The Neuroscience of Resilience

Kelsey N. Plummer[1*], Trent M. Filter[1*], and Anvith Chidananda[1*]
[1]Geisinger Commonwealth School of Medicine, Scranton, PA 18509
*Master of Biomedical Sciences Program
Correspondence: kplummer@som.geisinger.edu

Abstract

Resilience, a concept influenced by genetic, epigenetic, and neurophysiological factors, may offer biological protection against the diagnosis of a mental health disorder. Research identifying neurophysiological factors related to resilience has important implications in better understanding human behavior, determining therapeutic targets, and developing medical interventions. Such therapeutics may aid vulnerable individuals in combating their susceptibility to mental health disorders by optimizing their resilience.

Introduction

The concept of resilience refers to one's ability to overcome challenges and thrive in the face of adversity. Individuals who experience the same event may respond differently based on their capacity to be resilient. While some are able to learn from a trauma and grow stronger, others may experience an inability to cope, potentially resulting in the development of a mental health disorder if the incident is severe enough. This spectrum of potential reactions that varies between individuals is a result of combined genetic, epigenetic, and neurophysiological influences (1, 2). Understanding these factors and their role in determining whether one succumbs to stress or is resilient to it provides insight into human behavior. In addressing the neuroscience of resilience, progress can be made toward identifying neurophysiological factors that offer protection against mental health disorders (3). Investigating this topic may illuminate approaches to promoting resilience through medical interventions that would confer benefit to those with a greater susceptibility to stress (4).

Methods

Systematic procedures were implemented to ensure a thorough, high-quality review of the scientific literature on the neuroscience of resilience. In performing a search for relevant sources, databases including Google Scholar and PubMed were consulted to find recently published peer-reviewed journal articles that reference key topics such as the neuroscience of resilience and resilience versus vulnerability. Particular focus was given to studies that aimed to explain the relationship between resilience and mental health as well as to those that examined the neurophysiological factors, rather than genetic or epigenetic influences.

Discussion

Anatomy and physiology

Resilience involves coping, a type of behavioral adaptation that involves dynamic neurophysiological processing within the regions of the brain linked to stress, emotion, reasoning, and memory (5). These regions of the brain include the hypothalamic-pituitary-adrenal (HPA) axis, the prefrontal cortex, and the amygdala. The HPA axis is an interconnected network between the hypothalamus, pituitary gland, and adrenal gland that serves in responding to stress and regulating emotion (6). The prefrontal cortex, specifically the ventromedial and orbitofrontal regions, is involved in regulating emotions, evaluating risk and fear, and making decisions. The amygdala functions in processing fear and other emotions, making decisions, and forming memories.

One case report offers insight into a connection between the substantia nigra and transient acute depression (7). Identifying linkages such as these can offer targets for medically intervening to bolster resilience. In this case, a patient with Parkinson's disease and no previous history of mental illness was being treated for her condition with deep brain stimulation of the bilateral subthalamic nuclei. Four electrodes were implanted in her brain using stereotactic guidance to place them in the appropriate region; however, one of the electrodes was inadvertently placed below the left subthalamic nucleus in the left substantia nigra. Upon high-frequency stimulation through this particular electrode, the patient experienced an episode of transient acute depression. In a matter of minutes, she cycled through an array of severely depressive emotions, even expressing a desire to stop living. The symptoms lasted only while the electrode was being stimulated and ceased less than 2 minutes after stimulation was discontinued. This case report offers unexpected findings that may be useful in the search for mechanistic pathologies related to depression; however, it would be premature to apply these findings across the board. A study aimed specifically at measuring the response of high-frequency deep brain stimulation of the substantia nigra would be beneficial in demonstrating that these findings are consistent among a larger group. While other regions of the brain have been more consistently tied to mechanistic pathologies related to mental health disorders, the importance of this case report lies in its demonstration that neurophysiological pathways are directly tied to emotion and behavior and that an alteration of these pathways can have profound effects. Targeting these pathways and identifying possible pathologies within may offer further insight into the treatment of mental health disorders through medical interventions that aim to increase resilience.

Neuroplasticity

Neuroplasticity refers to the brain's ability to continually reorganize itself by creating new neural pathways to meet the needs of new functions (8). This restructuring occurs in response to stimuli in order to reinforce learning as well as in response to neural damage in order to mechanistically cope (8). The brain demonstrates learning by exhibiting neuroplasticity in response to emotional stimuli, forming positive memories as a result of positive stimuli and enhancing

preparedness as a result of negative stimuli (9). Thanks to experience-dependent neuroplasticity, the brain can learn from fear and more readily identify threatening situations in the future (9). The remodeling of neural circuitry in one region of the brain can have direct and indirect implications on activity in other regions. Due to the interconnectedness between the HPA axis, the prefrontal cortex, and the amygdala, neuroplasticity within these regions influences one another with regard to emotion and behavior (10).

