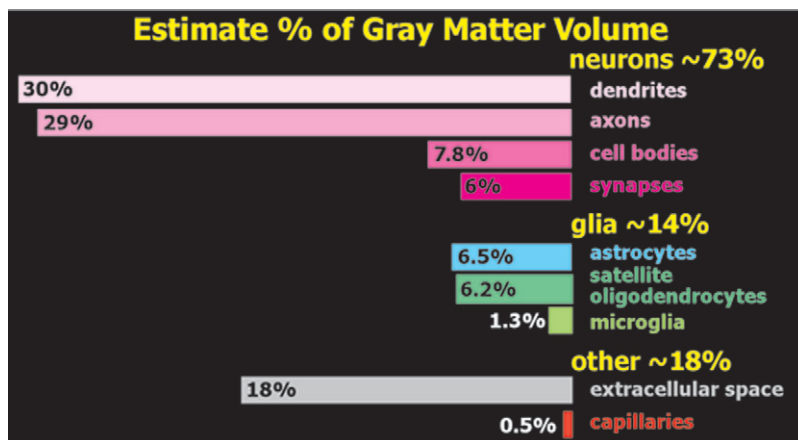
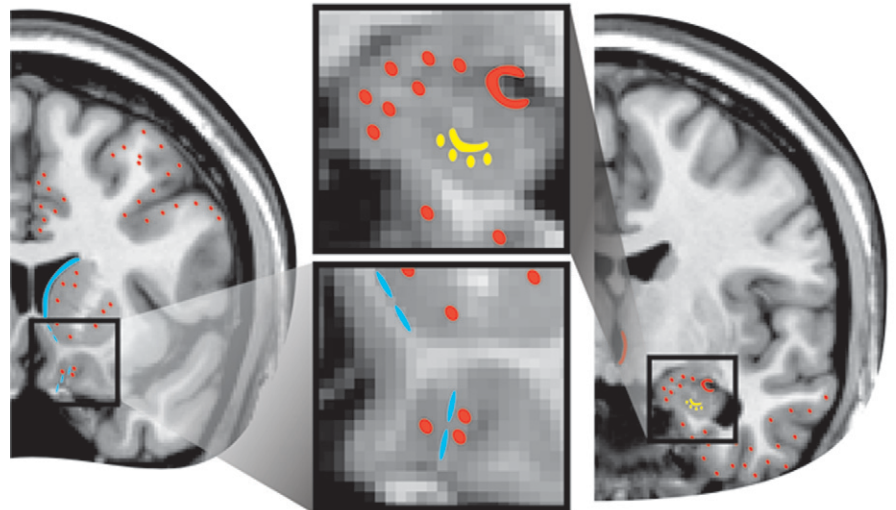


## The Dynamic Brain: Neuroplasticity and Mental Health

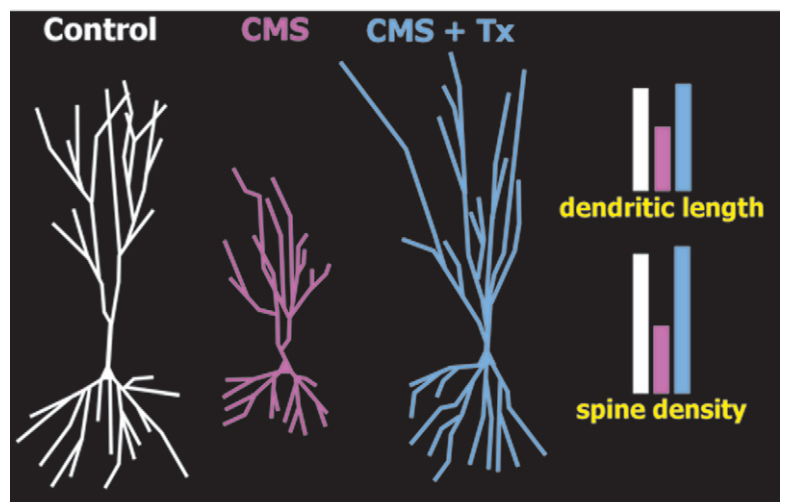
Jill L. Kays, Psy.D., Robin A. Hurley, M.D., Katherine H. Taber, Ph.D.

