

Claremont Colleges

Scholarship @ Claremont

Scripps Senior Theses

Scripps Student Scholarship

2020

Neuroscience of Stress & Addiction: A Digitally Animated Video on How these Brain Systems Interact and Influence Each Other from Early Life Stress to Withdrawal

Claire Bacon-Brenes
Scripps College

Follow this and additional works at: https://scholarship.claremont.edu/scripps_theses

 Part of the [Behavioral Neurobiology Commons](#)

Recommended Citation

Bacon-Brenes, Claire, "Neuroscience of Stress & Addiction: A Digitally Animated Video on How these Brain Systems Interact and Influence Each Other from Early Life Stress to Withdrawal" (2020). *Scripps Senior Theses*. 1580.

https://scholarship.claremont.edu/scripps_theses/1580

This Open Access Senior Thesis is brought to you for free and open access by the Scripps Student Scholarship at Scholarship @ Claremont. It has been accepted for inclusion in Scripps Senior Theses by an authorized administrator of Scholarship @ Claremont. For more information, please contact scholarship@cuc.claremont.edu.

**Neuroscience of Stress & Addiction: A Digitally Animated Video on How these Brain
Systems Interact and Influence Each Other from Early Life Stress to Withdrawal**

A Thesis Presented

By

Claire Bacon-Brenes

To the Keck Science Department

Of the Claremont Colleges

In partial fulfillment of

The degree of Bachelor of Arts

Senior Thesis in Neuroscience

Spring 2020

TABLE OF CONTENTS

Abstract.....	3
Acknowledgements.....	4
Introduction.....	5
Science Communication As a Means for Addressing Mental Health.....	6
Alcohol Addiction.....	8
Cycles of Addiction.....	9
Reward Pathway.....	12
Alcohol’s Actions on GABA and Glutamate.....	15
Stress Responses.....	17
Early Life Stress.....	21
Corticotropin Releasing Factor.....	24
Conclusion.....	27
Video Transcript.....	28
Introduction.....	28
Explanation of Alcohol Addiction & Stress Pathways.....	29
Early Life Stress.....	31
Corticotropin Releasing Factor.....	34
Conclusion.....	35
Video.....	37
Literature Cited.....	38

Abstract

Alcohol addiction and stress are both highly prevalent health conditions impacting our society. With stress on the rise in college students and alcohol addiction impacting 19.7 million Americans as of 2017, communication around the science of these issues is ever important because of stigma around them. This digitally animated video effectively explains alcohol addiction and stress on a neurobiological level with college science students as the audience, including two important examples of how stress and alcohol addiction interact. Stress experienced early in life is a known risk factor in developing addiction due to dysregulation of the reward pathway and altered limbic brain regions. Furthermore, corticotropin-releasing factor, a neuropeptide crucial in initiation of stress response pathways and present throughout the limbic brain regions, contributes to the continued administration of alcohol as well as heightened anxiety addicts experience during withdrawal. Ultimately this video aims to improve mental health by increasing awareness around alcohol addiction and stress, as well as inspire college students to pursue further neuroscience knowledge.

Acknowledgments

I would like to thank Professor Coleman and Professor Solomon-Lane for the continued feedback and support throughout this process. This science communication project would not have been possible without your guidance. I would also like to extend my gratitude to my friends and family who have not only been a constant support system, but provided encouragement of my endeavour in this novel thesis project.

Introduction

This thesis project about the neuroscience of alcohol addiction and stress is a unique combination of science communication, neuroscience, and design. The final product is a digitally animated video that tells the story of the neuroscience of stress and addiction and the points in the brain at which they intersect. This thesis is much more than just a scientific paper. It is personal, it is filled with passion, and ultimately it reflects my cumulative experience and growth throughout my time at Scripps College. As a fellow college student who has seen the demons of stress and addiction, I believe the stigma around these issues must end. Knowledge is powerful in not only combating the stigma, but also in healing. Understanding predispositions to and risk factors for addictive behaviors is important in attempting to recover from an alcohol addiction or help reduce stress. Through effective communication tools, this video aims to provide inspiration to college students to pursue knowledge around these issues, not only to further science, but to embody empathy towards those who are battling with mental health.

The motivation behind this thesis is three pronged. First, this video is personal. I hope to work in the field of science communication, and this video creation is an opportunity to gain experience for this field of work. I aim to share my passion for and understanding of neuroscience and make this knowledge more accessible to the general public, both in this video and in my future career.

Second, this video can be used as a learning tool. Throughout my college career, much of my own academic growth has been centered around understanding how I learn best. I believe that each student is capable of learning complex material if it is presented to them in a way that supports their learning style, and I am passionate about understanding these individual

differences in learning. I value the direction of academia at liberal arts schools that is moving away from purely lecture based learning, beginning to incorporate more alternative methods of consuming information. Research suggests that videos can be an effective learning tool as they offer a graphical, auditory, and visual component for various kinds of learners (Sevian and Gonsalves, 2008). This project has the potential to be impactful to science students as a supplementary classroom educational tool.

Finally, the video is targeted towards college students as viewers. Stress and addiction are both highly prevalent mental health conditions impacting our society. Stress is on the rise in current day college students, with the American Psychological Association reporting 61% of students seeking counseling services for anxiety and 45% of students seeking counseling services for stress as of 2017 (Winerman, 2017). While addiction is not on the rise, addiction affected 19.7 million Americans as of 2017, with 74% of those individuals being subject to alcohol addiction (Bose, 2017). As mental health issues continue to affect millions of lives each year, this video can be informative about these ever important mental health conditions. I hope college students will not only gain knowledge, but also empathy in supporting individuals who are experiencing stress and addiction.

Science Communication As a Means for Addressing Mental Health

Science gains power with understanding from the general public, in particular students. The scientific challenges such as population growth, climate change, disease, and rising mental health conditions are critical for the future of the world (Sevian and Gonsalves, 2008). Furthermore, building awareness and knowledge around the science of mental health conditions

is important in developing empathy and validity around these issues (Clark et al., 2016) (Corrigan and Wassel, 2008). This video intends to not only be a science education resource for college students, but a method to increase awareness around the mental health conditions; addiction and stress. In communicating this scientific material, trust is very important, both of the source of material, and the method of communication (Weingart and Guenther, 2016). This visual video presented by a college student studying neuroscience gains validity by a fellow student presenting the information. Furthermore, it will be an effective learning tool through the use of visual animation, aiming to inspire many young scientists to embody empathy around mental health.

Focus on effective science learning at the higher education level is also important. Strong methods of science communication at the college level have been seen to improve retention rates of material, as well as ensure higher numbers of qualified and diverse scientists who want to go into the field. Furthermore, some students are even inspired to become science educators themselves. Overall, effective teaching and communication of science is not prioritized at the college level, with poor science teaching cited as the top complaint by university students at 83% of higher education institutions surveyed (Sevian and Gonsalves, 2008). Sevian and Gonsalves further presented research on the most effective methods of science communication. They found that well organized and goal oriented presentations, interaction with the audience, and dividing the audience's attention between verbal and visual information, as well as providing imagery during presentation were best. Together, these science communication techniques lead to higher retention rates, building trust with students, and creating lasting mental images for the audience (Sevian and Gonsalves, 2008) (Clark et al., 2016). Finally, studies have shown the importance of

professors possessing not only scientific content knowledge, but pedagogical knowledge as well. Pedagogical knowledge includes structuring content clearly, awareness around student's prior knowledge, ability to provide feedback, moving at a pace that allows retention of knowledge, and prioritizing the classroom learning speed, according to Sevian and Gonsalves' rubric (2008).

Finally, methods used to communicate science must be explicitly designed to increase younger generations' awareness. Evidence-based communication tools that engage the audience, build rapport, and leave the audience inspired are vital. Studies have found that engagement in science education at the K-12 levels is beneficial for; student's learning, further engagement in and enthusiasm around scientific study, and breaking down the barrier between scientists and the general public (Clark et al., 2016). Furthermore, these educational outreach programs were seen to improve scientists' communication skills as well as their abilities to come up with novel research or hypotheses and design experiments (Feldon et al., 2011) (Clark et al., 2016). The pressure scientists face to continually produce papers and present novel research is clear, but focus on improving science communication skills and engagement in science outreach is also vital in furthering scientific progress (Clark et al., 2016) and decreasing the prevalence of and stigma around mental health conditions.

