cardiovascular responses to social threat, part I: reciprocal dorsal and ventral sub-regions of the medial prefrontal cortex and heart-rate reactivity. *Neuroimage*. 2009;47(3):821-835.

19. Gianaros PJ, Horenstein JA, Cohen S, et al. Perigenual anterior cingulate morphology covaries with perceived social standing. *Soc Cogn Affect Neurosci*. 2007;2(3):161-173.

20. Lederbogen F, Kirsch P, Haddad L, et al. City living and urban upbringing affect neural social stress processing in humans. *Nature*. 2011;474(7352):498-501.

21. Diorio D, Viau V, Meaney MJ. The role of the medial prefrontal cortex (cingulate gyrus) in the regulation of hypothalamic-pituitary-adrenal responses to stress. *J Neurosci*. 1993;13(9):3839-3847.

22. Pezawas L, Meyer-Lindenberg A, Drabant EM, et al. 5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: a genetic susceptibility mechanism for depression. *Nat Neurosci*. 2005;8(6):828-834.

23. Gianaros PJ, Sheu LK, Matthews KA, Jennings JR, Manuck SB, Hariri AR. Individual differences in stressor-evoked blood pressure reactivity vary with activation, volume, and functional connectivity of the amygdala. *J Neurosci*. 2008;28(4):990-999.

24. Salentin K. Diskriminierungserfahrungen ethnischer Minderheiten in der Bundesrepublik. In: Groenemeyer A, Wieseler S, eds. *Soziologie sozialer Probleme und sozialer Kontrolle: Realitäten, Repräsentationen und Politik: Festschrift für Günter Albrecht.* Wiesbaden, Germany: VS Verlag für Sozialwissenschaft; 2008:515-526.

25. Schouler-Ocak M, Bretz HJ, Penka S, et al; Psychiatry and Migration Working Group of the German Federal Conference of Psychiatric Hospital Directors. Patients of immigrant origin in inpatient psychiatric facilities: a representative national survey by the Psychiatry and Migration Working Group of the German Federal Conference of Psychiatric Hospital Directors. *Eur Psychiatry*. 2008;23(suppl 1):21-27.

26. Schouler-Ocak M, Schepker R, Bretz HJ, et al. Patients of immigrant origin in inpatient psychiatric facilities: differences between first and second generation: nationwide questionnaire of the Psychiatry and Migration Working Group of the German Federal Conference of Psychiatric Hospital Directors [in German]. *Nervenarzt*. 2010;81(1):86-94.

27. Eisenberger NI, Taylor SE, Gable SL, Hilmert CJ, Lieberman MD. Neural pathways link social support to attenuated neuroendocrine stress responses. *Neuroimage*. 2007;35(4):1601-1612.

28. Taylor DM, Wright SC, Moghaddam FM, Lalonde RN. The personal/group discrimination discrepancy: perceiving my group, but not myself, to be a target for discrimination. *Pers Soc Psychol Bull*. 1990;16(2):254-262. doi:10.1177/0146167290162006.

29. Operario D, Fiske ST. Ethnic identity moderates perceptions of prejudice: judgments of personal vs group discrimination and subtle vs blatant bias. *Pers Soc Psychol Bull*. 2001;27(5):550-561. doi:10.1177/0146167201275004.

30. Hariri AR, Mattay VS, Tessitore A, et al. Serotonin transporter genetic variation and the response of the human amygdala. *Science*. 2002;297(5580):400-403.

31. Meyer-Lindenberg A, Kolachana B, Gold B, et al. Genetic variants in *AVPR1A* linked to autism predict amygdala activation and personality traits in healthy humans. *Mol Psychiatry*. 2009;14(10):968-975.

32. Tost H, Kolachana B, Hakimi S, et al. A common allele in the oxytocin receptor gene (*OXTR*) impacts prosocial temperament and human hypothalamic-limbic structure and function. *Proc Natl Acad Sci U S A*. 2010;107(31):13936-13941.

33. Esslinger C, Kirsch P, Haddad L, et al. Cognitive state and connectivity effects of the genome-wide significant psychosis variant in *ZNF804A*. *Neuroimage*. 2011;54(3):2514-2523.

34. Esslinger C, Walter H, Kirsch P, et al. Neural mechanisms of a genome-wide supported psychosis variant. *Science*. 2009;324(5927):605.

35. Callicott JH, Egan MF, Mattay VS, et al. Abnormal fMRI response of the dorsolateral prefrontal cortex in cognitively intact siblings of patients with schizophrenia. *Am J Psychiatry*. 2003;160(4):709-719.