**Cover and FIGURE 1.** It is now generally accepted that adult neurogenesis occurs in two locations in all mammals, including humans.<sup>1-5</sup> Neurons born in the subventricular zone adjacent to the caudate (solid blue area) migrate ventrally, then rostrally (blue dashes), to be incorporated into the olfactory bulb. Neurons born in the subgranular zone of the dentate gyrus (solid yellow area) are incorporated into the dentate gyrus (yellow dots). Although controversial, there is evidence in adult primates for generation of new neurons in other ventricular regions (solid orange areas) and incorporation of new neurons into other cortical and subcortical areas (orange dots).<sup>2,6-10</sup>



**FIGURE 2.** Imaging-based studies provide estimates of gray-matter volume associated with particular psychiatric disorders or treatments, but do not allow identification differences at the cellular level.<sup>11</sup> Of particular interest is whether reduced neuronal numbers are likely to be present in areas with less gray-matter volume. A recent review provided estimates of the volume fractions occupied by the major constituents of cortex (right).<sup>12</sup> Note that much of the cortical volume is occupied by neurons (shades of pink). Their analysis concluded that most gray-matter volume differences reported in depression are likely due to synaptic pruning and dendritic regression, rather than cell loss.

**FIGURE 3.** Exposure of rats to 6 weeks of unpredictable chronic mild stress (CMS; pink) induces depressive-like behaviors (e.g., anhedonia, learned helplessness) and multiple detrimental effects in the hippocampus and medial prefrontal cortex (mPFC), including decreases in neurogenesis, dendritic length, and synaptic density, as compared with control conditions (white). Both behavioral and structural deficits can be reversed by administration of antidepressants (Tx) during the final 2 weeks of CMS (CMS + Tx; blue).<sup>13</sup> Schematic representations of mPFC neurons under the three conditions illustrate average dendritic changes. The authors of this study noted that these results were independent of neurogenesis, suggesting that restoration of normal dendritic length and synaptic density underlie behavioral recovery.



Until fairly recently, the adult brain was considered largely fixed and stable.<sup>14,15</sup> Although it was accepted that changes occurred in the context of learning and memory, the general consensus was that major processes essential to normal brain development (e.g., generation of new neurons, neuron migration, pruning) ceased once full development was reached. The relationship between physical illness, mental illness, and brain functioning or structure was not heavily considered. However, recent research has led to a major paradigm shift. Most important was the discovery of the birth of new neurons (neurogenesis) in the adult human brain.<sup>1-5</sup> Current perspectives suggest a dynamic brain, physically changed by both internal and external factors.<sup>15-20</sup> The processes by which the brain is remodeled are collectively referred to as “neuroplasticity.” Neuroplastic changes can be either adaptive or maladaptive. The concept of neuroplasticity is opening the doors to new ways of understanding illness and recovery, as well as how these processes can be utilized to influence and direct outcomes.

## NEUROPLASTIC PROCESSES

A variety of processes and mechanisms are included under the umbrella term *neuroplasticity*.<sup>16,17,20</sup> These include the formation of new neurons and glial cells (neurogenesis), as well as formation of new connections and alterations in existing ones through multiple processes (e.g., synapse formation and elimination, dendritic remodeling, axonal sprouting, and pruning). The importance of activity-level or demand in evoking remodeling has been emphasized. Research limitations largely prevent study of these processes directly in humans; thus, what is known has primarily been determined through animal studies. This work provides insight into processes that may be occurring in the human brain.

