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# Cerebral Damage after Stroke: The Role of Neuroplasticity as Key for Recovery

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## Abstract

Stroke remains global health care problem that constitutes world's second-leading perpetrator of mortality and third most pronounced cause of all disabilities. The hallmark of cerebral stroke is the persistent loss of cerebral function consequence of abnormality of the blood supply. The ultimate goal of stroke care is to recover and maximize the cerebral functions lost due to the cerebral damage. Therefore, understanding the mechanism of cerebral damage after stroke is fundamental to comprehension of mechanisms of recovery following stroke, as well as key towards eliminating devastating human disability as a result of stroke. Therapeutic strategies aim to harness and enhance neuroplasticity offers reasonable level of hope towards maximizing recovery from post stroke impairments. This paper therefore, highlighted the mechanism of cerebral damage after stroke as well as elucidates the concept of neuroplasticity as key for recovery following stroke.

**Keywords:** cerebral cortex, cerebral damage, stroke, neuroplasticity, stroke recovery

## 1. Introduction

Stroke also known as cerebrovascular accidents is the world's second death-perpetrating disease after cardiovascular diseases [1, 2], and it affects about 13.7 million people annually in the globe [3]. About one third of all strokes translate into fatalities, and another one third constitutes stroke survivors staying with residual disability that accounts as foremost noticeable root of long-term neurological disability in adults [4, 5] and third most common cause of all disabilities globally [6]. Stroke classically depicts a syndrome with sudden onset of acute focal injury of the central nervous system (CNS) of vascular origin that produces focal or global neurological deficit in accordance with affected area of blood supply [7]. Thus, based on the isolated territory of the brain involve, stroke can be cerebral stroke, brain-stem stroke, cerebellar stroke, or thalamic stroke, while based on underline cause it can be ischemic stroke (thrombotic, embolic, lacunar, watershed, or cryptogenic) which results from brain vascular occlusion, or hemorrhagic stroke (intraparenchymal or subarachnoid) which is due to blood-related aberrations [8].

Cerebral stroke results in loss of cerebral cortex related functions that manifests as motor impairment [9–11], sensory impairment [12–14], cognitive impairment [15–17], balance impairment [18] among others. The motor function of the

cerebral cortex is embedded in the motor cortex (primary motor area, premotor cortex, supplementary motor area, cingulate motor areas) located in the frontal lobe anterior to central sulcus, the motor cortex is responsible for planning, initiation, execution, and regulation of voluntary movement which is achieved through originating descending corticospinal tract and corticobulbar system to the spinal cord and brainstem respectively [19]. Cerebral cortex plays principal role in sensory/perceptual functions by providing meaning to all sensations (except sense of smell) through primary somatosensory cortex in the postcentral gyrus of the parietal lobe, and other primary cortical sensory areas such as auditory cortex in the temporal lobe and visual cortex in the occipital lobe. Cognitive function involves multifaceted domains of cognitive processes including memory, learning, attention, thought, comprehension, perception, language among others [20]. Each of these domains of cognition requires cerebral cortex, illustration can be seen in memory domain where memory acquisition involves sensory cortex, memory retrieval involves prefrontal cortex, and memory storage is distributed throughout the cortex [21]. Balance and coordination of movement involve integrated functioning of both pyramidal and extra-pyramidal systems, and the cerebral cortex is the main principal origin of pyramidal system.

The mechanism of cerebral damage after stroke determines the cerebral stroke impairments, and the mechanism of damage is relative to whether the type of stroke is ischemic or hemorrhagic. Ischemic stroke consists of five distinct pathophysiologic mechanism each of which has distinct time frame; these includes immediate (within minutes) peri-infarct depolarization and excitotoxicity, hours later by neuro-inflammation and oxidative stress, days later by apoptosis [8]. In addition to ischemia related cascade of events aforementioned, hemorrhagic stroke is associated with two additional unique pathophysiologic phases. The primary; acute phase which is due to physical effect of hematoma (mass effect) from the mass accumulated blood, and the secondary; subacute phase termed as cytotoxicity from secondary metabolites of blood components [22–24].

