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Review

Neurobiological basis of chemotherapy-induced cognitive impairment: A review of rodent research

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ABSTRACT

For some cancer survivors chemotherapy treatment is associated with lasting cognitive impairment, long after treatment cessation. Several candidate mechanisms have been suggested, yet clinical research has been unable to clearly tease apart these hypotheses. Rodent research has allowed a systematic study of these underlying mechanisms in the absence of potential patient confounds. Herein, this research is reviewed with emphasis on the role of the blood–brain barrier, neurogenesis, oxidative stress, white matter, immune system/(neuro) inflammation, HPA axis, blood flow, and cancer in chemotherapy-induced cognitive impairment. Furthermore, potential pharmacotherapy and behavioral intervention strategies are reviewed. This paper ends with methodological considerations in study of chemotherapy and cognition.

Contents

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1. Introduction

Chemotherapy is a frequently used adjuvant treatment strategy for cancer, often given in combination with surgery, radiation, and/or hormonal treatment. Besides affecting cancer cells, cytostatic agents also affect healthy cells in the body leading to a number of side effects that generally disappear over time after treatment cessation (Schagen et al., 2002). However, clinical evidence suggests for some cancer survivors chemotherapy treatment is associated with lasting cognitive impairment. This cognitive impairment ranges from very subtle to more severe, with memory, processing speed, and more complex aspects of attention being most affected. The decline in cognitive functioning is often noticed around two years after treatment although variation in this first awareness occurs (Correa and Ahles, 2008).

Despite the large increase in the number of clinical studies, cognitive decline is difficult to investigate in patients, partly due to methodological issues, such as relatively small samples sizes, differences in age of the patients, nature and location of the tumor(s), additional anti-cancer treatments (*e.g.* hormonal), and intensity of the adjuvant treatment. Further, not all cancer survivors suffer from cognitive decline due to their cancer treatment, with point estimates ranging between 17% and 34%. This suggests individual patient characteristics, related to IQ or level of education, may interact with chemotherapy-treatment effects (Ahles et al., 2002, 2008). Across studies, there is also large variation in the neuropsychological tests employed, as well as the criteria used to determine cognitive impairment. Furthermore, not every study uses appropriate control groups, study designs, or statistical measures (Schagen and Vardy, 2007), making definite conclusions difficult. This urges a need for animal studies objectively exploring cognitive impairment after peripheral cytostatic treatment and the associated underlying mechanism(s).

An animal model approach allows a systematic study of the underlying physiological mechanisms involved in cognitive decline due to chemotherapeutic treatment in the absence of cancer and other potential patient confounds. Increasing our knowledge of the potential mechanisms involved in cognitive impairment is essential for the improvement of chemotherapeutic strategies. However, the number of animal studies is still surprisingly scarce and the results from some studies are inconclusive. Most research has shown treatment with various cytostatic agents impairs performance in one or more tests of cognition in rodents free of cancer (Boyette-Davis and Fuchs, 2009; Elbeltagy et al., 2009; Fardell et al., 2009; Foley et al., 2008; Gandal et al., 2008; Konat et al., 2008; Li et al., 2008, 2010; Liedke et al., 2009; Macleod et al., 2007; Madhyastha et al., 2002; Mondie et al., 2010; Mustafa et al., 2008; Phillips et al., 1986; Reiriz et al., 2006; Seigers et al., 2008, 2009; Sieklucka-Dziuba et al., 1998; Stock et al., 1995; Winocur et al., 2006a; Yang et al., 2010; Yanovski et al., 1989) (see Table 1), but this appears to be highly dependent on treatment protocol and the learning task. One study even reports positive learning effects of cytostatic treatment (Lee et al., 2006).

This review will give an overview of animal studies exploring the effect of cytostatics on cognition and neurobiology. While many cytostatics have been used for cancer treatment, only a small number of chemotherapeutic agents have been studied for their effects on cognition and the brain. Therefore, we will first give a brief overview of the different classes of cytostatics, their working mechanisms, and demonstrated effects on cognition. We will further review potential mechanisms that may underlie these cognitive impairments as seen in patients and animals after adjuvant chemotherapy and potential intervention strategies. This review ends with an overview of differences between clinical and animal studies as well as discrepancies between the animal studies.

2. Cognitive and neurobiological effects of cytostatic agents in animal studies

2.1. Alkylating agents

Alkylating agents alkylate electron-rich atoms to form covalent bonds and the most important antitumor activities are reactions with DNA bases. Monofunctional alkylating agents react with only one DNA strand, whereas bifunctional alkylating agents react with an atom on each DNA strand to produce cross-links. This reaction of the alkylating agents with the DNA will prevent the cell from replicating (DeVita et al., 2005). Of the alkylating agents, the effect of cyclophosphamide on cognitive performance has most frequently been described in the literature. Furthermore, some work has shown thioTEPA treatment induces inhibition in hippocampal cell proliferation and impairments in both object placement recognition and novel object recognition (NOR, Table 1) (Mignone and Weber, 2006; Mondie et al., 2010).

Cyclophosphamide-associated cognitive impairment has been explored in a number of animal studies (Table 1). In these studies, mice or rats are treated with cyclophosphamide alone (Lee et al., 2006; Reiriz et al., 2006; Yang et al., 2010), or in combination with doxorubicin (Konat et al., 2008; Macleod et al., 2007). Briefly, cyclophosphamide does not affect anxiety behavior (Konat et al., 2008; Reiriz et al., 2006) or cued fear (Macleod et al., 2007). However, in rats it does impair passive avoidance task learning (Konat et al., 2008) and contextual fear conditioning (Macleod et al., 2007). In mice cyclophosphamide impairs memory retention as measured by a step-down inhibitory avoidance conditioning task (Reiriz et

Table 1
Summary of animal research investigating the effect of chemotherapeutic treatment on cognition.

First author	Cytostatic(s)	Animals[a]	Cognitive assessment	Cognitive outcome	Comments
Alkylating agents					
Konat	Cyclophosphamide + doxorubicin	Female Sprague-Dawley rats (10 months old)	Passive avoidance + open field	Impaired passive avoidance learning	No effect on anxiety behavior
Lee	Cyclophosphamide or 5-fluorouracil	Female Fischer-344 rats (young seven months and aged 18 months)	MWM + Stone 14-unit T-maze	No impairment	Transient improvement in MWM and Stone 14-unit T-maze seven to nine weeks post treatment
Macleod	Cyclophosphamide + doxorubicin	Female ovariectomized Sprague-Dawley rats (eight weeks old)	Cued and contextual fear conditioning	Impaired contextual fear memory	No effect on cued-fear or acquisition of fear response
Mondie	thioTEPA	Male C57BL/6J mice (five weeks old)	NOR + OLR	Impairment in NOR and OLR	No effect on depressive behavior
Reiriz	Cyclophosphamide	Male CF1 mice (70–90 days old)	Step-down inhibitory avoidance	Impaired inhibitory avoidance	No effect on anxiety behavior
Yang	Cyclophosphamide	Male ICR mice (8–10 weeks old)	Passive avoidance + NOR	Impaired passive avoidance learning Impaired NOR	
Cisplatin and analogues					
Fardell	Oxaliplatin + 5-fluorouracil	Male Sprague-Dawley rats (nine weeks old)	MWM + NOR + fear conditioning	Impairment in MWM, NOR and contextual fear memory	No impairment in cued-fear memory
Antimetabolites					
Elbeltagy	5-Fluorouracil	Male Lister-hooded rats (150–170 g)	Fear conditioning + OLR	Impairment in recall of fear conditioning memory and OLR	
Foley	Methotrexate + 5-fluorouracil	Male Swiss-Webster mice (20–35 g)	Operant conditioning	Combined MTX + 5-FU impair acquisition and retrieval of an operant response	No impairment due to MTX 5-FU failed to impair operant conditioning except at high doses
Gandal	Methotrexate + 5-fluorouracil	Male C57BL/6Hsd mice (seven to eight weeks of age)	Contextual fear conditioning + NOR	No impairment in NOR	Increased freezing during test of fear conditioning
Li	Cytosine arabinoside	Male Sprague-Dawley rats (200–250 g)	MWM	Impairment in remote recall of MWM	No impairment in MWM learning or recent recall
Li	Methotrexate	Male Long-Evans rats (12 weeks old) and young female and male Long-Evans (two weeks old)	NOR + OLR	Impaired OLR	No impairment in NOR + open field activity
Madhyastha	Methotrexate	Male Wistar rats (four months old)	Conditioned avoidance test	Impaired conditioned avoidance learning and memory	No effect on anxiety behavior
Mustafa	5-Fluorouracil	Male Lister-hooded rats (200–250 g)	OLR	Subtle impairment in OLR	
Seigers	Methotrexate	Male Wistar rats (three months old)	MWM + NOR + contextual fear conditioning	Impairment in MWM and NOR after MTX When trained prior to MTX treatment, impairment in MWM and fear conditioning memory	
Sieklucka-Dziuba	Methotrexate	Male and female Albino Swiss mice (20–25 g)	Passive avoidance task	Impaired passive avoidance learning	
Stock	Methotrexate	Male and female Sprague-Dawley rats. MTX treatment at 17 days old. Behavioral testing at 80 days old	Appetitive Pavlovian discrimination + conditioned taste aversion	No impairment in either appetitive or aversive conditioning	
Yanovski	Methotrexate	Male and female Lewis-inbred rats. MTX treatment at 16–17 days age. Behavioral testing at 12–14 weeks old	Conditioned emotional response + conditioned taste aversion	Impaired conditional emotional response learning Impairment in conditioned taste aversion acquisition	
Winocur	Methotrexate + 5-fluorouracil	Female BALB/C mice (approximately two months old)	Spatial MWM, cued memory, discrimination learning, NMTS, dNMTS	Impairment in spatial MWM, NMTS and dNMTS	No impairment in cued memory or discrimination learning
Topoisomerase interactive agents					
Liedke	Doxorubicin	Male Wistar rats (180–350 g)	Inhibitory avoidance conditioning	Impairment of memory retention	
Sieklucka-Dziuba	Doxorubicin	Male and female Albino Swiss mice (20–25 g)	Passive avoidance task	No impairment	
Antimicrotubule agents					
Boyette-Davis	Paclitaxel	Male Long-Evans rats	Five choice serial reaction time task	No impairment	

Abbreviations – MTX: methotrexate; 5-FU: 5-fluorouracil; NOR: novel object recognition; MWM: Morris water maze; OLR: object location recognition; NMTS: non-matching to sample; and dNMTS: delayed non-matching to sample.

[a] Age and weight of animals where provided.

al., 2006), passive avoidance learning (Yang et al., 2010) and NOR (Yang et al., 2010). Surprisingly, Lee et al. found that female rats show improved cognition as measured in a Morris water maze (MWM) and a Stone 14-unit T-maze seven weeks after treatment with cyclophosphamide or 5-Fluorouracil (5-FU). However, this relative improvement was gone seven months after treatment. The authors suggest that this unexpected beneficial effect of cyclophosphamide and 5-FU on learning behavior can be explained by the estrogen cycle. Cytostatic treatment causes premature menopause, and whereas lowered estrogen levels have a negative effect on cognition in humans, it has a positive effect on learning behavior in rats (Lee et al., 2006).

There has only been one animal study to address the causal relationship between cyclophosphamide treatment and behavioral changes (Konat et al., 2008). Konat et al. (2008) found treatment with N-acetyl cysteine, an antioxidant, ameliorated cognitive impairment due to cyclophosphamide and doxorubicin co-treatment, suggesting oxidative stress may in part cause the cognitive impairments associated with chemotherapeutic treatment. Several studies have shown cyclophosphamide treatment induces oxidative stress (Bhatia et al., 2006; Manda and Bhatia, 2003; Oboh and Ogunruku, 2010), decreases HPA axis activity (Navarra and Preziosi, 1997), decreases neurogenesis (Dietrich et al., 2006; Mignone and Weber, 2006; Yang et al., 2010), and induces apoptosis (Maslinska, 1986; Rzeski et al., 2004; Wick et al., 2004).

