

REGULAR RESEARCH ARTICLE

Early-Life Adversity, but Not Suicide, Is Associated With Less Prefrontal Cortex Gray Matter in Adulthood

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Abstract

Background: Suicide and major depression are prevalent in individuals reporting early-life adversity. Prefrontal cortex volume is reduced by stress acutely and progressively, and changes in neuron and glia density are reported in depressed suicide decedents. We previously found reduced neurotrophic factor brain-derived neurotrophic factor in suicide decedents and with early-life adversity, and we sought to determine whether cortex thickness or neuron or glia density in the dorsolateral prefrontal and anterior cingulate cortex are associated with early-life adversity or suicide.

Methods: A total of 52 brains, constituting 13 quadruplets of nonpsychiatric controls and major depressive disorder suicide decedents with and without early-life adversity, were matched for age, sex, race, and postmortem interval. Brains were collected at autopsy and frozen, and dorsolateral prefrontal cortex and anterior cingulate cortex were later dissected, postfixed, and sectioned. Sections were immunostained for neuron-specific nuclear protein (NeuN) to label neurons and counterstained with thionin to stain glial cell nuclei. Cortex thickness, neuron and glial density, and neuron volume were measured by stereology.

Results: Cortical thickness was 6% less with early-life adversity in dorsolateral prefrontal cortex and 12% less in anterior cingulate cortex ($P < .05$), but not in depressed suicide decedents in either region. Neuron density was not different in early-life adversity or with suicide, but glial density was 17% greater with early-life adversity in dorsolateral prefrontal cortex and 15% greater in anterior cingulate cortex, but not in suicides. Neuron volume was not different with early-life adversity or suicide.

Conclusions: Reported early-life adversity, but not the stress associated with suicide, is associated with thinner prefrontal cortex and greater glia density in adulthood. Early-life adversity may alter normal neurodevelopment and contribute to suicide risk.

Keywords: prefrontal cortex, adversity, immunocytochemistry, stereology, postmortem

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Significance Statement

Stress can result in structural and lasting reductions in brain volume, particularly in the prefrontal cortex and hippocampus. More recently, it has been shown that early-life adversity increases the risk for suicide behavior in adulthood. We have found reduced levels of chemical factors supporting neuronal health in postmortem human brain in suicide decedents, and the reduced levels were associated with early-life adversity. In the present study, we found that the prefrontal cortex is thinner in cases with early-life adversity, and there is an increased density of glial cells. Neither the thinner cortex nor the increase in glial cell density was associated with suicide. Our findings suggest that severe stress experienced early in life may alter the normal development of the brain with effects lasting into adulthood. The thinner prefrontal cortex may indicate reduced prefrontal cortex mediation of behavioral inhibition, which puts vulnerable individuals at risk for suicide.

Introduction

Stress and mental illness, including major depressive disorder (MDD), are associated with volumetric loss in medial prefrontal cortex (PFC) and hippocampus in vivo (see Belleau et al., 2018 for a recent review). The stress can be recent and associated with the mood disorder or distant and occurring in childhood, and both types of exposures can be associated with smaller brain regional volume. The early-life stress-associated volume loss in the PFC and hippocampus is hypothesized to be the result of severe stress impacting neuronal development at a critical period (Crews et al., 2007).

Early-life adversity (ELA) is associated with increased risk for suicide (Johnson et al., 2002; Labonte and Turecki, 2012; Turecki et al., 2012; Dykxhoorn et al., 2017; Youssef et al., 2018) and adult depression (Miniati et al., 2010; Harkness et al., 2012; Heim and Binder, 2012; Nanni et al., 2012). We found lower neuron density in depressed suicide decedents and hypothesized lower neuron density contributes to higher levels of postsynaptic 5-HT_{1A} and 5-HT_{2A} receptors (Underwood and Arango, 2011; Underwood et al., 2012). We also find higher levels of 5-HT_{1A} and 5-HT_{2A} receptor binding associated with ELA (Underwood et al., 2012). Changes in the density of neurons and glia have been reported in MDD by others (Rajkowska et al., 1999; Rajkowska, 2000; Cotter et al., 2001). Suicide and the mood disorder accompanying suicide are sources of current profound stress, potentially resulting in elevated cortisol and glutamate and in reduction in the brain trophic molecule brain-derived neurotrophic factor (BDNF) (Deveci et al., 2007; Kim et al., 2007; Dwivedi, 2012). We found lower levels of BDNF in the anterior cingulate cortex in individuals reporting ELA and in suicide decedents (Youssef et al., 2018), raising the possibility that less BDNF may lead to reduced trophic neuronal support and reduced brain region volume. Therefore, reduced volume of the PFC due to ELA could be due to loss of neurons, less interneuronal parenchyma, fewer glia, less vascular tissue, or some combination of these effects.

