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Increased frontal functional networks in adult survivors of childhood brain tumors

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ABSTRACT

Childhood brain tumors and associated treatment have been shown to affect brain development and cognitive outcomes. Understanding the functional connectivity of brain many years after diagnosis and treatment may inform the development of interventions to improve the long-term outcomes of adult survivors of childhood brain tumors. This work investigated the frontal region functional connectivity of 16 adult survivors of childhood cerebellar tumors after an average of 14.9 years from diagnosis and 16 demographically-matched controls using resting state functional MRI (rs-fMRI). Independent component analysis (ICA) was applied to identify the resting state activity from rs-fMRI data and to select the specific regions associated with executive functions, followed by the secondary analysis of the functional networks connecting these regions. It was found that survivors exhibited differences in the functional connectivity in executive control network (ECN), default mode network (DMN) and salience network (SN) compared to demographically-matched controls. More specifically, the number of functional connectivity observed in the survivors is higher than that in the controls, and with increased strength, or stronger correlation coefficient between paired seeds, in survivors compared to the controls. Observed hyperconnectivity in the selected frontal functional network thus is consistent with findings in patients with other neurological injuries and diseases.

1. Introduction

Advances in diagnosis and treatment have led to improved clinical outcomes of pediatric brain tumor patients. The 5-year survival rate of these patients has increased from 55% in the 1970s to over 70% in more recent cohorts (Armstrong et al., 2009; Gurney et al., 2003; Ostrom et al., 2015). With improved treatment and longer survival, adult survivors of pediatric brain tumors are more than likely to experience adverse health and disrupted cognitive functions that may impact quality of life and cause social-economic difficulties (Gurney et al., 2009; Kirchhoff et al., 2011; Robinson et al., 2013). Currently, the specific neural and functional substrates associated with childhood brain tumor and its treatment are not well understood. Recently, we demonstrated that adult survivors of childhood brain tumors indeed exhibit altered brain activation during a working memory executive function task in a functional magnetic resonance imaging (fMRI) study (King et al., 2015a) and also reduced white matter integrity in the regions associated with intelligence in a diffusion tensor imaging (DTI) study (King et al., 2015b). These findings suggest the critical need for additional examination of the interruption or reorganization of connectivity among the regions involving the specific cognitive functions. Improved understanding of the functional and structural changes in adult survivors of childhood brain tumors may lead to new interventions helping to reduce the challenges survivors experience and improve their quality of life.

In the past several years, resting-state fMRI (rs-fMRI) has been increasingly used for mapping the functional connectivity of different brain regions. This non-invasive imaging technique offers unbiased analysis of the region to region interactions and connections at the functional level based on the rudimentary and intrinsic activity of the resting brain (Fox and Raichle, 2007; Friston, 2011). It has been widely applied to investigate the complex functional networks and changes during brain development and aging (Qi et al., 2014; Zhou et al., 2014) as well as alterations caused by diseases (van den Heuvel and Hulshoff Pol, 2010). Despite a rapidly expanding body of literature studying normal and disease affected brains through mapping functional connectivity with rs-fMRI, we still lack a clear understanding of the influence of

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posterior fossa or cerebellar brain tumors on the cortical functional networks of adult survivors of childhood brain tumors.

In the present study, we hypothesize that functional and structural abnormalities observed in our early studies may lead to the disrupted or altered functional connectivity in the adult survivors of childhood brain tumors which can be examined by rs-fMRI. With the cohorts of adult survivors of childhood brain tumors and the demographically matched healthy controls who were included in our previous studies, we examined the triple unifying networks proposed by Menon and Uddin (2010). These three intrinsic connected networks are particularly important for understanding the brain connectivity at rest. This unifying networks include the executive control network (ECN), a frontoparietal cognitive system that controls and manages executive functions, such as working memory, and other cognitively demanding tasks that involve reasoning, planning and problem solving (Alvarez and Emory, 2006); default mode network (DMN), a set of brain regions that typically exhibit activations when an individual is in the state of wakeful rest (Broyd et al., 2009; Whitfield-Gabrieli and Ford, 2012) and is typically deactivated during most cognitive tasks, and is among the most commonly studied of the rs-fMRI analysis of connectivity networks; and salience network (SN), is the cingulate-frontal operculum system responsible for detecting and integrating "interoceptive, autonomic, and emotional" information (Menon and Uddin, 2010) and the coordination of behavioral responses (Medford and Critchley, 2010). These three RSNs have been shown to work synergistically in brain activations (Alexopoulos et al., 2012; Ham et al., 2013; Hellyer et al., 2014; Luo et al., 2014; Manoliu et al., 2014). Using the independent component analysis (ICA), a model-free approach for fMRI signal time course analysis, to identify and select the frontal regions that showed correlations in rs-fMRI data, functional connectivity analysis then revealed altered frontal functional networks, specifically increased functional connectivity, in adult survivors of pediatric brain tumors compared to the controls.