2.2. Cisplatin and its analogues

Cisplatin and its analogues form a variety of monofunctional and bifunctional adducts which may lead to the formation of intrastrand or interstrand DNA cross-links. Furthermore, this adduct formation interrupts certain cellular processes, such as separation, replication, and transcription of the DNA strands (DeVita et al., 2005). While the platinum drugs have not yet been extensively studied for their effects on cognition in animal models; unpublished work has shown when administered to healthy rats, oxaliplatin impairs novel object recognition, spatial reference memory, and contextual fear condition. Furthermore, when oxaliplatin is administered in combination with 5-FU, performance in these same tasks is worse (Table 1) (Fardell et al., in preparation). A number of animal studies have shown these drugs affect several neurobiological processes, including oxidative stress (Husain et al., 2001, 2003) and neurotoxic effects/apoptosis (Avella et al., 2006; Dietrich et al., 2006; Rzeski et al., 2004; Wick et al., 2004).

2.3. Antimetabolites

Antimetabolites are metabolic substances which disturb the biosynthesis or the function of nucleic acids and impair the formation of new DNA or RNA, which leads to an arrest in the cell cycle (DeVita et al., 2005). The most frequently studied antimetabolites in relation to cognitive behavior are methotrexate (MTX) alone (Foley et al., 2008; Li et al., 2010; Madhyastha et al., 2002; Mullenix et al., 1990; Phillips et al., 1986; Seigers et al., 2008, 2009; Sieklucka-Dziuba et al., 1998; Stock et al., 1995; Yanovski et al., 1989) and 5-FU alone (Foley et al., 2008; Mustafa et al., 2008) as well as their combination (Foley et al., 2008; Gandal et al., 2008; Winocur et al., 2006a) (Table 1). However, one paper has shown cytosine arabinoside appears to affect remote recall of MWM spatial location but not acquisition or recent recall in the MWM in rats (Li et al., 2008) (Table 1).

MTX is an inhibitor of dihydrofolate reductase, an important enzyme in folate metabolism. This enzyme maintains the intracellular folate pool which serves as a carrier for the synthesis of thymidylate, purine nucleotides, and certain amino acids (DeVita et al., 2005). 5-FU is a pyrimidine analogue that acts primarily by inhibiting thymidylate synthase resulting in blocked synthesis of thymidine which is important for DNA replication (DeVita et al., 2005). In a number of studies, MTX has been shown to decrease explorative behavior in rats in a variety of contexts (Madhyastha et al., 2002; Mullenix et al., 1990; Phillips et al., 1986). In contrast, Gandal et al. (2008) found mice treated with MTX and 5-FU show more exploration behavior in a NOR task, yet display increased anxiety behavior in fear conditioning. Rats treated with MTX show a variety of cognitive impairments; spatial MWM learning (Seigers et al., 2008), NOR (Seigers et al., 2008), object placement recognition (Li et al., 2010), conditioned emotional response (Yanovski et al., 1989), and operant response learning (Foley et al., 2008) have been found to be impaired post-MTX treatment. Similarly, 5-FU treatment alone impairs object placement recognition (Mustafa et al., 2008) and retrieval of a learned operant response (Foley et al., 2008). Further, MTX also impairs the ability to consolidate a previously learned memory when given directly after MWM training or contextual fear conditioning (Seigers et al., 2009). No cognitive impairment was seen in appetitive Pavlovian tasks (Stock et al., 1995), and impairment in a conditioned taste aversion task observed at two weeks post-MTX (Yanovski et al., 1989) was unaffected at nine weeks after treatment (Stock et al., 1995). Mice treated with MTX show impaired learning in a passive avoidance task (Sieklucka-Dziuba et al., 1998), and after treatment with MTX and 5-FU in spatial MWM, non-matching to sample learning, and delayed non-matching to sample learning (Winocur et al., 2006a). MTX has been found to have a number of neurobiological effects; being reduced neurogenesis (Seigers et al., 2008, 2009), reduced blood flow/glucose metabolism (Mizusawa et al., 1988; Phillips et al., 1989; Seigers et al., 2010b), increased neurotoxic effects/apoptosis (Billingsley et al., 1982; Gregorios et al., 1989; Igarashi et al., 1989; Madhyastha et al., 2002; Morris et al., 1995; Phillips et al., 1989; Silverstein and Johnston, 1986), oxidative stress (Rajamani et al., 2006; Uzar et al., 2006), and white matter damage (Gilbert et al., 1989; Gregorios et al., 1989; Seigers et al., 2009).

2.4. Topoisomerase interactive agents

DNA topoisomerases change the topology of DNA by forming single- (type I topoisomerases) or double-strand (type II topoisomerases) breaks in the double helix. This relaxes the torsional stress that occurs when the DNA double helix unwinds when DNA and RNA polymerases access the DNA. When topoisomerases are absent, the torsionally strained supercoiled DNA accumulates which will interfere with vital cellular functions. Topoisomerase interactive agents cause accumulation of DNA cleavage complexes of protein-linked DNA strand breaks. These lesions in the ongoing DNA replication or RNA transcription lead to cytotoxic DNA damage, causing cell-arrest, apoptosis, or cell necrosis (DeVita et al., 2005).

Of the different topoisomerase interactive agents, doxorubicin is the most studied agent for its effect on cognition given alone (Liedke et al., 2009; Sieklucka-Dziuba et al., 1998), or in combination with cyclophosphamide (Konat et al., 2008; Macleod et al., 2007) (Table 1). Together with cyclophosphamide, doxorubicin failed to affect anxiety (Konat et al., 2008), while doxorubicin alone did impair inhibitory avoidance conditioning in rats but not passive avoidance in mice (Sieklucka-Dziuba et al., 1998). In rats, combined doxorubicin and cyclophosphamide has been shown to impair context- but not cue-specific memory of fear (Macleod et al., 2007) and impair passive avoidance learning (Konat et al., 2008). Although doxorubicin is extensively distributed to tissues, the brain penetration of doxorubicin is low (Bigotte and Olsson, 1984). In part this is due to the fact that doxorubicin is a good substrate for P-glycoprotein, one of the most important drug transporters responsible for transporting drugs, such as doxorubicin, out of the

brain (see Section 3.1). However, in P-glycoprotein deficient mice the brain levels were only moderately (3-fold) higher than in wild-type controls and still 20–100-fold lower than in tissues like liver and kidney (van Asperen et al., 1999). This suggests that observed impairments in cognition may not be due to the direct effects of doxorubicin on brain regions protected by the blood–brain barrier that are associated with learning and memory. Furthermore, peripherally administered doxorubicin is associated with oxidative stress (Joshi et al., 2005; Montilla et al., 1997; Öz and Ilhan, 2006), and neurotoxicity/apoptosis in brain regions without a blood–brain barrier (Bigotte and Olsson, 1984).

2.5. Antimicrotubule agents

Microtubuli form the mitotic spindle that is necessary for the separation of replicated DNA; disruption of the dynamics of microtubuli by antimicrotubule agents interferes with cell division and proliferation. Furthermore, antimicrotubule agents may disrupt many of the nonmitotic functions of microtubules, such as chemotaxis; membrane and intracellular scaffolding; transport, secretion, and/or anchorage of organelles and receptors; adhesion; locomotion; and mitogenic signaling (DeVita et al., 2005).

Paclitaxel is an antimicrotubule agent associated with cognitive impairment in patients (Hurria et al., 2006; Tchen et al., 2003). However, similar to doxorubicin, paclitaxel does not cross the blood–brain barrier readily (Schiff et al., 2008). Paclitaxel is also a very good substrate for P-glycoprotein; knockout mice deficient in P-glycoprotein show brain exposure to paclitaxel 10-fold higher than wild-type controls (Kemper et al., 2003). The only animal study conducted so far found that rats treated with paclitaxel during the training phase of a five choice serial reaction time task displayed no cognitive impairment (Boyette-Davis and Fuchs, 2009) (Table 1). However, the authors suggest that the treatment with a single cytostatic given during the training phase does not accurately model the clinical setting where multiple cytostatics are given. Further, the effects of paclitaxel on cognition were explored only acutely after administration, yet cognitive deficits may only become apparent after longer delay periods (Boyette-Davis and Fuchs, 2009). The HPA axis (Navarra and Preziosi, 1997) and the immune system (Cata et al., 2008) appear to be important for the neurotoxicity/apoptosis effects (Rzeski et al., 2004; Wick et al., 2004) of the antimicrotubuli agents.

3. Neurobiological processes involved in cognitive impairment

3.1. The blood–brain barrier

The brain is effectively protected against potentially harmful compounds by the blood–brain barrier (BBB). This BBB is formed by the capillary endothelial cells of the brain, which are closely linked by tight junctions. Moreover, brain endothelial cells lack fenestrations and have low pinocytic activity, and together these characteristics build a rigid wall. On top of this, the physical architecture of the BBB is equipped with a range of efflux transporters that restrict the BBB penetration of drugs that might otherwise be able to accumulate. The best-known and most dominant drug transporter is ABCB1 (also called P-glycoprotein), with other ABC-transporters such as ABCG2 and ABCC4 also involved. Only drugs that are sufficiently lipophilic to allow passive diffusion and/or are able to (ab)use an inward directed transport system and that are also not recognized by any of the efflux transporters will penetrate the brain in appreciable amounts (de Vries et al., 2006). Nevertheless, all drugs, even those that do not fulfill these criteria may accumulate in the brain to some extent and, even at low concentrations, may negatively affect cognitive functioning. However, the behavioral and neurobiological effects of cytostatic agents may also be indirectly induced, potentially involving secondary and perhaps peripherally released, mediators.

3.2. Neurogenesis

Since cytostatics are aimed at the inhibition of the process of cell division, they will likely also affect cell proliferation in the brain if they are capable of passing the BBB. Stem cells can produce new neurons which can be integrated in specific brain regions in the process of neurogenesis. One of the most prominent regions in which neurogenesis occurs is the subgranular zone of the hippocampal dentate gyrus (Gould et al., 2000; Kempermann et al., 2004). Carmustine (Dietrich et al., 2006), cisplatin (Dietrich et al., 2006), cyclophosphamide (Yang et al., 2010), 5-FU (Han et al., 2008; Mustafa et al., 2008), MTX (Seigers et al., 2008, 2009), and thiotepa (Mignone and Weber, 2006; Mondie et al., 2010) have all been shown to decrease neurogenesis and/or hippocampal cell proliferation, and this correlates with increased cell death in the hippocampus for carmustine, cisplatin, and 5-FU treated animals (Dietrich et al., 2006; Han et al., 2008; Wick et al., 2004). The hippocampal formation is well known for its involvement in learning and memory processes (Gould et al., 2000; Kempermann et al., 2004). However, the functionality of neurogenesis in this area is highly debated; the role of the newly formed neurons in cognitive behavior is far from clear. While a number of studies report that neurogenesis plays a role in learning (Bendel et al., 2005; Bruel-Jungerman et al., 2005; Van der Borght et al., 2007; Wati et al., 2006), others report changes in hippocampal cell proliferation only have a partial, or no effect on learning and memory (Madsen et al., 2003; Raber et al., 2004; Shors et al., 2002; Snyder et al., 2005; Winocur et al., 2006b; Wojtowicz et al., 2008). Therefore it seems likely that more neurobiological processes, such as apoptosis and cell death (Courtney and Coffey, 1999; Koros and Kitraki, 2009; Rzeski et al., 2004; Wick et al., 2004) are involved in the development of cognitive impairment after chemotherapy, consistent with clinical studies showing cognitive impairment is mostly noticed in non-hippocampal dependent tasks (Ahles and Saykin, 2007).

