Modelling the Development of Hypercortisolism in Neurotypical Individuals and Individuals with Autism Spectrum Disorder using COBWEB

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Abstract

Biological and psychiatric literature postulates that high rates of comorbidity exist between Autism Spectrum Disorder and commonly known mental health disorders, including depression. One physiological process known as the hypothalamic-pituitary-adrenal axis is argued to be dysfunctional in depressed individuals. Various studies propose that this dysfunction is rooted in a stress-induced epigenetic effect on glucocorticoid receptors, which are responsible for regulating the axis following a stress response. Lastly, recent research suggests that those diagnosed with Autism Spectrum Disorder are at greater risk for chronic stress, hypothalamic-pituitary-adrenal axis dysfunction, and depression. The present study aims to propose a visual representation of hypothalamic-pituitary-adrenal axis dysfunction in the form of hypercortisolism in neurotypical individuals and individuals with Autism Spectrum Disorder respectively. COBWEB, an agent-based simulation software used to model complex systems, will be employed to build two related but separate functional models. Broadly speaking, the study combines findings from various scientific and clinical disciplines to explore the interconnected and synergistic dynamics of the aforementioned concepts and how they may contribute to the development of Major Depressive Disorder in those with Autism Spectrum Disorder.

Introduction

The comorbid relationship between Autism Spectrum Disorder (ASD) and Major Depressive Disorder (MDD) has garnered immense interest in recent literature (e.g., Chandrasekhar, 2015; Mayes et al., 2013). ASD is categorized as a developmental disorder by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association (APA), 2013). There has not been an identified cause of ASD; nonetheless, it is believed that a combination of genes and environmental factors contributes to developing this disorder (Chaste, 2012). Major Depression (MDD) is a major psychological disorder that negatively impacts one's mood (APA, 2013). Most individuals diagnosed with MDD experience persistent feelings of unhappiness, insomnia, and minimal response or interest in day to day activities (APA, 2013). The role of the hypothalamic-pituitary-adrenal (HPA axis), a bodily process responsible in part for the release of primary stress hormones such as cortisol, in MDD is a long-established finding in psychiatric research (Varghese & Brown, 2001). Notably, research on the HPA axis has provided a greater understanding of how individuals are physiologically affected by stress and the effect of chronic stress on the development of depression. The present study aims to model HPA axis dysfunction in the form of hypercortisolism, which is a precedent for the development of chronic stress (Herman et al., 2016). Additionally, this report will discuss issues that should be explored within research and society concerning the comorbidity of ASD and MDD.

Complex Organization and Behaviour within Environmental Bounds (COBWEB)

COBWEB is a software used to model agent-based systems through visual, two-dimensional grid simulations (Bass & Chan, 2017). Parameters within a COBWEB model, such as the size of the mapping grid, can be customized. COBWEB consists of several tabs representing a different set of biotic factors such as *Agents* and *Resources*. Abiotic factors may

also be altered in COBWEB and are often utilized to organize a system's environment. The *Agents* tab allows users to manipulate the movement and consumption behaviour of agents. Factors of the *Agents* tab include initial count, breed energy, and aging. The *Resources* tab is employed to provide sources of energy for agents. Some factors represented by *resources* in COBWEB are the spawn rate, growth rate, and depletion rate. The *Agents* tab and *Resources* tab are among the essential features of the current project's model.

Literature Review

ASD refers to a range of symptoms, including but not limited to: drawbacks in communication and social cues, limited interests, and other symptoms that hinder the daily functions of the individual (APA, 2013). These symptoms usually result in impeded linguistic, cognitive, and communication skills, leading to attention deficiencies, repetitive verbal cues (i.e., echolalia), and negative responses to slight routine alterations (APA, 2013). Seeing that ASD manifests heterogeneously, varying both in type and severity across individuals, it is referred to as a spectrum disorder (APA, 2013).

