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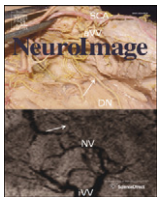

Integrating functional near-infrared spectroscopy in the characterization, assessment, and monitoring of cancer and treatment-related neurocognitive dysfunction

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ABSTRACT

Cancer and cancer treatment-related neurocognitive dysfunction (CRND) (e.g., impairments in key cognitive domains of attention, memory, processing speed, and executive function), commonly referred to as "chemobrain" or "chemo-fog", can negatively impact patients' psychosocial functioning and quality of life. CRND is a debilitating and enduring adverse effect experienced by 17% to 75% of patients during and after completion of treatment. However, few studies have systematically characterized and tested interventions to treat CRND. This paucity of data is due, at least partly, to difficulties understanding its etiology and a lack of consensus studies on best methods for assessing the presence and severity of CRND. This paper presents a comprehensive model for characterizing, assessing and monitoring cancer and treatment-related neurocognitive dysfunction, with functional near-infrared spectroscopy (fNIRS) as an important component of this model. The benefits of fNIRS to the characterization and longitudinal assessment and monitoring of CRND are discussed. Strategies for integrating optical imaging spectroscopy in biobehavioral oncology research, strength and limitations, and directions for future CRND studies using fNIRS are examined.

Introduction

Prevalence, adverse effects, and costs of cancer

Cancer is one of the topmost leading causes of death in the United States and worldwide, with a substantial and rapidly increasing financial burden to patients, their families and society (Kochanek et al., 2011; WHO, 2008). Approximately 11.9 million people in the United States were living with cancer in 2008 (Parry et al., 2011). The incidence of cancer has been steadily rising, perhaps because of exposure to known and/or unknown carcinogens, as well as other factors such as population growth and aging. Annual estimates of new cancers in the United States grew from 1.45 million in 2008 to 1.64 million in 2012 (ACS, 2012; Jemal et al., 2008, 2009, 2010; Siegel et al., 2011, 2012). The National Institutes of Health estimated the annual costs of cancer in the United States (including direct medical costs and indirect costs associated with lost productivity and premature cancer-related death) at approximately $226 billion in 2007 and $264 billion in 2010 (ACS, 2010, 2012). Adjusting for inflation, increases in prevalence, treatment expenses, and lost productivity, the annual costs of cancer in the United States could easily surpass $500 billion in the near future. Some of the key factors influencing lost productivity involve the debilitating biobehavioral and psychological adverse effects of cancer and cancer treatments (e.g., neurocognitive dysfunction, fatigue, sleep impairments, pain, and psychological distress) (Ancoli-Israel et al., 2006; Anton et al., 2012; Berger et al., 2012; Jean-Pierre, 2010; Jean-Pierre et al., 2010, 2012; McDonald et al., 2012; Ruge et al., 2011; Savard et al., 2009; Seklehner et al., 2013). Finding ways to reliably assess, prevent or treat these negative side effects can help improve treatment outcomes, enhance quality of life, and reduce lost productivity for cancer patients and survivors. The goal of this paper is to present a comprehensive model for characterizing, assessing and monitoring cancer and treatment-related neurocognitive dysfunction (CRND) that includes functional near-infrared spectroscopy (fNIRS) as an essential component of the model. The integration of fNIRS in the assessment and monitoring paradigm of CRND will enable continuous evaluation and collection of data to inform the development and testing of interventions to treat this adverse condition for patients and survivors.

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Cancer and treatment-related neurocognitive dysfunction (CRND)

Cancer and its treatments (e.g., chemotherapy, radiotherapy, immunotherapy, and hormonal therapy) are associated with impairments in key cognitive domains of attention, memory, processing speed and executive functioning. CRND, commonly referred to as "chemobrain", can negatively impact patients on multiple dimensions including psychosocial performance, intrapersonal and interpersonal relations, ability to return to work, quality of life, and survivorship (Ahles et al., 2002; Brezden et al., 2000; Jean-Pierre, 2010; Saykin et al., 2003; Scheibel et al., 2004). Previous studies have reported the incidence of CRND to be 17% to 75% of patients during and after completion of treatment (Wefel et al., 2004).

Possible causes of cancer and treatment-related neurocognitive dysfunction

The etiology of CRND is generally attributed to various biological (e.g., genetic predisposition to neurocognitive dysfunction, direct and/or indirect treatment-related neurotoxicity, failure of the blood–brain barrier, deoxyribonucleic acid damage, changes in brain biochemistry, oxidative stress, cerebral atrophy, microvasculature obstruction, and infarction of brain tissue), psychological (e.g., anxiety and depression), and behavioral (e.g., fatigue and sleep impairments) factors that can impact neuroanatomical structures (e.g., white matter atrophy), mental processes, and neurobehavioral outcomes such as attention and memory performance (Fig. 1) (Ahles and Saykin, 2007; Ahles et al., 2010; Bradbury, 2006; Christie et al., 2012; Dietrich et al., 2006; Joly et al., 2011; Joshi et al., 2010; Kannarkat et al., 2007; Rolig and McKinnon, 2000; Verstappen et al., 2003).