3.3. Oxidative stress

Oxidative stress is caused by the formation of reactive oxygen species (ROS) which are mainly produced by the respiratory chain of mitochondria. The formation of ROS can lead to mutations in mitochondrial DNA; in turn leading to errors in mitochondrial DNA coded proteins, altered electron transfer, and eventually again ROS generation, in a vicious circle (Lenaz et al., 1999). Since cytostatic agents in general disturb DNA, one can expect that mitochondrial DNA is also altered by chemotherapy treatment leading to ROS formation and oxidative stress. In fact, the presence of oxidative stress after cytostatic treatment has been shown for a number of agents, including carboplatin (Geller et al., 2001; Husain et al., 2001, 2003), cyclophosphamide (Oboh and Ogunruku, 2010), cytarabine (Geller et al., 2001; Koros et al., 2007; Koros and Kitraki, 2009), doxorubicin (Joshi et al., 2005; Montilla et al., 1997; Öz and Ilhan, 2006), and MTX (Rajamani et al., 2006; Uzar et al., 2006). Interestingly, Konat et al. (2008) found cognitive impairments due to chemotherapy were absent when rats were co-treated with an antioxidant. This suggests that oxidative stress indeed plays an important role in the development of cognitive impairment after treatment with the chemotherapeutic agents used in this study (cyclophosphamide and doxorubicin) and possibly after treatment with other substances that cause oxidative stress.

3.4. White matter

5-FU has been shown to decrease myelin sheets and deregulate Olig2 expression, crucial for generating functional oligodendrocytes, in the corpus callosum of rats (Han et al., 2008). Furthermore, carmustine, cisplatin, cytarabine, and 5-FU all affect oligodendrocyte precursors in vivo (Dietrich et al., 2006). Similarly, MTX is also associated with degeneration of white matter and white matter necrosis (Gregorios et al., 1989), and reduced thickness of the lateral corpus callosum (Seigers et al., 2009). White matter and oligodendrocytes are important for neuronal impulse conduction, and damage to white matter may explain the reduced speed of information processing noticed in patients after adjuvant chemotherapy (Han et al., 2008).

3.5. Immune system/(neuro) inflammation

Cytostatic agents may also indirectly affect cognition through their action on the immune system, since activation of the immune system is associated with cognitive impairment (Banks et al., 2002). Cytostatics can reduce cell proliferation in the gastrointestinal mucosa possibly leading to a decreased barrier function and an enhanced risk of developing infections caused by micro-organisms originating from the intestines (DeVita et al., 2005). This mucositis is associated with elevated cytokine release in the periphery (de Koning et al., 2006) which can induce inflammation, cytokine release, and sickness behavior in the central nervous system (CNS) (Seruga et al., 2008; Wilson et al., 2002). Central cytokine release can activate microglia (Hanisch and Kettenmann, 2007; Seruga et al., 2008) possibly leading to neuroinflammation, which is associated with cognitive impairment (Wilson et al., 2002). Furthermore, neuroinflammation and microglia activation are also known to have a negative effect on neurogenesis (Das and Basu, 2008; Ekdahl et al., 2003). This indirect route of cytostatic compounds via peripheral cytokines that may facilitate the process of neuroinflammation has hardly been explored. Recently, MTX has been shown to activate microglia; however, this activation was not associated with neuroinflammation, as no effect was seen in the uptake of a tracer for peripheral benzodiazepine receptors or in central cytokine levels, despite the observed cognitive impairment (Seigers et al., 2010b). This suggests that cognitive impairment after MTX treatment may not be caused by neuroinflammation.

3.6. HPA axis

The HPA axis appears to play an important role in the tolerability of several cytostatics; animals that have received hypophysectomy or adrenalectomy are more susceptible to the lethal effects of busulfan, carmustine, cyclophosphamide, 5-FU, and vindesine, possibly due to the omitted corticosterone (Navarra and Preziosi, 1997). Corticosterone inhibits nuclear factor kappaB (NF-κB), a transcription factor associated with apoptosis. This inhibition can occur via binding of the corticosterone–cytoplasmic receptor complex to NF-κb, or corticosterone can up-regulate synthesis of NF-κB inhibitors (Navarra and Preziosi, 1997). This is consistent with the observation that the toxicity of MTX in rats appears to be dependent on the corticosteroid plasma levels; MTX toxicity was decreased when supplementary corticosterone was given, whereas a low level of corticosterone resulted in increased toxicity (English et al., 1987).

3.7. Blood flow

A reduction in blood flow or damage to blood vessels can result in altered neuronal functioning and impaired cognition (de Vos et al., 2004). It is known that chemotherapy reduces local cerebral blood flow (Mizusawa et al., 1988) and has a negative effect on cerebral glucose metabolism in patients (Silverman et al., 2006) as well as in rats (Phillips et al., 1989). This effect may be caused by the anti-angiogenic effect of cytostatic agents, which also induce vascular toxicity (de Vos et al., 2004). Seigers et al. have shown that MTX indeed reduces the density of blood vessels in the hippocampal area. This reduced blood vessel density may be related to the decreased central glucose metabolism, as measured with [18F]FDG PET (Seigers et al., 2010b). Neurogenesis and angiogenesis appear to be closely related; up to 37% of the BrdU positive cells are positive for endothelial markers and brain microvascular endothelium secretes brain-derived neurotrophic factor (BDNF) which promotes the survival and differentiation of neuronal precursors (Palmer et al., 2000). This suggests that the reduction in blood vessel density with the accompanying reduction in energy supply and proliferative signals may be the cause of the decreased hippocampal cell proliferation which has been seen in a number of studies (Dietrich et al., 2006; Han et al., 2008; Mignone and Weber, 2006; Mustafa et al., 2008; Seigers et al., 2008, 2009).

3.8. Cancer

Almost all animal experiments described in this overview made use of healthy animals to test the effects of several cytostatics on cognition and biological processes. However, one should not forget that in the clinic, cytostatics are prescribed as an adjuvant treatment of cancer. Furthermore, cognitive impairment can also be noticed after the diagnosis of cancer and before the onset of any systemic treatment (Hermelink et al., 2007; Wefel et al., 2004a,b). In rats, the presence of a tumor appears to decrease the number of proliferating cells in the hippocampus (Seigers et al., 2010a), suggesting that the cancer itself may contribute to the cognitive impairment observed in patients before any treatment is initiated. However, in patients, additional explanations for this early cognitive impairment can be found in diagnosis related emotional stress, or DNA damage/deficiencies in DNA repair mechanisms (Hermelink et al., 2007; Wefel et al., 2004a,b) with the latter two being linked both to the development of cancer and neurodegenerative disorders.

4. Potential intervention strategies for chemotherapy-induced cognitive impairment

4.1. Pharmacotherapies and supplements

4.1.1. Targeting oxidative stress

As aforementioned in Section 3.3, oxidative stress has been found after administration of several chemotherapeutic agents; which suggests a possible mode of intervention targeting both the production and clearance of ROS by increasing antioxidant levels. Research suggests that antioxidants help improve normal age-related cognitive decline (Willis et al., 2009). Although the human evidence is somewhat equivocal regarding vitamin supplementation, several randomized control trials have shown a positive effect of Ginkgo biloba on cognitive performance (Kanowski and Hoerr, 2003; Le Bars et al., 1997). Further, long-term consumption of foods high in antioxidants (*e.g.* grape juice, berries, and walnuts) reduces vulnerability to oxidative stress and improves verbal memory performance in mildly cognitive impaired humans (Joseph et al., 2009). Animal models of senescence and neurodegenerative disorders, including Alzheimer's disease, which are associated with oxidative imbalance also show improvements in cognition after treatment with antioxidants either through diet (*e.g.* red fruits, spinach, and apple juice) or supplementation alone (*e.g.* Ginkgo biloba extract, vitamin E, and N-acetyl cysteine) (Ancelin et al., 2007; Yuede et al., 2007).

Given this brief review it is perhaps not surprising that Konat et al. (2008) found cognitive dysfunction induced by weekly co-administration of cyclophosphamide and doxorubicin over four weeks was ameliorated by administration of an N-acetyl cysteine. This promising result suggests that targeting oxidative stress during chemotherapeutic treatment for cancer may circumvent the occurrence of any cognitive dysfunction.

4.1.2. Targeting cytokine regulation and inflammation

Research suggests that cytokines are involved in cognition in the healthy population, and that the neurophysiological processes subserving complex cognition involve IL-1, IL-6, and TNF (McAfoose and Baune, 2009). On the other hand, high levels of pro-inflammatory cytokines have been associated with cognitive problems and dementias in the general population, and Alzheimer's disease in clinical cohorts (Dik et al., 2005; Holmes et al., 2003). As such targeting cytokines has proved useful in the treatment of Alzheimer's disease in clinical studies and in improving cognition in animal models. Use of etanercept, a TNF-alpha inhibitor, has improved cognition in Alzheimer's patients (Tobinick, 2008; Tobinick and Gross, 2008). In aged animals, treatment with nonsteroidal anti-inflammatory agents has led to improvements in water-maze performance (Casolini et al., 2002).

As yet no studies have trialed the use of cytokine inhibitors or nonsteroidal anti-inflammatory agents in the treatment of chemotherapy-induced cognitive impairment. However, since cytokine balance irregularities, particularly increased levels of pro-inflammatory cytokines, have been associated with some chemotherapeutic regimes (Seruga et al., 2008), targeting cytokine production may prove beneficial for the treatment of cognitive impairment due to chemotherapy.

4.1.3. Neural repair and neurotransmitters

Several key neurotransmitters involved in cognition are implicated in the effects of chemotherapy on the central nerves system (Ahles and Saykin, 2007). For example, Madhyastha et al. (2002) found that MTX treatment decreased brain levels of norepinephrine, dopamine, serotonin, and the serotonin metabolite 5-hydroxyindoleacetic acid in rats which was associated with cognitive impairments in conditioned avoidance testing. These same neurotransmitters are also implicated in other neurodegenerative diseases and treatments targeted accordingly have proved worthwhile. For example dopamine, which is implicated in Alzheimer's disease, Parkinson's disease, and Schizophrenia, has a key role in learning and memory modulation (Savitz et al., 2006). Furthermore, administration of L-DOPA, a commonly used Parkinson's treatment, improved long-term spatial memory in healthy rats (Reinholz et al., 2009). Similar effects have been found in a transgenic mouse model of Alzheimer's disease in which administration of L-DOPA improved object recognition as well as spatial learning (Ambree et al., 2009). Interestingly, impairments in object location recognition due to 5-FU treatment were improved with co-administration of fluoxetine, a selective serotonin reuptake inhibitor (Elbeltagy et al., 2009). Further, while 5-FU treatment was associated with a reduction in proliferating cells within the dentate gyrus relative to controls, treatment with fluoxetine abolished this difference (Elbeltagy et al., 2009).

In addition, therapies targeting neural growth factors may also be a beneficial intervention strategy. Of particular interest, in healthy populations BDNF appears to play an integral role in both the acquisition and retention of long-term memory, potentially through mediation of late-phase long-term potentiation (Lu et al., 2008). Perhaps not surprisingly, irregularities with BDNF production have been associated with cognitive impairment in Schizophrenic patients and animal models of dementia (Egan et al., 2003; Yu et al., 2009). The effects of BDNF on cognition have been well demonstrated in rodent models; blocking BDNF synthesis impairs contextual fear conditioning (Liu et al., 2004), while infusion of BDNF into the hippocampus after training in the Morris water maze improves retention of a spatial location (Alonso et al., 2002). Interestingly, Mustafa et al. found that healthy rats treated with 5-FU had significantly reduced levels of BDNF in the hippocampus, although this neurological difference was not reflected by an equally significant impairment in an object location recognition test (Mustafa et al., 2008). Taken together, this evidence suggests that targeting BDNF production may potentially provide some therapeutic relief to patients reporting cognitive dysfunction due to adjuvant chemotherapy.