In the present study, we sought to determine whether there is a loss of thickness of PFC associated with reported ELA and to distinguish effects of ELA from those associated with suicide. We also set out to determine whether the thickness of the cerebral cortex is associated with neuron density or glia density and how those associations are similar or different in depressed suicide decedents or nonsuicide controls with or without reported ELA.

METHODS

The respective Institutional Review Boards for Human Use Considerations of the New York State Psychiatric Institute, the University of Pittsburgh, and the Republic of Macedonia approved the procedures for collection and use of brain tissue.

Brain tissue samples were obtained from the respective medical examiner's offices from which the decedents originated. Upon removal of the brain from the cranium, the dura mater was stripped, and the brainstem and cerebellum were removed. The brain was bisected and the right hemisphere was cut into 2-cm-thick sections in the coronal plane. The tissue slabs were placed on a glass plate, frozen in liquid R-12 (Freon 12, dichlorodifluoromethane), placed in prelabelled plastic bags, and kept frozen at -80°C . A sample of cerebellar tissue was collected and used for brain toxicological analyses. The remaining tissue was placed in formalin for gross and microscopic neuropathological examination.

A total of 52 subjects were assigned to quadruplets, consisting of a nonsuicide with no reported history of ELA (control-no ELA), a suicide with no reported ELA (suicide-no ELA), a nonsuicide with ELA (control + ELA), and a suicide with ELA (suicide+ELA), matched for age (± 5 years), sex, race, and postmortem interval (± 5 hours and <24 hours). Control-no ELA ($n=13$) died of sudden death ($n=9$) or natural causes ($n=4$). Controls+ELA ($n=13$) died of heart attack ($n=10$) or accidental sudden death ($n=3$). Suicides-no ELA died from hanging ($n=6$), gunshot wound ($n=2$), physical trauma ($n=3$), or poisoning ($n=2$). Suicides+ELA died from hanging ($n=6$), gunshot wound ($n=2$), suffocation ($n=1$), or poisoning ($n=4$). See Table 1 for subject characteristics. All subjects were free of gross neuropathology and had negative toxicology screens in blood, urine, and bile for psychoactive drugs except for 2 suicide cases that were positive for benzodiazepines, one of whom also positive for barbiturates.

Tissue Preparation

Tissue blocks containing dorsolateral PFC (BA9) and anterior cingulate cortex (BA24) were dissected from frozen coronal slabs of the right hemisphere. The blocks were sectioned $60\mu\text{m}$ on a freezing microtome (Microm HM 440E, Walldorf, Germany) and slides were stored until used.

Immunohistochemistry

The sections on slides (3 sections from each Brodmann area in each ID at 1-mm intervals) were fixed in 4% paraformaldehyde/0.1 M phosphate buffer, pH 7.4 for 30 minutes. Then the sections were washed in 50 mM phosphate buffered saline, treated with 0.3% hydrogen peroxide, washed again, and blocked for 2 hours in NHS. The sections were incubated overnight in primary antibody to neuron-specific nuclear protein that we have named NeuN (Neuronal Nuclei, anti-NeuN mouse monoclonal antibody at 1:20 000; Chemicon, Temecula, CA; Figure 1) in 0.1% NHS and 0.3% Tx-100 at room temperature. The immunostained sections

