# Adversity, Trauma, Suicide, and Alzheimer's Disease

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This issue of the *Journal* is dedicated to the topics of adversity, trauma, and suicide, which are clearly intertwined with each other. Trauma and adversity are major factors that underpin psychopathology. While trauma is specifically linked to PTSD, trauma is also a transdiagnostic factor that increases the risk for almost all psychiatric illnesses. Adversity and trauma are also associated with an increased risk of suicidal ideation and suicide in both children and adults (1, 2). Adversity-related deleterious outcomes vary depending on the time of life during which the adverse events are experienced, the type of adversity, and their duration. These factors also interact with various individual factors (e.g., genetics, temperament, parental or social support), as well as community factors such as the availability of resources that can serve to mitigate the effects of trauma. There is no question that individuals from marginalized and underprivileged communities face greater levels of ongoing adversity, and it is important to emphasize that racism itself is traumatic. When occurring during childhood, adversity and associated trauma can be particularly damaging as their effects can have an impact on psychosocial, emotional, and cognitive development. One likely mechanism by which this occurs is via the influences of trauma on the brain systems that underlie the normal developmental trajectories of these functions. In particular, animal model research has elucidated the impacts of adverse environments on neuroplastic processes that support learning, memory, fear responding, and emotion regulation.

In this issue of the *Journal*, three papers are focused on adversity and trauma. The first is an overview by Dr. Dylan Gee from Yale University in which she provides an in-depth discussion on early-life and childhood adversity as it relates to psychobiological development and the vulnerability and resilience to develop psychopathology (3). This overview is accompanied by two original research papers, one focused on the differential effects of abuse and neglect on maturational patterns of gray matter in young girls, and another on developing biotypes that are predictive of psychiatric outcomes by using functional MRI data that is acquired 2–3 weeks after a traumatic experience. In addition to these papers, we include two papers on suicidal ideation, suicide attempts, and completed suicides. One paper uses data from U.S. Army soldiers presenting with suicidal ideation to characterize factors that are associated with later suicide attempts. The other paper, using a large Swedish registry, is focused on determining the relation between the genetic and environmental factors underlying suicide attempts and suicide completions.

In addition, we also include a review paper on Alzheimer's disease authored by Dr. Anand Kumar from the University of Illinois along with members of the APA Research Council (4). This review addresses the utility of using amyloid and tau proteins as Alzheimer's disease biomarkers and importantly emphasizes the distinction between their use as biomarkers versus their utility as treatment targets.

### Delayed Maturation of Gray Matter in Emotion Circuitry Is Associated With Childhood Abuse

It is well established that childhood adversity and abuse are prominent risk factors for the later development of psychopathology, especially for internalizing disorders such as depression, anxiety, and PTSD. Keding et al. (5) focus on understanding the impacts of childhood abuse (physical, sexual, emotional) on altered brain structure with the eventual goal of understanding neural mechanisms that are involved in mediating vulnerability and resilience to develop psychiatric disorders. In this study, the researchers used gray matter volume measurements obtained from structural MRIs to estimate the maturation of gray matter in a sample of "typically developing" girls (N=99, no history of abuse and no internalizing psychopathology) and comparing this maturation to that seen in a sample of abused girls that were further categorized into a "susceptible" group (N=85, history of abuse and internalizing psychopathology) or a "resilient" group (N=50, history of abuse and no internalizing psychopathology). In addition to performing analyses across the entire brain, an important feature of this study was to estimate the maturation of gray matter volume in selected brain regions constituting the language and emotion-related circuits. This approach allowed the authors to test the hypothesis, based on prior work, that abuse-related effects on structural brain maturation would be characterized by the accelerated maturation of emotion-related regions. While the findings demonstrated alterations that were selective to regions associated with emotion processing, they were in the opposite of the predicted direction,

