Biological Processes Underlying the Cognitive and Behavioural Effects of Neural Network Therapy®

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Biological processes underlying the cognitive and behavioural effects of Neural Network Therapy®

A Community-Based Research Project through the Trent Community Research Centre

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Introduction

In Canada, rates of mental illness are on the rise. Just in the past decade, the estimated chance of experiencing mental illness has increased from 1 in 5 individuals to 1 in 3 (Sunderland & Findlay, 2013). Of this population, 1 in 7 Canadians sought access to mental health services and supports (Public Health Agency of Canada, 2015). Many counselling approaches such as cognitive behavioural therapy, psychodynamic therapy, humanistic therapy, and mindfulness therapy promote understanding of oneself and the patterns of behaviour an individual exhibits in response to various situations. The Neural Network Therapy® technique takes this process further, utilizing current knowledge about neural pathways formed in response to stressful events to forge new networks that allow the individual to cope with these stressors. By understanding the biological basis of the cognitive and behavioural mechanisms occurring in the brain when one experiences mental disorder, one can make changes that directly target these pathways, diverging from habits and behaviours that seem to have become automatic.

The regions in the brain which are integral to the understanding of these biological mechanisms include the prefrontal cortex, the hippocampus, and the amygdala. These structures are heavily connected via neural networks and play modulatory roles towards each other, promoting or inhibiting behavioural, emotional, and learning processes (Chakraborty et al., 2021). Each neuron in the brain has the ability to make upwards of 1000 synaptic connections with nearby neurons, promoting strong connectivity and fast transmission of neural input (Stiles & Jernigan, 2010). These neural connections are highly dynamic, and the exposure to various stimuli has the ability to change where connections are made and how many are present (Stiles &

Jernigan, 2010). It is the neural pathways which are most often stimulated and form the most impactful connections which are maintained (Stiles & Jernigan, 2010). This is to ensure an increase in efficiency across the frequently used synaptic connection, allowing for rapid and accurate transmission of action potentials to other brain regions (Cohen et al., 2017). The ultimate strength, or weakness, of these neural networks is related to frequency of use, state of arousal, environment, and functionality of the regulatory brain regions (Stiles & Jernigan, 2010). It is these pathways that lead to an individual's behaviour, learning, memory, emotions, and coping outcomes, and it is these pathways which, when dysregulated, can have a negative impact on mental wellbeing.

This paper aims to provide an understanding of the biological basis of the human stress response, and how this response can lead to dysregulation and aberrant behaviour in the case of mental disorder. By breaking the mechanisms into subsections of neuroplasticity, learning and memory, behaviour, emotions, and coping and resilience, the overall impact of stressors on brain functionality is explained. These processes make up the biological basis of the Neural Network Therapy® technique and explain why exactly this method has an impact on clients.

The HPA Axis

The biological basis of the stress response is the result of a feedback loop which begins in the hypothalamus. This axis, called the hypothalamic-pituitary-adrenal (HPA) axis, ultimately leads to the production of the hormone cortisol which is responsible for the stress response. When a stressful stimulus is encountered, the hypothalamus secretes corticotropin-releasing

hormone (CRH), a hormone which acts on the anterior pituitary gland and stimulates the release of adrenocorticotropic hormone (ACTH). Upon release of ACTH into the bloodstream, the hormone travels to the adrenal cortex near the kidneys, a structure which produces and ultimately releases cortisol (Juruena et al., 2021). Within the brain, there are two types of cortisol receptors: mineralocorticoid receptors (MR) and glucocorticoid receptors (GR). MR has a much stronger affinity for the binding of cortisol, estimated to be ten-fold the affinity of GR (Oyamada et al., 2008), and therefore become saturated first following the release of cortisol. MR in the brain are found mainly in the hippocampus, while GR are dispersed throughout the hippocampus, amygdala, hypothalamus, and many other structures (Juruena et al., 2021). Enhanced cognitive function in the human brain is observed when most MR and some GR are saturated, however, this functioning decreases when increased GR binding occurs and glucocorticoid levels rise past this level (Young et al., 2016) Dysregulation of the HPA axis, resulting in either excessive or minimal cortisol release, it associated with an imbalance in binding to MR and GR (Oyamada et al., 2008), with negative effects on memory, arousal, and behavioural control (Juruena et al., 2021). The HPA axis is inhibited by the binding of cortisol to GR, especially within the hippocampus and medial prefrontal cortex (Roberts et al., 2022). Hippocampal cells have an extremely high concentration of GR, making the effects of stress quite significant on the area (Kim and Kim, 2019). Binding of cortisol to GR in the hippocampus and medial prefrontal cortex is associated with negative inhibition of the HPA axis and a subsequent decrease in cortisol release (Herman et al., 2005). In opposition, the binding of GR within the amygdala is responsible for prolonging the HPA stress response (Roberts et al., 2022). Typically, the excitability of the amygdala is counteracted by the inhibition of the prefrontal cortex and hippocampus, and connectivity between these areas is increased during the recovery period from

stress (Quaedflieg et al., 2015). However, when these structures are not integrated properly, regulation is not effective and dysfunction is likely, making it difficult to maintain homeostasis in regard to stress levels (Herman et al., 2005).