Table 1. Group Demographics

Group	Age (years)	Sex (M:F)	Race (W:B:H)	PMI (hours)	Brain pH	Cause of Death	Axis I Diagnosis (n)
Control, No ELA (n = 13)	37 ± 4	12:1	12:0:1	14.2 ± 1.5	6.50 ± 0.11	Cardiovascular (4) Accident (6) Homicide (3)	None (13)
Suicide, No ELA (n = 13)	37 ± 5	12:1	12:1:0	15.1 ± 1.4	6.44 ± 0.08	Hanging (6) GSW (2) Physical Trauma (3) Poisoning (2)	None (2) MDD (9) Schizophrenia (1)
Control, with ELA (n = 13)	38 ± 5	12:1	7:4:2	13.2 ± 1.1	6.56 ± 0.07	Cardiovascular (10) MVA (1) Accidental Electrocution (1) Hemorrhage (1)	None (11) Gambling Disorder (1) Conduct Disorder (1)
Suicide, with ELA (n = 13)	36 ± 5	12:1	9:1:3	19.2 ± 2.4	6.58 ± 0.07	Hanging (6) GSW (2) Suffocation (1) Poisoning (4)	MDD (10) MDD, Gambling Disorder, OCD (1) Conduct Disorder (1) MDD, Conduct Disorder, Cannabis Abuse, ADHD (1)

Abbreviations: B, black; ELA, early-life adversity; F, female; GSW, gunshot wound; H, Hispanic; M, male; MDD, major depressive disorder; MVA, motor vehicle accident; PMI, postmortem interval; W, white.

Age, PMI, and brain pH are expressed as mean ± SEM.

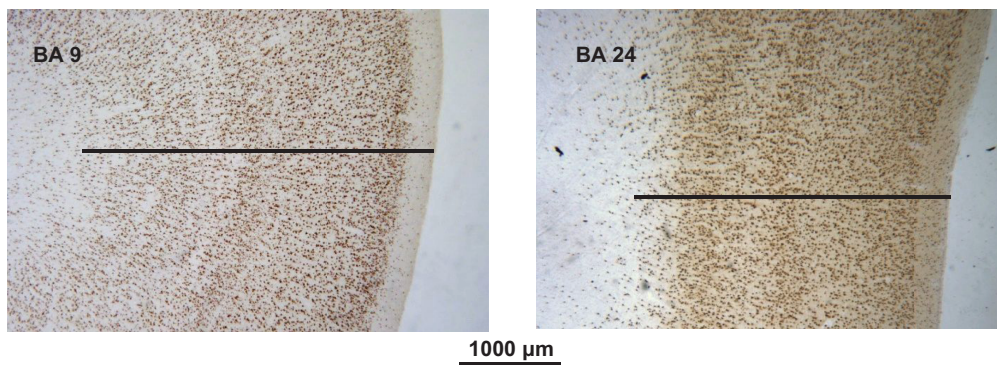


Figure 1. NeuN immunocytochemistry in representative tissue sections in dorsolateral prefrontal cortex (BA9) and anterior cingulate cortex (BA24). Cortex thickness measurement is depicted by the transept line.

and adjacent sections at 1-mm intervals were stained with cresyl violet.

Stereology

Length distances for each microscope objective were calibrated for linear measure by the software (Stereoinvestigator, MBF Bioscience, Williston, VT). The thickness of the cortex was measured at 40× drawing a transept line perpendicular to outer margin of layer I extending to the layer VI-white matter interface (Figure 1).

The total cell number could not be determined since the entirety of BA9 and BA24 was available for sampling, making NeuN⁺ and glial cell density the best possible metrics. The density of NeuN-IR⁺ neurons in BA9 and BA24 was determined stereologically using a personal computer-based imaging workstation equipped for stereology (Stereoinvestigator, MBF Bioscience). The computer was attached to a microscope (Leica, model Diaplan; Wetzlar, Germany) fitted with a motorized stage (Ludl Electronic Products, Hawthorne, NY) and stage position encoder (Heidenhain MT12, Schaumburg, IL). Neuronal and glial density was determined by 3-dimensional

stereology using the fractionator method (e.g., Gundersen et al., 1988a, 1988b). Slides were initially viewed at 16× total magnification under a Leica Wild M3Z stereoscope, and BA9 and BA24 margins were demarcated on each slide of each case using the Brodmann area map of Rajkowska and Goldman-Rakic (Rajkowska and Goldman-Rakic, 1995a, 1995b). The assumption was made that neuron density and glia density were representative of the region of interest throughout the rostrocaudal extent of the respective Brodmann area. We sought to maximize the sampling of each Brodmann area while having an adequately small coefficient of variation and sampled 3 slides 1 mm apart for each Brodmann area in each case. BA contours were drawn by the image analyst with the use of the computer pointing device and the microscope motorized stage. The contour corresponded to the recognized BA boundary. The dissector began 3 μm below the cut edge of the section. Immuno-positive neuron “tops” and glial cell nuclei were defined at a total magnification of 400×. Neuronal cell volumes were acquired using the nucleator probe (Gundersen, 1988, 1988b). Thionin stains glia nuclei but not their cell bodies so glia cell volume could not be measured.

