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Cognitive side effects of cancer therapy demonstrate a functional role for adult neurogenesis

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Abstract

Cancer therapies frequently result in a spectrum of neurocognitive deficits that include impaired learning, memory, attention and speed of information processing. Damage to dynamic neural progenitor cell populations in the brain are emerging as important etiologic factors. Radiation and chemotherapy-induced damage to neural progenitor populations responsible for adult hippocampal neurogenesis and for maintenance of subcortical white matter integrity are now believed to play major roles in the neurocognitive impairment many cancer survivors experience.

Keywords

hippocampal neurogenesis; radiation; chemotherapy; white matter; late effects; “chemobrain”

Therapies designed to kill proliferating cancer cells have profound and lasting effects on cognitive function. Cranial radiation, used in the treatment of primary brain tumors, cancer metastatic to brain, certain head and neck malignancies and historically in the management of acute leukemia, may result in a debilitating cognitive syndrome. Cognitive deficits associated with cancer therapy include prominent dysfunction of episodic memory, as well as deficits in speed of information processing and executive functions such as attention and calculation [1,2,3,4,5,6,7,8,9,10]. These symptoms appear several months to years following radiation exposure and worsen progressively [10-12]. Chemotherapy, especially when delivered directly to the central nervous system by intrathecal route, frequently results in a similar cognitive syndrome of variable severity and duration [10,13,14,9,15].

Patients treated systemically for various cancers can be affected by impairment of cognitive function [16]. This has been particularly well-studied in breast cancer patients, revealing that approximately 20%-40% of breast cancer patients demonstrate cognitive deficits on post-treatment evaluation. [17,18,19,20,21]

Symptoms may be especially accentuated in long-term survivors of cancer treated with both radiation and chemotherapy [22]. While the exact mechanisms underlying such cognitive deficits have been poorly understood for decades, recent studies have started to shed light on the cell-biological changes in the nervous system associated with cancer therapy. Radiation

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and chemotherapeutic agents can have deleterious effects on mature neural cell types and on vascular structures. Certainly, severe cognitive dysfunction may be associated with treatment-induced leukoencephalopathy and/or radiation-induced brain necrosis, changes evident on standard clinical neuroimaging. However, mild to moderate cognitive dysfunction is inconsistently associated with radiological findings, and frequently occurs in patients with normal-appearing brain scans using standard clinical neuroimaging protocols [23]. Clinically significant cognitive deficits in the absence of obvious radiological findings implicates damage to a subtle process with robust physiological consequences.

The cognitive side effect profile of many cancer therapies, particularly those targeted to the central nervous system, came as somewhat of a surprise to the medical community during a time when the brain was viewed as fully developed soon after birth. In the last two decades this view of the postnatal brain as a static organ has been debunked, and populations of dividing stem and progenitor cells are now recognized in the hippocampus [24] and subjacent to the ventricular system [25] (Figure 1). In addition, actively dividing oligodendrocyte precursor cells (OPCs) are found throughout the subcortical white matter [26,27,28](Figure 1).

Hippocampal stem and progenitor cells contribute to new neuron production in the dentate gyrus of all mammals studies to date, including humans [29]. Hippocampal neurogenesis appears crucial for at least some hippocampal-dependent memory tasks. In rodents, increased hippocampal neurogenesis results in improved performance in certain hippocampal-dependent memory tasks [30]. Neurogenesis is increased by voluntary physical exercise [30], exposure to an enriched environment [31] and by hippocampal-dependent learning [32]. The mechanism by which cognitive challenges increase neurogenesis appears to be mediated by increased activity flow through the hippocampal circuit [33,34]. Conversely, disruption of hippocampal neurogenesis generally results in decreased performance in certain hippocampal-dependent memory tasks, such as finding the way out of a maze [35,36,37,38,39,40]. Several exogenous and endogenous conditions negatively regulate neurogenesis in the hippocampus, including chemotherapy [35,41,42,43], radiation therapy [44,45,46,47], the glucocorticoid stress hormones [48] and certain inflammatory states [46,49]. Cranial radiation and chemotherapy each cause defects in hippocampal-dependent behavioral tests in rodents [40,39,38,42]. Whether human hippocampal neurogenesis is functionally significant remains a subject of debate [50,51]. In rodents, subventricular zone progenitors migrate via the rostral migratory stream to contribute to olfactory bulb neurogenesis. In humans the role of SVZ progenitors is less well understood, but despite conflicting reports [52] a rostral migratory stream appears to be present in the human adult brain [53]. Human SVZ stem cells may contribute to neurogenesis in yet-unknown forebrain regions, and also may replenish glial precursor populations throughout the white matter. Oligodendroglial precursor cells are found throughout white matter [28,27,26] and contribute to postnatal myelination, particularly in the frontal lobes, which do not complete myelination until the third decade of life.

