Selective Serotonin Reuptake Inhibitors, Phineas Gage, and Stress and the Adolescent Mind

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PSY 110: Introduction to Psychological Science

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One of the major sections of chapter three is a discussion on **neurotransmitters** and how they function. The specialization of these neurotransmitters was heavily emphasized and alluring. **Serotonin** was the major focus of a meta-analysis study conducted by researchers Jakubovski, Varigonda, Freemantle, Taylor, and Blotch. Their study, which consisted of multiple sets of meta-analyses, was designed to determine the best selective serotonin **reuptake** inhibitor (SSRI) dosage to use for people who suffer from major depressive disorder (MDD). SSRIs are drugs that prevent serotonin that has been released into the **synapse** from being taken back into the presynaptic **neuron** during the process of reuptake (Jakubovski et al., 2016).

According to ADA practice guidelines, it is safe to increase SSRI dosage, as long as the resulting symptoms are manageable and the "upper dose limit is not reached" (Jakubovski et al., 2016, p. 174). Though these are guidelines from a reputable source, previous meta-analyses disagreed with these recommendations. Other findings have suggested that increased doses significantly increase side-effect burden, but the researchers found this data to be suspect. This discrepancy prompted the researchers to conduct a new study. Previous studies grouped many different antidepressants together and labeled doses as categorical, rather than continuous outcomes. The researchers, however, designed a study that involved SSRIs exclusively to improve the existing evidence base on the association between increasing dosages and, ideally, improved outcomes. This improved outcome would result in a decrease in the burden and symptoms of MDD (Jakubovski et al., 2016).

The researchers first conducted a literature review, which influenced the requirements of their study. These requirements for inclusion in their meta-analysis were

“randomized controlled trials comparing all SSRIs versus placebo in short-term treatment” (Jakubovski et al., 2016, p. 175). The data also had to have been recorded at three different points at least--a baseline in the beginning, an additional middle value, and the end results--and the measurement used to quantify depression had to be both standardized and valid. Other critical information included the treatment responders, the number of people who dropped out and for what reason they left the study, the type of SSRI that was tested, the maximum dosage of the SSRI, the duration of the trial(s), and the year of the trial(s).

Ultimately, the meta-analysis study determined that an increase in SSRI dose was significantly associated with an increase in the likelihood of symptom improvement. This finding, however, is not as simple as one might hope. A noticeable consequence of an increase in SSRI dosage was a decrease in toleration of the side effects by the participants. Interestingly, the study reported that “overall dropout rates were reduced at higher doses of SSRIs” (Jakubovski et al., 2016, p. 181). This finding, the researchers concluded, could be attributed to the decrease in MDD symptoms that the study found were negatively associated with SSRI dosage.

Limitations of this study were thoroughly documented. The researchers identified publication bias, difficulty in measuring the frequency of some side effects, and strict inclusion criteria as aspects of the study that may have impeded generalizability to subjects beyond that narrow scope as the main limitations the study possessed (Jakubovski et al., 2016).

This peer-reviewed study was referenced in chapter three of the sixth edition of the textbook “Psychological Science.” The section covers the purpose of the

neurotransmitter serotonin and discusses the effect of some drugs on serotonin. Jakubovski and his colleagues' research is brought up in the concluding sentences of this section, and it is used, specifically, to introduce the concept of SSRIs and name some examples, such as Prozac. The section also emphasizes that, as found in Jakubovski's research, SSRIs are commonly used to treat forms of depression. Considering the detail of the article and the variety of scientific associations it discusses, the textbook uses its conclusions in a very rudimentary way--mainly as a means to introduce a new topic--and does not dedicate much time to the article's discussion or discoveries.

The textbook also cited a research study that analyzed the case study of Phineas Gage and drew major connections between his brain injury and what psychologists know about the brain today. Before his injury, he was very highly praised, responsible, and functioned typically. After his injury, however, it seemed that "Gage was no longer Gage" (Damasio et al., 1994, p. 1102). Though his intellectual abilities, motor functions, and communicative abilities remained intact, he suffered a huge personality shift and became a social outcast as well as unhirable.

Despite this shocking and intense transition, no autopsy was performed on Gage once he died (Damasio et al., 1994). Were it not for a man named John Harlow, scientists may not have learned much from Phineas Gage at all. Though many scientists thought otherwise and dismissed his claims, Harlow insisted that Gage's sudden changes could be correlated to the frontal region of his brain suffering damage. The lack of an autopsy hurt his theories significantly, but Harlow did not rest. Instead, he

had Gage's skull and the tamping iron excavated and kept as a medical record (Damasio et al., 1994).

