The Impact of Stress and Major Depressive Disorder on Hippocampal and Medial Prefrontal Cortex Morphology

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Abstract

Volumetric reductions in the hippocampus and medial prefrontal cortex (mPFC) are among the most well documented neural abnormalities in major depressive disorder (MDD). Hippocampal and mPFC structural reductions have been specifically tied to MDD illness progression markers, including greater number of major depressive episodes (MDE), longer illness duration, and non-remission/treatment resistance. Chronic stress plays a critical role in the development of hippocampal and mPFC deficits, with some studies suggesting that these deficits occur irrespective of MDE occurrence. However, preclinical and human research also points to other stress-mediated neurotoxic processes, including enhanced inflammation and neurotransmitter disturbances, which may require the presence of a MDE and contribute to further brain structural decline as the illness advances. Specifically, hypothalamic-pituitary-adrenal axis dysfunction, enhanced inflammation and oxidative stress, and neurotransmitter abnormalities (e.g., serotonin, glutamate, gamma-Aminobutyric acid) likely interact to facilitate illness progression in MDD. Congruent with stress-sensitization models of MDD, with each consecutive MDE, it may take lower levels of stress to trigger these neurotoxic pathways leading to more pronounced brain volumetric reductions. Given that stress and MDD have overlapping and distinct influences on neurobiological pathways implicated in hippocampal and mPFC structural decline, further work is needed to clarify which precise mechanisms ultimately contribute to MDD development and maintenance.

Keywords

hippocampus; medial prefrontal cortex; stress; depression; illness progression

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Major depressive disorder (MDD) is frequently a chronic, progressive illness. Approximately 60% of individuals with MDD will experience recurrent episodes and each successive episode carries a 10–20% risk of failing to remit with current therapeutic approaches (1). While several neural pathways have been linked to the development and recurrence of depression, the hippocampus and medial prefrontal cortex (mPFC) have been repeatedly implicated in the pathophysiology and progression of this illness (2,3).

In this review, we examine clinical and preclinical data pointing to the pivotal role of stress in the development of hippocampal and mPFC abnormalities in depression and a chronic (often treatment-refractory) course of the disorder. Based on existing evidence, we propose a model (Figure 1), by which chronic/severe life stress can trigger the initial development of mPFC and hippocampal volume reductions. However, these reductions are neither necessary nor sufficient for inducing a major depressive episode (MDE). On the other hand, stress also instigates other neurotoxic processes (hypothalamic pituitary adrenal (HPA) axis dysregulation, inflammation, oxidative stress, neurotransmitter disturbances) that interact and may drive the development of a chronic type of MDD marked by further reductions in hippocampal and mPFC volumes. Expanding on recent conceptualizations, we highlight how each of these stress-linked neurotoxic processes has been related to hippocampal and mPFC structural aberrations and the development of persistent courses of depression.

Hippocampus and mPFC volume reductions: Cause versus consequence of MDD?

MDD is phenomenologically, etiologically, and pathophysiologically highly heterogeneous. Consequently, identifying reliable biological or imaging markers has been significantly more challenging than anticipated. One exception has been structural imaging of the hippocampus and mPFC; several meta-analyses have demonstrated that, relative to healthy controls (HCs), individuals with MDD show reduced hippocampus and mPFC volumes, including dorsal and ventral mPFC portions (dmPFC/vmPFC) extending into the medial orbital frontal cortex (mOFC) as well as dorsal and rostral portions of the anterior cingulate cortex (rACC/dACC) (2,4–14). These meta-analyses have reported moderate effect sizes for reduced hippocampal volume in MDD (Cohen's d range = −0.41 to −0.47; 6,8,9). While most studies have examined the whole hippocampus due to spatial resolution limitations, those that have parcellated the hippocampus into different subfields have found evidence for reduced cornu ammonis 1–3, dentate gyrus/cornu ammonis 4, and subiculum volumes as well as both anterior and posterior subdivisions in MDD (e.g., 15,16). With respect to mPFC volume reductions, small to large effect sizes have been reported (Figure 2). Given that extant meta-analyses have also included portions of the PFC outside of the mPFC, we focused on calculating effect sizes for individual studies that targeted aspects of the mPFC, including the vmPFC/mOFC, the rACC/dACC, and the dmPFC (Figure 2 and Supplementary Table 1). Additionally, these estimates are likely impacted by antidepressant use and presence of other psychiatric comorbidities, given that they were not exclusionary in most studies. Notably, longitudinal studies have shown that common antidepressants lead to increases in hippocampus and mPFC volumes (17). Moreover, individuals with MDD and an anxiety disorder were found to have more pronounced mPFC reductions than those with just one

disorder (18). Despite these effects, the volume reduction findings remain significant even when accounting for antidepressant use and common psychiatric comorbidities (5,7,8).

