

Published in final edited form as:

Nat Rev Cancer. 2007 March ; 7(3): 192–201. doi:10.1038/nrc2073.

Candidate mechanisms for chemotherapy-induced cognitive changes

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Abstract

The mechanism(s) for chemotherapy-induced cognitive changes are largely unknown; however, several candidate mechanisms have been identified. We suggest that shared genetic risk factors for the development of cancer and cognitive problems, including low-efficiency efflux pumps, deficits in DNA-repair mechanisms and/or a deregulated immune response, coupled with the effect of chemotherapy on these systems, might contribute to cognitive decline in patients after chemotherapy. Furthermore, the genetically modulated reduction of capacity for neural repair and neurotransmitter activity, as well as reduced antioxidant capacity associated with treatment-induced reduction in oestrogen and testosterone levels, might interact with these mechanisms and/or have independent effects on cognitive function.

Studies associating cognitive changes with cancer chemotherapy have been reported since the mid 1970s¹; however, systematic research on the cognitive side effects of chemotherapy did not appear until the 1990s. Over the past 10 years, neuropsychological studies of cancer survivors^{2–8} and emerging data from longitudinal studies that include pretreatment neuropsychological assessments^{9,10} have found evidence supporting the influence of chemotherapy on cognitive functioning, although negative studies have also been reported^{11–12}. The cognitive changes associated with chemotherapy are typically subtle (functioning is reduced but often remains in the normal range), and occur across various domains of cognition, including working memory, executive function and processing speed^{13–16}, but not the retrieval of remote memories (see BOX 1 for a description of the cognitive functions that can be affected by chemotherapy). Furthermore, although acute cognitive changes during chemotherapy are common^{14,15}, long-term post-treatment cognitive changes seem to persist in only a subgroup (17–34%) of cancer survivors. Historically, cognitive changes in cancer patients were assumed to be related to psychological factors such as depression or anxiety, or other side effects of cancer treatments like fatigue. However, most of the studies cited above have found evidence for persistent post-chemotherapy cognitive changes after statistically controlling for

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Competing interests statement

The authors declare no competing financial interests.

psychological factors or fatigue, or by studying patients without significant psychological distress or fatigue.

Studies that have used imaging techniques (FIG. 1) have reported structural and functional changes in the brain associated with chemotherapy^{17,18}. A reduction in the volume of brain structures important for cognitive functioning (such as the frontal cortex) and changes in the integrity of white-matter tracks that connect brain structures have been associated with changes in cognitive functioning, and have been seen using structural magnetic resonance imaging (MRI) on patients after chemotherapy. Recent data from a longitudinal study of breast cancer patients, who were evaluated with structural and functional MRI before treatment and 1 and 12 months after treatment, have suggested a pattern of reduced activation in frontal areas during a working memory task¹⁹. Decreased activation in frontal areas is indicative of dysfunction in brain areas crucial for normal working memory functioning. Finally, studies in patients with breast cancer treated with chemotherapy have examined the P-300 event-related brain potential of the electroencephalogram (EEG), which is important for the attention-dependent processing of information. These studies found that decreases in amplitude (intensity of neural activation) and latency (timing and duration of activation) of P-300 were associated with chemotherapy, which is consistent with changes in information-processing capacity^{20,21}.

Interestingly, several studies have found a higher than expected incidence of cognitive problems in cancer patients before the initiation of chemotherapy²²⁻²⁵, and the diagnosis of cancer has been proposed as a potential risk factor for cognitive impairment and Alzheimers disease in the elderly²⁶. These data suggest that cognitive changes associated with chemotherapy need to be examined within the broader context of risk factors and biological processes associated with the development of cancer.

The research so far suggests that performance changes in cognitive functioning can be seen in a subgroup of patients after chemotherapy, and that these changes might be associated with changes in brain structure and function. However, studies that examine the mechanism(s) by which chemotherapy can cause long-term cognitive changes are either in process or are yet to be conducted. When considering mechanisms of chemotherapy-induced cognitive changes, it is important to consider biological pathways that could lead to relatively subtle alterations in cognitive functioning in only a subgroup of people exposed to chemotherapy. The purpose of this Review is to describe candidate mechanisms for chemotherapy-induced cognitive changes (FIG. 2) and potential common risk factors for the development of cancer and cognitive problems. For each of the candidate mechanisms, genetic polymorphisms will be described that might account, in part, for variation in the cognitive effects of chemotherapy (TABLE 1). Unfortunately, data directly supporting the proposed mechanisms are limited; therefore, the goal of this Review is to present mechanisms that lead to logical hypotheses that can be tested empirically. Furthermore, although the focus of the Review is on chemotherapy-associated changes in cognitive function, much of the discussion might be relevant to other treatment modalities (such as radiation therapy, particularly in combination with chemotherapy) and other treatment-related toxicities (for example, peripheral neuropathy).

Chemotherapy and the blood–brain barrier

It has generally been assumed that most chemotherapeutic agents do not cross the blood–brain barrier (exceptions include methotrexate and 5-fluorouracil). However, recent reviews have suggested that nearly all frequently used chemotherapeutic agents can cause disorders of the central nervous system (CNS), including encephalopathy, leukoencephalopathy, ototoxicity and cerebellar symptoms, although these are fairly uncommon^{27,28}. In addition,

studies using positron emission tomography (PET) have shown that detectable levels of radiolabelled cisplatin²⁹, BCNU (1,3-bis (2-chloroethyl)-1-nitrosourea, also known as carmustine)³⁰ and paclitaxel³¹ were found in the brain after intravenous administration. The levels of these agents in the brain are low, which might explain why the intravenous administration of chemotherapeutic agents is not usually highly effective in the treatment of brain tumours. However, an unanswered question is whether the level of drug in the brain that could influence cognitive function might be lower than the dose needed to be efficacious for the treatment of tumours.