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The most surprising and exciting type of neuroplasticity is the actual measurement of birth, migration, maturation, and functional integration of new neurons in the adult brain.<sup>3-5,15</sup> Proliferated or newly-born cells are typically labeled using bromodeoxyuridine (5-bromo-2'-deoxyuridine; BrdU), a synthetic nucleoside that is incorporated into dividing cells in place of thymidine. Once labeled, cells can be subsequently traced through the maturation and integration process. By utilizing animal models, researchers are able to examine patterns and factors related to rates of cell proliferation, maturation, and survival associated with different experimental conditions (e.g., treatment, stress, environmental variables).<sup>3</sup> It is now generally accepted that adult neurogenesis occurs in two locations. Neurons born in the subventricular zone (SVZ) adjacent to the caudate are incorporated into the olfactory bulb; those born in the subgranular zone (SGZ) of the dentate gyrus are incorporated into the hippocampus (Figure 1).<sup>1-5,21</sup> Although controversial, there is evidence in adult primates for generation of new neurons in other ventricular regions and incorporation of new neurons into other cortical and subcortical areas (Figure 1).<sup>2,5-10</sup> Rates of survival for newborn cells vary by species and experimental conditions.<sup>3</sup> Survivors mature into neurons or glia cells, depending on their location and activity. Growth factors (e.g., brain-derived neurotrophic factor [BDNF]), vascular endothelial growth factor [VEGF], insulin-like growth factor [IGF]) play an important role in regulating the neurogenic process by increasing the rate of cell birth and promoting maturation and survival.<sup>21-24</sup> Glial cells are believed to play an important role in this process, directly and indirectly, both supporting and regulating the development of new neurons.<sup>25,26</sup>

When confronted with major changes or challenges, the brain can adapt by remodeling and refining existing connections.<sup>17-20,27</sup> Communication pathways can be strengthened or enhanced by outgrowth of dendrites, axonal sprouting, and increasing or strengthening synaptic connections. Conversely, various factors can contribute to loss of synapses, shrinkage or retraction of dendrites (de-branching), and pruning of axons, thereby reducing communication in those areas. After injury (e.g., stroke, traumatic brain injury), axonal sprouting and pruning can serve to re-establish connections and ultimately restore some functioning.<sup>18,20,28</sup> This area of neuroplasticity has particular relevance to humans in the study of cognitive rehabilitation.

Multiple factors have been found to modulate neuroplasticity in animal studies, pointing to internal and external variables that may influence this process in humans, as well. Factors that have been associated with increased neurogenesis include environmental enrichment, exercise, learning, electroconvulsive shock, and chronic administration of antidepressants and other psychotropic medications.<sup>15,18,21,24,29–34</sup> Reactive neurogenesis (increases after injury) has also been reported, which may be a confounding variable in some animal studies.<sup>3,15</sup> Chronic stress, depression, and illness have been associated with suppressed neurogenesis.<sup>22,24,34–36</sup> All of these factors, as well as altered sensory and motor experiences, appear to modulate dendritic remodeling in a dynamic manner.<sup>15,18,20–22,24,27,37,38</sup> Considerable variation has been found in all of these neuroplastic processes among species and even between strains.<sup>3</sup> This must be borne in mind, particularly when comparing studies or extrapolating from other mammalian lines to humans.

Extensive animal studies have focused on the effects of various types of stress on neuroplastic processes. In considering the effects of both acute and chronic stress, it is essential to differentiate negative (aversive) stress from positive (rewarding) stress.<sup>15,34</sup> Although both are associated with increased activation of the hypothalamic–pituitary–adrenal (HPA) axis, they can have opposite effects on measures of structural plasticity (e.g., neurogenesis, dendritic branching, spine number, synapse number) in the hippocampus. As noted previously, multiple animal studies have reported detrimental effects on both behavioral measures and neuroplastic processes associated with chronic negative stress. In contrast, successful coping with intermittent social stress enhanced both spatial learning and hippocampal neurogenesis in adult male squirrel monkeys.<sup>39</sup>