While the presence of hippocampal and mPFC volume reductions in first-onset MDD is mixed (2,7), they have been consistently associated with markers of a progressive course of MDD characterized by more recurrent episodes/relapses (3,19–25), longer illness duration (24,26–30), and non-remission/treatment resistance (28,31–38). Importantly, a meta-analysis found that hippocampus volume reduction was only found in patients who had been depressed for at least two years and had more than one episode (2). More critically, longitudinal work has shown that hippocampal and mPFC volume reductions become more pronounced when depressive symptoms do not remit (35,38). These findings suggest that hippocampal and mPFC volume reductions may be a selective marker for the propensity towards and/or the consequence of episodic recurrence. However, contrary to this, several other studies have found that these structural changes may reflect a pre-existing vulnerability to a MDE, particularly for individuals with certain genetic profiles and/or early life stress (ELS) histories (39–45).

Interestingly, a preclinical longitudinal study involving a chronic mild stress model of depression attempted to directly address the cause/consequence debate (46). This study found that both resilient rats and susceptible rats exhibiting a depressive phenotype were characterized by reduced hippocampal cell proliferation. Additionally, amongst the susceptible rats, the development of depressive behaviors occurred prior to reductions in hippocampal cell proliferation (46). These results contradict both causal and consequence hypotheses of hippocampal abnormalities in MDD. Instead, this study suggests that hippocampal changes result from stress and are likely independent of MDE development. Consistent with this hypothesis, other preclinical work has demonstrated similar stress-related microstructural changes in the hippocampus in both resilient mice and mice exhibiting depressive behavior (47). Additionally, longitudinal human imaging work has highlighted that greater baseline life stress was associated with the development of smaller hippocampal volumes three months later in a sample of HCs (48). A possible explanation for these seemingly contradictory findings may be that chronic stress drives initial hippocampal and mPFC abnormalities, but other risk factors need to be present (e.g., genetic, abnormal physiological response to stress) for development of a MDE. Moreover, possibly via the upregulation of stress-induced neurotoxic processes (e.g., inflammation, oxidative stress), further hippocampal decline occurs among individuals who develop chronic MDD. While the presence of hippocampal and mPFC damage alone may not be sufficient for inducing a MDE, recent work has shown that the induction of long-term potentiation within the hippocampus is sufficient to generate antidepressant effects (49). Thus, abnormalities within these structures may nevertheless contribute to the maintenance or exacerbation of depressive symptoms (see Table 1 for a cause versus consequence debate synopsis).

Stress and hippocampal/mPFC volume reduction in MDD

Two classes of stress-related models, the stress sensitization and stress autonomy models, have been proposed to explain how relationships between stress and depression change as a function of illness course (50). Both models posit that while first MDEs are highly likely to

follow periods of severe stress, the strength of this relationship declines as a function of illness course. However, while the stress sensitization model hypothesizes that with recurrent episodes of depression, more minor stressors are capable of triggering MDEs, the stress autonomy model posits that successive MDEs develop independently of stressful life events. In support of both models, prospective studies have found that the likelihood of a severe stressful life event occurring in the three months prior to an MDE onset was reduced amongst those with a prior history of depression compared to those experiencing their first MDE (51,52). However, more consistent with the stress sensitization model, these longitudinal studies also found that the likelihood of a MDE onset increased when nonsevere life stressors were present in the three months prior to the episode amongst those with a prior history of depression (51,52).

Additionally, cross-sectional research examining the role of stressful life events in hippocampal and mPFC anomalies in MDD is supportive of both stress models. A human study found that a greater number of stressful life events in the three-months prior to an initial MDE was linked to increased hippocampal volume reductions in males with a first MDE (53). However, a recent study demonstrated that individuals with a history of multiple MDEs exhibited smaller hippocampal and mPFC volumes, yet reported less perceived life stress, compared to those with fewer episodes (3). This suggests that while high levels of stress may have an important role in initiating hippocampal vulnerabilities amongst individuals with a first MDE, this relationship may be weaker amongst those with recurrent MDEs. However, given the cross-sectional nature of this study, it is unclear whether the hippocampal declines were driven by lower stress levels (supportive of a stress sensitization model) or are occurring independent of stress (supportive of a stress autonomy model). Future prospective work is needed to clarify whether hippocampal and mPFC volume decline related to MDD illness progression are linked to stress dependent or independent mechanisms.

