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Task-Positive and Default Mode Network Components and Their Relation to Attention and Working Memory in Adult Survivors of Childhood Brain Tumors

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TASK-POSITIVE AND DEFAULT MODE NETWORK COMPONENTS AND THEIR RELATION TO ATTENTION AND WORKING MEMORY IN ADULT SURVIVORS OF CHILDHOOD BRAIN TUMORS

by

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Under the Direction of Tricia King, PhD

ABSTRACT

Assessments of functional connectivity of resting state and task-based networks using independent component analysis (ICA) in this population may help describe long-term effects of childhood brain tumors and adjuvant treatments in hopes of identifying potential neuronal markers that may aid in prognosis and inform innovative interventions to optimize outcomes. The present study used ICA to evaluate presence and strength of functional connectivity networks in 23 adult survivors of childhood posterior fossa tumors (9 low grade, 14 high grade) at least 5 years past diagnosis compared to 40 age- and sex-matched healthy peers. Across groups, functional connectivity networks and their task-related engagement during attention and

working memory tasks were assessed, and relationships between task-based connectivity and cognitive task performance were evaluated. Resting state functionally connected networks were also extracted and evaluated for any group differences in recruitment patterns. High grade tumor survivors performed more poorly than their low grade tumor survivor or healthy peers on most attention and working memory measures. Task-based components demonstrated general trends in which default mode network (DMN) component recruitment decreased in task-relatedness with higher task load while cognitive network component recruitment increased. Low grade survivors showed distinct patterns in DMN component recruitment, and high grade survivors demonstrated limited recruitment of an executive control network component at higher task loads. Correlations between task relatedness and task performance did not survive correction but demonstrated different trends of interest across groups. Resting state components emerged with some overlap with task components, but group differences were not observed. Results reflect differences in functional network recruitment across long-term survivors of high grade and low grade brain tumors such that low grade tumor survivors may demonstrate more compensatory functions, while high grade tumor survivors may develop some compensatory functions alongside recruitment of other networks that do not improve performance. Findings also indicate the importance of cognitive intervention in both survivor groups and the necessity to track low grade tumor survivors despite their cognitive abilities often resembling that of their healthy peers.

INDEX WORDS: Brain tumor, Functional neuroimaging, Functional connectivity, Attention, Working memory, Cognitive outcomes

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1 INTRODUCTION

1.1 Brain Tumor Survivorship and Cognitive Outcomes

With an incidence rate of 5.81 per 100,000 individuals between the ages 0 and 19 years, brain and central nervous system (CNS) tumors affect children and adolescents at a rate greater than any other common cancer, and over half of brain and CNS tumors in this population are malignant (Ostrom et al., 2017). Innovations in diagnostics and treatment have led to significant improvements in rate and length of survival (Ostrom et al., 2016), but many survivors suffer from long-term sequelae across domains. These deficits include impairments in cognitive domains such as memory and attention (Conklin et al., 2012; Dennis et al., 1998; Jayakar et al., 2015; Riggs et al., 2014; Robinson et al., 2010; Wolfe et al., 2012), more complex cognitive abilities such as executive functioning (Lassaletta et al., 2015; Netson et al., 2016; Wolfe et al., 2012), elements of daily living such as academics and social functioning (Lannering et al., 1990; Moyer et al., 2012; Poggi et al., 2005; Zebrack et al., 2002), and general physical and emotional health (Hobbie et al., 2016). Much work in this area has also specifically focused on brain tumors of the posterior fossa, given that of the brain and CNS tumor diagnoses in children 0-19 years old, 11% of tumors are found in the brain stem and 13% are found in the cerebellum (Ostrom et al., 2017). These can include both higher and lower grade tumor types requiring different treatment regimens.

Posterior fossa tumor survivors display a range of cognitive outcomes in the years following their diagnoses and treatments. Those with higher grade tumors such as medulloblastoma that involve more adjuvant treatment consistently demonstrate greater impairment (Hanzlik et al., 2015; Wolfe et al., 2012), with areas of weakness including attention, executive functioning, processing speed, and memory. Fewer studies track low grade posterior

fossa tumor survivors over the long term, and while some indicate functioning similar to their healthy peers (Hanzlik et al., 2015; Mabbott et al., 2008), others find mild cognitive discrepancies within domains like attention and processing speed (Aarsen et al., 2009). With today's increased likelihood of and length of survival following brain tumors of all grades, it is imperative that research continue to investigate the long-term outcomes and their neurological bases in this vulnerable and growing population.

1.2 Structural Effects of Brain Tumors

Both before and after resection and regardless of adjuvant treatment, brain tumors will impact the structure of the brain (Ailion et al., 2017). Specifically, damage may be observed at the site of the tumor itself, around the area impacted by neurosurgery and shunting, and across the brain as a result of mass effect, shifting of the brain within the skull due to pressure from the tumor (Baris et al., 2016). Hydrocephalus, fluid buildup in the ventricles of the brain, is a common consequence as well (Krishnamurthy & Li, 2014). Atypical gray matter development has also been observed in long-term adult survivors of low grade juvenile pilocytic astrocytoma (JPA) cerebellar tumors, and researchers posit that gray matter changes in brain tumor survivors without adjuvant therapy may be partially driven by the presence of hydrocephalus (Moberget et al., 2015).

Adjuvant treatments such as chemotherapy and RT commonly result in further structural brain changes; chemotherapy administered to patients with tumors of various types and locations has been found to alter gray and white matter volumes, likely as a result of cytokines' interaction with the blood-brain barrier (Matsos et al., 2017; Ren et al., 2017; Simo et al., 2013). Results of studies examining gray matter changes following RT tend to vary; total gray matter rarely differs between brain tumor survivors treated with RT and healthy controls, but hippocampal volume

consistently emerges as lower in survivors (Jayakar et al., 2015; Nieman et al., 2015; Riggs et al., 2014). Following pediatric RT, one study observed a 3% hippocampal volume decrease relative to controls for each year of life after treatment (Nieman et al., 2015).

Adjuvant treatment also more consistently disrupts white matter throughout the brains of survivors of malignant brain tumors. Reduced white matter volume is frequently observed within survivors regardless of whether their tumors occurred in childhood or adulthood (Aukema et al., 2009; Mabbott et al., 2006; Riggs et al., 2014), and RT administered at a younger age is associated with reduced white matter volume (Connor et al., 2016; Reddick et al., 2005; Reddick et al., 2014). White matter reductions are noted across the frontal lobe, cerebellar hemispheres, and brainstem in these survivors (Khong et al., 2003; Mulhern et al., 2004a; Qiu et al., 2007), and white matter integrity of tracts such as the corpus callosum and uncinate fasciculus are diminished relative to those of healthy controls (Aukema et al., 2009; King et al., 2015b; Mabbott et al., 2005; Palmer et al., 2012; Riggs et al., 2014; Rueckriegel et al., 2010). Changes in white matter following chemotherapy and RT for brain tumors have been shown to correlate with cognitive deficits including attention, working memory, and processing speed regardless of tumor location (King et al., 2017; Mulhern et al., 2004a). Correlations between white matter changes and both executive function and processing speed have been observed in samples of survivors of posterior fossa region tumors treated with RT (Palmer et al., 2012; Wolfe et al., 2012).

Changes to white matter tracts following a tumor and surgery alone can include thinning, interruptions in tracts, and reductions in tract size (Lazar et al., 2005). White matter integrity is generally lower in brain tumor survivors than their healthy peers, especially when the survivors undergo radiation therapy (RT; Moberget et al., 2015; Rueckriegel et al., 2015), and such

differences have also been found to correlate with measures of intelligence (King et al., 2015a). Survivors of childhood brain tumors of the posterior fossa specifically experience lower white matter integrity of the right cerebellar-left frontal pathway (Ailion et al., 2017; Rueckriegel et al., 2015), and an investigation that used a sample with which the present study overlaps found that different segments of this pathway correlated with decreased gray matter volumes depending on whether survivors' included RT (Ailion et al., 2019). Integrity of this white matter pathway has also been shown to be related to working memory in child survivors of high grade medulloblastoma (Law et al., 2015b), which aligns with data on verbal working memory in adults with cerebellar damage suggesting that the cerebellum and left cerebello-thalamic-cerebral pathway supports initial phonological encoding (Ravizza et al., 2006). White matter integrity of the right cerebellar-left frontal pathway has also been found to be correlated specifically with auditory attention but not visual scanning in group of high and low grade posterior fossa tumor survivors (Ailion et al., in press), further implying the need for assessment of simultaneous neurological and cognitive functioning in this population.

Recent work in graph theory has also demonstrated structural differences in brain tumor survivors such as decreased network segregation and higher network integration (Aerts et al., 2016). Global efficiency is generally found to be higher in post-treatment brain tumor patients compared to pre-treatment patients or healthy controls (Bahrami et al., 2017; Huang et al., 2014). Global efficiency has also been demonstrated to mediate differences in cognitive flexibility between pediatric brain tumor survivors and healthy peers (Na et al., 2018).

1.3 Functional Effects of Brain Tumors

Functional neuroimaging also provides a window through which effects of brain tumors can be observed. Functional magnetic resonance imaging (fMRI) evaluating blood oxygen level-

dependent (BOLD) percent signal change has revealed differences between healthy controls and adult patients with brain tumors, both pre-surgically and years past diagnosis and treatment (Petrella et al., 2006). One well-established task, the letter n-back, is frequently used within fMRI paradigms as a measure of attention and working memory across populations. Within brain tumor survivors, performance on the task is often impaired compared to healthy controls, and patterns of BOLD signal vary. One study identified a significantly elevated BOLD response in the left superior frontal gyrus and left superior parietal lobe during working memory (2-back) trials compared to attention (0-back) trials in posterior fossa tumor survivors compared to controls (King et al., 2015b), while another identified elevated BOLD response in the left anterior cingulate in survivors whose tumor locations varied (Robinson et al., 2014). The latter study also observed less BOLD signal in survivors in bilateral frontal regions during the attention trials of the n-back. The general dearth of fMRI literature in this population of long-term brain tumor survivors limits the conclusions that may be drawn; however, the suggestion that survivors demonstrate increased neural activity across the brain compared to healthy peers aligns with theories from the traumatic brain injury (TBI) literature. Specifically, these findings support a latent resource hypothesis (Hillary, 2008; Hillary et al., 2015) wherein brain regions are recruited in the context high-effort scenarios when optimal pathways are limited or impacted by some sort of trauma (see Figure 1), a pattern that is commonly observed with the prefrontal cortex (PFC). However, instead of serving a compensatory function, TBI literature indicates that recruitment of these latent resources may not enhance task performance (Medaglia et al., 2012).