Statistical Analysis

Statistical tests were done using SPSS (Version 24, IBM Analytics, NY) and R (Version 3.5.1, R Foundation for Statistical Computing; <https://cran.r-project.org>).

There were 3 primary hypotheses: (1) cortical thickness is less in suicides, (2) there is a lower density of neurons in the PFC in suicide, and (3) there is a greater density of glia in the PFC in suicides. Linear models were used since the response variables were continuous (scalar) (SPSS Procedures UNIANOVA, CORRELATIONS, REGRESSION and t test). Suicide and ELA were fixed factors and Brodmann area was a random factor. All statistical models included age and sex as covariates, and when found to be significant, correlation analysis was performed. Because there were 3 hypotheses being tested, Bonferroni correction was employed and P values were considered statistically significant when $P < .017$. Correlations between continuous variables (e.g., thickness correlating with neuronal density or glia density) with age were examined using Pearson Product-Moment Correlation coefficients. Statistical tests were performed on raw values. Cortex thickness, neuron density, and glia density were examined in independent tests.

RESULTS

Cortical Thickness

In controls-no ELA, cortical thickness in BA9 was $4630 \pm 180 \mu\text{m}$ and in BA24 was $4691 \pm 252 \mu\text{m}$ ($n=13$). The thickness of BA9 (paired $t = -1.048$; $P = .3$) and BA24 (paired $t = 0.162$; $P = .872$) were not different.

Cortical thickness was not different in suicides in BA9 ($F = 0.830$, $df = 1, 12$, $P = .380$) or BA24 ($F = 2.861$, $df = 1, 12$, $P = .116$). Cortical thickness trended to be less with ELA in BA9 ($F = 5.269$, $df = 1, 12$, $P = .04$) and was less in BA24 ($F = 8.274$, $df = 1, 12$, $P = .014$). The effect of ELA was the same in suicides and controls as there was no interaction between suicide and ELA on cortical thickness in either BA9 ($F = 2.064$, $P = .179$) or BA24 ($F = 0.239$, $P = .638$).

Neuron and Glia Density

Neuron density in controls-no ELA in BA9 was $40\,611 \pm 4090$ neurons per mm^3 and in BA24 was $38\,301 \pm 2567$ per mm^3 and was not different between regions ($t = 0.750$, $P = .475$; Figure 2). Glial density was $58\,437 \pm 4459$ cells per mm^3 in controls-no ELA in BA9 and $58\,666 \pm 3895$ in BA24 and was not different between BA9 and BA24 (Figure 2). Across all groups, glial density ($53\,471 \pm 3696$ cells per mm^3 in BA9, $53\,311 \pm 2911$ in BA24) was greater than neuron density ($44\,791 \pm 2249$ cells per mm^3 in BA9, $42\,996 \pm 1692$ in BA24, $F = 21.779$, $P < .0001$, repeated-measures ANOVA).

In BA9, neuronal density was not different in suicides ($F = 1.052$, $P = .329$) or in association with ELA ($F = 0.064$, $P = .806$). Likewise in BA24, neuron density was also not different in suicide ($F = 0.212$, $P = .655$) or with reported ELA ($F = 1.011$, $P = .336$). Glial density in subjects with ELA was greater in BA9 ($F = 7.813$, $P = .023$) and in BA24 ($F = 5.194$, $P = .044$), but the difference was not statistically significant after Bonferroni correction. Glia density was not different in suicide decedents in either BA9 ($F = 0.025$, $P = .878$) or BA24 ($F = 0.001$, $P = .976$). There was no interaction between suicide and ELA ($F = 0.023$, $P = .884$). Neuron density correlated negatively with cortical thickness in both BA9 (Pearson coefficient $-.338$, $P = .014$) but not BA24 (Pearson coefficient $.583$, $P = .047$). Glia density did not correlate with cortical thickness when examined in all cases together in either BA9 (Pearson coefficient $.069$, $P = .629$) or BA24 (Pearson coefficient $.057$, $P = .699$), or in subgroups of either suicide decedents or in cases with ELA ($P > .05$).