Related to the last question, Dietrich and colleagues³² administered the commonly used chemotherapy agents BCNU, cisplatin and cytosine arabinoside (cytarabine) systemically to mice. These chemotherapy agents were associated with increased cell death and decreased cell division in the subventricular zone, the dentate gyrus of the hippocampus and the corpus callosum (areas important for normal cognitive functioning) in animals that received treatment; in some cases this pattern persisted for weeks after the discontinuation of the agents. Neural progenitor cells and oligodendrocytes were particularly vulnerable. Importantly, these results were seen at lower doses than were required to cause tumour cell death.

Another factor that might influence the dose of chemotherapy that reaches the CNS is genetic variability in drug transporters at the blood–brain barrier. The gene multidrug resistance 1 (*MDR1*) encodes the protein P-glycoprotein (P-gp), the role of which is to protect cells from toxic substances by transporting them out of the cell. P-gp is expressed in the capillary endothelial cells in the brain. At the blood–brain barrier, P-gp influences the amount of drug uptake into the brain. Most commonly used chemotherapeutic agents are substrates of P-gp; therefore, the levels and functionality of P-gp at the blood–brain barrier can influence the level of a chemotherapeutic agent in the brain. For the most part, P-gp serves to protect the brain by transporting chemotherapy agents out of the brain. Several polymorphisms of the *MDR1* gene have been identified³³ that might influence P-gp function. One of the most studied polymorphisms is C3435T in exon 26. People with the T allele have lower levels of P-gp (less efficient efflux); therefore, a higher concentration of a given drug that enters the cell or organ remains because less is pumped out. Studies have shown higher plasma concentrations of several drugs in people homozygous for the T allele compared with people homozygous for the C allele^{34,35}, and animal studies have shown that mice deficient in P-gp have higher concentrations of the chemotherapy agent vincristine³⁶ and steroid hormones in the brain after peripheral administration³⁷. Although studies have not examined the direct influence of *MDR1* polymorphisms on concentrations of cytotoxic agents given intravenously to patients, it is possible that such genetic variability might influence the dose of drug delivered to the brain. In our own research, we are examining whether patients treated with chemotherapy who have polymorphisms associated with lower expression or functionality of P-gp are more vulnerable to long-term cognitive side effects, presumably because they are exposed to higher doses of the chemotherapeutic agents. In addition, PET studies using radiolabelled chemotherapeutic agents, such as those described above, could compare concentrations of these agents in the brain across patients with different polymorphisms of *MDR1* or other transporter genes (for example, those that encode organic anion transport proteins)³⁵.

Many questions remain about the direct effect of chemotherapy on the brain, and the relationship between the doses of drug delivered to the brain and cognitive functioning. Given the current state of knowledge, it seems unlikely that a direct mechanism for chemotherapy-induced cognitive decline is the only or even the primary mechanism. Therefore, it is important to look for other potential mechanisms for these changes.

DNA damage, oxidative stress and cognition

The integrity of the human genome is crucial for the normal functioning of all biological systems, including the brain³⁸. Mistakes during DNA replication and damage to DNA are common, and elaborate mechanisms exist for base-excision, nucleotide-excision, mismatch and double-strand-break repair³⁹. Oxidative stress is a common source of DNA damage that causes single- or double-strand breaks^{40,41}, and is probably the most frequent cause of DNA damage in neuronal cells⁴². Oxidative stress occurs through exposure to exogenous toxins, as well as through endogenous mechanisms secondary to normal cellular metabolism^{41,42}. Many chemotherapy agents (for example, alkylating agents) commonly used for the treatment of cancer achieve their therapeutic efficacy, in part, through DNA damage^{27,43} leading to tumour cell apoptosis. Although the desired goal is to eliminate tumour cells, DNA in normal cells is also affected, resulting in many of the side effects of chemotherapy. Studies have found evidence for oxidative DNA damage in peripheral blood lymphocytes after chemotherapy for breast cancer^{44,45}, and an increased number of point mutations in mitochondrial DNA in patients with various cancer diagnoses treated with chemotherapy with or without radiation therapy⁴⁶. Furthermore, chemotherapy has been associated with increased levels of non-protein-bound iron⁴⁷ and free radicals⁴⁸, and reduced antioxidant capacity⁴⁸⁻⁵⁰, all of which can increase oxidative stress and DNA damage. Therefore, a logical candidate mechanism for chemotherapy-induced cognitive changes is DNA damage affecting the CNS⁴².

Several lines of evidence have linked DNA damage and repair systems to neurodegeneration. Clinical syndromes such as ataxia telangiectasia and xeroderma pigmentosum are caused by genetic defects in DNA-damage response systems, and are characterized by significant neurological deficits, including cognitive deficits³⁵. Furthermore, oxidative DNA damage has been associated with various neurodegenerative disorders, including Alzheimers disease and Parkinsons disease, that are characterized by significant cognitive symptoms⁵¹. Perhaps most relevant for this discussion, elderly patients diagnosed with mild cognitive impairment (a condition characterized by isolated memory deficits without a general loss of function and associated with an increased risk of Alzheimers disease) have been shown to have higher levels of oxidative DNA damage in peripheral leukocytes⁵² and in the brain on autopsy⁵³. These data suggest that links exist between DNA damage and cognitive problems; therefore, one obvious question is whether cancer patients who show cognitive problems also have higher baseline levels of DNA damage⁴². So far, no studies have related cognitive functioning to the level of DNA damage after treatment with chemotherapy.

The mechanism(s) by which DNA damage leads to damage in the nervous system is not well understood. The CNS might be vulnerable to increases in oxidative stress because of high endogenous metabolic rates and the production of reactive oxygen species (ROS). One proposed mechanism is the production of defective proteins that eventually lead to neuronal apoptosis. Harrison and colleagues⁵⁴ showed that a decreased capacity to repair mitochondrial DNA damage was associated with increased apoptosis in neuronal cell cultures. Alternatively, DNA damage might block transcription and cause the loss of essential gene products⁴⁰. One issue in much of the research that associates DNA damage with neurodegeneration or neurocognitive problems in humans is that DNA damage is assessed in peripheral leukocytes with the assumption that these measurements reflect systemic levels of DNA damage, including in the CNS. In support of this assumption, post-mortem studies have also identified higher levels of DNA damage in the brains of patients with mild cognitive impairment and Alzheimers disease⁵³; however, this issue requires further investigation.