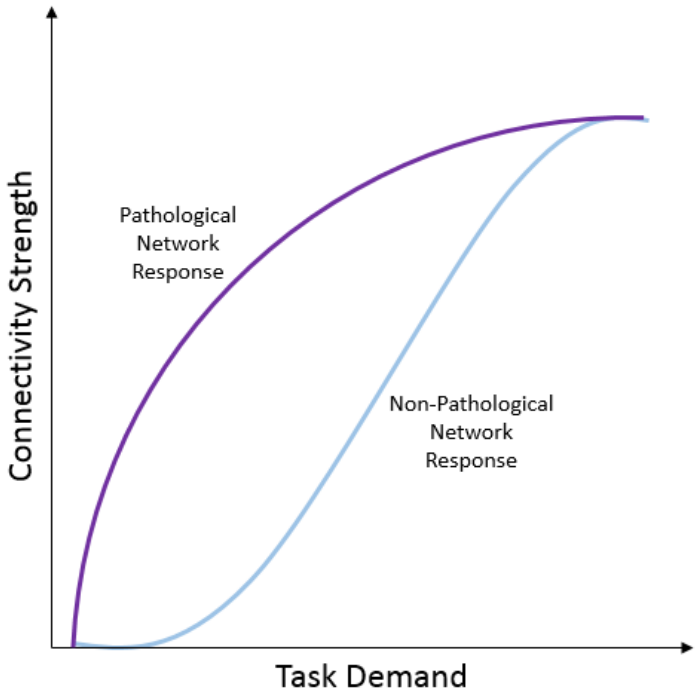

Figure 1. Hypothesized connectivity changes in neurological and non-neurological populations.

1.4 Functional Connectivity across Populations

Beyond using contrasts of BOLD activity in the brain during different tasks, functional connectivity, a measure of the presence and strength of neural networks (Broyd et al., 2009), is also now employed to examine clinical populations and further understand neurological differences. Functional connectivity is defined here as the measurement of how regions of the brain co-activate over a given time frame, either in a resting state or during a task (Biswal et al., 1997). Commonly co-activated regions are understood to form networks, and proper function of a network is believed to represent optimal architecture for exchange of information across the brain (Stam, 2014). Patterns of functional connectivity in various networks have been shown to relate to cognitive task ability and predict task-response properties of brain regions (Fox & Greicius, 2010). Changes in connectivity are observed throughout childhood and across the lifespan (Betzel et al., 2014).

A number of functionally connected networks are routinely observed across studies of healthy adults. The default mode network (DMN) was observed early on in functional connectivity research and is commonly studied today (Fox et al., 2005; Raichle, 2015). In healthy populations, this network is normally active during a resting wakeful state and is thought to be involved in self-referential processing, mind-wandering, and other behaviors unrelated to tending to tasks (Gusnard et al., 2001). Task-based analyses, on the other hand, have identified a set of task-positive networks including the salience network (SN) and executive control network (ECN) (Di & Biswal, 2014; Richiardi et al., 2015; Shirer et al., 2012). Some studies indicate that these networks' functional connectivity may be observed in the absence of a task as well (Damoiseaux & Grecius, 2009; Fox & Raichle, 2007; van den Heuvel & Hulshoff Pol, 2010). Other networks, such as the auditory (AN), visual (VN), language (LN), and sensorimotor networks (SMN), are also understood to be functionally connected during rest and tasks (Hart et al., 2016; Richiardi et al,. 2015; Shirer et al., 2012).

DMN activity and connectivity are often found to negatively correlate with task difficulty during a scan (i.e., greater DMN deactivation is observed at higher task levels; Anticevic et al., 2012; Ceko et al., 2015), whereas many task-positive networks are recruited more heavily as tasks become more challenging (Liang et al., 2016). Some researchers propose theories of competition of resources between the DMN and task-positive networks (Anticevic et al., 2012; Zhou et al, 2007). Methodology such as functional network connectivity (FNC) allows for exploration of the correlational relationships between independent network components (Allen et al., 2011; Jafri et al., 2008). Though sometimes weaker than intranetwork connectivity (Arbabshirani et al., 2013), it can be a useful tool for describing the interplay across components

with similar or differing functions in both healthy controls and clinical populations (Brody et al,. 2009; Jafri et al., 2008).

Standard patterns of functional connectivity are often disrupted in individuals with neurological or psychological disorders, and these changes frequently correlate with and may underlie functional impairments. For example, reduced functional strength in the DMN is observed in autism spectrum disorders, and persistent DMN functional connectivity has been observed in disorders related to attention deficits such as attention-deficit/hyperactivity disorder (ADHD) and schizophrenia during goal-directed activity, a time when it is decreased in healthy individuals (Broyd et al., 2009; Rubia, 2018; Sidlauskaite et al., 2016). Neurological insult such as TBI has also been shown to result in altered connectivity patterns compared to healthy controls (Nathan et al., 2015, Shumskaya et al., 2012), and chronic pain patients do not deactivate the DMN with increased task difficulty as effectively as healthy controls (Ceko et al., 2015). Patterns of alterations vary widely and may include decreased or increased connectivity within a network and/or topographical changes, i.e., physical shifts in location of network regions due to a lesion, and these will vary depending on the tools used for analysis (Fox & King, 2018). Additionally, some clinical populations demonstrate abnormal patterns such as stronger functional connectivity between different networks than within a network, which is theorized to be a biomarker for disease (Broyd et al., 2009). Furthermore, abnormal DMN connectivity has been established as a possible precursor to cognitive or behavioral changes in Alzheimer's disease that may precede amyloid deposition (Krajcovicova et al., 2014; Sheline et al., 2010).

Hyperconnectivity is an abnormality commonly observed in clinical populations. In particular, it is often observed following brain injury, with most research thus far focusing on

changes to DMN connectivity (Sharp et al., 2014). In the case of task-based connectivity, hyperconnectivity may be framed similarly to that of hyperactivity observed in TBI in that this pattern of increased connectivity is activation of a latent resource that is not necessarily functioning in a compensatory manner (Hillary et al., 2014). Resting state results are mixed; increased connectivity of the DMN and sensorimotor networks during rest has been shown to be correlated with increased performance on cognitive tasks in TBI patients (Shumskaya et al., 2017), and stroke patients who demonstrated greater network modularity in resting state networks following therapy performed better on a language task, though no control group was assessed to determine whether this reflected hyperconnectedness (Duncan & Small, 2016). However, multiple sclerosis patients demonstrated greater modularity than healthy controls during resting state, and the patients' increased modularity was related to poorer performance on a divided attention task (Gamboa et al., 2014). It must be noted that any relationship between resting state connectivity and performance involves assessing abilities outside of the scanner, but variable findings suggest the need for further investigation across clinical groups.

1.5 Functional Connectivity in Brain Tumor Populations

Similar to other clinical groups, adult brain tumor patients and survivors demonstrate significant functional connectivity disruption (Fox & King, 2018). Within this population, functional connectivity analyses have primarily been used in presurgical contexts, and networks such as the DMN and SMN commonly show decreased patterns of functional connectivity during times of expected intranetwork connectivity in this literature (Bottger et al., 2011; Ghumman et al., 2016; Harris et al., 2014; Maesawa et al., 2015; Mallela et al., 2016; Zhang et al., 2016). Individuals with higher grade tumors also generally present with decreased connectivity strength compared to those with lower grade tumors around the time of diagnosis

and treatment (Harris et al., 2014; Mallela et al., 2017; Zhang et al., 2016). Regarding effects of brain tumors over time, rare post-treatment assessments tend to capture an immediate decrease but later relative increase or recovery of functional connectivity strength in adult patients between 72 hours and 3 months after neurosurgery (Hart et al., 2015; Vassal et al., 2017). One study (Otten et al., 2012) followed up with some patients three to five months after neurosurgery and found that the single brain tumor patient who had experienced motor weakness that subsided also demonstrated a reconstitution of the SMN, and the patient who demonstrated a partial recovery of motor function also demonstrated a partial recovery of SMN connectivity to pre-operative levels. Thus, it appears that there is some degree of immediate change to functional connectivity following resection, particularly when the tumor is clearly within the network being assessed, but months of recovery may lead to return to pre-treatment levels of connectivity and correlated abilities in some cases.

A study of long-term survivors of high- and low-grade childhood posterior fossa tumors over 7 years past diagnosis observed greater DMN, ECN, and SN functional connectivity strength in brain tumor survivor participants than healthy controls during rest, indicating a potential continued pattern of functional connectivity increase following recovery (Chen et al., 2016). The utility of this relative hyperconnectivity, particularly during a resting state scan, remains uncertain, but authors posit that the survivor brain may be utilizing an "all hands on deck approach," even when at rest (Chen et al., 2016; Hillary et al., 2015).

In a task-based functional connectivity study of posterior fossa tumor survivors, long-term survivors of low grade tumors who did not undergo any adjuvant therapy demonstrated incomplete DMN deactivation (i.e., more unexpected activation during a task) as well as weaker task modulation of the left ECN and anterior SN in survivors compared to controls (Reichert et

al., 2017). Although these participants showed no difference in performance on the tasks where this was observed, authors indicate that there may have been ceiling effects due to the ease of the tasks. It is therefore still possible that a lack of DMN deactivation during tasks impedes performance. Weaker task modulation across more "task positive" networks in survivors suggested potential deficits in normal recruitment of these networks, but their lack of correlation with task performance led authors to speculate about effects of structural change or possible resting state hyperconnectivity as was observed by Chen and colleagues (2016). This study also discussed the presence of a "cerebellar network" that did not align with traditionally observed networks (Richiardi et al., 2015; Shirer et al., 2012).

The differences in participants between the two studies of long-term survivors is noteworthy, and one must consider effects of radiation and chemotherapy as well as the grade and growth pattern of the tumor itself. It will be necessary for future studies to consider this while investigating functional connectivity during both task and resting state scans and employing well-normed tasks with sufficient variability.