## NEUROPLASTICITY IN THE HEALTHY HUMAN BRAIN

Multiple studies have documented neuroplastic changes in healthy human brains as a result of normal processes, such as learning.<sup>16,17,19</sup> Studies using transcranial magnetic stimulation (TMS) to map motor cortex found significantly increased cortical representation with task practice for the involved muscle groups, suggesting increased neural connections to support task performance.<sup>16,17</sup> Similar results were found when the task was

practiced mentally, suggesting that mental rehearsal alone may produce neuroplastic changes in the brain. Both cross-sectional and longitudinal studies support the induction of neuroplastic changes by musical training.<sup>40</sup> A longitudinal study of adults in training to be London taxi drivers reported increased gray-matter volume in posterior hippocampus at the end of training (3–4 years) only in those who passed the stringent qualification examinations.<sup>41</sup> A longitudinal study in adults found that the number of stressful life events occurring during the 3-month study period was positively correlated with decreased gray-matter volume in several regions, further supporting the dynamic nature of acquired change in the healthy brain.<sup>42</sup>

The brain's ability to efficiently reorganize allocation of its resources to meet demands and compensate for deficits is uniquely illustrated in research utilizing individuals with congenital or acquired absence of a sensory modality. Both blind and deaf individuals often demonstrate superior skills in their remaining senses, as compared with individuals with all senses intact.<sup>43,44</sup> Also, areas of brain normally dedicated to the missing sense can be recruited for use by other sensory modalities. Braille reading, for example, has been shown to require participation of visual cortex.<sup>17,43,44</sup> Injury to visual cortex or temporary disruption by TMS impairs Braille reading, despite intact somatosensory cortex. The brain's ability to compensate in these ways can occur rapidly and reversibly, as evidenced by similar cross-modal recruitment in prolonged visual deprivation (e.g., blindfolding) of normal individuals.<sup>43</sup> There is growing evidence that sensory-specific areas (e.g., visual cortex, auditory cortex) receive direct (short-latency) inputs from other sensory modalities.<sup>43,45</sup> Such heteromodal connections may be the basis for the observed cross-modal compensatory plasticity. This supports the idea of redundancy in the brain, in which there are multiple pre-existing pathways with the potential to sustain similar functions, that are "unmasked" when needed.<sup>16,17,43</sup>

## NEUROPLASTICITY AND NEUROPSYCHIATRIC DISORDERS

Both animal and human research has provided supportive evidence that chronic stress and some forms of mental illness have deleterious effects on the brain, both structurally and functionally. Numerous studies of various neuropsychiatric disorders have found significant

structural differences between patients and healthy individuals.<sup>46,47</sup> For example, studies utilizing magnetic resonance imaging (MRI) have reported smaller hippocampal volume in both posttraumatic stress disorder (PTSD) and major depressive disorders (MDD), as well as correlations between volume, symptom severity, and symptom duration.<sup>48–52</sup> One study reported that veterans with current PTSD symptoms had significantly smaller hippocampal volumes than those who were recovered or who never developed PTSD.<sup>53</sup> The authors hypothesized the results may point to a possible reversal of any volume loss among veterans who had recovered or that a smaller hippocampus is a risk factor for chronic, non-remitting PTSD, rather than just for the development of PTSD. Other studies have also found a relationship between hippocampal volume and treatment outcomes, with larger hippocampal volume predictive of positive treatment outcomes and rates of remission.<sup>54,55</sup>

The cross-sectional design utilized in most studies makes it difficult to determine whether these structural differences were present before the psychiatric illness developed (possible risk factors) or if they are a result of the conditions themselves. This has continued to be an area of debate. For a period of time, it was assumed that stress and mental illness directly caused the observed differences in brain volume. However, a seminal study in pairs of identical twins suggested that smaller hippocampal volume served as a risk factor for developing PTSD, rather than an acquired trait.<sup>56,57</sup> Given the conflicting results regarding acquired versus predispositional differences, the field seems to be moving toward a more nuanced, multifaceted understanding of these variables, recognizing that both genetics and environment likely play a role in the etiology and course of mental illness, as well as the associated differences and changes in brain function and structure.<sup>52,57</sup> More research is needed, particularly twin and longitudinal studies, in order to clarify the relationship between genetic (i.e., predisposing traits) and environmental (i.e., experience, mental illness, stress) factors.