While stress-related models of MDD have historically focused on relationships between recent life stressors and MDE onset, researchers have expanded these models to incorporate ELS. Consistent with the stress sensitization model, longitudinal research examining relationships between ELS, recent life stressors, and development of MDEs has shown that individuals with an ELS history are more prone to developing an MDE under less amounts of recent life stress than those without an ELS history (54,55). Further bolstering connections between ELS and illness progression, a meta-analysis found that a history of childhood maltreatment was associated with a greater probability of developing recurrent and persistent cycles of depression as well as treatment-resistance (56). Imaging studies have also demonstrated that an ELS history was associated with hippocampal and mPFC volumetric decline (57–65). Some of these studies have noted that the relationship may be independent of the presence of MDD (61,64,65). However, the link between ELS and the development of chronic courses of depression marked by greater hippocampal and mPFC damage may be mediated by the persistent manifestation of neurotoxic processes that are triggered by even minor stressors. Congruent with this idea, one study found that individuals with an ELS history, both with and without an MDD diagnosis, exhibited increased adrenocorticotropic hormone (ACTH) levels in response to a moderate laboratory stressor compared to HCs and individuals with MDD without ELS. Individuals with both an MDD

diagnosis and an ELS history showed the highest stress-related ACTH response (66). Fitting stress sensitization models of MDD, there is also evidence that ELS enhances inflammatory responses to minor daily life stressors in adulthood (67). However, further longitudinal work linking ELS, recent life stress, neural deficits, and the development of recurrent depressive cycles is warranted to further clarity these relationships.

The role of HPA axis dysregulation in stress-mediated hippocampal and mPFC deficits

Animal models have established that prolonged stress can lead to HPA axis hyperreactivity and depressive behaviors along with hippocampal and mPFC abnormalities (68,69). Specifically, excessively high as well as blunted glucocorticoid receptor expression has been linked to reduced neurogenesis within the dentate gyrus (69). Higher circulating levels of glucocorticoids have also been shown to cause neuronal atrophy and dendritic retraction within the mPFC (70).

In accordance with the animal literature, a meta-analysis of clinical studies noted that individuals with MDD showed higher basal cortisol levels, particularly in the afternoon when cortisol levels should be dropping (71). However, this meta-analysis highlighted substantial variability in HPA axis functioning in MDD (71). Longitudinal studies have found that both enhanced and blunted cortisol levels predicted MDE recurrence amongst those with a prior history of MDD (72–74). Similarly, cortisol responses to a laboratory psychosocial stressor in MDD are mixed, with some showing cortisol hyperreactivity, while others hyporeactivity (75,76).

One of the factors complicating the interpretation of abnormal cortisol levels in MDD is the potential presence of glucocorticoid resistance (77). A lower cortisol output may reflect its bioavailability or it may be an indicator of reduced responsiveness to the presence of glucocorticoids (77). Additionally, even in the presence of cortisol hypersecretion, elevated cortisol may represent an attempt to counteract inflammatory responses in the presence of high glucocorticoid levels (77). Thus, a measure of glucocorticoid expression is also needed to clarify the pathophysiology of HPA axis aberrations leading to MDD-related neural abnormalities. Another confounding factor is antidepressant use, which has been found to reduce HPA axis activity (78). Thus, further research is needed to tease apart which mechanisms may contribute to different aspects of HPA dysregulation in depression.

Relatedly, HPA axis dysregulation has also been associated with hippocampal and mPFC structural abnormalities. Specifically, higher baseline cortisol levels as well as higher cortisol/dehydroepiandrosterone (DHEA) ratios have been linked to smaller hippocampal and mPFC volumes amongst HC and MDD samples (79,80), further highlighting the importance of stress (rather than the presence of MDD per se) in facilitating initial structural damage. Critically, animal models have shown that DHEA reduces the adverse effects of cortisol on the central nervous system (81), so it is likely important to consider other stress-related hormones when assessing cortisol levels.

However, in addition to these positive findings, several imaging studies in MDD have failed to find associations between cortisol and structural abnormalities (82–87). This may partly reflect evidence supporting the impact of chronic stress and persistent types of MDD on mPFC and hippocampal morphology. Importantly, these studies did not report on levels of life stress prior to neuroimaging assessment. Moreover, none of these studies examined whether relationships between structural deficits and cortisol levels vary as a function of clinical MDD illness progression markers (e.g., number of MDEs, illness duration) of MDD. Additionally, given that these studies are cross-sectional, and brain structural changes may occur long after stress exposure, prospective studies are needed to link distinct cortisol trajectories with different life stress profiles, structural deficits, and illness course. This would clarify potential HPA axis-related mechanisms leading to hippocampal and mPFC decline in MDD.

Stress-mediated inflammatory pathways to hippocampal and mPFC deficits in MDD

Another possible stress-related mechanism linking structural changes in the hippocampus and mPFC to MDD illness progression is inflammation (88). Particularly relevant to this review, animal models have demonstrated that chronic unpredictable stress promotes the production of pro-inflammatory cytokines in the hippocampus (89) and mPFC (90,91). Moreover, the stimulating effects of peripheral pro-inflammatory cytokines on brain microglia can result in reduced hippocampal neurogenesis (92). Thus, stress-mediated enhancement of central and peripheral pro-inflammatory cytokines may contribute to subsequent structural alterations. With respect to connections with MDD, a preclinical chronic stress study demonstrated that mice exhibiting anhedonic behavior (but not stress-resilient mice) showed enhanced inflammation in the mPFC (90). This suggests that some stress-related mPFC and hippocampal inflammatory processes may require the presence of depressive symptomology in addition to stress.