The researchers' work coincides with the sudden surge in interest in Phineas Gage across the scientific community; with the advancement of technology and brain imaging, scientists could now attempt to replicate Gage's injury. By taking many photographs of Gage's skull, Damasio and his colleagues were able to measure his skull and create a digital reconstruction of it. Then, using those measurements and the dimensions of the tamping iron, they simulated the different exit and entrance points the iron could have taken when it went through Gage's skull, thus creating five possible trajectories of the iron. The medical record of Gage's injuries were crucial in narrowing down the entry and exit points and, as a result, the possible trajectories the iron took when it made its way through Gage's skull.

One of the trajectories seemed to be a better fit than the other four, but all were simulated in a 3-D reconstruction, which allowed the researchers to see which areas of the brain the lesion hit and which areas of the brain the lesion missed. Crucially, the rod missed the supplementary motor area and Broca's Area, which accounted for Gage's continued ability to speak and ambulate post-injury (Damasio et al., 1994).

When Damasio and his colleagues compared Gage's presumed injury to other patients with similar frontal damage, they found that both Gage and the other patients had difficulty making rational decisions and processing emotion, which are both huge personal and social necessities in society. Despite this major loss in normal functioning, these patients, as well as Gage, did not suffer any difficulties with their logical thinking

and rational analysis abilities. This led the researchers to hypothesize that emotion has influence over social skills and that both are frontal processes (Damasio et al., 1994).

The researchers cite studies done with monkeys as further evidence of the specialization of regions of the frontal lobe, as well as the interconnectedness of the brain. Monkeys who were more socially adapted had a high concentration of serotonin **receptors** in their frontal lobe, while monkeys that were aggressive or uncooperative had less receptors (Damasio et al., 1994). This shows that not only is the frontal lobe highly specialized for motor, analytic, and social-emotional functions, it is also interconnected and greatly complex.

Unlike Jakubovski's research, Damasio and his colleagues' research is more wholly represented in the textbook. While the text does not go into depth about the researchers' methods for creating images and models of Gage's brain and injury, it does state the authors' findings: "the **prefrontal cortex** was the area most damaged by the tamping rod" (Gazzaniga, 2018, p. 91). The text also goes on to cite information the researchers gathered on patients with similar injuries to Gage and the behaviors they exhibit, specifically how their emotional and social performance became impaired and socially unacceptable while their learning and analytical capabilities remained intact. While the discussion the textbook dedicates to Damasio and his colleagues' work is not proportional to the detail of their research, the textbook represents their work fairly and ensures that the main ideas and impactful findings of their study are discussed.

Though the two articles seem vastly different, there are some underlying connections between them. The first is the involvement of serotonin and its importance in the brain. Jakubovski and his colleagues studied serotonin exclusively, working to

identify the most helpful doses of SSRIs to make the symptoms of MDD less severe or absent. The function of serotonin and its importance to normal brain functioning is mirrored in Damasio and his colleagues' study. In addition to damage in the frontal region of the brain, the presence or absence of serotonin receptors are major determinants of how socially and emotionally capable humans and animals are, which then impacts their functioning and subsequent rejection by, or acceptance from, their society.

Another similarity is in the complexity of the brain. Studying SSRI impact required a very delicate balance of the benefits of dosage versus the deleterious effects of increased dosage; a lack of serotonin and other deficiencies resulted in MDD, which was very harmful to patients, but efforts to correct those deficiencies are difficult because of how particular the brain is. In a similar way, Gage's case study also highlights the complexities of the brain. His damaged frontal lobe resulted in lesions in some areas of his brain, but the tamping iron missed other areas. This altered his social functioning, but he miraculously maintained his motor, analytical, and language abilities. In this way, the brain is specialized; certain areas are integral and have control over certain functions. Yet, Gage is also a landmark case that shows the interconnectedness of the brain. While Gage was still as intelligent as he ever was, his inability to understand social customs or make responsible choices caused him to be dismissed from numerous jobs. Gage's injury allowed scientists to learn more about the specializations and functions of the frontal lobe, while also showing that the different regions of the brain are interconnected.

Finally, both articles researched an impairment of normal functioning. For Jakubovski and his colleagues, impairment of normal functioning manifested as the condition MDD. For Damasio and his colleagues, impairment of normal functioning meant social and emotional deficits as a result of a brain injury. Though the impairments were fairly different, the articles find similarity in that they attempt to improve scientific understanding on their respective impairments and seek explanations for why they occur.