Interestingly, studies have found higher than expected rates of cognitive impairment in cancer patients before the initiation of chemotherapy²²⁻²⁵. In addition, higher levels of oxidative DNA damage have been found in women with breast cancer^{44,45}, and higher levels of oxidative stress were found in dogs with lymphoma⁵⁵ before the beginning of treatment. These data are consistent with research linking certain DNA-repair polymorphisms associated with a decreased capacity to repair damaged DNA to an increased risk of cancer (for reviews see REFS 39,56). Finally, patients with ataxia telangiectasia and xeroderma pigmentosum are also at a significantly increased risk of developing cancer³⁵. These data raise the possibility that deficits in DNA-repair mechanisms might be a common risk factor for both cancer and neurodegenerative disorders that include cognitive symptoms. Consequently, changes in cognitive function following chemotherapy need to be evaluated within the context of genetic factors that increase the risk of cancer but might also increase the risk of cognitive dysfunction before treatment.

Chemotherapy might also increase cognitive problems through its affect on telomere length. During the DNA replication process, telomeres shorten by 20–200 base pairs per replication. The shortening of telomeres to a crucial point leads to cell senescence and apoptosis, and has been associated with ageing, Alzheimers disease severity, cancer predisposition and mortality of people over 60 years of age⁵⁷. Several factors influence the rate of telomere shortening, including genetic variation⁵⁸, oxidative stress⁵⁹ and chemotherapy⁵⁹⁻⁶¹. Schroder and colleagues⁵⁹ reported that standard-dose and high-dose chemotherapy in patients with breast cancer resulted in telomere shortening in leukocytes for most patients, although a minority of patients showed telomere lengthening after treatment. Similarly, high-dose chemotherapy regimens given to patients with haematological malignancies who are undergoing allogeneic stem-cell transplantation have been associated with telomere shortening in haematopoietic stem cells⁶⁰. Most neuronal cells are post-mitotic; however, certain cells, such as glia in the CNS, remain mitotic and are susceptible to telomere shortening⁶². Consequently, chemotherapy might have a long-term effect on cognition by accelerating the ageing process, either through the general effect of telomere shortening on biological systems and genomic stability or through the direct effect on telomere length in mitotic cells in the CNS⁶¹.

This body of research suggests that both chemotherapy and factors that increase cancer risk might be important in understanding why a subgroup of patients experience long-term chemotherapy-induced cognitive problems. Specifically, people with deficiencies in DNA-repair mechanisms will probably have more DNA damage and shorter telomeres at the time of cancer diagnosis, related to their lifetime accumulation of endogenous and exogenous toxic exposures leading to DNA damage. Chemotherapy is a major cause of systemic DNA damage from which patients with inefficient repair mechanisms will have a more difficult time recovering. Consequently, one could predict that poorer cognitive functioning would be seen in patients with the most DNA damage before and after chemotherapy. As a first step in evaluating this hypothesis, our group is examining the relationships between DNA-repair polymorphisms and cognitive functioning within the context of two longitudinal studies of the effect of chemotherapy on cognitive function in patients with breast cancer and lymphoma. We are particularly focusing on polymorphisms in the base-excision repair pathway because of their importance in modulating oxidative stress⁴² and the risk of cancer⁵⁶.

Cytokines and cognition

In addition to their role in the regulation of inflammation, cytokines have important roles in normal CNS function, including the modulation of neuronal and glial cell functioning, neural repair and the metabolism of dopamine and serotonin, both of which are

neurotransmitters important for normal cognitive function⁶³. However, the deregulation of cytokine activity has been associated with neurotoxicity and various neurodegenerative disorders, including Alzheimers disease, multiple sclerosis and Parkinsons disease⁶⁴. In addition, cytokine-induced sickness behaviour is associated with cognitive disturbance, fatigue and depression^{65,66}. Animal and human studies that have used various methods for stimulating a cytokine response (for example, *Escherichia coli* endotoxin exposure) have shown an association between the deregulation of cytokines and deficits in cognitive performance⁶⁷⁻⁶⁹. For example, Krabbe and colleagues⁶⁹ reported an inverse association between levels of circulating interleukin 6 (IL6) and memory functioning following the administration of low-dose *E. coli* endotoxin in healthy volunteers. Other cytokines that have been studied in relation to cognitive function include IL1, IL2, IL10 and tumour necrosis factor- α (TNF α).

For many years, researchers had assumed that the brain was minimally influenced by changes in the peripheral immune system. However, recent research has shown that there is significant communication between cytokines outside the CNS and cytokines in the brain and spinal fluid through various mechanisms, including transport into the brain across the blood-brain barrier or by peripheral cytokines stimulating the release of central cytokines by communication through the vagus nerve^{63,66}.

In cancer patients, the relationship between cytokines and cognitive function is most clearly seen in the neuropsychological changes seen in patients who have received immunotherapies such as IL2 or interferon- α . Symptoms associated with immunotherapy include depression, weakness, fatigue and cognitive disruption⁷⁰. Longitudinal studies of interferon- α and IL2 treatments in cancer populations have shown decrements in cognitive performance, particularly in the domains of information processing speed, executive function, spatial ability and reaction time^{71,72} (BOX 1). These cognitive changes were independent of symptoms of depression that were also associated with the treatments.

Although not extensively studied, there is evidence that standard-dose chemotherapy is associated with increases in cytokine levels. Specifically, paclitaxel and docetaxel have been associated with increased levels of IL6, IL8 and IL10 (REFS 73-75). The studies cited above examined the acute effects of chemotherapy on cytokine levels; however, there are no direct data examining the associations between chemotherapy-induced cognitive changes and cytokine deregulation in long-term cancer survivors. However, in a related area, breast cancer survivors who experience persistent fatigue two years or more after chemotherapy have been shown to have elevations in several of the same cytokines described above^{76,77}.