A common, yet simplistic, assumption regarding volumetric changes is that they are directly due to changes in cell quantity (increase or decrease); however, this has not necessarily been well-supported by post-mortem studies.<sup>11</sup> Recent research suggests that other interpretations may be more accurate. A review of the documented changes in animal models of stress and depression in humans, coupled with the estimated volume fraction of each cortical component, supported

the hypothesis that the majority of gray-matter volume changes reported in depression are due to decreased synapses and dendritic regression, rather than a reduction in cell numbers (Figure 2).<sup>12</sup>

## UTILIZING NEUROPLASTICITY

Researchers have begun examining ways to harness neuroplasticity to promote healing and recovery. Although these efforts are still in the beginning stages, there is promising evidence that the dynamic qualities of the brain may play a pivotal role in how one copes with stress and mental illness.<sup>58,59</sup> Medications have been shown to affect neuroplasticity in animal models and a few human studies. As noted previously, antidepressant medications can reverse the effects of various types of chronic stress on both behavior and brain structure (Figure 3), although animal studies differ on which aspects of neuroplasticity (e.g., neurogenesis, dendritic remodeling, BDNF levels) are critical for therapeutic efficacy.<sup>60–62</sup> Several clinical studies have found that successful medication treatment can reverse hippocampal volume deficits in PTSD and depression, although contrary results have also been reported.<sup>51,63–65</sup> Induced stimulation of the brain focally or generally also effects neuroplasticity. Studies in multiple species, including non-human primates, have shown that electroconvulsive shock increases hippocampal BDNF levels, synaptic density, and neurogenesis.<sup>66</sup> A small longitudinal study in patients with depression reported increased hippocampal volume after electroconvulsive therapy (ECT) treatment.<sup>67</sup> A case study of a patient with schizophrenia reported that serum levels of BDNF increased during the course of ECT treatment in parallel with symptom improvement.<sup>68</sup> Other forms of stimulation (e.g., TMS, deep brain stimulation) have also been utilized in treatment for various conditions by modifying activation patterns in the brain with the intention of improving functioning.<sup>59</sup> Exercise, which has been shown to ameliorate behavioral symptoms of stress and enhance hippocampal neuroplasticity in animal models, has also been considered as a potential adjunctive treatment for neuropsychiatric conditions.<sup>21,59,69–71</sup> Physical activity attenuates many of the harmful effects of stress.<sup>70</sup> Reviews of the evidence indicate that exercise can be associated with reduced psychiatric symptoms (particularly of depression [MDD]) and cognitive deficits in multiple conditions (e.g. MDD, schizophrenia, Alzheimer's



dementia).<sup>69,71</sup> There is evidence that exercise, used as a supportive treatment, may delay or even prevent disease-onset and progression.<sup>71</sup>

## CONCLUSIONS

The brain, once considered to be a fixed and stable organ, is now viewed as dynamic, flexible, and adaptive. Efforts are beginning to focus on ways to harness the plastic qualities of the brain for treatment and recovery. There is much that is still unclear about the relationship

between neuroplasticity and mental health. Research capabilities for human studies are limited, so most questions must be addressed by study of animal models. This makes disentangling genetic, environmental, and experiential influences much more challenging. Although there is not yet consensus, it appears the field is moving toward a more multifaceted, nuanced understanding that recognizes the likely contribution of multiple factors, rather than a single explanation. Future research and advances in technology will continue to increase understanding of the human brain and its fascinating abilities and potential.

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