Alcohol Addiction

Understanding the neural basis of alcohol addiction and stress, including overlapping brain regions, pathways, and molecules, is critical to developing knowledge around these mental health conditions. Addiction is defined as a substance dependence or reward deficit disorder (Koob, 2008) and is characterized by an increase in emotional and psychological stress,

otherwise known as “negative effect,” a decrease in behavioral control, an increase in impulsivity, and an increase in chronic stress (Sinha, 2008). This chronic stress experienced during addiction is a risk factor for developing maladaptive behaviors (Sinha, 2008). Addiction extends to an array of addictive drugs and even objects beyond alcohol, specifically, addictive tendencies towards technology seem to be on the rise in humans (Hamissi et al., 2013). Nevertheless, alcohol addiction, or alcohol-use disorder as the DSM-5 has named it (Cooper, 2014), is still the most prevalent substance of abuse (Bose, 2017).

Alcohol use disorder is said to have two distinct components compared to healthy consumption of alcohol: tolerance and dependence (Sommer and Spanagel, 2012). Tolerance is defined as a decrease in behavioral or intoxicating effects when an addicted individual consumes alcohol (Sommer and Spanagel, 2012). In other words, when an individual becomes addicted to alcohol, they must increase their dose of alcohol consumed to achieve the same effect of intoxication. Dependence is an increase in withdrawal symptomatology and has both a physical and motivational component. The major withdrawal symptoms experienced by those who are dependent on alcohol include anxiety, dysphoria, irritability, and disruption of sleep (Sommer and Spanagel, 2012). When an individual develops both a tolerance of and a dependence to alcohol, they generally engage in chronic consumption of alcohol (Koob, 2013).

Cycles of Addiction

There are two well characterized cycles in which addiction operates, crucial in understanding how addiction develops. Alcoholism is not an individual constantly being intoxicated, rather, it is a mental health condition that undergoes a cyclical progression. The

three stages included in this cyclical model are the preoccupation/anticipation, binge/intoxication, and withdrawal/negative effect stages shown in Figure 1 (Koob, 2013). While this cycle of addiction is seen in each drug of abuse, the binge and intoxication state is prolonged in alcohol addiction due to the oral administration method of alcohol consumption (Sommer and Spanagel, 2012). Furthermore, the brain regions involved in the withdrawal/negative effect phase are particularly important in understanding continued administrative behavior of alcohol. In addicted individuals, these brain regions; the nucleus accumbens (NAcc), bed nucleus of the stria terminalis (BNST), and the central nucleus of the amygdala (CeA), become altered (Koob, 2008).

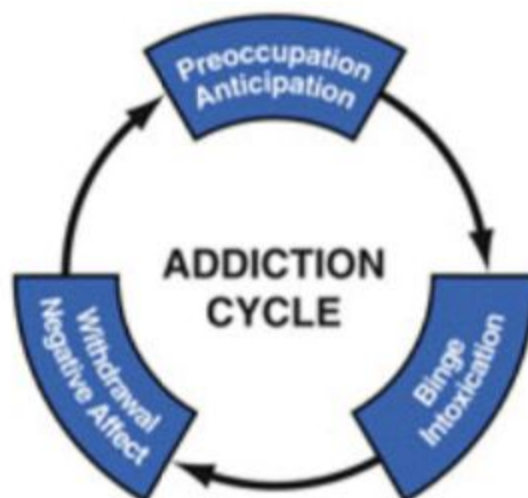


Figure 1 Schematic of addiction cycle highlighting three phases (Koob, 2013)

Alcohol addiction is also seen to operate in a cycle alternating between impulsive and compulsive behavioral patterns (Koob, 2013). Impulsive behavioral patterns are said to occur in the initial phases of addiction and include a rotation between feelings and behaviors of tension/arousal, impulsive acts, pleasure/relief/gratification, and relief/guilt/self reproach (Koob,

2013). As an individual moves to the compulsive behavioral stage, typically during the terminal phase of the addictive cycle, this individual will experience anxiety and stress, repetitive behaviors, relief of stress and anxiety, and finally obsessions in a cyclical manner (Koob, 2013). Both of these addictive cycles and the feelings in each respective schematic are important in understanding the continued administration of alcohol, characteristic of addicts.

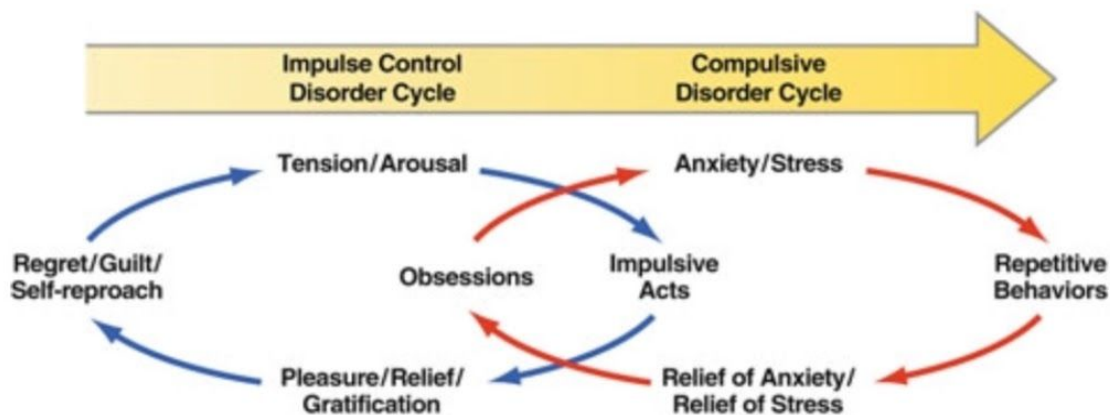


Figure 2 Second schematic of a cycle of addiction depicting the change from impulsive control to compulsive control of individuals consuming alcohol chronically (Koob, 2013)

Table 1 Brain region abbreviations and functions. These regions are important in understanding the development of alcohol addiction, the reward pathway, stress response pathways, limbic brain regions, and how alcohol addiction and stress overlap

Abbreviation	Brain Region	Function
NAcc	Nucleus accumbens	Located in the hypothalamus and involved in processing rewarding stimuli
VTA	Ventral tegmental area	Origin of dopaminergic cell bodies involved in the reward pathway and other dopaminergic pathways
PFC	Prefrontal cortex	Involved in a wide variety of executive functions, including reward initiated decision making and assessment of consequences
BNST	Bed nucleus of the stria terminalis	Limbic forebrain region involved in mediating neuroendocrine, autonomic, and behavioral responses (Crestani et al., 2013)
CeA	Central nucleus of the amygdala	Located in the amygdala, the CeA is involved in processing of painful stimuli, mediating fear and anxiety responses, as well as serving as a major output source of the amygdala (Kalin et al., 2004)
PVN	Paraventricular nucleus of the hypothalamus	Activated by physiological changes including stress and involved in many autonomic responses (Ferguson et al., 2008)

Reward Pathway

The reward pathway, otherwise known as the mesolimbic dopamine pathway, is further important in understanding the development of alcohol addiction. There are two components thought to be involved in reward: “wanting” and “liking.” Dopamine, the chemical associated with pleasure and many other functions throughout the body, is the main neurotransmitter involved in the reward pathway, alongside GABA and glutamate (Söderpalm and Ericson, 2013).

Specifically, dopamine is responsible for mediating the “wanting” phase in addiction (Berridge and Robinson, 1998). Berridge and Robinson showed this through dopamine antagonist studies in mice where an individual's desire to seek either food or drug was altered, but hedonic palatability seemed unaffected (Berridge and Robinson, 1998). When a non-addicted individual encounters something rewarding, such as alcohol, limbic regions of the brain become activated (Gilpin and Koob, 2008). Further, the ventral tegmental area (VTA) produces dopamine, and releases dopamine onto neurons in the nucleus accumbens (NAcc), depicted in Figure 3. Finally, dopaminergic neurons from the NAcc innervate the neurons in the prefrontal cortex (PFC), where a positive association is made between the behavior of consuming alcohol and the release of dopamine or this pleasurable experience (Heshmati and Russo, 2015).