Studies have supported the association between inflammation and an increased risk of developing several types of cancer, including bladder, cervical and ovarian^{78,79}. In addition, cytokines have been shown to be increased in cancer patients before treatment. In patients with advanced breast cancer, IL6 and TNF α were increased compared with healthy controls⁷³. Meyers *et al.*²³ studied patients with acute myeloid leukaemia or myelodysplastic syndrome, and found increased levels of IL1, IL1 receptor antagonist (IL1RA), IL6, IL8 and TNF α compared with normal values before treatment. Furthermore, higher levels of IL6 were associated with poorer performance on measures of executive function before treatment. Unfortunately, the number of patients available for post-treatment neuropsychological evaluation was too small to examine the relationships among chemotherapy, cytokine levels and cognitive performance. These data suggest that cytokine deregulation might be related both to the development of cancer and cognitive problems before treatment.

Genetic polymorphisms have been identified that influence cytokine activity and have been associated with disorders such as Alzheimers disease and depression^{64,80}. However, so far no studies have examined the relationships between these polymorphisms and chemotherapy-induced cognitive changes. Within the context of the genetic component of the longitudinal study of the cognitive side effects of chemotherapy described above, we are also examining various polymorphisms related to cytokine activity.

Cognitive changes associated with cytokine deregulation are probably associated with both direct and indirect mechanisms. Neuronal damage secondary to cytokine exposure can be caused by various mechanisms including excitotoxic glutamate receptor-mediated damage and oxidative stress⁶³. Indirect mechanisms include cytokine-induced appetite reduction leading to micronutrient deficiency, and impaired sleep regulation⁶³.

These data raise the possibility that the neurotoxic effects of cytokines triggered during the development of cancer and/or in association with chemotherapy might contribute to the development of post-treatment cognitive problems. Furthermore, cytokines might be triggered in response to DNA damage, which could set up a cycle of increasing DNA damage and cytokine activity³⁸, and chronic inflammation can increase oxidative stress⁶³, which might also contribute to this cycle. Therefore, understanding the independent and interactive effects of DNA damage, inflammation and cytokine deregulation might be important for a complete understanding of chemotherapy-induced cognitive changes.

Genetics of neural repair

Apolipoprotein E (APOE) is a complex glycolipo-protein that facilitates the uptake, transport and distribution of lipids. It seems to have an important role in neuronal repair and plasticity after injury⁸¹. A four-exon gene encodes *APOE* on chromosome 19 in humans. There are three main alleles: E2, E3 and E4. These alleles differ in amino acids at positions 112 and 158: E2 (cysteine–cysteine), E3 (cysteine–arginine) and E4 (arginine–arginine). Animal models suggest a link between the E4 allele and increased mortality, extent of damage and poor repair following brain trauma⁸²⁻⁸⁴. The human E4 allele has been associated with various disorders with prominent cognitive dysfunction, including otherwise normal patients with memory complaints, Alzheimers disease and poor outcomes in stroke and traumatic brain injury^{85,86}. Our group evaluated the relationship of the *APOE* genotype to neuropsychological performance in long-term cancer survivors treated with standard-dose chemotherapy. The results showed that survivors with at least one E4 allele scored significantly lower in the visual memory and spatial ability domains, with a trend to score lower in executive functioning compared with survivors who did not carry an E4 allele⁸⁷.

The mechanism by which the E4 allele exerts its negative effect is unclear. Rather than an active detrimental effect, it might be that the E4 allele of *APOE* is less effective than the E3 allele in promoting neuronal repair and neuritic growth and branching. However, data also suggest that E4 carriers, compared with people with other forms of *APOE*, might have morphological differences in the brain, specifically, lower hippocampal volume (an indication of a reduced functional capacity of the hippocampus, which is important for memory functioning⁸⁸).

Brain-derived neurotrophic factor (BDNF) is expressed in the brain, particularly in the prefrontal cortex and hippocampus, and has been associated with neuronal repair and survival, dendritic and axonal growth, and long-term potentiation^{89,90}. A functional polymorphism of *BDNF* is associated with a valine-to-methionine amino-acid substitution at codon 66. The methionine allele has been associated with poorer performance on measures of memory and executive function and lower hippocampal volume⁹¹⁻⁹³ in non-cancer populations. No chemotherapy studies have examined the relationship of *BDNF*

polymorphisms to chemotherapy-induced cognitive changes; however, this seems to be another important target for investigation⁹⁰.

Genetics of neurotransmission

Polymorphisms in neurotransmitters that affect their activity have also been linked to cognitive performance⁸¹. A polymorphism in catechol-O-methyltransferase (*COMT*) is one of the most commonly studied polymorphisms, and is so far the only polymorphism to be linked to the cognitive side effects of chemotherapy (see REFS 81,90,94 for potential candidate alleles that affect the activity of other neurotransmitters). *COMT* catalyses the metabolic breakdown of catecholamines through the methylation of dopamine and noradrenaline. A common functional polymorphism of *COMT*, characterized by a single nucleotide change from G to A at position 472, changes a valine to a methionine. The effect of this amino-acid substitution is a significant change in the efficiency of *COMT* enzymatic activity⁹⁵. *COMT* with the valine allele is almost four times as active as that with the methionine allele. Therefore, individuals homozygous for the valine allele presumably metabolize dopamine much more rapidly than those with the methionine allele. *COMT* is an important modulator of the amount of dopamine in the frontal cortex, accounting for ~60% of the metabolic degradation of dopamine⁹⁶. Dopamine is important for executive and memory functioning mediated by the frontal cortex, and research has shown that decreased dopamine levels associated with the valine allele of *COMT* are associated with poor performance on various measures of cognitive functioning⁹⁰ in non-cancer populations. Analyses of pilot data from our long-term survivor cohort showed that breast cancer and lymphoma survivors who had been treated with chemotherapy and carried the *COMT* valine allele scored significantly lower on measures of verbal memory and spatial ability compared with survivors who were homozygous for the methionine allele (T.A.A. and A.J.S., unpublished data).

