Cognitive Changes Associated With Cancer and Cancer Treatment: State of the Science

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Background: Cognitive impairment is a distressing, disruptive, and potentially debilitating symptom that can occur as a direct result of cancer or its treatment. National organizations have identified cognitive impairment as a challenge many survivors face and call for research to address this problem. Despite the priority, research is still relatively limited and questions remain unanswered about prevalence and impact on survivors, as well as coping strategies and effective treatment options available to address this potentially debilitating problem.

Objectives: The purpose of this article is to (a) analyze the prevalence and types of cognitive impairment that commonly affect survivors; (b) delineate the impact that cognitive impairment after cancer and cancer treatment has on self-esteem, social relationships, work ability, and overall quality of life among survivors; and (c) synthesize and appraise commonly used coping strategies used by survivors to address cognitive impairment and evidence-based interventions that may be incorporated into clinical practice.

Methods: A comprehensive review and synthesis of the literature was conducted.

Findings: Evidence-based interventions to address cognitive changes after cancer and cancer treatment are limited. However, emerging research has demonstrated that nonpharmacologic treatments, such as cognitive training, are likely to be effective.

Definition of Cognitive Impairment

Cognitive impairment has been defined as those cognitive changes that negatively affect higher-order mental processes (Hess & Insel, 2007). Although no single neurocognitive signature of cancer- and cancer treatment-related effects stands out (Castellon, Silverman, & Ganz, 2005), deficits in attention, memory, speed of processing, language (word finding), and executive functioning (problem solving) appear to be most common (Anderson-Hanley, Sherman, Riggs, Agocha, & Compas, 2003; Jansen, Miskowski, Dodd, Dowling, & Kramer, 2005; Vardy et al., 2008). Cognitive deficits following diagnosis and survivors as well as insufficient data to guide evidence-based interventions (Vardy, Wefel, Ahles, Tannock, & Schagen, 2008; Von Ah, Jansen, Allen, Schiavone, & Wulff, 2011; Von Ah, Storey, Jansen, & Allen, 2013).
treatment of cancer may be subtle, yet may have a significant impact on quality of life in cancer survivors (Mehnert et al., 2007; Von Ah, Russell, Storniolo, & Carpenter, 2009).

### Risk Factors

The exact etiology of cognitive deficits in cancer survivors is not fully understood and most likely is thought to be multifactorial (Bender & Thelen, 2013; Merriman, Von Ah, Miaskowski, & Aouizerat, 2013). Briefly, in cancer survivors, tumor- and/or treatment-related factors may directly or indirectly affect cognitive functioning through one or more of the following mechanisms: neurotoxic injury in the brain, microvascular injury, secondary central and/or systemic inflammatory processes, or dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis, resulting in changes in endogenous hormones (estrogen and serotonin) (Merriman et al., 2013). In addition, it has been hypothesized that cancer treatment may accelerate cognitive aging by influencing aging at a cellular level, including inflammation, DNA damage, oxidative stress, telomere length, and cell senescence (Ahles, Root, & Ryan, 2012; Mandelblatt et al., 2013). Individual differences in age, education level, intelligence, menopausal status, comorbid conditions, medication usage, and genetics also may contribute to cognitive deficits in cancer survivors (Bender & Thelen, 2013). Cognitive deficits also may be compounded by other related symptoms, including fatigue, depression, and anxiety (Bender, Ergyn, Rosenzweig, Cohen, & Sereika, 2005; Bender & Thelen, 2013). A summary of cancer- and treatment-related and non-cancer treatment–related factors that may influence an individual’s risk for cognitive impairment are displayed in Figure 1 (Bender & Thelen, 2013; Mandelblatt et al., 2013; National Comprehensive Cancer Network, 2013). The complexity associated with cognitive changes after cancer and cancer treatment contribute to the difficulty of understanding and effectively treating this symptom (Bender & Thelen, 2013).

### Scope of the Problem

Seventeen percent (van Dam et al., 1998) to 75% (Wieneke & Dienst, 1995) of survivors report some level of cognitive impairment (Anderson-Hanley et al., 2003; Falleti, Sanfilippo, Maruff, Weih, & Phillips, 2005; Jansen et al., 2005; Stewart, Bielajew, Collins, Parkinson, & Tomiak, 2006; van Dam et al., 1998; Wiencke & Dienst, 1995). In Von Ah, Harvison, et al. (2009), the author’s group found clinically significant memory deficits in 44% of breast cancer survivors (n = 52) who were, on average, 4.6 years (SD = 2.76) post-treatment. Five meta-analyses have also documented cognitive deficits that survivors experience, suggesting that impairments in memory, attention and concentration, speed of processing, and executive functioning are most common (Anderson-Hanley et al., 2003; Falleti et al., 2005; Jansen et al., 2005; Jim et al., 2012; Stewart et al., 2006). Although results of some prospective studies suggest cognitive impairment may attenuate over time (Jenkins et al., 2006; Tchen et al., 2005; Wefel, Lenz, Theriault, Davis, & Meyers, 2004), researchers have found that a substantial number of survivors continue to have objectively measured memory deficits for 5, 10, and even as long as 20 years post-treatment (Ahles et al., 2002; Jenkins et al., 2006; Koppelmans et al., 2012; Wefel et al., 2004).