Accordingly, recent imaging studies in depressed individuals have reported enhanced neuroinflammation in the hippocampus and mPFC compared to HCs (93,94). Additionally, higher levels of peripheral pro-inflammatory cytokines, greater expression of inflammation-related genes, and reduced expression of neuroprotective genes, have all been associated with greater hippocampal volume decline and mPFC thinning in MDD (95–97). Enhanced peripheral inflammation has also been related to MDD recurrence/relapse, number of episodes, illness duration, and treatment non-response (98–100). However, responders to antidepressant treatment showed reduced peripheral inflammation over the course of treatment compared to nonresponders (101).

Oxidative stress as a mechanism contributing to MDD-related brain structural deficits

Closely tied to inflammatory mechanisms, preclinical studies have also demonstrated that chronic stress initiates production of oxidative stress and impairment of antioxidant defense mechanisms in the hippocampus and mPFC (102). This can result in hippocampal and

mPFC cellular damage and reduced hippocampal neurogenesis (102), likely contributing to hippocampal and mPFC atrophy. With respect to MDD, increased oxidative stress, lower antioxidant levels, and imbalanced oxidant:antioxidant levels have been well documented within the hippocampus (103,104) and mPFC (104–106), resulting in associated markers of DNA/RNA damage in these regions. While few studies have examined relationships between oxidative stress and brain structural deficits in MDD, one found that lower antioxidant levels were associated with more pronounced hippocampal volume reductions in MDD (107). Consistent with neural markers of progressive illness, greater oxidative stress, lower antioxidant, and greater oxidative stress-related DNA/RNA damage have been linked to clinical markers of MDD illness progression, including greater chronicity, more MDEs, and treatment resistance (98,108–113). Conversely, response to antidepressant treatment has been shown to normalize the oxidant: antioxidant imbalance seen in MDD (108). Findings to date suggest a psychosocial stress-induced oxidative stress pathway that contributes to hippocampus and mPFC structural deficits in MDD.

Serotonin dysfunction contribute to brain structural decline and MDD illness progression

Neurotransmitter disturbances, such as serotonin dysfunction, are likely prominent pathways to illness progression in MDD. Preclinical chronic mild stress models of depression show reduced serotonin concentration, expression, release, and neurotransmission in both the hippocampus and mPFC (114–116). Interestingly, a study comparing stress-resilient mice versus those exhibiting anhedonic behavior noted that stress-elevated expression of $5HT_{2A}$ receptors within the mPFC occurred in both groups of mice, whereas additional 5-HT transporter elevations occurred exclusively in the depression-susceptible mice (90). This suggests that some stress-related serotonergic abnormalities are independent of the development of depressive behavior, whereas others were specific to anhedonia development.

While the animal literature has demonstrated clear pathways to serotonin dysregulation within specific brain regions that are linked to depressive behaviors, human imaging findings in MDD have been more mixed (117–119). There has been evidence of decreased $5HT_{1A}$ mRNA levels within the hippocampus of individuals with MDD compared to HCs (117). Conversely, two recent meta-analyses failed to find significant alterations in serotonin transporter binding/availability in the hippocampus and mPFC in MDD (118,119). Discrepancies may be due to clinical heterogeneity, including illness stage, particularly since greater serotonin dysfunction has been described amongst individuals with MDD who have experienced a greater number of past MDEs (120).

Few studies have examined associations between hippocampal/mPFC volume reductions and serotonin system dysfunction. Recent longitudinal studies have linked smaller hippocampal volumes to MDD onset among individuals with ELS and carrying the s allele of the serotonin transporter gene, which is associated with reduced serotonin uptake (44,45). One of these studies noted that greater parental display of positive behaviors was protective against hippocampal volume reductions amongst those carrying the s allele. However, these

connections have yet to be explored in conjunction with MDD illness progression markers, which is an important area for future research given the connection between greater serotonin dysfunction and number of MDEs. Additionally, more studies are needed to clarify which serotonergic disturbances are consequences of stress that do not necessarily lead to MDD, and which result in MDD development.

Glutamatergic contributions to MDD-related brain structural decline

The glutamate system is also highly impacted by stress. Chronic stress disrupts glutamate release, glutamate clearance from the synapse, and glutamate transmitter expression, but the direction of the effects is region-specific (121). Some studies have reported enhanced chronic stress-related glutamate release and glutamate receptor expression, but reduced glutamate clearance/metabolism in the hippocampus (122,123). A study that directly compared stress-resilient to stress-susceptible mice displaying depressive behaviors indicated that enhanced hippocampal glutamate expression was unique to depression-susceptible mice (122). A different pattern has been described in the mPFC, with some reporting reduced chronic stress-related glutamate receptor expression, which has been speculated as a potential protective mechanism against excessive glutamate signaling and excitoticity (e.g., 124–125). However, these studies did not examine potential differences between stress-resilient versus MDD susceptible mice. In contrast to these results, reduced glutamate clearance (and thus enhanced accumulation of glutamate in the mPFC) has been shown to produce anhedonic behaviors (126). Accordingly, increased chronic-stress related glutamate expression in the hippocampus and mPFC may be unique to those who develop the depressive phenotype.