Components of the HPA axis play a notable role in ASD and depression, primarily cortisol and glucocorticoid receptors (Spratt et al., 2012; Varghese & Brown, 2001). Cortisol, a neurobiological stress hormone, triggers an individual's acute stress response by elevating heart rate and blood pressure, sometimes disrupting homeostasis (Hannibal & Bishop, 2014). Compared to research on children without ASD, autistic children exhibit elevated cortisol levels (e.g., Sharpley, 2016). Sustained stress leads to increased cortisol and reduces the secretion of serotonin, dopamine, and other neurotransmitters that, when lacking, have been shown to have a direct connection to chronic depression (Belujon & Grace, 2017; Cowen & Browning).

Glucocorticoid receptors (GRs) in the brain interact with glucocorticoid hormones and the HPA axis and are responsible for the body's development, metabolism, and immunity (Vandevyver et al., 2014). In patients with MDD, increased levels of glucocorticoid hormones, such as cortisol, can decrease the expression of GRs and impair regularity of the HPA axis, both of which have been seen to further stress and MDD (Spratt et al., 2012; Varghese & Brown, 2001). Further research has provided evidence that irregularities of the HPA axis might lead to cortisol reuptake dysfunction and chronic stress (Fuld, 2015; Sivaratnam et al., 2015). Chronic stress, which can develop following adverse experiences, is a primary predictor of depression (Yang et al., 2015). Hence, this report will be looking at the relationship between ASD and depression. When exploring said association, it is important to identify the different determinants of HPA axis activity.

Research conducted after the publication of the DSM-5 suggests advancing the study of comorbidities in people with ASD, specifically concerning mental health disorders rooted in stress and trauma. Prior literature supports the existence of comorbid conditions with ASD, including but not limited to: depressive disorder, anxiety disorder, and attention deficit hyperactivity disorder (e.g., Chandrasekhar, 2015; Mayes et al., 2013). According to the DSM-5, 70 percent of people affected with ASD experience at least one mental health disorder and approximately 40 percent have two or more (APA, 2013). One study by Mayes et al. (2013) demonstrated a relationship between children with ASD and depression. Data from parent interviews suggested that contemplating or committing suicide was 28 times higher for children with ASD compared to neurotypical children (Mayes et al., 2013).

The Adverse Childhood Experience (ACE) studies (Felitti et al., 1998) have played a critical role in helping researchers to understand the impact of stress and trauma on the

development of ASD (Kerns et al., 2018). ACE studies conducted on children with ASD have discovered a significant association between the diagnosis of ASD and reporting one or more ACEs (Berg et al., 2016; Schilling et al., 2007). Additionally, adults with ASD report greater overall stress levels than neurotypical adults (Bishop-Fitzpatrick et al., 2015). Some research even argues that stress associated with ASD might be a key driver behind the disorder's relatively high comorbidity with mental health difficulties (Fuld, 2015).

The current project employs literature on the individual and synergistic components of ASD, MDD, stress, and HPA axis dysfunction. It hypothesizes that individuals with ASD are at greater risk for developing chronic stress and depression than neurotypical individuals due to an epigenetic decrease in GR expression associated with significant trauma and adversity. Two models will be created using COBWEB to offer a visual comparison of stress, hypercortisolism, and MDD in a brain with and without ASD, respectively.

Methods

In this study, two functional models were created using COBWEB to describe the stress response in a neurotypical brain and a brain affected by ASD. The results were collected and analyzed using Microsoft Excel. In both models, the Agent type 1 is symbolized by a triangle with a yellow circle and represents GRs. The Food type 1 represents cortisol and is shown as a yellow square. The Food type 2 is indicated by a blue square and represents stress.

Model 1: Hypercortisolism in a Neurotypical Brain

The stress response over time in a neurotypical brain is displayed in a two-step model. The complete simulation is run in a series of three functional cycles and three dysfunctional cycles, each with a first and second step. In functional cycles, the number of ticks per step remains constant throughout. The number of ticks varies for each step in dysfunctional cycles to represent a progressively prolonged cortisol response associated with HPA axis dysfunction.

In the first step, GRs (Agent 1), stress (Food 2), and cortisol (Food 1) enter the model, and cortisol increases for a specific amount of ticks to represent cortisol release during a stress response. This step utilizes three tabs: *Environment*, *Agents*, and *Resources*. The *Environment* tab is responsible for determining the structure of the model, such as the grid size and the number of factors that will be present. The *Agents* tab sets the behaviour and components of the glucocorticoid receptors (Agent 1), such as the initial amount of agents present on the grid. The Resources tab controls the properties of cortisol (Food 1) and stress (Food 2), such as its growth rate.