Oestrogen and testosterone

The influence of low levels of oestrogen and testosterone on cognitive functioning should be briefly mentioned within the context of chemotherapy-induced cognitive changes because chemotherapy can induce early, abrupt menopause in women. Reduction of oestrogen associated with natural menopause has been associated with changes in cognitive functioning, particularly working memory; therefore, although not well studied, one would assume that chemotherapy-induced menopause would have similar effects⁹⁷. In addition, certain treatments for cancer that reduce levels of these hormones (tamoxifen and aromatase inhibitors for breast cancer, and androgen ablation in prostate cancer) are often given in combination with chemotherapy or as single agents. Initial evidence suggests that these treatments have a detrimental effect on cognitive functioning even when given without chemotherapy^{98,99}. Research also supports the neuroprotective and antioxidant effects of both oestrogen¹⁰⁰ and testosterone¹⁰¹, and the importance of oestrogen for maintaining telomere length¹⁰². Therefore, reduced oestrogen or testosterone might have an independent effect on cognitive function or might interact with chemotherapy through a reduction of antioxidant capacity or the ability to maintain telomere length.

Conclusions and future directions

Despite increasing research in this area, the mechanisms by which chemotherapy-induced cognitive changes occur remain largely unknown. However, several potentially important candidate mechanisms have been identified that can be evaluated in future research. We suggest that there might be shared genetic factors for the development of cancer and cognitive problems. These include low-efficiency efflux pumps that lead to increased exposure to toxins in the brain, deficits in DNA-repair mechanisms that lead to greater DNA

damage, and deregulation of the immune response. Cancer patients with one or more of these risk factors might show cognitive deficits at diagnosis, and are probably the most vulnerable to cognitive side effects of chemotherapy. Exposure to chemotherapy causes DNA damage and telomere shortening in healthy cells and tumour cells, and triggers an immunological response, both of which can have neurotoxic effects. Furthermore, in certain patients, DNA damage and cytokine release could interact to create a cycle of chronic inflammation and DNA damage that is sustained after chemotherapy is discontinued. Reduced capacity for neural repair (for example through polymorphisms in *APOE* or *BDNF*) and neurotransmitter activity (for example by polymorphisms in *COMT*), as well as reduced antioxidant capacity associated with reduction in oestrogen and testosterone levels, might exacerbate this process and/or have independent effects on cognitive function.

Two additional mechanisms deserve to be mentioned, even though they have not been directly studied in relation to chemotherapy-induced cognitive changes. First, many chemotherapy agents are cardiotoxic; therefore, cognitive changes could be secondary to cardiovascular changes that could influence cerebrovascular function¹⁰³. Second, alterations in the neuroendocrine system have been associated with cognitive deficits¹⁰⁴. Corticosteroids, which are known to alter neuroendocrine functioning and cognition, are commonly used as part of chemotherapy regimens or to manage side effects such as nausea¹⁰⁵.

The tools for evaluating the candidate mechanisms proposed are, for the most part, currently available. As outlined at the 2003 Banff consensus conference on cognitive side effects of chemotherapy (BOX 2), large scale¹³, longitudinal studies of various patient groups who are evaluated before receiving chemotherapy and followed after chemotherapy with measures of neuropsychological functioning, brain structure and function (MRI and PET), genetic profiles and biomarkers relevant for candidate mechanisms (for example, DNA damage and immune response) are necessary to identify a large enough subgroup of patients who experience persistent cognitive problems secondary to chemotherapy. Ideally, comparison groups of patients with the same diagnoses who are treated with non-chemotherapy-based regimens and/or healthy controls will be evaluated with the same measures at analogous time periods. However, because investigators have proposed that chemotherapy might accelerate the ageing process⁶¹, cross-sectional studies of long-term survivors (for example, five or more years after treatment) who have been treated with chemotherapy compared with well-matched groups of patients not treated with chemotherapy and healthy controls might be necessary to examine the relationships among variables such as cognitive performance, DNA damage and/or telomere shortening, genetic profile and imaging-based measures of brain function. Finally, animal models of chemotherapy-induced cognitive changes, which are currently under development, will improve the ability of researchers to examine mechanistic questions^{106,107}.

In summary, several candidate mechanisms for chemotherapy-induced cognitive changes have been proposed, and it is likely that there are several pathways to cognitive decline depending on the treatment regimens and the particular vulnerabilities of the individual. Given that only some individuals seem to experience long-term cognitive changes following chemotherapy, it might be that several interacting mechanisms are necessary to produce changes in biological systems that translate into changes in cognitive ability.

Acknowledgments

The authors are supported by grants from the Office of Cancer Survivorship of the US National Cancer Institute and a National Institutes of Health Roadmap U54 Grant.

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Glossary

Magnetic resonance imaging	A noninvasive technique that produces high-resolution, computerized images of internal body tissues. Structural MRI enables abnormalities of brain structure to be evaluated and volumetric measurements of specific structures to be made. Functional MRI enables activation patterns in various brain areas in response to the performance of cognitive or motor tasks to be examined.
P-300	The P-300 is a neural-evoked potential component of the EEG. The P-300 is an event-related potential that is triggered approximately 300 milliseconds after the presentation of an unexpected or novel stimulus.
Encephalopathy	Encephalopathy refers to alterations in brain structure and/or function that can have several causes, including infection, exposure to toxic chemicals (for example, chemotherapy), poor nutrition or lack of oxygen or blood flow to the brain. The primary symptoms of encephalopathy are alterations in mental status.
Leukoencephalopathy	Alterations of the white matter of the brain owing to infection or exposure to toxic chemicals.
Ototoxicity	Toxicity associated with organs or nerves involved with hearing or balance.
Cerebellar symptoms	The cerebellum is an area of the brain that is important for the integration of sensory input and motor output. Disorders of the cerebellum include symptoms associated with equilibrium, posture, motor learning and fine motor control.
Positron emission tomography	A nuclear medicine imaging technique that produces a three-dimensional image of functional or metabolic processes in the body by scanning for a radioactive isotope (for example, a