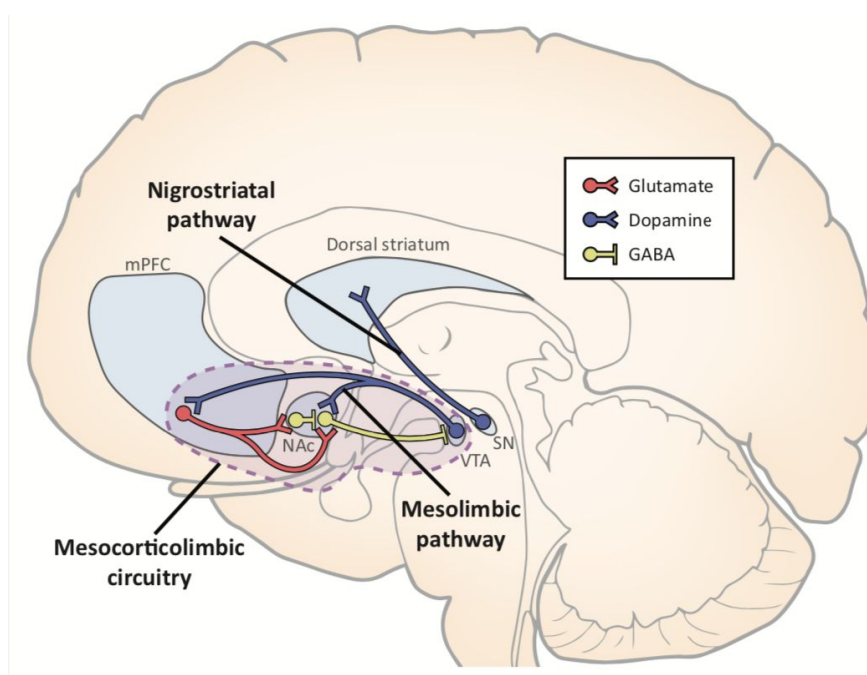


Figure 3 Diagram of mesolimbic pathway highlighting dopaminergic, glutamatergic, and GABAergic neuronal connections (Stanton et al., 2018)

Dopaminergic neurons from the VTA also innervate neurons in the hippocampus and allow for positive formation of memories to be made (Heshmati and Russo, 2015). When a

non-addicted individual seeks alcohol again, there are positive associations between consuming alcohol, dopamine release, and the euphoric effects of alcohol, causing alcohol consumption to be under the control of positive reinforcement (Gilpin and Koob, 2008).

In individuals who are addicted to alcohol, this reward pathway becomes dysregulated. In contrast to acute consumption of alcohol, chronic consumption of alcohol is under the control of negative reinforcement (Koob, 1992). Addicted individuals consume alcohol to alleviate the negative effect or anxiolytic feelings that occur during the withdrawal phase in the cycle of addiction, not because of the positive, euphoric feelings and dopamine release occurring following alcohol consumption (Gilpin and Koob, 2008). The dysregulation of the reward pathway is behind this change from positive reinforcement to negative reinforcement control in the development of addiction. Reward circuitry becomes dysfunctional due to constant activation occurring with chronic alcohol administration, ultimately making reward circuitry less sensitive to hedonic stimuli (Söderpalm and Ericson, 2013). Furthermore, in addicted individuals there is an enhanced decrease in dopamine when alcohol or the positive stimulus is removed during withdrawal. Compulsive behavior to seek alcohol is then triggered in order to alleviate this depletion of dopamine, highlighting negative reinforcement control of the withdrawal phase (Koob, 2013). This compulsive behavioral response to dopamine depletion is key to understanding the cycle that leads to a dysregulated reward pathway.

This dysregulation of dopaminergic transmission in the mesolimbic system occurs, in part, through alcohol's actions on GABA pathways and DAT receptors. GABA_A receptors are abundant throughout the mesolimbic dopamine system and are involved in influencing dopamine levels throughout the reward pathway, as seen in Figure 3 (Söderpalm and Ericson, 2013)

(Stanton et al., 2018). Acute ethanol consumption inhibits actions of GABA interneurons in the ventral tegmental area (VTA). This causes VTA dopaminergic neurons to be disinhibited and an increase in dopamine release in the NAcc is seen (Söderpalm and Ericson, 2013). This suggests that during chronic consumption of alcohol, VTA dopaminergic neurons are not as likely to be disinhibited and therefore there is less dopamine released in the reward pathways of addicted individuals. Additionally, DAT receptors, dopamine reuptake transporters throughout the reward pathway, particularly in the NAcc, are seen to be down regulated in alcohol dependent rats (Hirth et al., 2016). DAT receptors are known to be plastic, and human imaging studies suggest that with decreased receptor density, there are decreased levels of circulating dopamine throughout the reward pathway (Volkow et al., 2004). Altogether, this evidence further confirms dysregulation of reward pathways on a molecular level that lead to negative reinforcement motivation to consume alcohol in addicts.

Alcohol's Actions on GABA and Glutamate

The development of alcohol addiction, as well as alcohol as a depressant, are best understood through alcohol's actions throughout the nervous system on a molecular level. Ethanol, or the alcohol that we humans consume, acts as a central nervous system (CNS) depressant. Studies have shown that when alcohol is administered, it acts on both GABAergic and Glutamatergic neurons (Söderpalm and Ericson, 2013). GABA is the main inhibitory neurotransmitter in the CNS (Koob, 1992), while glutamate is the most prevalent excitatory neurotransmitter in the brain (Lovinger and Roberto, 2013). Neither GABA nor glutamate are specific to one brain region, but rather are prevalent throughout the nervous system. GABA acts

on both ionotropic and metabotropic GABA receptors. The GABA_A ionotropic receptor is where ethanol perpetuates GABA's inhibitory actions. When GABA binds to the GABA_A receptor, there is an increased flow of negatively charged chloride ions into the nerve cell, decreasing the likelihood for a cell to reach the threshold for an action potential to occur (Koob, 1992). With acute alcohol administration, ethanol molecules bind to GABA_A receptors and enhance further postsynaptic inhibition (Lovinger and Roberto, 2013). Additionally, studies have shown that administration of GABA_A receptor antagonists decrease some of the depressant behavioral effects of ethanol (Koob, 1992). Finally, the decrease in likelihood of an action potential is mechanistically showing alcohol's actions as a CNS depressant as GABAergic neurons become less active (Koob, 1992).

When administration of alcohol becomes chronic, GABAergic systems develop a tolerance to ethanol molecules. In order to experience the depressant actions of alcohol such as euphoria, decreased anxiety, and sedation, an addicted individual must consume larger amounts of alcohol (Koob, 1992). In addicts, ethanol no longer potentiates the release of GABA. In fact, studies have shown a decrease in GABA release when an addicted individual consumes alcohol (Lovinger and Roberto, 2013). Further, postsynaptic GABA_A receptors are altered and develop a decreased affinity for the binding of ethanol molecules (Lovinger and Roberto, 2013).

In terms of glutamate, ethanol inhibits glutamatergic neurotransmission (Lovinger and Roberto, 2013). Glutamate acts on both metabotropic and ionotropic receptors, with ionotropic receptor types including NMDA, AMPA, and kainate receptor subtypes. Upon acute consumption of alcohol, ethanol inhibits all classes of the ionotropic glutamate receptor, with most significant effects seen at the NMDA and kainate receptors. This further explains the

depressant actions of alcohol as glutamate is an excitatory neurotransmitter. On the other hand, when consumption of alcohol becomes chronic, the glutamatergic ionotropic receptors also develop a tolerance to the ethanol molecules and are no longer inhibited by ethanol. In fact, presynaptic glutamate release as well as NMDA receptor actions are seen to be increased (Lovinger and Roberto, 2013). While alcohol acts as a depressant upon acute consumption, addicted individuals experience different actions of ethanol molecules due to their chronic consumption. Alcohol's actions on the molecular level, as well as the development of addiction through the reward pathway, results in escape from the cyclical consumption of chronic alcohol incredibly difficult, evident by the many individuals who continually struggle with this mental health condition.

Stress Responses

Neuroscience background on different stress responses is needed to make connections between stress and alcohol addiction. While stress is a commonly used term and an understood feeling among the general population, its hormonal, biological, and behavioral components are not understood by many. Stress is defined by Dr. George Koob, an expert in the field of the neuroscience of stress and addiction, as the response to demands on the body (Koob, 2008). In other words, stress is the body adjusting to reinstate homeostatic balance. Generally there are considered to be two different kinds of stressors: physical and psychological stressors. Physical stressors put strain on the body and include experiences such as extreme cold temperatures, chronic illness, and pain, while psychological stressors are experiences humans perceive as negative or threatening, including emotional strain and cognitive stress (“Stressors – CESH /

CSHS,” n.d.). Additionally, stress is also categorized as acute or chronic, with acute stress being for a short period of time, while chronic stress is a prolonged endurance of a stressor (Jankord and Herman, 2008). When an individual encounters a stressor, the first step is the brain perceiving the type of stressor. As seen in Figure 4, the brain activates different neural circuits depending on if it is a physical or psychological stressor, but ultimately a stress response is triggered (Godoy et al., 2018).