1.6 Specific Aims and Hypotheses

Given these trends in cognitive and neurological changes in brain tumor survivors as well as the lingering gaps in the literature, the present study aimed to investigate long-term outcomes in survivors of childhood posterior fossa brain tumors of both low and high grades compared to age- and sex-matched healthy peers. Using functional connectivity data alongside data from performance on cognitive tasks and informant reports of daily functioning, we aimed to better describe long-term effects of brain tumors and treatment in hopes of identifying potential neuronal markers that may inform prognosis and making recommendations regarding rehabilitative intervention.

Specifically, we aimed to identify functional connectivity networks that were present among adult survivors of childhood brain tumors and age-matched healthy controls via independent component analysis (ICA). Two primary aims focused on functionally connected independent components (ICs) that emerged during a letter n-back task designed to evaluate attention (0-back, 1-back) and working memory (2-back, 3-back) abilities (Egli et al., 2018). Group ICA, a blind source separation technique, was used to identify components across all participants and all task levels and rest within a mask. Components were labeled based on spatial correlation with the individual networks established by the Stanford Functional Imaging in Neuropsychiatric Disorders (FIND) Lab (Richiardi et al., 2015; Shirer et al., 2012). ICA was used as opposed to a seed-based connectivity analysis in order to identify maximally independent networks throughout the brain without biasing results by selecting a seed region (Calhoun et al., 2003). This is valuable in the brain tumor population due to aforementioned structural changes that may result in impacts to regions of a given network. Aims 1 and 2 focused on task modulation of relevant components during different levels of the n-back task with hypotheses based on literature describing hyperactivity and hyperconnectivity in neurological populations. Aim 3 involved a more exploratory approach, identifying similarities between task-positive ICs present during the same participants' resting state scan and any anti-correlated ICs in order to better describe consistent or aberrant patterns of functional network activity in our sample.

1.6.1 Specific Aim 1

We aimed to evaluate how closely network functional connectivity is related to the task and probed for potential interactions or main effects of group and task load on network strength.

~~Hypothesis 1~~: DMN components were hypothesized to be identifiable during the task across all groups with an expected overall negative task-relatedness. During all task levels,

controls were expected to show relative disengagement, i.e., more negative task-relatedness of the DMN, i.e., survivors' DMN beta weights would be greater/less negative than controls', with a greater degree of this aberrant engagement observed in high grade tumor survivors than low grade tumor survivors. Following a pattern of disengagement with greater task difficulty, DMN connectivity was expected to be weaker in working memory tasks than attention tasks.

Hypothesis 2: Cognitive networks' [ECN, SN, LN, visuospatial network (VSN), higher visual network (HVN), basal ganglia network (BGN)] were hypothesized to be observed across groups during task conditions. Task-relatedness was predicted to be stronger during more complex working memory tasks than attention tasks, particularly in the executive control and salience networks following findings of Chen and colleagues (2016) in an overlapping sample and known patterns of hyperconnectivity in the prefrontal cortex in other populations. Following expectations of hyperactivity/hyperconnectivity, survivors were expected demonstrate greater recruitment (i.e., greater task-relatedness) of these networks during all tasks than controls, and greater task-relatedness in high grade tumor survivors than low grade tumor survivors is expected across the entire task.

Hypothesis 3: Sensory networks' [SMN, VN, AN] were predicted to be observed across groups during task conditions. Despite limited expected differences between task and the implicit crosshair baseline, some task-relatedness was expected to emerge given the requirements of button pressing (SMN) and silent reading of presented letters (VN, AN). Sensory network components were predicted to be similar between attention and working memory tasks. Survivors were expected to demonstrate greater recruitment of these networks compared to controls at all task levels. Analyses by tumor grade were broadly exploratory due to a dearth of literature comparing sensory networks' function between groups of high and low grade tumor

patients and survivors; however, rudimentary predictions were that sensory networks would follow the same pattern of hyperactivity/hyperconnectivity as cognitive networks wherein high grade tumor survivors would demonstrate the greatest task-relatedness of sensory ICs, followed by low grade tumor survivors, followed by controls.

1.6.2 Specific Aim 2

We aimed to evaluate relationships between functional network task-relatedness and cognitive performance in the interest of considering the latent resource hypothesis as an interpretation of the cognitive function of brain tumor survivors.

Hypothesis 1: Controls' performance across all cognitive tasks was expected to exceed survivors' performance across attention span, working memory, and fine motor tasks. When separated into high and low tumor grade groups, low grade tumor survivors were expected to perform better than high grade tumor survivors across all tasks. Literature suggested that low grade tumor survivors likely would not differ by overall IQ but might show relative weakness compared to controls across other cognitive tasks of attention and working memory.

Hypothesis 2: DMN IC task-relatedness during both the 0-back task and 2-back task was hypothesized negatively correlate with cognitive task performance, with the strongest negative correlations in the control group followed by the low grade tumor survivor group. Greater (i.e., less negative) DMN task-relatedness during tasks was expected to correlate with higher BRIEF Working Memory scores (i.e., greater impairment), with stronger correlations expected in survivors due to predicted lower variance in controls' BRIEF scores. No correlations were expected between DMN task-relatedness and Finger Tapping performance.

Hypothesis 3: In controls, cognitive networks' IC task-relatedness was expected to correlate with greater cognitive task performance and lower BRIEF scores. Across survivors,

cognitive network task-relatedness was expected to negatively correlate with cognitive task performance and higher BRIEF scores per the latent resource hypothesis, though stronger negative brain-behavior relationships were predicted between high grade tumor survivors than low grade tumor survivors. Differences in brain-behavior correlations as measured by Fisher z tests were therefore expected to be present between controls and survivors and between survivor groups. The strongest correlations in all directions were expected between 0-back task-relatedness and attention span measures (0-back d', DSF) and between 2-back network task-relatedness and working memory measures (2-back d', DSB). No correlations were expected between cognitive network task-relatedness and Finger Tapping performance.

Hypothesis 4: Sensory networks' task-relatedness was not expected to correlate with cognitive task performance or BRIEF scores in any group. SMN task-relatedness was expected to positively correlate with Finger Tapping scores in controls and negatively correlate with Finger Tapping scores in survivors, with a stronger negative relationship expected in high grade tumor survivors than low grade tumor survivors.

1.6.3 Specific Aim 3

In the interest of exploring the presence and interrelatedness of components during a resting state scan in the same sample, ICA was also run on participants' resting state data, and functional network connectivity (FNC) was assessed. Relationships between networks were compared among groups.

Hypothesis 1: Default mode network components, cognitive network components, and sensory components were expected to be observed during the resting state across participants. It was predicted that similar components would be observed during the resting state scan as the task scan. Given the results of a study with an overlapping sample (Chen et al., 2016), we

expected specifically to at least observe multiple default mode network components, multiple executive control network components, and a salience network component.

Hypothesis 2: Anti-correlations were predicted between default mode network components and task-positive cognitive components, while positive correlations were predicted among default mode network components and among task-positive cognitive components. It was predicted that all of these relationships would be strongest within the control group and a reflection of maximized neural efficiency, with similar but weaker patterns observed in the low grade followed by the high grade survivor groups.

2 METHODS

2.1 Participant Recruitment and Screening

The study was approved by the local institutional review board, and all participants provided informed consent. The participants included brain tumor survivors and healthy control groups. Survivor participants were recruited through a combination of referrals through Children's Healthcare of Atlanta and mailings sent to individuals who participated in a previous study as children. 676 adult survivors were sent mailings, and 88 letters were not delivered properly and returned. 127 responses were received. All participants included in the present study were at least 17 years old and at least 5 years past their initial diagnosis in order to evaluate effects of long-term survivorship in adult survivors of pediatric brain tumors. Only survivor participants with embryonal or astrocytic tumors of the posterior fossa region were included. Participants were excluded if they carried a diagnosis of pervasive developmental disorder or neurofibromatosis, resulting in 51 initially eligible participants, though 17 did not undergo a magnetic resonance imaging (MRI) scan due to lack of interest, metal in body, or other scanning

contraindications. Thirty-four survivors who met criteria and had no contraindications for MRI per a safety screener completed the neuropsychological testing battery and an MRI scan. One of these survivors was administered an abbreviated version of the MRI task due to difficulties learning the task and was therefore excluded. Ten individuals completed the full task, but their scans were not usable across the entire task due to technical issues, motion/artifact, or use of a different scanner. Thus, data from 23 survivor participants (9 low grade tumor survivors, 14 high grade tumor survivors) are included in the proposed study. The final ten excluded individuals did not differ significantly from the 23 included participants across any demographic, tumor, or treatment variables. Tumor and treatment variables of included survivor participants are presented in Table 1.

Table 1. Survivor participants' tumor and treatment variables.

	Survivors		*t*	X^2	*Fisher's Exact Value*
	Low Grade (N=9)	*High Grade (N=14)*			
Tumor Type (N)	Juvenile Pilocytic Astrocytoma=8 Fibrillary Astrocytoma=1	Medulloblastoma=12 Anaplastic Astrocytoma=1 PNET-NOS=1	-	23.00***	-
Age at Diagnosis (Years, M±SD)	10.44±5.22 Range: 3-18	7.79±5.00 Range: 1-17	1.22	-	-
Time since Diagnosis (Years, M±SD)	13.78±7.11 Range: 5.8-23.6	15.53±6.61 Range: 5.2-30.4	-0.60	-	-
Shunt Placement (N)	3	4	-	-	1.000
Radiation (N)	1	13	-	-	<.001
Focal Radiation Only (N)	1	1			
Craniospinal Irradiation with Boost to Site (N)	0	12	-	17.17***[t]	-
Chemotherapy (N)	0	13	-	19.22***	-
Hydrocephalus (N)	7	10	-	0.11	-
Presence of Seizures (N)	0	0	-	n/a	n/a
Presence of Hormone Deficiency (N)	1	13	-	-	<.001

Note: PNET=primitive neuroectodermal tumor; NOS=not otherwise specified
*p<0.05
**p<0.01
***p<0.001
[t]X^2 represents group differences in across type of radiation administered (none, focal, craniospinal with boost)

Healthy control participants were recruited through Georgia State University's Psychology Department research pool and fliers and advertisements posted throughout the Atlanta, Georgia community. Control participants had no reported history of neurological illness and were administered the Structured Clinical Interview for the DSM-IV, Second Edition (SCID-II; First, Spitzer, Gibbon, & Williams, 1997) to verify that they did not meet criteria for psychological or substance abuse disorders. This was done to ensure that the control sample was truly representative of a healthy population and that imaging results would not be influenced by neurological or psychological disorders. Control participants were also screened for MRI safety. The control sample for the proposed study was matched for mean age and male-to-female gender ratio with the survivor sample. Characteristics of the control and survivor samples are listed in Tables 2 and 3. To evaluate any demographic differences between survivors and controls, independent two-sample t-tests were run on continuous variables, and chi-square tests were run on discrete variables. Groups did not differ across demographic variables including years of education. Groups differed significantly by WASI FSIQ score such that, determined by Tukey's HSD post-hoc tests, controls did not significantly differ from low grade tumor survivors (p=0.185) but had significantly greater FSIQ scores than high grade tumor survivors (p<0.001), and low grade tumor survivors had greater FSIQ scores than high grade tumor survivors at trend level (p=0.060). Notably, both survivor groups' FSIQ means were within the average range.

