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CHALLENGES IN RESEARCH ON THE NEURAL BASIS OF „CHEMOBRAIN"

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Abstract

Cancer survivors treated with chemotherapy frequently complain about impairment of cognitive functions including attention and memory. While the contribution of factors like psychological distress, anxiety or fatigue to this "chemobrain" syndrome has been discussed, studies in rodents have demonstrated the toxicity of various chemotherapeutic substances to the adult central nervous system. In humans, structural brain imaging has revealed both reduced gray and white matter volume and decreased white matter integrity related to chemotherapeutic treatment. Studies of brain function have found alterations in brain activation patterns during different types of tasks. Nevertheless, further clinical research using prospective designs in larger samples is required to better understand the relationship between chemotherapy and cognitive deficits. Variables that need to be considered more systematically include drug dose, genetic variations, and psychological factors. Assessing both electroencephalographic and hemodynamic responses during tasks at different stages of the processing hierarchy and at different difficulty levels should help in pinpointing the cortical processes affected by chemotherapy.

Keywords

• Chemotherapy • Cognitive impairment • Brain imaging

Many cancer patients treated with chemotherapy report symptoms related to cognitive impairment. The most frequently affected functions include memory, attention, processing speed and multitasking [1-3]. This syndrome, which has been termed "chemobrain" or "chemo fog", significantly impairs the quality of life of patients undergoing active therapy and cancer survivors. It has been studied most extensively in the population of breast cancer patients with an estimated frequency of 20-40% of affected patients [4]. Cognitive dysfunction is revealed both by patients' self-reports and by neuropsychological tests, although both types of measures do not necessarily correlate with each other [5,6]. Most cognitive deficits tend to recover within the first year after treatment; however, some studies have convincingly demonstrated long-term effects years after treatment [7]. While the existence of cognitive dysfunction in cancer survivors is generally recognized, its causation remains controversial. Cognitive deficits may represent a general comorbidity of cancer. In addition, psychological reactions to the diagnosis of cancer, such as distress, anxiety or depression [8] affect cognitive performance. Some studies indicate the onset of cognitive impairment prior to the start of chemotherapy [9,10]. On the other hand, animal studies have clearly demonstrated detrimental effects of chemotherapeutic agents on the central nervous system (CNS), providing evidence for a contribution of chemotherapy to cognitive dysfunction.

Both *in-vitro* and *in-vivo* preclinical studies have shown that different types of chemotherapeutic substances are toxic to neural progenitor cells in the adult CNS with preferential vulnerability to the oligodendroglial lineage – the myelin forming cells of the CNS [11-13]. The resulting impairment of brain plasticity and neural repair and the damage to myelination and white matter integrity, respectively, may at least in part account for the cognitive sequelae of chemotherapy [14]. Additional evidence for this notion has been provided by an increasing number of animal studies using behavioral paradigms [15,16]. Exposure to chemotherapeutic agents was associated with decreased performance on different types of learning tasks utilizing hippocampal and frontal network functions [17-20].

Structural and functional brain imaging studies have started to elucidate the neural correlates of chemotherapy-related cognitive decline in humans [21-24]. Examinations of cortical structure using magnetic resonance imaging (MRI) have demonstrated reductions of both gray and white matter volume when comparing chemotherapy-treated patients with either healthy controls [25] or untreated patients [26]. Prospective studies have revealed that both frontal and temporal cortex showed the most pronounced volume reductions [27,28]. A recent cross-sectional investigation provided evidence for hippocampal damage that was related to decreased verbal memory performance [29]. In line with the findings from the animal work reported above, diffusion tensor imaging (DTI) studies have found chemotherapy-related reductions of white matter integrity that correlated with cognitive performance [30]. A prospective DTI study

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in children with hematological malignancies showed that chemotherapy predominantly affected frontal white matter [31].

Studies of functional changes related to chemotherapy have used both electroencephalography (EEG) and hemodynamic brain imaging methods. Only a few studies have investigated event-related EEG potentials in chemotherapy-treated patients. A consistent finding was an amplitude reduction of the P300 component in treated compared with untreated patients. This finding, suggesting sustained deficits in the allocation of processing resources, was obtained both during passive stimulus processing [32] and during a perceptual-motor task. Effects lasted for up to 5 years after treatment [33,34]. While these studies compared patients in cross-sectional designs, prospective studies comparing event-related potentials before and after therapy have yet to be performed.