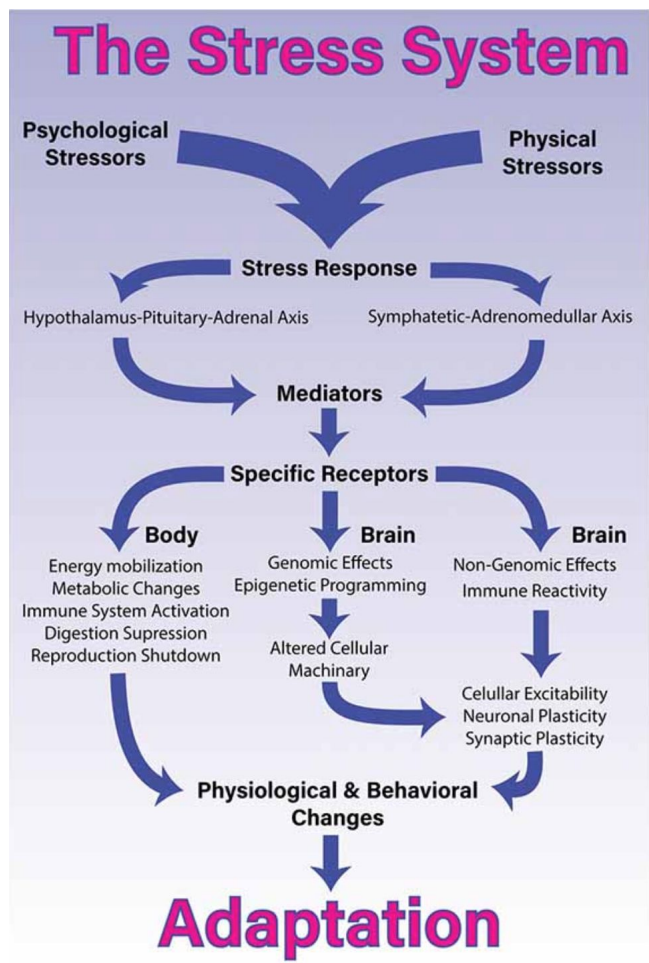


Figure 4 Stress responses involved in perception of and adaptation to physical and psychological stressors (Godoy et al., 2018)

There are many different ways in which a stress response occurs in the body. Generally, stressors that are physical demands on the body trigger an autonomic stress response while psychological stressors tend to cause both a physical and cognitive stress response. Brain regions specifically involved in responses to psychological stressors are the prosencephalic nuclei, components of limbic circuits such as the PFC, amygdala, hippocampus, PVN, VTA, and NAcc regions of the brain, with many GABAergic interneurons connecting PVN to limbic brain regions (Godoy et al., 2018). Furthermore, hormonal stress pathways are well understood as stress responses in the body. They include the hypothalamic-pituitary-adrenal axis, or HPA axis, which secretes glucocorticoids, and the sympathetic-adrenal-medullary axis, or SAM axis, which secretes epinephrine and norepinephrine. These two systems coordinate as the slow acting and fast acting stress responses, respectively, and work together to reinstate homeostatic conditions by releasing hormones that induce physiological and behavioral changes (Figure 4) (Godoy et al., 2018).

The HPA axis response to a stressor is a slow acting, hormonal response (Godoy et al., 2018). Activation of the HPA axis begins in the paraventricular nucleus (PVN) of the hypothalamus, considered a limbic brain region. Corticotropin releasing factor, or CRF, an important molecule in understanding the intersection of stress and addiction, is synthesized and then released from the PVN (Logrip et al., 2011). CRF in the blood stream then binds to CRF receptors present on the anterior pituitary gland, causing synthesis of adrenocorticotrophic hormone inside the anterior pituitary and then release into the circulatory system (Logrip et al., 2011). Finally, upon detection of high levels of adrenocorticotrophic hormone circulating, the adrenal glands paired with the autonomic nervous system cause cortisol and corticosterone to be

released (Jankord and Herman, 2008). Further, the PVN and anterior pituitary of the HPA axis are under control of negative feedback regulated by the PFC and hippocampus. When this negative feedback system becomes dysfunctional, as it does during chronic stress or other neuropsychiatric disorders, including addiction, the NAcc can become less active, and a positive feedback system now operates, resulting in overload on the stress system and high levels of circulating glucocorticoids (Godoy et al., 2018).

The SAM response to a stressor is also a hormonal response, but is considered the fast acting stress response associated with the autonomic nervous system. Activation of the SAM pathway also begins with neurons projecting from the PVN, as well as locus coeruleus (LC), amygdala, and rostral ventrolateral medulla (RVLM) to preganglionic sympathetic neurons present in the dorsal column of the spinal cord (Murison, 2016). This activation of the sympathetic nervous system turns on a variety of signaling pathways, specifically causing changes in blood vessels, glands, tissues, visceral organs, and smooth muscles. In the SAM pathway, the adrenal medullary glandular tissue is responsible for synthesizing and finally secreting norepinephrine and epinephrine into the body upon activation. Higher levels of circulating norepinephrine and epinephrine bind to the adrenergic G-protein coupled receptors, resulting in increased alertness, increased glucose production, and other physiological changes (Godoy et al., 2018). Beyond physiological actions, studies have shown norepinephrine's involvement in dopaminergic signaling of the reward pathway, crucial in the development of alcohol addiction (Weinshenker and Schroeder, 2007).

In addition to hormonal responses to stressors, knowledge around the brain's specific response to psychological stressors is critical in understanding addiction. Dopaminergic neurons

involved in the reward pathway are also involved in the perception of psychological stressors (Godoy et al., 2018). Increased firing of dopaminergic neurons innervating the NAcc from the VTA was seen in mice who were conditioned to be susceptible to social stress (Chaudhury et al., 2013). Additionally, the LC-Norepinephrine (LC-NE) system is crucial in interpretation of stressors in coordination with the PVN of the hypothalamus. Specifically, the LC-NE system is seen to be involved in regulation of stress induced anxiolytic behaviors via CRF. When an individual encounters a stressor there is release of CRF in the LC, by activation from the PVN, resulting in NE release throughout forebrain regions. Furthermore, CRF release from the LC is regulated by circulating corticosteroid levels. This coordination of the HPA axis and LC-NE system is important in individual's having flexible behavioral responses to stressors when in different environments (Godoy et al., 2018), as well as providing an example for extrahypothalamic actions of CRF. While there are many pathways that are involved in the perception of stressors, many of these brain regions and pathways overlap not only with each other, but also brain regions and neural pathways involved in addiction.

Early Life Stress

Substance use disorders are disproportionately experienced by individuals who have experienced early life stress (ELS), therefore understanding the dysregulation of brain stress systems that lead to addiction is crucial to ending this vicious predisposition. ELS is generally defined as chronic stress occurring during a critical period during development, and includes abuse, neglect, adoption, and other traumatic experiences (Maniam et al., 2014). Individuals who have experienced ELS are 21% more likely to develop a substance use disorder as an adult (Roos

et al., 2018). Additionally, upon exposure to chronic stress, ELS individuals in particular see lasting brain alterations, while adults experiencing chronic stress do not at the same rate (Godoy et al., 2018). Further evidence has shown that there is a correlation between the number of stressful early life events and the age of first drink. And a younger age of first drink further correlates with an increased likelihood of becoming addicted to alcohol (Schmid et al., 2010).

Altered brain structures involved in perception of psychological stressors and emotional processing is one way in which individuals who have experienced ELS are predisposed to developing addiction (Godoy et al., 2018). For example, human and primate studies show individuals who have experienced ELS show reduced hippocampal size (Pechtel and Pizzagalli, 2011) (Karten et al., 2005) (Hanson et al., 2016), as well as exaggerated early development and increased dendritic size of neurons in the amygdala as children (Roos et al., 2018). Roos et al. further showed that reductions in hippocampal volume lead individuals to be at risk of depression and lead to disruptive behaviors. This increased risk of depression is correlated with an increased likelihood of being in a negative emotional state, a step in the cycle of addiction (Roos et al., 2018). Additionally, the early development of the amygdala seems to lead to heightened reactivity of the amygdala, altered emotional processing and stress perception abilities, and eventual early cell death in the amygdala. Due to these altered limbic brain structures, individuals who have endured ELS are more likely to be in a negative emotional state. As alcohol is used as a coping mechanism to suppress this negative emotional state by addicts, ELS individuals are more likely to become addicted (Roos et al., 2018).