Table 2. Continuous demographic variables by participant group.

	Controls (N=40)	Survivors (N=23)		*F*
		Low Grade (N=9)	*High Grade (N=14)*	
Age at Examination (M±SD)	23.04±4.59 Range: 18-41	24.22±4.52 Range: 17-30	23.29±6.17 Range: 17-35	0.21
Years of Education (M±SD)	14.75±1.74	14.78±2.68	13.50±2.79	1.86
WASI FSIQ (M±SD)	111.72±0.24	104.78±7.46	94.29±15.05	14.29***

Note: WASI=Wechsler Abbreviate Scales of Intelligence; FSIQ=full scale IQ.
*p<0.05
**p<0.01
***p<0.001

Table 3. Discrete demographic variables by participant group.

	Controls (N=40)	Survivors (N=23)		X^2
		Low Grade (N=9)	*High Grade (N=14)*	
Sex (N)	Males=14 Females=26	Males=3 Females=6	Males=5 Females=9	0.01
Race/Ethnicity (N)	Caucasian/White=20 African-American/Black=8 Hispanic/Latinx=3 Asian-American=2 Mixed/Multi-Racial=1 Other=1	Caucasian/White=8 Mixed/Multi-Racial=1	Caucasian/White=10 African-American/Black=1 Hispanic/Latinx=1 Asian-American=1 Mixed/Multi-Racial=1	9.18
Mother's Education (N)	Junior High Graduate=2 Partial High School=2 High School Graduate=11 Partial College=9 College Graduate=14 Graduate Degree=2	High School Graduate=3 College Graduate=2 Graduate Degree=3	High School Graduate=3 Partial College=2 College Graduate=5 Graduate Degree=3	11.30

*p<0.05
**p<0.01
***p<0.001

2.2 Data Collection

2.2.1 Neuroimaging Parameters

Imaging data was acquired using a 3T Siemens Trio MRI scanner at the GSU/GaTech Joint Center for Advanced Brain Imaging (CABI). A total of 645 volumes were collected over twenty minutes of the n-back task. Functional data consisted of gradient-recalled echo-planar-imaging sequence (EPI) sensitive to blood oxygenation level-dependent (BOLD) signals (echo time [TE]=30ms; repetition time [TR]=2130 ms; field of view [FOV]=240 mm and flip angle=90 degrees). The imaging sequence was acquired as 40 axial slices in interleaved ascending order, with 3.0x3.0x3.0 mm voxel dimensions. 3D T1-weighted images were used for anatomical registration (TR=2250 ms, TE=3.98 ms, flip angle=9 degrees, voxel=1.0x1.0x1.0 mm).

During resting state fMRI data acquisition, participants rested with their eyes open, viewing a crosshair. 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=3.0×3.0×3.0 mm^3. The scan time was 275 s, with a total of 129 volumes recorded.

2.2.2 Letter N-Back Task

All included participants completed a letter “n-back” task (King et al., 2015b), a well-established working memory task, in the MRI scanner. So that they became familiar with the task and had the opportunity to ask any questions, participants were first trained on an untimed,

paper version of the task, then a brief timed, computerized version of the task before entering the scanner for the formal task. In each 1-, 2-, and 3-back trial, participants were instructed to indicate whether a letter presented on the screen is the same as the one presented n letters ago. The 0-back trials ran such that a participant was first presented with a screen reading "Target = B," for example, so in the sequence "b, a, B, c, D," a participant would be expected to indicate "yes" with a button box when the B/b was presented, that is, on the first and third displays, and "no" on all others. Each participant completed five runs in the scanner task, which was set up as a block design such that each participant had the same counterbalanced, pseudo-random order of blocks. Each run was comprised of a fixation period and five blocks (a crosshair block and 0-, 1-, 2-, and 3-back blocks), each preceded by instructions informing the participant as to the type of block they were about to begin. Each block lasted approximately four minutes, making the entire task last approximately 20 minutes. Each n-back block was comprised of a 3000 ms instruction screen and fifteen letters presented for 500 ms each with an inter-stimulus interval of 2500 ms.

To assess accuracy, we used the d' index (Haatveit et al., 2010; Macmillan & Creelman, 1990) that includes evaluation of hits, misses, false alarms, and correct recognition of non-targets (i.e., pressing the "no" button at the appropriate time). In the present sample, d' values demonstrated a more normal distribution than percentage correct values, though 0-back d' values still showed significant negative skew. For the purposes of the present study, 0-back d' values were used as an operationalization of attention span and 2-back d' values were used an operationalization of working memory in the scanner.

2.2.3 Additional Neuropsychological Measures

2.2.3.1 Digit Span

All participants were administered the Digit Span subtest from the Wechsler Memory Scale, Third Edition (WMS-III; Wechsler, 1997a). Within the first component of the task, Digit Span Forward (DSF), the examiner orally presented number sequences that the participant was instructed to repeat verbatim. In Digit Span Backward (DSB), the examiner orally presented number sequences, but the participant was required to repeat the numbers in reverse order. DSF is thought to reflect an individuals' attention span, whereas DSB is believed to reflect working memory abilities given the need for maintenance and manipulation of the information presented (Lezak et al., 2012). Z-scores based on participant's longest span, i.e., how many total digits they could accurately recall on at least one of two trials of the same length, were generated based on WMS-III norms for DSF and DSB.

2.2.3.2 Behavior Rating Inventory of Executive Function (BRIEF)

All participants were administered the Behavior Rating Inventory of Executive Function (BRIEF; Gioia et al., 2000) self- and informant-report forms. Participants 18 years and older completed the Adult version, and an informant completed the Adult Informant form. Informants were participants' parents, friends, or roommates who had known the participant for at least 6 months. Participants who were 17 years old completed the Child version and a parent completed the Parent Informant form. Questions varied slightly between versions, but both contained a Working Memory subscale with similar content. Higher BRIEF scores indicate greater impairment, and $T \geq 65/z \geq 1.5$ indicates significant impairment. Only the Working Memory subscale of the BRIEF was utilized in the present study.

2.2.3.3 Finger Tapping Test

All participants were administered the Finger Tapping Test (Reitan & Wolfson, 1993), a task which measures finger tapping speed in an individual's dominant and non-dominant hand averaged over at least five trials. Dominant hand finger tapping z-scores based on age- and sex-based norms will be included in this study as a measure of discriminant validity, as performance is not expected to correlate with functional connectivity strength of DMN or cognitive networks.

2.3 Data Analysis

2.3.1 MRI Preprocessing

Preprocessing of MRI data was conducted using SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/) implemented in MATLAB (Release 2017a, Mathworks Inc., Sherborn, MA, USA). T1 images were manually reoriented with the origin set at the anterior commissure, and subsequent preprocessing included slice time correction, realignment, coregistration, normalization to the Montreal Neurological Institute (MNI) template (Mazziota et al., 2001) and spatial smoothing with an 8 x 8 x 8 mm^3 full width at half-maximum Gaussian kernel. For resting state analyses, ICA-AROMA was utilized to identify and remove movement-related components before group ICA was conducted; this was not utilized for task data at the risk of removing task-related effects.

2.3.2 Independent Component Analysis

2.3.2.1 Task ICA

See Figure 2 for a graphical representation of task data analysis pathway. ICA was performed on the pre-processed data using the Group ICA of fMRI Toolbox (GIFT; Calhoun et al., 2001). Resting state and task data were analyzed separately, but all participants were

included in each analysis to ensure that the arbitrary order of components will be the same across groups. All task data were analyzed in one analysis with task level as a temporal regressor. A design matrix indicating task onsets and durations was generated with SPM. A binary mask including both cortical and subcortical regions but excluding the cerebellum and brainstem was used as a mask file within GIFT so as to exclude participants' potentially lesioned brain regions.

Minimum descriptive length (MDL) estimation within GIFT was conducted on task data. Results indicated an estimated 30 independent components, and this is what was utilized. MDL estimation of resting state data suggested 15 components.

Prior to the ICA decomposition, participant datasets were orthogonalized and whitened using principal component analysis (PCA). Subject-specific PCA was used. Temporal group ICA was run on task data; spatial group ICA was run on resting state data. Temporal ICA required that only 1 reduction step is conducted, whereas in resting state analyses in which we aimed to maximize spatial independence, 2 data reduction steps were conducted. For all analyses, the Infomax algorithm was repeated 10 times in ICASSO to assess the reliability of the decomposition. Participant-specific spatial maps and timecourses were estimated using the GICA back reconstruction method. The aforementioned mask modeled after the MNI152 mask but excluding the cerebellum was applied. Voxels from spatial maps were scaled into z-scores. Temporal regression beta weights indicating task-relatedness of each IC for each participant at each level were extracted.

The GIFT component labeler was used to label components using the FIND Lab network templates (Richiardi et al., 2015 Shirer et al., 2012). Components were correlated with the given templates, and the best template was determined by the maximum correlation value.

Components were then visually evaluated, and components deemed to be related to motion or otherwise artifactual were excluded. Criteria followed artifact exclusion criteria from prior GIFT-focused studies; components were excluded if peak activations were outside gray matter, components overlapped with known vascular, ventricular, motion, or susceptibility artifacts, or timecourses demonstrated excessive high-frequency fluctuations (Allen et al., 2012; Cordes et al., 2000).