When an individual experiences repeated activation and dysregulation of the HPA axis, the impact can be severe. In the inhibitory regions of the HPA axis, including the medial prefrontal cortex and hippocampus, the number of GR can be significantly downregulated (Chen et al., 2008) and neurogenesis impaired (Tripathi et al., 2017). Inhibition of long-term potentiation in medial prefrontal cortex-hippocampus pathways is also observed following chronic stress exposure, decreasing the rate and frequency of signal conduction along this pathway (Goldwater et al., 2009). A decrease in the volume of the hippocampus has also been reported (Pechtel and Pizzagalli, 2011), while the prefrontal cortex has been associated with hypervigilance towards threatening stimuli, causing a subsequent decrease in attention for information and environmental factors which are not related to the perceived threat (Raymond et al., 2018). Due to the high saturation of GR in the hippocampus, high levels of cortisol have been reported to contribute to necrosis of the hippocampus in mice treated with chronic, repeated stress, a process which may be related to the observed decrease in hippocampal volume (Kim and Kim, 2019). The effects of chronic stress are just as significant on the amygdala, but in an excitatory capacity. Mice treated with chronic stress experienced hypertrophy of dendritic spines in the amygdala which lasted for several weeks following termination of treatment (Vyas et al., 2004). Increasing exposure was positively correlated with the number of dendritic spines grown, and with dendritic retraction in the hippocampus (McEwan, 2003). The effect of this process is an increase in excitation of the HPA axis to future stimuli and a decrease in inhibition. Roberts et

al. (2022) demonstrated that the more hyperreactive the amygdala is to threat, due to this increased spinogenesis, the stronger and more prolonged the HPA response can be. Additionally, the slope of cortisol activation was positively correlated with activation of the amygdala (Roberts et al., 2022). Individuals with a higher amygdala activation saw a more rapid increase in cortisol as well as a higher baseline level of cortisol in between periods of stress (Roberts et al., 2022). Therefore, an effect of chronic stress can be morphological changes in excitatory and inhibitory regions of the HPA axis, lowering the threshold for activation of the stress response.

There are discrepancies in the understanding of the impact of chronic stress throughout the lifetime. There is some evidence that individuals who experience greater activation of the stress response during childhood experience a higher baseline cortisol level and more frequent activation of the HPA response in adulthood (Tarullo and Gunnar, 2006). The proposed mechanism for this process is a significant loss of GR receptors in inhibitory structures like the hippocampus and amygdala, as described above (Willner et al., 2013; Wilkinson and Goodyer, 2011). With less GR binding, the inhibition of the negative feedback loop of the HPA axis is impaired, making it more difficult to prevent and end activation (Juruena et al., 2022). However, some studies, including Chen et al. (2008) and Chiba et al. (2012), show the opposite effect of chronic stress exposure: a blunting of the cortisol response. Downregulation of CRH receptors has been reported due to chronic release of CRH, a mechanism which prevents release of cortisol (Raymond et al., 2018). Zorn et al. (2017) reported that cortisol levels following stress exposure were diminished in individuals diagnosed with major depressive disorder and who reported many adverse stressful events in childhood. A proposed mechanism is neurotoxicity brought on by hyperactivity of cortisol, promoting inflammation and mobilizing energy, impacting the structure

of activationary structures in the HPA axis (Fowler et al., 2021). Interestingly, this blunting and low levels of cortisol is observed only in adults, suggesting that blunting occurs in response to long term exposure of stressors and HPA activation, contradicting the theory that cortisol and HPA hyperactivity are responsible for onset and maintenance of mental disorders (Hakamata et al., 2022). However, an important confounding factor is that participants in most of these studies were already diagnosed with mental illness. This area has a variety of conflicting reports and evidence, and it is not yet known which process, if either, is correct. These are the proposed theories at this moment.

Neuroplasticity

The area of neuroplasticity refers to the ability of neurons and associated structure to modify their morphology in response to the individual needs of the brain. This can be associated with the formation of dendritic spines, small protrusions on the dendrites which can form additional connections to nearby neurons, arborization, in which the dendrites are pruned and grown according to patterns of use, or neurogenesis, which is the formation of a completely new neuron, to name a few. The basis of neuroplasticity can be described using the Associative Network Theory, which states that the less connections are used, the weaker the association between them will become, requiring a greater stimulus to activate the connection (Giotakos, 2020). Connections that are frequently used are strengthened, leading to a lower threshold for activation so that the response can be facilitated as quickly as possible. The formation of dendritic spines occurs following a series of action potentials in quick succession (Antic et al., 2010). This suggests that the neural connection is useful and will likely need to be used again

soon in the future, and the summation of these 10-50 action potentials leads to a strong depolarization and long-term potentiation (Vadakkhan, 2019). Long term potentiation is associated with a long-lasting strengthening of synapses between neurons, stabilizing and facilitating the connection to ensure speed and accuracy in the future (Hardie and Spruston, 2009).

The diameter and myelination of the axon, which transmits neural signals to a neuron's synapse, determines how quickly a signal is conducted (Friedrick et al., 2020). The more myelinated the axon and the smaller the diameter, the faster the signal. Fractional anisotropy is associated with the density of an axon, and therefore makes a technique for measuring the size of axons in the brain (Friedrick et al., 2020). The diameter of the axon is related to its placement from its termination site. The thicker the diameter, the further away the axon is from where it will form a connection with another neuron (Zikopoulos et al., 2018). This helps to visualize where the connections occur and between which structures. This can also be used to monitor synaptic plasticity, which is characterized by changes in connectivity and structure at the synapse (Negron-Oyarzo et al., 2016).

Degree of synaptic turnover is positively correlated with the level of environmental stress (Attardo et al., 2015; Kempermann et al., 1997). In contrast, enrichment, rest, and calm atmospheres promote the formation of new neurons, neurogenesis (Richards et al., 2017). In times of prolonged, high stress, atrophy of the dendrites is common, as is synaptic remodelling (Dominguez et al., 2019). These changes are seen in the prefrontal cortex, which can demonstrate retraction of dendritic spines and spinal loss (Goldwater et al., 2009; Tripathi et al.,

2019), as well as a decrease in volume of the medial prefrontal cortex (Croteau et al., 2017). Additionally, prolonged stress can have a similar impact in the hippocampus, including decreased expression of plasticity-related genes and peptides, dendritic atrophy, and impaired neurogenesis (McEwen, 2003; Monsey et al., 2014). In opposition, the amygdala has been shown to experience dendritic hypertrophy, an increase in spine density, and an associated increase in anxiety-related behaviour (Monsey et al., 2014). The impact of these morphological changes includes memory impairments (Dominguez et al., 2014), increasing strength of emotional reactions (Lim et al., 2020), and increased anxiety-related behaviours to a number of stimuli (Monsey et al., 2014).

