

# Stress-Induced Brain Atrophy: A Role for Orthomolecular Medicine

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**Abstract** *Brain structure can be shaped and remodeled by several important environmental factors throughout an individual's life course, with nutrition and chronic stress two of the most established environmental factors. Stress-induced atrophy in key brain regions is thought to play a central role in the development of mental health disorders including depression, psychosis, and cognitive decline. Conversely, nutrients, in particular the omega-3 fatty acids and homocysteine-lowering B vitamins, can improve mental health and are potent modulators of brain structure with evidence suggesting that personalized nutritional interventions may increase neurogenesis, restore brain structure and protect the brain from the damaging effects of stress. Furthermore, nutritional interventions may augment and improve the potential for behavioral therapies and lifestyle changes to reverse brain atrophy and, in turn, improve mental and physical wellbeing.*

## Introduction

Brain structure, especially that of the amygdala, hippocampus and prefrontal cortex, can be shaped and remodeled by several important environmental factors throughout an individual's life course.<sup>1</sup> The amygdala, hippocampus and prefrontal cortex are collectively involved in emotional processing, mood regulation, and higher functions such as memory and cognition, and thus these brain regions are crucial for maintaining resiliency to stress and subsequently safeguarding mental and physical wellbeing.<sup>2</sup>

Structural changes in the brain are thought to play a central role in the "neurotrophic hypothesis" of mental health disorders, including the development and maintenance of depression, anxiety, psychosis, and cognitive decline.<sup>3-6</sup> The neurotrophic hypothesis proposes that an individual's mental health may be influenced by underlying changes in brain structure as a result of factors that can decrease, or increase, the ability of neurons to survive and function.<sup>7</sup> The pre-

frontal cortex, hippocampus, and amygdala are particularly sensitive to stress-induced change, and can conversely be favorably influenced by interventions that harness their potential for rapid remodeling, thus these particular brain regions are primary targets for preventative and curative interventional therapies.<sup>8</sup>

Two major and well-established factors that influence brain structure are chronic psychological stress and nutrition. The evolutionary expansion of the human brain is thought to have not been possible without access to both a high quality diet and the appropriate nutritional substrate for neurogenesis, an understanding that has immediate relevance to mental health today.<sup>9</sup> Because of the ability of nutritional factors to influence mental health and neuroplasticity, nutritional therapy is an important means of influencing molecular pathways that influence brain structure.<sup>10</sup> Subsequently, a number of dietary components and nutritional supplements have received attention as candidates

for the treatment and prevention of mental illness because of their potential for improving brain plasticity including fatty acids, polyphenols, vitamins, minerals and amino acids.<sup>11-15</sup>

While optimal nutrition may improve brain structure, exposure to chronic stress, on the other hand, can have deleterious effects. Atrophy of nerve cells in the hippocampus (involved in learning and memory) and prefrontal cortex (working memory, executive function) and hypertrophy of amygdala (fear response) are consequences of chronic stress and biological features of stress-related illness.<sup>16</sup> These changes are thought to occur because of reduced brain plasticity, which, at least in part, appears to be the result of changes in glutamatergic activity and consequential shrinkage of hippocampal and prefrontal cortex neurons.<sup>17</sup> In addition, chronic stress results in an adaptive increase in the size and activity of the amygdala.<sup>18</sup>

Chronic psychological stress and nutrition may influence brain physiology and wellbeing in a synergistic and highly individualized fashion at both the molecular and environmental level.<sup>19</sup> Omega-3 polyunsaturated fatty acid (omega-3 PUFA) availability in the cerebral environment, for example, is influenced by dietary intake and can counteract the deleterious effects of stress on the brain, an effect that may in part explain the positive correlation between higher dietary omega-3 PUFA intake and lower incidence of stress-related disorders such as anxiety and depression.<sup>20</sup> Further, it is known that the ability to metabolize and synthesize omega-3 PUFAs is genetically determined and may be dramatically different between individuals, in turn influencing a person's nutritional requirements and disease susceptibility.<sup>21</sup>

