Spring 5-2014

The Impact of Serotonin and Dopamine on Human Aggression: A Systematic Review of the Literature

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A Thesis
Submitted to the Graduate School
of The University of Southern Mississippi
in Partial Fulfillment of the Requirements
for the Degree of Master of Arts

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May 2014

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Aggressive behaviors can have serious impacts on both the population at-large and the criminal justice system (Fish, DeBold, & Miczek, 2002); but despite these potential repercussions, no adequate treatment options have been identified to prevent (or reduce) such consequential actions. An increasing amount of research has, however, developed (over the years) in response to these treatment needs. Recently, the disciplines of neurobiology and neuropsychology have discovered specific anti-aggressive treatments. Studies on the prefrontal cortex specifically reveal that certain areas of the brain, along with an array of chemical imbalances, are related to aggressive behavior (Barrett, Edinger, & Siegel, 1990). Specifically, serotonin and dopamine imbalances in the prefrontal cortex were found to contribute to more aggressive behavior (Giammanco, Tabacchi, Giammanco, Di Majo, & La Guardina, 2005). Using a systematic review of the literature as the primary methodology, this study analyzed academic literature over a recent 20-year period (1992-2012) for indicators regarding the potential impact of serotonin and dopamine on human behavior.

ACKNOWLEDGMENTS

I would like to thank my thesis chair, Dr. Lisa Nored, for supporting every aspect of my Master's degree in Criminal Justice. Your professional and personal advice helped me mature into the researcher I am today. I also wish to thank Dr. Mary Evans and Dr. Thomas Panko for serving as committee members, and for their useful remarks and suggestions throughout the thesis-writing process. Lastly, I thank you all for continuously engaging over the course of the entire process, and for contributing to a final defense that was an enjoyable moment.

On a personal note, I thank my parents for their unconditional love. The two of you have been my strength since the beginning of this wonderful adventure. Finally, I thank all of my friends who occupied the "passenger seat" while I navigated this wonderful journey.

TABLE OF CONTENTS

LIST OF ILLUSTRATIONS

Figure

CHAPTER I

INTRODUCTION

Problem Statement

Impulsive aggression, understood as one's inability to control impulsive outbursts, can have a detrimental impact on a person's life (Coccaro & Siever, 2000). Research has shown that aggressive impulses in the presence of mental disorders can be comorbid, in that it creates (or perpetuates) a tendency toward substance abuse or suicide. Seo, Patrick and Kennealy's (2008) research (and their predecessors) have highlighted the relationship among serotonin hypofunction, dopamine hyperfunction, and aggressive behavior with other comorbid disorders (Hicks, Krueger, Iacono, McGue, & Patrick, 2004; Koller, Preub, Bottlender, Wenzel, & Soyka, 2002; Linnoila & Virkkunen, 1992; Placidi et al., 2001).

Research in neurology, biology and brain imaging illustrate the complexity of the behavioral phenomenon that is impulsive aggression. Indeed, impulsive aggression can be explained using chemical imbalances in multiple parts of the brain and its neurological system (Seo et al., 2008). Specifically, the serotonin transporter gene (5-HTTLPR) interacts with the likelihood of impulsive aggression in adolescents and adults when examining self-control (Asberg, Scalling, Trakeman-Bendz, & Wagner, 1987; Beaver, Ratchford, & Ferguson, 2009; Linnoila & Virkkunen, 1992).

Research in neurology and biology describe the serotonergic and dopaminergic systems as interacting with one another (Daw, Kakade, & Dayan, 2002; Kapur & Remington, 1996; Wong, Feng, & Teo, 1995). Specifically, in the prefrontal cortex, if levels of serotonin were to be lower, the serotonergic system would dysfunction, which would cause the dopaminergic system to be deregulated as well, which in turn could

cause a person to respond aggressively to a situation of perceived threat (Anderson, Bechara, Damasio, Tranel, & Damasio, 1999; Davidson, Putnam, & Larson, 2000; De Simoni, Dal Toso, Fodritto, Sokola, & Algeri, 1987).

Other studies on norepinephrine and testosterone have also argued that a chemical imbalance could cause someone to react in an aggressive manner (Barrett, Edinger, & Siegel, 1990; Giammanco et al., 2005). Therefore, there seems to be a link between neurotransmitters dysfunction and the likelihood of someone showing signs of aggressive behavior. Because of the abundant literature on the role of serotonin and dopamine on human aggression, with serotonin being involved in the regulation of levels of dopamine, which is linked to the regulation of emotions (Daw et al., 2002; Davidson et al., 2000; Volavka, 1999; Yan, 2002), this study will solely focus on these two neurotransmitters.

Significance of the Study: Biosocial Perspective

Given that science is a cooperative enterprise (Feldman & Cooper, 2010), the findings of past research are necessary building blocks in developing new knowledge. Yet, until twenty-five years ago, investigating, locating, evaluating, summarizing and interpreting past research was not common for social scientists. During the 1960s and 1970s when social science research expanded rapidly, scholars realized that there was a need to sift through all the new research being published in an efficient manner. Garvey and Griffith (1971) argue “The individual scientist is being overloaded with scientific information. Perhaps the alarm over an ‘information crisis’ arose because sometime in the last information doubling period, the individual psychologist became overburdened and could no longer keep up with and assimilate all the information being produced that was related to his primary specialty (p. 350)”. Since criminal justice and the social

sciences are expanding, specialization within these disciplines lack a means to make past research available to researchers. Except for a few areas of special interest, researchers today simply lack the time to wade through the volumes of research published every year.

A lot of research has been published on the role of serotonin and dopamine in human aggression, and it continues to expand rapidly. As a result of new ongoing research and potential advances for the promotion of treatment for people displaying aggressive behavior due to neuropsychological deficiencies, this research trend is very promising. However, having accumulated a vast body of research makes the task of locating the most useful information about the role of serotonin and dopamine on aggression more challenging. Hawking argued that "the greatest enemy of knowledge is not ignorance, it is the illusion of knowledge" (as cited in Duke, Begue, Bell, & Eisenlohr-Moul, 2013, p. 114). Due to the large number of articles published on the role of serotonin and dopamine in human aggression, a systematic review is essential to assess the current state of research on this topic. No previous systematic review of the literature has been performed regarding the role of serotonin and dopamine in human aggression. Thus, utilizing a biological perspective, this study will provide a systematic review of the literature on the role of serotonin and dopamine in human aggression from 1992 to 2012.

Research Questions

To assess the current role of serotonin and dopamine in human aggression, this systematic review of literature will attempt to answer the following research questions:

1. What are the elements that define aggression?
2. How is serotonin defined in the literature?
3. How is dopamine defined in the literature?

4. What is the role of the serotonin and dopamine in human aggression? Are serotonin and dopamine closely intertwined?

Definition of Terms

Comorbid "pertaining to a disease or other pathological process that occurs simultaneously with another" (Dorland's Medical Dictionary for Health Consumers, 2007, p. 54).

Dopamine is "a neurochemical made in the brain that is involved in many brain activities, including movement and emotion" (Gale Encyclopedia of Medicine, 2008, p. 74).

Enzyme is "a protein that catalyzes chemical reactions of other substances, without itself being destroyed or altered upon completion of the reactions" (Dorland's Medical Dictionary for Health Consumers, 2007, p. 23).

Human aggression is "is any behavior directed toward another individual that is carried out with the proximate (immediate) intent to cause harm" (Bushman & Anderson, 2001, pp. 273-279).

Metabolite is "a substance necessary for, or taking part in, a particular metabolic process" (Demain, 1980, pp. 582-587).

Neurotransmitter is "a chemical messenger that carries, boosts, and modulates signals between neurons and other cells in the body" (Thompson, 2000, p. 53).

Serotonin is "a chemical produced by the brain that functions as a neurotransmitter" (Gale Encyclopedia of Medicine, 2008, p. 94).

CHAPTER II

REVIEW OF THE LITERATURE

Theoretical Relevance

According to Simon (2007), “There are times when the most important questions of all are not what should we do, but how should we think” (cited in Kraska & Brent, 2010, p. 1). For much of our Western history, the common ground was to think that crime was the result of supernatural forces coming from Satan. People were said to be evil and that the devil made them have sinful behavior. In order to determine if people were possessed, very harsh and brutal methods were used. When someone was found guilty of possessing evil forces, he or she could be burned alive or tortured to death in some kind of public ceremony to make it more unbearable.

In reaction to the harsh, corrupt, and certainly arbitrary nature of the demonic perspective that was in place through the 1700s, a group of people who were known as “classical theorists,” led by Cesare Beccaria (1764/1963), challenged the prevailing beliefs about crime. Since laws were open to interpretation because of their lack of clarity, classical theorists proposed to reform the judicial system. Their reforms were based on the work of the philosopher Thomas Hobbes (1651/1985), who argued that human conduct is simple: people are selfish and will pursue acts that maximize pleasure while avoiding pain. Since seeking pleasure can lead to violating the law (and potentially harming others), classical theorists argued that swift, certain and severe punishments must be implemented to deter people from committing crime.

Although classical theory dominated criminology in the 1700s and 1800s, scholars were attempting to include a biological element to explaining crime. In 1876, Cesare Lombroso’s manuscript was perhaps the first attempt at linking biology and

crime. Lombroso (1876) used crime rates to show that despite so-called deterrent changes implemented into the penal system, crime was still increasing. As part of his research on prisoners, Lombroso (known as the father of positivism) compared traits of criminals' anatomy to the general Italian population. He argued that criminals were "genetic throwbacks" (as cited in Cullen & Agnew, 2010) who possessed certain characteristics (such as sharper teeth, bigger jaws, longer arms) that were conducive to crime. Based on his observations, Lombroso argued that he could determine whether a person was likely to be a criminal. Moreover, he described criminals as having an animal instinct void of free will, and thus should not be held responsible for their actions because they are only protecting themselves against a violent situation, as people always had over the course of human evolution. Tannenbaum (1938) explained that "In the mid-to-late thirties…the Positive School of Criminological thought was still dominant" (p. 2). Whereas the Classical school was known for its assertion that individuals are free to decide whether they will commit criminal acts, Positivism supports the idea that criminal acts are the product of things beyond one's control. Tannenbaum said: "The emphasis on biological determinism and internal explanations of crime were the preeminent forces in the theories of the early thirties" (p. 2).

Modern criminology refuted Lombroso's findings as not methodologically sound on the basis that he over-generalized conclusions and failed to consider how the environment and genetics may explain his proposed "criminal" physical traits. Thus, criminologists chose to focus on the social aspect of explaining crime. Tannenbaum (1938) mentioned "The dominance by the Positivist school changed in the late thirties with the introduction of conflict and social explanations of crime and criminality" (p. 2).

Many studies conducted around that time did not use random samples or include appropriate control groups to validate their claims. Additionally, many of Lombroso's criminal traits could have appeared because of environmental conditions such as lack of vitamins and nutrients, poor health, or untreated diseases, which could have caused missing teeth or a body that lacks certain characteristics that a healthy human being would exhibit, making them look deformed or abnormal. Moreover, not only did Lombroso fail to assess environmental conditions, he also did not consider the social factors that could have influenced prisoners to commit their crime. Maybe their family was hungry and they stole food to provide for their loved ones. Because of a lack of sound methodology, biological criminology was put to the side for several decades. During that time, criminologists used a more sociological approach to crime.

Nonetheless, biological criminology did not completely disappear. In the 1970s, Wilson (1975) declared "people are biosocial organisms whose behaviors are influenced by both their physical characteristics and the environmental conditions they are faced with" (p. 25). With the work of Wilson and others after him, criminologists argued that criminal behavior could not only be determined by physical traits but also that the environment played a role. Thus, criminologists started advocating for a combination of nature and nurture in saying that both genetics and the environment had a role to play in explaining aggressive human behavior. van den Berghe (1974) asked "When faced with the same environmental stressors, why do some people engage in violence while most people do not? (p. 779). Thus, the 1970s was an era during which criminologists viewed crime as better explaining both the environment and the societal conditions people lived in combined with biological traits that would make someone more prone to committing

crime. Even though a few criminologists argued for a bigger place given to biological traits determining criminality as the main factor, other biosocial criminologists advocated that someone's diet could have an impact on their behavior.

> Nutrition is usually taken to be important for physical health, but mental health – brain health in its widest sense – must be considered as equally important. A diet lacking essential nutrients or containing too many ingredients that are detrimental in excess is likely to have adverse consequences for brain function and thus mental health and behavior. It is widely agreed that a balanced diet is required to support physical health. (Benton, 2007, p. 753)

Biosocial criminologists maintain that minimum levels of vitamins and minerals acquired through a balanced nutrition are required for a human brain to function normally. Specifically, research has highlighted the importance of a balanced diet during childhood and adolescence (Neisser et al., 1996). Since children and adolescents' brains are still forming during this period of time, a balanced nutrition will prevent deficiencies that can have a detrimental impact on humans such as causing mental, physical or behavioral problems (Neisser et al., 1996; Schoenthaler & Bier, 2000).

> Correction of nutrient intake, either through a well-balanced diet or low-dose vitamin-mineral supplementation, usually corrects the low concentrations of vitamins in blood, improves brain function, and subsequently lowers institutional violence and antisocial behavior by almost half in both public schools and correctional facilities. (Schoenthaler & Bier, 2000, p. 16)

In his manuscript, *The Moral Sense*, renowned criminologist J. Wilson (1993) also argues that there is difference in behavior between males and females. Indeed, his

research shows that there is a difference in the exposure to certain hormones between males and females, which may in turn cause males to react more aggressively to a situation compared to women who are more nurturing and empathetic. Wilson explains "gender differences in exposure to androgens (male sex hormones) explain why males are naturally more violent than females and why females are more nurturing and empathetic. (p. 27)". Scientific studies present support about how exposure to chemicals such as mercury, chlorine and artificial coloring such as colorants use to color cakes or other types of food has an impact on the likelihood of someone being more aggressive (Rappaport & Thomas, 2004).

Furthermore, Beaver (2009), a biological criminologist, used the term "evidence-based" practices to describe the shift in criminal justice from a soft science to one with greater rigor. Robinson and Beaver (2010) argued that "The empirical evidence indicating that antisocial behavior is partially influenced by genetic factors has spawned some theorists to advocate for an integration of behavioral genetic findings into mainstream criminological theories" (as cited in Barnes, Beaver, & Boutwell, 2011, p. 925). Thus, criminologists such as Beaver (and colleagues) put strong emphasis on analyzing the methodologies that researchers use when publishing new knowledge. Thus, because the subject matter touches on understanding humans and the human life, it became primordial for research syntheses to be evidenced-based and to be postulated in order to help researchers and policy makers. Duke et al. (2013) argued that "The inverse relation between serotonin and human aggression is often portrayed as 'reliable', 'strong', and 'well established' despite decades of conflicting reports and widely

recognized methodological limitations" (p. 1148). Studies on serotonin and dopamine and their relationship with human aggression have thus been found methodologically sound.

Serotonin and Aggression

During the middle of the 1970s, research on the role of serotonin on human aggression became more popular. Serotonin was found to be a key component in the regulation of behavior, specifically deviant and aggressive behavior. In their study of suicide victims, Llyod, Farley, Deck, and Hornykiewicz (1974) found that suicide victims possessed lower levels of one of the metabolites of serotonin in their brain fluid: the 5-hydroxyindoleacetic acid (5-HIAA). More studies came to conclude that temperament, aggression, depression, suicidal behavior, alcoholism, drug use and impulsive behavior were attributed to a change in the brain chemical balance – and specifically how lower serotonin levels were linked to psychopathological behavior. This study, among others, confirmed previous findings on how lower levels of serotonin in human brain help regulate the mood and is linked to dangerous and self-destructing behaviors (Seo et al., 2008). Tops, Russo, Boksem, Maarten and Tucker (2009) explained that "Proposing that serotonin is involved in a drive to withdraw and seek contentment, instead of a drive to avoid may be compatible with several lines of evidence on serotonin function and may facilitate a better understanding of serotonergic neuromodulation in human psychopathology (para. 2)." Therefore, if there is an imbalance in the chemicals that come into contact with serotonin receptors in the brain, serotonin will not be produced and metabolized correctly, which in turn, will prevent the brain from regulating mood change, aggressiveness, impulsivity or even sexual impulses that an individual may have. Kyes, Botchin, Kaplan, Manuck and Mann (1995) demonstrated that this finding is true to both the human and animal species: "A propensity to exhibit impulsive, aggressive

behavior has been linked to reduced levels of central serotonergic (5-HT) activity in both human beings and animal models (p. 205)."