Following chronic stress, it is the basolateral amygdala which experiences the greatest increase in morphological changes. The basolateral amygdala displays a significant increase in dendritic spine density and dendritic remodelling (Mitra et al., 2005). This occurs following continuous exposure to the same stressor, increasing long term potentiation and leading to growth of the dendritic tree, strengthening its connectivity (Mitra et al., 2005). In an experiment by Tripathi et al. (2017), hypertrophy of the dendrites of the basolateral amygdala lasted for over three weeks following final exposure to chronic, repeated stress, and never did completely reverse during their time parameters. In opposition, the atrophy seen in hippocampal neurons reversed within just three days (Tripathi et al., 2017). This can help to correct the HPA imbalance of excessive amygdala excitation and excessively inhibited hippocampal action (Lakshminara and Chattarji, 2012). Since the changes in amygdala morphology are not corrected within the same timeframe, this can lead to an imbalance in HPA regulation, and an increase in emotional, anxiety-related behaviour (Lakshminara and Chattarji, 2012).

Memory and Learning

In terms of memory, it is the hippocampus which controls the contextual details of a situation, while the amygdala is responsible for the emotional valence (Palombo et al., 2021). One must know the significance of a memory in order for it to be consolidated (Negron-Oyarzo et al., 2016). This is done when the prefrontal cortex activates the amygdala, allowing it to produce arousal information and label the event as significant and necessary for consolidation in the hippocampus (Negron-Oyarzo et al., 2016). Memory is most easily retrieved when one's emotional state matches that at which the memory was encoded (Williams et al., 2022). This is why individuals struggling with negative emotions will often become trapped remembering negative memories, the body is attempting to bring forth information that may be helpful to deal with the stimulus. When feeling anxiety, the neurons of the amygdala and the hippocampus fire together (Huff et al., 2005). It appears that both structures are required for consolidation of negative memories, as when the amygdala is inactivated, the memory is less likely to be retrieved (Huff et al., 2005). Memories begin in the posterior hippocampus which handles rich, specific details as well as spatial representation and perception (Winocour and Moscovitch, 2011). They then move to the anterior hippocampus, which changes to a more universal, coarse, less detailed representation, also known as the 'gist'. (Winocour and Moscovitch, 2011). Upon entering the medial prefrontal cortex, the gist is then changed into a schema, incorporating parts of several memories which are similar to the original (Winocour and Moscovitch, 2011). It is the changes in neuronal connections which drives this movement to the schema of the prefrontal cortex, and this leads to a sort of generalization of many memories (Robin and Moscovitch, 2017), incorporating ideas which no longer came from the original. This is the result of synapses

being upregulated and frequently used, whereas the process of forgetting occurs when synapses are depressed (Richards et al., 2017). Negative experiences are unique in that they require more cognitive resources to encode the memory, increasing short-term memory and making it more likely to be remembered frequently in the long term (Talmi, 2013). It is highly emotional memories which are the most highly conserved (Christianson, 1992; Payne and Kensinger, 2018), and a switch from prefrontal integration, which considers context and the full picture, to sensory integration, commonly occurs (Bowen et al., 2018; Murray and Kensinger, 2014).

Chronic stress has many negative effects on memory, weakening explicit memory (Giotakos, 2020), working memory (Dominguez et al., 2019), and leading to behavioural deficits (Dominguez et al., 2019) and an increased response to negative stimuli (McCabe et al., 2009). The exposure is associated with epigenetic changes in memory-related genes, changing long-term expression (Monsey et al., 2014). Chronic stress can also be associated with a decrease in the volume of the hippocampus (Cole et al., 2010). Saturation of mineralocorticoid receptors promotes encoding of the experience and enhances retrieval of previously stored information that is related to the stressor (de Kloet et al., 2019). During this time, a shift from hippocampal-cognitive memory, which focuses on context and environmental details, to habit pathways in the dorsolateral striatum occurs (de Kloet et al., 2019). When similar stimuli are experienced frequently, increased activation and hypertrophy occurs in this habit pathway, bypassing cognitive integration in the hippocampus which would typically provide a more specific, targeted retrieval and subsequent reaction (de Kloet et al., 2019). High concentrations of glucocorticoids are associated with the consolidation and storage of emotionally salient memory, and retrieval of these memories can be blocked in mice by antagonizing mineralocorticoid receptors in a stressful

situation (de Kloet et al., 2019). Autobiographical memory has an optimal effect when mineralocorticoid receptors are saturated, but this effect decreases with binding to glucocorticoid receptors (Young et al., 2016). Mineralocorticoid receptor saturation is associated with accurate and specific memory recall independent of affect and mood, however, glucocorticoid receptor saturation correlates with an increase in amygdala activity, especially when responding to negative stimuli (Browning et al., 2010). This leads to a shift in emotional bias which prioritizes recall of memories associated with negative stimuli over positive (Browning et al., 2010).

Beyond the stress response, specific areas of the amygdala and hippocampus are necessary for the consolidation and storage of memories related to the fear response. These areas include the basolateral amygdala and ventral hippocampus, both of which are associated with aberrant consolidation of fear memories when treated with lesions (Cuccovia et al., 2022). The basolateral amygdala is the main site of storage for stressful events, and the ventral hippocampus mediates affect and motivation (Cuccovia et al., 2022). When the basolateral amygdala is inactivated prior to stress onset, deficits in learning and memory are prevented, suggesting this area has a role in the impairment of memory consolidation during acute stress (Tripathi et al., 2017). Ideally, during times of rest following a stressful stimulus, the default mode network is active. This network is a system which uses past experiences and memories to predict what situations are likely to occur in the future, and how to react to them (Vaisvaser et al., 2013). At the onset of stress, increased connectivity and action is seen between the medial prefrontal cortex and hippocampus, likely undergoing the process of reflecting on past memories and experiences and comparing to the current situation (Vasivaser et al., 2013). This increase in connectivity remains in effect for several hours following removal of the stressful stimulus while the

emotional memory is consolidated and encoded (Vasivaser et al., 2013). In individuals that have experienced chronic exposure to stress, this default network prioritizes the retrieval of emotional memories formed in response to stressful stimuli as this type of stimulus is commonly encountered (Vasivaser et al., 2013). This suggests a shift to a more negative memory bias.