4.2. Behavioral interventions

4.2.1. Exercise

There is a growing body of evidence that physical activity improves cognitive function (Hillman et al., 2008). Moreover, while physical activity has a mild effect on cognition in healthy people, it seems to have a particularly beneficial effect on people suffering cognitive impairment from disease (*e.g.* Alzheimer's disease, depression) or ageing (Colcombe and Kramer, 2003). Notably these effects are also found in both transgenic animal models of Alzheimer's disease and senescent rodents (Nichol et al., 2007; Parachikova et al., 2008; van Praag et al., 2005). Importantly, physical evidence improves the domains of cognition affected by chemotherapy; namely working memory and executive processing. In addition, exercise improves cognitive function by affecting the neural systems that have been shown to be impaired by chemotherapy: cell proliferation and survival in the hippocampus (van Praag et al., 1999); oxidative stress (Radak et al., 2001); white matter integrity (Marks et al., 2007); inflammation (Ajijola et al., 2009; Petersen and Pedersen, 2005); CNS blood flow via production of vascular endothelial growth factor (Fabel et al., 2003); and a range of neurotransmitter systems (Cotman and Berchtold, 2002). In addition, preliminary findings suggest that rats given wheel access after treatment with oxaliplatin and 5-FU performed better than those with no wheel access on NOR and MWM (Fardell et al., in preparation).

4.2.2. Reminding

In animal models of cognition, lesions of the hippocampus prior to training lead to poor acquisition of spatial memory, while lesions of the hippocampus post training also lead to poor performance in probe tests of spatial memory (D'Hooge and De Deyn, 2001). However, investigations into the retrieval of 'lost' spatial memory suggest that reminding procedures can reactivate dormant memory traces (de Hoz et al., 2004). Specifically, hippocampal lesions that occur after successful training of rodents to find the hidden spatial location of a platform in the standard MWM procedure, cause failures in spatial reference memory. However, if these lesions are partial, rats that are 'reminded' of the spatial location, simply by re-exposure to the task are able to recall the original pre-lesion location of the platform (de Hoz et al., 2004; Martin et al., 2005). Interestingly, these simple 'reminding' strategies may be effective in ameliorating cognitive impairments due to administration of methotrexate. Specifically, rats that show impaired spatial memory recall four months post treatment due to treatment with MTX were able to perform at a level indistinguishable from controls after 2 re-training trials were given (Fardell et al., 2009).

These animal studies may offer an explanation for Ferguson et al.'s successful behavioral intervention (Ferguson et al., 2007). They found that Memory and Attention Adaptation Training (MAAT) resulted in improved self-report of cognitive function, quality of life, and standard neuropsychological testing results. This training involved consultation with a trained clinician and development

of cognitive compensatory skills tailored to the individual's own cognitive complaints. These compensatory skills involved verbal rehearsal, list making and external cuing types of reminding.

5. Methodological considerations in study of chemotherapy and cognition

5.1. Differences between clinical and animal studies

5.1.1. Individual vulnerability for cognitive impairment

In the clinic, only a subgroup of patients suffers from cognitive impairment. Similarly it could be expected that only a subgroup of animals treated with chemotherapy show impairments in cognition and neurobiological processes, leading to false positive or false negative results. However, most animal studies use rodent species which are fairly genetically homogeneous in which individual difference is minimal; furthermore, developmental environment is kept fairly uniform, at least within suppliers. In contrast the developmental history of humans is highly varied, as are differences in gene expression, IQ, and other disease co-morbidities, which could lead to differences in cognitive reserve and subsequent impairment (Ahles et al., 2002, 2008). From an experimental point of view, it seems most appropriate to first explore the effects of chemotherapy on cognition and neurobiological processes involved in a homogenous set of animals. When the affected processes are fully explored, they should also be studied in a less homogenous group of animals as well, to examine the basis of the individual variation as seen in patients. These studies could be conducted in a wild-type population or in animals that have been genetically manipulated.

5.1.2. Differences in treatment strategy

In the clinic, cytostatic agents are always given in a chemotherapy cocktail which is repeatedly administered for a number of days/weeks since this treatment strategy increases the efficacy of the agents by enabling multiple pathways of cancer cell division to be attacked. In contrast, in the studies described in this review, the animals were generally treated with one or two chemotherapeutic agents for a small number of times. This suggests that a single treatment with only one cytostatic could yield an underestimation of the damage caused by chemotherapeutic cocktails. However, from an experimental point of view, treating animals with multiple cytostatics or multiple injections with one cytostatic has a number of downsides. First, when more than one cytostatic is given, it is impossible to state which cytostatic agent is responsible for which effect. Second, multiple injections of/or multiple cytostatics and the timing of the administrations increase the risk of side effects such as sickness, which in itself can also have an effect on cognition (Lee et al., 2006). Third, it is stressful for an animal to receive multiple injections, and stress is also known to have a negative effect on learning and memory (Alzoubi et al., 2009; Bowman, 2005; Kasar et al., 2009; Wang et al., 2010). To fully explore the effects of a chemotherapeutic agent on neurobiological processes, the agent should preferably be given alone in a single high dose, before combination or multiple dose studies are performed.

However, not all animal model researchers have employed this approach, making comparisons across studies difficult. For example, Lee et al. (2006) administered five intraperitoneal injections of 150 mg/kg cyclophosphamide to seven-month-old female Fischer-344 rats over 18 weeks and failed to find any cognitive dysfunction as measured by water maze and stone maze performance. In fact, as already mentioned in Section 2.1, Lee et al. (2006) found transient improvements in water and stone maze performance. Yet Macleod et al. (2007) found two-month-old female ovariectomized Sprague-Dawley rats administered three tail vein injections of combined 40 mg/kg cyclophosphamide and 4 mg/kg doxorubicin displayed impairments in contextual fear recall but not cued-fear recall. Similarly, Konat et al. (2008) found impairments in passive avoidance learning due to treatment with 25 mg/kg cyclophosphamide and 2.5 mg/kg doxorubicin. Taking these results together we may conclude that cyclophosphamide is less toxic than doxorubicin. However, Lee et al. (2006) note that cyclophosphamide induced toxicities in their animals; loss of weight, change in teeth and claw growth, and poor coat quality, and Yang et al. (2010) recently found mice treated with 40 mg/kg cyclophosphamide alone induced impairments in object recognition. Further complicating interpretation is the difference in route of administration; Lee et al. (2006) employed intraperitoneal injection, while Macleod et al. (2007) used tail vein injections, however this difference is unlikely to explain the discrepant in findings; as Yang et al. (2010) used a single intraperitoneal injection. The key differences between these papers appears to be the time frame over which the cytostatic(s) were administered, and when cognitive testing was commenced after treatment. In rodents, it appears that chemotherapeutic treatment schedules given over a shorter time are more toxic than those given over longer periods of time, even when the cumulative dose is similar. However, these questions are yet to be investigated thoroughly, and certainly differences in treatment strategies have important implications for patients.

5.1.3. Age and gender differences

A large difference between clinical and animal studies is the age of the subjects. Most clinical studies are performed in middle aged people, since this age group is most at risk to develop cancer. In contrast, the majority of animal studies are performed in young, healthy animals. Yet for both humans and rodents ageing increases the incidence of cognitive impairment either due to other age-related disorders or age-related changes in brain structure and function (Raz and Rodrigue, 2006; van Praag et al., 2005). Despite this, the research papers described in this review found young, healthy animals developed cognitive impairment after treatment with chemotherapy, suggesting that the process of aging is not prerequisite for these impairments. However, the impact of older age has yet to be fully examined, and one may anticipate that while young animals, show few impairments in cognition long after treatment, older animals may have less cognitive reserve and therefore demonstrate greater long-term impairments.

In most papers described in this review, male rats or mice were used to study the effect of chemotherapy on cognition. In contrast, the overwhelming majority of clinical studies are performed in women suffering from breast cancer. This may suggest women are at a disproportionately greater risk of developing cognitive impairments post chemotherapy, yet a (small) number of studies that have explored the effects of chemotherapy on cognition in men show that men are just as vulnerable as women to developing cognitive impairment (Ahles et al., 2002, 2005, 2003). Given that both female and male humans present with cognitive impairments post chemotherapeutic treatment, it suggests use of male rodents is as appropriate as using female rodents. Furthermore, there are large physiological differences between males and females. Most notably, males have constant hormone levels, whereas females show changes according to estrogen cycle. This variation in estrogen levels is associated with changes in cognitive performance in humans (Hampson, 1990) as well as in rodents (Bimonte-Nelson et al., 2003). However, this situation is not analogous; in women decreased estrogen is associated with decrements in verbal memory and fluency (Sherwin, 2000), yet low estrogen levels in female rodents are associated with increased learning ability (Bimonte-Nelson et al., 2004; Healy et al., 1999). Further complicating the issue, chemotherapy is known to induce premature menopause (Ganz, 2005; van Dam et al., 1998) which is associated with decreased estrogen levels (Buckler, 2005). While

this may explain cognitive impairments in female cancer survivors, it may not be so relevant for male cancer survivors [though it should be noted that hormonal anti-cancer treatments are associated with cognitive impairments in both sexes (Ahles and Saykin, 2007)]. Since changes in hormone levels appear to have an effect on cognition independent of chemotherapy, use of male rodents to explore the neurobiological processes underlying cognitive impairment, rather than female animals, may be advantageous.

5.1.4. What is the role of cancer in the development of cognitive impairment?

As mentioned in Section 3.8, only one study in this review was performed in tumor-bearing rats, to study the combined effect of MTX and cancer on hippocampal cell proliferation (Seigers et al., 2010a). In this study, no interaction effect between MTX and the presence of a tumor was found, meaning that the cancer did not have an additional negative effect on hippocampal cell proliferation when combined with MTX. This suggests that using a healthy, cancer-free animal model is sufficient to explore the potential neurobiological processes involved in cognitive impairment. However, no other animal studies have investigated the combined effect of chemotherapy and the presence of a tumor on cognition. While studies in healthy animals demonstrate that cytostatics alone are associated with cognitive dysfunction and provide a starting point for investigating the underlying neurological mechanisms, more work needs to be done on the interaction between cancer and anti-cancer treatments affects on cognition.

5.2. Which cognitive tasks to use?

5.2.1. Cognitive domains assessed

The results obtained from clinical studies employing neuropsychological testing show that verbal and visual memory, processing speed, attention, and executive function are most affected by chemotherapeutic treatment (Vardy and Tannock, 2007). These results suggest a profile of frontal and subcortical damage (Ahles and Saykin, 2007; Vardy et al., 2008). However, a large number of cognitive tasks employed in the animal research are hippocampal in nature. Most cognitive tasks in the clinical setting involve word/color recollection which is impossible to perform with rodents. It may be argued, since in animals spatial memory is affected after chemotherapeutic treatment, as seen in a Morris water maze paradigm (Eijkenboom and Van Der Staay, 1999; Li et al., 2008; Seigers et al., 2008, 2009; Winocur et al., 2006a), testing spatial memory in animals may be representative for cognitive impairment as seen in patients.