Neurophysiological pathologies, as they relate to mental health disorders, have been studied to provide a better understanding of the pathways involved so that therapeutic targets can be identified. Neuroplasticity may contribute to correcting for certain pathologies, as in the case of emotional remodeling (11,12). Recalling positive memories or ruminating on negative ones can enhance the effects of those original emotions. Symptoms of post-traumatic stress disorder (PTSD) can be triggered by intrusive negative memories. As these negative memories are continually called upon, the neural circuitry used to do so is strengthened and so are the feelings of trauma surrounding the memory. This neural pathway offers opportunity for therapeutic emotional remodeling to reverse these effects, alleviating negative emotions and replacing them with positive ones. Reminiscing about positive memories reinforces positive emotions and may have a direct impact on strengthening resilience. In the case of major depressive disorder (MDD), many individuals with this diagnosis have difficulty both recalling positive memories and sustaining positive emotions as well as a diminished capacity to engage in reward processing. This indicates that there is value in the recall of positive memories, both in increasing one's capacity to experience positive emotions and in benefiting from this action by being rewarded with increased resilience. The decreased capacity of individuals with MDD to perform this act of recall may be linked to their decreased resilience. This pathological neural pathway in those with MDD presents another opportunity for therapeutic emotional remodeling. Utilizing emotional remodeling to downregulate rumination of negative emotions and upregulate the recall of positive emotions enables those with mental health disorders to reap the benefits of increased resilience.

Oxytocin

A recent experiment examined the effects of oxytocin on emotional remodeling in rats (11). In this study, male rats, identified as having either a resilient or vulnerable baseline, were administered oxytocin, and the resulting degree to which their resilience increased was measured using specific neurophysiological markers. The premise of this experiment is that oxytocin's ability to reduce responsiveness to fear decreases symptomatology of PTSD and instead, promotes resilience.

To determine which rats had a natural baseline of resilience or vulnerability, the rats were subjected to adverse stimuli to induce a stress response. Trauma was induced in 50 rats by subjecting them to an inhibitory avoidance task and a single prolonged stress (SPS). The inhibitory avoidance task involved one light compartment and one dark compartment; while the rat was safe in the light compartment, once the rat entered the dark compartment, he received two shocks. Immediately following this inhibitory avoidance task, the rats were subjected to an SPS. This involved restraining the rats in a plexiglass device that restricted their breathing for 2 hours and then immediately placing them in a tank where they were forced to swim for 20 minutes without rest. Next, they were given the opportunity to rest for 15 minutes before being placed in a carbon dioxide chamber until loss of consciousness was induced. After the SPS, the rats were given an opportunity to recuperate. During the entire SPS procedure, a tone was sounded and an odor was released in order to achieve specific auditory and olfactory associations with this trauma that could later be repeated to remind the rats of the trauma. A control group of rats was exposed to the same auditory and olfactory cues, but was not subjected to the trauma.

Two weeks after the rats were subjected to the trauma, they were divided into groups based on anxiety profiling and were labeled as either resilient or vulnerable. Their anxiety profile was measured based on their activity in an elevated plus maze. The rats with a greater ability to explore open spaces and a decreased acoustic startle response (ASR) were placed in the resilient group. The rats with a hindered ability to explore open spaces and an increased ASR were described as having PTSD-like symptoms and were placed in the vulnerable group.

On day 21 of the study, the rats were implanted with a cannula device in the right lateral ventricle so that oxytocin could be administered to the rats. On days 29 through 31, within the experimental group of rats, one subgroup received a dose of oxytocin, while another subgroup was given a saline solution. Forty minutes after the oxytocin or saline infusion, the rats were subjected to stimuli to remind them of their previous trauma and their responses were recorded.

On day 54, the rats were euthanized and their brains were removed for examination. Two markers, immunofluorescence of c-fos-labeled cells and dendritic length extension, indicated resilience versus vulnerability in the rats. These two markers were measured in both the prelimbic (PL) region and the basolateral nucleus of the amygdala (BLA). Greater immunofluorescence of c-fos-labeled cells is indicative of greater neuronal activity, and longer dendritic extensions are indicative of greater neuronal complexity and connectivity.

Results of the study showed that the difference in the immunofluorescence of c-fos-labeled cells between the vulnerable group that received the saline solution and the vulnerable group that received the oxytocin infusion was significant ($0.05 > p > 0.01$) in both the PL region and the BLA. In addition, the difference in dendritic length between these same two groups was also significant ($0.05 > p > 0.01$). These findings indicate that oxytocin has a significant effect on increasing the resilience of vulnerable rats.

Oxytocin, synthesized in the hypothalamus and excreted by the posterior pituitary gland, modulates emotions, reducing those associated with fear, potentially by inhibiting processing within the amygdala and instead, enhancing feelings of social trust and attachment. The ability of oxytocin to increase resilience in rats with PTSD-like symptoms is a valuable concept worth exploring in human studies. This type of experimentation, in which oxytocin is administered

and its effects on resilience are measured, has not yet been performed in human clinical trials; however, the findings of this animal model experiment are encouraging. Inevitably, limitations may arise in translating the study from an animal model to a human clinical trial due to the fact that rat and human brains are not completely homologous.