Emotions

It is common for individuals struggling with mental illness to experience a negative valence or negative memory bias. This bias occurs when negative memories are enhanced and brought to the forefront of the mind much more frequently than positive memories (Zangani et al., 2021). This can be associated with aberrant control of dopaminergic systems, preventing the encoding of positive memories (Imbriano et al., 2022), however, it is more commonly associated with amygdala activation due to stress (Zangani et al., 2021). Negative memory bias can lead to an increase in amygdala activation coupled with decrease in activation of the frontal lobe (Browning et al., 2010). Without adequate activation of the frontal cortex, context and salience are not considered, and full attention is passed to the stressor (Browning et al., 2010). The amygdala is extremely important to the processing of emotion, both negative and positive (Zald, 2003). While positive emotions and stimuli decrease the activation of the amygdala, negative stimuli increase activation (Burgdorf and Panksepp, 2006).

There is an evolutionary reason to prioritize the consolidation and maintenance of negative memories and their emotional responses. Prioritization of memories is based on three factors: the state of arousal it caused, the strength of the amygdala response, and how relevant it

is likely to be in the future (Williams et al., 2022). Memories that lead to a heightened amygdala response are associated with strong, negative emotions, and evolutionarily, this is something worth remembering so that if that stimulus is encountered again, a fast, adequate response is possible. However, the intensity of these emotions and related memories can cause them to be retrieved much more frequently than positive memories, especially when one is stressed or experiencing negative emotions (Williams et al., 2022). This frequent retrieval can convince individuals that negative experiences are much more common than they actually are, despite the ability to experience positive emotions just as frequently (Williams et al., 2022). Intensity is not the same as frequency and understanding the reason negative memories and emotions are prioritized can aid in lifting this negative bias.

Behaviour

Increased exposure to stress throughout the lifetime has the ability to change the way an individual responds to a stressful stimulus (Segal et al., 1996). This can include changes in gene expression, increasing vulnerability to anxious behaviours, and developing patterns of behaviour which are greater in magnitude than the stressor might require (Post, 1992). It is the medial prefrontal cortex which has the greatest role in coordinating behavioural methods of an individual's defense response (Croteau et al., 2017). When an individual experiences chronically elevated glucocorticoid levels, a reduced medial prefrontal cortex volume is possible, coupled with alterations in the morphology of its dendrites (Corteau et al., 2017). This can be associated with aberrant regulation of behaviour in response to stress.

The typical, immediate behavioural response to a stressor is to process all available information, appraise the situation in its context, and make a decision as to the level of threat and the best way to proceed (Liberzon et al., 2007). When an individual experiences frequent elevation of glucocorticoid levels, behavioural networks can become more sensitive, preparing for a rapid response to a stimulus that is likely to occur frequently (Croteau et al., 2017). In this situation, it is common to see increased activity in the dorsolateral striatum, a circuit involved in habitual, fast behaviour driven by a strong stimulus (de Kloet et al., 2019). This circuit acts habitually, inducing a behavioural response that was utilized when exposed to the stimulus, or a similar one, in the past (de Kloet et al., 2019). This response is not specific to the current context and may not have the desired outcome, but it occurs quickly to save time and react to the threat before taking too much time to think about it.

Behavioural impact is also controlled by factors other than activation of the HPA axis. When studying the reaction of rats to controllable and uncontrollable stressors, Maier and Watkins (2010) observed that despite the same HPA response in both groups, uncontrollable stressors led to long-lasting changes in behaviour. When the group was given the opportunity to end the stressor, therefore making it controllable, the behavioural impact was prevented (Maier and Watkins, 2010). When the stimulus was changed from something that could not be controlled to something that could, the habitual pathway via the dorsolateral striatum was no longer required, and prefrontal activation was able to assess the context and adjust accordingly.

There is some evidence that repeated, chronic exposure to stress leads to decreased corticosterone levels, and this decrease is associated with a downregulation of glucocorticoid receptors as many are no longer needed (Arnett et al., 2015). The consequence of this is a decrease in glucocorticoid receptors in the central nucleus of the amygdala, and subsequent decrease in anxiety and fear behaviours leading to risky, thrill-seeking behaviour (Arnett et al., 2015). In rats, this process was mimicked using glucocorticoid receptor antagonists, and when the antagonists were removed, receptor activity was restored and this behaviour resolved itself (Arnett et al., 2015). It is not currently understood whether this process occurs in humans, especially since there is conflicting evidence for and against the blunting hypothesis of chronic stress. However, it is clear that behavioural patterns in response to stressors depend on multiple factors including the HPA axis, perception of control, and habit formation.

Coping Mechanisms and Resilience

The way that an individual copes with perceived stress has a great impact on one's ability to move on from current adversity and persevere in similar future situations. Individuals who have experienced great levels of stress throughout life can potentially experience a decreased resistance to stressful stimuli and emotional situations (Schore, 2003). There are two types of coping mechanisms: active and passive. Active coping mechanisms are characterized in animal models by a desire to investigate the environment, display aggressive behaviour towards stressors and peers, and demonstrate a less robust glucocorticoid response (Bowen et al., 2014). This type of coping style is associated with better prolonged physical health and a decrease in risk for mental disorders (Bowen et al., 2014). Alternatively, passive coping styles are

characterized by intense fear and avoidance. Individuals with a passive style will avoid the stimulus as much as possible, experience a strong stress response, and react consistently when exposed to the same stressor (Bowen et al., 2014). The passive style individual will also likely generalize this behaviour to other stimuli and situations, while active copers will have a tailored response to each specific situation (Bowen et al., 2014). In humans, coping style can be divided into problem-solving or emotion-focused (Maier and Watkins, 2010). Problem-solving coping is similar to active in that the individual will display a less intense stress response, less anxiety-related behaviours, and will conduct an action which is specific to the stimulus (Maier and Watkins, 2010). Emotion-focused coping is similar to passive in that it is easily generalized amongst various stimuli, leads to a very strong stress response, and is controlled mainly by the amygdala (Maier and Watkins, 2010).