Between the 1990s and the 2000s, numerous studies focused on the importance of biochemical and brain imaging studies to explain crime. They rapidly linked suicidal and aggressive behavior to low serotonin levels. Indeed, Seo et al. (2008) demonstrated that "Impulsive aggression is characterized by an inability to regulate affect as well as aggressive impulses, and is highly comorbid with other mental disorders including depression, suicidal behavior, and substance abuse (p. 383)." It became clear that there is a relationship between the physiological, biological and chemical consequences of lower levels of serotonin and the exhibition of impulsive and aggressive behavior in humans. They pointed out "In an effort to elucidate the neurobiological underpinnings of impulsive aggression and to help account for its connections with these disorders, this paper reviews relevant biochemical, brain imaging, and genetic studies (p. 383)." From that point forward, brain imagining studies and biological criminology became inextricably linked in order to make sense of the relationship between lower levels of neurotransmitters in the brain and regulating aggressive and impulsive behavior.

Virkkunen et al. (1994) studied 58 alcoholic offenders (43 impulsive and 15 non-impulsive) and 21 healthy volunteers, and found that impulsive alcoholic offenders who exhibited antisocial behaviors were the ones with lower levels of serotonin in the brain. The authors concluded that lower levels of serotonin in the brain were associated with poor impulse control, which is an important factor for alcoholics (and criminal behavior in general). The question, then, is since the study targeted only a small portion of the

population, and given the importance of evidence-based practice, are these findings generalizable to all species?

In 1995, Kyes et al. answered yes to this question. In their study of monkeys, they found that monkeys with low serotonin levels exhibited more aggressive behavior when encountering unexpectedly stressful or threatening situations. Monkeys with lower levels of serotonin "displayed significantly more aggressive gestures in response to a threatening slide of a human being than did the high responders (p. 207)." The authors generalized their findings as follows: "The data support related findings in people and nonhuman primates linking reduced serotonergic activity and aggression" (p. 208). Concomitantly (in 1995), unprecedented violence was witnessed in French and American laboratories studying mice. Scientists found that chemical imbalances in the brains of mice turned "normal" mice into more violent and sexually aggressive creatures. Cases and colleagues (1995) studied enzymes, specifically the monoamine oxidase A (MAOA), an enzyme that transports serotonin to the brain and found out that mice displaying a lack of MAOA were significantly more likely to exhibit aggressive behaviors compared to mice with normal levels of MAOA enzymes.

During that time, American researchers from Johns Hopkins University were studying strokes in genetically-modified mice. Nelson and colleagues' (1995) results were astonishing: "Upon routine morning examinations, we often discovered one or two dead mice in each cage" (p. 278). They studied the mice's genes to solve the mystery of all these deaths. They discovered that the aggressive mice who were killing other mice were lacking a specific gene linked to the production of a neurotransmitter called nitric oxide: "it is highly probable that the behavioral abnormalities we have observed are

direct, selective consequences of the loss of enzyme necessary for formation of nitric oxide and not secondary to global physiological disruptions (p. 282).” Nitric oxide regulates aggressive behavior. Additionally, the authors found that aggressive behaviors were not evidenced in female mice lacking that gene. Thus, this finding confirmed previous studies on how males and females differ in the presence of certain genes and the interaction of these genes with the likelihood to be more aggressive. However, the researchers cautioned that, “[t]hough direct comparisons are not feasible, the sexual and aggressive aberrations of mice lacking the gene seem more pronounced than those reported with deletion of other genes. Accordingly, nitric oxide may be a major mediator of sexual and aggressive behaviors, relevant for studies of their biological determination in humans as well as mice” (p. 283).

The publication of behavioral studies linking highly aggressive mice with the lack of a specific enzyme necessary for the production of nitric oxide provoked considerable criticisms. Since the production of nitric oxide was linked to strokes, researchers began looking for a way to inhibit or control the creation of nitric oxide. Subsequently, drugs inhibiting such enzyme production were introduced. Demas et al. (1997) investigated the efficacy of these new drugs. In their study, they found that injected mice demonstrated substantially increased aggression. Since the nitric oxide synthase inhibitor increased aggression, it implied that nitric oxide has an impact on the mediation of aggression. This study increased researchers’ interest on the effects of inhibitors. At the same time, however, it raised concerns about the unexpected behavioral consequences of some pharmacological products.

In France, Saudou et al. (1994) conducted an experiment on mice which lacked a receptor for the serotonin in their brains. These researchers discovered 14 types of serotonin receptors, and subsequently created mutant mice to investigate the role of each. They determined that mice missing one type of receptor for serotonin "attacked normal mouse intruders faster and more intensely than did wild-type mice suggesting the participation of these receptors in aggressive behavior" (p. 1877). From the findings, the authors concluded that in the event of a stressful or threatening interaction, this type of receptor may be activated. "When the mutants are housed as a group …they are not more aggressive than other mice. However, after a month of isolation and in the presence of an intruder, the mutants are significantly more aggressive than the other mice" (p. 1878).

One intriguing new study on monkeys lends support to the idea that lower levels of serotonin are linked to aggressive and dangerous behavior. In a four-year study, Higley et al. (1996) examined the serotonin levels and aggressiveness of 49 male monkeys who were going through stressful and dangerous events. During that period, a significant number of monkeys died. The researchers measured each of the monkey's brain levels of 5-HIAA, one of the most important metabolites of serotonin, and subsequently placed the monkeys into one of four groups depending on those levels (from low level to high level). Twenty-seven monkeys were then placed into a wilderness-like environment so the researchers could record levels of aggressiveness. All 49 monkeys were also observed while in captivity to determine their level of aggressiveness in that type of environment. At the end of the study, the researchers wrote "The 11 subjects who died or were presumed dead had significantly lower serotonin levels during their first capture than the subjects who remained alive" (p. 540). They added that the monkeys who died had also

engaged in more aggressive behaviors and had higher rates of escalated aggression and were overall more aggressive than the other primates in the group. The authors concluded "Our findings, suggest that death rate is not randomly distributed across the overall male population. Instead, it appears that subjects with low concentrations of serotonin are much more likely to die during this period of life than the rest of the male population" (p. 543). A partial explanation for why the lowest-serotonin monkeys died prematurely can be attributed to their dangerous personality traits. Interestingly, the first monkey to die during the study was also the one which exhibited the lowest level of serotonin in its brain: "He was three years old and weighted less than half of a mature adult male…The night of his death, two of us observed this young male repeatedly attack a pair of fully mature males (p. 538)." Not only did this monkey exhibit lower serotonin levels, but it also exhibited sensation-seeking behavior, in that the thrill of fighting two bigger monkeys outweighed the risk of being killed due to the difference in size and strength.

Following this research, the question became: "Can these findings be generalized to humans?" Higley and colleagues (1996) paralleled their findings on monkeys with findings from another one of their studies on male psychiatric patients. Between 1976 and 1990, they studied a group of 73 psychiatric patients (seven of which died prematurely due to suicide, homicide or suspicious deadly accident). The researchers opined that these premature deaths among both humans and monkeys with low serotonin levels "suggest that low serotonin metabolite (5-HIAA) concentrations may be a marker for early death among humans as well" (p. 543). Thus, there is a relationship between lower levels of serotonin in the brain and premature death of people who exhibit this trait.

Since the 1990s, studies on humans from childhood to adulthood have documented the relationship between serotonergic deregulation and aggression. In their study of 43 male offenders between the ages of 13 and 17, Unis et al. (1997) confirmed previous findings that observed aggressive behaviors or conduct disorders such as "chronic stealing, aggression, truancy, property destruction, arson, lying, fighting, cruelty to animals and people, weapons use, and running away from home." Thus, they found a positive correlation between serotonin levels and delinquency, onset of delinquency and severity of delinquency. These findings are consistent with previous studies showing a relationship between serotonin hypofunction and aggressive behavior.

Cleare and Bond (1997) did not achieve the same result when they tested the link between low levels of serotonin in males who did not exhibit psychiatric problems and aggressive behavior. In their study, fenfluramine, a drug that releases more serotonin in the brain, was administered to 35 male and female subjects. They found that healthy males with low serotonergic activity did not exhibit a greater tendency for aggressive behavior, and concluded that their data "provided modest support for the theory of a link between reduced serotonergic activity and increased trait aggression in healthy males (p. 92)." Thus, since healthy males with low serotonergic activity did not exhibit a greater tendency for aggressive behavior, the idea that psychological deficiencies and low serotonin levels are correlated with more aggressive behaviors for males is confirmed. Unfortunately, their study and others before them have not yet fully explored the same relationship for females. In addition, New and colleagues (1997) studied the link between abnormal serotonin levels and aggression. They gave fenfluramine to 97 patients with personality disorder and found that patients who had a history of hurting themselves or

had attempted to commit suicide before exhibited an abnormal serotonergic system. They concluded that "Self-injurious behavior…represents a form of self-directed aggression, and may be associated with a decrease in central serotonin function (p. 17)." For people with personality disorder, when the levels of serotonin fluctuate too much, they are more likely to exhibit impulsive and aggressive behavior. Thus, there is a link between psychological disorders, low levels of serotonin and aggressive and impulsive behaviors.

Throughout the 1990s, research managed to show that there actually is a relationship between serotonin levels and aggressive behavior, specifically between low levels of 5-HIAA, the metabolite of serotonin in the brain and aggressive and impulsive behavior. However, investigating the same linkage among females is limited or inexistent. In 1999, Westergaard, Suomi, Higley, and Mehlman conducted a study that included sixty-one female macaques from two different but very similar species: rhesus and pigtailed macaques. Rhesus macaques are a very aggressive macaque species, pigtailed macaques are supposed to be friendlier. The authors measured the levels of serotonin metabolite 5-HIAA in the macaques' brain after being placed into only female macaque groups. They found that rhesus macaques exhibited higher levels of aggression and had lower levels of serotonin in their brain fluid. The researchers also found that female monkeys with high levels of serotonin metabolite dominated macaques, in both species, with lower levels of serotonin. Moreover, researchers noted that low serotonin levels, while sometimes depicted as detrimental, may be the result of adaptation. Indeed, the most aggressive macaques lived in a much bigger social group in a much bigger environment, and as such they concluded "the resulting increased competition for resources may have led to higher rates of aggression in rhesus over evolutionary history

and suggests a possible adaptive purpose for the high rates of aggression in this species" (p. 446). A major conclusion from this study was that there is a link between serotonin hypofunction and aggressive behavior and that serotonin plays a role in controlling impulses and dominance in both male and female monkeys.

In 1994, Virkkunen et al. identified an enzyme known as tryptophan hydroxylase that catalyzes serotonin. Among violent offenders, they found tryptophan hydroxylase necessary to the proper functioning of the serotonergic system. They also found a relationship between this specific genetic variation and suicide attempts, and thus showed there was a link between the synthesis of serotonin from dietary tryptophan, serotonin hypofunction, and the likelihood of exhibiting more aggressive behavior. As a result, altering the elements of a diet which produces tryptophan may have behavioral consequences. Along a similar vein, Mehlman et al. (1994) found that macaques who were prevented from having tryptophan-containing food exhibited decreased serotonin levels and increased tendency for aggression and violence, especially during social interactions such as feeding or copulating.

Young, Pihl, and Ervin (1988) observed human subjects who drank a "special" beverage lacking tryptophan. They found that this special "unbalanced mixture not only deprived the body of new tryptophan for making serotonin, it also interfered with the body's utilization of the tryptophan already in the brain" (p. 212). To confirm these findings, Collins et al. (1998) gave this low tryptophan beverage to ten healthy men who were separated into two groups. The first group of men was administered a low dose of tryptophan beverage while the second group was given a higher dosage. After five hours, the higher-dose tryptophan male subjects exhibited aggressive behavior. Thus, reaction to

high tryptophan consumption showed that there is a relationship between drugs that alter the serotonergic system and the likelihood of exhibiting aggressive behavior.

Halperin and colleagues (1994) studied eleven-year-old boys with attention deficit hyperactivity disorder (ADHD) and aggressiveness. Both groups consumed fenfluramine, which alters serotonin levels in the brain and causes a loss in appetite (fenfluramine is often prescribed as an obesity cure). Boys who exhibited aggressive behaviors responded more strongly to the drug fenfluramine and the subsequent lowering of serotonin levels. This study confirms previous studies linking low levels of serotonin to the likelihood of aggressive and impulsive behavior, and also highlights the relationship between appetite-related drugs, lower levels of serotonin, and violent and aggressive behavior. Following this study and because of an apparent increase in the depression and suicide rates in the United States, researchers (and the general public) began paying greater attention to prescribed drugs, specifically anti-cholesterol drugs. Could it be that drugs intended to reduce the risks of stroke and heart disease led to greater depression, suicide, or premature death? Is serotonin the missing link when trying to explain the relationship between low cholesterol and the increase in aggressive behavior, depression and suicide?

Kaplan et al. (1994) observed young monkeys for eight months. Some were given a high-fat high-cholesterol diet and others a high-fat low-cholesterol diet. They found that the monkeys who were given the low-cholesterol diet had lower levels of serotonin and demonstrated a more aggressive behavior (such as more impulsive fights) compared to the monkeys who were given the high-cholesterol diet. They concluded by asking, “Can a low-fat, low-cholesterol diet actually do some people more harm than good?” (p. 479). Following this train of thought, can a low-cholesterol diet influence the behavior of

people who already have low levels of serotonin to the extent that they would engage in activities they would otherwise have avoided? There has been no specific study of this relationship but a few researchers have made some important assumptions.

Kaplan et al. (1994) described cholesterol as very important to brain cells and their membranes. They stated that “Primary prevention trials which have shown that the lowering of serum cholesterol concentrations in middle-aged subjects by diet, drugs, or both leads to a decrease in coronary heart disease have also reported an increase in deaths due to suicide or violence” (p. 823). In other words, overly reducing cholesterol may have a detrimental impact on the cells that contain serotonin receptors. Ploeckinger et al. (1996) used a physiological model of decreasing cholesterol concentration in humans to test its relationship to behavior. The study included 20 healthy pregnant women. They found a significant relationship between women having a lower cholesterol concentration in their blood and them experiencing postpartum symptoms such as depression. Indeed, women whose cholesterol concentrations dropped furthest after delivering their baby were more likely to experience postpartum depression. Thus, studies suggest that there is a relationship between low cholesterol and aggressive behavior (Hawthon, Cowen, Owens, Bond, & Elliott, 1993; Ploeckinger et al., 1996)

Steegmans et al. (1996) hypothesized that as a result of low cholesterol and low serum-free tryptophan, the synthesis of serotonin would be reduced. They studied 30,359 men aged 40 to 70 in Rotterdam in 1990 and 1991. They found that plasma serotonin levels in the low-cholesterol group surpassed those of the normal-cholesterol subjects, indicating disruption of serotonin synthesis due to a change in cholesterol concentration. Serotonin levels and cholesterol were a significant measure of central nervous serotonin

activity. It is also a major factor in increasing the risks of aggressive behavior and violent death. Moreover, there seems to be a relationship among low levels of cholesterol, violent and aggressive behavior, death, and how serotonin is metabolized.

When studying animals, especially rats, Pihl and Peterson (1993) found that some drugs designed to lower serotonin levels actually increased the consumption of alcohol. However, in cases where the same animals were injected drugs that contained serotonin or tryptophan, their alcohol consumption decreased. They did an inverse study to see if it would produce similar findings, and found that rats who had been raised to prefer drinking alcohol rather than water exhibited reduced serotonin activity in comparison to "normal" rats' serotonin activity. They also tested the theory on humans and found that chronic alcohol use appears to increase serotonin levels. However, they also found that levels of serotonin simultaneously decrease when drinking stops. Consequently, the decrease in serotonin and alcohol symptoms may contribute to simultaneous craving for alcohol. If the urge to drink is not satisfied, serotonin levels gradually recede.