In addition, researchers have explored cognitive changes associated with cancer using multiple neuroimaging techniques (Holohan, Von Ah, McDonald, & Saykin, 2013). Electrophysiological and imaging studies reveal differences in central nervous system structure and function among survivors exposed to chemotherapy compared to baseline prechemotherapy or control participants (Brown et al., 1998; Ferguson, McDonald, Saykin, & Ahles, 2007; Inagaki et al., 2007; Kreueks et al., 2005; Saykin, Ahles, & McDonald, 2003; Schagen, Hamburger, Muller, Boogerd, & van Dam, 2001; Silverman et al., 2007). Results from imaging studies also have documented reduced regional volumes of gray and white matter, with studies demonstrating both short-term (Brown et al., 1998; Ferguson, McDonald, et al., 2007; Inagaki et al., 2007) and long-term effects (Saykin et al., 2005). In addition, in a review of the empirical literature, Holohan et al. (2013) identified 35 separate neuroimaging studies and noted that the majority identified structural and/or functional alterations which also were accompanied by increases in self-reported cognitive concerns, neuropsychological testing deficits, or both. Taken together, findings from these studies provide clear and convincing evidence that cognitive deficits are prevalent after cancer and cancer treatment.

### Impact on Quality of Life and Work-Related Outcomes

Cognitive impairment can dramatically affect quality of life in survivors (Mehnert et al., 2007; Myers, 2013; Von Ah, Habermann, Carpenter, & Schneider, 2013). In a survey of 471 survivors, 62% stated that cognitive problems were disruptive to their functioning and relationships at home and at work (Hede, 2008). In qualitative interviews with 22 breast cancer survivors, cognitive impairment affected survivors’ self-confidence, self-esteem, social relationships, and perceived work ability (Von Ah, Habermann, et al., 2013). Survivors related that they often were embarrassed when they could not remember names, dates, or places and often would withdraw from social situations. In addition, many identified that dealing with cognitive changes...
after cancer and cancer treatment was most difficult when family, friends, or healthcare providers did not acknowledge or validate their concerns. Previous work by Von Ah, Russell, et al. (2009) with 135 African American (47%) and Caucasian (53%) breast cancer survivors also demonstrated that subjective cognitive impairment was related to poorer health-related quality of life, including more depressive symptoms, lower well-being, poorer physical functioning, and greater fatigue.

Results from multiple studies also have shown that cognitive impairment, as demonstrated on objective neuropsychological tests, is associated with higher levels of depressive symptoms, fatigue, and anxiety (Bender et al., 2006; Cimprich, 1992, 1993; Mehrert et al., 2007; Stewart et al., 2008; Wefel et al., 2004). In preliminary work conducted by Von Ah et al. (2010), which included 444 breast cancer survivors compared to 355 healthy women, the authors found that cognitive impairment on neuropsychological tests (deficits in immediate [short-term] and delayed memory, processing speed, and executive functioning) was significantly related to depressive symptoms and fatigue. Findings are supported by research results in which cognitive impairment commonly co-occurs with fatigue and depressive symptoms across the cancer trajectory (Bender et al., 2005; Bender & Thelen, 2013). In addition, many researchers have demonstrated that cognitive impairment affects perceived work ability in survivors (Calvio, Peugeot, Bruns, Todd, & Feuerstein, 2010; de Boer et al., 2008; Feuerstein, Hansen, Calvio, Johnson, & Ronquillo, 2007; Hansen, Feuerstein, Calvio, & Olsen, 2008; Pryce, 2007; Taskila, Martikainen, Hietanen, & Lindbohm, 2007; Von Ah, Habermann, et al., 2013). In a large cohort study of 1,490 employed survivors and 2,796 reference participants, survivors had significantly lower levels of perceived work ability than healthy controls (Lindbohm et al., 2012). Perceived work ability, or the capability to manage job demands (Ilmarinen & Tuomi, 2004), has been associated with job stress (Kinnunen, Parkatti, & Rasku, 1994), and several studies have confirmed that poor work ability predicts loss of work productivity, retirement intentions, long-term absence, early retirement, need for rehabilitation, and work disability (Alavinia, de Boer, van Duivenbooden, Frings-Dresen, & Burdorf, 2009; Kuoppala, Laminpaa, Vaananen-Tomppo, & Hinkka, 2011; Salonen, Arola, Nygard, Huhtala, & Koivisto, 2003; Sell et al., 2009). Overall, research has consistently documented the significant and negative impact of cancer- and cancer treatment-related cognitive impairment on survivor’s self-confidence, social relationships, quality of life, and work-related outcomes (Myers, 2013).