With respect to *in vivo* human imaging work in MDD, magnetic resonance spectroscopy (MRS) studies have provided evidence of glutamate dysfunction in MDD (e.g., 127,128). However, the glutamate measures are primarily intracellular, so it is difficult to interpret relationships with glutamate neurotransmission. Additionally, many of these studies have reported on combined glutamate and glutamine (Glx) metabolite levels or metabolite ratios, further complicating interpretations. Generally, studies have found reduced Glx/glutamate levels in the mPFC and hippocampus in MDD, with those having a more chronic course showing greater declines compared to individuals experiencing a first episode (127,128). While difficult to interpret, reduced glutamate levels may reflect cellular abnormalities associated with decreased glutamate availability resulting from hyperactive glutamate neurotransmission (129). While yet to be applied to MDD samples, a human imaging study noted associations between increased extracellular glutamate levels and hippocampal volume reductions (130).

There is also emerging evidence of impaired glutamate-glutamine cycling in the mPFC and hippocampus amongst those with MDD. Glutamate is produced in neurons from glutamine by glutamase. Astrocytes uptake glutamate once it is released from the synaptic terminal and convert glutamate back to glutamine via glutamine synthase. A preclinical study showed that inhibiting glutamine synthase and glutamine transport in the mPFC led to the development of depressive behavior (131). Additionally, another preclinical study showed that enhanced stimulation of glutamate cycling in the mPFC via three different classes of antidepressants

was associated with the onset of rapid antidepressant action (132). Several human postmortem studies have also shown reductions in the expression of several components critical to astrocyte function, largely in the mPFC, but also some evidence in the hippocampus, suggesting impaired glutamate-glutamine cycling (133). Together, these findings indicate that glutamate dysregulation likely has a strong role in neural and clinical markers of MDD illness progression MDD.

GABAergic disturbances associated with brain structural decline and chronic MDD

GABA is also likely centrally involved in hippocampal and mPFC abnormalities in MDD (134). With respect to preclinical models of depression, chronic stress has been shown to decrease GABA expression in the hippocampus and mPFC (135,136). Serotonin is known to regulate the GABAergic system (137). Therefore, when the serotonin system is dysregulated, this can contribute to reduced GABAergic inhibitory control, resulting in enhanced glutamate and HPA axis reactivity, and ultimately reduced hippocampal neurogenesis (124,138).

Several human MRS studies have reported lower mPFC GABA levels in MDD (139–141). Reduced mPFC GABA levels in MDD have been associated with smaller hippocampal volumes (139) and treatment resistance (142,143). However, antidepressants known to target the monoaminergic system have also shown to counteract GABAergic abnormalities (134). This suggests that GABA may have a key role in multiple pathways leading to hippocampal and mPFC structural deficits in MDD and treatment resistance.

A common pathway leading to MDD illness progression-related hippocampal and mPFC volume reductions

Based on the above evidence, it is likely that these neurotoxic processes interact to form multiple pathways leading to hippocampal and mPFC volume decline and MDD illness progression. One possible common pathway involves chronic stress triggering HPA axis dysfunction and enhanced production of cell-mediated immune cytokines, which activate indoleamine 2,3-dioxygenase (IDO;68). IDO is an enzyme that catabolizes tryptophan leading to serotonin depletion and production of kynurenine. Kynurenine is then converted to neuroprotective metabolites (kynurenic acid (KynA)) or neurotoxic metabolites (3-hydroxykynurenine (3HK), and quinolinic acid (QA)) (68). The production of neurotoxic 3HK and QA leads to increased glutamate and oxidative stress as well as reduced GABAergic inhibitory control. Given the connection between serotonin and GABA, reduced serotonin also contributes to decreased GABA expression. Together, this pathway may trigger hippocampal and mPFC cellular damage and volume reductions (138,144,145). In line with stress sensitization models, with each successive MDE, it may take smaller amounts of stress to trigger these pathways and produce further brain structural decline. Early life stress and genetic risk profiles may program this vulnerability early on by enhancing psychological and biological reactivity to minor stressful life events (Figure 3). In support of this pathway, a study found that a lower KynA/3HK ratio correlated with reduced

hippocampal volumes in MDD and partially mediated the relationship between MDD and mPFC cortical thinning (146,147). Additionally, preclinical evidence suggests that neurotoxic dorsal hippocampal kynurenine metabolism may drive depressive behavior when inflammation is enhanced (148).