Interestingly in the only (known) animal models study of attention, executive function, and information processing speed, as noted in Section 2.5, Boyette-Davis and Fuchs (2009) found treatment with paclitaxel had no affect on performance of the five choice serial reaction task. However, several experimental design factors may explain these results. Firstly, a low dose was used; animals were treated with four intraperitoneal injections of 1 mg/kg paclitaxel, though this was sufficient to induce mechanical sensitivity. Second, while it may be optimal to assess peripheral neuropathy within 24 h of treatment (Weng et al., 2005), it may not be the optimal time to assess cognition (discussed in Section 5.3 below). Finally, it is difficult to conclude that paclitaxel has no affect on cognition without assessment in other cognitive domains, such as those measured by the Morris water maze paradigm. Indeed, others have found that treatment with chemotherapeutic agents induces differential effects on cognition, similar to those found in the clinic. For example, Winocur et al. (2006a) found mice treated with MTX and 5-FU had impaired non-matching to sample rule learning, impaired delayed-non-matching to sample learning, and impaired spatial reference memory while both cued memory and discrimination learning were intact. These results show that tasks that rely on the hippocampus and frontal lobe structures are impaired after treatment with MTX and 5-FU, while tasks more reliant on caudate nucleus and related striatal structures appear to be left undamaged (Winocur et al., 2006a). This urges a need for researchers to employ a battery of cognitive tests, similar to that employed in the clinic, to explore the domains of cognitive function affected by chemotherapy.

5.2.2. Sensitivity of tests

One of the biggest problems facing clinical studies is the sensitivity of the cognitive tests employed. Not all clinical studies have found that chemotherapeutic treatment for cancer is associated with cognitive impairment, with some finding only a small degree of impairment, a transient effect, or no impairment at all (Hermelink et al., 2008). The majority of animal studies reviewed here demonstrate that treatment with various different cytostatics is associated with cognitive dysfunction (Table 1), however, a few studies have failed to find an effect of chemotherapy on cognition (Boyette-Davis and Fuchs, 2009; Gandal et al., 2008; Lee et al., 2006; Sieklucka-Dziuba et al., 1998; Stock et al., 1995). As highlighted in Section 5.1.2, it appears that differences in experimental design likely account for these discrepant findings. However, animal model researchers need also to be mindful of the sensitivity of the tests employed to assess cognitive effects of chemotherapy. For example, Gandal et al. (2008) found in C57BL/6 mice combined MTX and 5-FU treatment did not significantly affect novel object recognition two weeks after treatment completion, yet others have found combined MTX and 5-FU impairs spatial memory one week post treatment (Winocur et al., 2006a) and operant condition at 24 h post treatment (Foley et al., 2008). The results of Gandal et al. (2008) are surprising, particularly as the treatment schedule was near identical to that of Winocur et al.'s (2006a) where mice received three intraperitoneal injections of 37.5 mg/kg MTX and 75 mg/kg 5-FU over three weeks; whereas Gandal et al. (2008) administered the combined treatment for a total of four weeks instead of three. Since different cognitive tests were employed in these papers this once again highlights that animal model researchers should be more aware of the sensitivity of the tasks preformed.

5.3. Duration of cognitive impairment post-chemotherapeutic treatment

A large difference between clinical and animal studies is the time period in which cognitive impairment can be seen. In cancer survivors the cognitive impairment after adjuvant chemotherapy can be noticed up to years after treatment (Bender et al., 2006; Correa and Ahles, 2008; Wefel et al., 2008). However, in the animal studies most cognitive tests are executed shortly after treatment, with time periods ranging from minutes (Boyette-Davis and Fuchs, 2009; Foley et al., 2008; Phillips et al., 1986) to days or weeks (Eijkenboom and Van Der Staay, 1999; Gandal et al., 2008; Konat et al., 2008; Li et al., 2008; Macleod et al., 2007; Madhyastha et al., 2002; Reiriz et al., 2006; Seigers et al., 2008, 2009; Sieklucka-Dziuba et al., 1998; Winocur et al., 2006a). Though a few studies have examined rodent cognitive function up to several months post treatment there have been mixed findings; with some research suggesting that chemotherapy is associated with long-lasting cognitive impairment (Li et al., 2008; Yanovski et al., 1989), while others have failed to find lasting impairments (Lee et al., 2006; Stock et al., 1995). This suggests that chemotherapy may induce only transient changes in cognition in rodents. However, Han et al. (2008) found mice administered 5-FU displayed progressive damage to myelin tracts with time. That is, while there was cell death acutely after treatment, cell proliferation and white matter integrity was sig-

nificantly decreased up to six months post 5-FU treatment. Though the authors did not assess cognition, it is likely these changes in the CNS are associated with cognitive impairment as reduced myelin integrity is associated with impairments in processing speed and memory in humans (Bucur et al., 2008). Interestingly, Li et al. (2008) found rats treated with cytosine arabinoside displayed no impairment in learning or failure to remember the location of a hidden platform in the Morris water maze when trained and tested one week after treatment completion. However, when the same animals were tested again 30 days later, memory impairments in the treated animals became apparent and were associated with a significant reduction in dendritic length, number of branch points, and spine density of apical dendrites of pyramidal neurons in the anterior cingulate cortex but not the basal neurons of the hippocampus relative to control animals. This data fits with the suggestion that CNS damage induced by treatment with cytostatic agents may only become apparent with time. As such, attention should be paid to differences in the time course of chemotherapy-induced cognitive changes when designing experiments.

6. Concluding remarks

For some cancer survivors cognitive impairment is a long-term side effect of adjuvant chemotherapy which can have a large impact on quality of life. While many clinical studies have been performed to describe the nature and severity of cognitive impairment, these studies have been unable to adequately explore and identify possible causal mechanisms involved due to, for example, methodological and ethical constraints. Furthermore, these studies have been unable to clearly show which cytostatics are causally involved in cognitive impairment and which individuals are most at risk of developing cognitive impairment (Ahles and Saykin, 2007).

Due to the impact of cognitive impairment on the quality of life and the individual variation in the occurrence and severity of this phenomenon, there has been an increase in the number of animal studies performed during the last years. However, comparisons between these studies are difficult due to differences in species, gender, age of the animals, cytostatic used, treatment strategy, route of administration, time between treatment and testing, and behavioral tasks used in the various studies. Despite this, several possible pathways that may contribute to the cognitive impairment observed after chemotherapy have been elucidated including inhibition of neurogenesis (Dietrich et al., 2006; Han et al., 2008; Mignone and Weber, 2006; Mondie et al., 2010; Mustafa et al., 2008; Seigers et al., 2008, 2009; Yang et al., 2010), oxidative damage (Geller et al., 2001; Husain et al., 2001, 2003; Joshi et al., 2005; Konat et al., 2008; Koros et al., 2007; Koros and Kitraki, 2009; Montilla et al., 1997; Oboh and Ogunruku, 2010; Öz and Ilhan, 2006; Rajamani et al., 2006; Uzar et al., 2006), white matter damage (Dietrich et al., 2006; Gregorios et al., 1989; Han et al., 2008; Seigers et al., 2009), decreased HPA axis activity (English et al., 1987; Navarra and Preziosi, 1997), and reduced brain vascularization/blood flow (Mizusawa et al., 1988; Phillips et al., 1989; Seigers et al., 2010b). While the studies are based on a variety of cytostatic agents, this review indicates that each of these pathways may contribute to the behavioral consequences of chemotherapy. However, it is hard to conclude which brain pathways are directly affected by cytostatic agent, and which pathways are secondarily affected via changes in *e.g.* vascularization or peripheral factors. There is still a clear lack of systematic studies exploring effects of single cytostatic compounds within different classes on a range of neurobiological mechanisms paired with an appropriate cognitive-behavioral measure.

While far from complete, the research conducted thus far suggests that several cytostatics are implicated in cognitive changes post-treatment in rodents. These investigations are important as using animal models has enabled researchers to explore likely causal mechanisms and provide targeted candidates for therapeutic and remedial intervention.

References

Ahles, T.A., Saykin, A.J., 2007. Candidate mechanisms for chemotherapy-induced cognitive changes. Nat. Rev. Cancer 7, 192–201.

Ahles, T.A., Saykin, A.J., Furstenberg, C.T., Cole, B., Mott, L.A., Skalla, K., Whedon, M.B., Bivens, S., Mitchell, T., Greenberg, E.R., Silberfarb, P.M., 2002. Neuropsychologic impact of standard-dose systemic chemotherapy in long-term survivors of breast cancer and lymphoma. J. Clin. Oncol. 20, 485–493.

Ahles, T.A., Saykin, A.J., Furstenberg, C.T., Cole, B., Mott, L.A., Titus-Ernstoff, L., Skalla, K., Bakitas, M., Silberfarb, P.M., 2005. Quality of life of long-term survivors of breast cancer and lymphoma treated with standard-dose chemotherapy or local therapy. J. Clin. Oncol. 23, 4399–4405.

Ahles, T.A., Saykin, A.J., McDonald, B.C., Furstenberg, C.T., Cole, B.F., Hanscom, B.S., Mulrooney, T.J., Schwartz, G.N., Kaufman, P.A., 2008. Cognitive function in breast cancer patients prior to adjuvant treatment. Breast Cancer Res. Treat. 110, 143–152.

Ahles, T.A., Saykin, A.J., Noll, W.W., Furstenberg, C.T., Guerin, S., Cole, B., Mott, L.A., 2003. The relationship of APOE genotype to neuropsychological performance in long-term cancer survivors treated with standard dose chemotherapy. Psychooncology 12, 612–619.

Ajijola, O.A., Dong, C., Herderick, E.E., Ma, Q., Goldschmidt-Clermont, P.J., Yan, Z., 2009. Voluntary running suppresses proinflammatory cytokines and bone marrow endothelial progenitor cell levels in apolipoprotein-E-deficient mice. Antioxid. Redox. Signal. 11, 15–23.

Alonso, M., Vianna, M.R., Depino, A.M., Mello e Souza, T., Pereira, P., Szapiro, G., Viola, H., Pitossi, F., Izquierdo, I., Medina, J.H., 2002. BDNF-triggered events in the rat hippocampus are required for both short- and long-term memory formation. Hippocampus 12, 551–560.

Alzoubi, K.H., bdul-Razzak, K.K., Khabour, O.F., Al-Tuweiq, G.M., Alzubi, M.A., Alkadhi, K.A., 2009. Adverse effect of combination of chronic psychosocial stress and high fat diet on hippocampus-dependent memory in rats. Behav. Brain Res. 204, 117–123.

Ambree, O., Richter, H., Sachser, N., Lewejohann, L., Dere, E., de Souza Silva, M.A., Herring, A., Keyvani, K., Paulus, W., Schabitz, W.R., 2009. Levodopa ameliorates learning and memory deficits in a murine model of Alzheimer's disease. Neurobiol. Aging 30, 1192–1204.

Ancelin, M.L., Christen, Y., Ritchie, K., 2007. Is antioxidant therapy a viable alternative for mild cognitive impairment? Examination of the evidence. Dement. Geriatr. Cogn. Disord. 24, 1–19.

Avella, D., Pisu, M.B., Roda, E., Gravati, M., Bernocchi, G., 2006. Reorganization of the rat cerebellar cortex during postnatal development following cisplatin treatment. Exp. Neurol. 201, 131–143.

Banks, W.A., Farr, S.A., Morley, J.E., 2002. Entry of blood-borne cytokines into the central nervous system: effects on cognitive processes. Neuroimmunomodulation 10, 319–327.

Bendel, O., Bueters, T., von, E.M., Ove, O.S., Sandin, J., von, E.G., 2005. Reappearance of hippocampal CA1 neurons after ischemia is associated with recovery of learning and memory. J. Cereb. Blood Flow Metab. 25, 1586–1595.

Bender, C.M., Sereika, S.M., Berga, S.L., Vogel, V.G., Brufsky, A.M., Paraska, K.K., Ryan, C.M., 2006. Cognitive impairment associated with adjuvant therapy in breast cancer. Psychooncology 15, 422–430.