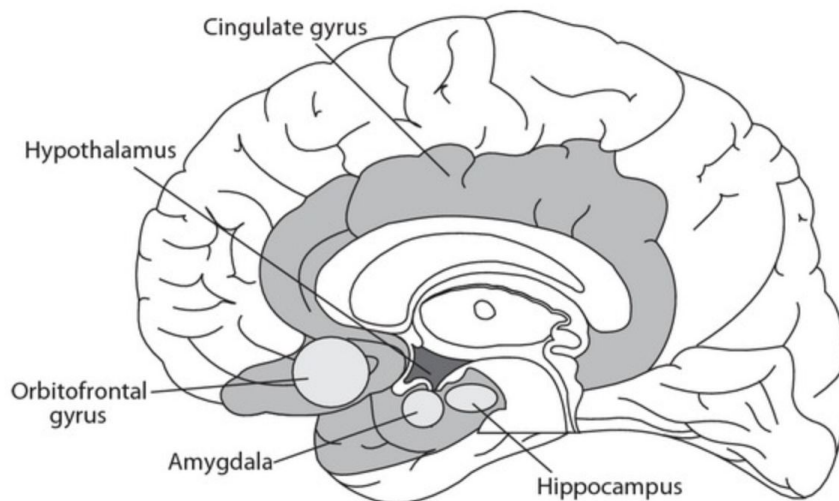


Figure 5 Limbic brain regions; important in emotional processing, memory consolidation, and perception of emotional and stressful stimuli. Critical in understanding dysregulation of neural pathways seen in ELS individuals (Roxo et al., 2011).

In addition to regulation of emotional processing, ELS is seen to affect reward pathway neural networks (Pechtel and Pizzagalli, 2011) (Hanson et al., 2016). When ELS individuals were exposed to rewards such as money or positive social cues, there was reduced activation of brain regions involved in processing rewards (Roos et al., 2018). This altered perception of rewarding stimuli appears to be correlated with the dysregulation of reward circuitry seen when an individual develops addiction, further highlighting how ELS individuals are predisposed to developing addiction (Roos et al., 2018). This dysregulation of reward circuitry is likely due to the chronic stress endured by ELS individuals. Human and primate studies show that when an ELS individual undergoes chronic stress, there is reduced firing of dopaminergic neurons along the reward pathway, specifically those that innervate the PFC. On the other hand, there is increased firing of dopaminergic neurons connecting the VTA and NAcc seen in susceptible mice who have undergone chronic social stress (Chaudhury et al., 2013) (Godoy et al., 2018). While studies have shown findings with upregulation and downregulation of dopamine levels

throughout the reward pathway, dysregulation of the pathway is clear. In conclusion, ELS individuals have altered neural activity pertaining to reward circuitry, stress perception, and emotional processing, predisposing them to being in a negative emotional state more frequently and more likely to develop alcohol addiction given the same exposure to alcohol.

Corticotropin Releasing Factor (CRF)

CRF's control of stress response pathways as well as other actions throughout the nervous system contributes to an individual maintaining addictive consumption of alcohol (Koob, 2008). CRF acts on both the hypothalamic and extrahypothalamic level during the withdrawal phase of addiction to maintain addictive behaviors. On the hypothalamic level, CRF acts on the well known HPA axis to control alcohol consumption. Generally, upon acute consumption of alcohol, there is increased activation of the HPA axis. On the other hand, when dependence to alcohol has developed, there is decreased activity of the HPA axis, implying dysregulation (Logrip et al., 2011). While there is decreased activation of the HPA axis during consumption of alcohol, when an addicted individual is in the withdrawal phase of the addictive cycle, there is an increase in CRF release in the brain, triggering a stress response via the HPA axis (Roberto et al., 2017). Furthermore, studies have shown that when a CRF antagonist is administered to mice undergoing the withdrawal phase of addiction, there are lower rates of self administration. Increased activation of the HPA axis via hypothalamic CRF during the withdrawal phase leads to motivation to consume more alcohol (Logrip et al., 2011).

CRF's main actions in maintaining addictive behavior are on the extrahypothalamic level. Extrahypothalamic CRF is involved in mediating negative reinforcement mechanisms involved

in the withdrawal phase of addiction. Increased CRF plays a crucial role in this negative emotional state, as CRF is seen to increase likelihood of relapse in both rat and human studies (Figure 6) (Lê et al., 2000) (Logrip et al., 2011). This increase in likelihood to relapse is due to the withdrawal phase of addiction being characterized by increased anxiety. In other words, the withdrawal phase is under control of negative reinforcement. When an individual is in ethanol withdrawal, CRF is released in the amygdala, triggering a stress response via the SAM pathway, as well as heightened anxiolytic feelings (Roberto et al., 2017) (Lê et al., 2000). Furthermore, when a CRF antagonist was administered, the anxiety experienced during withdrawal, excessive drug intake associated with dependence, and stress induced reinstatement of drugs are all blocked (Koob, 2008).

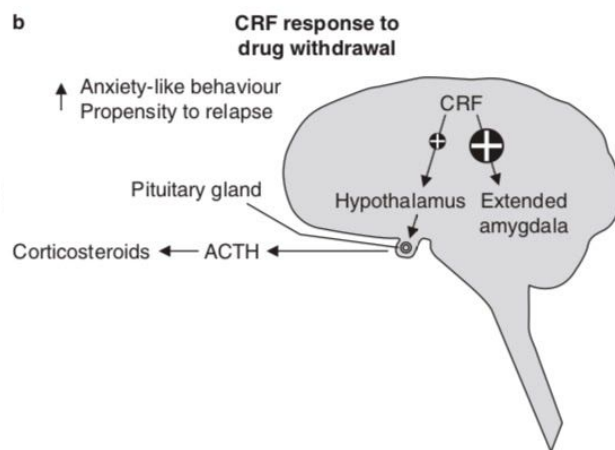


Figure 6 Increased CRF release seen in extended amygdala during withdrawal paired with an increase in anxiolytic feelings and an increase in relapse potential (Logrip et al., 2011)

CRF has additional limbic system involvement: control of the reward pathway, further connecting a neuropeptide crucial in the stress response and alcohol addiction. CRF has effects on dopaminergic neurons in the reward pathway. Specifically, VTA dopaminergic neurons express CRF receptors and receive CRF input from limbic forebrain regions and the PVN.

Furthermore, an increase in CRF results in increased firing of these dopaminergic neurons via the fast acting NMDA glutamate receptor. This suggests that increased CRF levels may lead to dysregulation of an individual's reward circuitry (Lovinger and Roberto, 2013).

GABA, whose actions are enhanced upon consumption of alcohol, is also involved in modulating extrahypothalamic CRF concentrations, and vice versa. GABAergic activity has been seen to increase CRF in the amygdala. Additionally, CRF has been seen to affect GABAergic transmission. Specifically, CRF is thought to enhance GABA's postsynaptic inhibitory actions (Koob, 2013) (Söderpalm and Ericson, 2013). As GABA's actions are altered upon consumption of alcohol and CRF is a factor in influencing stress responses as well as withdrawal and relapse behavior, the influence of the two molecules on one another may act to maintain addictive behaviors.

Finally, differences in genes coding for the CRHR1, a type of CRF receptor, have been indicated to increase the likelihood of an individual developing addiction. The CRHR1 is a G-protein coupled receptor and known to mediate behavioral stress responses via binding of CRF (Heinrichs and Koob, 2004). Genetic variation in this CRHR1 can lead to heavy alcohol drinking associated with stress. Rat studies and initial human studies have shown that upregulation of CRHR1 in limbic regions were related to alcohol drinking motivation, ultimately driving excessive alcohol intake. Furthermore, CRHR1 moderates the impact of childhood stress exposure on drinking age onset in humans. Finally, the T allele encoding for the CRHR1 has been seen to have a protective effect for developing addiction (Schmid et al., 2010). In all, this evidence is suggesting a genetic predisposition to developing addiction due to mutations in a receptor involved in stress response.

CRF, the neuropeptide involved in initiating stress responses as well as acting throughout limbic regions of the nervous system, contributes to maintenance of addictive behaviors in many ways. This neuropeptide's actions on the HPA axis, amygdala, GABA, the reward pathway, as well as genetic variations in the CRHR1 receptor are all important in understanding its actions in increasing likelihood of consuming alcohol, heightened anxiety during the withdrawal phase of addiction, as well as other behaviors that perpetuate the cycle of addiction.

Conclusion

Understanding brain systems involved in stress is crucial to understanding the development and maintenance of addictive behaviors. While there are many examples that can explain the intersection of stress pathways and the development of alcohol, CRF actions throughout the nervous system and the chronic stress endured during ELS, highlight important understanding around dysregulation of the HPA axis and reward pathway, in addition to heightened anxiety during the withdrawal phase of addiction. Knowing these predispositions to and risk factors for maintaining the addictive behaviors is important in attempting to combat the disease and help reduce stress. In conclusion, this project communicates the knowledge of how stress and addiction can contribute to one another, many times in a cyclical fashion. In this day in age, addiction is manifesting in many different ways as our world becomes more and more isolated with technology. I hope this video can be used as a resource and inspire continued education around the topics of stress, addiction, and mental health as a whole. Furthermore, I hope this video is another step in combating the stigma around mental health, while increasing empathy around stress and addiction by viewers.