In the second step, cortisol production halts and GRs (Agent 1) begin getting rid of the cortisol (Food 1) to depict the reuptake of cortisol as signalled by GRs (Agent 1) at the end of a stress response. This step uses the aforementioned tabs in addition to the Food Web tab. This additional tab dictates which resources may be consumed by the agents. For instance, the glucocorticoid receptors (Agent 1) are set to deplete cortisol (Food 1) using the Food Web tab. See Table 1 and 2 for details on Model 1.

Model 2: Hypercortisolism in a Brain with ASD

The stress response over time in a brain with ASD is displayed in a two-step model that follows the same format as Model 1 but uses different values within each tab. The most significant differences are present within the ticks, Agents tab, and Resources tab. In Model 2, functional cycles run for 100 ticks, and each dysfunctional cycle lasts for 110, 120, and 130 ticks, respectively. In the first step of functional cycles, the number of ticks allotted to cortisol (Food 1) release is 25 ticks. In the first step of dysfunctional cycles, cortisol (Food 1) increases to 35, 45, and 55 ticks, respectively. Similar to Model 1, the initial amount for cortisol (Food 1) is set to 50 in the Resources tab. However, it experiences an increased growth rate of 10 to

represent greater cortisol release in those with ASD than neurotypical individuals. Additionally, unlike Model 1, stress (Food 2) has an initial amount of 50 to represent a greater number of stressors by those with ASD compared to those without. Altogether, the cycles in Model 2 are manipulated to be longer than those in Model 1 to represent significant HPA axis dysfunction in ASD. See Table 3 and 4 for details on Model 2.

Results

Neurotypical Dysfunctional Cycles

Table 1

Neurotypical Dysfunctional Cycles: Cortisol Build-up and Shut-off

Cycle	Tick	Phase
1	0 - 30	Cortisol Build-up
	31 - 105	Cortisol Shut-off
2	0 - 35	Cortisol Build-up
	36 - 110	Cortisol Shut-off
3	0 - 40	Cortisol Build-up
	41 - 115	Cortisol Shut-off

Table 1 represents the cortisol build-up phase and cortisol shut-off phase in the neurotypical model's dysfunctional cycles. There were a total of three cycles performed on this model where the ticks allocated for cortisol to build-up and shut-off increased as each cycle progressed. There were a total of 105 ticks in cycle one, and the first 30 ticks involved cortisol build-up. The second phase of cycle one was then performed when cortisol was shut off from ticks 31 to 105. In cycle two, there were a total of 110 ticks, an increase of five ticks from the

previous cycle, and while the first 35 ticks involved cortisol build-up, ticks 36 through 110 involved cortisol being shut off. Finally, cycle three had 115 ticks - an increase of five ticks from the previous cycle - and cortisol was shut off during ticks 41 through 130.

As will be seen in subsequent tables, the ticks allotted for each dysfunctional cycle in a model increase at a constant rate. For example, Table 1 shows that the number of ticks per cycle only increased by five ticks. However, Table 3, which pertains to the ASD model, depicts a total of 110 ticks in cycle one which is greater than the initial amount of ticks in Table 1. As each cycle progressed in Table 1, a total of 10 ticks was added to each cycle. Therefore, even though the dysfunctional cycles in both the ASD and Neurotypical models increased at a constant rate, the rate of increase differed.

Table 2

Neurotypical Dysfunctional Cycles: The Onset of Chronic Stress and the Rate of Cortisol Decline by GRs

Cycle	Tick	Cortisol	Phase	Rate of Cortisol Decline by GRs
1	0	50	Cortisol Build-up	1.44 units/tick
	105	156	Cortisol Shut-off	
2	0	50	Cortisol Build-up	0.88 units/tick
	110	336	Cortisol Shut-off	
3	0	50	Cortisol Build-up	0.64 units/tick
	34	405*	Cortisol Build-up	
	115	473	Cortisol Shut-off	

Note. *Chronic Stress enters in Cycle 3

Table 2 represents data from the neurotypical dysfunctional cycles. The rate of cortisol decline by GRs is the rate at which GRs got rid of cortisol, measured by the number of cortisol consumed per tick. Within the neurotypical model, this rate declines overall. The onset of chronic stress occurs when the amount of cortisol is greater than 400.

