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Is there a biological relationship between autism and suicide?

Abbie Storan

Around 800,000 people lose their lives to suicide each year. The World Health Organisation propose that for every person lost to suicide, there will be 20 more attempting suicide. Autistic people are 7.55 times more likely to die by suicide than the general population. Approximately 1% of the population is Autistic, but many will remain undiagnosed1.

When you consider a relationship between Autistic Spectrum Disorder, Mental Illness, and Suicide you will not fall short for evidence relating to the psychological nature of their connection. Such as the JAMA network report published this January, which states that Autistic people have a “more than 3-fold higher rate of suicide attempt and suicide than neurotypical individuals, and that over 90% of people with ASD who attempted or died by suicide had another comorbid mental health condition2. But what if we want to go deeper; can we establish a biological explanation for why Autistic people are at such an exaggerated risk of mental illness, suicidal ideation, and death from suicide compared to the Neurotypical population?

What is autism?

Autistic Spectrum Disorder [ASD] is a neurodevelopmental condition which affects how a person experiences the world around them, how they perceive others, and the way in which they communicate. With ASD, everything is different, and everyone is different. Due to the phenotypic heterogeneity as well as the accompanying differences in things like brain connectivity, it has been extremely hard for research to completely describe ASD neurobiology. However, promising progress is being made with identifying the molecular pathways underpinning ASD[3]. With the increasing success in neuroimaging data and genetic analysis, it is likely we could see breakthroughs in the diagnosis and treatment of ASD and co-morbidities in the future.

Before exploring the biology of ASD and Suicide, we should make note of the psychiatric evidence for relationships between ASD and Mental Illness. In 2017 AUTISTICA – the UK’s leading Autism research charity – partnered with the National Suicide Prevention Alliance. They produced a report wherein it was mentioned that depression is present in 30- 50% of adults with Autism[4]. Meanwhile in a meta-analysis of 21,797 Autistic participants, 11.8% of were also diagnosed with Schizophrenia Spectrum Disorders[5]. Another large-scale meta-analysis of 26,070 people with ASD reported that the prevalence of co-morbid Anxiety Disorders was 42%. This same study also reported the lifetime prevalence of OCD within participants was 22%[6].

In the UK there are approximately 500,000 adults with Autistic Spectrum Disorder (ASD). Eight in ten of these adults will also suffer from mental illness[7]. From a study of 374 adults with ASD researchers found that 66% had experienced suicidal thoughts, and 35% had attempted suicide[1].

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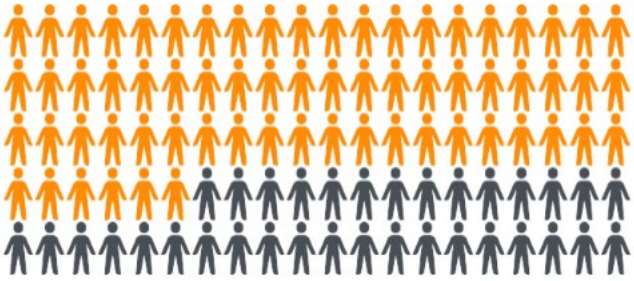
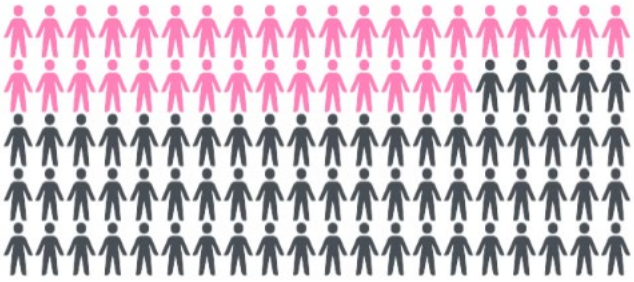
8/10 ALSO SUFFER MENTAL ILLNESS



66% HAVE EXPERIENCED SUICIDAL THOUGHTS



35% HAVE ATTEMPTED SUICIDE

Genetic links between mental illness and autism

Thanks to a fascinating review of genetic associations with psychiatric disorders, from Andrade et al, we can now outline a direct biological relationship between ASD, Depression and Anxiety[8]. This connection is facilitated by the dysfunction of genes encoding voltage-gated calcium channels (CaVs). CaV1.2 and CaV1.3 encourage neuronal firing and also couple excitation to gene expression; studies show this activity is linked to a number of psychiatric disorders.

In particular, CaV1.3 is encoded by CACNA1D genes, which have been associated with conditions such as ASD, Major Depressive Disorder, Schizophrenia, ADHD, and Bipolar Disorder. Andrade et al report that, “The non-coding SNP rs893363, located in the 3’ UTR of CACNA1D and the putative promoter region of the choline dehydrogenase gene was found in a genome- wide analysis of these five major psychiatric disorders”[8].

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We can go on to consider the roles of Cortisol and the Hypothalamus-Pituitary-Adrenal axis (HPA) in relation to Autism and Suicide. Cortisol is colloquially referred to as the 'stress hormone', stress is a known biological and psychological response to experiencing threatening stimuli. The effect of acute stress is the Fight or Flight response, wherein the Hypothalamus stimulates the adrenal medulla to secrete adrenaline – which decreases activity of the parasympathetic nervous system while increasing activity of the sympathetic nervous system.

Meanwhile chronic stress is regulated by the HPA axis[9]. Secretion of cortisol is controlled by actions of the paraventricular nuclei in the hypothalamus. Those nuclei secrete Corticotrophin-Releasing Factor to the pituitary, leading to the release of Adrenocorticotropic hormone into the bloodstream which stimulates cortisol synthesis and release from the adrenal glands. The HPA axis is under direct circadian regulation by the hypothalamic body clock, leading to diurnal rhythms in all components including cortisol[10].