Impairment of hippocampal neurogenesis may explain the profound difficulties patients experience encoding new episodic memories following treatment for brain tumors and other cancers requiring cranial radiation therapy. Cranial radiation therapy profoundly inhibits the generation of new hippocampal granule cell neurons in both rodents [44,45,46] and in humans [54]. Of note, radiation does not simply ablate the hippocampal stem and precursor pool [45], but rather alters the neurogenic microenvironment. Radiation-induced activation of local microglia and the subsequent elaboration of pro-inflammatory cytokines such as interleukin-6 produce a specific blockade in neuronal differentiation [46]. This microenvironmental perturbation can be mitigated by non-steroidal anti-inflammatory therapies, offering a possible clinical intervention for patients suffering from radiation-induced memory dysfunction [46,12]. Chemotherapeutic agents also impair hippocampal

neurogenesis in experimental models [41,55,42]. A recent immunohistochemical analysis of human postmortem brain tissue shows that pediatric and adult subjects treated with surgery, radiation therapy and chemotherapy for medulloblastoma exhibited near complete ablation of hippocampal neurogenesis compared to age and sex-matched control subjects [54].

White matter damage also occurs as a result of exposure to many chemotherapeutic agents. For example, methotrexate, an anti-metabolite with a particularly high incidence of neurotoxic effects, induces cell death in multiple neural cell types [56]. Particularly vulnerable to methotrexate toxicity are the glial progenitor cells that form myelinating oligodendrocytes and astrocytes, both critical to white matter integrity [57]. Further studies have confirmed and delineated the particular chemo-sensitivity of neural precursor cells, including both neural stem cells as well as glial progenitor cells that form, among other cell types, the myelinating oligodendrocytes in the frontal white matter [58,59]. Importantly, chemotherapeutic agents may not simply target proliferating cells, but appear to alter fate decisions and cellular functions of neural progenitor cells [58,60,58,60].

Alterations of the progenitor cell pool and disruption of the functionally significant postnatal production of new neural cells offers a plausible explanation for the cognitive side effect profile seen in many patients treated with anticancer therapies (Figure 1). If current theories of postnatal neurogenesis and gliogenesis hold true in humans, then halting new cell production in the central nervous system should produce cognitive deficits that localize neurologically to the hippocampus and subcortical white matter, producing impairment of verbal and visual episodic memory function as well as a clinical picture reminiscent of subcortical dementia (slowed information processing, impaired attention – symptoms often referred to as “processing” issues). This is, in fact, what a great number of patients treated with cancer therapy targeted to the central nervous system experience. Damage to postnatal neurogenesis and gliogenesis is now believed to be the cellular basis for much of the cognitive dysfunction that follows treatment for cancer with cranial radiation and chemotherapy [12,10]. The clinical consequences associated with inadvertent medical inhibition of postnatal neurogenesis suggest a crucial role for new neural cell production in the postnatal brain.

Future studies designed to unravel the mechanisms and signals required for adult neurogenesis and progenitor cell proliferation will likely suggest strategies to minimize or even prevent the detrimental long-term cognitive consequences seen in many cancer patients. A clinically meaningful cognitive benefit gleaned from restoring postnatal stem and progenitor function after cancer therapy would further support the idea that these cells are relevant to normal human brain function.