Recovery to some extent from post stroke impairments observed among stroke survivors was one of the early evidences that led to move away from outdated dogma widely misconceived previously that; there was no possibility for repair or change within the CNS after it had suffered a lesion; and that once there is damage such as stroke that leads to neuronal demise inadvertently, the brain structures and functions are lost forever [25, 26]. It is now well-established fact that CNS repair or change itself but it just that it relatively does not do well enough, and that functional recovery after damage relies on neuroplasticity [27, 28]. Neuroplasticity is life-long natural capability of the CNS to rearrange itself in both molecular form and function in response to new experience or stimulus. Brain plasticity is pivotal to functional recovery after cerebral stroke, and this spontaneous, endogenous and intrinsic capacity of the brain is what restorative rehabilitation approaches for stroke explore, promote and remodel in the right direction to achieve optimal functional recovery after stroke [29, 30].

There is exploding surge among scientists to pay more attention in searching for various therapeutic strategies that can enhance neuroplasticity to augment functional recovery with rehabilitation after stroke [31–34]. Although this strategy is still in developmental stage but the reasons for this shift in attention are not far-fetched. Firstly, the thrombolytic/thrombectomy clinical treatment available for acute stroke has a very restrictive time window of administration of 4–5 hours of lesion onset [35]. This is in contrast to restorative/rehabilitative interventions that has unlimited therapeutic window of lifelong applicability [36]. Secondly, rehabilitation interventions are still far from sufficiency for optimal and ideal

recovery from impairments after stroke [37], as about 50% of stroke survivors still leaves with residual disability and remain functionally dependent despite rehabilitative management [38]. Understanding the mechanisms of cerebral damage and their recovery after cerebral stroke is essential towards development of strategies that harness and enhance neuroplasticity in combination with rehabilitation processes [39]. This paper therefore discusses the mechanism of cerebral damage after stroke as well as elucidates the concept of neuroplasticity as key for recovery following stroke.

## **2. Mechanism of cerebral damage after stroke**

In ischemic stroke, irreversible cascade of damage to the brain tissue ensue once the cerebral blood flow (CBF) reduces to less than 12 ml/100 g/min of the normal range of 50–60 ml/100 g/min. Within seconds of this abrupt ischemic insult, neuronal cells in the center of ischemic region termed as ischemic pre-numbra undergoes anoxic depolarization due to loss of ATP-dependent ionic pump homeostasis, and they never repolarize [40]. This necrotic core of ischemic prenumbra is enclosed by a zone of relatively lesser impacted tissue termed as ischemic penumbra, which is abridged functionally silent by the reduced blood flow but maintains metabolically active and therefore can repolarize at the expense of further energy consumption [41]. This repetitive depolarization and repolarization of ischemic penumbra are termed peri-infarct depolarization and the important period of time during which this volume of brain tissue is salvageable is referred to as the window of opportunity. The energy failure in the functioning of ATP dependent sodium potassium pump in the ischemic prenumbra results in massive uncontrolled anoxic depolarization that results in opening of voltage-gated calcium channels, mitochondrial dysfunction which further deplete energy required to maintain ion gradient, and abnormally extracellular buildup of excitatory amino acids [42, 43].

Consequently, excitatory glutamate and other excitatory amino acids such as aspartate becomes excessively released, and glutamate hyperexcitation of glutamate N-methyl-D-aspartate (NMDA) receptor, which is arguably the most calcium-influx allowing ionotropic glutamate receptor; results in massive influx of calcium ion ( $\text{Ca}^{++}$ ) into hypoxic neuron. Calcium ion triggers series of cascading events that ultimately lead to neuronal demise through activation of proteolytic enzymes, stimulation of pathogenic genes, lipid peroxidation and free radical generation [44]. For this; glutamate and other excitatory amino acids are cumulatively termed excitotoxins, and their accompanying neuronal damage termed excitotoxicity [45]. Calcium activates key number of disparaging intracellular enzymes such as proteases, kinases, lipases, and endonuclease that not only wildly permits release of cytokines and other mediators that result in the loss of cellular integrity but also orchestrated triggering of intrinsic apoptotic pathway of neuronal death. Specifically, calcium through mobilizing phospholipases hydrolyses membrane bound glycerophospholipids to yield free fatty acids, which enable free radical peroxidation of other membrane bound lipids. Calcium through mobilizing proteases lyses integral structural proteins and activates nitric oxide synthase enzyme that triggers free radical machinery [46].