Emerging evidence suggests that personalized nutritional therapy, or orthomolecular medicine, is an important means of supporting optimal mental health by the provision of nutrients involved in the remodeling and building of a healthier, more resilient brain. The aim of this review is to explore recent evidence for nutritional interventions that can favorably influence the structure of the brain, in particular the prefrontal cortex, hip-

pocampus, and/ or amygdala while ultimately improving mood and cognition. Emphasis will also be placed on a basic principle of orthomolecular medicine; that is, that the optimization of nutritional intake through dietary modification or nutritional supplementation will vary from person to person based on their unique biological individuality.<sup>22</sup>

### **Omega-3 Polyunsaturated Fatty Acids**

In 1972, an essential role of the fatty acids arachidonic (AA) and docosahexaenoic acid (DHA) in brain development and function was first established by Crawford and Sinclair who then went on to demonstrate that a dietary deficiency of omega-3 PUFAs can result in behavioral changes.<sup>23-25</sup> Subsequently, a number of studies have shown that dietary reduction in omega-3 PUFAs results in reduced brain DHA levels and important alterations in brain function including impaired brain development, reduction in the size of neurons and impaired learning, memory and the development of aggressive and depressive behavior.<sup>26</sup> And importantly, DHA has been shown to increase hippocampal neurogenesis and rapidly restore neurite length after experimental deficiency.<sup>27,28</sup>

Some of the first evidence that supplemental omega-3 PUFAs may improve brain structure in humans came from a study in which DHA was administered to five peroxisomal disorder patients.<sup>29</sup> This study found that treatment with DHA normalized or significantly improved brain white matter on MRI imaging.

Subsequently, a pioneering case report detailed symptomatic improvement in a patient with schizophrenia that corresponded with reversal of brain atrophy within 6 months.<sup>30</sup>

Then, in perhaps the first study to directly explore a relationship between dietary omega-3 PUFAs and brain structure, it was found that higher reported consumption of the omega-3 fatty acids eicosapentaenoic (EPA) and DHA was associated with greater volume of the anterior cingulate cortex, amygdala and hippocampus.<sup>31</sup> The authors hypothesized that the observed relation-

ship between dietary omega-3 PUFA and increased brain size in these regions could be due to direct effects of EPA and DHA on neurogenesis and their ability to mitigate stress-induced neuronal atrophy and preserve brain structure.

More recently, a number of studies have found an association between plasma or red blood cell (RBC) omega-3 PUFAs and total brain and hippocampal volumes. Lower plasma EPA was associated with hippocampal and amygdala atrophy in people over 65 years, and in turn was associated with a greater 4-year decline in memory and the development of depressive symptoms.<sup>32</sup> Older age dementia-free women with either low DHA or a low omega-3 index score were found to have lower total brain volumes and higher clinical signs of cognitive aging.<sup>33</sup> In a relatively large study of some 1,111 postmenopausal women, a higher omega-3 index (a well-established measure of omega-3 PUFA status) was associated with larger total brain volume and hippocampal volumes.<sup>34</sup>

In a recent 18-month long clinical study, however, supplementation with DHA (2,000 mg from algae per day) in people with mild to moderate Alzheimer's disease found no measurable decline in the rate of whole brain or hippocampal atrophy compared to placebo.<sup>35</sup> Nonetheless, when taken as a whole compelling evidence suggests that omega-3 PUFAs, in particular DHA, may positively influence brain structure, which may, at least in part, explain observed benefits on cognition and mood.<sup>36</sup>

From a clinical standpoint, advice to increase fatty cold water fish consumption, or optimize intake through supplemental purified DHA or DHA-containing fish oil may be preferred interventions for improving brain structure and mitigating brain atrophy as the biosynthesis of DHA from the precursors alpha-linolenic acid (ALA) or EPA is negligible.<sup>37</sup> For example, in otherwise healthy individuals supplemental ALA conversion to DHA ranged from 0% to 0.04%.<sup>38</sup>