In order to determine task components of interest, beta weights for all control participants for all remaining ICs at each task level (0-, 1-, 2-, and 3-back) were subjected to one-sample t-tests. ICs were excluded if no significant (uncorrected $p<.05$) task-relatedness was observed at any task level in controls.

2.3.2.2 Rest ICA

Minimum descriptive length (MDL) estimation within GIFT was conducted on resting state data. Results indicated an estimated 15 independent components, and this is what was utilized.

Similar to procedures with task data, prior to the ICA decomposition, participant datasets were orthogonalized and whitened using principal component analysis (PCA). Subject-specific PCA was used, and spatial group ICA was run on resting state data, thus, 2 data reduction steps were conducted. For all analyses, the Infomax algorithm was repeated 10 times in ICASSO to assess the reliability of the decomposition. Participant-specific spatial maps and timecourses were estimated using the GICA back reconstruction method. The aforementioned mask modeled after the MNI152 mask but excluding the cerebellum was applied. Voxels from spatial maps were scaled into z-scores.

Similar to the procedure with task data, the GIFT component labeler was used to label components using the FIND Lab network templates (Richiardi et al., 2015 Shirer et al., 2012). Components were correlated with the given templates, and the best template was determined by the maximum correlation value. Components were then visually evaluated, and components deemed to be related to motion or otherwise artifactual were excluded. Criteria followed artifact exclusion criteria from prior GIFT-focused studies; components were excluded if peak activations were outside gray matter, components overlapped with known vascular, ventricular, motion, or susceptibility artifacts, or timecourses demonstrated excessive high-frequency fluctuations (Allen et al., 2012; Cordes et al., 2000).

2.3.3 Statistical Analyses

Task-relatedness of components was assessed by multiple regression of the component timecourses with the design matrix containing the onsets of task blocks convolved with a hemodynamic response function. The regression output was subject-specific beta weights for each task regressor that indicated the extent to which each component timecourse was related to the task. 0-back and 1-back task performance were defined as attention span tasks and 2-back and 3-back task performance were defined as working memory tasks for certain analyses. A high beta weight was interpreted as representing a large task-related modulation of the component for the given regressor. Beta weights were extracted from GIFT and analyzed in SPSS 25.0 (IBM Corp., Released 2017. IBM SPSS Statistics for Windows, Version 25.0, Armonk, NY: IBM Corp.). For resting state data, functional network connectivity correlations among all networks of interest were extracted for each participant. Differences by group will be analyzed in SPSS 25.0. False discovery rate (FDR) correction were conducted to mitigate effects of multiple analyses when applicable. Low-pass and high-pass filters were not used on task data due to the frequency

information for component decomposition that can be lost when they are utilized in ICA (Pignat et al., 2013).

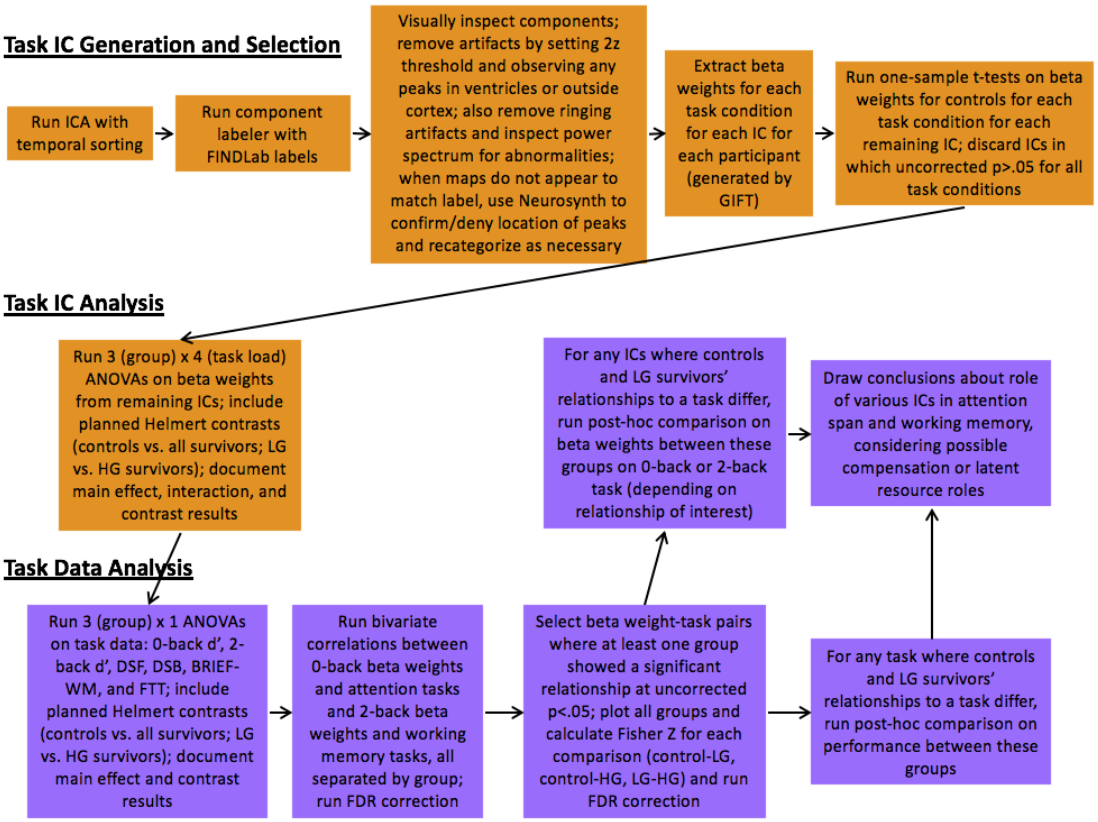

Figure 2. Task data analysis pathway.

2.3.3.1 Aim 1 Statistical Analyses

The purpose of the first aim was to identify networks of interest then evaluate potential interactions or main effects of group and task load on component strength. The significance of beta weights was evaluated by one-sample t-tests for each group. A two-way ANOVA (group X load) with planned contrasts was run with participants' beta weights of each component of interest as the dependent variable. Greenhouse-Geisser estimates were used to determine significance of task load and interaction effects to mitigate significant tests of sphericity. Helmert contrasts among groups were controls vs. all survivors followed by low grade tumor survivors

vs. high grade tumor survivors. Games-Howell post-hoc comparisons between controls and low grade survivors were probed when group or interaction effects were significant and appeared to differ from predicted group differences as assessed with Helmert contrasts.

2.3.3.2 Aim 2 Statistical Analyses

The purpose of the second aim was to establish group differences in cognitive abilities and potential relationships between the strength of various networks and participants' performance on cognitive measures. One-way ANOVAs with planned contrasts were first run to compare task performance among groups on the following data: 0-back d', 2-back d', WMS Digit Span Forward (DSF) z-scores, WMS Digit Span Backward (DSB) z-scores, and BRIEF-Informant Working Memory subscale T-scores. Planned Helmert contrasts among groups were controls vs. all survivors and low grade tumor survivors vs. high grade tumor survivors. Hochberg's GT or Games-Howell (if variances were unequal) post-hoc tests were also run to compare controls to low grade tumor survivors when valuable for interpreting findings.

Participants' components' beta weights from the 0-back task and 2-back task were utilized as proxy for the components' relation with attention span and working memory, respectively. Separated by group, correlations were run between 0-back beta weights and standardized from the attention measures, 0-back d' and DSF. Correlations were also run between 2-back beta weights and standardized scores from the working memory measures, 2-back d' and DSB. Benjamini-Hochberg corrections with $q<0.05$ were used to adjust significance thresholds for each set of beta weight by performance correlations. Fisher z transformations were conducted to compare the strength of relationships among the three groups whenever one or more group demonstrated a significant correlation, and FDR corrections were used to increase the significance threshold for each set of comparisons, thereby decreasing the likelihood of a

Type 1 error. For any IC for which beta weights were significantly correlated with an attention span or working memory measure, correlations were run between beta weights and BRIEF-Working Memory subscale T-scores. Correlations were also run between beta weights and Finger Tapping z-scores for all included components, and Fisher Z transformations were conducted as appropriate.

2.3.3.3 Aim 3 Statistical Analyses

The purpose of the third aim was to identify which components of interest from the task were also observed during resting state, and functional network connectivity (FNC) was assessed using the Mancovan toolbox in GIFT to determine interrelatedness among task-positive components and default mode components and differences by group. To generate FNC values, subject-specific timecourses were detrended and despiked with 3dDespike and filtered using a fifth-order Butterworth low-pass filter with a high frequency cutoff of 0.15. The default p-value significance of p=.01 was utilized. FDR corrections were utilized in initial Mancovan-based calculations.

3 RESULTS

3.1 Aim 1

3.1.1 Task Default Mode Network Components

Of the 30 task ICs generated by GIFT, 17 met criteria as non-artifactual components. Two of these 17 were removed from further analyses due to non-significant one-sample t-tests in controls across all levels of task (IC6: precuneus network; IC10: anterior salience network), resulting in 15 ICs analyzed (see Table 4 and Appendix A for details). Eight of the 15 remaining ICs were identified as DMN components; seven ICs were initially identified as overlapping best

with the FIND Lab dorsal DMN template and one reportedly overlapped best with the ventral DMN template.

Table 4. Task-based components identified and analyzed.