Video Transcript

Introduction

Speaker: Stress and addiction are both highly prevalent mental health conditions impacting our society. Stress is on the rise in current day college students, with the American Psychological Association reporting 61% of students seeking counseling services for anxiety and 45% of students seeking counseling services for stress as of 2017 (Winerman, 2017).

Speaker: With the exception of opioids, addiction rates have been rather stable over the past decade (Abuse, 2015). However, 19.7 million Americans battled with a substance use disorder in 2017, with 74% of those individuals battling alcohol addiction (Bose, 2017).

Speaker: There is a great deal of evidence that stress increases the probability of developing alcohol addiction. This video will explain the widely accepted neuroscience behind stress response pathways and the development of alcohol addiction. To highlight the connection between stress, and the development and maintenance of alcohol addiction, research of two examples will be explained: Early Life Stress and its changes on the brain that increase the chance of developing alcohol addiction, as well as Corticotropin Releasing Factor, or CRF, a neuropeptide involved in the stress response pathway and contributing to an increased negative emotional state experienced by addicts during withdrawal from alcohol.

Speaker: So, first off, what is alcohol addiction? Alcohol addiction is considered a substance use disorder or reward deficit disorder (Koob, 2008). Generally, alcohol addiction is characterized by an increase in emotional and psychological stress, a decrease in behavioral control, an increase in impulsivity, and an increase in chronic stress (Sinha, 2008).

Speaker: Alcohol addiction affects individuals via a cycle of three stages: the preoccupation/anticipation stage, the binge/intoxication stage, and the withdrawal/negative effects stage (Koob, 2017)

Speaker: And, what is stress? Stress is defined as the body's response to demands that disrupt homeostasis in an attempt to maintain homeostatic conditions (Koob, 2008).

Explanation of Alcohol Addiction and Stress Pathways

Speaker: There are three crucial components to understanding alcohol addiction: How addiction develops, the reward pathway, and where alcohol acts on the brain.

Speaker: Addiction develops because addicts gain both a tolerance of and dependence to alcohol. Tolerance is when more alcohol is needed to reach intoxication, while dependence includes symptoms such as anxiety, dysphoria, hyperalgesia, and disruption of sleep that occur during the withdrawal stage of addiction (Lovinger and Roberto, 2013).

Speaker: The mesolimbic dopamine pathway, better known as the reward pathway, is also crucial in understanding the development of alcohol addiction. When an individual first consumes alcohol, their drinking behavior is under control of positive reinforcement, where alcohol induced euphoria becomes associated as a pleasurable reward stimuli (Gilpin and Koob, 2008). Dopamine is a neurotransmitter in the brain that is involved in this "wanting" phase of reward (Berridge and Robinson, 1998). When alcohol is administered, or even thought of, dopamine is produced in the ventral tegmental area, or VTA, of the brain. The VTA has dopaminergic neurons that connect to, or innervate, the nucleus accumbens (NAcc). Dopaminergic neurons from the NAcc synapse to the prefrontal cortex, where associations

between behavior and their consequences are made (Heshmati and Russo, 2015). The VTA also has dopaminergic neurons that innervate the hippocampus, where memories are created, and thereby making positive associations between consuming alcohol and the euphoric experience that occurs following consumption (Gilpin and Koob, 2008). The consumption of alcohol at this phase is under the positive reinforcement of euphoria.

Speaker: In addition, the consumption of alcohol is now under the control of negative reinforcement: addicted individuals consume alcohol to alleviate the feelings of withdrawal (Sommer and Spanagel, 2012) (Gilpin and Koob, 2008). As an individual begins to develop an addiction, this reward circuitry becomes dysfunctional due to constant activation of the mesolimbic dopamine pathway (Söderpalm and Ericson, 2013). In terms of the reward circuitry, there is decreased dopamine in the ventral striatum, where the NAcc is located, during withdrawal. This triggers compulsive behavior of individuals to consume more alcohol to alleviate this depletion of dopamine (Koob, 2013).

Speaker: Finally, alcohol's actions on the nervous system. Alcohol acts as a central nervous system depressant, by acting on the two most prevalent neurotransmitters of the brain: GABA and glutamate (Koob, 1992).

Speaker: When GABA binds to the GABA_A receptor, it is inhibitory by allowing negative chloride molecules to enter the cell, making the nerve cell more negative and decreasing the probability that an action potential will occur (Koob, 1992). Ethanol molecules, the alcohol that we drink, binds to GABA_A receptors and perpetuates the inhibitory actions of GABA. This decreased likelihood of an action potential is what makes ethanol a CNS depressant.

Speaker: Now that we have a better understanding of how alcohol acts and addiction develops in the brain, it is interesting to explore who is likely to develop addiction. Experiencing chronic stress early in life is one risk factor for developing addiction (Roos et al., 2018). Now, let's take a look at the brain stress response.

Speaker: There are several stress response pathways in the brain. They include activation of the hypothalamic-pituitary-adrenal axis, or HPA axis, which signals for the release of glucocorticoids, and the release of norepinephrine and epinephrine via the sympathetic-adrenal-medullary, or SAM, pathway in a hormonal response to stress. Behavioral responses to stressors generally involve activation of limbic regions of the brain (Godoy et al., 2018) When the HPA axis is activated, first, corticotropin releasing factor, or CRF, is released from the periventricular nucleus of the hypothalamus. Second, CRF triggers production and release of adrenocorticotrophic hormone from the anterior pituitary, and finally adrenocorticotrophic hormone causes glucocorticoids, namely cortisol, to be released from the adrenal glands and trigger a slow acting physiological response to stress (Maniam et al., 2014) (Koob, 2008). CRF can also be released in extrahypothalamic regions. Specifically, CRF released in the amygdala and other limbic brain regions, is known to be involved in the behavioral response to stressors (Koob, 2009).

Early Life Stress

Speaker: So how do the stress response pathways and alcohol addiction interact? There are many ways in which stress has been hypothesized to interact with addiction and vice versa, this

video will just focus on two components: Early Life Stress and Corticotropin Releasing Factor's involvement in both stress and alcohol addiction.

Speaker: Early life stress is a known risk factor for developing addiction (Hanson et al., 2016).

Adults who have experienced early life stress are 21% more likely to develop some kind of addiction compared to those who have not (Roos et al., 2018).

Speaker: In order to understand how early life stress increases the chances that an individual will develop an addiction, it is crucial to understand the limbic regions of the brain.

Speaker: The limbic system is involved in emotional processing, memory consolidation, and perception of emotional and stressful stimuli. There are many brain regions considered to be a part of the limbic region, but most research pertaining to addiction and stress has focused on actions of the amygdala, hypothalamus, and hippocampus.

Speaker: Individuals who have endured ELS show alterations in limbic brain regions and a reduced ability to process difficult emotions, suggesting a causal relationship. Human and primate studies show limbic brain alterations due to ELS include reduced hippocampal size (Pechtel and Pizzagalli, 2011) (Karten et al., 2005). The hippocampus innervates important brain regions involved in the stress response, emotional processing, and reward including the amygdala, PFC, and HPA axis (Pechtel and Pizzagalli, 2011).

Speaker: Additionally, altered amygdala volume, and altered long term connectivity in the amygdala region has been seen. In kids experiencing ELS, dendritic spines of neurons increase in size in the amygdala. However, as adults these same individuals experience early cell death of these extensive neural connections in the amygdala (Roos et al., 2018). This altered structure and connectivity of limbic regions negatively impacts emotional processing. Alcohol can be a way in

which individuals cope with these negative emotional states such as stress, depression, and anxiety (Roos et al., 2018).

Speaker: Early life stress can also lead to long term dysregulation of the reward circuitry involved in addiction (Pechtel and Pizzagalli, 2011) (Godoy et al., 2018) When an individual has experienced ELS they are more likely to have decreased motivation and an increase in hedonic or pleasure seeking behavior (Pechtel and Pizzagalli, 2011). Furthermore, when individuals who have endured ELS encounter rewards such as money or positive social cues, there is decreased activation of reward circuitry compared to controls (Hanson et al., 2016) (Sinha, 2008). This appears to be correlated with the dysregulation of reward circuitry seen when an individual develops addiction, highlighting how ELS individuals are predisposed to developing addiction (Roos et al., 2018).