Conclusions

The proposed model provides numerous directions for future research. Much of the preclinical literature has focused on the impact of chronic stress on the hippocampus and mPFC, without directly comparing animals that did not exhibit depressive behaviors (resilient phenotype) versus those exhibiting depressive behaviors (susceptible phenotype). Those studies that directly compared the two groups have provided some promising leads on identifying which neurotoxic processes affecting hippocampal and mPFC structure are unique to the development of depression. This work can inform which neurotoxic components to target in future prospective studies of MDD and brain structural decline. Prospective studies focusing on "at risk" samples by virtue of living in highly stressful environments, would address which stress-related neurotoxic processes affecting hippocampal and mPFC structure are relevant to MDD onset and which processes are implicated at different stages of MDD illness. Additionally, these studies would clarify temporal relationships between neurotoxic processes, hippocampal and mPFC structural aberrations, and MDD illness progression. This would allow for a more precise identification of stress-related mechanisms signifying biomarkers of MDD, which could lead to more effective treatment targets.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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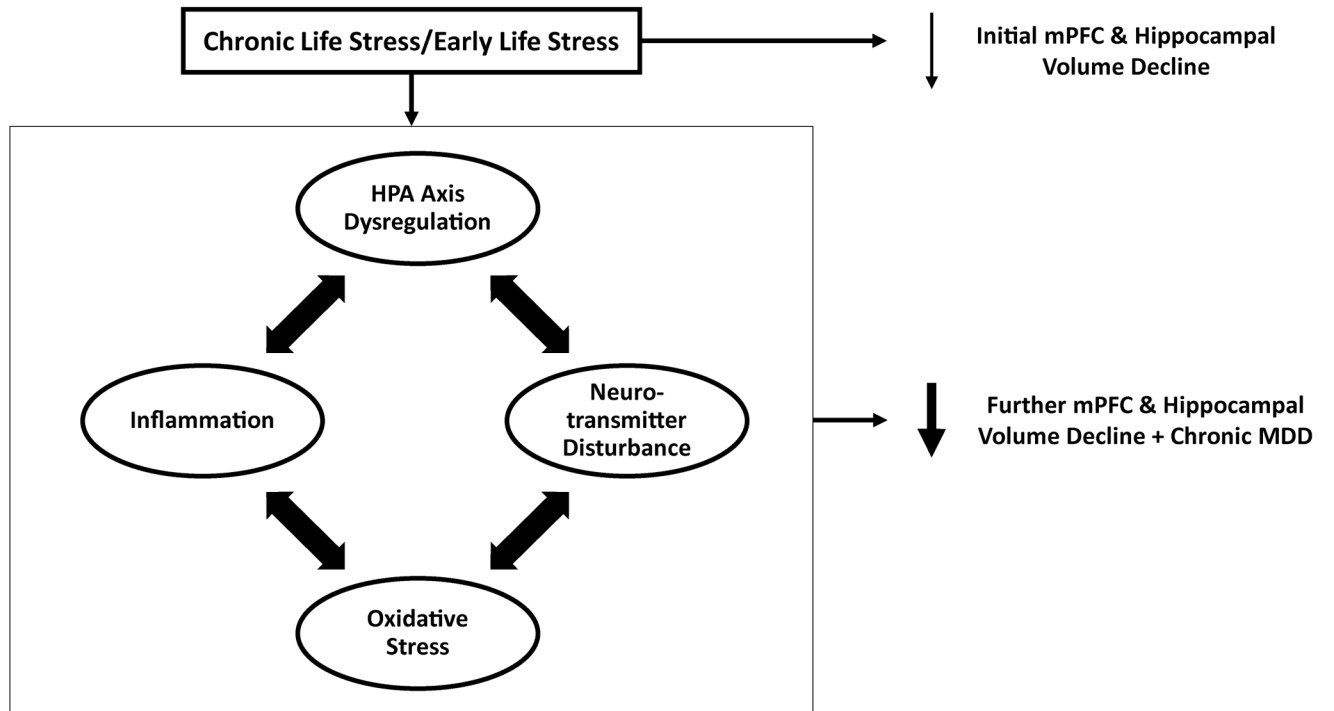
Figure 1. The Role of Chronic Stress and Neurotoxic Processes on Brain Volumetric Reductions and MDD Illness Progression.
Chronic life stress can trigger the initial development of medial prefrontal cortex (mPFC) and hippocampal volume reductions. However, these reductions are neither necessary nor sufficient to produce a major depressive episode. On the other hand, stress also initiates a set of neurotoxic processes (hypothalamic pituitary adrenal (HPA) axis dysregulation, inflammation, neurotransmitter disturbances) that interact and may drive the development of a more chronic type of MDD marked by further reductions in hippocampal and mPFC volume reductions.
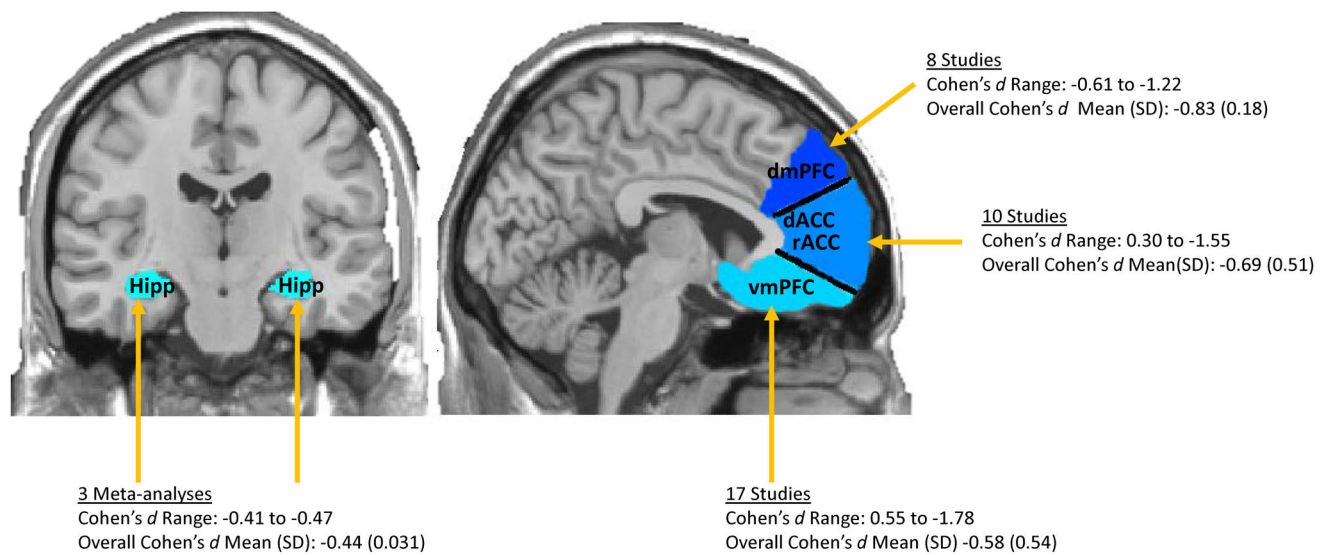
8 Studies
Cohen's *d* Range: -0.61 to -1.22
Overall Cohen's *d* Mean (SD): -0.83 (0.18)