Coping Strategies to Address Cognitive Impairment

Although cognitive impairment after cancer and cancer treatment is a prevalent and significant problem, little research has focused on addressing these cognitive changes. Interviews with survivors provide some insight regarding how survivors live with and manage cognitive changes after cancer (Myers, 2013; Von Ah, Storey, et al., 2013). Figure 2 displays a summary of positive and potentially negative coping strategies used by survivors to address cognitive impairment. The majority of the research reviewed identified positive methods for coping with cognitive changes after cancer. In previous work (Von Ah, Storey, et al., 2013), the author’s group was able to identify and classify these positive coping strategies into five overarching and distinct categories: organizational and self-management, management of the physical environment, management of the social environment, stress and attention fatigue-reducing methods, and engaging in mind-stimulating activities. However, the literature also reported that survivors identified potentially negative coping strategies, such as avoiding social activities, avoiding substantive social interactions, and leaving demanding employment situations (Myers, 2013). Although removal from a stressful social or work situation may be appropriate depending on the context and extent used, these avoidant strategies may not produce the long-term positive adjustment that is necessary to address cognitive changes after cancer.

Interventions for Cognitive Changes After Cancer and Its Treatment

Evidence-based interventions for cognitive impairment after cancer and cancer treatment remain limited. Researchers have explored pharmacologic and nonpharmacologic approaches to address cancer- and cancer treatment-related cognitive impairment (Von Ah et al., 2011; Von Ah, Jansen, & Allen, 2014). Table 1 displays the pharmacologic interventions trialed, including the use of donepezil, an acetylcholinesterase inhibitor often used for Alzheimer disease (Jatoi et al., 2005; Shaw et al., 2006); methylphenidate, a psychostimulant often used in children with attention deficit hyperactivity disorder (Bruera, Miller, Macmillan, & Kuehn, 1992; Butler et al., 2007; Escalante et al., 2014; Gagnon, Low, & Schreier, 2005; Gehring et al., 2012; Lower et al., 2009; Mar Fan et al., 2008; Meyers, Weitzner, Valentine, & Levin, 1998; Schwartz, Thompson, & Massoud, 2002); memantine, an N-methyl-D-aspartate receptor antagonist, which has been shown to be neuroprotective in preclinical trials (Brown et al., 2013); and modafinil, a psychostimulant often used for narcolepsy (Blackhall, Petroni, Shu, Baum, & Farace, 2009; Gehring et al., 2012; Kohli et al., 2009; Lundorff, Jonsson, & Sjogren, 2009). Table 2 highlights the nonpharmacologic treatments used to address cognitive impairment, including
TABLE 1. Pharmacologic Interventions for Cognitive Impairment in Survivors

