REVIEW

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# Gamification as a Solution for Cancer-Induced Cognitive Impairment

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**ABSTRACT** Cancer-induced cognitive impairment is a critical issue for cancer survivors. It has a clear negative impact on the quality of life of cancer survivors. A growing body of literature has substantiated that brain exercises can improve cognitive functions and lower the symptoms of anxiety and depression, although the neural plasticity of human brains diminishes with growing age. Gamification, which is the adaptation of game characteristics and elements into non-game concepts to achieve a goal or overcome a problem, can also employ some psychological strategies such as helping to focus on a virtually appealing environment cognitively to positively manage the issue. Studies that implemented gamification for brain exercises with the appropriate consideration of the principles of neural plasticity have yielded significant evidence supporting the efficacy of evidence-based brain exercises in clinical settings in combating cancer-induced cognitive impairment. In this paper, we have reviewed pertinent studies on cancer-induced cognitive impairment and have further discussed how the gamification of brain exercises could be utilized for cancer survivors.

**Keywords:** Cognitive decline; cancer survivors; chemotherapy; cognition; memory; neuronal plasticity

The overall survival rate for all cancers has increased over the past decades.[1] This has, in turn, substantially increased the amount of effort required to address the side effects of cancer therapies. Healthcare professionals should proactively adopt strategies to improve the quality of life of cancer survivors and maximize their reintegration into the community and daily work routine after recovery from cancer. A significant challenge that might decelerate or prevent the social rehabilitation of cancer survivors is cancer-induced cognitive impairment, also colloquially known as “chemobrain” or “chemofog.” It has been reported that 10-40% of all cancer patients suffer from cancer-induced cognitive impairment.[2] Most importantly, several cancer patients with this complication eventually quit or change their professions; around 30% fail in their previous positions within two years after cancer therapy.[3,4] Cancer-induced cognitive impairment can be associated with the disease and its treatments such as chemotherapy, radiotherapy, hormone therapy, and novel anticancer treatments.[5-9]

Existing evidence originating from both preclinical animal models and human trials has demonstrated that chemotherapy regimens, especially those containing anti-metabolic agents such as methotrexate, may cause long-lasting cognitive impairment.[5,10] Chemotherapy-related cognitive impairment (CRCI) encompasses a range of mild neurological impedi-

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ments such as self-recognized mental slowness, impaired concentration, and memory loss during and after chemotherapy.[11-13] Generally, the complaints of this phenomenon are transitory; however, in some cases, they can present as protracted symptoms.[5] Janelsins et al. evaluated the self-reported cognitive functions of 581 women with breast cancer from pre-chemotherapy to post-chemotherapy and from pre-chemotherapy to 6-month follow-up after post-chemotherapy.[12] They reported that the self-reported cognitive functions of the patients deteriorated drastically from pre-chemotherapy to post-chemotherapy. They also observed that pre-chemotherapy anxiety and depression had a significant effect on the perceived intellectual abilities of the patients. Owing to the complex nature of CRCI, the study of this phenomenon requires the identification and elimination of confounding variables such as depression, anxiety, fatigue, comorbid medical conditions, genetic predisposition, surgical impact, and hormonal therapy as much as possible to tackle the adverse impact of CRCI on patients.[14-16]

To date, predicting which patients will be affected and how to protect them from this problem remains unclear.[17] Rigorous research has been conducted during recent years to understand this issue and several potentially associated mechanisms such as direct neuronal injury, glial-modifying effects of chemotherapeutics, cytokine deregulation-associated neurotoxicity, accelerated aging of neuronal structures, and hormonal changes have been identified (Figure 1).[7,9,10,18-25] Thus, the etiology of CRCI can be considered as multifactorial, which corroborates with the considerable variation observed among different sub-populations of patients.[26] Future research is required to identify the susceptible sub-populations and develop effective interventions to combat CRCI. No pharmacological interventions toward CRCI have been proven as effective to date, although evidence from contemporary research indicates that non-pharmacological approaches, including cognitive rehabilitation programs, physical exercise, and electroencephalographic bio-feedback, have a promising future.[27]

IL-1: Interleukin-1; IL-6: Interleukin-6; TNF: Tumor necrosis factor-alpha; 5-FU: 5 fluorouracil. The pathophysiology of chemotherapy-related cognitive impairment includes different mechanisms such as direct neurotoxicity, glial modification, cytokine deregulation associated with neurotoxicity, and hormonal changes.