10 Studies
Cohen's *d* Range: 0.30 to -1.55
Overall Cohen's *d* Mean(SD): -0.69 (0.51)

3 Meta-analyses
Cohen's *d* Range: -0.41 to -0.47
Overall Cohen's *d* Mean (SD): -0.44 (0.031)

17 Studies
Cohen's *d* Range: 0.55 to -1.78
Overall Cohen's *d* Mean (SD) -0.58 (0.54)

Figure 2. Estimated Effect Sizes of Hippocampal and mPFC Volume Reductions in MDD.
The medial prefrontal cortex (mPFC) includes ventral portions of the mPFC (ventral medial prefrontal cortex; vmPFC, medial orbitofrontal cortex; mOFC) and dorsal portions of the mPFC (dorsal medial prefrontal cortex; dmPFC) as well as rostral anterior cingulate cortex; rACC and dorsal anterior cingulate cortex; dACC). In this figure, we provide a range, mean (standard deviation) of effect sizes calculated from individual studies for each of the mPFC subdivisions. We also provide a range, mean (standard deviation) of effect sizes for reduced hippocampal volumes in MDD calculated from three prior meta-analyses. Negative effect size values indicate that those with MDD have reduced mPFC and hippocampal volumes compared to healthy controls.
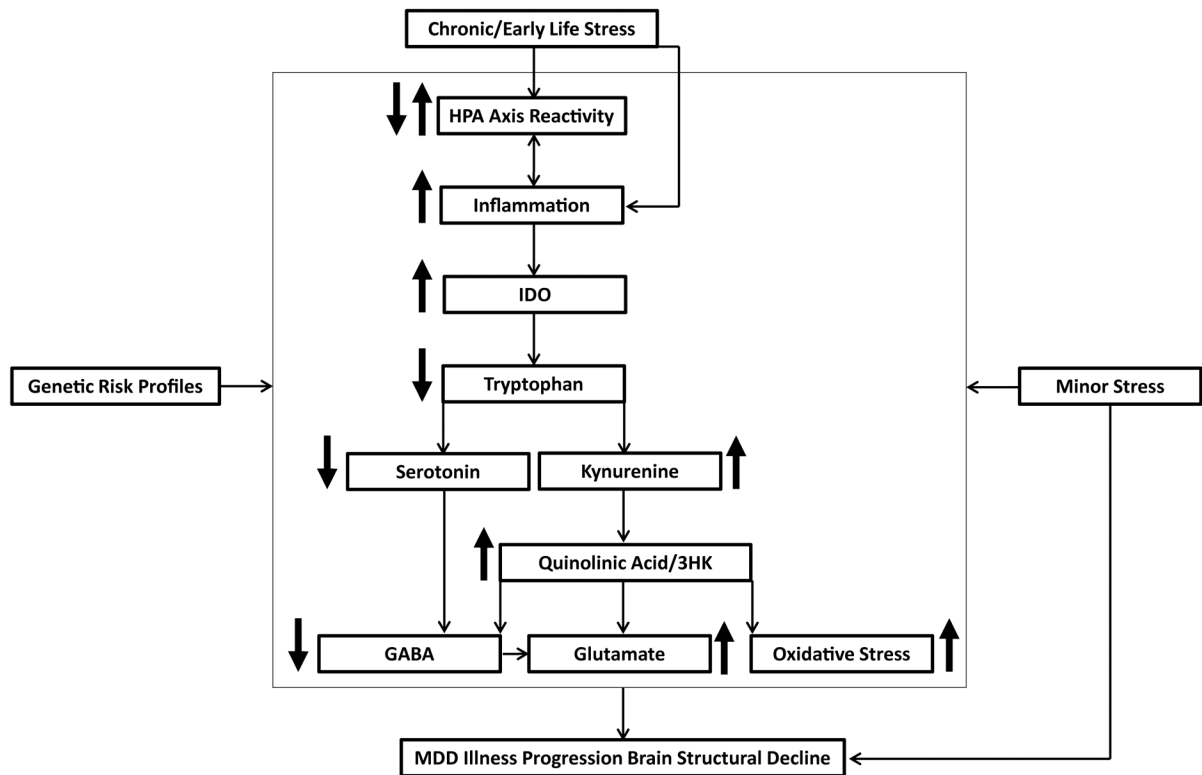
Figure 3. A Stress-Mediated Neurotoxic Pathway Leading to Chronic MDD Hippocampal and mPFC Volume Reduction.

Chronic stress sets off a cascade of neurotoxic processes. The presence of chronic stress triggers dysregulation of the hypothalamic pituitary adrenal (HPA) axis, which can either be enhanced or blunted due to glucocorticoid resistance. This HPA axis dysregulation triggers the immune system, leading to enhanced inflammation (stress can also have a direct effect on inflammation not mediated by the HPA axis). In turn, enhanced inflammation can produce further dysregulation of the HPA axis. Pro-inflammatory cytokines then activate indoleamine 2,3-dioxygenase (IDO), an enzyme that catabolizes tryptophan, which leads to serotonin depletion and the production of kynurenine. Kynurenine can be converted to neurotoxic 3HK and quinolinic acid, which can increase glutamate release and oxidative stress, as well as reduce GABA inhibitory control. Dysregulated serotonin levels lead to further reductions in GABA inhibitory control. This reduction in GABA inhibitory control can lead to further glutamate release. With successive major depressive episodes, even minor levels of stress can trigger this pathway, leading to further hippocampal and mPFC volume decline. Genetic risk profiles can also increase vulnerability to chronic stress triggering of these neurotoxic pathways to illness progression and brain structural decline.

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Table 1.

A summary of the cause versus consequence debate of hippocampal and medial prefrontal cortex (mPFC) volume reductions in major depressive disorder (MDD). A body of human research has supported the hypothesis that hippocampal and mPFC volume reductions occur prior to the onset of depression, and ultimately cause a first major depressive episode (MDE). However, independent evidence has shown that hippocampal and mPFC deficits are only found amongst those with a history of major depressive episodes and greater illness progression. Further, a third hypothesis has emerged from preclinical and human research, demonstrating that hippocampal and mPFC deficits are produced by stress and occur irrespective of whether depressive symptomology emerges.

Cause *mPFC and hippocampal volume reductions cause initial MDD onset*	**Consequence** *mPFC and hippocampal volume reductions occur as a result of having multiple major depressive episodes*	**Independence** *mPFC and hippocampal volume reductions are a result of stress and independent of MDD development*
• Longitudinal human studies showing mPFC and hippocampal volume reductions occur prior to MDD onset (40, 44, 45)	• mPFC and hippocampal volume reductions correlate with MDD illness progression markers (3, 19–38)	• Chronic stress animal models show that hippocampal abnormalities occur in both stress-resilient and MDD-susceptible animals (46,47)
• Human studies showing hippocampal and mPFC volume reductions in unaffected samples at increased risk for MDD (39, 41–43)	• Longitudinal studies show mPFC and hippocampal volume reductions are more pronounced when MDD does not remit (35,38)	• Studies have linked chronic life stress with hippocampal volume reductions in healthy individuals (48)