

Loneliness in the Mind

Hari Balachandran

In times of unprecedented levels of social isolation, loneliness has affected more people than normal. Loneliness is defined as a complex set of feelings encompassing reactions to the absence of intimate and social needs (Ernst, 1999). Typically, the terms lonely and alone are used interchangeably, but they are not the same. Being alone simply means being by oneself. A person being alone does not necessarily mean they suffer from the feelings of social isolation. Likewise, a lonely person may be in a room full of people, and still lack the sufficient personal connections to satisfy their social needs.

Loneliness, like other feelings, can be caused by a lack of positive emotional states and an excess of negative emotional states (Matthews, 2016). Examples of positive states include interactions with others, which leads to security and reduces the total energy needed to survive. An absence of these interactions can lead to loneliness, which is, in other words, a negative emotional state (Eisenberger, 2012). The negative state prompts a neurological change which pushes the organism to seek social interaction. The carrot of interaction and the stick of isolation constitute the feelings of loneliness, and push humans to a much more interconnected existence.

To study the neurological effects of loneliness, testing must often be done; however, given the ethical issues of isolating humans, rodents are used instead of humans. Rodents, like humans, are social animals, and have been shown to prefer interaction over isolation (Loo et al., 2001). While rodent models are not perfect substitutes for human testing, especially in the field of neuroscience, rodents have been used in the development of new drugs and are primarily used for their accuracy in modeling parts of human physiology and function.

The physical effects of loneliness are not centralized to one specific region of the brain. However, one particular region of note is the dorsal raphe nucleus (DRN), a region in the brain stem found in the midbrain and pons. To test methods that the brain uses to reward interaction and punish isolation, an *in vivo* calcium image was taken of rodents. *In vivo* calcium imaging works by using calcium indicators, special chemicals that light up when they bond to Calcium (II) ions. These ions are released within a cell when an extracellu-

lar messenger, such as dopamine, interacts with the cell. The entire process works like a series of dominos, as the dopamine movement triggers a release of calcium ions, which interact with the luminescent indicators that are then observed by researchers. Following a period of isolation, an increase in dopamine receptor activity in the dorsal raphe nucleus was found once the rodents were able to interact with other rodents (Matthews, 2016). The increased activity of dopamine, the “happiness hormone” brought about a pleasurable feeling to the rat. Similar to the rush a person might feel after exercise, this new rush incentivized the rat to pursue similar social activities, thus increasing their dopamine levels.

Another region important to understanding the effects of loneliness is the prefrontal cortex. The prefrontal cortex is a region of the brain that governs decision making, personality, complex thought, and moderation of social behavior. Within the prefrontal cortex, small-conductance calcium-activated potassium channels, or SK channels, were found to be responsible for the changes in the serotonergic neurons, neurons in charge of serotonin synthesis. Serotonin, the “feel-good hormone,” is a mood stabilizer and is frequently produced when participating in group activities or exercise. The SK channels changed the serotonergic neurons by reducing the rate they fire following a period of social isolation, which resulted in mice having elevated levels of aggression, anxiety, depression, and antisocial behavior. However, a treatment of an excitation of serotonergic neurons was able to curb those behaviors. This treatment differed from previous trials, which used traditional pharmacological means to control serotonin levels within the mice. The new treatment was done using optogenetic and chemogenetic control. Researchers were able to excite the serotonergic neurons by changing the DNA in the mice themselves. The new DNA attaches either light-sensitive or chemical-sensitive receptors to the serotonergic neurons, which the researchers were then able to manipulate. These manipulations resulted in a decrease in aggression and an increase in social behavior in the mice (Sargin, 2009). Isolation deprived the mice of contact with others, which starved them of serotonin, and led to a variety of psychological issues. For this reason, treatments for loneliness may be found

by addressing the serotonin deficiency. Addressing the symptoms of serotonin deficiency, such as the aforementioned anxiety and depression, via anti-anxiety/depressant medication is likely the best place to start when attempting to curb the effects of loneliness.

There is another method in which social isolation can be observed within the brain. This is visible with the presence of the neuropeptide tachykinin 2 (Tac2)/neurokinin B (NkB), two different chemicals used to transmit messages between neurons in the brain. When mice were isolated for two weeks, Tac2 concentrations spiked across the entire brain. Like the previous study, aggressive behavior was noted in the animals, yet interestingly there were also defensive behaviors present in the mice. The presence of Tac2 triggered the “freeze” response in many mice. Prolonged loneliness, it was found, triggered fear responses in mice, in addition to anxiety and aggression. (Zelikowsky, 2018). The heightened fear response likely suggests that social isolation may have been causing harm to the mice. Fear is typically associated with the perception of danger, and being alone for nearly two weeks was enough for the mice to feel threatened by their environment.