Neuron Soma Volume

Mean neuron soma volume was $2639 \pm 94 \mu\text{m}^3$ in BA9 and 2564 ± 80 in BA24 and was not associated with suicide (BA9: $F = 0.001$, $P = .975$; BA24: $F = 0.282$, $P = .607$) or ELA (BA9: $F = 0.242$, $P = .634$; BA24: $F = 2.281$, $P = .159$). Similarly, when soma volumes were binned into sizes and compared, the distribution of soma volumes was not different in suicide decedents or with ELA (Figure 3).

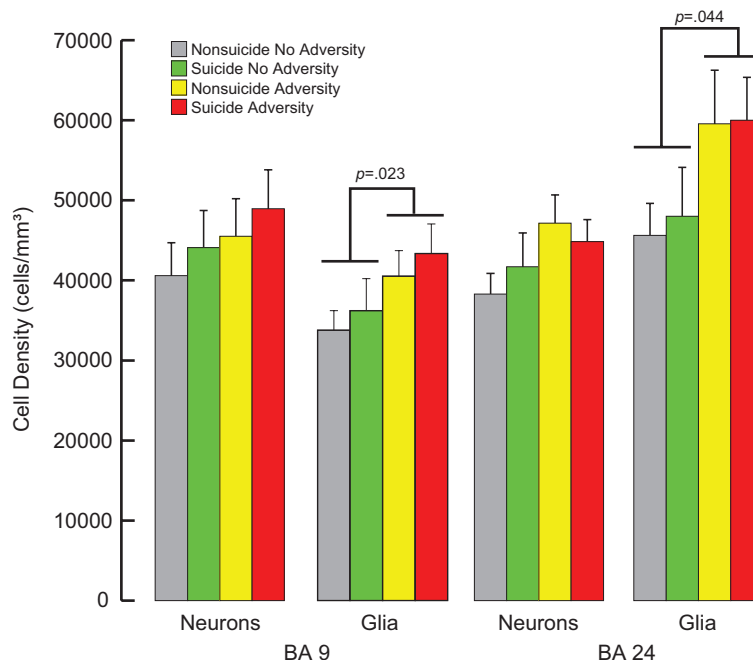


Figure 2. Neuron and glia density in dorsolateral prefrontal cortex (BA9) and anterior cingulate cortex (BA24). In both BA9 and BA24, glial density was greater in cases with reported early-life adversity (ELA), independent of suicide status. Bars represent mean \pm SEM.