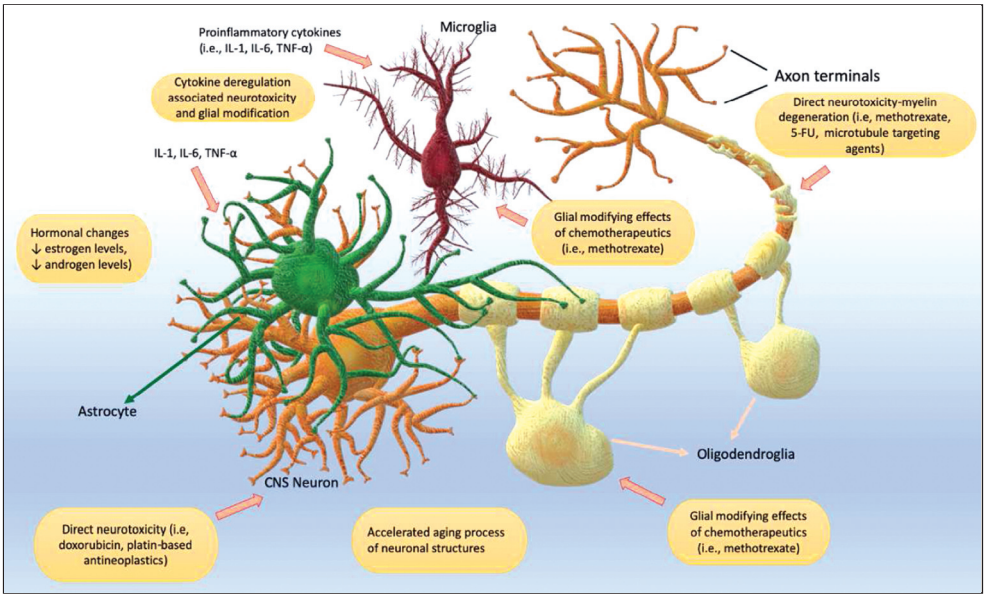



**FIGURE 1:** Possible pathophysiological mechanisms in chemotherapy-related cognitive impairment. IL-1: Interleukin-1; IL-6: Interleukin-6; TNF: Tumor necrosis factor-alpha; 5-FU: 5 fluorouracil. The pathophysiology of chemotherapy-related cognitive impairment includes different mechanisms such as direct neurotoxicity, glial modification, cytokine deregulation associated with neurotoxicity, and hormonal changes.

## GAMIFICATION CAN BE A STRATEGY TO TACKLE "CHEMOBRAİN"

Neural plasticity has aroused the interest of neuroscientists for decades. It has been argued that human brains possess this ability for their entire lives, although it declines over time.[28] Therefore, neuroscientists have developed mental exercises to palliate the decline of neural plasticity and thus sustain cognitive functions.[29] It has been proposed that brain exercises improve cognitive functioning. However, the underlying mechanisms of this effect remain to be elucidated.[30] Harnessing these brain exercises in clinical practice necessitates prior clinical trials to prove their effectiveness.