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<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Findings</th>
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<tbody>
<tr>
<td><strong>Donepezil</strong></td>
<td>5 mg per day for four weeks increased to 10 mg per day plus vitamin E 1,000 IU per day</td>
<td>No treatment effect</td>
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<tr>
<td><strong>Shaw et al., 2006</strong></td>
<td>5 mg per day for six weeks; 10 mg per day for 18 weeks; followed by six weeks washout</td>
<td>Improvement on attention and concentration, verbal memory, and figural memory</td>
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<tr>
<td><strong>Methylphenidate/Dexmethylphenidate (MPH/dMPH)</strong></td>
<td>10 mg per day for two days</td>
<td>Improvement in alertness, attention, and memory</td>
</tr>
<tr>
<td><strong>Butler et al., 2007</strong></td>
<td>10–30 mg per day during and eight weeks after radiation therapy</td>
<td>No treatment effect</td>
</tr>
<tr>
<td><strong>Escalante et al., 2014</strong></td>
<td>18 mg per day for two weeks followed by placebo for two weeks</td>
<td>Improvement in speed of processing and recall</td>
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<tr>
<td><strong>Gagnon et al., 2005</strong></td>
<td>10 mg test dose; increased to 20 mg per day and increased by 5 mg per day until resolution of delirium or maximum tolerated dose</td>
<td>Improvement in overall cognitive functioning, alertness, psychomotor functioning, and slurred speech</td>
</tr>
<tr>
<td><strong>Gehring et al., 2012</strong></td>
<td>20 mg per day MPH or 18 mg per day sustained release MPH versus 200 mg per day modafinil for four weeks</td>
<td>Improvement in speed of processing and executive function; MPH improved attention, modafinil improved processing speed</td>
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<tr>
<td><strong>Lower et al., 2009</strong></td>
<td>10 mg per day</td>
<td>No treatment effect</td>
</tr>
<tr>
<td><strong>Mar Fan et al., 2008</strong></td>
<td>10 mg per day for one week; if tolerated, increase up to 20 mg per day</td>
<td>No treatment effect</td>
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<tr>
<td><strong>Meyers et al., 1998</strong></td>
<td>10 mg per day; increase by 5 mg BID until response or dose-limiting toxicity</td>
<td>Improvement in psychomotor speed, memory, visual-motor function, executive function, motor speed, and dexterity</td>
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<tr>
<td><strong>Schwartz et al., 2002</strong></td>
<td>20 mg per day, long-acting, for four months and 15–20 minutes of exercise</td>
<td>Improvement in perceived mental health and executive function in MPH group</td>
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<tr>
<td><strong>Memantine</strong></td>
<td>Total dose of 20 mg per day</td>
<td>Reduced decline in memory processing speed and executive function; no improvement in delayed recall</td>
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<tr>
<td><strong>Modafinil</strong></td>
<td>100 mg per day for two weeks; 200 mg per day for two weeks</td>
<td>Improvement in cognitive flexibility; no intervention effect on verbal learning, memory, verbal fluency, motor and eye-hand coordination, attention, or motor speed</td>
</tr>
<tr>
<td><strong>Gehring et al., 2012</strong></td>
<td>20 mg per day MPH or 18 mg per day sustained release MPH versus 200 mg per day modafinil for four weeks</td>
<td>Improvement in speed of processing and executive function; MPH improved attention, modafinil improved processing speed</td>
</tr>
<tr>
<td><strong>Kohli et al., 2009</strong></td>
<td>200 mg day for four weeks; responders continued 200 mg day or placebo for four weeks</td>
<td>Improvement in speed of memory and episodic memory but not working memory</td>
</tr>
<tr>
<td><strong>Lundorff et al., 2009</strong></td>
<td>200 mg per day for four days</td>
<td>Improvement noted in attention and psychomotor speed</td>
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*a Indicates interventions that combine pharmacologic and nonpharmacologic approaches*

Nursing Implications and Need for Future Research

Oncology nurses are in a prime position to address cognitive changes after cancer and cancer treatment. Nurses need to recognize the cancer- and non-cancer-related factors that may place a survivor at higher risk for cognitive changes. In addition, nurses must fully...
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<th>Study</th>
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<td><strong>Cognitive-Behavioral Training</strong></td>
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<tr>
<td>Cherrier et al., 2013</td>
<td>Seven one-hour sessions for seven weeks</td>
<td>Improvement in perceived cognitive function</td>
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<tr>
<td>Ferguson, McDonald, et al., 2007</td>
<td>Memory Attention Adaptation Training (MAAT), 30–50 minutes for four months</td>
<td>Improvement over time in perceived cognitive functioning, verbal memory, attention, and executive psychomotor functioning</td>
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<tr>
<td>Ferguson et al., 2012</td>
<td>MAAT training</td>
<td>Improvement in verbal memory</td>
</tr>
<tr>
<td>Goedendorp et al., 2014</td>
<td>Individualized training (5–26 sessions, (\bar{x} = 12.5, \text{SD} = 4.7)) focused on reducing fatigue</td>
<td>Improvement in perceived concentration; no improvement on neuropsychological assessment</td>
</tr>
<tr>
<td>Locke et al., 2008</td>
<td>Six sessions of cognitive rehab and six sessions of problem-solving therapy for two weeks</td>
<td>Improvement in mood; unable to obtain follow-up on objective cognitive functioning</td>
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<tr>
<td>McDougall, 2001</td>
<td>75 minutes, eight sessions for four weeks with MT and self-efficacy</td>
<td>Improvement in perceived cognitive functioning; memory efficacy, and metamemory; no improvement in memory performance</td>
</tr>
<tr>
<td>McDougall et al., 2011</td>
<td>30 minutes per week for eight weeks of MT with four, two-hour booster sessions</td>
<td>Improvement in perceived cognitive functioning and visual memory</td>
</tr>
<tr>
<td>Schuurs &amp; Green, 2012</td>
<td>Two hours per week for four weeks; includes psycho-education and problem-solving approaches</td>
<td>Improvement in immediate (short-term) and delayed memory, visuospatial skills, and language and attention; these were sustained at three months postintervention except for language and attention.</td>
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**Cognitive Training**