	radiolabelled chemotherapy agent) that has been injected into the bloodstream.
Ataxia telangiectasia	A disorder caused by a mutation of the ataxia telangiectasia mutated (<i>ATM</i>) gene, which is important for DNA repair. Ataxia telangiectasia causes progressive immunological and neurological problems, including cognitive symptoms, and people with ataxia telangiectasia have a significantly increased risk of cancer.
Xeroderma pigmentosum	A genetic DNA-repair disorder in which the body is unable to repair DNA damage or mutations caused by ultraviolet light.
Glia	A group of non-neuronal cells in the brain that provide support and nutrition, form myelin and influence signal transmission in the nervous system.
Sickness behaviour	Physiological response to infection that includes symptoms such as decreased activity level, fatigue, decreased motivation and cognitive problems.
Vagus nerve	The vagus nerve is the only cranial nerve that extends from the brainstem to all the organs in the abdomen.
Excitotoxicity	The process by which neurons are damaged or killed through the over-activation of receptors for the excitatory neurotransmitter glutamate.
Long-term potentiation	Long-lasting increase in the functioning of a synapse, which is thought to be related to neural plasticity and the cellular basis for learning and memory.

At a glance

- Evidence for chemotherapy-induced cognitive changes comes from studies that have used neuropsychological testing, imaging (structural and functional magnetic resonance imaging (MRI) and positron emission tomography (PET)) and electrophysiological (electroencephalogram) assessments. Emerging data from animal studies also support the effect of chemotherapy on cognitive function.
- Most chemotherapy agents administered systemically do not cross the blood–brain barrier in significant doses; however, the amount that enters the brain can be modified by genetic variability in blood–brain barrier transporters. In addition, recent data from animal studies suggest that very small doses of common chemotherapy agents can cause cell death and reduced cell division in brain structures crucial for cognition, even at doses that do not effectively kill tumour cells.
- Chemotherapy might cause cognitive changes through DNA damage caused directly by the cytotoxic agents or through increases in oxidative stress. Many chemotherapeutic agents also cause the shortening of telomeres, thereby accelerating cell ageing. Genetic variability in DNA-repair genes might influence the extent of, and recovery from, chemotherapy-associated DNA damage.
- Chemotherapy-induced cognitive changes might also be related to the neurotoxic effects of cytokine deregulation. Cytokine deregulation and inflammation can also lead to increased oxidative stress, which could establish a cycle of increased DNA damage that triggers additional cytokine release.
- Variability in genes that regulate neural repair and/or plasticity, such as apolipoprotein E (*APOE*) and brain-derived neurotrophic factor (*BDNF*), and neurotransmission, such as catechol-O-methyltransferase (*COMT*), might increase the vulnerability of an individual to chemotherapy-induced cognitive changes.
- Changes in levels of oestrogen and testosterone are associated with cognitive decline, and can be influenced by chemotherapy (for example, chemotherapy-induced menopause) or hormonal treatments, such as tamoxifen or aromatase inhibitors for breast cancer or androgen ablation for prostate cancer.
- The effects of chemotherapy-associated cardiovascular toxicity and alterations in neuroendocrine function on cognitive function require investigation.

Box 1**Cognitive functions and brain regions relevant to chemotherapy-induced cognitive changes****Memory**

Working memory: The ability to temporarily store and manipulate information (bilateral prefrontal and parietal regions).

Episodic memory: The ability to learn and retain new context-dependent information (medial temporal lobes and prefrontal cortex).

Remote memory: The ability to retrieve memories from the past (frontal and temporal lobes).

Modality-specific memory

Verbal memory: Memory for words and narrative material presented verbally or in writing (left hemisphere).

Visual memory: Memory for objects, faces, figures or locations presented visually (right hemisphere).

Executive function

The control system that manages other cognitive processes, including planning, rule acquisition, initiating appropriate action, inhibiting competing responses and selecting relevant information (bilateral dorsal lateral prefrontal cortex).

Processing speed

The speed and efficiency with which information is used in completing a task (distributed frontal subcortical network).

Visual, spatial and constructional ability

The ability to visualize and manipulate two and three-dimensional objects (right parietal and bilateral frontal regions).

Attention and concentration

Attention is the ability to focus on certain information or stimuli at the same time as ignoring other information or stimuli. Concentration refers to the ability to maintain attention without being distracted by competing stimuli (distributed frontal subcortical network).

Reaction time

Simple reaction time is the time it takes for a person to react to a stimulus (for example, pressing a button when a light goes on), whereas complex or choice reaction time is the period of latency before a decision is made regarding a stimulus (for example, deciding if a sequence of letters represents a word) (distributed frontal subcortical network).

Motor speed and dexterity

The speed and accuracy with which a person can perform simple motor tasks and manipulate objects (for example, placing pegs in holes on a board) (bilateral frontal and pyramidal and extrapyramidal motor systems).

Box 2**Recommendations from the Banff conference¹³**

- Conduct longitudinal studies that include pre- and post-treatment neuropsychological assessments that enable the evaluation of acute and longterm cognitive changes, and that include appropriate comparison groups such as cancer patients not treated with chemotherapy and/or matched healthy controls.
- Design studies that examine factors that increase the risk of cognitive changes (for example, genetic factors) and define the mechanism(s) that underlies chemotherapy-induced cognitive changes.
- Use advanced imaging techniques such as magnetic resonance imaging (MRI) and positron emission tomography (PET) to define structural and functional changes in the brain associated with chemotherapy.
- Develop animal models that will aid in identifying the mechanism(s) of chemotherapy-induced cognitive changes.
- Identify the neuropsychological tests that are the most sensitive to the cognitive side effects of chemotherapy and develop new tests that are more closely related to cognitive functioning in the real world.
- Develop and evaluate medication and cognitive rehabilitation interventions.