There were a total of three cycles in the neurotypical model, and similar to the ASD model, each cycle started from tick zero with the initial amount of cortisol being 50. Cycle one ran for a total of 105 ticks. The initial amount of cortisol was 50, and this gradually increased to 156 at tick 105. In cycle two, the cortisol grew to 336 at 110 ticks. There were 115 ticks in cycle three, and the first step experienced an exponential build-up in cortisol from 50 to 405 at only 34 ticks. Finally, in the second step of cycle three, the number of cortisol increased to 473 after 115 ticks, thereby indicating the onset of chronic stress.

ASD Dysfunctional Cycles

Table 3

ASD Dysfunctional Cycles: Cortisol Build-up and Shut-off

Cycle	Tick	Phase
1	0 - 35	Cortisol Build-up
	36 - 110	Cortisol Shut-off
2	0 - 45	Cortisol Build-up
	46 - 120	Cortisol Shut-off
3	0 - 55	Cortisol Build-up
	56 - 130	Cortisol Shut-off

Table 3 represents the cortisol build-up phase and cortisol shut-off phase in the ASD dysfunctional cycles. There were three cycles performed in the ASD Dysfunctional model where the ticks allocated for each phase increased as each cycle progressed. In cycle one, there were a total of 110 ticks, and the first 35 ticks involved cortisol build up. The second phase of cycle one consisted of shutting off cortisol from ticks 36 to 110. In cycle two, there were a total of 120 ticks, where the first 45 ticks represented cortisol build up and ticks 46 through 120 simulated cortisol being shut off. Finally, cycle three had a total of 130 ticks with an increase of 10 ticks from the previous cycle, and the cortisol was shut off for ticks 56 through 130. As each cycle progressed, there was an increase of 10 ticks.

Table 4

ASD Dysfunctional Cycles: The Onset of Chronic Stress and the Rate of Cortisol Decline by GRs

Cycle	Tick	Cortisol	Phase	Rate of Cortisol Decline by GRs
1	0	50	Cortisol Build-up	1.31 units/tick
	110	215	Cortisol Shut-off	
2	0	50	Cortisol Build-up	0.93 units/tick
	39	409*	Cortisol Build-up	
	120	438	Cortisol Shut-off	
3	0	50	Cortisol Build-up	0.19 units/tick
	35	403	Cortisol Build-up	
	130	764	Cortisol Shut-off	

Note.*Chronic Stress enters in Cycle 2

Table 4 represents data from the ASD dysfunctional model created in COBWEB. Within the ASD model, the rate of cortisol depletion declines. Each cycle started with an initial cortisol value of 50. In cycle one, cortisol grew to 215. The first step of the second cycle experienced cortisol build-up of 409 and signified the onset of chronic stress as the amount of cortisol passed the threshold of 400. Finally, in cycle three, the amount of cortisol climbed to 764.

Discussion

Prior literature posits that compared to neurotypical people, autistic individuals respond differently to environmental stressors (e.g., Spratt et al., 2012). In a study by Spratt et al. (2012), twenty children from ages three to 10 were split into an autistic and neurotypical group according to their developmental diagnosis. After comparing the HPA axis stress response in children with and without autism, the researchers found that the autistic group produced higher cortisol levels after receiving a blood stick stressor (Spratt et al., 2012). A heightened serum cortisol response involves higher peak cortisol levels, which prolongs the recovery of cortisol elevation and the HPA axis's reactivity to stressors (Brady et al., 2012). This is represented in our ASD dysfunctional cycles, in which the build-up period of cortisol is 35 ticks, while the build-up period for the functional cycles is 25 ticks. Both the literature and our model indicate that autistic individuals may have a lowered ability to turn off the increase of cortisol compared to their neurotypical peers when exposed to stressors in their environment.