Because preformed DHA appears to be the only means of raising DHA status it has been argued that DHA is in fact a truly es-

sential fatty acid, and that a dietary reference for optimal intake should be established.<sup>39,40</sup> Although an optimal daily intake equivalent is not known, a comprehensive review of evidence from epidemiological, peripheral and central omega-3 PUFA composition studies, and placebo-controlled trials concluded that a daily DHA dose of 400–700 mg per day for children and 700–1,000 mg per day for adults would optimize DHA status for the prevention and management of affective disorders.<sup>41</sup>

Individual variations in omega-3 PUFA status and responses to supplementation are significant and may in turn influence treatment outcomes.<sup>42</sup> A number of factors have been shown to influence omega-3 PUFA status and dose response including genetic factors, body weight, baseline omega-3 PUFA status, age, physical activity, and sex.<sup>43,44</sup> The Omega-3 Index, a measure of the EPA and DHA content of erythrocytes expressed as a percent of total identified fatty acids, may help personalize nutritional recommendations.<sup>45</sup> Although originally established as a cardiovascular risk assessment, the omega-3 index has demonstrated utility in the optimization of nutritional status for mental health. A higher omega-3 index has been correlated with larger total normal brain volume and hippocampal volume, lower depressive symptoms, and better neurocognitive performance under stress.<sup>46-49</sup>

## B Vitamins

As early as the 1960s, B vitamins were being used to lower hereditary homocystinuria, a condition associated with severe mental health disorders and cerebral atrophy.<sup>50-52</sup> It is now known that suboptimal intake of B vitamins can result in hyperhomocysteinemia and that homocysteine is a neurotoxin, which, even at low levels, may have adverse neurological effects including a causal role in brain atrophy.<sup>53</sup> In the central nervous system homocysteine levels are normally kept low by folate and vitamin B<sub>12</sub>-dependent re-methylation to methionine, however elevated homocysteine in the extracellular space is not uncommon and may promote

excitotoxicity, DNA damage and neuronal cell death.<sup>54</sup>

In an illustrative study conducted in otherwise healthy middle-aged women, a robust relationship between retrospective and current plasma homocysteine and total brain volume was discovered.<sup>55</sup> Indeed, a relationship between homocysteine and brain atrophy has been widely reported in people with cognitive impairment, Alzheimer's disease and alcohol-related brain atrophy.<sup>56</sup> Associations between psychiatric illness, overt and sub-clinical folate deficiency, elevated homocysteine and brain atrophy have been made in a number of investigations.<sup>57</sup>

B vitamin therapy has been extensively studied for the treatment and prevention of cognitive decline, with higher quality studies generally finding that certain study subgroups, in particular people with low folate or vitamin B<sub>12</sub> status and/or hyperhomocysteinemia, consistently experience cognitive benefits.<sup>58</sup> More recently, attention has turned directly to the potential for using B vitamin therapy to prevent brain atrophy related to cognitive decline and Alzheimer's disease.

The first study to examine the effects of B vitamin treatment on homocysteine levels and brain atrophy contrasted the effects of B vitamin supplementation (providing 800 mcg folic acid, 500 mcg vitamin B<sub>12</sub> and 20 mg vitamin B<sub>6</sub> daily) to placebo over a 2-year period. The study group consisted of adults with mild cognitive impairment living in England. At the end of the intervention it was found that the group receiving the B vitamins had a slower rate of total brain atrophy with a rate of 0.76% with B vitamins vs. 1.08% for placebo, equating to a reduction in the rate of brain atrophy of almost 30%. Treatment response was associated with baseline homocysteine levels, showing a 53% lower rate of atrophy in the group with the highest quartile of homocysteine (>13.1 mmol/L).<sup>59</sup>

The clinical outcomes of this study have also been reported, with greater cognitive benefits in the group receiving B vitamins compared to placebo.<sup>60</sup> In a more detailed

data analysis, B vitamin treatment was associated with reduced atrophy in specific brain regions, including the medial temporal lobe and hippocampus.<sup>61</sup> Both clinical outcomes and reductions in atrophy of key brain regions were greater in those with higher baseline homocysteine levels.