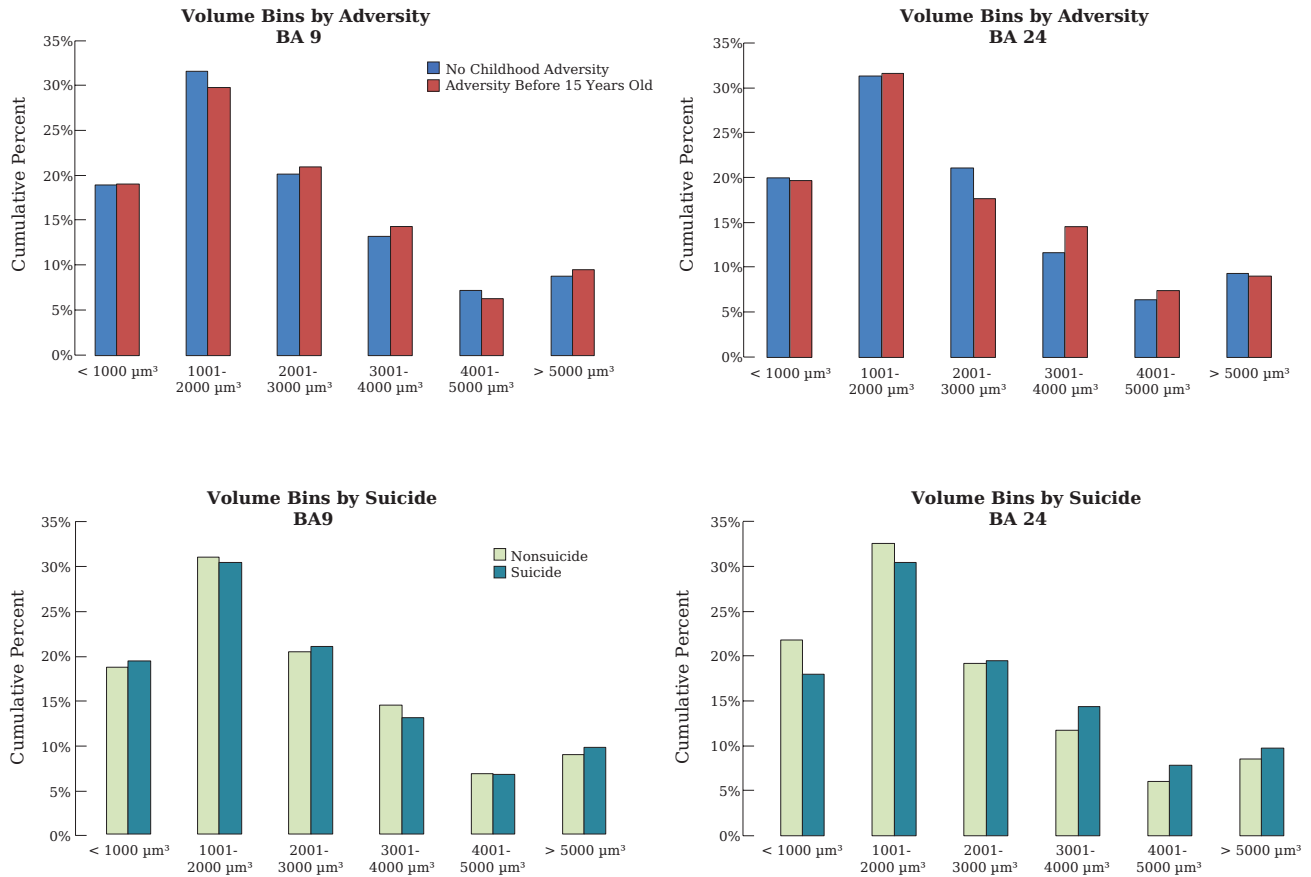


Figure 3. Neuronal cell volume. Neuron soma volume was measured using the Nucleator Method. Soma volumes were aggregated by volume range into bins of $1000 \mu\text{m}^3$. Cell soma volumes did not differ between cases with and without early-life adversity (ELA) in either dorsolateral prefrontal cortex (BA9) and anterior cingulate cortex (BA24) (top) or between nonsuicide and suicide decedents (bottom).

Age

Neuron density increases with age in nonsuicides independent of ELA in BA24 ($r=0.547$, $P=.008$). In all cases without ELA, neuronal soma volume decreases with age BA24 ($r=-0.566$, $P=.006$); in that group, BA9 thickness also decreases with age ($r=0.555$, $P=.006$). In cases with ELA, there was no relationship between neuron density, glial density, or neuronal volume with age.

Discussion

We found that ELA but not suicide was associated with less cortical thickness and greater glial density but no difference in neuron density or neuron soma size. Less cortex thickness is previously reported in ELA (McCrorry et al., 2010) and also in MDD (Rajkowska et al., 1999), but the present study clarifies and extends the previous published literature by separating ELA from MDD and suicide and suggesting that it is the ELA that is the more important factor. We believe this is the first report of increased glia density associated with ELA.

Cortical thickness is reported to be less in rostral orbitofrontal cortex in MDD postmortem (Rajkowska et al., 1999) and attributed to a shift in the size of neurons from large to small with a decrease in the density of large neurons and an increase in the density of small neurons, suggesting neuronal shrinkage and not neuron loss accounted for the difference in neuron density.

Glia are implicated in suicide and the major depression that often accompanies it. Glial density has also been observed to be decreased in density in MDD (Rajkowska et al., 1999; Cotter et al., 2001) in contrast to schizophrenia or Huntington's disease, which are associated with increases in glia density (Rajkowska et al., 1998). Glia include astrocytes, oligodendrocytes, and microglia. Astrocytes are specifically implicated in suicide and MDD based on studies using markers specific for astrocytes such as glial fibrillary acidic protein. In contrast, studies using nonspecific markers report that astrocytes are increased in density or unchanged (Miguel-Hidalgo et al., 2000; Davis et al., 2002; Webster et al., 2005). It has been argued that there is a reduction in oligodendrocytes in MDD (Uranova et al., 2004; Vostrikov et al., 2007) that accounts for the overall reduction in glia density in MDD.