	Peak Location in MNI coordinates	Cluster Locations at ±2z	Beta weights ANOVA results summary	Additional Notes
Default Mode Network Components				
IC5: Dorsal DMN	(-11.5, 29.5, -16.5)	Bilateral vmPFC	Load effect (negative)	
IC27: Dorsal DMN	(-32.5, 11.5, -36.5)	Bilateral temporal lobes; midline vmPFC	Load effect (negative)	
IC19: Dorsal DMN	(-0.5, 59.5, 7.5)	Midline mPFC; midline precuneus (negative)	Load effect (negative)	
IC1: Dorsal DMN	(15.5, -30.5, 76.5)	Bilateral somatosensory cortex; L frontal pole	Load effect (negative); group effect (LG survivors show least reduction across task load levels)	
IC16: Dorsal DMN	(-0.5, 55.5, -18.5)	Midline vmPFC; bilateral superior temporal lobe	Load effect (negative); group effect (LG survivors show least reduction across task load levels)	
IC17: Dorsal DMN	(56.5, -21.5, -24.5)	Bilateral inferior temporal lobe; midline vmPFC; L mPFC (negative); L hypothalamus (negative)	Load effect (negative); group effect (LG survivors show greatest reduction across task load levels)	
IC22: Dorsal DMN	(-6.5, -12.5, 77.5)	Bilateral supplementary motor cortex; bilateral parieto-occipital junction;	Load effect (negative); group effect (LG survivors show greatest reduction	

		midline vmPFC (negative)	across task load levels)	
IC29: Ventral DMN / "Frontal pole"	(24.5, 64.5, -3.5)	Bilateral frontal pole; midline hypothalamus (negative)	Load effect (positive)	Recategorized from ventral DMN
Cognitive Network Components				
IC26: ECN	(-3.5, -18.5, 77.5)	Midline primary motor cortex; L lateral inferior frontal lobe; bilateral frontal pole (negative)	Load effect (positive)	
IC8: ECN	(29.5, 59.5, -6.5)	Bilateral lateral OFC; R lateral and posterior parietal lobe; midline vmPFC (negative)	Load effect (positive)	Recategorized from SMN
IC30: ECN	(-20.5, 62.5, -6.5)	L lateral OFC; L lateral inferior frontal lobe; R inferior occipital lobe; midline vmPFC (negative)	Interaction effect (positive increase in beta weights with increased task load but to a lesser extent in HG survivors at 2-back and 3-back levels)	
IC15: VSN/ECN	(-24.5, 62.5, -3.5)	L anterior PFC; R anterior PFC (negative)	Load effect (negative)	VSN clusters were positive; ECN clusters were negative
IC7: HVN/ECN	(-3.5, -91.5, -16.5)	L lateral PFC; L inferior occipital (negative)	Load effect (positive)	HVN clusters were negative; ECN clusters were positive
Sensory Network Components				
IC12: PVN	(-3.5, -91.5, -15.5)	Midline primary visual cortex; midline mPFC (negative); R	Load effect (negative)	

		vmPFC (negative)		
IC4: SMN	(-17.5, -24.5, 74.5)	Bilateral sensorimotor cortex	Interaction effect (negative increase in beta weights with increased task load but to a lesser extent in HG survivors at 2-back and 3-back levels)	Recategorized from anterior salience network

DMN=default mode network; ECN=executive control network; HVN=higher visual network; mPFC=medial prefrontal cortex; OFC=orbital frontal cortex; PFC=prefrontal cortex; PVN=primary visual network; SMN=sensorimotor network; vmPFC=ventromedial prefrontal cortex; VSN=visuospatial network

See Table 5 for detailed mixed-effects ANOVA DMN component results. Assumptions of sphericity were commonly violated for within-subjects effects; in these cases, Greenhouse-Geisser-corrected values were reported. Three DMN components' (IC5, IC19, IC27) demonstrated significant effects of only task load on beta weights ($.000<p<.006$) with overall trends of more negative beta weights as task load increased. IC5 and IC27 beta weights were significantly lower for working memory (2- and 3-back) levels than attention (0- and 1-back) levels ($p's<.001$).

Four DMN components (IC1, IC16, IC17, IC22) demonstrated significant effects of both task load ($p's<.001$) and group ($.012<p<.041$) with overall trends of more negative beta weights as task load increased and significantly lower beta weights for working memory levels than attention levels ($p's<.001$). Group differences varied by component. Planned Helmert contrasts for IC1 and IC16 indicated significant differences between controls and all survivors ($p_{IC1}=.006$, $p_{IC16}=.028$) with controls demonstrating more negative beta weights but no significant difference between survivor groups. Games-Howell post-hoc tests also indicated significant differences between controls and LG survivors alone ($p_{IC1}=.010$, $p_{IC16}=.043$) with controls demonstrating

more negative beta weights. Planned Helmert contrasts for IC17 also indicated significant differences between controls and all survivors (p=.035) with survivors demonstrating more negative beta weights. The LG-HG contrast approached significance, with LG survivors demonstrating a trend of more negative beta weights than HG survivors (p=.079). Games-Howell post-hoc tests indicated significant differences between controls and LG survivors alone (p=.026) with LG survivors demonstrating more negative beta weights. Planned Helmert contrasts for IC22 did not indicate a significant difference between controls and all survivors, but LG survivors differed from HG survivors (p=.009) with LG survivors demonstrating more negative beta weights. Games-Howell post-hoc tests also indicated significant differences between controls and LG survivors alone (p=.019) with LG survivors demonstrating more negative beta weights.

The component categorized as a ventral DMN component (IC29) demonstrated a significant effect of task load only (p<.001) with a presentation of more positive beta weights as task load increased. Participants had higher IC29 beta weights at working memory levels than attention levels (p<.001). Of note, visual inspection indicated that this network was comprised of inter-hemispheric frontal pole clusters (Brodmann area 10). While these regions are not traditionally considered part of the DMN, limited research suggests that these lateral frontal pole clusters are functionally connected to DMN regions during rest (Moayedi et al., 2015), while medial frontal pole clusters are functionally connected to the ECN. As a result, IC29 remained labeled as a DMN component for the remainder of the manuscript; however, the unexpected pattern of recruitment during the task is further elaborated upon within this unique context in the Discussion section.

Table 5. Mixed-effects ANOVA default mode network component results.

DEFAULT MODE COMPONENTS	SS	*df*	MS	F	*p*	Partial η^2
IC1						
Group	9.81	2	4.91	4.75	0.012	0.14
Error	61.90	60	1.03			
**Task Load*	4.62	2.42	1.91	29.64	<0.001	0.33
**Task Load*Group*	0.58	4.84	0.12	1.86	0.107	0.06
**Error*	9.35	145.14	0.06			
IC5						
Group	2.37	2	1.18	1.03	0.364	0.03
Error	68.95	60	1.15			
**Task Load*	9.22	2.35	3.93	46.50	<0.001	0.44
**Task Load*Group*	0.07	4.69	0.02	0.19	0.962	0.01
**Error*	11.90	140.76	0.08			
IC16						
Group	12.17	2	6.08	3.42	0.039	0.10
Error	106.64	60	1.78			
**Task Load*	2.84	2.18	1.30	20.28	<0.001	0.25
**Task Load*Group*	0.42	4.37	0.10	1.51	0.200	0.05
**Error*	8.42	130.96	0.06			
IC17						
Group	8.93	2	4.47	3.36	0.041	0.10
Error	79.72	60	1.33			
**Task Load*	4.26	2.64	1.62	20.71	<0.001	0.26
**Task Load*Group*	0.04	5.27	0.01	0.09	0.995	0.00
**Error*	12.35	158.16	0.08			
IC19						
Group	1.30	2	0.65	0.38	0.685	0.01
Error	102.62	60	1.71			
**Task Load*	0.94	2.40	0.39	4.81	0.006	0.07
**Task Load*Group*	0.12	4.79	0.02	0.30	0.908	0.01
**Error*	1.69	143.73	0.08			
IC22						
Group	13.37	2	6.68	4.06	0.022	0.12
Error	89.87	60	1.65			
Task Load	3.49	3	1.16	18.00	<0.001	0.23
*Task Load*Group*	0.76	6	0.13	1.96	0.079	0.06
Error	11.64	180	0.06			
IC27						
Group	1.54	2	0.77	0.66	0.519	0.02
Error	69.57	60	1.16			
**Task Load*	12.14	2.53	4.80	51.33	<0.001	0.46
**Task Load*Group*	0.69	5.06	0.14	1.46	0.204	0.05
**Error*	14.18	151.82	0.09			

IC29						
Group	3.32	2	1.66	1.42	0.250	0.05
Error	70.38	60	1.17			
**Task Load*	3.22	2.40	1.34	18.01	<0.001	0.23
**Task Load*Group*	0.38	4.80	0.08	1.06	0.384	0.03
**Error*	10.72	144.04	0.07			

*Note: These Within-Subjects values recorded are Greenhouse-Geisser corrected values due to violations of the assumption of sphericity; otherwise, Within-Subjects sphericity-assumed values are reported

3.1.2 Task Cognitive Network Components

See Table 6 for detailed mixed-effects ANOVA results for cognitive networks. Assumptions of sphericity were commonly violated for within-subjects effects; in these cases, Greenhouse-Geisser-corrected values were reported. One right executive control network (ECN) component (IC30) was identified, and a significant interaction between group and task load on beta weights was observed (p=.001). Beta weights increased overall with higher task load such that more positive beta weights were observed at working memory levels than attention levels (p<.001), but this increase was less pronounced in HG survivors than other groups. Hochberg GT post-hoc testing indicated that groups differed at working memory levels with HG survivors demonstrating weaker beta weights than controls during 2-back (p=.045) and weaker beta weights than both LG survivors (p=.011) and controls (p=.001). Groups did not differ at attention levels.

One left ECN component (IC26) demonstrated a significant effect of only task load on beta weights (p<.001) with more positive beta weights as task load increased. Participants demonstrated higher beta weights at working memory levels than attention levels (p<.001).

One IC was initially categorized in GIFT as a sensorimotor network component, but visual and quantitative assessment of clusters suggested that it was more likely an attention-based component (IC8; peak z=3.98; x=30, y=49, z=-8). Of note, an equally strong negative

cluster of the component was located in the medial PFC (z=-2.63; x=-3, y=65, z=-7). The component demonstrated a significant effect of task load on beta weights (p<.001) with presentations of more positive beta weights as task load increased. Participants demonstrated higher beta weights at working memory levels than attention levels (p<.001).

One IC was identified as a visuospatial network component (IC15) due to its positive left mPFC and occipital clusters. Negative clusters within the IC were located in the right executive control regions, specifically the right precentral gyrus (peak z=-2.19) and right dlPFC (z=-2.14). This component demonstrated a significant effect of task load on beta weights (p<.001). Beta weights were more negative as task load increased, and more negative beta weights overall were observed at working memory levels than attention levels (p<.001).

One IC was identified as a higher visual network component (IC7), though clusters traditionally related to visual function were sorted as negative (e.g., the negative peak in the left occipital lobe; z=-3.28), while the positive clusters were in regions related to memory and task-related function (e.g., the positive peak in the left dlPFC; z=3.66). This component demonstrated a significant effect of task load on beta weights (p<.001) with presentations of more positive beta weights as task load increased. Participants demonstrated higher beta weights at working memory levels than attention levels (p<.001).

Table 6. Mixed-effects ANOVA cognitive network component results.