It is important to note that despite these observations, it may be that brain atrophy is related to B vitamin deficiency independently of hyperhomocysteinemia. In a prospective 5-year study of older adults vitamin B<sub>12</sub> status was associated with brain atrophy whereas homocysteine was not.<sup>62</sup> This was consistent with a subsequent study that also found an association between vitamin B<sub>12</sub> status and total brain volume over a similar time period.<sup>63</sup>

Personalization of dietary or supplemental B vitamin intake may be important as nutrient-gene interactions can influence circulating homocysteine levels and accelerate brain atrophy. A common single nucleotide polymorphism (C677T) in the gene for methylenetetrahydrofolate reductase (MTHFR) is thought to account for the majority of genetic variance in plasma homocysteine levels and increase folate requirements (it is important to note that vitamin B<sub>2</sub> has been shown to lower homocysteine levels in people with the MTHFR 677TT genotype, an effect that may be related to its role as cofactor for the MTHFR enzyme).<sup>64</sup> The importance of this nutrient-gene interaction is supported by an analysis of two independent cohorts that found a significant association between the MTHFR 677T genotype, homocysteine levels in the blood, and brain atrophy in people with mild cognitive impairment.<sup>65</sup>

Finally, it is interesting to note that both acute and chronic psychological stress has been associated with increased homocysteine levels. In men, chronic job-related stress was associated with homocysteine levels, and a study in women found that acute stress, in this case a mental arithmetic and speech stressor, resulted in rapid elevations in homocysteine that returned to baseline during recovery.<sup>66,67</sup> These observations may be explained by the ability of glucocorticoids

to reduce homocysteine metabolism by inhibiting the transcription of cystathionine beta synthase.<sup>68</sup> When the evidence above is taken as a whole it is plausible to suggest that long-term treatment with a combination of homocysteine-lowering B vitamins may benefit mood and cognition and have the effect of preventing brain atrophy, which is likely due to direct effects on neurogenesis, indirectly through homocysteine lowering, and perhaps by modifying the adverse effects of psychological stress on homocysteine levels.

## Discussion

An integrative approach to mental health care involves the simultaneous use of conventional approaches, evidence-based complementary medicine, and therapeutic lifestyle changes.<sup>69</sup> The effect of an integrative intervention would be expected to be additive and are likely to have synergistic, or more than simply additive, effects with the individual components of an intervention enhancing the effects of others.<sup>70</sup>

With the potential synergy of various therapies in mind, it is interesting to note that McEwen has suggested that psychiatric medications with evidence for neurotrophic effects, such as conventional anti-depressants, should not be used without behavioral therapy.<sup>71</sup> The basis for his suggestion is (1) that a medication that increases neurogenesis would be more effective with a behavioral intervention because such interventions are also associated with positive structural brain changes and (2) because pharmacotherapy without a positive behavioral intervention could make matters worse by wiring the brain for stress if the adverse conditions persist. This suggestion has strong relevance to orthomolecular medicine as it implies that the integration of behavioral therapy with nutritional therapy would be a better approach than either therapy alone.

Lending support to this notion successful psychotherapy has been associated with increased brain plasticity and structural and functional changes in the brain.<sup>72</sup> Cognitive behavioral therapy has also been shown to

reduce amygdala size in anxiety sufferers and increase prefrontal cortex volume in patients with chronic fatigue syndrome.<sup>73,74</sup> And an exploratory open label study suggested that omega-3 PUFA supplementation immediately after trauma might prevent posttraumatic stress disorder by improving brain plasticity.<sup>75</sup>

## Conclusion

Based on the evidence presented in this review, it would appear that optimizing and individual's unique requirements for omega-3 PUFAs, in particular DHA, along with the homocysteine-lowering B vitamins would augment neurogenesis and mitigate stress induced brain atrophy. Further, personalized nutritional therapy would work synergistically with behavioral therapies and therapeutic lifestyle changes to improve brain structure and mental health.

## Competing Interests

The author is Technical Director at Viridian Nutrition, who supply dietary supplements including B vitamin and omega-3 PUFA containing products, however the author or company hold no proprietary rights or patents on these widely available nutrients.

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