Speaker: Finally, dysregulation of the HPA axis has been shown in individuals who have experienced ELS. Glucocorticoids, released from the adrenal glands, are responsible for negative feedback mechanisms in the HPA axis via glucocorticoid receptors located in the hippocampus, hypothalamus and anterior pituitary. This negative feedback is important in adapting and recovering from stress. However, chronic stress, like that experienced during ELS can lead to dysregulation of these negative feedback mechanisms and result in high levels of circulating glucocorticoids (Maniam et al., 2014).

Speaker:

In conclusion, given the same alcohol exposure, an individual who has experienced stress early in their life is...

1. More likely to be in a negative emotional state

2. More likely to use alcohol to cope with this negative emotional state or stressors
3. And given the alcohol use, more likely to become addicted

Corticotropin Releasing Factor

Speaker: Corticotropin releasing factor is also a crucial factor in understanding how stress and addiction are connected. Corticotropin releasing factor, or CRF, is involved in regulation of anxiety behaviors through the HPA axis as well as acting in extrahypothalamic brain regions (Logrip et al., 2011). CRF controls both hormonal and sympathetic responses to stressors via the HPA axis and other stress response pathways (Koob, 2008).

Speaker: At the hypothalamic level, CRF plays a role in the administration of alcohol. When the production of corticosterone is blocked by decreased CRF, reduced alcohol self-administration is seen (Logrip et al., 2011). Rodent studies suggest that increased activation of the HPA axis leads to increased self administration of alcohol (Logrip et al., 2011).

Speaker: CRF also acts on the extrahypothalamic level. In order to understand CRF's actions on the extrahypothalamic level, we have to go back to the three stages in the cycle of addiction. CRF, plays a crucial role in the negative emotional state or withdrawal phase of addiction by increasing the likelihood of relapse (Lê et al., 2000) (Logrip et al., 2011). When an individual is in ethanol withdrawal, CRF is released in the amygdala, triggering a stress response (Roberto et al., 2017).

Speaker: The negative emotional state or withdrawal phase of addiction is characterized by increased anxiety. According to rodent studies studies, this increased anxiety is thought to be a result of the increase in CRF present in the amygdala. This increased anxiety thereby increases

the likelihood that an individual will self administer alcohol during withdrawal (Koob, 2008).

Furthermore, when a CRF antagonist, a chemical that blocks the actions of CRF throughout the body, is administered, the anxiety experienced during withdrawal, excessive drug intake associated with dependence, and stress induced reinstatement of drugs are all blocked (Koob, 2008).

Speaker: Finally, there are several other mechanisms by which CRF may be involved in addiction. First off, GABA, whose actions are increased upon consumption of alcohol, have been seen to increase CRF in the amygdala (Koob, 2008). CRF has also been seen to affect GABAergic transmission. CRF affects dopamine neurotransmission in the VTA, involved in the reward pathway, potentially leading to the dysregulation of the reward pathways seen in addicted individuals. VTA dopamine neurons express CRF receptors, while the VTA receives CRF inputs from both limbic forebrain and PVN hypothalamic regions of the brain (Lovinger and Roberto, 2013). Lastly, there are several other chemicals that interact with CRF and have been seen to further contribute to this negative emotional state including norepinephrine, dynorphin, neuropeptide Y and urocortins (Sommer and Spanagel, 2012).

Conclusion

Speaker: This video is a broad overview of some of the many factors that link stress and addiction. These are serious mental health conditions impacting our society that need to be better understood among the general population. This message is particularly important for college students because of rising rates of stress and anxiety, as well as new exposure and pressure to engage in various drugs and alcohol seen in the college student population. Understanding

around stress and addiction will not only foster a culture of empathy towards those struggling with mental health, but will also work to combat psychiatric stigma while providing increased knowledge to inform decisions around drugs and alcohol use (Pinfold et al., 2005). Ultimately, the hope is that this video left you with a deeper understanding of how alcohol addiction and stress operate and interact on a neurobiological level. Listed below are a list of addiction and mental health resources, please contact these resources if you are in need of support. Both of these experiences can be incredibly isolating, but you should know you are not alone. Thank you for watching and please remember to take care of yourself!

Video

<https://scrippscollege.box.com/s/sra0m8ui8k3pg406qztp15ahkbi0c5>

Literature Cited

- Abuse, N.I. on D., n.d. Nationwide Trends [WWW Document]. URL <https://www.drugabuse.gov/publications/drugfacts/nationwide-trends> (accessed 2.20.20).
- Berridge, K.C., Robinson, T.E., 1998. What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? *Brain Res. Rev.* 28, 309–369. [https://doi.org/10.1016/S0165-0173\(98\)00019-8](https://doi.org/10.1016/S0165-0173(98)00019-8)
- Bose, J., 2017. Key Substance Use and Mental Health Indicators in the United States: Results from the 2017 National Survey on Drug Use and Health 124.
- Chaudhury, D., Walsh, J.J., Friedman, A.K., Juarez, B., Ku, S.M., Koo, J.W., Ferguson, D., Tsai, H.-C., Pomeranz, L., Christoffel, D.J., Nectow, A.R., Ekstrand, M., Domingos, A., Mazei-Robison, M.S., Mouzon, E., Lobo, M.K., Neve, R.L., Friedman, J.M., Russo, S.J., Deisseroth, K., Nestler, E.J., Han, M.-H., 2013. Rapid regulation of depression-related behaviours by control of midbrain dopamine neurons. *Nature* 493, 532–536. <https://doi.org/10.1038/nature11713>
- Clark, G., Russell, J., Enyeart, P., Gracia, B., Wessel, A., Jarmoskaite, I., Polioudakis, D., Stuart, Y., Gonzalez, T., MacKrell, A., Rodenbusch, S., Stovall, G.M., Beckham, J.T., Montgomery, M., Tasneem, T., Jones, J., Simmons, S., Roux, S., 2016. Science Educational Outreach Programs That Benefit Students and Scientists. *PLOS Biol.* 14, e1002368. <https://doi.org/10.1371/journal.pbio.1002368>
- Cooper, R., 2014. Diagnosing the Diagnostic and Statistical Manual of Mental Disorders: Fifth Edition. Routledge, London, United Kingdom.
- Corrigan, P.W., Wassel, A., 2008. Understanding and Influencing the Stigma of Mental Illness. *J. Psychosoc. Nurs. Ment. Health Serv.* 46, 42–48. <https://doi.org/10.3928/02793695-20080101-04>
- Crestani, C.C., Alves, F.H., Gomes, F.V., Resstel, L.B., Correa, F.M., Herman, J.P., 2013. Mechanisms in the Bed Nucleus of the Stria Terminalis Involved in Control of Autonomic and Neuroendocrine Functions: A Review. *Curr. Neuropharmacol.* 11, 141–159. <https://doi.org/10.2174/1570159X11311020002>
- Feldon, D.F., Peugh, J., Timmerman, B.E., Maher, M.A., Hurst, M., Strickland, D., Gilmore, J.A., Stiegelmeier, C., 2011. Graduate Students' Teaching Experiences Improve Their Methodological Research Skills. *Science* 333, 1037–1039. <https://doi.org/10.1126/science.1204109>
- Ferguson, A.V., Latchford, K.J., Samson, W.K., 2008. The Paraventricular Nucleus of the Hypothalamus A Potential Target for Integrative Treatment of Autonomic Dysfunction.