When scientists in the Zelikowsky study increased the expression for the Tac2 gene in mice that had not faced social isolation, the mice began to exhibit aggressive and anxious behaviors, similar to those that had undergone isolation. Thus, it was shown that Tac2 was likely the primary culprit for the feelings of loneliness in mice, and that more importantly, finding a way to inhibit that may cure the mice. As stated earlier, mice that were isolated displayed various hostile behaviors, such as chronic fear, increased aggression and an increased sensitivity to threatening stimuli. These mice were all found to have elevated levels of Tac2 in both the amygdala and the hypothalamus. Providing doses of Osanetant, a former schizophrenia medicine that also acts as a way to block the processing of NkB chemicals, showed a reduction in these traits, resulting in a mitigation of the effects of social isolation. Interestingly, the researchers discovered different effects when blocking the expression of the Tac2 gene in different regions of the mice’s brains. When blocking the expression in the amygdala, the mice lost many behaviors related to the increased fear, such as hypersensitivity and chronic fear. When blocking the Tac2 expression in the hypothalamus, the mice retained the increase in fear, yet saw a decrease in the increased aggression brought about from social isolation (Zeli-

kowsky, 2018).

Not only are there different chemical reactions that occur in the brain when a person experiences loneliness, but the shape of the brain is also subject to change. Using Voxel-Based Morphology, individuals suffering from chronic loneliness were found to have less gray matter in the Left Posterior Superior Temporal Sulcus (pSTS). This region of the brain is associated primarily with social perception. Accounting for other factors, such as empathy, other disorders individuals face, and the size of their social circles, there was a direct correlation found between loneliness and basic social perception. In other words, loneliness directly hindered an individual’s ability to process social cues. It is unknown whether loneliness contributes to a loss in gray matter in the pSTS or if a person born with less gray matter in the pSTS is more likely to be lonely. Given the harmful, stress-inducing effects of an increase in Tac2 expression, and the fact that stress has already shown to cause neuron death in other parts of the brain, such as the hippocampus (Lee, 2002), it is not outside of the realm of possibility for Tac2 expression to result in a loss of gray matter. However, until further research is done, this question remains unsolved.

Loneliness is a rather insidious chemical process in the brain. Although mice were primarily used in testing, many of the processes observed are homologous in humans. It can be difficult to define loneliness, as the needs for every person changes. The difference between an individual’s needs and the amount of interaction an individual feels is one way to determine how lonely a person feels. The important factor is not actual social interaction, but perceived social interaction. A poor perceived social interaction leads to a worse cognitive function, higher negativity, and greater chance of death (Cacioppo, 2009).

As shown in the 2018 study by Zelikowsky, a fear response in rodents was triggered after prolonged isolation. In humans, this likely manifests itself in a cognitive bias to social context (Spithoven, 2017, Kanai 2012). Loneliness was shown to lead to people having a much more negative outlook in all stages of a Social Interaction Processing model. An unfortunate circumstance of this behavior is that it becomes increasingly difficult for those with a negative outlook to gain the interaction they need, which leads to increasing levels of loneliness. In essence, a dangerous feedback loop is created. However, as more experimentation is done, more is being found to combat this issue. Serotonin treatments have already shown promise, and future

treatments to limit Tac2 production may yield fruitful results.

While these results are promising, no trials have been conducted on humans. For now, it has yet to be seen if one day a viable cure to loneliness can be found. Aside from pharmacological means, other forms of treatment are being explored. Technology has shortened the distance between people, and for individuals that are unable to meet face-to-face, it can serve as a way for them to connect. More research is needed to determine the effectiveness of technology in bolstering connections between humans, but as our world revolves around technology more, it will be interesting to see the effects of these changes. Given the recommended social-distancing policies due to COVID-19 in place at the time of writing, it will be interesting to see the short and long term effects of isolation. No doubt cases of loneliness amongst the population in the world have increased, but the extent to which social isolation has contributed to loneliness, and the societal outcomes of these cases have yet to be seen and studied. Future studies may combine the two ideas and attempt to discern a connection between a society's level of technology use and the effects of loneliness on the populace. Loneliness has become more prevalent in recent months. It is worth our effort to study and understand this debilitating disease.

References

Dorsal Raphe Dopamine Neurons Represent the Experience of Social Isolation.
<https://www.ncbi.nlm.nih.gov/pubmed/26871628>

Serotonin Regulation of the Prefrontal Cortex: Cognitive Relevance and the Impact of Developmental Perturbation.

Social Isolation Co-opts Fear and Aggression Circuits
[https://www.cell.com/cell/fulltext/S0092-8674\(18\)30524-5](https://www.cell.com/cell/fulltext/S0092-8674(18)30524-5)
"Chronic social isolation stress triggers an increase in neuronal tachykinin signaling across distinct brain regions that mediate fear and aggression, elucidating the neural basis of these maladaptive responses."

The Neuropeptide Tac2 Controls a Distributed Brain State Induced by Chronic Social Isolation Stress
[https://www.cell.com/cell/fulltext/S0092-8674\(18\)30361-1#secsectitle0010](https://www.cell.com/cell/fulltext/S0092-8674(18)30361-1#secsectitle0010)

Perceived Social Isolation and Cognition
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2752489/>

Social Relationships and Health: A Flashpoint for Health Policy
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3150158/>