Less gray matter volume and cortical thickness are also reported in the frontal cortex in subjects with mood disorders using magnetic resonance imaging by some investigators (see Drevets et al., 1997; Bora and Pantelis, 2011; Belleau et al., 2018), though not all (Bora and Pantelis, 2011; Gifuni et al., 2016; Rizk et al., 2018) Bora et al. (2011) performed a meta-analysis of voxel-based morphometry from 23 studies involving 986 MDD patients and found cortical gray matter volume was reduced in rostral anterior cingulate cortex and dorsolateral and dorsomedial cortex as well as in hippocampus. The smaller gray matter volume was related to illness duration, leading the authors to conclude that chronic MDD has deleterious but regionally restricted effects on PFC (Bora

et al. (2011). The volume deficits related to MDD and also to stress (Belleau et al., 2018). It is not known, however, whether the reduced cortex thickness was attributable to the mood disorder, a suicide component of the psychopathy, or to both.

The majority of suicide decedents in the current study had MDD. However, we did not find cortex thickness different in these MDD suicides in either BA9 or BA24. BA24 was not examined by Rajkowska and colleagues, and 5 of 12 of the MDD cases studied by Rajkowska died from causes other than suicide. Interestingly, the meta-analysis performed by Bora and colleagues (2011) did find smaller BA9 and BA24 gray matter volume in MDD, but there was no indication of whether any of the MDD cases ever made suicide attempts, leaving open the possibility there may be a different effect of suicide and MDD on cortex thickness.

ELA is one of the biggest risk factors for adult suicide and can affect the trajectory of neurodevelopment with lasting effects on brain structure and dysfunction (Teicher et al., 2003). Childhood maltreatment can increase the risk of psychiatric problems in adulthood, including anxiety, depression, and conduct disorder (Gilbert et al., 2009). There is a growing literature in live subjects with ELA reporting reduced cortex thickness and/or gray matter volume (McCrorry et al., 2010). Reduced cortical thickness in maltreated children is reported in the anterior cingulate and superior frontal gyrus (Andersen et al., 2008; Kelly et al., 2013), suggesting an impact on brain morphology from exposure to ELA. Such structural differences in the PFC and other brain regions may represent an enduring effect on brain development that might lead to the emergence of psychiatric illness later during development or in adulthood (Teicher et al., 2003).

There are critical periods for brain development during which genetic and environmental factors affect neurogenesis, innervation, and synaptic pruning and lead to vulnerability for developing psychiatric illness (see Crews et al., 2007 for review). Andersen and colleagues (2008) found reductions in frontal cortex volume, hippocampus volume, and corpus callosum area in women with repeated episodes of childhood sexual abuse. The authors not only concluded there were effects of the childhood sexual abuse on regional brain development but also that there are sensitive windows during which the brain regions are affected with the frontal cortex most sensitive to abuse at ages 14–16 years. Vulnerability windows may explain why not all individuals exposed to ELA have alterations in brain anatomy. Susceptibility to adversity also likely depends on other factors, including frequency and intensity of the stress (Edwards et al., 2003), the type of adversity (Heim et al., 2013; McLaughlin et al., 2014), and genetics (Caspi et al., 2002, 2003). As such, the lack of significant change in neuronal density for both BA9 and BA24 in the present study may be due to different insults received at different times in early life (Andersen et al., 2008). The lack of association with suicide may reflect an adaptation gained over adolescence and further suggest a critical window of sensitivity of region-specific vulnerability.

The thinner PFC and greater glial density associated with ELA is suggestive of neuropathology. Acute stress causes alterations in the function of the hypothalamic-pituitary axis, most notably elevated levels of cortisol and cortisol hyperreactivity (Horowitz and Zunszain, 2015). Acute stress elevates glutamate to toxic levels, causing dendritic loss (see McEwen, 2017 for review). Likewise, mood disorders are associated with excess glutamate that can lead to synaptic and neuronal loss (see Haroon et al., 2017). However, in vivo imaging studies have not found associations between cortisol and PFC structure (Drevets, 1999; Gold et al., 2002). Inflammation and neurotoxic sequelae of neuroinflammatory processes are increasingly shown in