There is little hesitation that important alcohol consumption and low levels of serotonin are a dangerous combination. But how does serotonin synthesis influence alcoholics' responses? What is it about serotonin synthesis that would make a person who chronically drinks more likely to have impulsive and violent responses? Pihl and Peterson (1993) speculated that serotonin may modify the response to threat. Anxiety is the normal response to threat. In their article, they described that humans who have normal levels of serotonin are less likely to respond violently to a threat or situation that increases their anxiety. On the contrary, humans with low serotonin levels will be unable to refrain from acting in a violent or aggressive manner when anxiety increases, even if people are

watching. Thus, chemical imbalances provoke emotional imbalances in people with low levels of serotonin. They stated that "people with low serotonin are likely to appear depressed and aggressive, more driven by appetites (food, water, sex, drugs), and more impulsive in the face of a threat (p. 115)." When it comes to alcohol, these researchers believed "The combination of impulsivity due to low serotonin, with alcohol-induced fearlessness and hyperactivity appears prone to produce aggressive acts or to culminate in victimization (p. 115)." Therefore, in some cases, it seems like low levels of serotonin may cause someone to not be able to stop drinking once drinking has started.

By examining the 1990s biochemical research on serotonin hypofunction and its consequences, would it be possible to find a way to reverse the serotonin insufficiency in an individual? Is there a way for an individual to have his or her serotonergic activity maintained at a most favorable level to decrease depression, alcoholism, aggression, violence, strokes, and appetite disorders? Some researchers suggested adding tryptophan to drinking water. Others sanctioned taking dietary supplements to reduce cholesterol and instead to have a balanced and healthy diet, and a reduction of soft drinks. The diminution of drinking alcoholic beverages would be one of the best answers to the question, "What are the most favorable things to do in order to decrease or never increase depression, alcoholism, violence and appetite disorder" (Pihl & Peterson, 1993, p. 115)?

Dopamine and Aggression

Dopamine is responsible for rewards and punishment, along with motivation and behavior regulation such as sensation-seeking or aggressive and impulsive behaviors (Everitt & Robbins, 2000; Ikemoto & Panksepp, 1999). Furthermore, it seems that animals' impulsivity tends to increase when their dopaminergic system is high such as

during a violent fight (Harrison, Everitt, & Robbins, 1997; Miczek, Hussain, & Faccidomo, 1998). The same is true for humans. When their dopaminergic system is high, they are more likely to experience aggression (Lawrence, Calder, McGowan, & Grasby, 2002). Thus, it is possible to say that dopaminergic hyperfunction is related to impulsive and aggressive behavior (Bergh, Eklund, Sodersten, & Nordin, 1997).

The relationship between dopaminergic hyperfunction and aggressive behavior has been found in studies of people with ADHD and personality disorders (Sostek, Buchsbaum, & Rapoport, 1980). It has been found that even for people who do not have ADHD, taking stimulants increase dopaminergic systems and consequently increase the likelihood of violent behavior. If a person's dopaminergic system is hyperfunctioning, he or she will be more likely to exhibit violent and impulsive behavior (Chotai, Kullgren, & Asberg, 1998). When dopamine levels are altered through the use of medication, results also reveal an impact on patients' aggressiveness and willingness to respond violently (Ossowska, Klenk-Majewska, & Zebrowska-Lupina 1996). On the other hand, drugs that have an antipsychotic effect are likely to lower the dopaminergic system and to lower the likelihood of aggressive and impulsive behavior in people who take them (Brizer, 1988). As a conclusion, even if the literature is not as advanced on the topic, there seems to be a relationship between dopamine and human aggressive.

Serotonin and Dopamine Interaction

In the human brain, serotonergic and dopaminergic systems interact anatomically and functionally. Specifically, serotonin's role is to modulate the dopaminergic system in the human brain (Kelland & Chiodo, 1996). When studying instances of withdrawal-related behaviors, serotonin and dopamine activities have been found to be determinant

(Wong et al., 1995). Indeed, higher levels of dopamine trigger the sensation-seeking aspect of an individual, whereas serotonin discourages such a behavior, thereby provoking a feeling of withdrawal from an exciting and sensational, but risky, activity (Daw et al., 2002). The fields of anatomy and pharmacology have been combined in order to better grasp the implications of the role that dopamine and serotonin can have on the human body. These fields have demonstrated how neurons and brain cells in contact specific to the dopaminergic system are also in contact with numerous serotonin neurons. As a result, at such a small level that a neuron is, that is where the behaviors are modulated through connections between serotonin metabolites and the dopaminergic system (Kapur & Remington, 1996). In other words, the serotonin receptors' role is to inhibit the dopaminergic activity in the brain when the system is in hyperfunction. Serotonin receptors will regulate dopaminergic levels in the brain, which will in turn regulate human aggressive and impulsive behavior. Thus, as serotonin can inhibit the dopaminergic system in the human brain, interactions between serotonergic and dopaminergic systems have been found to be a good frame of reference when analyzing impulsive and aggressive behavior (Shi, Nathaniel, & Bunney, 1995). Indeed, if there is a serotonergic hypofunction in the brain, regulation does not happen in the dopaminergic system and this dopaminergic hyperfunction may result in more impulsive and aggressive behaviors in humans. Van Erp and Miczek (2000) found similar results in their studies of rats. After a fight, rats' serotonin levels had decreased and dopamine levels had increased in their brains compared to before the fight. Other studies have looked at this inverse relationship and confirmed that there is a relationship between increased dopamine levels, decreased serotonin levels and impulsivity in rats (Ferrari, Van Erp, Tornatzky, &

Miczek, 2003; Harrison et al., 1997). Additionally, clinical studies on violent offenders and sex-offenders also illustrate the relationship between serotonergic hypofunction, dopaminergic hyperfunction, and exhibiting psychopathic tendencies (Kapur & Remington, 1996; Soderstrom, Blennow, Sjodin, & Forsman, 2003). These studies highlight the potential genetic basis of serotonin deficiencies, and its impact on human aggressive and impulsive behavior due to a lack of inhibition of the dopaminergic system.

Neuroanatomical Mechanism of Impulsive Aggression

Brain abnormalities

Aggression in humans is related to the idea that one cannot control their violent impulses. The part of the brain called prefrontal cortex is responsible for the processing and regulation of moods, emotions and behaviors (Davidson et al., 2000), and specifically exerts control over impulsive and aggressive emotions (Bechara, Tranel, & Damasio, 2000). Studies have even shown that people who exhibit antisocial behavior have a gray matter volume that is 11% lower in their prefrontal cortex compared to people who do not exhibit antisocial behavior (Raine, Lencz, Bihrle, LaCasse, & Colletti, 2000). Individuals with deficiencies in the prefrontal cortex are more likely to experience behavior regulation issues and to respond to a stressful situation using socially unacceptable behavior such as aggressiveness or violence (Bechara et al., 2000). This inability to face negative emotions and response in a socially acceptable manner have been found in patients with personality disorders (Goyer et al. 1994), murderers (Raine et al., 2000), and alcoholics (Hirono, Mega, Dinov, Mishkin, & Cummings, 2000).

These findings indicate that there is a relationship between prefrontal cortex deficiencies and the regulation of aggressive and impulsive behavior when a negative

(real or perceived) situation occurs. Brain imagining studies argue that prefrontal cortex connectivity experiencing hypofunction is related to defective behavior regulation, as activity in the amygdala will increase due to impaired functioning in the brain and will cause emotional deregulation and more aggressive behavior (Phan et al., 2005).

Emotion regulation and neural transmission

Serotonergic and dopaminergic systems are neurotransmitters that operate in the prefrontal cortex of the brain and are linked to emotion and behavior regulation (Biver et al., 1996; Daw et al., 2002; Kapur & Remington, 1996). Serotonin neurotransmitters are responsible for inhibiting neurotransmissions in the synapses of the prefrontal cortex – which are linked to mood, emotion and behavior regulation. After the administration of fenfluramine, healthy patients exhibited higher levels of activity in the prefrontal cortex, whereas patients who exhibited impulsive and aggressive behavior experienced lower activity levels in the prefrontal cortex (Frankle et al., 2005; Mann et al., 1996; New et al., 1997). Thus, a decrease in serotonergic activity in the prefrontal cortex will increase the likelihood of the regulatory system also being impaired, causing more aggressive and impulsive emotions. Furthermore, studies on people with personality disorders revealed that they exhibited a lower response to serotonin functions in their prefrontal cortex. Thus, there is a relationship between serotonin and aggressive behavior (Soloff, Meltzer, Greer, Constantine, & Kelly, 2000). Specifically, as the dopaminergic system is linked to rewards and punishments in the prefrontal cortex, its hyperfunctioning is likely to cause an increase in impulsive and aggressive behavior (Everitt & Robbins, 2000).

Overall, studies have demonstrated that when there is dopaminergic hyperfunction and serotonin hypofunction in the brain, subjects are more likely to exhibit aggressive

behavior (Everitt & Robbins, 2000. This is due to the fact that serotonin regulates the dopaminergic system and also has an impact on aggression. In studies of mammals, when there is an increase in the dopaminergic system due to a fight, levels of serotonin in the prefrontal cortex will decrease during and after a fight. Thus, if the serotonergic system is experiencing a dysfunction, the dopaminergic system will too, causing someone to have a harder time regulating emotions when in a situation of aggression, threat or discomfort. Nonetheless, more studies have been conducted about the role of serotonin on human aggression compared to the role of dopamine on human aggression. More research needs to be done on the matter (Van Erp & Miczek, 2000).

Aggression and Comorbid Disorders

Depression and aggression

Impulsive aggression can be highly comorbid. Disorders such as depression, anger substance abuse or suicides have been linked to impulsive aggression, whether if it is the same person experiencing both or a person who has been the victim of aggression. Koller et al. (2002) studied people who had experienced depression and found that 44% of such people had at some point experienced a violent encounter with another person. Research also has indicated that the response to being given the drug fenfluramine has lowered depression for depressed patients and aggressiveness in aggressive patients (Newman, Shapira, & Lerer, 1998). Additionally, if drugs to inhibit serotonin are given to patients, symptoms of aggressiveness and impulsivity are likely to increase (Zanarini, Frankenburg, & Parachini, 2004). Thus, lower levels of serotonin are linked to impulsive aggression, and are also linked to several of its comorbid disorders such as depression

(Newman et al., 1998). In conclusion, there is a relationship between serotonin hypofunction, human aggression and depression.

Suicide and aggression

People demonstrating suicidal tendencies also demonstrate greater impulsivity, irritability and aggressiveness. In their study of 625 humans, Conner, Meldrum, Wieczorek, Duberstein, and Welte (2004) presented support for the relationship between impulsivity, irritability, aggressiveness and suicide. In the study of mood disorders in humans, Michaelis and colleagues (2004) found that people with suicidal tendencies exhibited higher impulsivity and aggressiveness compared to people who did not have suicidal tendencies. Moreover, serotonergic hypofunction has been linked to impulsive aggression and its comorbid disorders such as suicide or suicide attempts (Coccaro & Siever, 2002; Mann et al., 1996). Further, brain-imaging research reported that people who had suicidal tendencies exhibited the same neurotransmission dysfunction in the prefrontal cortex as impulsive aggressive people. Thus, because of its inhibitory power in the prefrontal cortex, serotonin can have an impact on human aggression toward other humans but also toward their own selves (Kamali, Oquendo, & Mann, 2001). As a conclusion, the regulation of human aggression and suicide seem to happen in the same part of the brain: the prefrontal cortex and seem to be heavily influenced by the serotonergic system.

Substance abuse and aggression

Studies have demonstrated that substance abuse likely causes someone to experience impulsive reactions to situations. However, studies also demonstrate that impulsive aggression may not always be caused by substance abuse (Higley & Bennett,

1999). Thus, if someone experiences impulsive aggressiveness, he or she may also be more inclined to have substance abuse issues. As the prefrontal cortex play an important role in behavior regulation (Davidson et al., 2000), research on aggression and substance abuse, and brain imagining research were performed, and revealed that people with substance abuse issues exhibited poor control over impulsive behavior along with prefrontal cortex dysfunction, and in some cases with uncontrollable drug taking (Volkow et al., 2006). For instance, studies on cocaine usage have demonstrated how cocaine is responsible for modifications of the prefrontal cortex (Robinson, Galetta, McCluskey, Forman, & Balcer, 2001). Additionally, this prefrontal cortex alteration is associated with the inability to regulate impulsive and aggressive emotions. Similarly, brain imaging research has revealed a link between impulsive aggression, substance abuse and a biological dysfunction in the brain. Specifically, dopamine has been linked to the addictive feeling one often experiences after drug consumption (Volkow et al., 2006). As the dopaminergic system is involved in pleasure seeking, an impaired dopaminergic system can have detrimental consequences, such as processing drug taking as a good or pleasurable thing. Therefore, there is a relationship between aggressive behavior, substance abuse and a biological factor caused by an impaired dopaminergic system. However, results have been different for alcoholism.

Cloninger (1987) defined two types of alcoholism. Type I alcoholism is related to "a later age of onset and the presence of anxiety symptoms (p. 411)." Type II alcoholism is related to "an early age of onset, impulsivity, and antisocial behavior (p. 412)." Type I alcoholism appears with the dopaminergic system is hypofunction, whereas Type II alcoholism appears when the dopaminergic system is in hyperfunction. Since it has been

previously demonstrated that serotonergic hypofunction is related to dopaminergic hyperfunction (Everitt & Robbins, 2000; Kapur, & Remington, 1996; Van Erp & Miczek, 2000) the dopaminergic hyperfunction experienced in alcoholism of Type II may be explained by lower levels of serotonin. Higley and Bennett's (1999) study likewise supported such a statement, finding that monkeys with low serotonin metabolite concentration in the brain exhibited Type II alcoholism behaviors. These monkeys showed risk-taking behavior, impulsive and aggressive behavior, and consumed alcohol in large quantities (the study does not mention why alcohol was given to a monkey).

Studies demonstrate that low levels of serotonin facilitate the use of drugs and alcohol through the mechanism of facilitating impulsivity (Virkunnen et al., 1994). Specifically, low serotonin levels have been linked to a higher likelihood of Type II alcoholism compared to Type I alcoholism (Cloninger, 1987; Higley & Bennett, 1999). Thus, a lower serotonergic system impacts the dopaminergic system, which can then result in disinhibited behavior such as impulsivity, aggressiveness and substance abuse.

Conclusion

Impulsive aggression is linked to the idea that a person is incapable of refraining impulses to hurt oneself or hurt others when in a threatening or perceived threatening situation or when experiencing negative emotions (Davidson et al., 2000; Seo et al., 2008). Serotonergic hypofunction in the prefrontal cortex has been linked to increase the likelihood of aggression and its comorbid disorders such as depression, suicide, anger and suicide (Koller et al., 2002; New et al., 1997; Placidi et al., 2001; Ploeckinger et al., 1996). Additionally, low levels of serotonin in the human brain can cause levels of dopamine to increase, causing a higher likelihood of aggressive responses to a stressful,

threatening or negative situation (Miczek, Fish, De Bold, & De Almeida, 2002). Serotonin has an inhibitory effect on dopamine. If the serotonergic system is impaired, it will result in dopaminergic hyperfunction, failure to regulate one's behavior which can cause someone not to be able to regulate their emotions and to react violently or exhibit aggressive tendencies toward oneself or others (Everitt & Robbins, 2000). Moreover, dopaminergic hyperfunction has been linked to a higher likelihood of substance abuse such as drugs and alcohol abuse (Koller et al., 2002).

Understanding how the brain functions is primordial to identify what causes aggression, and to find an effective treatment strategy. Pharmacological research indicates that drugs which regulate serotonin receptors could increase serotonin levels, decrease dopamine levels, and reduce aggressive behavior (Miczek et al., 2002). This biological component of explaining aggression in humans must be coupled with findings on the social environment, which plays an equally important role in regulating aggression (Raine et al., 2000). Treatment for aggressive behavior should consider the impact aggressive impulsive behavior has on other comorbid disorders and the environment in which one would be experimenting new treatment (Miczek et al., 2002).