COGNITIVE COMPONENTS	**SS**	***df***	**MS**	**F**	***p***	**Partial η^2**
IC2						
Group	4.22	2	2.11	1.15	0.323	0.04
Error	109.89	60	1.83			
**Task Load*	1.35	2.24	0.60	8.50	<0.001	0.12
**Task Load*Group*	0.46	4.49	0.10	1.45	0.215	0.05
**Error*	9.56	134.58	0.07			
IC7						
Group	1.65	2	0.83	0.66	0.522	0.02
Error	75.51	60	1.26			

Task Load	4.02	3	1.34	25.02	<0.001	0.29
*Task Load*Group*	0.44	6	0.7	1.37	0.230	0.04
Error	9.23	180	0.05			
IC8						
Group	1.21	2	0.60	0.47	0.627	0.02
Error	77.08	60	1.28			
**Task Load*	13.01	2.00	6.51	64.66	<0.001	0.52
**Task Load*Group*	0.44	4.00	0.11	1.08	0.369	0.03
**Error*	12.07	119.99	0.10			
IC15						
Group	0.97	2	0.48	0.30	0.740	0.01
Error	95.61	60	1.59			
**Task Load*	11.62	2.43	4.78	60.16	<0.001	0.50
**Task Load*Group*	0.70	4.86	0.14	1.82	0.14	0.06
**Error*	11.49	145.93	0.08			
IC21						
Group	3.30	2	1.65	0.95	0.391	0.03
Error	103.95	60	1.73			
**Task Load*	1.52	2.38	0.64	8.56	<0.001	0.12
**Task Load*Group*	0.38	4.76	0.08	1.08	0.373	0.03
**Error*	10.65	142.85	0.07			
IC26						
Group	0.18	2	0.09	0.07	0.932	0.00
Error	78.75	60	1.31			
**Task Load*	5.36	2.55	2.10	23.81	<0.001	0.28
**Task Load*Group*	0.36	5.10	0.07	0.80	0.56	0.03
**Error*	13.50	152.91	0.09			
IC30						
Group	6.32	2	3.16	2.28	0.112	0.07
Error	83.27	60	1.39			
Task Load	17.21	3	5.74	91.56	<0.001	0.60
*Task Load*Group*	1.47	6	0.24	3.90	0.001	0.12
Error	11.28	180	0.19			

*Note: These Within-Subjects values recorded are Greenhouse-Geisser corrected values due to violations of the assumption of sphericity; otherwise, Within-Subjects sphericity-assumed values are reported

3.1.3 Task Sensory Network Components

See Table 7 for detailed mixed-effects ANOVA sensory network results. Assumptions of sphericity were violated for within-subjects effects for both sensory network components; as a result, Greenhouse-Geisser-corrected values were reported. One IC was identified as a primary

visual network component (IC12) and demonstrated a significant effect of task load on beta weights (p=.003) with presentations of more negative beta weights as task load increased. There was not a significant difference between beta weights at attention versus working memory levels (p>.05).

One IC was initially identified as an anterior salience network component, but visual and quantitative assessment of its clusters and peaks (z=4.43; x=-18, y=-24, z=73) suggested that it was more likely a sensorimotor-related component (IC4). In in this component, a significant interaction between group and task load on beta weights was observed (p=.047). Beta weights were more negative as task load increased, more negative beta weights overall were observed at working memory levels than attention levels (p<.001), and this decrease appeared less pronounced in HG survivors than other groups. However, HG survivors did not differ from LG survivors as measured by planned Helmert contrasts, nor did post-hoc Hochberg's GT analyses suggest that groups differed significantly at any task level.

Table 7. Mixed-effects ANOVA sensory network component results.

SENSORY COMPONENTS	**SS**	***df***	**MS**	**F**	***p***	**Partial η^2**
IC4						
Group	0.56	2	0.28	0.23	0.792	0.01
Error	72.23	60	1.20			
**Task Load*	7.72	2.32	3.34	35.25	<0.001	0.37
**Task Load*Group*	1.04	4.63	0.22	2.37	0.047	0.07
**Error*	13.15	138.92	0.09			
IC12						
Group	3.869	2	1.93	1.45	0.243	0.05
Error	80.06	60	1.33			
**Task Load*	0.86	2.37	0.36	5.38	0.003	0.08
**Task Load*Group*	0.23	4.75	0.05	0.71	0.61	0.02
**Error*	9.60	142.45	0.07			

*Note: These Within-Subjects values recorded are Greenhouse-Geisser corrected values due to violations of the assumption of sphericity; otherwise, Within-Subjects sphericity-assumed values are reported

3.2 Aim 2

3.2.1 Task Performance

ANOVAs with planned Helmert comparisons were run to assess task performance across groups. Groups differed significantly on the 0-back d' measure ($p<.001$) where controls performed better than survivors overall ($p=.014$) and LG survivors performed better than HG survivors ($p=.003$). Of note, the 0-back d' scores demonstrated significantly unequal variance across groups and heteroskedasticity, suggesting that all 0-back d' findings should be interpreted with caution. Groups did not differ significantly on the 2-back d' measure ($p>.05$), though group means trended in the same general direction as 0-back d' scores and the effect size was small to medium ($\eta_{p2}=.05$). See Table 8 for details.

Groups differed significantly on Digit Span Forward z-scores ($p=.006$) where controls performed better than survivors overall ($p=.020$). LG survivors' mean DSF z-score was higher than HG survivors' but the difference was not significant ($p=.067$). However, post-hoc Hochberg GT testing demonstrated a significant difference between controls' and HG survivors' DSF z-scores ($p=.005$) while controls' and LG survivors' scores did not differ. Groups differed significantly on Digit Span Backward z-scores ($p=.001$) where controls performed better than survivors overall ($p=.027$) and LG survivors performed better than HG survivors ($p=.007$). Post-hoc Hochberg GT testing demonstrated a significant difference between controls' and HG survivors' DSB z-scores ($p=.001$) but none between controls' and LG survivors' scores.

Groups differed significantly on T-scores on the Working Memory subscale of the BRIEF ($p<.001$). Controls' T-scores were lower (less impaired) than survivors overall ($p=.031$), and LG survivors' scores were lower than those of HG survivors ($p=.001$). Post-hoc Hochberg

GT testing demonstrated a significant difference between controls' and HG survivors' BRIEF Working Memory T-scores ($p<.001$) but none between controls' and LG survivors' scores. Groups differed significantly on Finger Tapping Test z-scores ($p<.001$) where controls performed better than survivors overall ($p=.003$) and LG survivors performed better than HG survivors ($p=.002$). Post-hoc Hochberg GT testing demonstrated a significant difference between controls' and HG survivors' FTT z-scores ($p=.006$) but none between controls' and LG survivors' scores. Of note, FTT z-scores demonstrated significantly unequal variance across groups and heteroskedasticity, suggesting that FTT findings should be interpreted with caution.

Table 8. Task performance by group.

	Controls (N=40[t])	Survivors (N=23)		*F*
		Low Grade (N=9)	*High Grade (N=14)*	
0-back d' (M±SD)	3.95±0.22	3.94±0.29	3.33±0.90	9.50***
2-back d' (M±SD)	2.78±0.83	2.63±0.71	2.32±0.91	1.60
Digit Span Forward z-score (M±SD)	0.15±0.84	-0.06±0.91	-0.76±0.97	5.53**
Digit Span Backward z-score (M±SD)	0.13±0.75	0.13±0.65	-0.74±0.70	7.75**
BRIEF-Informant Working Memory T-score (M±SD)	45.65±7.57	44.56±6.69	56.50±10.41	9.85***
Finger Tapping Test Dominant Hand T-score (M±SD)	0.16±0.93	-0.03±1.23	-1.68±1.80	11.81***

Note: BRIEF=Behavior Rating Inventory of Executive Function
*p<0.05
**p<0.01
***p<0.001
[t]BRIEF-Informant data and Finger Tapping Test data were each available for only 37 healthy control participants.

3.2.2 Task Default Mode Network Correlations

No correlations survived Benjamini-Hochberg FDR correction. However, the following uncorrected results with significance of $p<.05$ are presented in the interest of considering trends within relatively small samples that may be replicated in larger future studies. Uncorrected correlations were run between 0-back beta weights and attention task scores as well as 2-back beta weights and working memory task scores, all separated by group. With respect to the relationship between beta weights and performance on the correlating task, controls demonstrated a negative relationship between IC29 0-back beta weights and 0-back d' scores; controls who performed better on 0-back demonstrated less engagement of this supposed DMN component, in which a positive relationship between beta weight and task load had been observed. Both survivor groups' relationships trended in the same direction but did not reach significance. There were no significant relationships between DMN component 2-back beta weights and 2-back d' scores.

Contrary to hypotheses about correlations between network engagement on an attention task inside the scanner and attention span outside the scanner, no groups' 0-back beta weights of any DMN component were correlated with DSF z-scores.

Reflective of hypotheses, DSB z-scores were relatively frequently related to 2-back task-relatedness, though not consistently in the expected direction. In controls, IC29 2-back beta weights were positively correlated with DSB performance such that increased recruitment of this network during a working memory task in the scanner was reflective of better working memory performance outside the scanner. This was in the context of positive mean beta weights that increased as task load increased. In LG survivors, IC5 2-back beta weights were positively correlated with DSB such that more negative task-relatedness (more disengagement) was related

to poorer working memory scores outside the scanner. This same pattern was observed with LG survivors' IC16 2-back beta weights and DSB performance, though in IC16, this relationship was significantly different from the beta weight-DSB relationships of controls and HG survivors. Of note, post-hoc comparison of IC16 2-back beta weights indicated much less disengagement of this dorsal DMN component in LG survivors compared to controls.

HG survivors demonstrated a negative relationship between IC19 2-back beta weights and DSB z-scores. HG survivors who more successfully disengaged this dorsal DMN component performed better on the working memory measure outside the scanner.

No significant relationships emerged between DMN component beta weights and FTT z-scores. Correlations between BRIEF-Working Memory T-scores and beta weights for components in which task-based relationships were run; none of these emerged as significant.