Functional MRI (fMRI) studies have used both passive and active paradigms. Resting-state investigations revealed altered cortical functional network properties in patients treated with chemotherapy compared with healthy controls [35]. Connectivity patterns also served to discriminate between patients and controls [36], supporting altered cortico-cortical wiring and possibly white matter damage associated with cancer and its treatment. Differences between the activation patterns of treated patients and controls were observed also during the active performance of tasks tapping memory and executive functions. Paradigms included verbal long-term memory [37,38], verbal working memory [39,40], and tasks requiring rule testing or planning, both involving prefrontal cortex [41,42]. Activation differences between groups were frequently found in frontal cortex and other task-relevant regions. Depending on the study, patients were characterized either by reduced or increased activations, which were interpreted as deficient resource mobilization or compensatory hyper-activations, respectively. However, given that most fMRI studies did not find correlations between brain activity and behavioral performance measures, such conclusions should be treated with caution. As compensation may be possible only up to a certain level of task complexity, prospective studies with tasks at different difficulty levels might shed more light on the effects of chemotherapy on human brain function.

In summary, while animal studies have yielded solid evidence for toxic effects of chemotherapeutic agents on the CNS (for review see [16]), we are only beginning to understand how these effects manifest themselves in non-invasive measures of human brain structure and function. Moreover, the question of how closely these measures are associated with cancer survivors' subjective complaints about "chemobrain" symptoms is still open. Clearly there is a need for further clinical research in cancer patients. To advance existing knowledge, future studies should take into account several critical issues, some of which have been recognized and discussed in detail previously [21,43].

Preclinical studies in rodent models have been able to elucidate both structural and functional effects of various chemotherapeutic compounds on the adult brain. In contrast, clinical studies in cancer patients have paid little attention to correlating the effects of distinct treatment regimens and drug doses to clinical outcomes. Patient heterogeneity and various other factors (e.g., concurrent medications, such as anti-depressants and steroids) are also likely to contribute and modulate neurocognitive function and will need to be recognized and studied in greater detail in future studies.

The study of genetic risk factors includes screening for genetic polymorphisms of drug resistance genes and other genetic factors that might alter brain vulnerability. Correlating such studies with imaging and neurocognitive outcome measures in cancer patients will be helpful to understand the differential vulnerability of patients to chemotherapy. It is also critical to identify patients who are at greatest risk to develop neurocognitive decline as a consequence of cancer treatment.

Both fMRI and EEG data have a limited reliability especially for more complex paradigms [44], making between-group comparisons difficult. Large numbers of participants would help to avoid over-estimating group differences. Also, as the vast majority of previous research on the functional and structural correlates of chemotherapy was performed in breast cancer patients, including patients with other types of tumors would increase the generalizability of the results. Frequent findings of pre-treatment group differences [39,45,46] underscore the need for longitudinal approaches with measurements before and after chemotherapy. While healthy individuals may not represent the ideal control group, comparisons between treated and untreated patients may also be affected by confounding factors related to disease severity like psychological distress, anxiety, depression or fatigue. For example, Lopez Zunini *et al.* [38] found activation differences between patients and healthy controls pre-chemotherapy to be related to differences in anxiety and fatigue. If groups differ on these variables, they need to be included as covariates in the statistical analyses.

Whereas functional imaging studies in chemotherapy patients have used memory paradigms or tests of executive functions, it would be interesting to assess whether treated patients show generalized deficits at different levels of the processing hierarchy ranging from passive perceptual processing to high-level cognitive tasks, or whether impairments are specific to certain types of tasks and levels of difficulty. Assessing the latency and amplitude of early event-related potentials can demonstrate early perceptual processing abnormalities as found in mice [12]. This would be indicative of fundamental damage to neural transmission that could affect subsequent, higher-order functions. On the other hand, chemotherapy-treated patients may be able to compensate such deficits for tasks of moderate complexity or difficulty, whereas compensation should break down for more demanding tasks. We would therefore recommend applying tests of different functions along the processing hierarchy starting from passive sensory processing via simple attention/detection paradigms up to more demanding memory tasks at variable difficulty levels. It would be useful to combine different methods for the analysis of temporal and spatial aspects of cortical activation like EEG and fMRI, respectively. Given the

evidence for chemotherapy-related damage to cortico-cortical connections [47], measures of task-related functional connectivity should be investigated during paradigms tapping integrated processing such as working memory tasks requiring the interplay between fronto-parietal executive networks and sensory storage regions. In addition, comparing structural and functional connectivity measures could elucidate the mechanisms underlying possible integration deficits.

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