Future research should pursue the identification of which genetic factors are the highest predictors of aggressive behavior in humans. Learning more about the human brain is invaluable when trying to understand why some people are more likely to exhibit aggressive behaviors than others and finding treatment to help people regulate their negative emotions (Seo et al., 2008).

CHAPTER III

METHODOLOGY

Overview

Since the 1980s and the study by Brown, Goodwin, Ballenger, Goyer and Major (1979), there has been considerable enthusiasm for identifying the neurochemical origins of human aggression. They discovered that the neurotransmitter serotonin was a major predictor in human aggression, and suggested that serotonin hypofunction resulted in an increase in aggressive behavior for a group of military men diagnosed with personality disorders. A decade later, when studying the prefrontal cortex, researchers found that several neurotransmitters other than serotonin were related to aggressive behavior (Barrett et al., 1990). Therefore, chemical imbalances in the prefrontal cortex (such as serotonin hypofunction, dopamine hyperfunction, or a dysfunction in the levels of norepinephrine or testosterone in the human brain) were found to increase the likelihood of aggressive behavior (Giammanco et al., 2005; Raine et al., 2000; Shi et al., 1995).

This study focuses solely on the role of serotonin and dopamine imbalances in the likelihood of aggressive behavior in humans. Reporting relationships between serotonin and dopamine systems will provide a framework to better understand why some people are more likely to express impulsive aggression. Hence, a systematic review of modern literature in regard to these serotonin and dopamine functions will be provided.

Method

The System Literature Review

To provide evidence-based practice on how to treat a symptom or a deficit, researchers, professionals, physicians and other professions will turn to the most recent

literature. As White and Schmidt (2005) wrote, reviewing literature can "provide the historical background on a particular style of reflexology to finding out how safe or effective a particular treatment is (p. 54)." The purpose of a literature review is to research, summarize and present the latest findings on a specific topic. This method is used to sift through vast amounts of information and resolve questions about strategies that work or do not work. Literature reviews also identify niches in the field of research where new studies need to be conducted.

Petticrew and Roberts (2006) argued that

> The science of systematic reviewing for social policy purposes is still relatively young, and we do not assume that systematic reviews as presently constituted are perfect, or that they are appropriate for all purposes. Nor do we assume that every review has to be 'systematic' to be useful (or even that every 'systematic' review is useful). We therefore acknowledge and discuss the limitations of systematic reviews, and the criticisms that have been made of them. However, we believe that they can be used more widely than at present, can often be made more useful, and are essential scientific tools that any scientist (social or otherwise) should know how to use. (p. 6)

It is important to distinguish between genuine and assumed knowledge. The systematic review is based on clearly formulated questions such as: What are the prevailing definitions of serotonin, dopamine, and aggression? What are the effects of serotonin and dopamine on human aggression? What is the nature of the relationship between serotonin and dopamine regarding human aggression? Through what processes do neurotransmitters influence the risk of human aggression? Thus, systematic reviews of

the literature can identify relevant information to help researchers create new knowledge based on what we already know. Literature reviews also help in putting research into context, into perspective. It helps identify the different research questions within a research or the important points that are made and may be overlooked because of the mass amount of information that is produced every day (Cooper & Feldman, 2010).

Why is a systematic literature review needed?

Because of the plethora of published articles on any given subject, it has become increasingly difficult to keep pace with primary research (Hemingway & Brereton, 2009). Increased Internet access to published articles has created a plentitude of "hits" to read or skim through. In addition, all the research on a given topic is not regrouped in one place, sometimes it can take hours to dig through all the different software and internet sites to find the grail of research. Additionally, reviews of the literature can be of different kind. The type of reviews that helps to compile the most recent and accurate research on a topic is called a "systematic review" (Cooper & Feldman, 2010). This type of review has a rigorous procedure that allows any researcher to gather information the same way and end up with the same (or almost the same) list of relevant articles for their research. Thus, systematic reviews can be replicated and the results will likely be the same no matter who does it (Antman, Lau, Kupelnick, Mosteller, & Chalmers, 1992).

As a result of the rapid increase in publications concerning the role of serotonin and dopamine on human aggression, the present study will index and summarize the plethora of recent literature which has been published on the topic.

Procedures

The main steps for carrying out a systematic review can be summarized as follow (Higgins & Green, 2006):

- Step 1: define search terms.
- Step 2: identify data bases and search engines.
- Step 3: determine which filters will be applied to include and exclude articles.
- Step 4: make sure that the articles found are relevant and representative of the study by repeating the first three steps.

In a systematic literature review, the protocol needs to be carefully documented in a transparent manner so any researcher can replicate the process and obtain the same results. This process increases a study's external validity (Higgins & Green, 2006).

This study reviewed literature published during a twenty year time frame (from 1992 to 2012). The research questions guiding this study were:

- What are the prevailing definitions of serotonin, dopamine, and aggression?
- What are the effects of serotonin and dopamine on human aggression?
- What is the nature of the relationship between serotonin and dopamine with regard to human aggression?
- Through what processes do neurotransmitters influence the risk of human aggression?

All available and pertinent research databases were searched online using the EBSCO search engine. The 16 databases were Academic Search Premier, PsycINFO, Psychology and Behavioral Sciences Collection, CINAHL (full text), SPORT (full text), Criminal Justice Abstract (full text), SocINDEX (full text), Education source, Health source: Nursing/Academic Edition, Environment Complete, MasterFILE Premier,

Business Source Complete, ERIC, Green File, Human Resources Abstracts, and Legal Collection.

The key terms “aggression,” “serotonin,” and “dopamine” were introduced to cull articles from peer reviewed academic journals published between 1992 and 2012. This procedure produced 276 articles. Major headings of the articles were then examined for the words “aggression,” “serotonin,” and “dopamine”. This procedure generated fifty relevant articles.

Despite the significant amount of literature devoted to aggressive behavior in animals, this systematic review focused solely on aggressive behavior in humans. The literature review examined research about humans and animals to better contextualize the evolution and the degree of progress in researching the role of serotonin and dopamine on aggression. Consequently, the total number of articles for the systematic literature review was re-evaluated. All 50 articles containing the words “serotonin”, “dopamine”, and aggression were examined. Articles whose main research focus was on animals were deleted. As a result, the number of relevant articles for this study (articles focusing on human aggression) decreased to 24. An additional article published in Italian was likewise excluded. Figure 1 illustrates the method used to select relevant articles for this study. Figure 2 displays the repartition of the 23 articles relevant to this study during the twenty-year period from 1992 to 2012.

Systematic reviews of the literature are very common when developing research. For instance, Niazi, Ikram, Bano, Imtiaz, and Khan (2013) published a systematic literature review about computers using 18 sources. Krause, Subklew-Sehume, Kenyon, and Colebunders (2013) published a systematic literature review about the acceptability

of HIV self-testing, using eleven articles. As a result, the 23 articles for this research appear to be an acceptable number.

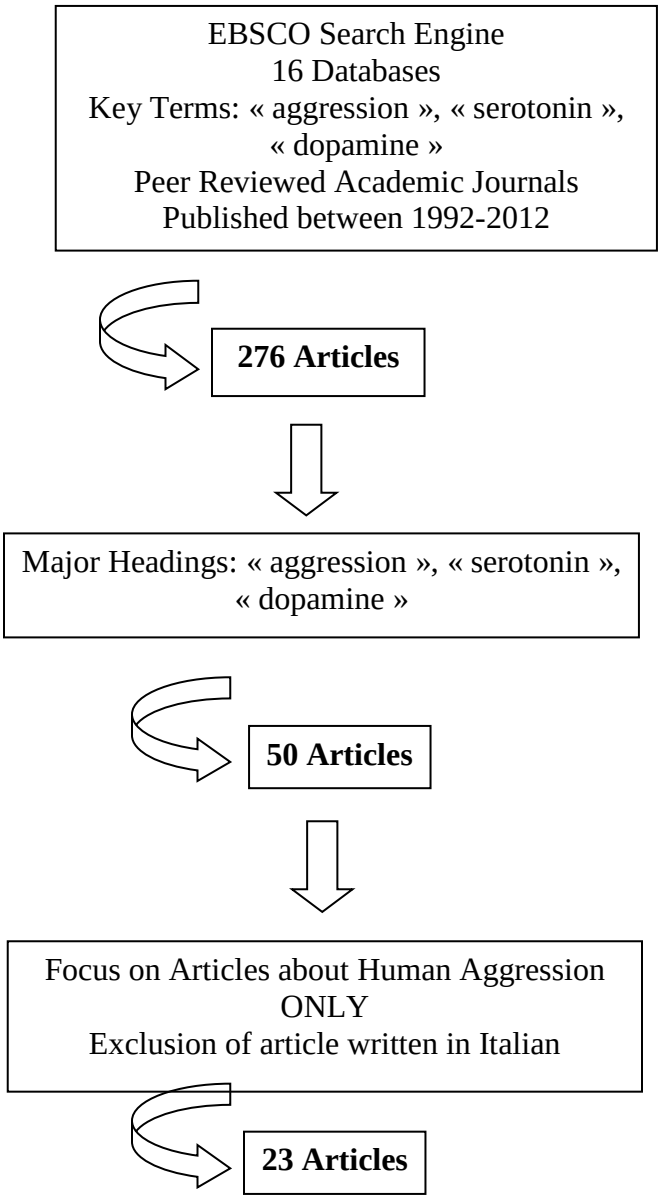

Figure 1. Selection of relevant articles. This figure illustrates how relevant articles for this study were selected.

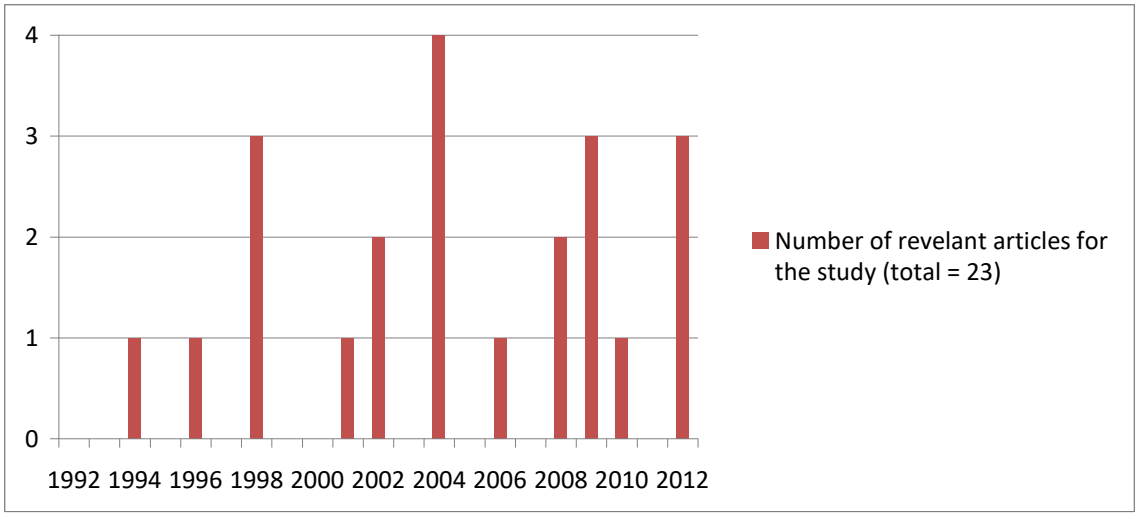

Figure 2. Distribution of relevant articles: 1992-2012. This figure illustrates how recent studies on the impact of serotonin and dopamine on human aggression have been.

Data Analysis

This study's systematic review of the literature on the role of serotonin and dopamine on human aggression from 1992 to 2012 analyzed and summarized the content of 23 articles (Figure 1). Coding sheets were created to define the relationship between serotonin and dopamine and their role on human aggression. The coding sheets incorporated relevant information from previous studies, appraised their quality, and summarized the findings in tabular form. Conclusions were drawn about the cumulative state of research on the role of serotonin and dopamine on aggression.

Each article was indexed and summarized within a coding sheet with 12 sections:

- Title
- Author
- Journal Name
- Year Published
- Purpose of the article

- Research Question(s)/Hypothesis(es)
- Methodology used by the researcher(s)
- Key Variables (Independent and Dependent Variables)
- Findings
- Outcomes
- Comments or key thoughts about the article
- Source and full reference

The "Outcomes" section was divided into several subsections:

- How are aggression, serotonin and dopamine defined?
- Is there a relationship between serotonin and dopamine being described in the article? If so, how is it described?
- How is the impact of serotonin and dopamine on aggression explained?

Each coding sheet was then placed into a computerized table in order to ensure that a clear representation of the literature concerning the role of serotonin and dopamine on aggression during the past 20 years could be visualized.

Limitations

While the systematic review of the literature process is a very thorough strategy, limiting key words in the search engine restricts the scope of the relevant literature for this study. A second potential limitation is the exclusion of non-journal articles which may contain important information from valuable sources other than published literature. Excluding research articles on aggressive behavior in animals may have led to the exclusion of some important parallels between animal and human aggressive behavior.

CHAPTER IV

FINDINGS

After analyzing 23 scholarly articles, the current study produced mixed results. Appendix A illustrates the findings for each article. One article was a study on rats. However, the decision was made to keep the article for the purpose of the study because of the numerous parallels drawn between findings in animal study and findings in human study. Moreover, a few articles reviewed some of the literature on certain area of interest for this study. Since the reviews were very thorough, the reader was under the impression that the researchers actually led the research they are describing. Consequently, the decision was made to keep these articles because of their value to the study.

What are the prevailing definitions of serotonin, dopamine, and aggression?

Serotonin is defined several different ways depending on the context. Longe (2006) defines serotonin as "a chemical produced by the brain that functions as a neurotransmitter." According to the research articles selected for this study, "Serotonin is one of the main neurotransmitters…whose actions contribute to virtually all aspects of behavior and cognition" (Damasio in Levinson et al., 2004, p. 490). "Serotonin is a fundamental neuromodulator in both vertebrate and invertebrate nervous systems, with a suspected role in many human mental disorders" (Tops et al., 2009, p.1). Additionally, Seo et al. (2008) define the neurotransmitter serotonin as "exerting an inhibitory action in the brain and is deeply involved in the regulation of emotion and behavior, including the inhibition of aggression" (p. 384). Therefore, serotonin is one of the major neurotransmitters in the prefrontal cortex influencing mood regulation (Schmidt, Fox, Rubin, Hu, & Hamer, 2002). Consequently, a dysfunction in the serotonergic system can

have severe consequences such as low self-control, mood swings, and low self-esteem (Hohmann et al., 2009; Tops et al., 2009).

Dopamine as defined by Seo et al. (2008) is a "system is involved in behavioral activation, motivated behavior, and reward processing. It also plays an active role in the modulation of aggressive behaviors" (p. 386). Dopamine is related to mechanisms of reward and punishment; once a goal is achieved, a person should feel pleasure in the fulfillment of the goal (Berman & Coccaro, 1998; Friedel, 2004; Schmidt et al., 2002).

Aggression is expressed by Miczek and colleagues in 2002 as behavior that "relies on the intent to harm someone being motivated by fear, anger, or pleasure (p. 435)." Behavioral scientists define aggression as "an overt behavior, the goal of which is to inflict harm or injury" (Berman & Coccaro, 1998, p. 304). Hohmann et al. (2009) argued that "Aggressive behavior defined as behavior that causes or threatens physical harm to others often occurs in the context of other types of antisocial behaviors, such as lying, stealing and truancy, and is an essential component of the diagnosis of conduct disorders" (p. 1621). They added "Aggressive behavior in young people is highly predictive of violence in adulthood and is strongly associated with a greater risk of alcohol and drug abuse, accidents, violent crimes, suicide attempts, and depression" (p. 1621).

Baron defined aggression as "any form of behavior directed towards the goal of harming or injuring another living being which is motivated to avoid such treatment" (cited in Felthous, Barratt, & Kent, 1994, p. 133). "Antisocial aggression" behaviors are directed toward harming another living being, or the destruction of useful property, after thoughtful consideration and with the purpose of self-gain. "Impulsive aggression" refers to behaviors directed toward the injury or harm of to another living being, or the

destruction of useful property, with little evidence of thoughtful consideration or self-gain trough the deed except for the reduction of tension (p. 133).