2. Materials and methods

2.1. Participants

The study was approved by the Georgia State University and Emory University Institutional Review Boards. Sixteen adult survivors of childhood brain tumors (10 females, age range: 17–34 years, mean age: 22.5, standard deviation: 5.2) participated in this study. All survivors were diagnosed and had been treated for pediatric cerebellar brain tumors on average 14.9 years prior to the exam (SD = 7.3), and on average at the age of 7.6 years (SD = 5.1). All participants were at least 7 years past their most recent diagnosis and treatment. They were recruited from a cohort of individuals who participated in an initial longitudinal childhood brain tumor study and later in the neuroimaging study (King et al., 2015a, 2015b). Written consent was obtained from all adult participants, while the parental written consent and participant assent were obtained from two individuals who were 17 years old. Information on the diagnosis of brain tumors and treatments was obtained from a retrospective review of the available medical records. None of the survivors included in this study was found to have a history of tumor progression or recurrence, neurofibromatosis or other significant neurological insult (e.g. stroke, traumatic brain injury or seizure). There is no indication of pervasive developmental disorders in these participants.

For comparison, sixteen healthy volunteers (10 females, age range: 18–34 years, mean age: 22.7, standard deviation: 4.1) were recruited as controls. The statistical analysis showed that the survivor and control subjects were matched in age ($p = 0.8816$, two sample two-tailed t-test) and gender ($p = 1$, chi-square test) with no statistically significant difference. Control participants were screened for current and history of neurological or developmental conditions and psychopathology based on the Structured Clinical Interview for DSM-IV-TR Axis 1 (First et al., 1997) to ensure that these individuals represented a healthy comparison group.

2.2. Resting state fMRI

MRI data were collected using a 3T Siemens Trio Tim MRI scanner with a 12-channel head coil. Participants were placed in the scanner in the supine position. Cushions and forehead straps were used to immobilize the head to minimize movement.

A routine clinical neuroimaging protocol, including diffusion weighted imaging, T_1-weighted spin echo and T_2-weighted FLAIR imaging was applied for each participant to ensure that there were no abnormal neuroradiology indications. In addition, T_1-weighted sagittal anatomic images with an isotropic resolution were acquired using a three-dimensional magnetization prepared rapid gradient echo (MP-RAGE) sequence with repetition time (TR) = 2250 ms, echo time (TE) = 3.98 ms, inversion time (TI) = 850 ms, flip angle (FA) = 9 degrees, matrix = 256 × 256, field of view (FOV) = 25.6 × 25.6 cm^2, slice thickness = 1.0 mm, no slice gap. Typically, a total of 176 slices were used to cover the whole brain.

During rs-fMRI data acquisition, participants were instructed to rest with their eyes open and looking at the crosshairs and keep their heads still during MRI scans. Blood oxygenation level-dependent (BOLD) image series were collected using a gradient-recalled T_2*-weighted echo-planar-imaging (EPI) sequence. The imaging parameters included: field of view of 240 mm, 40 slices, 3-mm slice thickness and no slice gap, TR = 2130 ms, TE = 30 ms, FA = 90 degrees giving a nominal resolution = 3 × 3 × 3 mm^3. The scan time of each rs-fMRI was 275 s, with a total of 129 volumes recorded.

2.3. Image processing and analysis

2.3.1. Data preprocessing

All rs-fMRI data were preprocessed using the software of Data Processing Assistant for Resting-State fMRI (DPARSF, http://www.restfmri.net/forum/DPARSF) (Chao-Gan and Yu-Feng, 2010) based on Statistical Parametric Mapping (SPM8, http://www.fil.ion.ucl.ac.uk/spm) and Resting-state fMRI Data Analysis Toolkit (REST, http://www.restfmri.net) (Song et al., 2011). All time course data were first evaluated for movement distortion and motion artifacts. The time course data were not included in the analysis if they exhibited displacement greater than 1.5 mm or rotation larger than 1.5° (Luo et al., 2014; Luo et al., 2012; Lou et al., 2014). There was no group difference in frame-wise head displacement after discarding data. In addition, the first 10 volumes of each time series of echo-planar images were discarded to minimize the effect of the un-equilibrium of tissue magnetization that may affect the BOLD signal (Burton et al., 2014; Liao et al., 2011). Thus, the remaining 119 time points of each time course image series were used for analysis. The selected time course images were subsequently corrected for slice timing and realigned to the image of the first time point for the correction of the rigid-body head movement. A band filter (0.01–0.08 Hz) installed in the "Functional Connectivity Toolkit" in the REST software was also applied to remove the low-frequency physiological noise. The time course images (3 × 3 × 3 mm^3) were then spatially normalized into the standard Montreal Neurological Institute (MNI) space, and smoothed using an isotropic Gaussian filter with full width at half maximum (FWHM) of 6 × 6 × 6 mm^3.

2.3.2. Independent component analysis (ICA) and component identification

Independent component analysis is well documented and applied in many statistical analyses literatures and research, although it has been increasingly applied to analyze imaging data in recent years. In contrast to traditional model-based fMRI data analysis, ICA offers a model-free, probability driven pattern or feature recognition approach. In our early study, we showed that using this model free approach is critical to capture the activation pattern or signal time course characteristics