ELSEVIER

NeuroImage

www.elsevier.com/locate/ynimg
NeuroImage 24 (2005) 61–69

BOLD responses to visual stimulation in survivors of childhood cancer

Ping Zou,[a,b] Raymond K. Mulhern,[c] Robert W. Butler,[d] Chin-Shang Li,[e] James W. Langston,[a] and Robert J. Ogg[a,b,*]

[a]*Department of Radiological Sciences, St. Jude Children's Research Hospital, Memphis, TN 38105, USA*
[b]*Department of Biomedical Engineering, University of Tennessee, Health Science Center, Memphis, TN 38163, USA*
[c]*Department of Behavioral Medicine, St. Jude Children's Research Hospital, Memphis, TN 38105, USA*
[d]*Department of Pediatrics, Oregon Health and Science University, Portland, OR 97201, USA*
[e]*Department of Biostatistics, St. Jude Children's Research Hospital, Memphis, TN 38105, USA*

Received 16 January 2004; revised 2 July 2004; accepted 23 August 2004
Available online 18 November 2004

Children surviving certain cancers have a high incidence of cognitive deficits caused by central nervous system (CNS) disease or treatments directed at the CNS. To establish the feasibility of using blood oxygen level-dependent (BOLD) functional magnetic resonance imaging (fMRI) to study cognitive deficits in survivors of childhood cancer, we tested the hypothesis that this population has the same BOLD response to visual stimulation as healthy subjects. We used BOLD fMRI to measure spatial and temporal patterns of brain activity after brief visual stimulation in 16 survivors of childhood cancer, 11 age-similar healthy siblings of survivors, and 16 healthy adults. Functional data for the survivors were analyzed with two general linear models, one used a canonical hemodynamic response function (HRF) and the other used a Fourier set as basis functions. The measured BOLD signal and brain activation patterns were similar in the survivors with both models. The BOLD signal for survivors was qualitatively similar in timing and shape, but there were significant quantitative differences as compared with healthy subjects. The activation was normally located in the primary visual cortex in 13 survivors, but the activation volume was significantly smaller in brain tumor survivors than in other groups. These findings demonstrate the feasibility of using BOLD fMRI to investigate brain function in survivors of childhood cancer. However, fMRI studies in this population must take into account effects of quantitative differences in their BOLD responses as compared to healthy subjects.

Keywords: Functional magnetic resonance imaging; Blood oxygen level-dependent contrast; Primary visual cortex; Neuroimaging; Cognition; Cerebral vasculature; Brain; Human

Introduction

As cure rates of childhood cancers have increased in recent decades, the quality of life of long-term survivors has become a new concern. Children surviving certain types of cancer, particularly acute lymphoblastic leukemia (ALL) and brain tumors, have a high incidence of cognitive deficits that can be caused by central nervous system (CNS) disease or treatments directed at the CNS, for example, cranial radiation therapy (RT) and intrathecal chemotherapy (Butler et al., 1994; Moore et al., 1994; Mulhern et al., 1988a,b; Palmer et al., 2001).

Cognitive impairments associated with cranial RT and intrathecal chemotherapy include disturbances in attention or concentration, intelligence, memory, academic skills, and motor abilities (Copeland et al., 1996; Moore et al., 1992a; Mulhern et al., 1988c; Pfefferbaum-Levine et al., 1984). These deficits can be sufficiently severe to hinder normal academic achievement, vocational attainment, and quality of life.

Cognitive deficits in ALL and brain tumor survivors after treatment directed at the CNS have been associated with structural abnormalities and altered patterns of brain electrical activity. Structural abnormalities observed in CT and MRI scans of the brain include cortical atrophy, intracerebral calcification, leukoencephalopathy, gray matter changes, and white matter loss, and these imaging abnormalities have been associated with behavioral problems and decreased scores in neuropsychological tests. (Brouwers and Poplack, 1990; Brouwers et al., 1984, 1985; Mulhern et al., 1999, 2001; Riccardi et al., 1985). Electroencephalography (EEG) results and event-related potentials (ERP) during attention and memory tasks in survivors of childhood cancer suggest that cognitive deficits in this population are associated with prolonged information processing time, use of ineffective cognitive strategies, or both (Lahteenmaki et al., 1999, 2001; Moore et al., 1992b). These findings establish associations between cognitive impairments and the presence of imaging abnormalities. However, no relation between the location of

* Corresponding author. Department of Radiological Sciences, Mail Stop 212, St. Jude Children's Research Hospital, 332 North Lauderdale, Memphis, TN 38105. Fax: +1 901 495 4398.
E-mail address: robert.ogg@stjude.org (R.J. Ogg).
Available online on ScienceDirect (www.sciencedirect.com.)

1053-8119/$ - see front matter © 2004 Elsevier Inc. All rights reserved.
doi:10.1016/j.neuroimage.2004.08.030

imaging abnormalities in important functional areas of the brain and specific deficits has been recognized. The functional neural correlates (Coull, 1998) of cognitive deficits in this population are largely unknown.