Many studies on post-mortem brain samples from neurotypical people who died by suicide, and those who died by other means have highlighted higher concentrations of corticotropin-releasing hormone[12]; suggesting that people who commit suicide biologically possess higher levels of cortisol, thus higher levels of stress. This has been supported by a particularly interesting study by McGowan et al in 2009, outlining the direct role of the HPA axis in suicide.

From observations of the hypothalamus in people who died from suicide they found evidence of hypermyelination as well as reduced expression of the NR3C1 gene – a glucocorticoid receptor responsible for weakening cortisol signalling - compared to their control group of people who had died by other means. Their work also revealed that early-life adversity can have lifelong detrimental effects on function of the HPA axis[13]. Autistic children are 63% more likely to suffer from bullying than neurotypical children; wider research confirms that 16.6-18% of Autistic children are physically or sexually abused[14], and that autistic children are over 2.5 times more likely to be reported to child protection services for abuse[15]. So how is this relevant to ASD? The Diurnal Fluctuation of the HPA axis leads to a maximum concentration of salivary cortisol during the first half hour of waking, which decreases throughout the day[10]. We know that an increase in cortisol synthesis can dysregulate the HPA axis, and research states that children with ASD have elevated plasma and salivary cortisol concentrations, which we know to be associated with suicide.

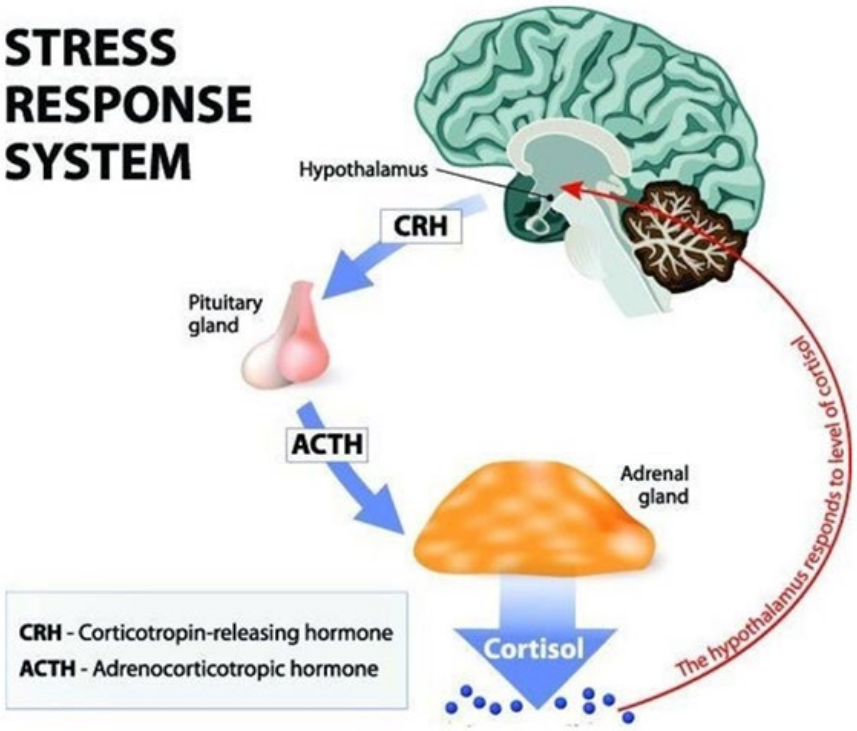

Figure 1. A schematic representation of the HPA

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The role of serotonin

We can now consider how serotonin plays a part in Autism and suicide. Hyperserotonaemia – elevated levels of whole blood serotonin - was the first biomarker identified from ASD in 1961, and it is present in more than 25% of autistic people. We can also note that elevated whole blood serotonin has been attributed to OCD too. Although we still do not completely understand how the serotonergic system contributes to ASD pathophysiology, neuroimaging and genetic research has concluded that the following clinical findings are related to both ASD and the serotonergic system:

Reduced brain and platelet 5-HT binding, Since 5-HT is degraded by aromatic acid decarboxylase into 5-hydroxyindoleacetic acid (5-HIAA), this means reduced 5-HIAA levels are characteristic too.

Intensified by tryptophan depletion Genetic link to chromosome 17q in males Rare SLC6A4 amino acid variants leading to low expressions of the Serotonin Transport (SERT) receptor – associated with increase in cerebral cortex grey matter volume[16]

Post-mortem studies of people who died by suicide have revealed low levels of 5-HIAA in the brainstem, as well as in the prefrontal cortex. These low levels are also observed in suicide victims known to have depression and schizophrenia. Dysregulation of the serotonergic system predisposes individuals to suicidal and other self-injurious acts - The amount of 5-HIAA metabolite in the cerebrospinal fluid (CSF) is strongly correlated to current and future suicidal behaviour. So, we know that not only do low levels of CSF 5-HIAA predict a higher rate of suicidal acts, but also indicate more lethal suicide attempts.

Most serotonin receptor studies focus on SERT, with results showing reduced amounts of SERT binding sites in suicide victims[17]. This information highlights more neurochemical evidence for the biological relationship between Autism and Suicide.

Hope for the future

There is a lot of work to be done to further our understandings of both Autism biology and the biological basis of suicide respectively. Therefore, primary research into the direct biological relationship of suicide and Autism is understandably lacking. From past investigations discussed here, we can be positive this work is underway, and remain hopeful that in the future we may have answers that could keep more autistic people alive. Unfortunately, Autistic people are more prone to experience discrimination throughout their lives from other individuals and even from services expected to keep them safe – undoubtedly having a severe impact on their mental health. There still are not enough resources or support specifically for Autistic individuals with mental health issues, which tells us that equally as much progress is desperately needed on a societal basis to reduce Autistic suicides.

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