Coping style is very clearly associated with the onset of anxiety behaviours. Individuals who display ineffective coping strategies often also experience decreased connectivity between the amygdala and prefrontal cortex, preventing adequate inhibition of the HPA axis and a decreased ability to differentiate between the strength of various stressors (Quaedflieg et al., 2015). These individuals often experience a robust and fast stress response to stressors which would not cause the same reaction in individuals with active coping mechanisms (Bowen et al., 2014). It is the posterodorsal medial amygdala which is involved in the determination of coping style, and Bowen et al. (2014) have reported reduced activity in this region in subjects displaying a passive coping style. In opposition, the neuropeptide Arginine Vasopressin (AVP) is found in high levels in the medial amygdala of subjects experiencing active coping and is associated with a decrease in serum cortisol (Bowen et al., 2014). In a study investigating the effect of chronic,

repeated stress on passive and active coping rats, passive copers experienced higher levels of corticosterone after a rest period, as well as increased AVP promoter methylation (Bowen et al., 2014). This demonstrates a biological basis for coping style and identifies a key area of study, the posterodorsal medial amygdala, for the adjustment of coping methods.

Beyond coping, it is common for individuals to report better future reactions to stressors when controllable stress was experienced in the past. A study by Goodman et al. (2019) used this idea to study how perceived degree of life stress is associated with seizure frequency in patients with epilepsy. This study demonstrated that the feeling of being in control of seizure-causing stressors was associated with a decrease in seizure frequency, and interestingly, the groups did not differ in cortisol levels during this study (Goodman et al., 2019). This suggests that the difference was not obviously due to the stress response, but the individual's resilience and feeling of control. The dorsal raphe nucleus (DRN) has an important role in the propagation of fear and freeze-like behaviour in response to a fearful stimulus (Maier and Watkins, 2010). When individuals experience uncontrollable stress, a stronger activation of serotonin 5-HT receptors in the DRN is observed, and in lesion studies, loss of function in this area is associated with prevention of negative behavioural fear responses (Maier and Watkins, 2010). The DRN does not cause fear or mediate it, but it does have the ability to amplify it, and this action occurs strongly in individuals experiencing uncontrollable stress (Maier and Watkins, 2010). It appears that the ventromedial prefrontal cortex, which has many inhibitory connections formed with the DRN serotonin receptors, inhibits these receptors in response to a perceived sense of control, dulling the fear response (Maier and Watkins, 2010). This phenomenon has also been shown to alter response to future stressors. In a process termed behavioural immunization, Amat et al.

(2006) demonstrated that when rats experienced a controllable stress treatment a week before an uncontrollable treatment, there was increased inhibition of the DRN serotonin receptors, demonstrating a controllable response to an uncontrollable situation. This suggests that exposure to a controllable stressor affects one's reaction to an uncontrollable one in the future. Additionally, hypofunction of the ventromedial prefrontal cortex has been identified in individuals suffering from several mental disorders including anxiety and depression (Amat et al., 2006). Restoring function to this area may have a role in mediating these strong stress responses.

Conclusion

In all, there are many factors which contribute to the onset and maintenance of mental disorders, and at this point, there is not a clear understanding of all the exact mechanisms. That being said, the relationships between the prefrontal cortex, hippocampus, and amygdala are undoubtedly important to our understanding of the biological and cognitive mechanisms of mental illness. Through understanding of these three regions and the contribution of the HPA axis, it is possible to understand how neuroplasticity, behaviour, learning and memory, emotion, and resilience are related to the heterogeneity in outcomes and experiences observed in individuals seeking counselling.

In individuals experiencing the effects of a stressful stimulus, the HPA axis is clearly affected by the modulatory factors of the prefrontal cortex, hippocampus, and the amygdala. It is the counteractive actions of these regions which maintain homeostasis and allow for activation

and inhibition of the axis, and when this balance is upset, dysfunction occurs. This dysfunction over time has the ability to change the morphology of these structures, increasing the excitability of the amygdala and decreasing the inhibitory actions of the hippocampus and prefrontal cortex, exacerbating the dysregulation. The repeated activation of the HPA axis in response to a large number of stressors is associated with a shift in encoding of memory with specific, context-dependent details in the hippocampus to a generalized schema of similar stimuli which also produced a negative valence. Since these negative memories are quite emotionally salient, they are prioritized due to the level of arousal, amygdala activation, and relevance at encoding. This places emotional, negative memories at the forefront of the mind, increasing risk of developing a negative memory bias. The more negative memories and situations encountered, the more poorly behaviour is regulated by the medial prefrontal cortex. There is a shift from planned, context-dependent behaviour mediation to habitual pathways formed in response to past stress exposure. Despite this, there is evidence that active coping mechanisms and feelings of control when facing a stressor lead to more positive behaviours and change the way individuals face uncontrollable stressors in the future. By focussing on resilience and ways to actively cope with stressful situations, there seems to be evidence that these effects of chronic stress can be changed.

By understanding the actions of the amygdala, hippocampus, and prefrontal cortex in the regulation and maintenance of mental illness, these mechanisms can be actively targeted for treatment. That being said, this is an area that is not completely understood. It is possible that there are other mechanisms and regions involved in this circuitry which have not been discovered yet. Contradictory evidence can be found in several areas of research, including the understanding of how the HPA axis responds to long term exposure to stress. We see this

inconsistent reporting in the support for a blunting of cortisol levels and a theory of excess cortisol and increased activity in adulthood. There is evidence for both of these processes, so there is likely an explanation connecting the two or explained by heterogeneity and variability in humans and lived experiences. As technology advances and this field becomes more important due to societal needs, these specifics can be more accurately researched and described. In the meantime, counselling techniques like Neural Network Therapy® which utilize the understanding of these regions and promote self-understanding and self-directed changes can have an impact on the response to stressors. By understanding the processes occurring in the brain during times of stress, one feels more control in the response and in handling future stressors. Neural Network Therapy® exercises, including the Rolodex and Telephone Poles, utilize these specific principles and provide clients with an understanding of the neurobiological mechanisms underlying brain function. This understanding, combined with participation in exercises, allows clients to direct changes to counteract these mechanisms and promote emotional well-being.