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<tr>
<td>Gehring et al., 2009</td>
<td>Two hours per week for six weeks of cognitive training</td>
<td>Improvement in perceived cognitive function immediately and at six months postintervention; improvement in attention and memory at six months postintervention only</td>
</tr>
<tr>
<td>Hassler et al., 2010</td>
<td>90 minutes per week for 10 weeks of CT</td>
<td>Improvement in learning, perception, concentration, attention, memory, retentiveness, and verbal memory</td>
</tr>
<tr>
<td>Kesler et al., 2013</td>
<td>48 executive function training sessions for 12 weeks</td>
<td>Improvement in cognitive flexibility, verbal fluency, and processing speed</td>
</tr>
<tr>
<td>Miotto et al., 2013</td>
<td>Minimum of five 30-minute sessions of semantic organizational strategies</td>
<td>Improvement in verbal recall and increased activation</td>
</tr>
<tr>
<td>Poppelreuter et al., 2009</td>
<td>Two intervention groups: four one-hour sessions of (a) attention and memory training in person or (b) attention and memory per computer compared to control</td>
<td>No intervention effects</td>
</tr>
<tr>
<td>Von Ah et al., 2012</td>
<td>10 one-hour sessions for 6–8 weeks; two groups (MT or ST compared to control)</td>
<td>Improvement in perceived cognitive function both groups; MT had improvement in immediate and delayed memory, ST had improvement in immediate and delayed memory as well as processing speed.</td>
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<tr>
<td>Zucchella et al., 2013</td>
<td>16 one-hour sessions for four weeks</td>
<td>Improvement in visual attention and verbal memory</td>
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**EEG/Neurofeedback**

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<tr>
<td>Alvarez et al., 2013</td>
<td>20-session neurofeedback regimen</td>
<td>Improvement in perceived cognitive function</td>
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**Exercise Programs: Combined or Alone**

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<tr>
<td>Baumann et al., 2011</td>
<td>60 minutes of resistance training two times per week for 12 weeks</td>
<td>Improvement in attention and working memory; no improvement in verbal memory; no baseline control group</td>
</tr>
<tr>
<td>Korstjens et al., 2006</td>
<td>Two-hour sessions two times per week for 12 weeks of physical fitness, plus seven two-hour psychoeducation sessions</td>
<td>Improvement in perceived cognitive function</td>
</tr>
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*Interventions that combine pharmacologic and nonpharmacologic approaches

CT—cognitive training; EEG—electroencephalography; MBSR—mindfulness-based stress reduction; MT—memory training; ST—speed-of-process training

(Continued on the next page)
assess each survivor for this late and long-term effect of treatment. Survivors often will express concerns regarding memory lapses (remembering names, dates, and places), inability to concentrate, and difficulty following instructions or completing tasks. These concerns should be fully assessed and referred to other healthcare professionals (e.g., neuropsychologist, psychiatrist) for evaluation if they disrupt everyday functioning (Jansen, 2013). At a minimum, nurses should acknowledge the survivors’ cognitive concerns because research has suggested that the acknowledgement alone can reduce distress. In addition, nurses should thoroughly assess and treat other symptoms that commonly co-occur with cognitive impairment, such as depression and anxiety. Addressing these other co-related symptoms may also help ameliorate the perception of cognitive impairment. Nurses should be aware of and refer survivors with concerns to reputable resources, such as the PEP resource for cognitive impairment (www.ons.org/practice-resources/pep/cognitive-impairment). This site is routinely updated with the most relevant empirical research in this area.

Based on the current research, cognitive training has shown to be useful in addressing cognitive impairment and has been identified as likely to be effective in improving cognitive impairment in cancer survivors (Von Ah et al., 2014). More research is needed, however, to fully identify effective interventions that are feasible and cost effective. Much of the current research is still limited by the research design (e.g., lack of randomized, controlled trials; lack of an attention control comparison group; laboratory versus home-based programs), small sample sizes,
limited sample diversity (mostly conducted in brain tumor or breast cancer survivors with well-educated and Caucasian participants), and lack of assessment using standardized neuropsychological tests. Research in this area is vital to fully address cancer- and cancer treatment–related cognitive impairment, which has been shown to be a prevalent, bothersome, and potentially debilitating symptom.

References


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