Bhatia, A.L., Manda, K., Patni, S., Sharma, A.L., 2006. Prophylactic action of linseed (*Linum usitatissimum*) oil against cyclophosphamide-induced oxidative stress in mouse brain. J. Med. Food 9, 261–264.

Bigotte, L., Olsson, Y., 1984. Cytotoxic effects of adriamycin on the central nervous system of the mouse—cytofluorescence and electron-microscopic observations after various modes of administration. Acta Neurol. Scand. Suppl. 100, 55–67.

Billingsley, M.L., Hall, N., Mandel, H.G., 1982. Trauma-induced glial proliferation: possible involvement of the immune system. Immunopharmacology 5, 95–101.

Bimonte-Nelson, H.A., Singleton, R.S., Hunter, C.L., Price, K.L., Moore, A.B., Granholm, A.C., 2003. Ovarian hormones and cognition in the aged female rat: I. Long-term, but not short-term, ovariectomy enhances spatial performance. Behav. Neurosci. 117, 1395–1406.

Bimonte-Nelson, H.A., Singleton, R.S., Williams, B.J., Granholm, A.C., 2004. Ovarian hormones and cognition in the aged female rat: II. Progesterone supplementation reverses the cognitive enhancing effects of ovariectomy. Behav. Neurosci. 118, 707–714.

Bowman, R.E., 2005. Stress-induced changes in spatial memory are sexually differentiated and vary across the lifespan. J. Neuroendocrinol. 17, 526–535.

Boyette-Davis, J.A., Fuchs, P.N., 2009. Differential effects of paclitaxel treatment on cognitive functioning and mechanical sensitivity. Neurosci. Lett. 453, 170–174.

Bruel-Jungerman, E., Laroche, S., Rampon, C., 2005. New neurons in the dentate gyrus are involved in the expression of enhanced long-term memory following environmental enrichment. Eur. J. Neurosci. 21, 513–521.

Buckler, H., 2005. The menopause transition: endocrine changes and clinical symptoms. J. Br. Menopause Soc. 11, 61–65.

Bucur, B., Madden, D.J., Spaniol, J., Provenzale, J.M., Cabeza, R., White, L.E., Huettel, S.A., 2008. Age-related slowing of memory retrieval: contributions of perceptual speed and cerebral white matter integrity. Neurobiol. Aging 29, 1070–1079.

Casolini, P., Catalani, A., Zuena, A.R., Angelucci, L., 2002. Inhibition of COX-2 reduces the age-dependent increase of hippocampal inflammatory markers, corticosterone secretion, and behavioral impairments in the rat. J. Neurosci. Res. 68, 337–343.
Cata, J.P., Weng, H.R., Dougherty, P.M., 2008. Behavioral and electrophysiological studies in rats with cisplatin-induced chemoneuropathy 1230, 91–98.
Colcombe, S., Kramer, A.F., 2003. Fitness effects on the cognitive function of older adults: a meta-analytic study. Psychol. Sci. 14, 125–130.
Correa, D.D., Ahles, T.A., 2008. Neurocognitive changes in cancer survivors. Cancer J. 14, 396–400.
Cotman, C.W., Berchtold, N.C., 2002. Exercise: a behavioral intervention to enhance brain health and plasticity. Trends Neurosci. 25, 295–301.
Courtney, M.J., Coffey, E.T., 1999. The mechanism of Ara-C-induced apoptosis of differentiating cerebellar granule neurons. Eur. J. Neurosci. 11, 1073–1084.
D'Hooge, R., De Deyn, P.P., 2001. Applications of the Morris water maze in the study of learning and memory. Brain Res. Brain Res. Rev. 36, 60–90.
Das, S., Basu, A., 2008. Inflammation: a new candidate in modulating adult neurogenesis. J. Neurosci. Res. 86, 1199–1208.
de Hoz, L., Martin, S.J., Morris, R.G., 2004. Forgetting, reminding, and remembering: the retrieval of lost spatial memory. PLoS Biol. 2, E225, 1233–1242.
de Koning, B.A., van Dieren, J.M., Lindenbergh-Kortleve, D.J., van der, S.M., Matsumoto, T., Yamaguchi, K., Einerhand, A.W., Samsom, J.N., Pieters, R., Nieuwenhuis, E.E., 2006. Contributions of mucosal immune cells to methotrexate-induced mucositis. Int. Immunol. 18, 941–949.
de Vos, F.Y., Willemse, P.H., De Vries, E.G., Gietema, J.A., 2004. Endothelial cell effects of cytotoxics: balance between desired and unwanted effects. Cancer Treat. Rev. 30, 495–513.
de Vries, N.A., Beijnen, J.H., Boogerd, W., van, T.O., 2006. Blood–brain barrier and chemotherapeutic treatment of brain tumors. Expert Rev. Neurother. 6, 1199–1209.
DeVita, V., Hellman, S., Rosenberg, S., 2005. Cancer: Principles & Practice of Oncology, 7th edition, pp. 332–422.
Dietrich, J., Han, R., Yang, Y., Mayer-Proschel, M., Noble, M., 2006. CNS progenitor cells and oligodendrocytes are targets of chemotherapeutic agents in vitro and in vivo. J. Biol. 5, 22.1–22.23.
Dik, M.G., Jonker, C., Hack, C.E., Smit, J.H., Comijs, H.C., Eikelenboom, P., 2005. Serum inflammatory proteins and cognitive decline in older persons. Neurology 64, 1371–1377.
Egan, M.F., Kojima, M., Callicott, J.H., Goldberg, T.E., Kolachana, B.S., Bertolino, A., Zaitsev, E., Gold, B., Goldman, D., Dean, M., Lu, B., Weinberger, D.R., 2003. The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. Cell 112, 257–269.
Eijkenboom, M., Van Der Staay, F.J., 1999. Spatial learning deficits in rats after injection of vincristine into the dorsal hippocampus. Neuroscience 91, 1299–1313.
Ekdahl, C.T., Claasen, J.H., Bonde, S., Kokaia, Z., Lindvall, O., 2003. Inflammation is detrimental for neurogenesis in adult brain. Proc. Natl. Acad. Sci. U.S.A. 100, 13632–13637.
Elbeltagy, M., Mustafa, S., Umka, J., Lyons, L., Salman, A., Chur-Yoe, G.T., Bhalla, N., Bennett, G., Wigmore, P.M., 2009. Fluoxetine improves the memory deficits caused by the chemotherapy agent 5-fluorouracil. Behav. Brain Res. 208, 112–117.
English, J., Aherne, G.W., Arendt, J., Marks, V., 1987. The effect of abolition of the endogenous corticosteroid rhythm on the circadian variation in methotrexate toxicity in the rat. Cancer Chemother. Pharmacol. 19, 287–290.
Fabel, K., Fabel, K., Tam, B., Kaufer, D., Baiker, A., Simmons, N., Kuo, C.J., Palmer, T.D., 2003. VEGF is necessary for exercise-induced adult hippocampal neurogenesis. Eur. J. Neurosci. 18, 2803–2812.
Fardell, J.E., Vardy, J., Johnston, I.N., 2009. Chemotherapy produces persistent subtle cognitive deficits in laboratory rodents. Asia Pac. J. Clin. Oncol. 5, A174.
Fardell, J.E., Vardy, J., Shah, D., Johnston, I.N. Cognitive impairments induced by oxaliplatin and 5-fluorouracil chemotherapy are ameliorated by physical activity, manuscript in preparation.
Ferguson, R.J., Ahles, T.A., Saykin, A.J., McDonald, B.C., Furstenberg, C.T., Cole, B.F., Mott, L.A., 2007. Cognitive-behavioral management of chemotherapy-related cognitive change. Psychooncology 16, 772–777.
Foley, J.J., Raffa, R.B., Walker, E.A., 2008. Effects of chemotherapeutic agents 5-fluorouracil and methotrexate alone and combined in a mouse model of learning and memory. Psychopharmacology (Berl.) 199, 527–538.
Gandal, M.J., Ehrlichman, R.S., Rudnick, N.D., Siegel, S.J., 2008. A novel electrophysiological model of chemotherapy-induced cognitive impairments in mice. Neuroscience 157, 95–104.
Ganz, P.A., 2005. Breast cancer, menopause, and long-term survivorship: critical issues for the 21st century. Am. J. Med. 118, 136–141.
Geller, H.M., Cheng, K.Y., Goldsmith, N.K., Romero, A.A., Zhang, A.L., Morris, E.J., Grandison, L., 2001. Oxidative stress mediates neuronal DNA damage and apoptosis in response to cytosine arabinoside. J. Neurochem. 78, 265–275.
Gilbert, M.R., Harding, B.L., Grossman, S.A., 1989. Methotrexate neurotoxicity: in vitro studies using cerebellar explants from rats. Cancer Res. 49, 2502–2505.
Gould, E., Tanapat, P., Rydel, T., Hastings, N., 2000. Regulation of hippocampal neurogenesis in adulthood. Biol. Psychiatry 48, 715–720.
Gregorios, J.B., Gregorios, A.B., Mora, J., Marcillo, A., Fojaco, R.M., Green, B., 1989. Morphologic alterations in rat brain following systemic and intraventricular methotrexate injection: light and electron microscopic studies. J. Neuropathol. Exp. Neurol. 48, 33–47.
Hampson, E., 1990. Estrogen-related variations in human spatial and articulatory-motor skills. Psychoneuroendocrinology 15, 97–111.
Han, R., Yang, Y.M., Dietrich, J., Luebke, A., Mayer-Proschel, M., Noble, M., 2008. Systemic 5-fluorouracil treatment causes a syndrome of delayed myelin destruction in the central nervous system. J. Biol. 7, 12.1–12.22.
Hanisch, U.K., Kettenmann, H., 2007. Microglia: active sensor and versatile effector cells in the normal and pathologic brain. Nat. Neurosci. 10, 1387–1394.
Healy, S.D., Braham, S.R., Braithwaite, V.A., 1999. Spatial working memory in rats: no differences between the sexes. Proc. Biol. Sci. 266, 2303–2308.
Hermelink, K., Henschel, V., Untch, M., Bauerfeind, I., Lux, M.P., Munzel, K., 2008. Short-term effects of treatment-induced hormonal changes on cognitive function in breast cancer patients: results of a multicenter, prospective, longitudinal study. Cancer 113, 2431–2439.
Hermelink, K., Untch, M., Lux, M.P., Kreienberg, R., Beck, T., Bauerfeind, I., Munzel, K., 2007. Cognitive function during neoadjuvant chemotherapy for breast cancer: results of a prospective, multicenter, longitudinal study. Cancer 109, 1905–1913.
Hillman, C.H., Erickson, K.I., Kramer, A.F., 2008. Be smart, exercise your heart: exercise effects on brain and cognition. Nat. Rev. Neurosci. 9, 58–65.
Holmes, C., El-Okl, M., Williams, A.L., Cunningham, C., Wilcockson, D., Perry, V.H., 2003. Systemic infection, interleukin 1beta, and cognitive decline in Alzheimer's disease. J. Neurol. Neurosurg. Psychiatry 74, 788–789.
Hurria, A., Hurria, A., Zuckerman, E., Panageas, K.S., Fornier, M., D'Andrea, G., Dang, C., Moasser, M., Robson, M., Seidman, A., Currie, V., VanPoznak, C., Theodoulou, M., Lachs, M.S., Hudis, C., 2006. A prospective, longitudinal study of the functional status and quality of life of older patients with breast cancer receiving adjuvant chemotherapy. J. Am. Geriatr. Soc. 54, 1119–1124.
Husain, K., Whitworth, C., Hazelrigg, S., Rybak, L., 2003. Carboplatin-induced oxidative injury in rat inferior colliculus. Int. J. Toxicol. 22, 335–342.
Husain, K., Whitworth, C., Somani, S.M., Rybak, L.P., 2001. Carboplatin-induced oxidative stress in rat cochlea. Hear. Res. 159, 14–22.
Igarashi, H., Inomata, K., Tateno, A., 1989. The effect of methotrexate on the development of synapses in the neonatal rat hippocampus. Neuropediatrics 20, 196–198.
Joseph, J.A., Shukitt-Hale, B., Willis, L.M., 2009. Grape juice, berries, and walnuts affect brain aging and behavior. J. Nutr. 139, 1813S–1817S.
Joshi, G., Sultana, R., Tangpong, J., Cole, M.P., St Clair, D.K., Vore, M., Estus, S., Butterfield, D.A., 2005. Free radical mediated oxidative stress and toxic side effects in brain induced by the anti cancer drug adriamycin: insight into chemobrain. Free Radic. Res. 39, 1147–1154.
Kanowski, S., Hoerr, R., 2003. Ginkgo biloba extract EGb 761 in dementia: intent-to-treat analyses of a 24-week, multi-center, double-blind, placebo-controlled, randomized trial. Pharmacopsychiatry 36, 297–303.
Kasar, M., Mengi, M., Yildirim, E.A., Yurdakos, E., 2009. Different effects of tianeptine pretreatment in rats exposed to acute stress and repeated severe stress. Methods Find. Exp. Clin. Pharmacol. 31, 157–163.
Kemper, E.M., van Zandbergen, A.E., Cleypool, C., Mos, H.A., Boogerd, W., Beijnen, J.H., van, T.O., 2003. Increased penetration of paclitaxel into the brain by inhibition of P-Glycoprotein. Clin. Cancer Res. 9, 2849–2855.
Kempermann, G., Wiskott, L., Gage, F.H., 2004. Functional significance of adult neurogenesis. Curr. Opin. Neurobiol. 14, 186–191.
Konat, G.W., Kraszpulski, M., James, I., Zhang, H.T., Abraham, J., 2008. Cognitive dysfunction induced by chronic administration of common cancer chemotherapeutics in rats. Metab. Brain Dis. 23, 325–333.
Koros, C., Kitraki, E., 2009. Neurofilament isoform alterations in the rat cerebellum following cytosine arabinoside administration. Toxicol. Lett. 189, 215–218.
Koros, C., Papalexi, E., Anastasopoulos, D., Kittas, C., Kitraki, E., 2007. Effects of AraC treatment on motor coordination and cerebellar cytoarchitecture in the adult rat. A possible protective role of NAC. Neurotoxicology 28, 83–92.
Le Bars, P.L., Katz, M.M., Berman, N., Itil, T.M., Freedman, A.M., Schatzberg, A.F., 1997. A placebo-controlled, double-blind, randomized trial of an extract of Ginkgo biloba for dementia. North American EGb Study Group. JAMA 278, 1327–1332.
Lee, G.D., Longo, D.L., Wang, Y., Rifkind, J.M., bdul-Raman, L., Mamczarz, J.A., Duffy, K.B., Spangler, E.L., Taub, D.D., Mattson, M.P., Ingram, D.K., 2006. Transient improvement in cognitive function and synaptic plasticity in rats following cancer chemotherapy. Clin. Cancer Res. 12, 198–205.
Lenaz, G., Bovina, C., Formiggini, G., Parenti, C.G., 1999. Mitochondria, oxidative stress, and antioxidant defences. Acta Biochim. Pol. 46, 1–21.
Li, C.Q., Liu, D., Huang, L., Wang, H., Zhang, J.Y., Luo, X.G., 2008. Cytosine arabinoside treatment impairs the remote spatial memory function and induces dendritic retraction in the anterior cingulate cortex of rats. Brain Res. Bull. 77, 237–240.
Li, Y., Vijayanathan, V., Gulinello, M.E., Cole, P.D., 2010. Systemic methotrexate induces spatial memory deficits and depletes cerebrospinal fluid folate in rats. Pharmacol. Biochem. Behav. 94, 454–463.
Liedke, P.E., Reolon, G.K., Kilpp, B., Brunetto, A.L., Roesler, R., Schwartsmann, G., 2009. Systemic administration of doxorubicin impairs aversively motivated memory in rats. Pharmacol. Biochem. Behav. 94, 239–243.
Liu, I.Y., Lyons, W.E., Mamounas, L.A., Thompson, R.F., 2004. Brain-derived neurotrophic factor plays a critical role in contextual fear conditioning. J. Neurosci. 24, 7958–7963.
Lu, Y., Christian, K., Lu, B., 2008. BDNF: a key regulator for protein synthesis-dependent LTP and long-term memory? Neurobiol. Learn. Mem. 89, 312–323.
Macleod, J.E., DeLeo, J.A., Hickey, W.F., Ahles, T.A., Saykin, A.J., Bucci, D.J., 2007. Cancer chemotherapy impairs contextual but not cue-specific fear memory. Behav. Brain Res. 181, 168–172.