"Insight" from Posit Science is a computerized neurocognitive learning program based on the neuroplasticity model, which uses adaptive exercises aimed at improving cognition through the speed and accuracy of information processing. The program targets cognitive areas that are often affected in patients with cancer, such as visual sensitivity, divided attention, working memory, the field of view, and visual processing speed. Bray et al. demonstrated the potential of a cognitive rehabilitation program (Insight) to alleviate CRCI.[31] This program was applied in 242 adult cancer patients who had reported persistent cognitive symptoms and had been administered three or more chemotherapy cycles as adjuvant therapy for a primary malignancy (except for malignancies of the central nervous system) during the previous 6 to 60 months. Of the patients, 230 (95%) were female. The median age of the patients was 53 years (23 to 74 years). A total of 216 patients had breast cancer, and 13 patients had colorectal cancer. The participants were divided into two groups; one randomly assembled group was assigned to a 15-week home-based cognitive rehabilitation program (Insight), and the other group was provided standard care. The primary outcome was self-reported cognitive function Functional Assessment of Cancer Therapy Cognitive Function (FACT-COG), with perceived cognitive impairment (PCI) as the subscale. The researchers evaluated the difference between the groups immediately upon the completion of the program and after six months. The PCI of the intervention group was significantly lower than that of the control group at both time points (the first evaluation point [-7.47; 95% confidence interval (CI), -10.80 to -4.13; p<0.001], the second evaluation point [-6.48; 95% CI -9.85 to -3.11; p=0.001]). Also, the analysis of the other subscales of FACT-COG indicated that the intervention was effective. The symptoms of anxiety, depression, and fatigue were significantly lower in the intervention group. Although there was no significant difference in the quality of life between the two groups at the first assessment (immediately upon completion of the 15-week program) (21.20; 95% CI, 22.20 to 20.20; p=0.02), the intervention group showed better quality of life after six months (21.0; 95% CI, 22.10 to 0.01; p=0.06).

Advanced Cognitive Training for the Independent and Vital Elderly (ACTIVE) was a unique clinical trial that focused on older adults who were potentially at risk of loss of independence, linking specific cognitive and perceptual interventions to broader behavioral outcomes.[32] It was originally designed to examine the effects of perceptual and cognitive interventions on the primary outcomes such as the cognitively demanding daily life tasks and secondary outcomes such as the health-related quality of life, mobility, and utilization of health services. Von Ah et al. evaluated a cognitive rehabilitation program in a randomized controlled trial, which was single-blinded and comprised of 82 breast cancer survivors.[33] They analyzed the efficacy of the intervention program, which was previously utilized in the ACTIVE study, by collecting data at baseline, post-intervention, and 2-month follow-up. They reported that the interventions significantly improved the objective neuropsychological tests, as well as the perceived cognitive functioning and quality of life.

The National Cancer Institute (NCI) of the US National Institute of Health has requested a team consisting of brain exercise program developers to submit their evidence for the evaluation of NCI. In 2018, NCI included the commercially available "Insight" program (Posit Science®, USA, Brain HQ) in its database of evidence-based cancer interventions and program materials34. The "Insight" program was a part of the ACTIVE trial and was subsequently upgraded and refined32. The other commercially available applications developed to improve cognitive functioning are listed in Table 1.

**TABLE 1:** Available commercial applications to improve cognitive functions.

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| Brain HQ | Aims to provide brain exercises that are designed to improve memory, attention, people skills, and navigation. | www.brainhq.com |
| Lumosity | A service that specializes in memory training. | www.lumosity.com |
| Happy Neuron | Intriguingly designed personalized brain exercises. | http://www.happy-neuron.com/ |

## EMPLOYING GAMIFICATION FOR CANCER PATIENTS

Patients living with cancer often focus on the negativity of the situation in a vicious circle and cannot get rid of negative ideas quickly, which causes further anxiety and depression. Gamification can help such patients focus on a virtually appealing environment cognitively, which will aid in breaking their vicious and precluded ruminative thought process. Gamification is the adaptation of game characteristics and elements into non-game concepts to achieve a goal or overcome a problem. Areas of application of gamification range across education, business, and healthcare settings.

It is vital to remember that gamification is often applied in business and marketing areas, wherein the targeted audience is generally healthy individuals. A cancer patient does not fit into this group of people because the holistic well-being of cancer patients holds significant importance during and after their treatment. After all, cancer is more than a physiological disease. Therefore, one limitation while designing a gamification approach is the consideration of the mental and physical status of cancer patients; the general gamification approach might not be as practical as it is over the general public and a specific approach to gamification needs to be developed.