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such that abused girls appeared to have delayed maturation of this circuit. Interestingly, using a dimensional approach within the sample of abused girls, the authors found that the severity of childhood physical neglect was associated with advanced maturation of whole brain gray matter volume. In addition, the presence or absence of an internalizing disorder diagnosis was associated with regional differences in how gray matter volumes contributed to the observed maturation effects. There are a number of insights to be gleaned from this study, but perhaps the most interesting is the opposite effects on gray matter maturation that are associated with abuse as compared with physical neglect. In their editorial (6), Drs. Anaïs Stenson and Tanja Jovanovic, both from Wayne State University, discuss the findings from this study, highlighting the meaningfulness of the reported differential effects of abuse and neglect.

### Neuroimaging-Based Biotypes Relevant to Post-Trauma Outcomes

This paper by Stevens and colleagues (7) represents the efforts of a large group of investigators involved in an ongoing multisite longitudinal study focused on understanding the deleterious consequences of trauma exposure. Participants were between 18 and 75 years of age and were recruited from the ER within 72 hours of their traumatic experience. Functional MRI data were obtained using three tasks (a threat-related task, an inhibitory control task, and a reward task) an average of 18 days after enrollment. Follow-up data on the participants were collected for at least 8 weeks. The initial "discovery cohort" (N=69) consisted of participants that experienced motor vehicle trauma. To validate the findings from this group, the researchers used another group of participants as a "replication cohort," which consisted of 77 individuals that had recently experienced various types of trauma, including interpersonal trauma. Using an agnostic clustering method to analyze the imaging data, the researchers found three imaging clusters that replicated across the discovery and replication cohorts, labeled "reactive/disinhibited," "low reward/high threat," and "inhibited." These statistically determined imaging clusters were then examined with respect to outcomes. Of interest, there was a relation between clusters and PTSD symptoms such that the reactive/disinhibited group had the greatest amount of PTSD symptoms. There also was an effect associated with the longitudinal modeling of anxiety symptoms, which were also higher in the reactive/disinhibited cluster. Importantly, when accounting for PTSD symptoms prior to the current traumatic exposure, the relation between PTSD symptoms and clusters was no longer significant. However, the relation between longitudinal anxiety and clusters remained significant when accounting for pretrauma anxiety severity. Taken together, these findings suggest the possibility that functional MRI data acquired shortly after a traumatic event, in combination with machine learning techniques, can be helpful in predicting psychological and psychiatric outcomes during the posttrauma period. The findings point to the reactive/disinhibited group as the "biotype" that is most likely to develop substantial PTSD and anxiety symptoms. At a neural level, the reactive/disinhibited cluster was associated with activation of threat- and reward-related regions (insular cortex, dorsal anterior cingulate cortex, nucleus accumbens, median raphe nucleus, and the ventral tegmental area) with little activation of regulatory regions associated with the expression of threat or inhibition. The authors also suggest that the inhibited cluster might be associated with active coping, as this cluster was characterized by increased activity in the ventromedial prefrontal cortex and the hippocampus, regions that have previously been associated with resiliency. In his editorial (8), Dr. David Knight from the University of Alabama points out the important and somewhat unique features of this study, which include using multiple neurocognitive measures to assess brain function, the prospective longitudinal design linking brain function to transdiagnostic outcomes, and the analytic methodology used as a prototype for future work aimed at linking psychiatric outcomes to biotypes.