36. Rosenberg M. *Conceiving the Self.* New York, NY: Basic Books; 1979.

37. Schulz P, Schlotz W, Becker P. *Trierer Inventar zum chronischen Stress.* Göttingen, Germany: Hogrefe; 2004.

38. Rammstedt B, John OP. Measuring personality in one minute or less: a 10-item short version of the Big Five Inventory in English and German. *J Res Pers*. 2007;41(1):203-212. doi:10.1016/j.jrp.2006.02.001.

39. Schulz U, Schwarzer R. Soziale Unterstützung bei der Krankheitsbewältigung: die Berliner Social Support Skalen (BSSS). *Diagnostica*. 2003;49(2):73-82.

40. Adler NE, Epel ES, Castellazzo G, Ickovics JR. Relationship of subjective and objective social status with psychological and physiological functioning: preliminary data in healthy white women. *Health Psychol*. 2000;19(6):586-592.

41. Kemper CJ, Lutz J, Neuser J. Konstruktion und Validierung einer Kurzform der Skala Angst vor negativer Bewertung (SANB-5). *Klinische Diagnostik und Evaluation*. 2012;4:343-360.

42. Graf A. Eine deutschsprachige Version der Self-Monitoring-Skala. *Zeitschrift für Arbeits-und Organisationspsychologie*. 2004;48(3):109-121. doi:10.1026/0932-4089.48.3.109.

43. Snyder M. Self-monitoring of expressive behavior. *J Pers Soc Psychol*. 1974;30(4):526-537. doi:10.1037/h0037039.

44. Ruggiero K, Taylor DM. Coping with discrimination: how disadvantaged group members perceive the discrimination that confronts them. *J Pers Soc Psychol*. 1995;68(5):826-838. doi:10.1037/0022-3514.68.5.826.

45. Schlotz W, Kumsta R. *The Subjective-Emotional Response Scale (SERS).* Southampton, England: School of Psychology, University of Southampton; 2011.

46. Meyer-Lindenberg A, Straub RE, Lipska BK, et al. Genetic evidence implicating DARPP-32 in human frontostriatal structure, function, and cognition. *J Clin Invest*. 2007;117(3):672-682.

47. Cohen J. A power primer. *Psychol Bull*. 1992;112(1):155-159.

48. Johansen-Berg H, Gutman DA, Behrens TE, et al. Anatomical connectivity of the subgenual cingulate region targeted with deep brain stimulation for treatment-resistant depression. *Cereb Cortex*. 2008;18(6):1374-1383.

49. Ochsner KN, Ludlow DH, Knierim K, et al. Neural correlates of individual differences in pain-related fear and anxiety. *Pain*. 2006;120(1-2):69-77.

50. Critchley HD, Melmed RN, Featherstone E, Mathias CJ, Dolan RJ. Volitional control of autonomic arousal: a functional magnetic resonance study. *Neuroimage*. 2002;16(4):909-919.

51. Eisenberger NI. The pain of social disconnection: examining the shared neural underpinnings of physical and social pain. *Nat Rev Neurosci*. 2012;13(6):421-434.

52. Kubota JT, Banaji MR, Phelps EA. The neuroscience of race. *Nat Neurosci*. 2012;15(7):940-948.

53. Richeson JA, Baird AA, Gordon HL, et al. An fMRI investigation of the impact of interracial contact on executive function. *Nat Neurosci*. 2003;6(12):1323-1328.

54. Hayes AF, Preacher KJ. Statistical mediation analysis with a multicategorical independent variable. http://www.afhayes.com/. Accessed March 1, 2013.

55. Bickart KC, Hollenbeck MC, Barrett LF, Dickerson BC. Intrinsic amygdala-cortical functional connectivity predicts social network size in humans. *J Neurosci*. 2012;32(42):14729-14741.

56. Bickart KC, Wright CI, Dautoff RJ, Dickerson BC, Barrett LF. Amygdala volume and social network size in humans. *Nat Neurosci*. 2011;14(2):163-164.

57. Zammit S, Lewis G, Rasbash J, Dalman C, Gustafsson JE, Allebeck P. Individuals, schools, and neighborhood: a multilevel longitudinal study of variation in incidence of psychotic disorders. *Arch Gen Psychiatry*. 2010;67(9):914-922.

58. Zink CF, Tong Y, Chen Q, Bassett DS, Stein JL, Meyer-Lindenberg A. Know your place: neural processing of social hierarchy in humans. *Neuron*. 2008;58(2):273-283.