Madhyastha, S., Somayaji, S.N., Rao, M.S., Nalini, K., Bairy, K.L., 2002. Hippocampal brain amines in methotrexate-induced learning and memory deficit. Can. J. Physiol. Pharmacol. 80, 1076–1084.
Madsen, T.M., Kristjansen, P.E., Bolwig, T.G., Wortwein, G., 2003. Arrested neuronal proliferation and impaired hippocampal function following fractionated brain irradiation in the adult rat. Neuroscience 119, 635–642.
Manda, K., Bhatia, A.L., 2003. Prophylactic action of melatonin against cyclophosphamide-induced oxidative stress in mice. Cell Biol. Toxicol. 19, 367–372.
Marks, B.L., Madden, D.J., Bucur, B., Provenzale, J.M., White, L.E., Cabeza, R., Huettel, S.A., 2007. Role of aerobic fitness and aging on cerebral white matter integrity. Ann. N. Y. Acad. Sci. 1097, 171–174.
Martin, S.J., de, H.L., Morris, R.G., 2005. Retrograde amnesia: neither partial nor complete hippocampal lesions in rats result in preferential sparing of remote spatial memory, even after reminding. Neuropsychologia 43, 609–624.
Maslinska, D., 1986. Effect of alkylating drugs on rat cerebellum. Folia Histochem. Cytobiol. 24, 47–52.
McAfoose, J., Baune, B.T., 2009. Evidence for a cytokine model of cognitive function. Neurosci. Biobehav. Rev. 33, 355–366.
Mignone, R.G., Weber, E.T., 2006. Potent inhibition of cell proliferation in the hippocampal dentate gyrus of mice by the chemotherapeutic drug thioTEPA. Brain Res. 1111, 26–29.
Mizusawa, S., Kondoh, Y., Murakami, M., Nakamichi, H., Sasaki, H., Komatsu, K., Takahashi, A., Kudoh, Y., Watanabe, K., Ono, Y., 1988. Effect of methotrexate on local cerebral blood flow in conscious rats. Jpn. J. Pharmacol. 48, 499–501.
Mondie, C.M., Vandergrift, K.A., Wilson, C.L., Gulinello, M.E., Weber, E.T., 2010. The chemotherapy agent, thioTEPA, yields long-term impairment of hippocampal cell proliferation and memory deficits but not depression-related behaviors in mice. Behav. Brain Res. 209, 66–72.
Montilla, P., Tunez, I., Munoz, M.C., Soria, J.V., Lopez, A., 1997. Antioxidative effect of melatonin in rat brain oxidative stress induced by Adriamycin. Rev. Esp. Fisiol. 53, 301–305.
Morris, G.M., Hopewell, J.W., Morris, A.D., 1995. A comparison of the effects of methotrexate and misonidazole on the germinal cells of the subependymal plate of the rat. Br. J. Radiol. 68, 406–412.
Mullenix, P.J., Kernan, W.J., Tassinari, M.S., Schunior, A., Waber, D.P., Howes, A., Tarbell, N.J., 1990. An animal model to study toxicity of central nervous system therapy for childhood acute lymphoblastic leukemia: effects on behavior. Cancer Res. 50, 6461–6465.
Mustafa, S., Walker, A., Bennett, G., Wigmore, P.M., 2008. 5-Fluorouracil chemotherapy affects spatial working memory and newborn neurons in the adult rat hippocampus. Eur. J. Neurosci. 28, 323–330.
Navarra, P., Preziosi, P., 1997. Disruptions of the hypothalamo-pituitary-adrenal axis increase anticancer drug lethality in the rat. Toxicol. Lett. 91, 219–227.
Nichol, K.E., Parachikova, A.I., Cotman, C.W., 2007. Three weeks of running wheel exposure improves cognitive performance in the aged Tg2576 mouse. Behav. Brain Res. 184, 124–132.
Oboh, G., Ogunruku, O.O., 2010. Cyclophosphamide-induced oxidative stress in brain: Protective effect of hot short pepper (*Capsicum frutescens* L. var. abbreviatum). Exp. Toxicol. Pathol. 63, 227–233.
Öz, E., Ilhan, M.N., 2006. Effects of melatonin in reducing the toxic effects of doxorubicin. Mol. Cell Biochem. 286, 11–15.
Palmer, T.D., Willhoite, A.R., Gage, F.H., 2000. Vascular niche for adult hippocampal neurogenesis. J. Comp. Neurol. 425, 479–494.
Parachikova, A., Nichol, K.E., Cotman, C.W., 2008. Short-term exercise in aged Tg2576 mice alters neuroinflammation and improves cognition. Neurobiol. Dis. 30, 121–129.
Petersen, A.M., Pedersen, B.K., 2005. The anti-inflammatory effect of exercise. J. Appl. Physiol. 98, 1154–1162.
Phillips, P.C., Thaler, H.T., Allen, J.C., Rottenberg, D.A., 1989. High-dose leucovorin reverses acute high-dose methotrexate neurotoxicity in the rat. Ann. Neurol. 25, 365–372.
Phillips, P.C., Thaler, H.T., Berger, C.A., Fleisher, M., Wellner, D., Allen, J.C., Rottenberg, D.A., 1986. Acute high-dose methotrexate neurotoxicity in the rat. Ann. Neurol. 20, 583–589.
Raber, J., Rola, R., LeFevour, A., Morhardt, D., Curley, J., Mizumatsu, S., VandenBerg, S.R., Fike, J.R., 2004. Radiation-induced cognitive impairments are associated with changes in indicators of hippocampal neurogenesis. Radiat. Res. 162, 39–47.
Radak, Z., Kaneko, T., Tahara, S., Nakamoto, H., Pucsok, J., Sasvari, M., Nyakas, C., Goto, S., 2001. Regular exercise improves cognitive function and decreases oxidative damage in rat brain. Neurochem. Int. 38, 17–23.
Rajamani, R., Muthuvel, A., Senthilvelan, M., Sheeladevi, R., 2006. Oxidative stress induced by methotrexate alone and in the presence of methanol in discrete regions of the rodent brain, retina and optic nerve. Toxicol. Lett. 165, 265–273.
Raz, N., Rodrigue, K.M., 2006. Differential aging of the brain: patterns, cognitive correlates and modifiers. Neurosci. Biobehav. Rev. 30, 730–748.
Reinholz, J., Skopp, O., Breitenstein, C., Winterhoff, H., Knecht, S., 2009. Better than normal: improved formation of long-term spatial memory in healthy rats treated with levodopa. Exp. Brain Res. 192, 745–749.
Reiriz, A.B., Reolon, G.K., Preissler, T., Rosado, J.O., Henriques, J.A., Roesler, R., Schwartsmann, G., 2006. Cancer chemotherapy and cognitive function in rodent models: memory impairment induced by cyclophosphamide in mice. Clin. Cancer Res. 12, 5000–5001.
Rzeski, W., Pruskil, S., Macke, A., Felderhoff-Mueser, U., Reiher, A.K., Hoerster, F., Jansma, C., Jarosz, B., Stefovska, V., Bittigau, P., Ikonomidou, C., 2004. Anticancer agents are potent neurotoxins in vitro and in vivo. Ann. Neurol. 56, 351–360.
Savitz, J., Solms, M., Ramesar, R., 2006. The molecular genetics of cognition: dopamine, COMT and BDNF. Genes Brain Behav. 5, 311–328.
Schagen, S.B., Muller, M.J., Boogerd, W., Rosenbrand, R.M., van, R.D., Rodenhuis, S., van Dam, F.S., 2002. Late effects of adjuvant chemotherapy on cognitive function: a follow-up study in breast cancer patients. Ann. Oncol. 13, 1387–1397.
Schagen, S.B., Vardy, J., 2007. Cognitive dysfunction in people with cancer. Lancet Oncol. 8, 852–853.
Schiff, D., Kesari, S., Wen, P., 2008. Cancer Neurology in Clinical Practice. Neurologic complications of chemotherapy, second ed. Humana Press Inc., Totowa, NJ, pp. 287–326.
Seigers, R., Pourtau, L., Schagen, S.B., van Dam, F.S., Koolhaas, J.M., Konsman, J.P., Buwalda, B., 2010a. Inhibition of hippocampal cell proliferation by methotrexate in rats is not potentiated by the presence of a tumor. Brain Res. Bull. 81, 472–476.
Seigers, R., Schagen, S.B., Beerling, W., Boogerd, W., van Tellingen, O., van Dam, F.S., Koolhaas, J.M., Buwalda, B., 2008. Long-lasting suppression of hippocampal cell proliferation and impaired cognitive performance by methotrexate in the rat. Behav. Brain Res. 186, 168–175.
Seigers, R., Schagen, S.B., Coppens, C.M., van der Most, P.J., van Dam, F.S., Koolhaas, J.M., Buwalda, B., 2009. Methotrexate decreases hippocampal cell proliferation and induces memory deficits in rats. Behav. Brain Res. 2, 279–284.
Seigers, R., Timmermans, J., van der Horn, H.J., de Vries, E.F., Dierckx, R.A., Visser, L., Schagen, S.B., van Dam, F.S., Koolhaas, J.M., Buwalda, B., 2010b. Methotrexate reduces hippocampal blood vessel density and activates microglia in rats but does not elevate central cytokine release. Behav. Brain Res. 207, 265–272.
Seruga, B., Zhang, H., Bernstein, L.J., Tannock, I.F., 2008. Cytokines and their relationship to the symptoms and outcome of cancer. Nat. Rev. Cancer 8, 887–899.
Sherwin, B.B., 2000. Oestrogen and cognitive function throughout the female lifespan. Novartis Found. Symp. 230, 188–196.
Shors, T.J., Townsend, D.A., Zhao, M., Kozorovitskiy, Y., Gould, E., 2002. Neurogenesis may relate to some but not all types of hippocampal-dependent learning. Hippocampus 12, 578–584.
Sieklucka-Dziuba, M., Saczonek, J., Dziuba, J., Kleinrok, Z., 1998. Central action of some cytostatics—methotrexate (MTX) and doxorubicin (DXR): II. The influence on the seizure activity and the learning and memory processes in mice. Ann. Univ. Mariae Curie Sklodowska [Med.] 53, 81–88.
Silverman, D.H., Dy, C.J., Castellon, S.A., Lai, J., Pio, B.S., Abraham, L., Waddell, K., Petersen, L., Phelps, M.E., Ganz, P.A., 2006. Altered frontocortical, cerebellar, and basal ganglia activity in adjuvant-treated breast cancer survivors 5–10 years after chemotherapy. Breast Cancer Res. Treat. 103, 303–311.
Silverstein, F.S., Johnston, M.V., 1986. A model of methotrexate encephalopathy: neurotransmitter and pathologic abnormalities. J. Child Neurol. 1, 351–357.
Snyder, J.S., Hong, N.S., McDonald, R.J., Wojtowicz, J.M., 2005. A role for adult neurogenesis in spatial long-term memory. Neuroscience 130, 843–852.
Stock, H.S., Rosellini, R.A., Abrahamsen, G.C., McCaffrey, R.J., Ruckdeschel, J.C., 1995. Methotrexate does not interfere with an appetitive Pavlovian conditioning task in Sprague-Dawley rats. Physiol. Behav. 58, 969–973.
Tchen, N., Juffs, H.G., Downie, F.P., Yi, Q.L., Hu, H., Chemerynsky, I., Clemons, M., Crump, M., Goss, P.E., Warr, D., Tweedale, M.E., Tannock, I.F., 2003. Cognitive function, fatigue, and menopausal symptoms in women receiving adjuvant chemotherapy for breast cancer. J. Clin. Oncol. 21, 4175–4183.
Tobinick, E., 2008. Perispinal etanercept produces rapid improvement in primary progressive aphasia: identification of a novel, rapidly reversible TNF-mediated pathophysiologic mechanism, Medscape. J. Med. 10, 135.
Tobinick, E.L., Gross, H., 2008. Rapid improvement in verbal fluency and aphasia following perispinal etanercept in Alzheimer's disease. BMC Neurol. 8, 27.
Uzar, E., Koyuncuoglu, H.R., Uz, E., Yilmaz, H.R., Kutluhan, S., Kilbas, S., Gultekin, F., 2006. The activities of antioxidant enzymes and the level of malondialdehyde in cerebellum of rats subjected to methotrexate: protective effect of caffeic acid phenethyl ester. Mol. Cell Biochem. 291, 63–68.
van Asperen, J., van Tellingen, O., Tijssen, F., Schinkel, A.H., Beijnen, J.H., 1999. Increased accumulation of doxorubicin and doxorubicinol in cardiac tissue of mice lacking mdr1a P-glycoprotein. Br. J. Cancer 79, 108–113.
van Dam, F.S., Schagen, S.B., Muller, M.J., Boogerd, W., vd, W.E., Droogleever Fortuyn, M.E., Rodenhuis, S., 1998. Impairment of cognitive function in women receiving adjuvant treatment for high-risk breast cancer: high-dose versus standard-dose chemotherapy. J. Natl. Cancer Inst. 90, 210–218.
Van der Borght, K., Havekes, R., Bos, T., Eggen, B.J., Van der Zee, E.A., 2007. Exercise improves memory acquisition and retrieval in the Y-maze task: relationship with hippocampal neurogenesis. Behav. Neurosci. 121, 324–334.
van Praag, H., Christie, B.R., Sejnowski, T.J., Gage, F.H., 1999. Running enhances neurogenesis, learning, and long-term potentiation in mice. Proc. Natl. Acad. Sci. U.S.A. 96, 13427–13431.
van Praag, H., Shubert, T., Zhao, C., Gage, F.H., 2005. Exercise enhances learning and hippocampal neurogenesis in aged mice. J. Neurosci. 25, 8680–8685.
Vardy, J., Tannock, I., 2007. Cognitive function after chemotherapy in adults with solid tumours. Crit. Rev. Oncol. Hematol. 63, 183–202.
Vardy, J., Wefel, J.S., Ahles, T., Tannock, I.F., Schagen, S.B., 2008. Cancer and cancer-therapy related cognitive dysfunction: an international perspective from the Venice cognitive workshop. Ann. Oncol. 19, 623–629.
Wang, H.N., Peng, Y., Tan, Q.R., Chen, Y.C., Zhang, R.G., Qiao, Y.T., Wang, H.H., Liu, L., Kuang, F., Wang, B.R., Zhang, Z.J., 2010. Quetiapine ameliorates anxiety-like behavior and cognitive impairments in stressed rats: implications for the treatment of posttraumatic stress disorder. Physiol Res. 59, 263–271.
Wati, H., Kudo, K., Qiao, C., Kuroki, T., Kanba, S., 2006. A decreased survival of proliferated cells in the hippocampus is associated with a decline in spatial memory in aged rats. Neurosci. Lett. 399, 171–174.