References

Amat, J., Paul, E., Zarza, C., Watkins, L. R., & Maier, S. F. (2006). Previous Experience with Behavioral Control over Stress Blocks the Behavioral and Dorsal Raphe Nucleus Activating Effects of Later Uncontrollable Stress: Role of the Ventral Medial Prefrontal Cortex. *Journal of Neuroscience*, *26*(51), 13264–13272.

Antic, S. D., Zhou, W.-L., Moore, A. R., Short, S. M., & Ikonomu, K. D. (2010). The decade of the dendritic NMDA spike. *Journal of Neuroscience Research*, *88*(14), 2991–3001.

Arnett, M. G., Pan, M. S., Doak, W., Cyr, P. E. P., Muglia, L. M., & Muglia, L. J. (2015). The role of glucocorticoid receptor-dependent activity in the amygdala central nucleus and reversibility of early-life stress programmed behavior. *Translational Psychiatry*, *5*(4).

Attardo, A., Fitzgerald, J. E., & Schnitzer, M. J. (2015). Impermanence of dendritic spines in live adult CA1 hippocampus. *Nature*, *523*(7562), 592–596.

Bowen, H. J., Kark, S. M., & Kensinger, E. A. (2018). NEVER forget: negative emotional valence enhances recapitulation. *Psychonomic Bulletin & Review*, *25*(3), 870–891.

Bowen, M. T., Hari Dass, S. A., Booth, J., Suraev, A., Vyas, A., & McGregor, I. S. (2014). Active coping toward predatory stress is associated with lower corticosterone and progesterone plasma levels and decreased methylation in the medial amygdala vasopressin system. *Hormones and Behavior*, *66*(3), 561–566.

Browning, M., Holmes, E. A., & Harmer, C. J. (2010). The modification of attentional bias to emotional information: A review of the techniques, mechanisms, and relevance to emotional disorders. *Cognitive, Affective, & Behavioral Neuroscience*, *10*(1), 8–20.

Burgdorf, J., & Panksepp, J. (2006). The neurobiology of positive emotions. *Neuroscience & Biobehavioral Reviews*, *30*(2), 173–187.

Chakraborty, R., Vijay Kumar, M. J., & Clement, J. P. (2021). Critical aspects of neurodevelopment. *Neurobiology of Learning and Memory*, *180*.

Chen, J.-X., Tang, Y.-T., & Yang, J.-X. (2008). Changes of Glucocorticoid Receptor and Levels of CRF mRNA, POMC mRNA in Brain of Chronic Immobilization Stress Rats. *Cellular and Molecular Neurobiology*, *28*(2), 237–244.

Chiba, S., Numakawa, T., Ninomiya, M., Richards, M. C., Wakabayashi, C., & Kunugi, H. (2012). Chronic restraint stress causes anxiety- and depression-like behaviors, downregulates glucocorticoid receptor expression, and attenuates glutamate release induced by brain-derived neurotrophic factor in the prefrontal cortex. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *39*(1), 112–119.

Christianson, S.-Å. (1992). Emotional stress and eyewitness memory: A critical review. *Psychological Bulletin*, *112*(2), 284–309.

Cohen, E. J., Quarta, E., Bravi, R., Granato, A., & Minciacchi, D. (2017). Neural plasticity and network remodeling: From concepts to pathology. *Neuroscience*, *344*, 326–345.

Cole, J., Toga, A. W., Hojatkashani, C., Thompson, P., Costafreda, S. G., Cleare, A. J., Williams, S. C., Bullmore, E. T., Scott, J. L., Mitterschiffthaler, M. T., Walsh, N. D., Donaldson, C., Mirza, M., Marquand, A., Nosarti, C., McGuffin, P., & Fu, C. H. (2010). Subregional hippocampal deformations in major depressive disorder. *Journal of Affective Disorders*, *126*, 272–277.

Croteau, J. D., Schulkin, J., & Shepard, J. D. (2017). Behavioral effects of chronically elevated corticosterone in subregions of the medial prefrontal cortex. *Behavioural Brain Research*, *316*, 82–86.

Cuccovia V Reis, F. M., Novaes, L. S., dos Santos, N. B., Ferreira-Rosa, K. C., Perfetto, J. G., Baldo, M. V. C., Munhoz, C. D., & Canteras, N. S. (2022). Predator fear memory depends on glucocorticoid receptors and protein synthesis in the basolateral amygdala and ventral hippocampus. *Psychoneuroendocrinology*, *141*.

de Kloet, E. R., de Kloet, S. F., de Kloet, C. S., & de Kloet, A. D. (2019). Top-down and bottom-up control of stress-coping. *Journal of Neuroendocrinology*, *31*(3).

Dominguez, G., Henkous, N., Prevot, T., David, V., Guillou, J.-L., Belzung, C., Mons, N., & Béracochéa, D. (2019). Sustained corticosterone rise in the prefrontal cortex is a key factor for chronic stress-induced working memory deficits in mice. *Neurobiology of Stress*, *10*.

Fowler, C. H., Bogdan, R., & Gaffrey, M. S. (2021). Stress-induced cortisol response is associated with right amygdala volume in early childhood. *Neurobiology of Stress*, *14*.

Friedrich, P., Fraenz, C., Schlüter, C., Ocklenburg, S., Mädler, B., Güntürkün, O., & Genç, E. (2020). The Relationship Between Axon Density, Myelination, and Fractional Anisotropy in the Human Corpus Callosum. *Cerebral Cortex*, *30*(4), 2042–2056.

Giotakos, O. (2020). Neurobiology of emotional trauma. *Psychiatriki*, *31*(2), 162–171.