According to Seo et al. (2008), "Impulsive aggression is a behavioral disposition characterized by the inability to regulate negative affect and impulses to harm oneself or others. It is highly comorbid with depression, substance use, and suicidal behaviors" (p. 395). They added "Impulsive aggression plays a critical role in the manifestation of violent and criminal behavior and is considered an important psychopathological symptom of several mental disorders including borderline and antisocial personality disorders" (p. 383). As a result, it is possible that aggressive behavior is a multifaceted phenomenon that involves different components such as genetics, neurology, biology, and psychology and can be the result of a dysfunction in the serotonergic system and/or the dopaminergic system (Comai, Tau, Pavlovic, & Gobbi, 2012).

What are the effects of serotonin and dopamine on human aggression?

Research has demonstrated that there is a relationship between the dopaminergic and serotonergic systems and human aggression (Butovskaya et al., 2012). For instance, Seo and colleagues (2008) argue that "Serotonin hypofunction may represent a biochemical trait that predisposes individuals to impulsive aggression, with dopamine hyperfunction contributing in an additive fashion to the serotonergic deficit" (p. 383). Thus a dysfunction in the serotonergic system can cause someone to experience lower self-esteem, swinging moods, and lower self-control (Tops et al., 2009). Recent research on Alzheimer's and schizophrenia suggest that deficits in the serotonergic system can also be associated with psychosis and aggression in patients exhibiting signs of Alzheimer's disease and schizophrenia (Glazer & Dickson, 1998; Mintzer, 2001).

Both serotonin and dopamine have been linked to personality characteristics (Hennig et al., 1998). Specifically, a dysfunction of the serotonergic system and or dopaminergic system has been associated with impulsive as opposed to premeditated aggressive behavior. This association between the dysfunction of serotonergic and dopaminergic systems and aggressive behavior has been observed in different categories of individuals (such as psychiatric patients, criminal offenders, and children who experienced abuse). Surprisingly the association was also observed in healthy patients (Comai et al., 2012). This suggests that some form of abuse or aggression experienced at an earlier age can cause a dysfunction in one or both systems, and increase the likelihood of aggressive behavior during adulthood.

What is the relationship between serotonin and dopamine regarding human aggression?

Seo et al. (2008) argue "dysfunctional interactions between serotonin and dopamine systems in the prefrontal cortex may be an important mechanism underlying the link between impulsive aggression and its comorbid disorders in that decreased serotonergic activity in the context of aggressive behavior is closely associated with increased dopamine activity (p. 387)." Essentially, then, as serotonin levels go down, dopamine levels go up and may influence the inhibition of aggressive behavior. In other words, if the dopaminergic system is so dysregulated by serotonin hypofunction, the exacerbated dopaminergic activity can cause more sensation seeking, and violent and aggressive behavior (Hohmann et al., 2009). As serotonin seems to balance dopamine increases and decreases in the body, and as dopamine is associated with novelty seeking, aggression and emotional reactivity, a body having more dopamine and less serotonin is

more likely to respond to external stimuli with aggressive responses (Berman & Coccaro, 1998; Hennig et al., 1998).

Through what processes do neurotransmitters influence the risk of human aggression?

Research has shown that there is a relationship between serotonin hypofunction and aggressive behavior (Glazer & Dickson, 1998). Additionally, biological research has produced interesting results linking serotonin dysfunction and genes. The serotonin transporter gene interacts with self-control, and thus a dysfunction in serotonergic transporters likely will produce a chemical imbalance in the body, which may result in a higher likelihood of aggressive behavior (Kochanska, Philibert, & Barry, 2009). A functioning serotonergic system is important, especially when unpleasant events occur. Serotonin helps balance chemicals in the brain to avoid feelings of depression or anxiety frequently caused by severe psychosocial stressors (Tops et al., 2009).

Hohmann and colleagues (2009) demonstrated the association between low levels of 5-HTT (serotonin neurotransmitter) and an increased rate of aggressive behavior. As the prefrontal cortex corresponds to areas of the brain related to judgment, impulses and impulsive behaviors, people exhibiting low levels of 5-HTT in the prefrontal cortex were shown to have a higher likelihood to respond with antisocial and aggressive behaviors. Therefore, people exhibiting a dysfunction in the orbital region of their brain had restricted foresight, failure to plan, and indifference over difficulties, which are characteristics that can lead to antisocial and aggressive behaviors. People who presented neuropsychological deficits and lower brain activity are likely to develop aggressive responses to negative stimuli (such as the presence of violence, discrimination or what they perceive as an aggressive environment). Oppositely, when the environment is prone

to positive stimuli, they are more likely to have a positive response to that environment (Simons et al., 2012).

CHAPTER V

DISCUSSION

Interpretation of the Data

Research indicates that there are more than 50 molecules that are related to human aggression, of which serotonin and dopamine serve as the two major neurotransmitters used to study human aggression. Serotonin is the more extensively studied of the two neurotransmitters, and its hypofunction in the human brain has clearly been linked to a higher likelihood of aggression. Therefore, there is a biological component to explaining crime and delinquency. The human brain is a complex actor in understanding aggression but without it, we would miss a very important part in explaining why some people are more likely to react aggressively to a situation compared to others.

In combination with one's environment, studying the brain and biological factors around it has been on criminologists' agenda to have a better understanding of human behavior. Thus, studies have revealed that some people are genetically more inclined to be sensitive to their environment, this is referred to as "differential susceptibility model" (Simons et al., 2012). Because of the availability of data on genetics, researchers in behavioral neurobiology, psychology and social behavior, child development and family relationships, cognitive psychology, and neuropsychobiology have drawn similar conclusions on the impact that genetics can have, in combination with social context, in explaining aggressive behavior in humans.

Overall, definitions of serotonin remained consistent across the articles. Often times the definitions provided great detail while equally often providing only simplistic detail, such as "Serotonin is one of the main neurotransmitters…whose actions contribute

to virtually all aspects of behavior and cognition" (Damasio in Levinson et al., 2004, p. 490). Serotonin and dopamine have been shown to be related with serotonin having a regulatory function on dopamine. In instances of aggression and depression, the brain exhibited a chemical imbalance, with lower serotonin levels and higher dopamine levels. When that is the case, individuals will be more likely to engage in violent or aggressive responses when faced with a stressful or what is perceived as being a threatening situation. On the contrary, when serotonin levels are high, people will experience a state of lethargy with a decreased feeling of motivation to do anything.

Studies using drugs and placebos to increase serotonin levels in human bodies have concluded that some drugs modulate the serotonergic system, and in turn attenuate the likelihood of aggression in human behavior. If the serotonin inhibitors are modified, this will likely have an impact on human aggression. Specifically, if serotonin levels are being better balanced, violent individuals may be less likely to feel as if they were completely out of control and could not stop themselves from committing violent acts.

On the other hand, dopamine has been described as acting on motivation, rewards and the regulation of aggressive behavior. Unfortunately, much less research has been done on dopamine and its role in modulating aggressive behavior. There also is very little research regarding the similarities of the functions of dopamine and serotonin receptors, such as whether higher dopamine levels inhibit the effects of serotonin, or whether low serotonin levels elevate dopamine levels.

Definitions of aggression appear to vary across the spectrum of articles. Although essentially the same, some authors made distinctions between "impulsive" and "antisocial" aggression. Felthous et al. (1994) defined "antisocial aggression" as

"behaviors directed towards the harm of another living being or the destruction of useful property after thoughtful consideration with self-control and with the purpose of self-gain" (p. 133); "impulsive aggression" was defined as "behaviors directed towards the injury or harm of another living being or the destruction of useful property with little evidence of thoughtful consideration, of self-control, or of self-gain trough the deed except for the reduction of tension" (p. 133). "Maladaptive behaviors" and "inappropriate behaviors" are terms which for years have been applied to problem behaviors.

Aggressive behavior in humans can have detrimental effects on society. As a result, young people are often labeled as aggressive or violent – a stigma which ultimately may exclude them from society, especially for juveniles with intellectual disabilities. Unfortunately, little research has been conducted on the impact of serotonin hypofunction on children and adolescents. Studies of shyness and anxiety have been conducted but nothing concrete has been extracted about such a relationship between juvenile delinquency and aggression.

Theory Implication

Studies of aggressive behavior have rarely been based on theory. "While they might have been more closely linked to theory when they were initially proposed, these models have often been restated and reinterpreted, and the original tight linkage with theory is lost. This process is analogous to repeatedly copying copies of originals; over time, the original signal is attenuated, and the meaning can be lost" (Sales, Smith, Curran, & Kochevar., 2006, p. 44). Biosocial and biochemical criminologists give greater credit to theory. As Robinson and Beaver (2010) argued, "The empirical evidence indicating that antisocial behavior is partially influenced by genetic factors has spawned some

theorists to advocate for an integration of behavioral genetic findings into mainstream criminological theories" (as cited in Barnes et al., 2011, p. 925).

As van den Berghe (1974) predicted, evidence exists on the relationship between biology, sociology and human aggression. A combination of environment and human biology explain more about human aggression and crime than when singularly examined. There is a relationship between serotonin and dopamine in explaining human aggression; however, other factors also must be considered. Genetic variability, social environment, ADHD, use of drugs or alcohol, diet, pre-natal / post-natal malnutrition, drugs during pregnancy, and traumatic brain injury all may increase the likelihood of externalizing aggressive behaviors. Using existing biosocial and biochemical theories of criminal behavior, along with empirical support from 23 articles, this study aims to benefit anyone interested in exploring the role of serotonin and dopamine on human aggression.

Limitations

Studies on the role of serotonin on human aggression are recent, but have already been highly criticized due to their reliance on self-reported data from small sample sizes, or the lack of consideration for certain confounding factors. For instance, few studies included females, which made the generalizing of such findings quite problematic. Much research lacked psychopathological concepts and instruments related to the definition of aggression. Additionally, because several different definitions of aggression are used, resulting measures are not precise, and thus inhibits assumptions due to errors in measurements. There is a need for better methodologies in studies analyzing the role of serotonin and dopamine in human aggression. Moreover, more clinical studies need to be conducted to confirm previous findings that serotonin hypofunction and dopamine

hyperfunction in the brain are linked to a higher likelihood of human aggression. Specifically, certain drugs can influence chemical imbalances in the prefrontal cortex. For example, there are no drugs directed toward specific dopamine or serotonin receptors; but some studies have proven that antipsychotic drugs (such as clozapine) have an impact on the dopaminergic system, and if used reasonably, perhaps such antipsychotic drugs can help regulate imbalances in the brain and impact aggression.

More research needs to be developed to discover why so many patients with psychiatric disorders also share a tendency for aggression. Is aggression the common denominator or is it psychiatric disorders? If researchers find which comes first, treatment can then be oriented toward reducing one tendency to reduce the other one and improve people's quality of life and reduce violence and maybe crime in the long term.

APPENDIX A

ANALYSIS

Article Name	**Author(s)**	**Journal Name**	**Date**	**Research Question(s)**	**Method**	**IV/DV**	**Definitions**	**Findings**
Aggression, Digit Ratio, and Variation in the Androgen Receptor, Serotonin Transporter, and Dopamine D4 Receptor Genes in African Foragers: The Hadza.	Butovskaya, M. L., Vasilyev, V. A., Lazebny, O. E., Burkova, V. N., Kulikov, A. M., Mabulla, A., Shibalev, D. V., & Ryskov, A. P.	Behavior Genetics	2012	Lower allelic frequency in AR genes differs depending on the population. Men with lower serotonergic activity are more likely to exhibit a higher 2D:4D ratio on the right hand and exhibit more aggressive behavior.	Study of the Hadza population Interviews with Aggression Questionnaire: 29 statements grouped into 4 subscales: physical and verbal aggression, anger and hostility. Anthropometric measurements (p. 651). Buccal	<u>IV:</u> Heritability Finger ratios associated with androgen receptor alleles <u>DV:</u> Aggression Competition for sexual partners among men	The serotonin transporter (5-HTT) plays an important role in serotonergic neurotransmission by facilitating the reuptake of 5-HT from the synaptic cleft (p.652).	The dopaminergic system serves as an important pathway to pathological aggression in childhood and adolescence (p. 649). The D4 human dopamine receptor plays an important role when examining aggression. AR gene polymorphis

					epithelium samples for DNA analysis (p. 651). Data analysis via SPSS-13 for Windows (p. 652).			m is not directly involved in the link between testosterone exposure and the degree of sexual differentiation (p. 654). Results were obtained from a population very different than the human population we are accustom to. Indeed, the selected population is still one conducting a foraging lifestyle. Because of

								their harsh environment and little access to medical care, they are the subjects of a very harsh selection process. As such, their way of life calls for an egalitarian culture favoring all individuals on the same level. Thus, aggressive behavior is not common in this type of culture. Nobody is competing for power. Masculinity and aggression are present

								in this culture, which explains not finding a relationship between low DRD4E3, lower 2D:4D and aggressiveness in this culture.
Role of Serotonin and Dopamine System Interactions in the	Seo, D., Patrick, C. J., & Kennealy, P. J.	Aggression and Violent Behavior	2008	Neurochemical bases of impulsive aggression, with a particular	Review of literature	IV: Neurochemical mechanisms Dysfunctional brain	Impulsive aggression is characterized by an inability to regulate	Structural and functional brain imaging studies

Neurobiology of Impulsive Aggression and its Comorbidity with other Clinical Disorders.				focus on interactions between the serotonin and dopamine systems. Review of neuroanato mical bases of impulsive aggression with an emphasis on structural and functional abnormalitie s in the prefrontal cortex. Description of the role of serotonin and dopamine systems associated with		regions <u>DV:</u> Impulsive aggression and its comorbid disorders	affect as well as aggressive impulses, and is highly comorbid with other mental disorders including depression, suicidal behavior, and substance abuse (p. 383). The neurotransmit ter serotonin can inhibit aggression and plays a role in the regulation of emotions (p. 384). The dopaminergic system is involved in	indicate that hypofunction ing of the PFC, particularly the orbitomedial area, is related to impaired regulation of emotion and aggressive behaviors (p. 388). Borderline personality disorder (BPD) showed decreased responses to serotonergic stimulation in the prefrontal cortex, in particular the medial and orbitofrontal

				emotion regulation.			behavioral activation, motivated behavior, and reward processing. It also modulates aggressive behaviors (p. 386). Impulsive aggression is a behavioral disposition characterized by the inability to regulate negative affect and impulses linked to depression, substance use, and suicidal behaviors (p. 395).	488666PFC (p. 389). Serotonergic function can have comorbid consequences. Low serotonin activity is associated with high-lethality suicide attempts, as well as impulsive and aggressive behaviors (p. 390). Serotonin hypofunction has been implicated as a possible

								source of comorbidity in individuals with depression and accompanying impulsive aggression (p.390). Abnormalities, specifically in the dopaminergic system, have been observed in individuals at risk for aggressive behavior as well as substance abuse (p. 391). This study demonstrates the

								importance of identifying risk factors that are conducive to impulsive aggressive behavior. To do so, research needs to look at ways to make the environment people live in better along with finding appropriate treatment for people who exhibit symptoms of impulsive aggressive behavior. Treatment for impulsive

								aggressive behavior should consider comorbid factors associated with violent, aggressive, impulsive behavior. Additionally, this study shows that developing neurobiologi cal measures of genetic risk factors conducive to aggressive, impulsive behavior would be a great asset to finding the best treatment for each stage of the

								neuropsychological disorder that is serotonin hypofunction and dopamine hyperfunction (and its consequences of higher likelihood of aggressive and impulsive behavior)
Social Adversity, Genetic Variation, Street Code, and Aggression: A Genetically Informed Model of Violent Behavior.	Simons, R. L., Lei, M. K., Stewart, E. A., Brody, G. H., Beach, S. R. H., Philibert, R. A., & Gibbons, F. X.	Youth Violence Juvenile Justice	2012	How much does genetics account for some of the differences in response to a hostile/demoralizing environment (p. 4)? Environmental	Longitudinal data collection of hundreds of African American males (p. 3) data from waves 2 (1997-1998; and 1999-2000) through 5 FACHS (p. 9).	<u>IV</u> Social environment Genotypes Community violence Exposure to discrimination Family environment <u>DV</u> Commitment to the		Strong support for the differential susceptibility perspective. Adverse environmental conditions are more likely to lead to problem behaviors when

				conditions interact serotonin and dopamine alleles in a "for better or worse" manner to predict violent and illegal behavior (p. 5). The extent to which genetic polymorphisms modulate the effect of a hostile, demoralizing environment on adoption of the street code and aggressive behavior in a manner	Analysis of how having differences in serotonin and dopamine alleles can modulate the effect of the environment on the adoption of the street code and aggression (p. 3). Why humans with particular variants serotonin and dopamine alleles show higher rates of aggression	street code Aggression		individuals possess a particular genotype (p. 4). Some people's genes will have an impact on whether or not they are sensible to the environment around them. Individuals high on genetic plasticity showed greater violence than other genotypes in response to an adverse environment (p. 15).