response to stress and in major depression (Slavich and Irwin, 2014; Setiawan et al., 2015; Lindqvist et al., 2017; van Velzen et al., 2017; Holmes et al., 2018). And higher levels of pro-inflammatory cytokines are associated with thinning of the medial PFC (Savitz et al., 2013; van Velzen et al., 2017). We did not find evidence of neuron loss associated with ELA history or death by suicide as there was no difference in neuron density observed in the present study compared with controls. Our measured neuronal density was comparable with those reported in the literature (e.g., Cotter et al., 2001; Underwood et al., 2012; Lew et al., 2017) but less than that reported by Rajkowska and colleagues who used a celloidin preparation producing considerable shrinkage and greater cell density (Rajkowska and Goldman-Rakic, 1995b), suggesting that our not finding a difference in neuron density was somehow a confound of the immunostaining or stereologic methods. We did detect a greater density of glial cell nuclei with ELA history, and this difference is also not likely a confound since the glia density we measured was comparable with that reported in the literature (e.g., Öngür et al., 1998; Cotter et al., 2001; Miguel-Hidalgo et al., 2002). Neuron soma volumes were not different in suicide decedents or with reported ELA and were therefore not informative for neuropathology. We were not able to measure glia soma volume since the thionin staining only labelled nuclei and not cell membranes.

Serotonergic differences in the PFC are reported in depressed suicide decedents (see Underwood et al., 2012 for review). Serotonin (5-HT) is also a trophic agent for neurons during neurodevelopment and in adulthood (Booij et al., 2015) and the 5-HT metabolite 5-HIAA is lower in suicide attempters (see Bach and Arango, 2012; Bach et al., 2013 for recent reviews), raising the possibility that cortical thinning may be the result of neurotransmitter alterations associated with the mental illness. Alternatively, 5-HT is a regulator of BDNF, which has trophic actions on neurons (Mattson et al., 2004). We previously reported lower BDNF levels in anterior cingulate cortex in subjects who had been exposed to ELA and/or died by suicide compared with controls with no reported ELA (Youssef et al., 2018). The 52 cases and controls in the present study were examined for BDNF levels in the study of Youssef et al. (2018). We examined the relationship between BDNF level and the morphometric measures in the present study and found the levels of BDNF correlated with glial density, neuronal volume, and cortical thickness (data not shown), raising the possibility that lower amounts of BDNF may underlie the reduced cortical thickness we observed with reported ELA.

Limitations

Differences in cortex morphometry in depressed suicide decedents do not distinguish between effects attributable to MDD vs those to suicide. Making such a distinction is particularly problematic in postmortem studies when the majority of suicides have MDD or some other mood disorder or psychiatric illness. Cellular changes in suicide implicate the PFC, including glia alterations and gray matter volume that reflect a diathesis for suicide (for reviews, see Ernst et al., 2009; van Heeringen and Mann, 2014; Balcioglu and Kose, 2018). It is also not possible to determine from postmortem studies, which by their nature examine the brain at a single point in time, whether the thinner cortical thickness reported in studies of MDD patients is state dependent (and perhaps reversible) or a trait (and indicative of neuropathology). Associations with multiple depression episodes or the summed duration of multiple episodes, however, suggest the changes in thickness progress with illness duration.

Our study is also limited by the underrepresentation in females. This may be more than just a confound since sex differences are reported not only in differences in the prevalence of MDD or ELA in females compared with males but also that males and females have opposite molecular profiles (Seney et al., 2018). Conclusions should not be extended to females based on the present findings. Lastly, postmortem studies are not able to demonstrate causality so it is unresolved whether or how the ELA leads to increased glia density or reduced cortex thickness.

CONCLUSION

Our study went beyond the gross assessment of PFC thickness and sought to determine the underlying components of neuron density, neuron size, and glial density in neocortex and to separate the effects of depression and suicide from those of ELA. We found no differences in neuron density or neuron size in the depressed suicide decedents or with ELA, yet cortex thickness was less with ELA, suggesting there was neuron loss. Neuron loss, or fewer neurons, with early adversity and combined with the greater glial density may be part of an ongoing pathology or a chronic change. The lack of differences in neuron or glia density in depressed suicides, who suffer severe stress, suggest that acute stress is not as important as childhood adversity or chronic stress experienced over many years. Future studies should not only seek to replicate the finding in a larger sample size but also examine the phenotype of glia involved.

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Interest Statement

Dr Mann receives royalties for the commercial use of the C-SSRS from the Research Foundation for Mental Hygiene. Dr Arango, Dr Underwood, Mrs. Kassir, Ms Escobar, and Mr. Bakalian declare no conflicts of interest.

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