The Neurobiological Relationship Between Childhood Maltreatment and Major Depressive Disorder (MDD)

Childhood maltreatment is a tragically common occurrence that takes place across different cultures and societies. In fact, according to the Centers for Disease Control and Prevention, at least 1 in 7 children have experienced child abuse and/or neglect in the past year alone. Childhood maltreatment is defined as a spectrum of sexual, physical, and emotional abuse, including physical and emotional neglect, and it has been identified as the leading preventable cause of mental illness (Teicher, Anderson, & Polcari, 2012).

While childhood maltreatment puts individuals at risk for a number of emotional disorders, the greatest risk is associated with a diagnosis of major depressive disorder, or MDD (Frodl, Reinhold, Koutsouleris, Reiser, & Meisenzahl, 2010). To begin, MDD is defined as "the presence of loss of pleasure or interest in usually pleasurable activities (anhedonia), together with an array of other features, including anergia, changes in sleep and appetite, sadness, and suicidal ideation" (Willner, Scheel- Krüger, & Belzung, 2013, p. 2332). MDD has been identified as one of the most debilitating diseases worldwide, with the social and economic burden of the disorder posing a major challenge to private and public health (Opel et al., 2014). Furthermore, individuals diagnosed with MDD often experience challenges in their interpersonal relationships, early pregnancy, low educational attainment, poor occupational functioning, unstable employment, and increased suicidality (Rao et al., 2010). While there are a variety of potential causes for MDD (e.g. genetics, life stressors, substance abuse, or medical conditions), childhood maltreatment poses one of the greatest risks for later development of the disorder. In fact, individuals who experienced childhood maltreatment are twice as likely as those without a history of childhood maltreatment to develop later depression (Nanni, Uher, & Danese, 2012).

Furthermore, there are certain brain structures implicated in both childhood maltreatment and MDD. To begin, the hippocampus—a structure known to atrophy in MDD—is key to learning, memory, and stress regulation (Stein et al., 2012). It works to consolidate declarative, or conscious, memories and is greatly influenced by environmental factors due to its plastic nature and life-long neurogenesis (Opel et al., 2014). Its involvement in consolidating memories and ease to which it can be influenced by environmental factors (e.g. stress) lends support to the idea that the hippocampus is altered by childhood maltreatment. Additionally, the amygdala is another brain structure involved in both childhood maltreatment and MDD. A central structure of the limbic emotion processing circuit, the amygdala participates in emotional regulation, the processing of threat-related stimuli, and the body's fear response (Dannlowski et al., 2012). Its volume and reactivity are subject to change in MDD, likely for the role it plays in consolidating memories for emotional experiences (van der Werff et al., 2012). With this knowledge, it is safe to assume that both the hippocampus and amygdala are at work in childhood maltreatment, an experience marked by fear, negative stimuli, and traumatic memories.

This literature review is of value because childhood maltreatment is a common experience, one that reportedly 30-40% of adults in Western countries experience, that puts an individual at risk for later mental illness (Dannlowski et al., 2012). Not only is childhood maltreatment a risk factor for MDD, but it could also be associated with a more severe course of illness. This means that individuals with MDD who also experienced childhood maltreatment are likely to experience a longer duration of illness, earlier onset of illness, more depressive episodes, greater suicidality, and higher levels of dysfunctional attitudes (Chaney et al., 2014). Therefore, my research question is as follows: does MDD and a history of childhood maltreatment cause hippocampal atrophy and amygdala hyperresponsiveness? I hypothesize that

individuals with MDD and a history of childhood maltreatment will experience a more severe course of illness because MDD and childhood maltreatment independently cause the aforementioned changes to the brain which, when combined, amplify the severity of illness.

Results

To begin, Chaney et al. (2014) conducted a study that used high-resolution magnetic resonance imaging to compare patients with major depressive disorder (MDD) to healthy controls with and without the experience of childhood maltreatment. Researchers observed that childhood maltreatment is associated with significant hippocampal atrophy, rendering individuals susceptible to a more severe course of depression. They found that childhood maltreatment is associated with hippocampal atrophy regardless of sex, age, or history of depression. In addition to confirming that MDD can cause independent morphological changes to the brain, Chaney et al. (2014) verified that childhood maltreatment is associated with this change in brain structure that is traditionally attributed to MDD.