				consistent with the differential susceptibility hypothesis (p. 6). Individuals with a combination of l-allele DRD4, s-allele 5HTTLPR, and l-allele MAOA to score higher than others on code of the street when hostile and demoralizing conditions are highly prevalent, but to score lower than others on code of the street in the	no matter the environment. Two-hour long questionnaires were administered in the respondent's home (p. 10). Regression models were employed to test the differential susceptibility hypothesis (p. 12).			Overall, this study highlights the fact that a lot of people are predisposed in their genetic make-up to respond to their environment. Thus, genetics and social environments need to be more studied and more tested in order to have a greater understanding of human impulsive and aggressive behavior.

				absence of such adverse conditions (p. 9).				
Social and neural determinants of aggressive behavior: pharmacotherapeutic targets at serotonin, dopamine and γ-aminobutyric acid systems.	Miczek, K. A., Fish, E. W., De Bold, J. F., & De Almeida, R. M. M.	Psychopharmacology	2002	Focus on the behavioral characteristics and determinants of intense aggression will ultimately produce a more adequate clinical approach to aggression (p. 435). How antecedents and consequences modify aggressive behavior (p. 436). What are the	Examine new pharmacological and molecular tools that target the neural mechanisms for different kinds of aggressive behavior more selectively than previously possible, and to outline potential pharmacotherapeutic opportunities (p. 435).	<u>IV:</u> Serotonin Dopamine γ-aminobutyric <u>DV:</u> Aggressive behavior	The most general definition of aggressive behavior relies on the intent to harm (p.435). Psychological approaches portray aggressive behavior as being motivated by fear, anger or pleasure (p. 435).	The dynamic changes in frontal cortical serotonin that are triggered by engaging in aggressive behavior show that the receptors' state is important when the drug is administered (p. 434). Serotonin deficiency is mostly found in individuals who engage in aggressive behavior in

				implications for neurobiological mechanisms of aggressive behavior (p. 440). Focus on antipsychotic drugs (p. 446).	Focus on antipsychotic drugs (p. 446).			an impulsive manner (without regard for its consequences) rather than in individuals with other forms of aggressive behavior (p. 441).
Molecular genetics of shyness and aggression in preschoolers.	Schmidt, L. A., Fox, N. A, Rubin, K. H., Hu, S., & Hamer, D. H.	Personality and Individual Differences	2002	Whether children with long alleles for their dopamine receptors would be defined by their mothers as exhibiting more aggressive behaviors at 4 years old.	Followed four separate cohorts of children who have been participating in a larger longitudinal study on socio-emotional development (p. 228).	IV: Molecular genetic differences in childhood development DV: Shyness Aggressive social behavior	Dopamine has been implicated as a major neuromodulator of novelty seeking because of the role it plays in inducing euphoria in humans (p. 229). Serotonin has	Children with long alleles for their dopamine receptors were defined by their mothers to have significantly more problems with aggression at age four

				(p. 230). Whether children with short alleles for their serotonin receptors would be defined by their mothers are shyer at four years old (p. 230).	Collect DNA samples (p. 228). Complete data on 161 children (p. 230). Maternal perceptions of childhood behavior problem were assessed (p. 230). Videotapes of the play group sessions (p. 231). Buccal swabs Analyses of		a role in anxiety-related personality traits in adults (p. 229) Serotonin has been implicated as a major neurotransmitter of anxiety and withdrawal because of its effects on regulating mood and emotional states (p. 229). Dopamine has been implicated as a major neurotransmitter involved in euphoria	compared with children with short allele repeats (p. 234). Children who engage in aggressive and disruptive behaviors have problems with attending and staying on-task (p. 235). The study did not find any significant associations of the DRD4 and the serotonin genes with the observed behavioral

					variance with dopaminergic, serotonergic systems (p. 231).		and approach and reward seeking behaviors (p. 234).	measures collected (p. 235). One possible explanation might be that mothers were more accurate in detecting temperamental and behavioral differences in their children than our observational methods because mothers have the opportunity to observe their everyday children throughout development (p. 235).

								Additionally, this study did not find a relationship between the 5-HTT gene and shyness. One way to explain this finding is due to the complexity of what being shy is. Being shy involves a cognitive knowledge of what it means. Thus, shyness in for very young children may not resemble shyness experienced by adults. Thus, the

								relationship between shyness and 5-HTT in young children may very likely different from adults. Nonetheless, this study demonstrates that DRD4 receptor genes in young children is somewhat related to their level of aggression as they develop through the years.
Serotonin: Modulator of a drive to withdraw.	Tops, M., Russo, S., Boksem, Maarten, A. S, &	Brain and Cognition	2009	Whether the function of the phylogenetically old	Review support ort for a novel hypothesis, that a	<u>IV:</u> Serotonin <u>DV:</u> Human	"Serotonin is a fundamental neuromodulator in both	Increasing serotonin decreases reactivity to sensory

	Tucker; D. M.			brainstem sourced serotonergic neuromodulator system can most likely be conceptualized as a primitive drive, orienting behavior in a certain direction (p.430). Whether serotonin facilitates withdrawal from the perspective of senses but this does not mean that serotonin necessarily decreases motoric output and if	phylogenetically old function of serotonin – as a neuromodulator of a drive to withdraw – provides a common framework for interpreting the apparently diverse functions of serotonergic systems in modern humans (p. 427). Identify a common denominator of the functions of the two serotonergi	psychopathology	vertebrate and invertebrate nervous systems, with a suspected role in many human mental disorders" (p. 427). Impaired function of this serotonergic projection results in low mood, low self-esteem, hopelessness, pessimism and reduces stress resilience (p. 427). Despite serotonin being involved in	stimuli and protects against overstimulation, while low serotonin states elicit an exaggeration of signal saliency and amplified signal passage. Behaviors modulated by serotonin appear to be especially facilitated by decreased serotonin and causes increased propensity for affective instability and created stress reactivity

				serotonin drives withdrawal for people to protect themselves thanks to community support (p. 427 and p. 429).	c projection groups originating from the raphe (p. 428).		temperature regulation, feeding, sexual behavior, and stressful situations, most of these response systems continue to function without serotonin (p. 429). Serotonin influences the termination rather than the initiation of eating, and has been suggested to mediate the satiation that motivates meal termination and withdrawal	and greater stress reactivity (p. 429). The majority of findings in humans relate serotonin function to impulsivenes s and depression (p. 429). Serotonin is known to inhibit approach behavior in conflict situations. In contrast, data from human studies emphasize serotonin modulation of negative emotional processing

							(p. 428).	(p.431). Depression is characterized by defective serotonergic neurotransmission (p. 431). Compromised serotonergic system may prevent effectivey disengaging from a situation in timely and mannered fashion which can cause stress and depression (p.431). The high ratio of

								serotonin to dopamine favors tiredness, lethargy and decreased motivation (p.432). Serotonin may also facilitate social behaviors by decreasing responsivene ss to current motivational stimuli and retarding gratification. A recent study in healthy volunteers demonstrate d that tryptophan depletion induced a

								shift away from cooperative behavior (p. 432). Serotonergic sanguinity and comfort may be important to the facilitation of social interactions (p. 432). When trying to understand mental disorders, serotonin hypofunction is very important. This particular study hypothesized that threat

								avoidance and serotonin functioning were related. The authors argue that serotonin plays a role in one's will power to withdraw from a dangerous situation, which can cause individuals to remove themselves from a situation that could cause harm. In their recommendations, the authors mention how medication

								that inhibits serotonin in the brain to reduce psychopathologies may not exactly target the pathology's origin. They argue that new treatment should be created to target what caused the psychopathology in the first place (they do not believe that a hypofunction in serotonin brain levels caused the psychopathology. The hypofucntion only accentuated

								it).
Evidence for epistasis between the 5-HTTLPR and the dopamine D4 receptor polymorphisms in externalizing behavior among 15-year-olds.	Hohmann, S., Becker, K., Fellinger, J., Banaschewski, T., Schmidt, M. H., Esser, G., & Laucht, M.	Journal of Neural Transmission	2009	Whether the serotonergic system functionally regulates dopaminergic neurotransmission and therefore plays an important role in controlling dopamine-mediated externalizing behavior (p. 1622). Whether the polymorphisms are related to adolescent externalizing behavior either alone or in interaction	The initial sample comprised 384 predominantly Caucasian infants, born between 1986 and 1988, who were recruited from two obstetric and six children's hospitals of the Rhine-Neckar region of Germany. At age 15, 298 adolescents completed the Youth Self Report, 296 primary	<u>IV:</u> 5-HTTLPR DRD4 Gene-gene interaction <u>DV:</u> Aggression Externalizing behavior	Aggressive behavior defined as "behavior that causes or threatens physical harm to others often occurs in the context of other types of antisocial behaviors, such as lying, stealing and truancy, and is an essential component of the diagnosis of conduct disorders." (p. 1621). DRD4 has a relationship with seeking new adventures, which is	The authors argue "Aggressive behavior in young people is highly predictive of violence in adulthood and is strongly associated with a greater risk of alcohol and drug abuse, accidents, violent crimes, suicide attempts, and depression" (p. 1621). Dopamine is associated with the activation

				with each other (p. 1623). Whether aggressive behavior in adolescents was link to an allele variation (p. 1625)	caregivers the Child Behavior Checklist and 253 teachers completed the Teacher Report Form. DNA samples were gathered too (p. 1621-1623). Use of self-reports to assess the adolescent psychopathological behaviors in eight subscales (p. 1623). Substance use inventory (p. 1624).		closely related to externalizing behavior, such as impulsivity, sensation seeking, and aggression (p. 1622).	and intensity of response in situations of reward, while serotonin is assumed to be linked to the inhibition of behavioral and emotional responses (p. 1622). The serotonin transporter (5-HTT) assumes a key position within the regulation of central serotonergic functioning and is responsible for the reuptake of

					Self-rating of stage of pubertal maturation (p. 1624).			5-HT from the synaptic cleft (p. 1622). In individuals with impulsive and aggressive behavior, a lower density of 5-HTT in the brain has been found and associated with violent behavior in individuals following methamphetamine abuse (p. 1622). As the receptors 5-HTTLPR and 5-HT are

								said to be involved in the regulation of dopaminergic neurotransmission, a dysfunction at this level could lead to a disequilibrium of these two neurotransmitter systems and therefore to a dopaminergic hyperfunction (p. 1626). The authors demonstrate the need to incorporate the degree of sexual development

								in subjects while investigating aggression in children and adolescents.
Serotonin and Dopamine as Mediators of Sensation Seeking Behavior.	Netter, P., Hennig, J., & Roed, I. S.	Neuropsychobiology	1996	How are the subscales of sensation seeking associated with measures of impulsivity, aggression, and psychoticism? (p. 156). What is the relationship of the serotonergic and the dopaminergic system to the sensation seeking subscales? (p.157).	Disinhibition and experience seeking were chosen based on their representation of the two major factors obtained in a factor analysis: disinhibition represents a factor of lack of impulse control and experience seeking a factor of novelty	<u>IV:</u> Serotonin Dopamine <u>DV:</u> Disinhibition Sensation seeking	Sensation seeking represents the behavior of approach and reward seeking which is described as being dominated by the dopaminergic system (p. 156).	There is abundant literature relating personality disorders as defined by the psychiatric classification to deficiencies or abnormalities of the serotonergic system but has not been widely confirmed that the underlying neurotransmitter-related abnormalitie

					seeking (p.155). Factor analysis on 224 male students relating the four subscales of sensation seeking to impulsivity (p.157). Sensation seeking subscales were analyzed with respect to their relation to cortisol, (p. 157). 20 healthy male students were assigned to			s represent a continuum for pathology to the normal range (p. 156). A constantly low serotonergic transmission may dysregulation of the nervous system and to a lowering of the threshold of sensitivity to aversive stimuli with the consequence of increased hypersensitivity and hyperirritability, then the increased

					either the placebo or the ipsapirone group (blood and saliva samples were taken) (p. 157). Analyses of covariance (p. 157). Since $5HT_{1a}$ agonists have been claimed to have anti-aggressive properties; the second study compared the effects of ipsarione to placebo in an aggression-			cortisol responses to the 5-HT_{1a} agonist in subjects with high trait aggression and irritability could be plausibly related to their low 5-HT activity (p. 162). With respect to the dopaminergic system it was surprising that neither of the two subscales of sensation seeking tested showed a relationship

					inducing condition in 40 healthy males randomly assigned to an aggression induction or a control condition with 10 subjects each tested under placebo and under ipsarione (p. 157). Because nicotine has been shown to exert its rewarding effects partly by release of mesolimbic dopamine, the effects			to PLR responses upon the dopamine agonist and antagonist (p. 163) Ipsapirone-induced cortisol responses are blunted or absent in high experience seeking as compared to low ones, but they did not seem to be related to the dimension of disinhibition (p. 162). Evidence seeking reflects the opposite of

					of dopamine agonist were investigated under the condition of smoking deprivation as compared to placebo using a balanced crossover design. Subjects were 36 healthy male heavy smokers divided into high and low experience seeking and low disinhibitio n subjects on the			irritable aggression and shares common variance with a positive stress-resistant attitude towards life (p. 162).

					sensation seeking subscales (p. 160).			
The anabolic androgenic steroid nandrolone decanoate affects mRNA expression of dopaminergic but not serotonergic receptors.	Birgner, C., Kindlundh-Högberg, A. M. S., Alsiö, J., Lindblom, J., Schiöth, H. B., & Bergström, L.	Brain Research I kept this article even if it was a study on rats, because the dosing paradigm aimed to mimic one cycle of human abuse.	2008	What are the long-term effects of androgenic steroids (AAS) upon monoamines, their receptors and metabolites in neurocircuitries? (p. 222). Whether gene-transcript expressions of dopaminergic and serotonergic receptor subtypes, transporters	Administered nandrolone decanoate for two weeks and measured expression of dopaminergic and serotonergic receptors, transporters and enzymes in brains of male rats (p. 221). One-year follow-up (p. 222).	IV: Serotonergic receptors Dopaminergic receptors DV: Aggression		Nandrolone decanoate administration causes alterations in the expression of dopamine receptors, but not in any of the investigated serotonin receptors (p. 222). Sub-chronic administration of the AAS nandrolone decanoate significantly changed the levels of dopamine receptors (p. 225).

				and enzymes, are implicated in AAS-induced effects in brain regions predominantly regulating cognitive functions, memory, inhibitory behavior and emotions (p. 222).				These findings may explain behavioral changes often observed in AAS abusers such as impulsivity and drug-seeking (p. 224). Additionally, levels of 5HT2A-receptor in the nucleus accumbens, even though were not significant, showed an increase in the study. An increase in serotonergic receptor was

								also found when testosterone was injected in rats that had been castrated. Overall, the study showed that when AAS was administered, levels of dopamine receptor in the brain changed, which could explains why some people who are AAS abusers exhibit impulsive, aggressive behavior.
Underlying Mechanisms of Psychosis	Mintzer, J. E.	The Journal of Clinical	2001	Discussion of recent data from	Review of the literature	IV: Conventional neuroleptic		Conventional neuroleptics

and Aggression in Patients with Alzheimer's Disease.		Psychiatry		clinical trials involving new antipsychotic agent risperidone and their implications for the future treatment of psychosis and depression in Alzheimer's disease (p. 23).		Serotonergic system Dopaminergic system DV: Psychosis Depression Aggressive behavior		are not indicated for aggression and their effectiveness in treating psychosis is counteracted by a high incidence of side effects (p. 23). Deficits in dopamine activity have been linked to psychosis in Alzheimer's disease and schizophrenia (p. 23). Conventional neuroleptic drugs with dopaminergic activity have been the

								mainstays of therapy (p. 23). More recent research suggested that deficits in the serotonergic system are associated with psychosis and aggression in Alzheimer's disease (p. 23). The development of antipsychotic drugs with serotonergic function may have strong therapeutic implications (p. 23).

