Evidence for Neurodegeneration and Neuroplasticity as Part of the Neurobiology of Suicide

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Two manuscripts appear in this issue of Biological Psychiatry involving suicide. Ernst et al. (1) found reduced expression of connexin 30 and connexin 43, which regulate calcium transients in the lateral prefrontal cortex of suicide completers. It is thought that astrocytes express connexins and it is argued that altered connexins affect astrocyte function, which could contribute to suicide. Cyprien et al. (2) found that the size of the caudal third of the corpus callosum was reduced in a group of suicide attempters. Taken together, the findings support the notion that there may be a neurobiology of suicide distinct from the psychiatric disorders commonly associated with suicide, involving alterations in glia, white matter, and by extension, the regions where the astrocytes are derived from (1) and where the regions contribute fiber tracts to the corpus callosum (2). Given the markedly different substrates (astrocytes vs. white matter; prefrontal cortex vs. corpus callosum), there is the further likelihood that suicide neurobiology has multiple phenotypes involving not only neurodegeneration but also neurodevelopment and neuroplasticity.

The possibility that there is a neurobiology of suicide has been raised before (3). Although suicide as a cause of death was originally viewed as an extreme outcome of major depression and then later as a potential confound in studies of the neurobiology of mood disorder, suicide is increasingly thought to have its own unique biological phenotype (4). Psychological autopsy studies have found that major depressive disorder is present in approximately 60% of suicides, while there is an Axis I diagnosis in more than 90% of all suicides (e.g., see [5]). The conclusion most often reached is that suicide is not an extreme response to stress, adverse events, or disease in normal people, but rather that suicide is an extreme act of someone with a psychiatric illness compounded by one or more adverse life events and a biological predisposition or vulnerability.

Biological studies of suicides have found differences in neurotransmitter receptors, neurons, glia, and/or white matter in various anatomical regions (6). In those studies reporting differences, the brain regions most commonly involved were in the prefrontal cerebral cortex. Other studies report differences in subcortical regions, adding further biological complexity. Interestingly, not all studies report differences, and even in those studies where differences are found, the magnitude of the differences is small. There are multiple confounds that can compromise human postmortem studies (postmortem delay, medication, psychiatric diagnosis, method of death, anatomy, methodology, age, sex, race, religious affiliation, socioeconomic status, tissue storage duration, tissue storage method, time of death, season of death, family history, agonal state, and others [7]), making it almost remarkable that any findings are detectable at all. This view is overly pessimistic, as the majority of human postmortem studies, including the report in this issue of Biological Psychiatry, go to lengths to control and minimize potential confounding variables. Yet, even with carefully controlled conditions, replication of findings does not always occur (8). The likely explanations are that the original findings are either chance observations reflecting the random nature of the sampling, with subsequent replication studies approximating the statistical mean of the subject population, or alternatively, that not all suicides will have the same underlying neuropathology. We believe the latter is the case.

The conventional heuristic hypothesis about the neuropathology of suicide was that systems in brain, most commonly reported in the serotonergic and noradrenergic systems, were deficient in suicide. The pathology was manifest by reduced neurotransmission, receptor alterations, and/or neuronal or glia changes, leaving the individual neurobiologically predisposed or vulnerable to an adverse life event. If mitigating factors are absent, hopelessness ensues, with a worsening outlook making suicide the only perceived solution. Importantly, the altered brain regions are most often found in the prefrontal cortex where executive decision making takes place. The healthy brain would find alternative life-extending solutions; the diseased brain, having a deficient prefrontal cortex, would not find the reason not to commit suicide and the behavior becomes disinhibited.