Functional magnetic resonance imaging (fMRI) has emerged recently as an important tool for investigation of brain function in health and disease (Matthews, 2001) and as the preferred method to study development of brain function (Gaillard et al., 2000, 2001; Poldrack et al., 2002; Thomas and Casey, 1999). This noninvasive functional imaging technology may be useful to identify neural correlates of cognitive deficits in survivors of childhood cancer; fMRI also may be helpful in evaluating behavioral and pharmacological interventions (Butler and Copeland, 2002; Thompson et al., 2001) for cognitive deficits in the survivors. Ultimately, fMRI may play a role in refining cancer treatment protocols to minimize the damage to important functional brain areas.

In fMRI neuronal activity is measured indirectly through metabolic and hemodynamic responses that are coupled to changes in neuronal activity in the brain. The most commonly used method for functional brain imaging is blood oxygen level-dependent (BOLD) fMRI (Chen and Ogawa, 1999; Matthews, 2001). Disease- or treatment-induced changes in the coupling between neuronal activity and the hemodynamic response in childhood cancer survivors would affect the use of BOLD fMRI in investigating cognitive deficits in this group. It is well known that cranial RT has deleterious effects on cerebral vasculature (Burger and Boyko, 1991; Lacey, 1984). Radiation-induced vasculopathy includes fibrous wall thickening, thrombosis, luminal occlusion, and the loss of connective tissue. These histopathological changes occur more often in small cerebral arteries than larger ones (Butler et al., 1994; Laitt et al., 1995; O'Connor and Mayberg, 2000; Ozus et al., 2001; Paakko et al., 1994). Brain tumor survivors are more likely to have cerebral vasculopathy than are ALL survivors because of the higher dose cranial RT during treatment. It is unknown whether these vascular changes may alter the neurovascular coupling mechanism and in turn affect detection of brain activation via the BOLD signal in this group. To establish the feasibility of using BOLD fMRI to study cognitive deficits in survivors of childhood cancer, we used this method to test the hypothesis that long-term survivors of childhood ALL or brain tumor have the same BOLD response to visual stimulation as healthy subjects.

Materials and methods

Subjects

The study population included nine female and seven male survivors of childhood cancer, six female and five male healthy siblings of survivors, and eight female and eight male healthy adults. The patient group consisted of eight survivors of ALL and eight survivors of brain tumors [medulloblastoma (n = 3) ependymoma (n = 2), optic glioma, oligodendroglioma, and astrocytoma (n = 1 each)]. Demographic and medical data for the cancer survivors are summarized in Table 1. All patients received chemotherapy, radiation therapy, or both, directed at the

Table 1
Demographic, medical, and brain activation data for childhood cancer survivors

DX	Brain tumor location	Cranial RT (cGy)[a]	Chemotherapy	Vision	Age at DX	Years since treatment	Age at fMRI	Peak BOLD (%)	Brain activation (voxels)
ALL	–	–	Yes	Normal	2.9	9.1	14.4	3.8	55
ALL	–	–	Yes	Normal	3.2	6.5	11.7	4.9	447
ALL	–	–	Yes	Normal	5.4	6	13.4	3.5	108
ALL	–	–	Yes	Normal	2	5.5	9.8	3.1	20
ALL	–	–	Yes	Normal	7.1	1.7	11.3	3.6	96
ALL	–	–	Yes	Normal	9.3	3.3	13.5	2.5	60 (frontal lobe activation)
ALL	–	1800	Yes	Normal	4.3	8.4	15	4.3	230
ALL	–	1800	Yes	Normal	3.9	2.7	9.1	0.8	21
Glioma	L. optic nerve	–	Yes	Reduced (20/40) inferior field defect	3	5.5	10.4	2.7	77
Glioma	L. temporal	–	–	Normal	7.3	5.4	14.7	4.2	83
Astrocytoma	Optic pathway at L. temporal	5940	–	Normal vision, but R. homonymous hemianopsia	7.2	6.9	14.5	5	55 (no activation on left)
Ependymoma	Posterior fossa	6960	–	Normal vision with exotropia	7.9	8.6	16.9	3.5	16
Ependymoma[b]	Posterior fossa	5580	–	Normal vision with mild optic atrophy	10.4	4.7	15.6		no activation
Medulloblastoma	Posterior fossa	5320	Yes	Normal vision with nystagmus	8.2	5.4	14.7	4.8	28
Medulloblastoma	Posterior fossa	5580	Yes	Normal	10.9	3.8	15.1	3.1	16
Medulloblastoma	Posterior fossa	5580	Yes	Normal	7.3	2.7	10.5	2.3	30

[a] Primary site irradiation dosage for brain tumor patient.
[b] This patient had low Hgb level (8.5 g/dL). Others: 13 had normal Hgb level (12–16 g/dL) and 2 had no data available at the time of fMRI.