### Predictors of Suicide Attempts in U.S. Soldiers

It is well known that there is a high risk of suicide in military personnel. Herberman Mash et al. (9) used an administrative database from the Army Study to Assess Risk and Resilience in Servicemembers (Army STARRS) to investigate factors that are associated with suicide attempts that occurred within 30 days of reported suicidal ideation. Data analyzed from 2006–2009 included 975,057 service members, 11,178 of whom had documented suicidal ideation and no prior documented suicide attempts. The major factors that were associated with reports of suicidal ideation included being male, White, and less than 30 years of age. Additionally, half of the individuals with suicidal ideation were in their first 2 years of service. Of the 11,178 individuals with suicidal ideation, 830 (7.4%) attempted suicide and 387 of these individuals (46%) did so within 30 days of initial suicidal ideation documentation. This was the highest period of risk. Using a statistical model that incorporated demographic data and characteristics of military service, the authors found that being female (odds ratio of 1.4) or a combat medic (odds ratio of 1.6) increased the likelihood of making a suicide attempt within 30 days of documented suicidal ideation. Of interest was the finding that Black individuals with suicidal ideation were less likely to attempt suicide within 30 days (odds ratio of 0.6). Additional comorbid psychiatric risk factors included having an anxiety disorder prior to the documented suicidal ideation (odds ratio of 1.3) or a sleep disorder that was concurrent with the documented suicidal ideation (odds ratio of 2.2). While depression and other disorders associated with mood were very prevalent in the individuals with suicidal ideation, this did not distinguish those individuals that acted on their ideation

within 30 days of documentation from those that did not. In their discussion, the authors point out the importance of developing predictors for individuals that transition from suicidal ideation to suicide attempt and particularly so for those that are at imminent risk. They also discuss factors that may be associated with the reduced risk observed in Black individuals and the apparent lack of association with depression and PTSD diagnoses.

### Genetic and Environmental Relations Between Suicide Attempts and Deaths

Edwards and colleagues (10) used the large Swedish national registry, a database of 1,314,990 individuals born between 1960–1990, to provide insights into whether the factors underlying suicide attempts are the same as those underlying suicide completions. By focusing on the genetic relatedness among twins, siblings, and half-siblings, and controlling for sex, the authors estimated the magnitude of the genetic and environmental contributions to suicide attempts and deaths by suicide. Results demonstrated that both suicide attempts and deaths were moderately heritable, with heritability estimates ranging from 0.41–0.52. Importantly, there was a significant genetic correlation between suicide attempts and deaths, suggesting that a sizeable component of the genetic factors underlying attempts and death are shared. The converse of this finding points to the fact that there are some genetic factors that are unique to suicide attempts versus death. In relation to the contributing environmental factors that were not shared among siblings, the authors found weaker correlations between attempts and death ranging from 0.21–0.36. Another interesting finding from this study was the demonstration that age mattered, such that the influences of heritability on suicide attempts were greater in the 10–24 age group than in older members of the cohort. Taken together, these findings provide insights into the magnitude of the genetic and environmental contributors to suicide attempts and deaths and imply shared and distinct etiologies for these components of suicidality. In his editorial (11), Dr. John Mann from Columbia University discusses the significance of these findings in relation to current GWAS findings and polygenic risk scores. He points out that genes discovered from GWAS studies only account for a small fraction of the heritability of suicidal behavior and deaths by suicide, and with this, the editorial illustrates why our current understanding of specific genes is not sufficient to make valid predictions of the likelihood of engaging in suicidal behavior.

### Conclusions

The papers presented in this issue of the *Journal* address important issues related to abuse, trauma, and Alzheimer's disease that are relevant to resilience, susceptibility, and the development of psychopathology. The major findings include 1) differential patterns of gray matter maturation are associated with childhood abuse as compared with neglect, suggesting the possibility that different pathophysiological processes underly abuse versus neglect; 2) the potential feasibility of using functional imaging combined with machine learning to predict the development of PTSD and anxiety symptoms after a traumatic experience; 3) understanding the demographic factors and psychiatric symptoms that predict the transition from suicidal ideation to suicide attempts in soldiers; 4) demonstrating that suicidal behavior and death by suicide have some shared but also some distinct genetic underpinnings, and 5) amyloid beta and tau imaging can be used as biomarkers for Alzheimer's disease, but this does not necessarily mean that they are effective treatment targets; a number of clinical trials have not supported targeting amyloid beta as an effective therapeutic approach.


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