The findings of Cyprien et al. (2) fall into this neuropathological typology. In the brains of the suicide attempters studied, Cyprien et al. (2) found a reduced cross-sectional area of the caudal third of the corpus callosum. As previously mentioned, the majority of studies found alterations in the prefrontal cortex of suicides. A topographical representation of interconnection of brain regions through the corpus callosum has long been recognized, so interconnections arising from the prefrontal cortex utilize more anterior portions of the corpus callosum. Earlier studies examined brain lesions and fiber tract histopathology to identify Wallerian degeneration. More recently, studies have used magnetic resonance tractography by diffusion tensor imaging. The results are comparable. With respect to the observations of Cyprien et al. (2), the changes were in the caudal third of the corpus callosum. The portion identified would indicate regions in the temporal pole, including, but not limited to, the amygdala and hippocampus, insular cortex, and parahippocampal gyrus (9,10). Such regions are reported to be involved in a number of psychiatric conditions, including schizophrenia and major depression, but Cyprien et al. (2) controlled for such variables with a group of affective control subjects without a history of suicide but with a history of depression and a group of healthy control subjects. Furthermore, they statistically adjusted for age, sex, history of brain trauma, and brain volume.

Potentially problematic is why Cyprien et al. (2) did not observe differences in the anterior corpus callosum, the portion that contains interhemispheric fibers from the prefrontal cortex. One possible explanation may lie within the population studied, namely subjects that were 65 years of age or older, and given the study was of living subjects, the suicide behavior was of attempts. Hence, it is possible that the brain regions associated with suicide might be different in an older population than a younger population (most postmortem studies of suicide have groups of mean age of 40, such as the article here of Ernst et al. [11]). Alternatively, brain regions associated with suicide attempt may differ from those associated with suicide completion. The result in this case would be that the...
more typical/common younger suicide completers are not represented in this study by virtue of the demographics of suicide completion, and the population examined by Cyprien et al. (2) represents a suicide-resilient population. The observation that the caudal portion of the corpus callosum was reduced in size has predictive implications for future studies, suggesting temporal lobe involvements and reduced capacity for function of those regions in suicides.

Another relatively recent development in the thinking about suicide etiology is that suicide risk has origins early in life and the predisposition to suicide occurs as a result of altered neurodevelopment with consequences later in adulthood (11). The origins of these hypotheses lie in genetics studies where adverse early life events were found in greater numbers in suicides and biological studies that found suicides to have greater numbers of serotonergic neurons in the dorsal raphe nucleus than control subjects (12). The study of Ernst et al. (1) in this issue found reductions in the expression of astrocyte proteins. Conventional thinking regarding neuropathology and a degenerative process would predict increases in astrocytes and their related proteins as a consequence of neuronal reductions. For example, reduced numbers of neurons are reported in prefrontal cortex of major depressives and suicides (6), a condition that would otherwise lead to predictions about reactive astrocytes in response. Astrocytes are also reported to be reduced in number in major depression and schizophrenia, and astrocytes are increasingly being recognized as providing trophic and other support to their local neurons. Hence, a reduction in astrocyte support to neurons becomes another potential mechanism whereby neuronal and regional deficits can occur. It is not clear at this time whether astrocyte reductions are a primary event occurring in the development of a region or whether astrocyte numbers might be reduced for other reasons and become reduced in number as a secondary event, with the consequence being reduced support to the neuronal infrastructure.

We believe the evidence increasingly indicates that suicide may have a unique neurobiology. However, given the findings, including different neurotransmitter systems, different brain regions, different aged populations, different relative involvement of neurons, and as reported in this issue, astroglia and white matter fiber tracts, there may be different mechanisms that can lead to the biological predisposition or vulnerability to suicide. The different mechanisms may be rooted in substantially different etiology, namely neurodegenerative or neurodevelopmental in origin, but resulting ultimately in substantially similar functional outcome with compromised brain function and a hopeless outlook on the acute or chronic adverse event precipitating the suicide behavior. These differing etiologies have the potential to be overlapping and co-existing or, if absent, perhaps conferring resilience in outlook, a better functioning prefrontal cortex, and/or emotional tone as modulated by temporal lobe regions such as the amygdala or hippocampus. These differences could therefore constitute different phenotypes of suicide neural constitution and explain the presence and absence of the complex findings increasingly being reported in the literature as associated with suicide behavior.

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