Cortisol

A human study investigated the relationship between cortisol and resilience (13). The study evaluated stress-induced cortisol levels of 120 healthy male participants between the ages of 18 and 30. Due to the fact that cortisol levels have a normal fluctuation pattern associated with the diurnal rhythm, the study was careful to measure cortisol levels consistently in order to eliminate possible confounding factors. The participants were exposed to either a stressful or neutral movie clip and then were immediately shown images of fearful and happy faces. They were then asked to identify the emotions present in the images, while being monitored by functional magnetic resonance imaging. Results of the study showed that the participants who watched the stressful movie clip were in a stress-induced state when viewing the images and as a result, demonstrated a slower response time in identifying the emotions of the facial expressions shown in the images when compared to the participants who watched the neutral movie clip. This indicates that stress may have an effect on the ability to concentrate and perform mental tasks. Interestingly, apart from the differences between the experimental and control groups, there were also differences between individuals within the experimental group, indicating that an underlying mechanism may cause certain individuals to be more resilient to stress and others to be more vulnerable to it.

Conclusion

Investigation into the neuroscience of resilience is of great importance because of the connection between resilience and mental health. While optimal resilience may serve as a protective factor, decreased resilience has been linked to individuals with mental health disorders (1–3). This concept is especially relevant in light of the predicted rise in mental health disorders as a result of the COVID-19 pandemic. Current events are inducing worldwide hardship, and those individuals that are least resilient are most at risk for developing a mental health disorder. By determining distinguishing factors between resilient and vulnerable individuals, therapeutic targets can be identified and medical interventions can be developed to optimize resilience and combat mental health disorders.

Current research offers clues as to the neurophysiological factors involved in conferring resilience. Emotional remodeling in humans, which relies on the brain's neuroplastic nature, has been shown to successfully reconfigure triggering memories by tailoring the emotions associated with them (12). Administration of oxytocin has been shown to bolster resilience in rats (11). Experiments monitoring cognition in humans during stress-induced situations reveal individuals to be either resilient or vulnerable (13). While these findings are non-competing, there are still gaps of knowledge in explaining how these findings relate to one another, and the concept of resilience remains largely abstract. Expanding this field of research to include not only neurophysiological factors but genetic and epigenetic influences as well, may bring to light an even better understanding of the biological components that contribute to resilience.

References

1. Han MH, Nestler EJ. Neural substrates of depression and resilience. *Neurotherapeutics*. 2017; 14(3):677-86.
2. Osório C, Probert T, Jones E, Young AH, Robbins I. Adapting to stress: understanding the neurobiology of resilience. *J Behav Med*. 2017; 43(4):307-22.
3. Holz NE, Tost H, Meyer-Lindenberg A. Resilience and the brain: a key role for regulatory circuits linked to social stress and support. *Mol Psychiatry*. 2019; 18:1-8.
4. Spencer-Segal JL, Akil H. Glucocorticoids and resilience. *Horm Behav*. 2019; 111:131-4.
5. Sinha R, Lacadie CM, Constable RT, Seo D. Dynamic neural activity during stress signals resilient coping. *Proc Natl Acad Sci USA*. 2016; 113(31):8837-42.
6. Siegel A, Sapru HN. Essential Neuroscience. Fourth Edition. Philadelphia: *Wolters Kluwer*; 2019.
7. Bejjani BP, Damier P, Arnulf I, Thivard L, Bonnet AM, Dormont D, et al. Transient acute depression induced by high-frequency deep-brain stimulation. *N Engl J Med*. 1999; 340(19):1476-80.
8. Mateos-Aparicio P, Rodríguez-Moreno A. The impact of studying brain plasticity. *Front Cell Neurosci*. 2019; 13:66.
9. Pignatelli M, Umanah GK, Ribeiro SP, Chen R, Karuppagounder SS, Yau HJ, et al. Synaptic plasticity onto dopamine neurons shapes fear learning. *Neuron*. 2017; 93(2):425-40.
10. McEwen BS, Morrison JH. The brain on stress: vulnerability and plasticity of the prefrontal cortex over the life course. *Neuron*. 2013; 79(1):16-29.
11. Le Dorze C, Borreca A, Pignataro A, Ammassari-Teule M, Gisquet-Verrier P. Emotional remodeling with oxytocin durably rescues trauma-induced behavioral and neuro-morphological changes in rats: a promising treatment for PTSD. *Transl Psychiatry*. 2020; 10(1):1-3.
12. Speer ME, Bhanji JP, Delgado MR. Savoring the past: positive memories evoke value representations in the striatum. *Neuron*. 2014; 84(4):847-56.
13. Henckens MJ, Klumpers F, Everaerd D, Kooijman SC, Van Wingen GA, Fernández G. Interindividual differences in stress sensitivity: basal and stress-induced cortisol levels differentially predict neural vigilance processing under stress. *Soc Cogn Affect Neurosci*. 2016; 11(4):663-73.