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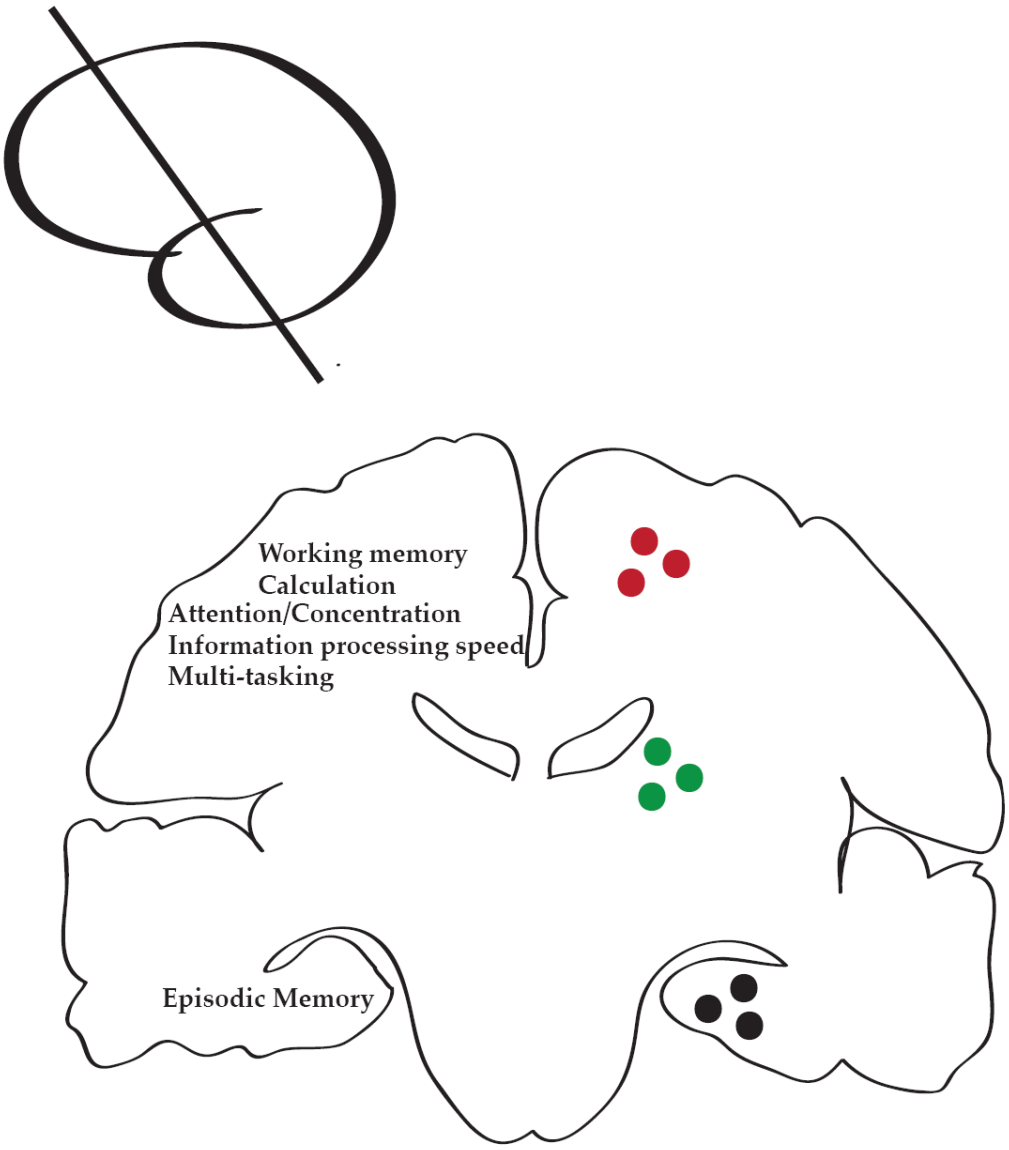

Figure 1. Neural precursor populations in the postnatal brain

Coronal section of brain (at the level indicated by the schematic in the upper). Postnatal neural precursor populations of the forebrain include hippocampal stem and progenitor cells (black dots), subventricular zone stem and progenitor cells (green dots) and white matter oligodendrocyte progenitor cells (red dots). Neuroanatomical localization of cognitive functions affected by cancer therapy are described on the left half of the figure.