Prior excitotoxicity activates microglia and astrocytes which are the brain resident innate immunity to reacts and release cytokines, chemokines (chemotaxis cytokines), and matrix metalloproteases (MMPs). This constitutes neuro-inflammation, and microglia activation institutes the initial vital



neuro-inflammatory response in acute stroke, which together with blood-borne innate immune cells and later adaptive immune cells support the course. This neuro-inflammatory response supposedly aims to reduce injury processes but this response under stroke pathology develops improperly more reactive and aggressive to yield numerous inflammatory mediators that trigger apoptosis and orchestrate lethal neuronal injury [47, 48]. Activated microglia becomes phagocytes that can release plethora of substances, some of which are neuroprotective such as neurotropic factors; nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), insulin-like growth factor I (IGF-I), and growth associated protein (GAP-43/B-50), while some are neurotoxic such as tumor necrosis alpha (TNF- $\alpha$ ), interleukin-1 $\beta$  (IL-1 $\beta$ ), and interleukin-6 (IL-6). Blood-brain barrier (BBB) which confers brain with protection against systemic toxins is disrupted by matrix metalloproteinases (MMPs) with MMP-2 (gelatinase A) and MMP-9 (gelatinase B) being the leading concerns in cerebral ischemia [49]. MMP-2 that is normally expressed at low levels becomes increased during cerebral ischemia to galvanizes MMP-9, which abolishes components of the basement membrane in the vascular wall leading to BBB distraction, thus allowing further infiltration of inflammatory mediators and other potential toxins [50].

Oxidative stress signifies disparity in the high-level oxidants (free radicals) with respect to corresponding nonconforming low level of antioxidants. Long term cerebral hypo-perfusion produces abnormal proportions of reactive oxygen species (ROS) and/or reactive nitrogen species (RNS) oxidants through several mechanisms of injury, such as mitochondrial inhibition, calcium ions overload, ischemia-reperfusion injury, and neuroinflammation [51]. During cerebral ischemia, there is mitochondrial inhibition of oxidative phosphorylation due to the lack of sufficient oxygen, and the oxygen depleted cell shift to glycolytic pathway of ATP generation that results in lactate and hydrogen ion (H<sup>+</sup>) build-up in the mitochondria and the consequent reversal of the H<sup>+</sup> uniporter on the mitochondrial membrane that results in superfluous cytosolic H<sup>+</sup> buildup and acidosis [52]. Acidosis partly lead to oxidative stress by supplying excessive H<sup>+</sup> for the successive progression in the generation of hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) and the final hydroxyl radicals ( $\bullet$ OH) either in the turnout of transition metal ions (Fenton reaction) or in the presence of superoxide radical (Haber-Weiss reaction), with this effect more pronounced in neurons due to inherently low anti-oxidant defense. In addition, the compelling protein and lipid oxidant peroxynitrite (OONO<sup>-</sup>) of RNS is favorably generated in the oxygen depleted cell by the reaction of nitric oxide (NO) and superoxide (O<sub>2</sub> $\bullet$ -), thereby also contributing to oxidative stress.

Calcium overloads, as a result of glutamate mediated NMDA receptor excitotoxicity, also contributes in neuronal oxidative stress at cytosolic and mitochondrial level. At cytosolic level, excessive calcium ion activation of key intracellular enzymes such as neuronal nitric oxide synthase (nNOS) via Ca<sup>2+</sup> binds calmodulin to induce subsequent downstream effect, as nNOS catalysis results in generation of nitric oxide (NO) free radical from L-arginine [53, 54]. At the mitochondrial level, excessive calcium ion influx into mitochondrial matrix leads to the inner mitochondrial accumulation of momentous level of Ca<sup>2+</sup> via mitochondrial calcium uniporter (MCU) which proliferates disturbance of usual bio-energetic, mitochondrial ROS, and membrane permeability [55].