A cancer patient understandably has several questions about their disease. These questions are accompanied by anxiety, fear, and concerns. In some cases, the fear of death, which is the basis of all our fears, can turn into a vicious circle that creates spiraling anxiety. Subsequently, this anxiety can lead patients to consciously lose positive expectations about the effectiveness of cancer treatment. Because expectations can be influenced by modifying perception and cognition, gamification might employ some psychological strategies to put a positive spin on these. It can also become a companion during the treatment journeys of cancer patients. The application should provide useful information to tackle confusion and use visual and auditory signals to improve brain activity while being flexible. In other words, the application should be responsive to the feedback of users and accordingly provide meditative services such as breathing exercises, calming visuals, and soothing melodies or sounds.

Fancourt et al. reported that long-term participation in a choir resulted in reduced levels of anxiety and improved the quality of life of more than 1,000 cancer patients.[35] It was observed that singing was associated with a decrease in the levels of cortisol, beta-endorphin, and oxytocin, indicating stress reduction and general activation of the cytokine network that helps regulate immunity.

Rabin et al. conducted a study on increasing physical activity (PA) and reducing stress among young people with cancer.[36] Participants were told they would be guided in gradually increasing the frequency and duration of their moderate-intensity aerobic activity toward a final goal of 30 minutes per day on at least 5 days a week. The project director also provided participants with an introduction to the philosophy and practice of mindfulness meditation. Participants were given a mindfulness CD and asked to practice meditation on at least 4 days a week. The results were feasible and acceptable. 97% of participants gave one of the two highest satisfaction ratings for the PA component of the intervention (i.e., 4 or 5 out of 5), and 61% gave one of the two highest satisfaction ratings for the meditation component. All of those completing the participant evaluation indicated that they would recommend the intervention to others. An increase in PA has been demonstrated as an intervention that can help improve fitness and enhance mood.

Competition is an important aspect of our daily lives; people are always in a race to be the best at

what they do to improve their well-being. Games also adopt this principle to increase their popularity and sales. Several genres of games include competitive game modes, wherein people play against one another to either advance to a better "league" or acquire unique rewards that are not available to every player to have the "bragging rights." However, for someone who is living with cancer and undergoing its treatment and the burdens of its side effects, competition may not be as sensible as it is for healthy individuals. A competitive environment in which someone has certain disadvantages due to their necessary treatment can remind them that they are isolated from society, which can cause negative thoughts and depression that will inevitably have adverse effects on their treatment process.

Nevertheless, there still needs to be a motivating factor for patients to pursue the goals of the game. As discussed above, competitive superiority might not be the best goal for motivating patients. Instead of having to compete with other individuals to achieve a reward, the player may be put in a vast environment by themselves with several hidden awards. Thus, the game can motivate the patient to progress further within the game, while also making sure that the patient does not feel overwhelmed or as being put in a race.

Besides, it may be necessary to consider the ages of the people in interventions such as gamification for improving their mood. Likewise, the difference in moods depending on the type and stage of the cancer is a crucial factor that needs consideration. The environment a person finds themselves in can also be another factor. Based on these factors, gamified interventions may have varying intensities. The combination of gamification with such activities can achieve more than gamification or other activities can do on their own.-

The main advantage of interventions such as gamification in the virtual world is that they have multiple goals. For example, because of being embedded in a story, the player will be closer to the real world than intelligence-stimulating games on paper. Also, while potentially challenging puzzles on paper, such as sudoku, may diminish the morale of the patient, computer-based games can be duly adjusted to the level of cognitive capability of the individual patient. Increasing the level of intervention according to the person is possible with gamification. One drawback of gamification is that there is a substantial lack of requisite technological hardware for bringing this novel method into widespread use, and such technologies are not accessible to certain segments of the population, such as the elderly. Besides, if a system is not designed considering the screen time, different health issues may also occur. Nevertheless, an array of studies has demonstrated the potential benefits of gamification in general.

Consequently, cognitive rehabilitation programs should be applied more and developed further in the appropriate gamification settings. The primary goal of gamification in cognitive rehabilitation programs should be to develop a system that will ameliorate the cognitive dysfunction of cancer patients, as well as educate and empower them to sustain a healthy approach towards cancer. To this end, engineers, program developers, and physicians should collaborate closely, along with effective communication with the patients, and be motivated to apply gamification to circumvent this issue with the benefits of technology.

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***Conflict of Interest***

*No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.*

***Authorship Contributions***

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