An outside source that was not mentioned in the textbook, but that has numerous relations to the previous two articles, discussed the stress response in adolescent brains. Authored by Russell D. Romeo, who works at Barnard College of Columbia University's Department of Psychology and Neuroscience and Behavior Program, the article explores how the changes in the type of stressors, and how animals respond to those stressors, affect the brain in both animals and humans. The studies evaluated and explained by Romeo were based on "basic animal models," which is how "most of our mechanistic understanding of changes in stress reactivity and neurobiological function is derived" (Romeo, 2013, p. 140).

The stress response outlined in the article has two main pathways: the instant response by the **sympathetic nervous system** and the **hypothalamus**-pituitary-adrenal (HPA) axis. Through the HPA axis, corticotropin-releasing hormone (CRH) is released, which then stimulates the **pituitary gland** to release adrenocorticotropic hormone (ACTH), which then stimulates the adrenal glands to create glucocorticoids. These **hormones** provide negative feedback once the stressful stimulus has ended and

signal the pituitary gland and the forebrain to stop producing the other two hormones (Romeo, 2013).

Both adolescent and adult humans and animals have stress responses, but there are underlying differences in adolescent hormone responses that may influence brain functioning and psychological and behavioral responses to stressors. These subtle differences lie in the amount and the duration of hormone release (Romeo, 2013). The mechanisms that contribute to differences in adolescent stress responses are unclear, though there are some plausible explanations that Romeo notes. One explanation is that there may be an activation difference, meaning adolescents often produce more CRH. The other explanation is that the negative feedback provided by the glucocorticoids may be less effective and/or not as well received by receptors in the brain (Romeo, 2013).

It has also been shown that previous experience may have a significant impact on stress. In adult animals, continued exposure to a consistent stimulus resulted in a habituated hormonal response; the animals were less stressed when faced with a stimulus they had experienced many times. In adolescents, however, even a stressor they had repeated exposure to elicited a sensitized response. (Romeo, 2013). Additionally, adults and adolescents showed similar sensitization to new stressors, yet adolescents took longer to recover from the hormonal responses than the adults (Romeo, 2013).

This lack of recovery and prolonged hormonal activity is concerning when evaluating the effects of stress on the brain. Prolonged stress has been linked to the impediment of the **hippocampus** and prefrontal cortex, leading to numerous deleterious

effects, such as decreased spatial learning and impaired cognitive abilities (Romeo, 2013). While stress decreases **neuroplasticity** in some areas of the brain, others become more plastic. The **amygdala**, in response to prolonged stress, enlarges and increases fear-based learning in that organism (Romeo, 2013).

Ultimately, the differences in stress response and the heightened feelings and damage of stress to various brain regions seem to be influenced by a variety of factors. Differences in adolescent brain functioning combined with the natural development and maturation of the hippocampus, prefrontal cortex, and amygdala during adolescence makes the adolescent brain vulnerable to the deleterious effects of stress and hormones (Romeo, 2013). These trends can be seen in both animals and humans.

The article is more credible than it is suspect. Though the article admits to a lack of studies conducted that compare adolescent and adult brains and stress responses, and its information mainly relies on animal, rather than human studies, there are numerous factors that make it credible. While there are few studies comparing adolescent and adult stress responses and brain composition in animals, other areas of study, such as studying the effects of chronic and acute stress, are growing (Romeo, 2013). Additionally, the article and its findings were supported by the National Institutes of Health Grant and the National Science Foundation Grant. Finally, the article was published in a peer-edited journal focused on contemporary psychological science and was found using the scholarly database JSTOR.

All three of these articles, despite their varying focuses, can be applied to my future goal of becoming a physical therapist. The brain is a fascinating organ, and all three of these articles highlight how complex and delicate the brain is. There are many

aspects of the brain that scientists have yet to research or understand. This complexity of the mind reflects the complexity of the body; both aspects have to work in harmony for people to be able to function properly and happily. When there is a disconnect between these two areas or a problem with one, people rely on doctors, physical therapists, and other medical professionals. Understanding how serotonin works and affects the brain, as well as how to mitigate symptoms of depression and anxiety as highlighted in the first and third articles, is vitally important for a physical therapist to understand. Additionally, the sensitivity and specialization of the brain is important to understand when it comes to injuries like concussions that physical therapists or trainers may work to heal. Overall, the best thing for a physical therapist to understand, outside of what they are taught in terms of physical healing, is their patients. Psychology can be applied in all aspects of our lives, as psychology is the study of the mind and of people. It is even more important to understand and have a strong foundation in psychology when your goal is to help others, especially when you want to work with those who are struggling and vulnerable. In addition to my personal interest in psychology, I believe it is very important for those in the medical field, including physical therapists, to have a strong understanding of psychological principles to help them better work and empathize with others.