Goldwater, D. S., Pavlides, C., Hunter, R. G., Bloss, E. B., Hof, P. R., McEwen, B. S., & Morrison, J. H. (2009). Structural and functional alterations to rat medial prefrontal cortex following chronic restraint stress and recovery. *Neuroscience*, *164*(2), 798–808.

Goodman, A. M., Allendorfer, J. B., Heyse, H., Szaflarski, B. A., Eliassen, J. C., Nelson, E. B., Storrs, J. M., & Szaflarski, J. P. (2019). Neural response to stress and perceived stress differ in patients with left temporal lobe epilepsy. *Human Brain Mapping*.

Hakamata, Y., Suzuki, Y., Kobashikawa, H., & Hori, H. (2022). Neurobiology of early life adversity: A systematic review of meta-analyses towards an integrative account of its neurobiological trajectories to mental disorders. *Frontiers in Neuroendocrinology*, *65*.

Hardie, J., & Spruston, N. (2009). Synaptic Depolarization Is More Effective than Back-Propagating Action Potentials during Induction of Associative Long-Term Potentiation in Hippocampal Pyramidal Neurons. *Journal of Neuroscience*, *29*(10), 3233–3241.

Herman, J. P., Ostrander, M. M., Mueller, N. K., & Figueiredo, H. (2005). Limbic system mechanisms of stress regulation: Hypothalamo-pituitary-adrenocortical axis. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *29*(8), 1201–1213.

Huff, N. C., Wright-Hardesty, K. J., Higgins, E. A., Matus-Amat, P., & Rudy, J. W. (2005). Context pre-exposure obscures amygdala modulation of contextual-fear conditioning. *Learning & Memory*, *12*(5), 456–460.

Imbriano, G., Waszczuk, M., Rajaram, S., Ruggero, C., Miao, J., Clouston, S., Luft, B., Kotov, R., & Mohanty, A. (2022). Association of attention and memory biases for negative stimuli with post-traumatic stress disorder symptoms. *Journal of Anxiety Disorders*, *85*.

Juruena, M. F., Bourne, M., Young, A. H., & Cleare, A. J. (2021). Hypothalamic-Pituitary-Adrenal axis dysfunction by early life stress. *Neuroscience Letters*, *759*.

Kempermann, G., Kuhn, H. G., & Gage, F. H. (1997). More hippocampal neurons in adult mice living in an enriched environment. *Nature*, *386*, 493–495.

Kim, E. J., & Kim, J. J. (2019). Amygdala, Medial Prefrontal Cortex and Glucocorticoid Interactions Produce Stress-Like Effects on Memory. *Frontiers in Behavioral Neuroscience*, *13*.

Lakshminarasimhan, H., & Chattarji, S. (2012). Stress Leads to Contrasting Effects on the Levels of Brain Derived Neurotrophic Factor in the Hippocampus and Amygdala. *PLoS ONE*, *7*(1).

Liberzon, I., King, A. P., Britton, J. C., Phan, K. L., Abelson, J. L., & Taylor, S. F. (2007). Paralimbic and Medial Prefrontal Cortical Involvement in Neuroendocrine Responses to Traumatic Stimuli. *American Journal of Psychiatry*, *164*(8), 1250–1258.

Lim, L., Howells, H., Radua, J., & Rubia, K. (2020). Aberrant structural connectivity in childhood maltreatment: A meta-analysis. *Neuroscience & Biobehavioral Reviews*, *116*, 406–414.

Maier, S. F., & Watkins, L. R. (2010). Role of the medial prefrontal cortex in coping and resilience. *Brain Research*, *1355*, 52–60.

McCabe, C., Cowen, P. J., & Harmer, C. J. (2009). Neural representation of reward in recovered depressed patients. *Psychopharmacology*, *205*, 667–677.

McEwen, B. S. (2003). Mood disorders and allostatic load. *Biological Psychiatry*, *54*(3), 200–207.

Mitra, R., Jadhav, S., McEwen, B. S., Vyas, A., & Chattarji, S. (2005). Stress duration modulates the spatiotemporal patterns of spine formation in the basolateral amygdala. *Proceedings of the National Academy of Sciences*, *102*(26), 9371–9376.

Monsey, M. S., Boyle, L. M., Zhang, M. L., Nguyen, C. P., Kronman, H. G., Ota, K. T., Duman, R. S., Taylor, J. R., & Schafe, G. E. (2014). Chronic Corticosterone Exposure Persistently Elevates the Expression of Memory-Related Genes in the Lateral Amygdala and Enhances the Consolidation of a Pavlovian Fear Memory. *PLoS ONE*, *9*(3).

Murray, B. D., & Kensinger, E. A. (2014). The Route to an Integrative Associative Memory Is Influenced by Emotion. *PLoS ONE*, *9*(1).

Negrón-Oyarzo, I., Aboitiz, F., & Fuentealba, P. (2016). Impaired Functional Connectivity in the Prefrontal Cortex: A Mechanism for Chronic Stress-Induced Neuropsychiatric Disorders. *Neural Plasticity*, *2016*, 1–16.

Oyamada, N., Sone, M., Miyashita, K., Park, K., Taura, D., Inuzuka, M., Sonoyama, T., Tsujimoto, H., Fukunaga, Y., Tamura, N., Itoh, H., & Nakao, K. (2008). The Role of Mineralocorticoid Receptor Expression in Brain Remodeling after Cerebral Ischemia. *Endocrinology*, *149*(8), 3764–3777.

Palombo, D. J., Elizur, L., Tuen, Y. J., Te, A. A., & Madan, C. R. (2021). Transfer of negative valence in an episodic memory task. *Cognition*, *217*.

Payne, J. D., & Kensinger, E. A. (2018). Stress, sleep, and the selective consolidation of emotional memories. *Current Opinion in Behavioral Sciences*, *19*, 36–43.

Pechtel, P., & Pizzagalli, D. A. (2011). Effects of early life stress on cognitive and affective function: An integrated review of human literature. *Psychopharmacology*, *214*, 55–70.

Post, R. M. (1992). Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. *American Journal of Psychiatry*, *149*(8), 999–1010.