								Low levels of serotonin have been associated with violent behavior and suicide in depressed patients. In addition, aggressive patients with personality disorder show a lack of prolactin response to challenge with fenfluramine, a serotonin-releasing uptake-inhibiting agent. These results suggest that such patients have a

								reduced central serotonergic function (p.23).
Delay aversion: Effects of 7-OH-DPAT, 5-$HT_{1A/1B}$-receptor stimulation and D-cycloserine.	van den Bergh, F. S., Bloemarts, E., Groenink, L., Olivier, B., & Oosting, R. S.	Pharmacology, Biochemistry, and Behavior.	2006	What are the new therapeutic targets in impulsive patients unconscious of long-term consequences associated with immediate reward (p.736)? How do we now treat impulsivity knowing the relationship between impulsivity and other constructs (p.737)?	Test drugs with known effects on receptor systems involved in several different known behaviors (p.737). Two analyses were made. Repeated measures ANOVA and Post-hoc tests were conducted (p. 738). Drugs and dosages	IV: The psychostimulant D-amphetamine The dopamine D3-receptor agonist 7-OH-DPAT The 5HT 1A-receptor agonist flesinoxan The 5-HT 1A/1B-receptor agonist eltoprazine The NMDA-receptor agonist D-cycloserine	Impulsivity is an important symptom of many psychiatric disorders, in particular aggression, addiction, attention-deficit hyperactivity disorder (ADHD) and mania (p.736). Different types of impulsivity, or pathways leading to impulsivity, are no longer seen as mutually	Patients suffering from impulsivity want immediate action or reinforcement (p. 736). Patients suffering from other impulsivity disorders, such as abuse of alcohol, nicotine, cocaine, heroin, and even gambling also display a preference for

					were chosen because of their relationship with impulsivity (p. 739).	DV: Aggression	exclusive, but rather as complementing accounts. Sometimes both types of impulsivity (aversion to delays for one's reward and the incapability of planning one's behavior) are present in a single patient (p. 736).	immediate gratification compared to control groups (p.736). Delay aversion may be studied in humans and animals by repeatedly presenting subjects with a choice between a small, immediately available reward or a larger reward that they will have to wait for a longer time (p. 736). In the

								present study, the effects of a variety of psychoactive drugs were assessed on delay aversion. D-amphetamine was the drug of reference for this study because it increased choice for the large reward (p. 740). Several lines of evidence support the link between delay aversion and substance abuse

								disorders. First, delay aversion predicts acquisition of cocaine self-administration. Second, people addicted to alcohol, nicotine, cocaine, heroin, and gambling all display delay aversion, and discount delayed rewards faster than controls (p. 740). The study demonstrated that aggressive persons are impulsive in

								the delayed reward task, lending further credibility to the dopamine D3receptor as a potential target for treatment of pathological delay aversion (p.740). This study demonstrates a relationship between delay aversion and substance abuse. D3 receptors have been shown to decrease addictive or substance

								abuse behaviors when blocked. When they are not, there is a higher likelihood of violent behavior. As such, D3 receptors could be targeted by substance abuse or impulsive aggressive behavior regulation treatments.
Pharmacotherapy of Pervasive Developmental Disorders in Children and Adolescents.	Masi, G.	CNS Drugs	2004	Whether it is true that the pervasive developmental disorders (PDDs) begin in the first 3 years of life, and that timely,	Review of the literature.	IV: Serotonin Dopamine Norepinephrine Psychotropic medications DV:	Serotonergic agents may be effective in some children with PDDs, especially when repetitive phenomena	Available evidence suggests that atypical antipsychotics (mainly risperidone and olanzapine) are

				effective treatment (both psychosocial and pharmacological) help to improve prognosis (p. 1039). What are the pharmacodynamic effects of drugs on the developing brain (p. 1039)?		Pharmacological efficacy and safety on drugs Aggression Self-injurious behaviors Hyperactivity	or affective syndromes are prominent (p. 1047).	particularly indicated when more serious behavioral symptoms, such as aggression, self-injurious behaviors and hyperactivity, are prominent. Serotonergic agents may be effective in children with repetitive phenomena or affective symptoms (p. 1032). Autistic patients had higher levels of serotonin in their blood

								compared with healthy controls have been found in several studies. Levels are elevated in about one-third of patients, with a 25% increase in mean serotonin levels compared with normal subjects (p. 1033). The appropriate use of medications in patients with PDD can improve some maladaptive

								behavior and increase patient's ability to benefit from nonpharmacological interventions (p. 1032). Symptoms of attention-deficit hyperactivity disorder (ADHD) are frequently reported in children with PDDs (p. 1045). Vitamins and other nutritional agents have been repeatedly used to treat PDDs over recent decades

								(p.1046). Pharmacological treatment can be considered a symptomatic intervention in children and adolescents with behavioral disorders associated with the autistic core symptomatology (p. 1047).
On the therapeutic action of SSRI medications.	Levinson, M. H., Ostow, M., Wolpert, E., Sandberg, L. S., Levine, F. J., & Gottlieb,	Journal of the American Psychoanalytic Association	2004	What is the mechanism of SSRIs action? (p. 491). Do SSRIs directly affect aggression?	Five letters addressing Gottlieb's article « A psychoanalytic hypothesis concerning the therapeutic	<u>IV:</u> SSRI (selective serotonin reuptake inhibitor) medication <u>DV:</u> The	"Serotonin is one of the main neurotransmitters…whose actions contribute to virtually all aspects of behavior and	When used in the treatment of these syndromes, SSRIs and their serotonergically active properties

	R. M.			(p. 491). Whether the benefits of any other psychotropic medications may derive from their effects on aggression or other impulses (p. 492).	action of SSRI medications » (JAPA 50/3, pp. 969-971) and a reply by its author (p. 483).	treatment of depression	cognition." Meaning that serotonin reuptake inhibitors do not have a specific action (Damasio p. 490).	can have an impact on predispositio ns (p. 485). Given the generally accepted importance of aggression in mental functioning among psychoanaly sts, the improvement of any individual by any means will of necessity result in a modification of aggression in a favorable direction (p.490). SSRIs have

								been shown in this study to decrease the effect of aggression, depression and the risk to react aggressively to a situation. However, the authors warn the reader that SSRIs only mitigate the effect of aggression when aggression is linked to depression. SSRIs do not have an effect on aggression associated with any other syndrome.

Personality Correlates of +/- Pindolol Induced Decreases in Prolactin.	Hennig, J., Kroeger, A., Meyer, B., Prochaska, H., Krien, P., Huwe, S., & Netter, P.	Pharmaco psychiatr y	1998	What are the possible mechanisms of action of substances that are discussed controversia lly with respect to their serotonergic or dopaminergi c activity (p.19)? Whether the aforementio ned findings on personality and neurotransm itter systems can be fruitfully applied to shed light on the difficult question as	Replicate previous findings on pindolol-induced PRL decreases (p. 20). Investigate the relationship between specific personality traits and PRL responses after treatment with +/- pindolol (p. 20). 40 healthy male volunteers aged between 20 and 33 years were	<u>IV:</u> Serotonin Dopamine <u>DV:</u> Personality traits	Dopaminergi c agonists, which lowers prolactin levels, has been found to be related to personality (the amount of PLR reduction has been positively correlated with positive emotionality extraversion (p. 19). The serotonergic (5-HT) neurotransmit ter system has been successfully related to personality traits (p. 19). Impulsivity,	The major dimensions in different theories of personality extraversion, neuroticism, and psychoticism , positive emotionality, constraint, and negative emotionality and sensation seeking have frequently been related to neurotransmi tter systems (serotonin, dopamine, and norepinephri ne) (p. 19). There is evidence that the higher

				to whether pindolol affects prolactin (PRL) via serotonergic or dopaminergic pathways (p. 20). If pindolol affects PRL by a serotonergic mechanism, subjects high in aggressive impulsivity should have a lower PRL decrease after treatment with pindolol than nonimpulsive due to their	randomly assigned to a placebo or a +/- pindolol group (p. 19). Blood samples were gathered (p. 19). Questionnaires on personality were given (p. 19). Based on the theoretical assumptions of traits related to the sensitivity of serotonin, dopamine and norepinephrine,		excitability, aggression and disinhibition are significantly correlated with +/- pindolol induced PRL (p. 21).	the amount of impulsive aggression the lower the increase in PRL which points in the direction of low serotonergic responsiveness. The same seems to be true for the subscales of sensation-seeking, disinhibition and boredom susceptibility (p. 19). Subjects in the group receiving +/- pindolol had higher numbers in the scale "psychoticism" which

				postulated serotonin receptor subsensitivity. Whether dopamine mediates the observed changes in PRL after pindolol, for positive emotionality or extraversion and related traits to be associated with higher decreases in PRL (p. 20).	measures should cover impulsivity, extraversion and neuroticism as well as their primary factors and correlates like sensation seeking (p. 20). An analysis of covariance for repeated measures was computed for demonstrating the effect of +/- pindolol on PRL concentrati			reaches statistical significance (p. 21). Impulsivity and related traits like excitability, aggression and disinhibition are positively correlated with mean changes in PRL concentrations after treatment with +/- pindolol. These traits are associated with low serotonergic responsivity (but not dopaminergi

					ons using the baseline values as covariates (p. 21).			c mechanisms) (p. 23). The example of +/- Pindolol in the present study demonstrates that substances usually applied to identify receptor specificity of agonists can also lead to some problems of interpretation when given alone. Serotonin seems to constantly inhibit dopamine-induced

								increases in motor activity, exploratory activity of novel stimuli, aggression, and reactivity to reward and general emotional reactivity (p. 22).
The Psychopharmacology of Aggressive Behavior: A Translational Approach. Part 1: Neurobiology.	Comai, S., Tau, M., & Gobbi, G.	Journal of Clinical Psychopharmacology	2012	What are the recent advancements in the treatment of aggression, integrating pharmacological findings from clinical research with neurobiological knowledge	Using a translational medicine approach, this review examines the neurobiology of aggression, discussing the major neurotransmitter systems implicated	IV: Serotonin Glutamate Norepinephrine Dopamine γ-aminobutyric acid Their respective receptors DV: Impulsivity Agitation	Aggressive behavior exhibits high comorbidity with a range of psychiatric conditions, including schizophrenia, bipolar disorder, dementia, personality disorders (in particular,	Aggression is a Aggression is a complex phenomenon associated with genetic, neurobiological, and psychosocial factors. Impairments of many neurotransmitter systems, including

				gained from basic science research (p. 83)?	in its pathogenesis, namely, serotonin, glutamate, norepinephrine, dopamine, and γ-aminobutyric acid, and also their respective receptors (p. 83). In this review, the aggressive behavior was considered as a unique entity (p. 83). The scope of this review is to link this preclinical	Violence	borderline and antisocial personality disorders), posttraumatic stress disorders, traumatic brain injury, addiction, and pervasive developmental disorders (p. 83). The neurobiological mechanisms accounting for aggression in these distinct disorders may change (p. 83). The etiology of aggression is multifaceted	serotonin (5-HT), dopamine (DA), and norepinephrine (NE), are implicated in the biology of aggression (p. 83). Self-rated aggression and impulsivity are inversely correlated with neuroendocrine response to fenfluramine challenge in healthy controls (p. 86). In humans, empirical evidence

					knowledge to the fundamental framework of human therapeutics.		and is influenced by several neurobiological factors, including genes and the environment (p. 83).	suggests that 5-HT dysfunction is typically connected with impulsive, rather than pre-meditated aggression (p. 86). Serotonergic abnormalities have been associated with impulsive aggression in various populations, including psychiatric patients, criminal offenders, and healthy subjects. This serotonergic

								dysfunction is frequently reported as an attenuated concentration of 5-HIAA in the CSF (p. 86). It has been hypothesized that the link between aggression and low 5-HIAA is specific to impulsive behavior (p.86). Similar correlations were also reported in children and adolescents with disruptive behavior disorders,

								even though for some measures of aggression the negative correlation with CSF 5-HIAA levels was not significant (p.86). This suggests that childhood abuse might lead to an adult serotonergic dysfunction, which could represent a possible mechanism for the appearance of pathological aggressivene ss in adulthood (p.

								86).
The Psychopharmacology of Aggressive Behavior: A Translational Approach. Part 2: Clinical Studies Using Atypical Antipsychotics, Anticonvulsants, and Lithium.	Comai, S., Tau, M., Pavlovic, Z., & Gobbi, G.	Journal of Clinical Psychopharmacology	2012	Whether a translational medicine approach from the neurotransmitters to human studies, combining the neurobiology of aggression along with the pharmacology and clinical outcomes of each drug, would help understand the therapeutics of aggression (p. 237).	A Critical review of all clinical trials using atypical antipsychotics, anticonvulsants, and lithium are presented (p. 237). Identified relevant clinical studies by searching PubMed using the names of the putative drugs along with the keywords ‘‘aggression,’’ ‘‘hostility,’’ and ‘‘agitation.’	<u>IV:</u> The major neurotransmitter systems implicated in pathogenesis: Serotonin, Glutamate, Norepinephrine, Dopamine and γ-aminobutyric acid Antipsychotics Anticonvulsants Lithium <u>DV:</u> Aggressive behavior	The neurobiology of aggression is multifaceted, implying different neurotransmitters and the involvement of different brain areas/nuclei at the cortical and subcortical levels (p. 237).	The typical antipsychotics interact the most with dopaminergic neurotransmission, compared to atypical antipsychotics, which interacts with serotonin, norepinephrine, histamine, and glutamate (p.237). The association of atypical antipsychotics with antiepileptics and/or lithium can

					’			represent a valid therapeutic strategy because this combination covers an even larger spectrum of membrane receptors, ion channels, and intracellular elements (p. 237). The main challenge in the immediate future is to develop novel antipsychotics with a more selective target spectrum and with a

								low risk of metabolic adverse effects (p. 253). Overall, aggressive behavior seems to be best treated using a long-term treatment targeting several neurobiological factors conducive to aggression at once. Lithium can be used as a treatment to aggression, but for best result, it needs to be used in conjunction

								with therapy and antipsychotic drugs. Zotepine was also described as having positive results in decreasing aggressive behaviors in patients.
Dopamine Dysfunction in Borderline Personality Disorder: A Hypothesis.	Friedel, R. O.	Neuropsychopharmacology	2004	Whether dopamine dysfunction is associated with three dimensions of borderline personality disorder (BDP), that is, emotional dysregulation, impulsivity, and cognitive-	Review articles identified by Medline searches of relevant topics, books, references from bibliographies and conference proceedings from 1975 to 2003 (p. 1029).	IV: Cognitive-perceptual impairment Disturbed relationships DV: Borderline personality disorder Emotional dysregulation Impulsivity	Dopamine activity is linked to the positive reinforcement of conditioned, goal-directed behaviors and the experience of pleasure of goal achievement (p. 1032).	Levels of pessimistic attitudes correlate directly with serotonin receptors in depressed subjects, but not in those with BPD (p. 1033). This shows that there are abnormalities in the

				perceptual impairment (p. 1029). Whether dopamine dysfunction in specific neural pathways is associated with one or more of the behavioral dimensions of BPD (p. 1029).				structure and function in brain regions that mediate emotion information processing, impulsivity, and cognition. However, there are no published neuroimaging studies that evaluate DA turnover or DA-binding potential in subjects with BPD (p. 1033). More neuro imaging studies need to be conducted in conjunction with genetic research in

								order to find strategies to limit aggressive impulsive behavior
Clozapine Reduces Violence and Persistent Aggression in Schizophrenia.	Glazer, W. M., & Dickson, R. A.	The Journal of Clinical Psychiatry	1998	Whether the reduction in violence and persistent aggression with clozapine treatment improve the chances for integration of the schizophrenia patient into the community and provide cost savings to society (p. 8).	Review evidence for the efficacy of clozapine in the treatment of aggression and violence in the treatment-refractory patient (p. 8).	IV: Clinical factors Sociodemographic factors DV: Violent acts	A violent episode refers to an unwanted physical contact, an unwanted sexual act, or a threat that includes specific statements of intent to harm (p. 8). Clozapine has relatively weak dopaminergic activity. It blocks receptors for the D_2 dopamine subtype.	The connection between serotonin and violence has been established with the repeated observation that abnormalities in central 5-HT function correlate with persistent aggression (p.9). The major metabolite of serotonin is found to be