Glossary

Amygdala (3.6): a brain structure that serves a vital role in learning to associate things with emotional responses and in processing emotional information. In studies of rats, the amygdala was found to grow/become more plastic when the rats were exposed to stressors. This increased the prevalence of fear-based learning.

Hippocampus (3.6): a brain structure that is associated with the formation of memories. When exposed to prolonged stress, the hippocampus often becomes impeded. This is especially prominent in adolescent animals due to the vulnerability of the maturing/growing hippocampus.

Hormones (3.11): chemical substances released from endocrine glands that travel through the bloodstream to targeted tissues; the tissues are subsequently influenced by the hormones. A variety of hormones are released when an animal or a human is presented with a stressor. These hormones perform various functions and make up the stress-response.

Hypothalamus (3.6): a brain structure that is involved in the regulation of bodily functions, including body temperature, body rhythms, blood pressure, and blood glucose levels; it also influences our basic motivated behaviors. The hypothalamus is a major component of the HPA axis. This axis is one of two main stress-responses in the brain.

Neuron (3.1): the basic units of the nervous system; cells that receive, integrate, and transmit information in the nervous system. They operate through electrical impulses, communicate with other neurons through chemical signals, and form neural networks. SSRIs prevent neurons from taking serotonin back that has been released into the

synapse. Neurons are also vital for the detection of stressors and to signal the hormonal responses and changes in the brain.

Neuroplasticity (3.12): a property of the brain that allows it to change as a result of experience or injury. The plasticity of the brain is what allowed Gage to survive and recover from his injury. Additionally, prolonged stress results in certain areas of the brain becoming less plastic, while others become more plastic and sensitized.

Neurotransmitters (3.3): Chemical substances that transmit signals from one neuron to another. A specific type of neurotransmitter, serotonin, was the focus of the study about major depressive disorder. Neurotransmitters are also vital on a broader scale as they trigger the firing of other neurons and thus cause communication to and within the brain.

Pituitary Gland (3.11): a gland located at the base of the hypothalamus; it sends hormonal signals to other endocrine glands, controlling the release of hormones. The pituitary gland is an important part of the HPA axis. Additionally, in response to a stressor, the pituitary gland is stimulated to produce the hormone ACTH.

Prefrontal Cortex (3.7): the foremost portion of the frontal lobes, especially prominent in humans; important for attention, working memory, decision making, appropriate social behavior, and personality. The prefrontal cortex faced the brunt of Gage's injury. This could explain his sudden change in personality and his alarming lack of social graces.

Receptors (3.3): in neurons, specialized protein molecules on the postsynaptic membrane; neurotransmitters bind to these molecules after passing across the synapse. In a study of social behavior in monkeys, those with more serotonin receptors in their frontal lobe were more sociable and those who had less were more aggressive

and antisocial. This research coincides with the findings developed from Phineas Gage, showing how social and emotional functions are found in the frontal lobe of the brain.

Reuptake (3.3): the process whereby a neurotransmitter is taken back into the presynaptic terminal buttons, thereby stopping its activity. The purpose of SSRI medications are to prevent the process of reuptake, thereby leaving serotonin in the synapse, which can be used by postsynaptic neurons. This lack of reuptake can help to mitigate MDD symptoms.

Serotonin (3.3): a monoamine neurotransmitter important for a wide range of psychological activity, including emotional states, impulse control, and dreaming. Serotonin is a major component in symptoms of MDD, which may be caused by a lack of serotonin or inefficient binding and processing of serotonin to receptors. Serotonin has also been seen in other studies, such as the monkey study, to affect sociability and group behavior.

Sympathetic Nervous System (3.10): a division of the autonomic nervous system that prepares the body for action. The sympathetic nervous system is the first to respond when an animal or human is presented with a stressor. This activation and the hormones that follow it comprise our stress-response.

Synapse (3.1): the gap between the terminal buttons of a “sending” neuron and the dendrites of a “receiving” neuron; the site at which chemical communication occurs between neurons. Serotonin, a vitally important neurotransmitter, travels from the presynaptic neuron, through the synapse, to the postsynaptic neuron. SSRI medications prevent serotonin from being taken from the synapse, which helps to alleviate the hardships of MDD.

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