59. Krabbendam L, van Os J. Schizophrenia and urbanicity: a major environmental influence—conditional on genetic risk. *Schizophr Bull*. 2005;31(4):795-799.

60. Kenny DA. Mediation. http://davidakenny.net/cm/mediate.htm. Accessed March 1, 2013.

61. LeDoux JE. Emotion circuits in the brain. *Annu Rev Neurosci*. 2000;23:155-184.

62. Etkin A, Egner T, Peraza DM, Kandel ER, Hirsch J. Resolving emotional conflict: a role for the rostral anterior cingulate cortex in modulating activity in the amygdala. *Neuron*. 2006;51(6):871-882.

63. Herman JP, Ostrander MM, Mueller NK, Figueiredo H. Limbic system mechanisms of stress regulation: hypothalamo-pituitary-adrenocortical axis. *Prog Neuropsychopharmacol Biol Psychiatry*. 2005;29(8):1201-1213.

64. Rocha-Rego V, Pereira MG, Oliveira L, et al. Decreased premotor cortex volume in victims of urban violence with posttraumatic stress disorder. *PLoS One*. 2012;7(8):e42560.

65. Masten CL, Telzer EH, Fuligni AJ, Lieberman MD, Eisenberger NI. Time spent with friends in adolescence relates to less neural sensitivity to later peer rejection. *Soc Cogn Affect Neurosci*. 2012;7(1):106-114.

66. Radua J, Borgwardt S, Crescini A, et al. Multimodal meta-analysis of structural and functional brain changes in first episode psychosis and the effects of antipsychotic medication. *Neurosci Biobehav Rev*. 2012;36(10):2325-2333.

67. Palaniyappan L, Liddle PF. Does the salience network play a cardinal role in psychosis? an emerging hypothesis of insular dysfunction. *J Psychiatry Neurosci*. 2012;37(1):17-27.

68. Kapur S. Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. *Am J Psychiatry*. 2003;160(1):13-23.

69. Erk S, Meyer-Lindenberg A, Schnell K, et al. Brain function in carriers of a genome-wide supported bipolar disorder variant. *Arch Gen Psychiatry*. 2010;67(8):803-811.

70. Ohi K, Hashimoto R, Yasuda Y, et al. Impact of the genome wide supported *NRGN* gene on anterior cingulate morphology in schizophrenia. *PLoS One*. 2012;7(1):e29780.

71. Rietschel M, Mattheisen M, Degenhardt F, et al; Genetic Risk and Outcome in Psychosis (GROUP Investigators); SGENE-Plus Consortium. Association between genetic variation in a region on chromosome 11 and schizophrenia in large samples from Europe. *Mol Psychiatry*. 2012;17(9):906-917.

72. Carless MA, Glahn DC, Johnson MP, et al. Impact of DISC1 variation on neuroanatomical and neurocognitive phenotypes. *Mol Psychiatry*. 2011;16(11):1096-1104.

73. Thurin K, Rasetti R, Sambataro F, et al. Effects of ZNF804A on neurophysiologic measures of cognitive control. *Mol Psychiatry*. 2013;18(8):852-854.

74. Meyer-Lindenberg A, Tost H. Neural mechanisms of social risk for psychiatric disorders. *Nat Neurosci*. 2012;15(5):663-668.

75. Poeggel G, Helmeke C, Abraham A, Schwabe T, Friedrich P, Braun K. Juvenile emotional experience alters synaptic composition in the rodent cortex, hippocampus, and lateral amygdala. *Proc Natl Acad Sci U S A*. 2003;100(26):16137-16142.

76. Kassem MS, Lagopoulos J, Stait-Gardner T, et al. Stress-induced grey matter loss determined by MRI is primarily due to loss of dendrites and their synapses. *Mol Neurobiol*. 2013;47(2):645-661.

77. Spinelli S, Chefer S, Suomi SJ, Higley JD, Barr CS, Stein E. Early-life stress induces long-term morphologic changes in primate brain. *Arch Gen Psychiatry*. 2009;66(6):658-665.

78. Baker LM, Williams LM, Korgaonkar MS, Cohen RA, Heaps JM, Paul RH. Impact of early vs late childhood early life stress on brain morphometrics. *Brain Imaging Behav*. 2013;7(2):196-203.

79. Cohen RA, Grieve S, Hoth KF, et al. Early life stress and morphometry of the adult anterior cingulate cortex and caudate nuclei. *Biol Psychiatry*. 2006;59(10):975-982.