Certain cancer and treatment-related adverse effects (e.g., nausea and emesis, pain, and fatigue) have been more systematically studied (Bloechl-Daum et al., 2006; Phillips et al., 2010; Ryan, 2010). Therefore, researchers and clinicians tend to have a better understanding of the underlying mechanisms and ways to treat these negative side effects for cancer patients and survivors. In contrast, CRND has been less systematically studied. Consequently, the underlying neurobiological and neuropsychological mechanisms involved in CRND are not yet clearly described. This lack of both understanding and consensus data on CRND is associated with inherent difficulties involved in characterizing and assessing the presence and severity of this debilitating adverse effect (Jean-Pierre et al., 2012).

Challenges in the characterization, assessment, and monitoring of CRND

The negative impact of cancer and its treatments on brain function is increasingly recognized as a significant problem for patients and survivors. CRND is generally characterized by mild to moderate impairments in cognitive functioning, and is normally determined based on patients' self-reported subjective complaints of cognitive problems (e.g., difficulties in routine attention and memory tasks) or their performance outcomes on psychometrically validated neuropsychological tests (Ahles et al., 2002; Brezden et al., 2000; Falleti et al., 2005; Joly et al., 2011; Saykin et al., 2003; Schagen et al., 1999; Tannock et al., 2004; Wefel et al., 2004). These two methods for determining CRND are often criticized because of issues related to subjective biases of self-report questionnaires and the ecological validity of currently available neuropsychological measures for cancer populations. Additionally, previous studies have reported inconsistencies between patients' self-reported subjective complaints of CRND and their scores on validated neuropsychological tests (Hermelink et al., 2010; Mehnert et al., 2007; Wefel et al., 2004). The lack of "gold standard" measures presents a clinical and research challenge that underscores the need to develop and validate multi-method approaches to cogently describe CRND.

An assessment paradigm that includes patients' self-reported subjective complaints of cognitive impairments, performance scores on psychometrically validated neuropsychological measures, blood or tissue biomarkers analysis, and neuroimaging during emotional and cognitive operations could prove beneficial to the understanding of CRND. Brain-imaging techniques such as fNIRS, an important component of the proposed comprehensive evaluation model for CRND depicted in Fig. 2, can help bridge the gap between cancer patients' self-reported complaints of cognitive impairments and their scores on psychometrically validated neuropsychological tests. To date, however, studies that assess ways to successfully integrate neuroimaging techniques in the characterization, evaluation, and monitoring of CRND are still lacking.

Neuroimaging and cancer and treatment-related neurocognitive dysfunction

Advances in neuroimaging provide a wide range of tools and techniques to ascertain normal and abnormal brain functioning and behavioral outcomes such as attention and memory performance (Diers et al., 2012; Goulden et al., 2012; Habeck et al., 2012; Linden et al., 2012; Penke et al., 2012; Versace et al., 2011). Neuroimaging can be used to obtain key data to support the development and testing of neurocognitive models that describe the underlying mechanisms of the brain and cognitive impairments in the context of cancer and its treatments. Many neuroimaging tools are currently available and are being utilized in brain research, including structural and functional magnetic resonance imaging (MRI and fMRI), magnetic resonance spectroscopy (MRS), diffusion tensor imaging (DTI), magneto-encephalography (MEG), computed tomography (CT), positron emission tomography (PET), single photon emission computed tomography (SPECT), electroencephalography (EEG), and functional near-infrared spectroscopy (fNIRS). These neuroimaging

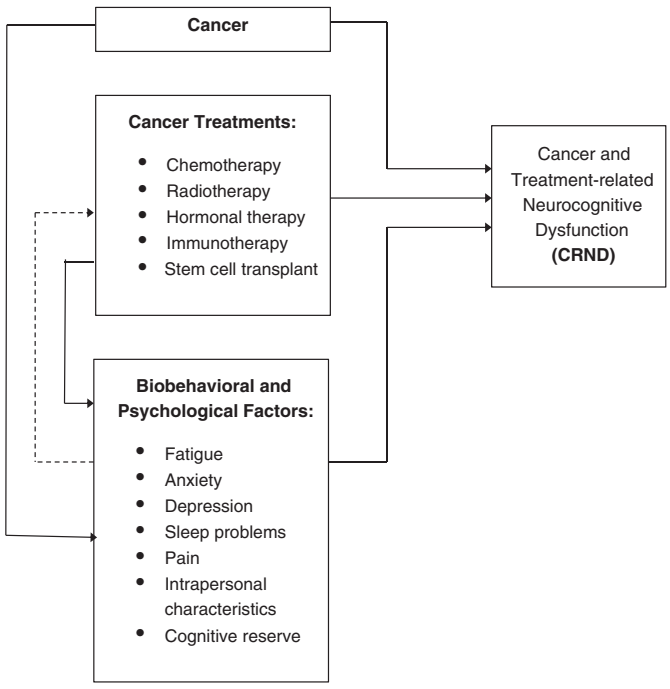

Fig. 1. Convergent and indirect causal structure of CRND.