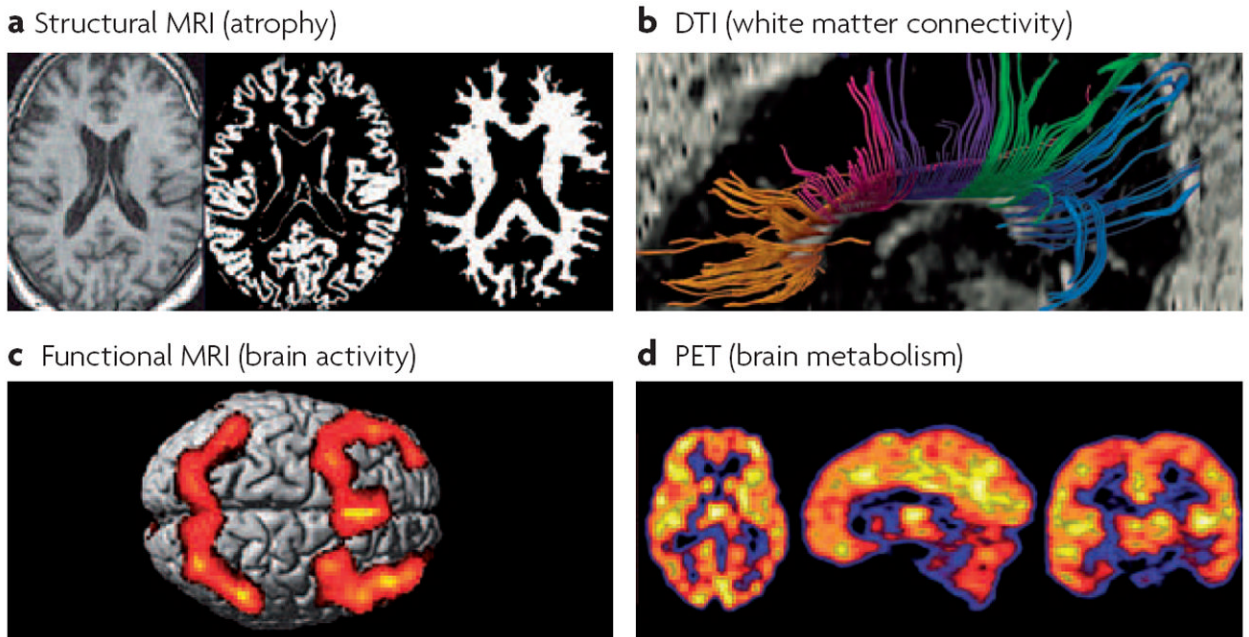


Figure 1. Neuroimaging methods relevant to the assessment of cognitive changes

a | Structural magnetic resonance imaging (MRI) provides a high resolution picture of normal neuroanatomic details and atrophy (T1-weighted scans), and visible pathology such as microvascular and inflammatory lesions (T2-weighted scans; fluid-attenuated inversion recovery (FLAIR) scans). Semi-automated methods can be used to segment or classify the structural images into the main tissue compartments, including grey and white matter, cerebrospinal fluid and hyperintense lesions, which reflect microvascular changes or areas of demyelination. Software is available to quantify the volume and other characteristics of each tissue type. **b** | Diffusion tensor imaging (DTI) is a recently developed technique that can be used to assess pathological changes in grey matter (increased mean diffusivity) and the loss of integrity of white matter fibre bundles (decreased fractional anisotropy). Tractography software enables the identification of directional fibre bundles such as subregions of the corpus callosum (shown). **c** | Functional MRI (fMRI) uses blood-oxygen-level dependent (BOLD) contrast or perfusion measurements to assess the functional activation of cortical and subcortical regions during the performance of cognitive or sensorimotor tasks in the scanner. Bilateral frontal and parietal activation can be seen, representing the mean activation observed in a group of healthy individuals performing a working memory task. **d** | Positron emission tomography (PET) using the fluorodeoxyglucose (FDG) radiotracer provides a measure of neuronal metabolism. Other applications of molecular imaging methods such as PET provide data on cerebral blood flow or specific neurotransmitter–receptor systems. Most of these methods have not yet been examined in systematic, prospective studies of chemotherapy-induced or cancer-associated cognitive changes, but these approaches hold promise for identifying the neural bases of such changes.