According to Taylor and Corbett (2014), the HPA axis "tends to recover slower in individuals with ASD." Analogous to the literature, cortisol release following stress lasts longer in our ASD dysfunctional cycles compared to our NT dysfunctional cycles. This disparity results from a more significant decline in the availability of GRs, which detect excessive amounts of cortisol and "restore the homeostasis" (Finsterwald et al., 2015), in the ASD model compared to

the NT model. Altogether, the literature postulates that the fewer GRs present in the brain, the less likely the HPA axis will turn off cortisol release after a stressful situation (Laryea et al., 2013), and this is depicted in both of our models through the progressive decline in GR efficiency in dysfunctional cycles. Additionally, the GR efficiency rate is lower at the end of each dysfunctional cycle in the ASD model than in the NT model.

Chronic stress due to diminished GR availability within each model was determined to occur when cortisol built up to at least a volume of 400. Chronic stress develops in cycle two of the ASD model, whereas this occurs in cycle three of the NT model. The dysregulation of GRs in the HPA axis is widely suggested to be a cause of MDD, primarily among psychotic depressives (Bao & Swaab, 2019; Keller et al., 2017). Furthermore, hypercortisolemia, or Cushing's syndrome, which commonly results from chronic stress and excess cortisol build-up, is shown to affect more than 40 to 60 percent of depressed individuals (Keller et al., 2017). These studies explain the accelerated development of chronic stress shown in this study's ASD dysfunctional model and elucidate the rapid onset of and quadrupled likelihood of a comorbid diagnosis of MDD in individuals with ASD (Hudson, Hall, & Harkness, 2019).

The heightened stress response experienced by autistic individuals can be attributed to social, language, cognitive, and motor impairments unique to autism (American Speech-Language-Hearing Association, 2020), which result in abnormal reactions to environmental changes (Brady et al., 2012), and increased difficulty in social situations (Bishop-Fitzpatrick et al., 2016). As a result, the reduction of these stressors can be beneficial to the treatment of MDD in groups with ASD. Other useful methods include adrenocorticotropic hormone (ACTH) stimulation, which lowers both cortisol serum response and morning basal levels (Corbett & Taylor, 2015). Psychotropic medications such as antidepressants and antipsychotics, which

reduce basal and post-dexamethasone-corticotrophin-releasing hormone cortisol values, are effective treatments as well (Subramaniam et al. 2019).

Although the current project focuses primarily on the development of MDD among autistic individuals, hypercortisolism has implications in the pathophysiology of other mood and cognitive disorders (Keller et al., 2017), including anxiety, concentration, memory impairments, and insomnia (Middleman, 2004). However, the focus of only HPA axis hyperactivity creates a limitation, as both high and low HPA axis activity is connected to depression, with 25 to 40 percent of depressed individuals exhibiting cortisol levels lower than median values in neurotypical populations (Maripuu, 2015). However, statistics on hypercortisolism solely among individuals with comorbid diagnoses of ASD and MDD were unavailable.

Due to insufficient data present in the literature, this study can only focus on the general analysis of MDD among populations with ASD and is not representative of all comorbid cases. Individual stress responses and cortisol levels of autistic individuals vary based on their areas and levels of impairment. Although this model can be applied to other depressive disorders, the statistics to confirm this hypothesis are currently unavailable in the scientific literature.

Future Directions

ACTH is a hormone that is released when one is exposed to stress. Once the adrenal glands detect an increase of ACTH, cortisol will also be released into the blood (Society for Endocrinology (SFE), 2019). The hypothalamus will sense the rise of cortisol and then slow down the corticotropin-releasing factor (CRF) which causes the secretion of cortisol (SFE, 2019). Afterwards, ACTH production will also be slowed down. When CRF is given to a depressed patient, there is a blunted ACTH response but cortisol levels remain normal (SFE,

2019). This effect of cortisol may be because depressed individuals produce more cortisol per molecule of ACTH than non-depressed individuals (e.g., Holsboer et al., 1984; Yang et al., 2015). After symptoms of MDD are treated, CRH will go back to the way it was before. As a result, we would like to explore what would happen to cortisol and other glucocorticoid hormones in our dysfunctional cycles if ACTH were to decrease or increase. We would also like to see what would occur in our dysfunctional models if one was treated for major depressive disorder.

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