As mentioned in the previous study, one of the structural brain changes observed in both childhood maltreatment and MDD is hippocampal atrophy, or the loss of hippocampal neurons and neuronal volume. Willner, Scheel-Krüger, and Belzung (2013) claimed that the hippocampal atrophy observed in childhood maltreatment and MDD is due to the effect of stress on the brain. In a review of literature on neuroendocrine function and glucocorticoid-relevant pathologies in stress-related mental disorders, Willner, Scheel-Krüger, and Belzung (2013) stated that increased glucocorticoids, released due to activation of the hypothalamus-pituitary-adrenal (HPA) axis, leads to a loss of glucocorticoid receptors in the hippocampus. Although acute exposure to glucocorticoids helps the body by decreasing inflammation, prolonged exposure is neurotoxic because it causes atrophy of hippocampal dendrites and granular cell death, resulting in a

reduction of hippocampal volume. In regard to MDD, a mental illness associated with increased stress levels, the degree of hippocampal shrinkage is proportional to the number and duration of prior depressive episodes in a person (Willner, Scheel-Krüger, & Belzung, 2013).

In addition to hippocampal atrophy, increased amygdala responsiveness is observed in both childhood maltreatment and MDD. In a study on amygdala hyperresponsiveness in childhood maltreatment and MDD, Dannlowski et al. (2012) recruited 148 healthy individuals via public notices (e.g. newspaper advertisements), screened the participants for psychiatric disorders, and measured amygdala responsiveness via functional magnetic resonance imaging. They used an emotional face-matching paradigm to activate the amygdala in response to threat-related faces, used voxel-based morphometry to study hippocampal atrophy, and assessed childhood maltreatment via the 25-item Childhood Trauma Questionnaire (CTQ). Dannlowski et al. (2012) observed that childhood maltreatment had a robust effect on increased amygdala responsiveness and decreased hippocampal volume, two neuroimaging markers previously associated with emotional disorders. Dannlowski et al. (2012) concluded that amygdala hyperresponsiveness and hippocampal atrophy might mediate between the experiences of childhood adversity and the development of emotional disorders such as MDD. Therefore, it is likely that childhood maltreatment increases the susceptibility for stress in later life with increased amygdala responsiveness and decreased hippocampal volume representing two independent yet related aspects of this vulnerability for later stress (Dannlowski et al., 2012).

In addition to the aforementioned neurobiological changes caused by childhood maltreatment and MDD, adults who experienced childhood maltreatment also showed increased amygdala-hippocampal connectivity. Jedd et al. (2015) observed this increase in connectivity by collecting structural and functional magnetic resonance imaging data while participants

completed an emotion-matching task. Many researchers speculate that this strong amygdala-hippocampal connectivity might indicate that maltreated individuals link threatening stimuli processed by the amygdala to negative memories reactivated by the hippocampus. Jedd et al. (2015) concluded that childhood maltreatment might exacerbate the illness course of MDD because this change to the amygdala-hippocampal interaction during emotional processing shows that negative stimuli and traumatic memories influence later emotional interpretation.

Expanding on the previous study by Jedd et al. (2015), Willner, Scheel-Krüger, and Belzung (2013) claimed that the reciprocal nature of the amygdala-hippocampal interaction can shed light on the respective changes to these structures observed in childhood maltreatment and MDD. Willner, Scheel-Krüger, and Belzung (2013) stated that the amygdala and hippocampus have opposite influences on the HPA axis, evidenced by the fact that inhibited hippocampal functioning (due to hippocampal lesions) led to a reciprocal increase in amygdala activity and enhanced amygdala coding. Therefore, hippocampal atrophy due to stress (in either childhood maltreatment or MDD) results in a compensating, hyperresponsive amygdala.

In regard to the statement that childhood maltreatment might contribute to the development and maintenance of MDD, it is important to note significant findings from Rao et al. (2010). In their study, 30 adolescents with MDD, 22 high-risk adolescents (considered high-risk due to parental depression) with no personal history of psychiatric illness, and 35 adolescents with no personal or family history of psychiatric illness underwent volumetric magnetic resonance imaging. Researchers used standard interviews to gather information on adverse experiences. Seeing hippocampal atrophy in individuals with depression as well as in those who experienced early-life adversity, Rao et al. (2010) proposed that early-life adversity such as childhood maltreatment may interact with genetic vulnerability to induce hippocampal

changes, thereby increasing a person's risk for MDD. Rao et al. (2010) concluded that early stress (e.g. the stress associated with childhood maltreatment) sensitizes the HPA axis to later stress, supporting the idea that childhood maltreatment might promote and maintain MDD.

