# Biological mechanisms underlying susceptibility to traumatic stress

Chapter 9

# Impact and valorization

Mental health and neurodegenerative disorders pose enormous personal and socioeconomic burdens worldwide. Among the mental disorders, schizophrenia and bipolar disorder have the lowest prevalence. However, they are associated with severe impairment, while major depressive disorder has a median prevalence rate of more than 5 % of the population with an enormous impact, as measured in disability-adjusted life years. Over the past generation, the global burden of neurodegenerative disorders like Parkinson's and Alzheimer's disease has more than doubled due to the increasing number of older people. The neurodegenerative disease frequently disrupts emotional, cognitive, and social behavior. However, many patients and their families do not receive adequate care. Besides, neurodegenerative disorders are most common among older adults who usually have a pension, while stress-induced psychiatric disorders are most common among young and middle-aged people who should be the most productive power in society. Therefore, research on psychiatric disorders could potentially improve the lives of many of the most productive age groups and benefit a country's GDP.

Treating psychiatric disorders suppresses symptoms and may induce various side effects. Similarly, treating neurodegenerative diseases does not cure them but may (at best) reduce the progression. A better understanding of the mechanism underlying mental health and neurodegenerative disorders is needed to pave the way to better treatment and prevention.

The current widely accepted framework in stress-related mental disorders is the Gene-Environment interaction model. The idea of the framework results from two common findings: one is that mental disorders have environmental causes, and the other is that people respond differently to the same environmental stressors. Later, the model is better revised as poly-gene-environmental causation of mental illness. To fulfill the framework's potential, we join the forces of neuroscience. The work presented in this dissertation attempts to understand several genetic players underlying susceptibility to traumatic stress in the neurons of patients or rodent models. Besides, scientific work should always have societal implications. We discuss chapter by chapter.

In **chapter 2**, the review highlights that *dusp* family genes have a close relationship with mental and neurodegenerative diseases. The *dusp* family genes are not fully understood in the mechanism of mental disorders. Most studies are correlational, not causal. Therefore, this thesis highlights more research on the future causal relationship between *dusp* genes and mental disorders. Besides, the involvement of the *dusp* family gene in mental disorders fits the poly-gene-environmental framework. The poly-genetic causes of mental disorders could relieve a small amount of the blame game within families while treating adolescents diagnosed with mental disorders. For example, parental barriers are very common in providing health care to adolescents diagnosed with depression. More than half of the adolescents do not have access to treatment due to parental motivation and support. The major concern is that parents do not want to get blamed for their upbringing style (environmental factor) that might bring about their child's mental disorders. Although this thesis does not deny the environmental factors in the onset of mental disorders, the poly-genetic findings could partly relieve the guilty feelings of parents or the anger of the sick child.

In **chapter 3**, we focus on the protein expression pattern of these related genes and the change of their expres-

sion in response to stress in the brains of mice. One of the genes, *dusp22,* which belongs to the limbic brain regions involved in psychiatric disorders, is expressed prevalently in the mouse brain. This finding is another evidence of studying brain evolution: our brains evolved from vertebrates' simpler and smaller brains. The phylogenetic approach assumes that living mammals contain primitive traits or features maintained from a distant ancestor. Thus, traits common to clade members are considered to be most likely inherited from a common ancestor rather than independently evolved specializations. The common traits between mice and the human brain are likely to originate from the common ancestors of mammals. Stress-related gene *dusp22* and its translated protein DUSP22 are expressed prevalently in the stress-related brain regions, the prefrontal cortex. The common features of DUSP22 expression can be evidence of the common ancestor of humans and mice. In addition, this common feature legitimates studying the human brain via investigating mice brains alongside other common features. Although other primates are more closely related to humans, mice are more available and have fast reproductive rates, which is ideal for scientific research.

In **chapter 4**, MBP protein expression increased in the CA1 of the hippocampus of mice in response to social defeat. MBP is a marker of myelination, and many psychiatric disorders show alterations in myelin. Myelin ensheathment allows fast and efficient conduction of nerve impulses through the nodes of Ranvier, improving the overall function of neuronal circuits [569]. Our study demonstrates the myelin alterations in the hippocampus of mice exposed to social defeat, indicating that stress is associated with the myelin alterations in the brain. This gives insight into the impact of stress and the potential harm to the human brain in modern society. Morden humans are suffering from more chronic stress than ever before. Penn State researchers looked at data from 1,499 adults collected in 1995 and then from 782 different adults 17 years later in 2012. Both different groups were interviewed daily for eight straight days. They were asked about stressful experiences they had over the past 24 hours. Researchers found that day-to-day stress and a sense of lower overall well-being were much higher in the 2010s compared to the 1990s [519]. Reducing stress practices could be a healthy lifestyle in modern society.

In addition, our study shows brain alterations in the hippocampus, which might indicate memory deficits, and future research could focus on memory and MBP in the hippocampus for further understanding.

Besides the *mbp*genes, *myt1l* in **chapter 5** is expressed prevalently in the limbic brains of mice. Meanwhile, variations in *myt1l* have been associated with autism, intellectual disability, and schizophrenia in humans. This finding shows the common gene between humans and mice and could be a basic foundation for studying autism, intellectual disability, and schizophrenia via mouse models. Recent manipulation of *myt1l* in mice successfully mimics the human phenotype of autism-related social impairments, especially in males [520].

**Chapter 6** tested the neuronal firing pattern in awake-behaving mice exposed to fox-urine odor chemicals 2MT. This study is different from previous studies because it tests the real-time neuronal reactions of mice to stress-related odors. With the availability problem of TMT fox odor in research materials, 2MT is a substitute for widely researched TMT. However, the related research literature is scarce, and this study provides a reference for

future research on fox-odor-induced stress in mice. In addition, AON is a brain structure receiving information from the hippocampus, and this connection gives a good foundation for researching traumatic experiences recalled by the odor. For instance, the burning BBQ might remind the combat soldiers of their traumatic memories of burning flesh during wartime. As we know, a war is going on in Ukraine, and the Ukrainian soldiers are traumatized by the odor in the warzone, including burning gasoline, bodies, and gun powders. I hope this study could benefit the research aimed at combat soldiers.

Furthermore, the study found that most non-predator odors induced excitatory responses in AON. In contrast, the predator odor 2MT induced predominantly inhibitory AON responses. This result indicates that predatory odor inhibits neuronal activity in AON, and this discovery does not show direct application but indirectly gives implications for future research, like neuronal response between natural innate fear and conditioned fear in mice.

We used the social defeat paradigm as a stress model. The social defeat paradigm is one stress paradigm that successfully induces psychiatric disorders-like behavior in rodents. In **chapter 7**, we did an animal experiment using social defeat, showing surprising results contrary to other studies. For instance, socially defeated mice showed increased social behavior. Physical exercise did not promote resilience to stress inflicted by social defeat.

Further investigation is needed to confirm the results by modifying the social defeat paradigm to avoid severe injuries or animal loss. Another modification of the experiment is the homogeneous control of mice or randomization. For example, the mice's arrival should be under the same circumstances between the long-term and short-term cohorts. The third modification is the daily handling of the control and stress groups to avoid bias between stress and non-stressed control groups. Lastly, the physical exercise should be arranged along with the experiment timeline until the end.

So, upon reflection on the impact of my work on various levels, I cannot find a once-and-for-all answer to mental disorders. The progression of a tiny step requires much work, which can not help the suffering people right now, but hopefully for the people in the future.