Apoptosis is a physiological mechanism of cell death through programmed cellular machinery of either extrinsic or intrinsic pathways [56]. Under stroke pathology, neuronal demise by necrosis preponderance in the ischemic penumbra is marked by excitotoxicity, while additional process of neuronal demise by apoptosis which is more delayed and predominant in the ischemic penumbra occur in a fashion where

apoptosis becomes dysregulated [57]. Thus, while the neurons within the core infarct die by immediate necrosis due to insufficient ATP, the penumbra die by ATP requiring process of apoptosis, supporting the established evidence that cellular demise after cerebral ischemia transpires through both necrosis and apoptosis [58]. Multiple pre-existing pathophysiologic mechanisms that can induce apoptosis after cerebral ischemia includes pro- calcium influx, pro-inflammatory cytokines and oxidative stress [59]. Apoptosis can be caspase-dependent or caspase-independent, and the most common is caspase-dependent which is initiated and triggered through distinctively intrinsic (or mitochondrial) pathway or extrinsic (or death receptor) pathway. Both intrinsic and extrinsic pathways share similar terminal phase termed execution phase where caspase 3 leads to the destruction of cellular components and cell death [60].

In hemorrhagic stroke, the mechanism of damage begins with additional process of mass effect from the mass accumulated blood, and cytotoxicity from the secondary metabolites of blood components, in addition to shared common damaging caused by ischemia such as excitotoxicity, neuroinflammation, oxidative/nitrosative stress, and apoptosis. The initial bleed from the cerebral hemorrhage causes immediate physical disruption of the cellular cytoarchitecture of the brain and increases local pressure which can cause compressions, hypothetically disrupting blood flow and principally causing brain herniation [61]. The subsequent expansion of hematoma causes mass effect of hematoma growth leading to further rise in intracranial pressure, brain herniation, and impacted blood flow that is correlated with neurologic deterioration and degraded clinical outcomes. Depending on the dynamic of hematoma expansion (growth), the primary damage ensues within minutes to hours subsequent to the onset of bleeding and is basically due to mechanical damage associated with the mass effect [62].

Secondary injury after cerebral hemorrhage termed as cytotoxicity occurs due to series of events initiated by the prior primary injury mechanism (mass effect), that is specifically due to body response to the hematoma for instance inflammatory response, and from the multiple blood components released from hematoma [61]. The extravasated blood components released from hematoma being implicated to cumulatively imposed cellular toxicity includes; majorly the erythrocytes and plasma proteins, and the damage-associated molecular patterns (DAMPs) which are nucleic acids, extracellular matrix components, proteins, lipid mediators, ATP and uric acid released from necrotic tissues [63]. At the early stage of cytotoxicity, the toxicity of extravasated blood plasma components such as coagulation factors, complement components, and immunoglobulins are known to be the main contributing factor of cellular damage. Subsequently, erythrocytes lysis leads to release of its major intracellular component hemoglobin (Hb), which when metabolize via hemoglobin metabolic pathway release degradation products; heme and iron (Fe). Both Hb and its degradation products are potent cytotoxic chemicals capable of causing death to many brain cells through mechanism of free radical generation with substantial increase oxidative stress and subsequent damage to DNA [62].

### **3. Concept of recovery after post stroke cerebral damage**

The ultimate goal of stroke management is to promote optimal recovery of lost functions and reduce further injury. This recovery depends majorly on brain plasticity; a spontaneous regeneration process that encompasses neural plastic changes in the lesioned hemisphere to reestablish its structural and functional

reorganization. Brain plasticity under pathological condition completely differs from plasticity under properly functioning brain. For instance, plasticity in normally functioning brain is a prerequisite basis of learning and memory that involves plastic adaptation such as long-term potentiation (LTP). This is opposed to plastic changes observed using MRI in cerebral stroke pathology, that involves modification in intracortical myelin, augmented neurogenesis, improved spine density in neuronal dendrites and alterations in astrocyte volume [64].

Stroke recovery to certain extent also depends on severity extent of the initial injury deficit as the severity of the damage is inversely related to the prognosis for recovery [65]. But it was also observed that recovery differs even among post stroke patients with similar clinically assessed severity. This apparently stress the recovery role of other brain endogenous survival mechanism such as extent to which collateral circulation bypass to supply blood to the perilesional neurons, angiogenesis, inhibitory neurotransmitters that counteract excitotoxicity, and multiple representations of the same function in different cortical areas [66]. Appropriate rehabilitation and drug treatment that target underline cause of stroke are also critical to recovery after post stroke cerebral damage. Rehabilitation aims to maximize optimum recovery of lost functions as a result of impairments deficit after stroke but overall, brain plasticity underlies recovery promoted by rehabilitation [67–69].