							Clozapine is also a potent 5-HT_2-serotonergic receptor antagonist (p. 11).	less in the brain of subjects who have experienced aggression and violence, as compared to those with no such history (p. 9). There is also preliminary evidence for a genetic disturbance in serotonergic function that might predispose individuals to impulsive aggressive behavior (p.9). Serotonergic drugs in

								particular have been studied for use in aggression. Drugs with 5-HT_2-antagonist and those with 5-HT_1-agonist properties show an antiaggressive effect (p.10). Schizophrenia increases the risk of aggressive and violent behavior against parents, friends, care providers and society in general that comes in contact with

								patients Therefore, more studies need to be conducted in order to find the best treatment for patients with schizophrenia, to ultimately decrease the risks of substance abuse, violence and aggression.
Psychosocial and neurological factors in the development of impulsive aggression.	Felthous, A. R., Barratt, E. S., & Kent, T. A.	Psychiatria Danubina (Croatia)	1994	What are the neurobiological and neuroendocrine factors and early influence from the social environment that are related to	Review of the literature	IV: Family background: past physical abuse or witnessed violence in childhood Serotonergic system and brain functioning	Baron has defined aggression as "any form of behavior directed towards the goal of harming or injuring another living being which is motivated	Among the biogenic amine neurotransmitter systems which have been implicated in behavior and aggression, serotonin is one of the most

				impulsive aggression? (p. 133). Can a defective serotonin transmitter system itself be a neurophysio logical dysfunction that leads to impulsive behaviors? (p. 135). Is low 5-HT and presumably CNS serotonin simply a sign of subtle damage with dysfunction in the CNS, which is important		<u>DV:</u> Aggression Impulsive behaviors	to avoid such treatment" (p. 133). "Impulsive aggression" refers to behaviors directed towards the injury or harm of another living being or the destruction of useful property with little evidence of thoughtful consideration , of self-control, or of self-gain trough the deed except for the reduction of tension (p. 133).	extensively studied (p. 134). The 5-HT2 receptor subtype especially predominate s in the prefrontal cortex which is known for behavioral control (p. 134). Structural damage of the frontal lobes leads to poor judgment and weak impulse control and, impulsive aggression. A dysfunction

				for behavioral regulation? (p.1 35). Does low serotonin and damage in certain regions of the brain constitute an important association between early physical abuse, especially abuse involving brain damage and later impulsive aggressivene ss? (p. 135).			"Antisocial aggression": behaviors directed towards the harm of another living being or the destruction of useful property after thoughtful consideration with self-control and with the purpose of self-gain (p. 133).	in the orbital region leads to restricted foresight, failure to recognize the results of one's actions, failure to plan, and indifference over difficulties, which are striking characteristic s that can lead to antisocial behaviors (p. 134). Individuals who commit impulsive, diffuse, antisocial acts of violence often have

								an early history of having been raised in an unstable family with at least one violent or brutal parent (p. 135). Those with specific predisposing psychosocial factors and with neurological dysfunction of the brain structures involved the generation and control of aggressive impulses are especially likely to develop a behavioral pattern of

								impulsive and antisocial aggression (p. 135).
Neurobiologic Correlates of Violence: Relevance to Criminal Responsibility.	Berman, M. E., & Coccaro, E.F.	Behavioral Sciences and the Law	1998	What is the role of neurotransmitter functioning in violent crime? Whether monoamine such as serotonin, dopamine and norepinephrine are related to human aggressive behavior?	Review and discuss existing studies of neurotransmitter functioning and violent crime (p. 305). Representative studies on neurotransmitter functioning and impulsive aggressive behavior are included to illustrate the state of this research	IV: Neurotransmitters such as serotonin, dopamine, and norepinephrine DV: Violent crime Aggressive behavior	Behavioral scientists, with minor variations, have defined aggression as to hurt or injure people (p. 304). Aggressive behavior can be seen as being on a continuum of severity. Given the impact of violent criminal behavior on society, and the stakes for individuals accused of	More than 50 molecules have been identified as neurotransmitters. Unfortunately, not all 50 have been used in regard to explaining human aggression. Among these, serotonin (5-HT), norepinephrine (NE), and dopamine (DA) have drawn the most

					area and to provide a framework to discuss the limitations of existing studies (p. 305). Problems inherent in putting forth a criminal defense based on neurotrans mitter defects will be discussed (p. 305). Case study of neurotrans mitter functioning testimony in a		such acts, factors relevant to determining the criminal culpability of an individual charged with a violent crime can take on enormous importance (p. 304). Dopamine is considered to play a role in behavioral activation, reward mechanisms, and goal-directed behavior (p. 309).	attention) (p. 305). Despite these findings, the authors argue that there is very little change that genetics will be brought into the courtroom. Indeed, even if criminal acts are the result or are related to a neurobiologi cal deficiency, jurors and judges do not see it as an excuse for the harm that was done. These

					homicide defense (p. 310).			disorders are not considered by the court to be so strong that they would influence someone's ability to know the difference between right and wrong and ultimately the difference between a criminal and a non-criminal act. Nonetheless, with more and more research being conducted in biology and neuropsycho

								logy, the authors hope for a reconceptualization of our way of thinking about criminal culpability.
Selecting Treatments for Repetitive Behaviors in Pervasive Developmental Disorders.	King, R., Fay, G., Prescott, H., Turcotte, P.& Preston, M.	Psychiatric Annals	2004	What are the various types of repetitive behavior in individuals with pervasive developmental disorder (PDD) (p. 221)? What are the differences between the signs and	Developmental Disabilities Program of the North Bay Psychiatric Hospital in North Bay, Ontario, Canada' files were reviewed The Program is modeled based on	<u>IV:</u> Selective serotonin reuptake inhibitor (SSRI) Prescribed medication <u>DV:</u> Pervasive developmental disorder Obsessive compulsive disorder Aggression	No definition was given	OCD is prevalent in patients with developmental disabilities (DD) and that compulsions could be diagnosed reliably and distinguished from stereotypies (p. 222). Patients with autistic

				symptoms of obsessive-compulsive disorder and core features of PDD (p. 221) What are the psychotropic medication options for observed repetitive behavior in patients with PDD (p. 221)?	biopsychosocial principles and uses interdisciplinary teams employing objective monitoring of operationalized definitions of signs and symptoms of mental illness, to support or refute diagnostic hypotheses and assess the efficacy of treatment recommendations (p. 225). Case examples illustrate:			disorders are less likely to exhibit repetitive behaviors associated with cleaning, checking, or counting (p. 223). In addition, patients with autistic disorders are less likely to have aggressive, contamination, sexual, religious, symmetry, or somatic thoughts (p. 223). Aggression, contamination, and a need for

					the complexity of the interplay between different types of repetitive behaviors in the presentation of individuals with PDD and challenging behaviors and mental health concerns, the manner in which response to prescribed medication can both heighten and diminish confidence in			symmetry are the most common obsessions (p.223).

					diagnostic hypotheses (p. 225).			
Brain serotonin transporter in human methampheta mine users.	Kish, S. J., Fitzmauric e, P. S., Boileau, I., Schmunk, G. A., Ang, L. C., Furukawa, Y., Chang, L. J., Wickham, D. J., Sherwin, A., & Tong, J.	Psychoph armacolo gy	2009	Whether protein levels of serotonin transporter (SERT), a key marker of serotonin neurons are decreased in brain of chronic MA users (p. 649).	SERT immunorea ctivity was measured using an immunoblot ting procedure in 16 autopsied brains of people who had used MA drugs (p. 650) Scalp hair samples for drug analyses could be obtained from 19 of the 24 controls and 11 of the 16 MA users (p. 650).	<u>IV:</u> Serotonin transporter (SERT) Dopamine <u>DV:</u> Brain of methamphet amine users	No definition was given	Post-mortem brain data provide limited support for the involvement of the serotonin system in behavior consequence s of MA exposure (p. 658). Findings of the autopsied human brain suggest that exposure to ecstasy may be related to lower levels of serotonin markers but has

					To establish whether there might be any substantial on the protein levels of SERT caused by time after death, biopsied temporal cerebral cortex was obtained immediatel y following operations for the treatment of intractable temporal lobe epilepsy (p. 650). Statistical			relatively little effect on markers of the dopamine system (p. 656). Decreased concentratio n of serotonin markers in orbitofrontal cortex may be related to higher suicide attempts (p. 658). SSRI effects might be exaggerated in MA users via decreased serotonin clearance from low SERT,

					analyses were performed by using the StatSoft STATISTICA 7.1. Two-way ANOVA to examine differences in levels of the outcome measures between control and MA cases and between the brain regions (p. 650).			possibly explaining poor SSRI response or high incidence of medication side effects during abstinence (p.658).

Pharmacotherapy for aggressive behaviors in persons with intellectual disabilities: treatment or mistreatment?	Tsiouris, J. A.	Journal of Intellectual Disability Research	2009	Can the overuse of antipsychotics in persons with intellectual disabilities (ID) be justified if their aggressive behaviors were associated with mostly psychotic disorders and not other psychiatric disorders or factors? Whether the anti-aggressive properties of the antipsychotics have been supported	The literature on aggressive behaviors, their associations with psychiatric disorders and treatments for aggressive behaviors in persons with and without ID was reviewed (p. 1). In addition, the literature on basic research regarding the brain receptors implicated in	<u>IV:</u> Antipsychotic medications Brain neurotransmitters <u>DV:</u> Psychotic disorders Aggressive behavior	Maladaptive behaviors and inappropriate behaviors are the terms used through the years for problem behaviors. Currently, the accepted term in the USA is 'challenging behaviors' and includes behaviors such as: physical aggression against others (assaultive behavior), aggression towards objects (destructive behavior), aggression toward self (self-injurious	Selective serotonin reuptake inhibitors (SSRIs) improved aggressive behaviors in 50% of persons with ID, and the most pronounced effect was in persons with an underlying anxiety disorder including obsessive-compulsive disorder (p. 4). Most aggressive persons with ID have no diagnosis of psychotic

				by basic research or reviews of clinical studies (p. 1).	aggressive behaviors and research on the anti-aggressive properties of antipsychotics was reviewed (p. 1).		behavior, or SIB) and also verbal aggression, screaming and tantrums (p. 3). Estimated prevalence of challenging behaviors in the ID population has ranged from 10-15% and up to 60 % (p. 3).	disorder, and there is a lack of strong evidence supporting anti-aggressive properties of antipsychotics (p. 1). Antipsychotic overuse in this population may be explained by old, faulty notions that aggressive behaviors in persons with ID are mostly associated with psychotic disorders (p. 1).

								Pharmacotherapy of aggressive behaviors in the ID population is not evidence-based (p. 4).

APPENDIX B

CODING SHEET

Coding Sheet	
Title	
Author	
Journal Name	
Year Published	
Purpose	
Research Questions	
Methodology	
Key Variables	Independent variables
	Dependent variables
Findings	
Outcomes	Definitions of aggression, serotonin, dopamine
	Relationship between serotonin and dopamine
	Impact of serotonin and dopamine on aggression
Comments/ Key thoughts	
Source/Full reference	

APPENDIX C

LIST OF RELEVANT ARTICLES

Article Name	Author(s)	Journal Name	Date
Psychosocial and neurological factors in the development of impulsive aggression.	Felthous, A.R.; Barratt, E.S.; Kent, T.A.	Psychiatria Danubina (Croatia)	1994
Serotonin and Dopamine as Mediators of Sensation Seeking Behavior.	Netter, P.; Hennig, J.; & Roed, I.S.	Neuropsychobiology	1996
Personality Correlates of +/- Pindolol Induced Decreases in Prolactin.	Hennig, J.; Kroeger, A.; Meyer, B.; Prochaska, H.; Krien, P.; Huwe, S.; Netter, P.	Pharmacopsychiatry	1998
Clozapine Reduces Violence and Persistent Aggression in Schizophrenia.	Glazer, W.M.; Dickson, R.A.	The Journal of Clinical Psychiatry	1998
Neurobiologic Correlates of Violence: Relevance to Criminal Responsibility.	Berman, M.E.; Coccaro, E.F.	Behavioral Sciences and the Law	1998
Underlying Mechanisms of Psychosis and Aggression in Patients with Alzheimer's Disease.	Mintzer, J.E.	The Journal of Clinical Psychiatry	2001
Social and neural determinants of aggressive behavior:	Miczek, K.A.; Fish, E.W.; de Bold, J.F.; de	Psychopharmacology	2002

pharmacotherapeutic targets at serotonin, dopamine and γ-aminobutyric acid systems.	Almeida, R.M.M.		
Molecular genetics of shyness and aggression in preschoolers.	Schmidt, L.A.; Fox, N.A.; Rubin, K.H.; Hu, S.; & Hamer, D.H.	Personality and Individual Differences	2002
Pharmacotherapy of Pervasive Developmental Disorders in Children and Adolescents.	Masi, G.	CNS Drugs	2004
On the therapeutic action of SSRI medications.	Levinson, M.H.; Ostow, M.; Wolpert, E.; Sandber, L.S.; Levine, F.J.; Gottlieb, R.M.	Journal of American Psychoanalytic Association	2004
Dopamine Dysfunction in Borderline Personality Disorder: A Hypothesis.	Friedel, R.O.	Neuropsychopharmacology	2004
Delay aversion: Effects of 7-OH-DPAT, 5-$HT_{1A/1B}$-receptor stimulation and D-cycloserine.	van den Bergh, F.S.; Bloemarts, E.; Groenink, L.; Olivier, B.; & Oosting, R.S.	Pharmacology, Biochemistry, and Behavior	2006
Role of Serotonin and Dopamine System Interactions in the Neurobiology of Impulsive Aggression and its Comorbidity with	Seo, D.; Patrick, C.J.; & Kennealy, P.J.	Aggression and Violent Behavior	2008

other Clinical Disorders.			
The anabolic androgenic steroid nandrolone decanoate affects mRNA expression of dopaminergic but not serotonergic receptors.	Birgner, C.; Kindlundh-Högberg, A.M.S.; Alsiö, J.; Lindblom, J.; Schiöth, H.B.; & Bergström, L.	Brain Research	2008
Serotonin: Modulator of a drive to withdraw.	Tops, M.; Russo, S.; Boksem, M., Maarten, A.S; & Tucker; D.M.	Brain and Cognition	2009
Evidence for epistasis between the 5-HTTLPR and the dopamine D4 receptor polymorphisms in externalizing behavior among 15-year-olds.	Hohmann, S.; Becker, K.; Fellinger, J.; Banaschewski, T.; Schmidt, M.H.; Esser, G.; & Laucht, M.	Journal of Neural Transmission	2009
Brain serotonin transporter in human methamphetamine users.	Kish, S.J.; Fitzmaurice, P.S.; Boileau, I.; Schmunk, G.A.; Ang, L.C.; Furukawa, Y.; Chang, L.J.; Wickham, D.J.; Sherwin, A.; Tong, J.	Psychopharmacology	2009
Pharmacotherapy for aggressive behaviors in persons with intellectual disabilities: treatment or mistreatment?	Tsiouris, J.A.	Journal of Intellectual Disability Research	2009

The Psychopharmacology of Aggressive Behavior: A Translational Approach. Part 1: Neurobiology.	Comai, S.; Tau, M.; Gobbi, G.	Journal of Clinical Psychopharmacology	2012
Social Adversity, Genetic Variation, Street Code, and Aggression: A Genetically Informed Model of Violent Behavior.	Simons, R.L.; Lei, M.K.; Stewart, E.A.; Brody, G.H.; Beach, S.R.H.; Philibert, R.A.; & Gibbons, F.X.	Youth Violence Juvenile Justice	2012

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