- Expert Opin. Ther. Targets 12, 717–727. <https://doi.org/10.1517/14728222.12.6.717>
- Gilpin, N.W., Koob, G.F., 2008. Neurobiology of Alcohol Dependence. *Alcohol Res. Health* 31, 185–195.
- Godoy, L.D., Rossignoli, M.T., Delfino-Pereira, P., Garcia-Cairasco, N., de Lima Umeoka, E.H., 2018. A Comprehensive Overview on Stress Neurobiology: Basic Concepts and Clinical Implications. *Front. Behav. Neurosci.* 12. <https://doi.org/10.3389/fnbeh.2018.00127>
- Hamissi, J., Babaie, M., Hosseini, M., Babaie, F., 2013. The Relationship between Emotional Intelligence and Technology Addiction among University Students. *Int. J. Collab. Res. Intern. Med. Public Health* 5
- Hanson, J.L., Albert, D., Iselin, A.-M.R., Carré, J.M., Dodge, K.A., Hariri, A.R., 2016. Cumulative stress in childhood is associated with blunted reward-related brain activity in adulthood. *Soc. Cogn. Affect. Neurosci.* 11, 405–412. <https://doi.org/10.1093/scan/nsv124>
- Heinrichs, S.C., Koob, G.F., 2004. Corticotropin-releasing factor in brain: a role in activation, arousal, and affect regulation. *J. Pharmacol. Exp. Ther.* 311, 427–440. <https://doi.org/10.1124/jpet.103.052092>
- Heshmati, M., Russo, S.J., 2015. Anhedonia and the brain reward circuitry in depression. *Curr. Behav. Neurosci. Rep.* 2, 146–153. <https://doi.org/10.1007/s40473-015-0044-3>
- Hirth, N., Meinhardt, M.W., Noori, H.R., Salgado, H., Torres-Ramirez, O., Uhrig, S., Broccoli, L., Vengeliene, V., Roßmanith, M., Perreau-Lenz, S., Köhr, G., Sommer, W.H., Spanagel, R., Hansson, A.C., 2016. Convergent evidence from alcohol-dependent humans and rats for a hyperdopaminergic state in protracted abstinence. *Proc. Natl. Acad. Sci.* <https://doi.org/10.1073/pnas.1506012113>
- Jankord, R., Herman, J.P., 2008. Limbic Regulation Of Hypothalamic-Pituitary-Adrenocortical Function During Acute And Chronic Stress. *Ann. N. Y. Acad. Sci.* 1148, 64–73. <https://doi.org/10.1196/annals.1410.012>
- Kalin, N.H., Shelton, S.E., Davidson, R.J., 2004. The Role of the Central Nucleus of the Amygdala in Mediating Fear and Anxiety in the Primate. *J. Neurosci.* 24, 5506–5515. <https://doi.org/10.1523/JNEUROSCI.0292-04.2004>
- Karten, Y., Olariu, A., Cameron, H., 2005. Stress in Early Life Inhibits Neurogenesis in Adulthood. *Trends Neurosci* 28, 171–172.
- Koob, G.F., 2017. Antireward, compulsivity, and addiction: seminal contributions of Dr. Athina Markou to motivational dysregulation in addiction. *Psychopharmacology (Berl.)* 234, 1315–1332. <https://doi.org/10.1007/s00213-016-4484-6>

- Koob, G.F., 2013. Theoretical Frameworks and Mechanistic Aspects of Alcohol Addiction: Alcohol Addiction as a Reward Deficit Disorder, in: Sommer, W.H., Spanagel, R. (Eds.), *Behavioral Neurobiology of Alcohol Addiction, Current Topics in Behavioral Neurosciences*. Springer, Berlin, Heidelberg, pp. 3–30.
https://doi.org/10.1007/978-3-642-28720-6_129
- Koob, G.F., 2009. Brain stress systems in the amygdala and addiction. *Brain Res., Stress, Coping, and Disease* 1293, 61–75. <https://doi.org/10.1016/j.brainres.2009.03.038>
- Koob, G.F., 2008. A Role for Brain Stress Systems in Addiction. *Neuron* 59, 11–34.
<https://doi.org/10.1016/j.neuron.2008.06.012>
- Koob, G.F., 1992. Drugs of abuse: anatomy, pharmacology and function of reward pathways. *Trends Pharmacol. Sci.* 13, 177–184. [https://doi.org/10.1016/0165-6147\(92\)90060-J](https://doi.org/10.1016/0165-6147(92)90060-J)
- Lê, A.D., Harding, S., Juzysch, W., Watchus, J., Shalev, U., Shaham, Y., 2000. The role of corticotropin-releasing factor in stress-induced relapse to alcohol-seeking behavior in rats. *Psychopharmacology (Berl.)* 150, 317.
- Logrip, M.L., Koob, G.F., Zorrilla, E.P., 2011. Role of corticotropin-releasing factor in drug addiction: potential for pharmacological intervention. *CNS Drugs* 25, 271–287.
<https://doi.org/10.2165/11587790-000000000-00000>
- Lovinger, D.M., Roberto, M., 2013. Synaptic effects induced by alcohol. *Curr. Top. Behav. Neurosci.* 13, 31–86. https://doi.org/10.1007/7854_2011_143
- Maniam, J., Antoniadis, C., Morris, M.J., 2014. Early-Life Stress, HPA Axis Adaptation, and Mechanisms Contributing to Later Health Outcomes. *Front. Endocrinol.* 5.
<https://doi.org/10.3389/fendo.2014.00073>
- Murison, R., 2016. Chapter 2 - The Neurobiology of Stress, in: al'Absi, M., Flaten, M.A. (Eds.), *Neuroscience of Pain, Stress, and Emotion*. Academic Press, San Diego, pp. 29–49.
<https://doi.org/10.1016/B978-0-12-800538-5.00002-9>
- Pechtel, P., Pizzagalli, D.A., 2011. Effects of early life stress on cognitive and affective function: an integrated review of human literature. *Psychopharmacology (Berl.)* 214, 55–70.
<https://doi.org/10.1007/s00213-010-2009-2>
- Pinfold, V., Stuart, H., Thornicroft, G., Flórez, J.A., 2005. Working with young people: the impact of mental health awareness programmes in schools in the UK and Canada. *World Psychiatry* 5.
- Roberto, M., Spierling, S.R., Kirson, D., Zorrilla, E.P., 2017. Corticotropin-Releasing Factor (CRF) and Addictive Behaviors. *Int. Rev. Neurobiol.* 136, 5–51.

<https://doi.org/10.1016/bs.irn.2017.06.004>

Roos, L.E., Horn, S., Berkman, E.T., Pears, K., Fisher, P.A., 2018. Leveraging translational neuroscience to inform early intervention and addiction prevention for children exposed to early life stress. *Neurobiol. Stress* 9, 231–240.
<https://doi.org/10.1016/j.ynstr.2018.10.004>

Roxo, M.R., Franceschini, P.R., Zubaran, C., Kleber, F.D., Sander, J.W., 2011. The Limbic System Conception and Its Historical Evolution. *Sci. World J.* 11, 2428–2441.
<https://doi.org/10.1100/2011/157150>

Schmid, B., Blomeyer, D., Treutlein, J., Zimmermann, U.S., Buchmann, A.F., Schmidt, M.H., Esser, G., Rietschel, M., Banaschewski, T., Schumann, G., Laucht, M., 2010. Interacting effects of CRHR1 gene and stressful life events on drinking initiation and progression among 19-year-olds. *Int. J. Neuropsychopharmacol.* 13, 703–714.
<https://doi.org/10.1017/S1461145709990290>

Sevian, H., Gonsalves, L., 2008. Analysing how Scientists Explain their Research: A rubric for measuring the effectiveness of scientific explanations. *Int. J. Sci. Educ. - INT J SCI EDUC* 30, 1441–1467. <https://doi.org/10.1080/09500690802267579>

Sinha, R., 2008. Chronic Stress, Drug Use, and Vulnerability to Addiction. *Ann. N. Y. Acad. Sci.* 1141, 105–130. <https://doi.org/10.1196/annals.1441.030>

Söderpalm, B., Ericson, M., 2013. Neurocircuitry Involved in the Development of Alcohol Addiction: The Dopamine System and its Access Points, in: Sommer, W.H., Spanagel, R. (Eds.), *Behavioral Neurobiology of Alcohol Addiction, Current Topics in Behavioral Neurosciences*. Springer, Berlin, Heidelberg, pp. 127–161.
https://doi.org/10.1007/978-3-642-28720-6_170

Sommer, W., Spanagel, R., 2012. *Behavioral Neurobiology of Alcohol Addiction*. Springer Science & Business Media.

Stanton, C., Holmes, A., Chang, S., Joormann, J., 2018. From Stress to Anhedonia: Molecular Processes through Functional Circuits. *Trends Neurosci.* 42.
<https://doi.org/10.1016/j.tins.2018.09.008>

Stressors – CESH / CSHS, n.d. URL <https://humanstress.ca/stress/what-is-stress/stressors/> (accessed 5.1.20).

Volkow, N.D., Fowler, J.S., Wang, G.-J., Swanson, J.M., 2004. Dopamine in drug abuse and addiction: results from imaging studies and treatment implications. *Mol. Psychiatry* 9, 557–569. <https://doi.org/10.1038/sj.mp.4001507>

Weingart, P., Guenther, L., 2016. Science communication and the issue of trust | JCOM. J. Sci. Commun. 15, C01. <https://doi.org/10.22323/2.15050301>

Weinshenker, D., Schroeder, J.P., 2007. There and back again: a tale of norepinephrine and drug addiction. *Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol.* 32, 1433–1451. <https://doi.org/10.1038/sj.npp.1301263>

Winerman, L., 2017. By the numbers: Stress on campus. <https://www.apa.org> 48