Recovery from stroke has also been attributed to be dependent on resolution of early local processes in the brain that includes resolve of perilesional edema, re-emergence of circulation within the ischemic penumbra, resolution of remote functional depression of neurological function induced by process of diaschisis [70]. As previously stated stroke recovery majorly depends on brain reorganization process of plasticity which in turn dictates recovery promoted by rehabilitation. Mechanism through which rehabilitation mediates brain plasticity to promote recovery has been studied and explained. Rehabilitation such as physical therapists stroke interventions modifies neurotrophic factor expression in the CNS especially brain derived neurotrophic factor (BDNF), which in turn upon binding with its tyrosine kinase B (TrkB) cognate receptor recruits a cascade of signaling pathways that ultimately mediates activity-associated plasticity of neurons [71, 72]. Activity-associated plasticity signifies a means of functional and structural neuroplasticity that is tailored by the depolarizing behavior of neurons, and the mechanisms governing activity-associated plasticity includes LTP and activity-associated development of corticospinal circuitry among others [72]. Therefore, through brain plasticity after cerebral stroke, reorganization by recruiting cortical or subcortical structures to adopt the function of the injured tissue, reinforcement of remaining synaptic pathways and then creating new connections, recruitment of other pathways that are functionally alike the damaged tissue but anatomically distinct, strengthening of existing but weaker and functionally silent connections, can all be achieved to recover lost cerebral functions [73].

#### **4. Neuroplasticity and its basic physiology**

Neuroplasticity is a general term that covers all available processes of neuronal reorganization possible [66], such as neurogenesis, synaptogenesis, dendritic arborization, axonal sprouting, LTP, recruitment of other pathways, reinforcement of functionally silent synapses. Neurogenesis is the process of generating of neurons of neural cell types from precursors neural stem cells and/or neural progenitor cells (NPCs) [74]. Synaptogenesis is a broad term that encompasses the complex process



of synaptic contacts formation, maturation and maintenance which form the basis for establishing neural circuits [75]. Dendritic arborization describes a process of neuronal dendrites tree-like branching out to make new synaptic connection through mechanisms of dendrite morphogenesis [76]. Sprouting is a form of plastic changes in the synapses in which there is axonal synaptic reorganization to modify the efficacy of synapses [77]. LTP is the fundamental form of synaptic plasticity where synapses become strengthened and this forms the cellular basis of learning and memory [78].

Neuroplasticity is regulated by the corresponding cascade of intracellular events that translates into plastic changes. However, the plastic changes may either be adaptive, where it is related with an upsurge in function or maladaptive where it is linked with adverse consequences such as loss of function or augmented damage [79, 80]. This brings about the concept that not all plasticity effect positively on clinical status, that maladaptive plastic changes from dys-regulated neuroplasticity result in an aberrant neural organization [79]. Typical example of situation where neuroplasticity becomes maladaptive can be seen in new onset of seizures after long period of cerebral trauma, where aberrant progressive plastic changes in the brain in the form of inappropriate synaptogenesis and axonal sprouting accounts for this late development. Neuroplasticity can also be seen as structural where the plastic changes involves the organization and number of synapses such as synaptogenesis, axonal sprouting and dendritic arborization, or functional where the plastic changes involves the efficacy and strength of synaptic connections such as LTP.

The basis of plastic changes that allows for neuroplasticity to become realistic depend upon factors such as neuronal excitability, which define the ability of a nerve to produce an action potential and in turn depends on the permeability, electrical and chemical state of the neuron [81]. This is then followed by adaptive changes termed plasticity, in which there are stable functional transformations that occur in specific neuronal systems as a result of specific stimuli or the combination of stimuli [82]. Furthermore, it has been revealed that effective and repeated action potentials are required from the presynaptic neuron to stimulate the postsynaptic to cause a change in the strength of an interneuron connection [83]. Cumulatively, the aforementioned process leads to biochemical changes, and anatomical adaptations which reinforce the connections between neighboring neurons, thus accounting for molecular, cellular, systems, and behavioral perspectives of explaining neuroplasticity [84].