Wefel, J.S., Lenzi, R., Theriault, R., Buzdar, A.U., Cruickshank, S., Meyers, C.A., 2004a. 'Chemobrain' in breast carcinoma?: a prologue. Cancer 101, 466 A–475 A.

Wefel, J.S., Lenzi, R., Theriault, R.L., Davis, R.N., Meyers, C.A., 2004b. The cognitive sequelae of standard-dose adjuvant chemotherapy in women with breast carcinoma: results of a prospective, randomized, longitudinal trial. Cancer 100, 2292B–2299B.

Wefel, J.S., Witgert, M.E., Meyers, C.A., 2008. Neuropsychological sequelae of non-central nervous system cancer and cancer therapy. Neuropsychol. Rev. 18, 121–131.

Weng, H.R., Aravindan, N., Cata, J.P., Chen, J.H., Shaw, A.D., Dougherty, P.M., 2005. Spinal glial glutamate transporters downregulate in rats with taxol-induced hyperalgesia. Neurosci. Lett. 386, 18–22.

Wick, A., Wick, W., Hirrlinger, J., Gerhardt, E., Dringen, R., Dichgans, J., Weller, M., Schulz, J.B., 2004. Chemotherapy-induced cell death in primary cerebellar granule neurons but not in astrocytes: in vitro paradigm of differential neurotoxicity. J. Neurochem. 91, 1067–1074.

Willis, L.M., Shukitt-Hale, B., Joseph, J.A., 2009. Modulation of cognition and behavior in aged animals: role for antioxidant- and essential fatty acid-rich plant foods. Am. J. Clin. Nutr. 89, 1602S–1606S.

Wilson, C.J., Finch, C.E., Cohen, H.J., 2002. Cytokines and cognition—the case for a head-to-toe inflammatory paradigm. J. Am. Geriatr. Soc. 50, 2041–2056.

Winocur, G., Vardy, J., Binns, M.A., Kerr, L., Tannock, I., 2006a. The effects of the anti-cancer drugs, methotrexate and 5-fluorouracil, on cognitive function in mice. Pharmacol. Biochem. Behav. 85, 66 A–75 A.

Winocur, G., Wojtowicz, J.M., Sekeres, M., Snyder, J.S., Wang, S., 2006b. Inhibition of neurogenesis interferes with hippocampus-dependent memory function. Hippocampus 16, 296 B–304 B.

Wojtowicz, J.M., Askew, M.L., Winocur, G., 2008. The effects of running and of inhibiting adult neurogenesis on learning and memory in rats. Eur. J. Neurosci. 27, 1494–1502.

Yang, M., Kim, J.S., Song, M.S., Kim, S.H., Kang, S.S., Bae, C.S., Kim, J.C., Wang, H., Shin, T., Moon, C., 2010. Cyclophosphamide impairs hippocampus-dependent learning and memory in adult mice: possible involvement of hippocampal neurogenesis in chemotherapy-induced memory deficits. Neurobiol. Learn. Mem 93, 487–494.

Yanovski, J.A., Packer, R.J., Levine, J.D., Davidson, T.L., Micalizzi, M., D'Angio, G., 1989. An animal model to detect the neuropsychological toxicity of anticancer agents. Med. Pediatr. Oncol. 17, 216–221.

Yu, H., Wang, Y., Pattwell, S., Jing, D., Liu, T., Zhang, Y., Bath, K.G., Lee, F.S., Chen, Z.Y., 2009. Variant BDNF Val66Met polymorphism affects extinction of conditioned aversive memory. J. Neurosci. 29, 4056–4064.

Yuede, C.M., Dong, H., Csernansky, J.G., 2007. Anti-dementia drugs and hippocampal-dependent memory in rodents. Behav. Pharmacol. 18, 347–363.