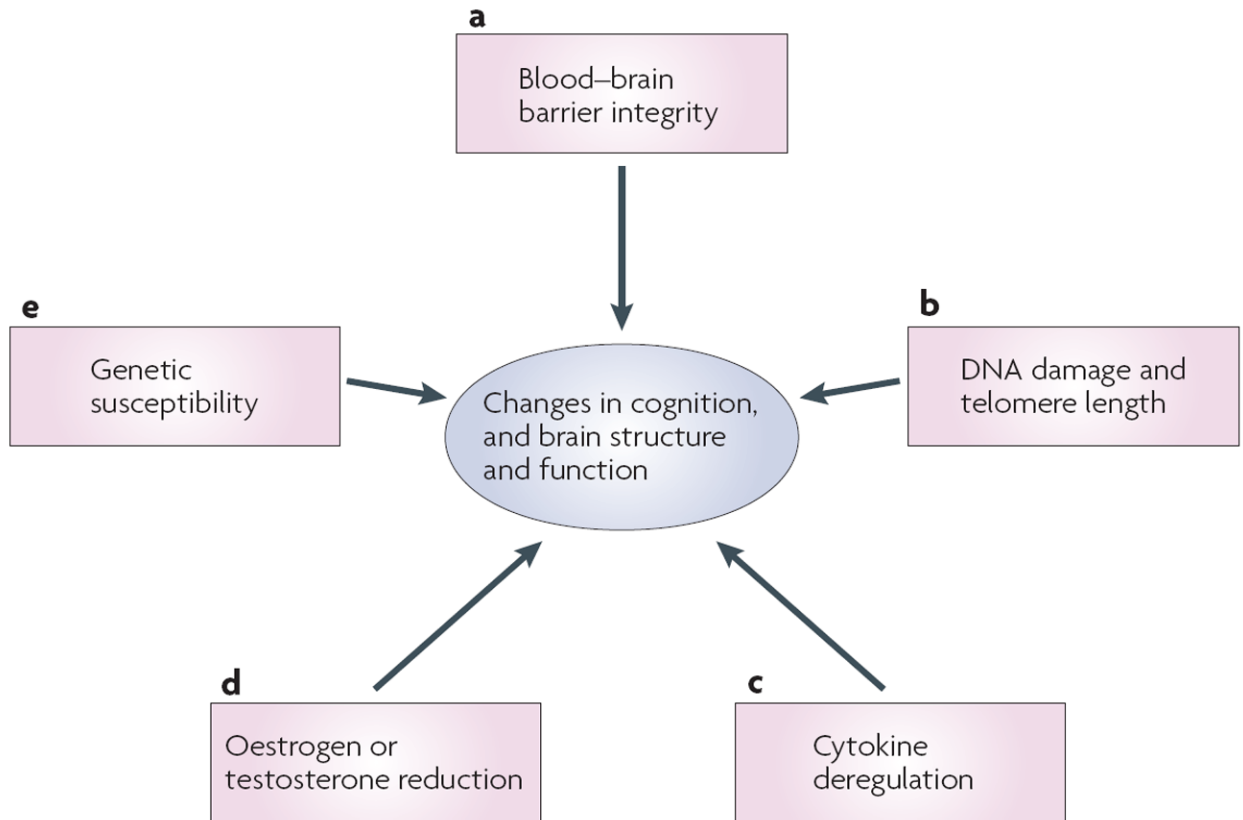


Figure 2. Candidate mechanisms

Several candidate mechanisms for chemotherapy-associated changes in cognitive function and brain structure and function are proposed. **a** | Although common chemotherapeutic agents do not readily cross the blood–brain barrier, recent data from animal studies suggest that even small doses of chemotherapy can cause cell death and reduce cell division in structures relevant for cognition. **b** | Chemotherapy has been associated with DNA damage and telomere shortening, both of which have been implicated in neural degeneration and the development of neurodegenerative disorders with cognitive components (for example, Alzheimers disease and mild cognitive impairment). **c** | Chemotherapy-induced cognitive changes might be associated with neurotoxic effects of inflammation and cytokine deregulation. **d** | Oestrogen and testosterone levels can be reduced secondary to chemotherapy and as a result of hormonal treatments for cancer. Reduction in hormonal levels has been associated with cognitive decline. **e** | Genetic variability in blood–brain barrier transporters, DNA-repair mechanisms, rate of telomere shortening, cytokine regulation, neuronal repair and plasticity, and neurotransmission could all increase vulnerability to cognitive changes associated with chemotherapy.

Table 1

Candidate mechanisms for chemotherapy-induced cognitive changes

Mechanism	Prediction	Findings relevant to cognition in cancer	Candidate genes *	Refs
Blood–brain barrier	Patients with one or more alleles associated with less efficient efflux pumps will be more likely to have cognitive problems before and after treatment		<ul style="list-style-type: none"> Multidrug resistance 1 (<i>MDR1</i>, which encodes P-glycoprotein (P-gp)) Organic anion transporting polypeptide (<i>Oatp</i>) 	32-34
DNA damage	<ul style="list-style-type: none"> Cognitive changes will be associated with the degree of DNA damage Patients with higher levels of DNA damage before treatment will be more likely to meet criteria for cognitive impairment Patients with one or more alleles associated with lower efficiency DNA-repair mechanisms will be more likely to have cognitive problems before and after treatment 		<ul style="list-style-type: none"> 8-oxoguanine DNA glycosylase (<i>OGG1</i>) Apurinic/aprimidinic endonuclease 1 (<i>APEX1</i>) X-ray repair cross complementing protein 1 (<i>XRCC1</i>) 	38,55
Telomere length	Lower telomere length and telomerase activity will be associated with poor cognitive performance		<i>DDX11</i> (a DNA helicase)	57
Cytokine regulation	<ul style="list-style-type: none"> Higher levels of proinflammatory cytokines (for example, interleukin 1 (IL1), IL2, IL6, IL10 and tumour necrosis factor-α (TNFα)) will be associated with greater likelihood of cognitive problems, both before and after treatment Patients with one or more alleles 	<ul style="list-style-type: none"> Cognitive side effects of interferon and interleukin therapy Higher levels of IL6 are associated with reduced executive function 	<ul style="list-style-type: none"> IL1 IL6 TNFα 	23,66,70,71,79

Mechanism	Prediction	Findings relevant to cognition in cancer	Candidate genes*	Refs
	associated with cytokine deregulation will be more likely to have cognitive problems before and after chemotherapy			
Neural repair	<ul style="list-style-type: none"> • Apolipoprotein E (<i>APOE</i>) E4 allele carriers will have more cognitive problems after chemotherapy • Brain-derived neurotrophic factor (<i>BDNF</i>) Val66Met carriers will have more cognitive problems after chemotherapy 	The <i>APOE</i> E4 allele has been associated with poorer cognitive performance in cancer survivors	<ul style="list-style-type: none"> • <i>APOE</i> E4 allele • <i>BDNF</i> Val66Met 	80,86,89
Neurotransmitters	Patients with one or more alleles associated with decreased neurotransmitter activity will be more likely to have cognitive problems before and after treatment	Preliminary data suggest that the valine allele is associated with poorer cognitive performance in cancer survivors	Catechol-O-methyltransferase (<i>COMT</i>)	89,93,96

*Examples of candidate genes are provided. See the references for a more extensive list.