The strength of the excitation impulse must exceed the threshold value to increase the synaptic efficacy and the stability of the connections between neurons. Nevertheless, when neurons are stimulated only with subthreshold stimuli, the overall activity of the synapse may decrease [85]. Studies conducted on unilateral lesion of the hippocampus results in the formation of new synapses (synaptogenesis) by the axons from the remaining contra-lateral hippocampal system [86]. Thus, the postsynaptic portion of a synapse continues to function properly despite the degeneration of the presynaptic region, and the surviving axons form new synapses. The fibers that form the (new) synapses are homologous to the damaged synapses, which may significantly facilitate the restoration of normal function.

## 5. Strategies that enhances neuroplasticity

**Table 1** summarized various strategies that were found to enhance neuroplasticity and the mechanism through which modulate neuroplasticity.



Strategy	Proposed mechanism reported to modulate and promote neuroplasticity	References
Transcranial direct current stimulation (noninvasive)	Modification of neuronal membrane potentials, consequently persuading neuronal excitability which form part of the basis of neuroplasticity.	[87, 88]
Deep brain stimulation (invasive)	This by stimulating neuronal network connected to the stimulated region, the pathological neuronal network becomes altered by changes in the neurochemical components thereby inducing morphological changes in both the dendrites (dendritic arborization) and axons (axonal sprouting).	[89]
Functional Electrical Stimulation (FES noninvasive)	Hypothesized to modulate neuroplasticity through repeated generation of neurons synaptic activity that might facilitate synaptic remodeling, leading to neural reorganization.	[90]
Aerobic Exercise	Aerobic exercise is linked with surge in neurogenesis and angiogenesis, together with rise in neurotrophic molecules especially BDNF and other growth factors implicated in neurite outgrowth and synaptic plasticity	[91, 92]
Brain-derived neurotropic factor (BDNF) therapy	By binding of BDNF to its TrkB cognate receptor, two distinctive intracellular signaling pathways namely phosphatidylinositol 3-kinase (PI3K)/Akt and mitogen-activated protein kinase/extracellular-signal-regulated kinase (MAPK/ERK) becomes initiated, thereby regulating transcriptional gene activity of neurite outgrowth and neurogenesis.	[93, 94]
Statins	Proposed mechanism by which statins modulates neuroplasticity involves indirect effect through statin-mediated increase in proteins such as endothelial nitric oxide synthase (eNOS), vascular endothelial growth factor (VEGF), tissue plasminogen activator (tPA), and brain-derived neurotropic factor (BDNF) among others.	[95]
Erythropoietin (EPO) therapy	EPO and EPO receptor (EPOR) that both becomes upregulated in response to cerebral ischemia, when supplemented act to indirectly augment neurogenesis through EPO-mediated increase in the expression vascular endothelial growth factor (VEGF) and brain-derived neurotropic factor (BDNF).	[96]
Phosphodiesterase type 5 inhibitors (PDE-5 inhibitors)	PDE-5 inhibitors competitively inhibit phosphodiesterase enzymes responsible for converting cyclic guanylyl monophosphate (cGMP) back to GMP, thus fostering cGMP accumulation which has diverse cellular effect in the brain including angiogenesis, and neurogenesis which are requirements of neuroplasticity	[97]
Vascular endothelial growth factor (VEGF) therapy.	Proposed mechanism through which VEGF modulates neuroplasticity involves mediating the PI3K–AKT–nuclear factor kappa B signaling pathway; an intracellular pathway that regulate transcriptional factors involves in neurogenesis	[98, 99]

**Table 1.**  
*Various strategies that were found to enhance neuroplasticity.*

## 6. Conclusion

Advancement in the understanding of mechanism of cerebral damage after stroke and brain neuroplasticity have continue to be a cutting-edge landmark information towards reducing human disability as a result of stroke. Strategies aimed at harnessing and augmenting neuroplasticity in complement with neurorehabilitation offers reasonable level of hope to maximize stroke recovery and diminish cerebral stroke induced neurological impairments. Although these strategies are rapidly evolving towards achieving clinical viability and success, more is needed to be done especially pertaining to outcome measures of neuroplasticity that rely on biomarkers of neuroplasticity rather than functional or behavioral outcome.

## Conflict of interest

The authors declare no conflict of interest.

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