The Stress Epidemic: A New Perspective of Neuropsychiatric Ailments in the First World

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Introduction

When Poe wrote these words more than a hundred and fifty years ago, he tapped deeply into the root of what it means to be anxious and depressed. He eloquently described the condition of a home representing society at large and a human’s reflection on such conditions. Much in the same way that Poe reflects on a house in disrepair only to have utter depression cast over him, it is easy too to feel overwhelmed at the disrepair of society at large in modern times and wonder on our own state of affairs. At times this may evoke an overwhelmed or agitating feeling within us as well.

Background and Historical perspective

The word anxiety originates from the Greek anhos, meaning “to squeeze or throttle” and eventually transformed to the Latin anxietas meaning a “troubled in mind.” This however, does not really make clear just how unconformable a sensation it is to question your role in the environment or existence that comes with these states [1].

Michel Foucault wrote on mental illness states quite eloquently in his treatise Madness in Civilization, where in his text, Foucault asserts that madness is reflected by the society as a whole and is somewhat in flux with society itself. He also asserts that our modern-day view of loss of sanity is different than the same states of being in prior epochs, such as the Middle Ages and Renaissance [2].

Major depressive disorder (MDD), which usually a manifestation of anxiety, comes originally from the concept of melancholia, covering all major forms of insanity and discussed as long ago as by the Mesopotamians several hundred years before the birth of Christ. The word depression, coming from the Latin word for “to press down”, was not taken on as an epithet to further delineate these concepts until the 19th century, where it took on the meaning of sadness and lassitude [3].

The burden of disease with regards to Generalized Anxiety Disorder (GAD) and MDD has certainly never been higher within society overall, with a total world population fast approaching 7 billion people with an overall population that fits the diagnostic criteria for MDD reaching approximately 350 million people. These overall numbers may be an underestimation due to poor understanding and underreporting of these illnesses [4]. According to the National Center for Health Statistics (NCHS), the overall rate in modern society for mental illness is between 1 in 20; with approximately 1 in 10 people in the United States on anti-depressants and with it being the number one cause of long-term disability, MDD has surely become a public health crisis [5]. What is not known is whether the overall incidence has increased out of proportion to adjust for population size, as a result of modern “convenience” and shifting values. As Foucault posited—our understanding of mental illness changes with the times.

The Priming Hypothesis

There are common genes that predispose people to GAD, MDD, Bipolar Disorder, Schizophrenia and other neuropsychiatric illnesses, but the question of what differentiates the genes at play and the roles that they play, is still relatively unknown.

Further, it is unknown how stress truly affects the human body and mind, thereby making our understanding of neuropsychiatric illness limited. This can mostly be attributed to the fact that the human nervous system, in its sheer complexity, and seemingly infinite number of combinations of triggers, neurochemical activities, mood states, behaviors; and complexities of human interaction and relationships are made difficult and tarnished by inabilities to relate and to read social cues.

I would assert to liken it to a two-hit hypothesis, where people with predisposition to these illnesses are “primed” for an episode and the stress of the environment creates an insult enough to incite a mood episode. A possible mechanism for this is through pruning of synapses within the brain and the effects of too much or too little of this process [6,7]. I would also assert that Generalized Anxiety Disorder (GAD), or the mood state created by constant stress, ruminations and thoughts of chaos or dysphoria, is what creates the foundation or bedrock for a MDD and is on the same neuropsychiatric continuum. Mikael Cho reports in a TED Talk on stage fright that sums up the anxiety portion of this cycle quite well in a visual format, which may be more broadly applied to the state of generalized anxiety disorder (GAD), with only the duration of symptoms differentiating these states [8].

The common denominator between these systems, which are primed genetically to react aberrantly to external stimuli, is the external stimuli, which I will now be referring to as environmental stress henceforth.

Learned helplessness as a paradigm for human behavior

There exists a paradigm in neuroscience of the “learned helplessness” model. It predicts that when a subject is subjected to recurrent stressors that feel unavoidable or out of one’s control due to the environmental stressors they are faced, the subject reaches a state of “learned helplessness”, where it participates in avoidance behaviors (i.e. hiding, aversion to stress) [9,10]. Over time, these avoidance behaviors manifest as a sort of “sickness behavior” consisting of a flu-like malaise, locomotor alterations, decreased reaction time, stereotypic alterations, withdrawal from social situations, decreased ingestion of food and drink, other physical symptoms, and an overall decrease in goal-directed behavior and motivation [11].

It therefore may not be such a stretch to view neuropsychiatric ailments as a pro-inflammatory state, which affects humans much in
the same way that animals are affected by recurrent shocks during experimentation, buffeted at the whims of the environment, much in the same way as, subjecting a patient to monoclonal antibodies that are pro-inflammatory incite episodes of depression in patients who have never before experienced such symptoms [11]. These may be adaptive measures taken on by an organism to slow down and dedicate more resources to the healing of such illnesses.

It is likely that learned helplessness, which has been studied extensively in animals, has a correlation to neuropsychiatric states in that of human subjects, with the most striking examples being MDD and GAD in human adults and Autism Spectrum Disorder (ASD) seen in human children.