Public Health Agency of Canada. (2015). *Report from the canadian chronic disease surveillance system: mental illness in canada*, *2015*.

Quaedflieg, C. W. E. M., van de Ven, V., Meyer, T., Siep, N., Merckelbach, H., & Smeets, T. (2015). Temporal Dynamics of Stress-Induced Alternations of Intrinsic Amygdala Connectivity and Neuroendocrine Levels. *PLOS ONE*, *10*(5).

Raymond, C., Marin, M.-F., Majeur, D., & Lupien, S. (2018). Early child adversity and psychopathology in adulthood: HPA axis and cognitive dysregulations as potential mechanisms. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *85*, 152–160.

Richards, B. A., & Frankland, P. W. (2017). The Persistence and Transience of Memory. *Neuron*, *94*(6), 1071–1084.

Roberts, A. G., Peckins, M. K., Gard, A. M., Hein, T. C., Hardi, F. A., Mitchell, C., Monk, C. S., Hyde, L. W., & Lopez-Duran, N. L. (2022). Amygdala reactivity during socioemotional processing and cortisol reactivity to a psychosocial stressor. *Psychoneuroendocrinology*, *144*.

Robin, J., & Moscovitch, M. (2017). Details, gist and schema: hippocampal–neocortical interactions underlying recent and remote episodic and spatial memory. *Current Opinion in Behavioral Sciences*, *17*, 114–123.

Schore, A. (2003). *Affect dysregulation & disorders of the self* (1st ed.). W.W. Norton.

Segal, Z. v, Williams, J. M., Teasdale, J. D., & Gemar, M. (1996). A cognitive science perspective on kindling and episode sensitization in recurrent affective disorder. *Psychological Medicine*, *26*(2), 371–380.

Stiles, J., & Jernigan, T. L. (2010). The Basics of Brain Development. *Neuropsychology Review*, *20*(4), 327–348.

Sunderland, A., & Findlay, L. C. (2013). Perceived need for mental health care in Canada: Results from the 2012 Canadian Community Health Survey. *Health Reports*, *24*(9), 3–9.

Talmi, D. (2013). Enhanced Emotional Memory. *Current Directions in Psychological Science*, *22*(6), 430–436.

Tarullo, A. R., & Gunnar, M. R. (2006). Child maltreatment and the developing HPA axis. *Hormones and Behavior*, *50*(4), 632–639.

Tripathi, S. J., Chakraborty, S., Srikumar, B. N., Raju, T. R., & Shankaranarayana Rao, B. S. (2017). Inactivation of basolateral amygdala prevents chronic immobilization stress-induced memory impairment and associated changes in corticosterone levels. *Neurobiology of Learning and Memory*, *142*, 218–229.

Tripathi, S. J., Chakraborty, S., Srikumar, B. N., Raju, T. R., & Shankaranarayana Rao, B. S. (2019). Prevention of chronic immobilization stress-induced enhanced expression of glucocorticoid receptors in the prefrontal cortex by inactivation of basolateral amygdala. *Journal of Chemical Neuroanatomy*, *95*, 134–145.

Vadakkan, K. I. (2019). A potential mechanism for first-person internal sensation of memory provides evidence for the relationship between learning and LTP induction. *Behavioural Brain Research*, *360*, 16–35.

Vaisvaser, S., Lin, T., Admon, R., Podlipsky, I., Greenman, Y., Stern, N., Fruchter, E., Wald, I., Pine, D. S., Tarrasch, R., Bar-Haim, Y., & Hendler, T. (2013). Neural traces of stress: cortisol related sustained enhancement of amygdala-hippocampal functional connectivity. *Frontiers in Human Neuroscience*, *7*.

Vyas, A., Pillai, A. G., & Chattarji, S. (2004). Recovery after chronic stress fails to reverse amygdaloid neuronal hypertrophy and enhanced anxiety-like behavior. *Neuroscience*, *128*(4), 667–673.

Wilkinson, P. O., & Goodyer, I. M. (2011). Childhood adversity and allostatic overload of the hypothalamic–pituitary–adrenal axis: A vulnerability model for depressive disorders. *Development and Psychopathology*, *23*(4), 1017–1037.

Williams, S. E., Ford, J. H., & Kensinger, E. A. (2022). The power of negative and positive episodic memories [Article]. *Cognitive, Affective, & Behavioral Neuroscience*, *22*(5), 869–903.

Willner, P., Scheel-Krüger, J., & Belzung, C. (2013). The neurobiology of depression and antidepressant action. *Neuroscience & Biobehavioral Reviews*, *37*(10), 2331–2371.

Winocur, G., & Moscovitch, M. (2011). Memory Transformation and Systems Consolidation. *Journal of the International Neuropsychological Society*, *17*(05), 766–780.

Young, K. D., Preskorn, S. H., Victor, T., Misaki, M., Bodurka, J., & Drevets, W. C. (2016). The Effect of Mineralocorticoid and Glucocorticoid Receptor Antagonism on Autobiographical Memory Recall and Amygdala Response to Implicit Emotional Stimuli. *International Journal of Neuropsychopharmacology*, *19*(9).

Zald, D. H. (2003). The human amygdala and the emotional evaluation of sensory stimuli. *Brain Research Reviews*, *41*, 88–123.

Zangani, C., Giordano, B., Stein, H., Bonora, S., D'Agostino, A., & Ostinelli, E. G. (2021). Efficacy of amisulpride for depressive symptoms in individuals with mental disorders: A systematic review and meta-analysis. *Human Psychopharmacology: Clinical and Experimental*, *36*(6).

Zikopoulos, B., Liu, X., Tepe, J., Trutzer, I., John, Y. J., & Barbas, H. (2018). Opposite development of short- and long-range anterior cingulate pathways in autism. *Acta Neuropathologica*, *136*(5), 759–778.

Zorn, J. v., Schür, R. R., Boks, M. P., Kahn, R. S., Joëls, M., & Vinkers, C. H. (2017). Cortisol stress reactivity across psychiatric disorders: A systematic review and meta-analysis. *Psychoneuroendocrinology*, *77*, 25–36.