In addition to human research, animal research using rodent models has been used to study the effects of early life adversity on the brain. Many animal studies have created paradigms representing emotional maltreatment in humans (e.g. maternal separation) to demonstrate the effect of maltreatment on brain structure and animal behavior. In fact, van der Werff et al. (2012) claimed that in rodents, maternal separation most largely affects the hippocampus, amygdala, and medial prefrontal cortex, which are all constituents of the limbic network involved in the stress response and emotional regulation. Researchers hope to be able to apply this knowledge to our understanding of the long-term neurobiological consequences of childhood maltreatment.

In conclusion, these results appear to confirm my hypothesis that individuals with MDD and a history of childhood maltreatment are likely to experience a more severe illness course due to the fact they exert similar changes (decreased hippocampal volume and increased amygdala responsiveness) on the brain. Childhood maltreatment is also associated with increased amygdala-hippocampal connectivity, suggesting that early-life adversity might induce additional neurobiological changes that could further exacerbate the illness course of MDD.

Discussion

In summary, the results of this literature review reveal that childhood maltreatment and major depressive disorder (MDD) exert similar effects on the brain. Because both childhood maltreatment and MDD are associated with a decrease in hippocampal volume and an increase in amygdala responsiveness, an adult with MDD who was also maltreated as a child would experience a great degree of neurobiological change and a severe course of illness.

One of the greatest applications of this research pertains to the prevalence of childhood maltreatment in the world. Despite how common this detrimental experience is, the literature on childhood maltreatment has yet to fully evaluate which brain networks are most vulnerable to adversity (Jedd et al., 2015). Therefore, the fronto-limbic circuitry described in this literature review is likely just one of the many brain networks affected by early adversity. Additionally, although MDD was the focus of this literature review, childhood maltreatment has also been associated with the development of other mental illnesses, such as PTSD, anxiety disorders, and substance abuse (Chaney et al., 2014). With such a large proportion of the adult population having experienced childhood maltreatment, it is imperative we continue research on the long-term physiological, especially neurobiological, effects of childhood maltreatment.

Another application of this research regards the pervasiveness of MDD, the world's most common psychiatric disorder and most disabling medical condition (Willner, Scheel-Krüger, & Belzung, 2013). In fact, Willner, Scheel-Krüger, and Belzung (2013) reported that depression is projected to be the world's greatest contributor to the burden of disease by 2030. Therefore, continued research in the neurobiology of depression can help the scientific community to uncover new and more effective antidepressant drug therapies. With more knowledge and alternative treatment plans, there is a greater likelihood that patients will be able to manage their MDD and potentially be freed from their debilitating depressive symptoms altogether.

In regard to future studies, researchers should aim to investigate how neurobiological consequences might differ among the various forms of childhood maltreatment (e.g. verbal abuse, sexual abuse, physical abuse, emotional neglect, and physical neglect). In order to do this, however, researchers need sample sizes that are large enough to detect significant differences between the various forms of childhood maltreatment. This proves to be difficult because many

individuals are wary about participating in research that recognizes their abuse or recalls traumatic memories of early adversity. As a result, researchers should strive to develop other recruiting methods that encourage participation by this population.

In addition to distinguishing between the neurobiological effects of the various forms of childhood maltreatment, future research should also aim to clarify whether altered hippocampal structure is a risk factor for or a consequence of MDD. I mention this because some researchers believe that hippocampal atrophy is a symptom of MDD and not the cause. For instance, Willner, Scheel-Krüger, and Belzung (2013) propose that depression is due less to hippocampal size and more due to its connections to other brain regions. Future research should therefore strive to explicitly define the role of the hippocampus in MDD. Additionally, future research studies should seek to eliminate any confounding that the experience of childhood maltreatment has on hippocampal atrophy in MDD. This potential confounding is due to the high rates of childhood maltreatment in populations diagnosed with MDD. In general, understanding the precise role of hippocampal atrophy in MDD will help clinicians best detect individuals at risk for the disorder.

In conclusion, the literature presented in this review holds great value due to the prevalence and pervasiveness of both childhood maltreatment and MDD. While research remains to be conducted, it is obvious that the similar neurobiological effects of childhood maltreatment and MDD is key to the maintenance of depression as well as a more severe illness course.

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