Ontologically, we have not divorced ourselves so far from lower order animals that the limbic system and gray matter composing the motor cortex is very dissimilar from the animals that we branched from. Our dense cap of white matter forming the cerebral cortex however, is what separates us from all other hominids, primates and animals. This “mind” or thinking organ portion of our nervous system is essentially disengaged during periods of extreme duress, allowing for a fight or flight mentality during these states and is thus, adaptive. Therefore, anxiety is an uncoupling of our higher order mind from the lower order, more primal, more emotional brain and allowing our rogue “primal brain” to take over.

**Depression**

It is generally accepted that GAD, and therefore MDD, is ignited or exacerbated by certain insults. It is now generally agreed upon that there is also a connection between certain states of inflammation (i.e. autoimmune disease, cancer, etc.) and MDD.

Peripheral inflammation mediated by stress hormones and pro-inflammatory cytokines (i.e. IL-1β, TNF-α, IL-6 etc.) can evoke alterations in mood states and therefore affect behavior directly in a way that depression may be soon looked at as an inflammatory illness, like atherosclerosis and diabetes mellitus, with a mechanism of dysregulation of the hypothalamic-pituitary axis (HPA-axis) to environmental stressors [11].

**Autism**

Autism spectrum disorder (ASD) is now the most common neurodevelopmental disorder, with the CDC predicting a rate as low as 1:68, it consists of delays in social interaction and repetitive stereotypies in the pediatric and adolescent populations [12]. Cases of probable Autism in cases described in literature date back to at least the 18th century, but the incidence is starkly increased and increasing [13]. This may not have to do with a specific factor or teratogen, but rather, there is a nascent body of research concerning how steroids, cytokines and mediators from maternal circulation pass the placental barrier and may cause an intrauterine milieu that is inhospitable to normal human development due to the porous nature of the developing blood brain barrier (BBB) [14-16]. The placenta is an organ with the ability to produce its own compounds and acts a selective filter for other compounds. What remains unknown is how and why there is a connection between placental transmission, and production, of cytokines and various other pro-inflammatory mediators; and the later manifestation of neuropsychiatric conditions, such as Autism, depression or other neuropsychiatric ailments. There are seemingly a multitude of immune factors at play here and the increasing neuropsychiatric burden of adults may be manifesting itself in their progeny through enhanced stress states. There are numerous examples of this, including a paper published by the Zalcman lab, which correlate stress states invoked in peri-adolescent animals symptoms consistent with Autism and early childhood neuropsychiatric states [17].

Even in clinics, there are studies correlating the effects of gut inflammation on the exacerbation of neuropsychiatric symptoms in children with ASD from the degree of food restriction, aversion or allergies (as seen in Food Protein Induced Enterocolitis Syndrome (FPIES)) and in sudden onset illness (i.e. Rett’s, Pediatric Autoimmune Neuropsychiatric Syndromic, regressive forms of Autism, etc.) that these illnesses are environmental as well as genetic [16,18-25]. There may be evidence to support interplay between the gut microbiome and how “leakiness” in the intestines, much how the BBB developmentally is porous and made so in inflammatory states, may be inciting further inflammation in these patients and so may be exacerbating their neuropsychiatric symptoms. What is also interesting is that this is not restricted to a developmental setting in that gut inflammation leads to exacerbation of neuropsychiatric illness in older adults, especially those predisposed to symptoms, as in Alzheimer’s dementia [26,27].

**Conclusion**

It is unknown whether the incidence of neuropsychiatric symptoms is truly increasing, although it seems evident that it is. What we have discovered through animal models and population studies in humans is that increased environmental stress leads to an increase in neuropsychiatric symptoms. We actually may be seeing the rise of a stress crisis in the first-world, which is attributed to our lifestyles (i.e. pro-inflammatory states, long work hours, low compensation, poor diet, etc.). The journal Science recently produced an article on the disparity of poverty, which noted that poverty leads to less risk-taking and causes a 1.5 to 2.0 increase in MDD [28]. This is exacerbated by the cost of modern pharmacological intervention and the cost of missed work, which accounts for the number one cause of disability in first-world countries, and is not only costly, but also alarming. For instance, suicide rates amount to one million deaths globally annually.

Also striking to note, is that the neuropsychiatric ailments that affect adults and children are similar in their overall mechanism through pro-inflammation, but that the symptoms that they experience are so starkly different.

Children do not have the memory or life experience of adults, whom, when faced with adversity, predominantly adapt to the various circumstances of life. Consequently, children do not have the necessary perspective to cope and rather than hobbling along, withdraw from the inner-thinking of the mind and become enamored with the external world or regress from a certain level of realization. They just simply may not have the means to cope with such environmental stressors.

What we need to recognize is that much like having cancer or an autoimmune condition, GAD and MDD are pro-inflammatory states. We can treat them as illnesses and blame people or we can try to have more compassion for our mothers, brothers, sisters and lovers who have to cope with an illness that shakes the very core of their being and dredges up existential questions while trying to discover treatments that work at reducing the negative cycles created by our lifestyle that creates stress and inflammation.
Just as Poe reflected in "The Fall of the House of Usher", we can stand back and reflect on the home that is modern society and get washed over in a pale of depression, or we can recognize that it is a symptom of how we live our lives and how we may do so in a less detrimental manner.

References