3.2.3 Task Cognitive Network Correlations

Contrary to hypotheses about correlations between network engagement on an attention task inside the scanner and attention span outside the scanner, no groups' 0-back beta weights of any cognitive network component were correlated with DSF z-scores. With respect to the 2-back, HG survivors demonstrated a significant positive relationship between the ECN component IC8 2-back beta weights and 2-back d' scores such that increased task-relatedness on the working memory task related to better performance on the working memory measure in the scanner. No other group demonstrated significant relationships between beta weights and performance on the correlating task.

Furthermore, a significant relationship emerged in LG survivors between ECN component IC8 2-back beta weights and DSB z-scores wherein LG survivors who demonstrated

greater task-relatedness of this component during the working memory task in the scanner did more poorly on the working memory task outside the scanner.

Finally, in controls, ECN network component IC8 0-back beta weights were negatively correlated with FTT z-scores such that greater recruitment of this network during a simple task was related to poorer fine motor performance.

Correlations between BRIEF-Working Memory T-scores and beta weights for components in which task-based relationships were run; none of these emerged as significant.

3.2.4 Task Sensory Network Correlations

With respect to the relationship between beta weights and performance on the correlating task, LG survivors demonstrated a significant positive relationship between the primary visual motor component IC12 2-back beta weights and 2-back d' scores such that increased task-relatedness on the working memory task related to better performance on the working memory measure in the scanner.

Correlations between BRIEF-Working Memory T-scores and beta weights for components in which task-based relationships were run; none of these emerged as significant.

3.2.5 Post-Hoc Exploratory 3-Back Analyses

In the interest of assessing possible relationships between beta weights and task performance at a more demanding task load, correlations were run between 3-back d' values and the 15 component beta weights. Analyses were conducted separately for each group.

In controls, three relationships remained significant following Benjamini-Hochberg FDR correction of q=0.05 for 15 correlations. Two DMN ICs' beta weights showed significant inverse relationships with 3-back d' scores (IC5, r=-0.50, p=.001; IC1, r=-0.42, p=.007). One cognitive IC, an ECN component, demonstrated a significant positive relationship between beta weights

and 3-back d' scores (IC30, r=0.43, p=.006). No components demonstrated relationships at p<.05 before or after FDR correction in the LG survivor group. Beta weights of one cognitive IC, an ECN component, were significantly positively correlated with 3-back d' scores for HG survivors (IC8, r=0.75, p=.002).

3.3 Aim 3

3.3.1 Resting State Components

Fifteen ICs were generated by GIFT as determined by MDL estimation. Thirteen of these met criteria as non-artifactual components and were included in the following analyses. The GIFT component labeler suggested the presence of four DMN components, seven cognitive components, and two sensory components (see Table 9 and Appendix A for details). However, but visual and quantitative assessment of clusters suggested that one sensory component (restIC10) was more likely a DMN component. A cognitive component (restIC11) was also recategorized from BGN to anterior SN in this process. As predicted, components included DMN, ECN, and SN network components.

Visual inspection suggested that certain task and resting state ICs overlapped anatomically. Within the DMN components, restIC6 overlapped with task IC19 in the medial prefrontal cortex. RestIC10 also overlapped somewhat with task IC19, though with restIC10's medial PFC cluster being located more ventrally, it displayed greater anatomical overlap with task IC16. Within the task-positive networks, ECN components restIC5 and task IC7 overlapped in the left dorsolateral PFC. Five same-network IC pairs consisted of adjacent but not overlapping clusters when thresholds were z=±2. The remaining five resting state ICs were anatomically distinct from task ICs.

Table 9. Resting state functional networks identified and analyzed.

	Peak Location in MNI coordinates	Cluster Locations at ±2z	Notes
Default Mode Network Components			
restIC2: Dorsal DMN	(-0.5, 7.5, -10.5)	Ventral striatum	
restIC4: Ventral DMN	(-27.5, -1.5, -39.5)	Bilateral medial temporal lobe	
restIC6: Dorsal DMN	(29.5, 61.5, -0.5)	R anterior PFC; midline PFC	
restIC10: Dorsal DMN	(-0.5, 61.5, -6.5)	Bilateral vmPFC	Recategorized from PVN
restIC12: Ventral DMN	(0.5, -79.5, 41.5)	Midline precuneus	
Cognitive Network Components			
restIC1: Anterior SN	(3.5, -9.5, 74.5)	Bilateral premotor cortex	
restIC3: ECN	(56.5, -22.5, -22.5)	Bilateral inferior temporal lobe	
restIC5: ECN	(29.5, 61.5, 20.5)	Bilateral anterior PFC	
restIC8: HVN	(-26.5, 64.5, -0.5)	L anterior PFC	
restIC11: Anterior SN	(-0.5, 32.5, -24.5)	Bilateral vmPFC	Recategorized from BGN
restIC13: LN	(-50.5, 22.5, -6.5)	Bilateral inferior frontal lobes	
restIC14: HVN	(11.5, -97.5, -12.5)	R inferior occipital lobe	
Sensory Network Components			
restIC9: SMN	(-48.5, 14.5, 32.5)	R inferior frontal lobe; R IPS; L lateral frontal lobe (negative)	

BGN=basal ganglia network; DMN=default mode network; ECN=executive control network; HVN=higher visual network; IPS=inferior parietal sulcus; PFC=prefrontal cortex; PVN=primary visual network; SMN=sensorimotor network; SN=salience network

3.3.2 Resting State Component Functional Network Connectivity

The 13 ICs of interested were organized by network and entered in order into the Maconvan toolbox. Mancovan was used to conduct a MANCOVA with group (control, LG, HG)

as a covariate with FDR correction. No significant univariate results were found at $p<0.05$, nor were any significant group differences were observed among FNC values at $p<0.05$.

4 DISCUSSION

4.1 Review of Task-Related Findings

As hypothesized, with control and survivor groups combined, non-artifactual independent components emerged across default mode, cognitive, and sensory domains. Patterns of network recruitment and relationships between recruitment and task performance varied by group.

4.1.1 Task-Relatedness of Functional Connectivity in Healthy Controls

By first considering the patterns of task-relatedness and task performance observed in healthy controls, some broad conclusions may be drawn about functional network recruitment and healthy individuals' attention span and working memory abilities. Such findings were generally commensurate with prior literature; relative to baseline, the most default mode network components consistently demonstrated negative task-relatedness, and most task-positive networks demonstrated positive task-relatedness. Greater task demand increased the degree to which such relationships were observed.

In controls, more negative task-relatedness of the DMN was observed as task difficulty increased, echoing the literature (Esposito et al., 2006; Esposito et al., 2009). Healthy young adults appear to be minimizing mind-wandering and self-reflective behaviors guided by the DMN (Andrews-Hanna et al., 2014; Mak et al., 2017) when tasks require greater effort and more focus in order to perform. The component that was initially categorized as a ventral DMN component but consisted of bilateral frontal pole clusters, however, demonstrated an inverted pattern; this component was more heavily positively recruited by all groups as task difficulty increased. One prior study indicated that these medial frontal pole regions are functionally

connected to other DMN regions during rest in healthy controls (Moayedi et al., 2015), which, along with a lack of overlap with other networks of interest, prevented the author of the present study from recategorizing the component. However, this pattern of increased positive task-related connectivity with increased task load ran counter to the presentation of other DMN components and better resembled that of task-positive network components for both healthy controls and survivors. The same study that determined that medial frontal pole regions were functionally connected to DMN regions also found that lateral frontal pole regions were functionally connected to ECN regions (Moayedi et al., 2015), and given these complexities, further reference to IC29 results will be described as a "frontal pole component" that may or may not be a component of a task-positive, cognitive network such as a fronto-parietal network. Further research should be conducted in healthy participants to better clarify the functional connectedness of these frontal pole regions.

Healthy controls also demonstrated consistent increases in executive control network components' task-relatedness as task difficulty increased, commensurate with results found by Reichert and colleagues (2017), such that working memory levels of a task were related to greater engagement of the components than the simpler attention-based levels. These patterns of increased ECN involvement being related to greater load on the n-back task also support findings from studies using other methodology to assess connectivity between regions of the ECN (e.g., Liang et al,. 2016; Repovs & Barch, 2012).

In one instance within our study, a component was initially sorted as a visuospatial component with positive clusters in visually-related regions and negative clusters in right ECN regions. As a result, beta weights reflecting component task-relatedness were negative and trended more negative as task difficulty increased, but this can be conceptualized as an increase

in ECN recruitment, matching other ECN beta weight patterns. A component labeled as a higher visual network component was also composed of a combination of negatively task-related visual regions and positively task-related clusters, suggesting that disengagement from these more basic networks co-occurs with the increased recruitment of the task-positive executive control network. Such a theory is bolstered by findings of negative task-relatedness in visual networks during cognitive tasks in the literature (Reichert et al., 2017), and the observed trade-off between the higher visual network and ECN may reflect a healthy coordination of bottom-up and top-down processing, respectively, in the face of attention and working memory tasks (Parks and Madden, 2013).

With the component inclusion criteria that in controls, a component must demonstrate significant task-relatedness in at least one level of the task, it was expected that sensory networks might emerge with significant differences relative to baseline and be selected for analysis; however, it was not predicted that differences would be observed across task level. Still, both sensory components that emerged during the task demonstrated a trend; a sensorimotor network component and a primary visual network component each demonstrated decreased engagement as task difficulty increased. Similar to the visuospatial and higher visual components, this may reflect a reallocation of resources to specific task-positive networks as less attention is paid to basic processes and more is paid to the demanding task at hand. However, it may also be a reflection of the established overlap between default mode nodes and those belonging to visual and sensory systems (Power et al., 2011); these lower-level sensory networks' negative task relatedness may be driven by the disengagement of the DMN as task demands increase. The cingulate gyrus in particular is specifically believed to regulate sensory attention and allocate resources to the appropriate stimulus (Heilman et al., 2000; American Academy of Neurology,

2013) and may therefore be the juncture resulting in coupling between default mode nodes and sensory cortices.

With further respect to controls, who performed within normal limits on all tasks on average, some uncorrected significant relationships emerged with respect to component recruitment and task performance. Prior literature has indicated that in the case of greater cognitive demand, individuals with the greater cognitive control show less mind-wandering, a DMN-based function (Andrews-Hanna et al., 2014; Kane et al., 2007), suggesting that those who successfully disengage would presumably perform better across both attention and working memory tasks. However, none of the DMN components in the present study demonstrated relationships with performance for the healthy control group at 0-back or 2-back levels. When assessing relationships between 3-back recruitment and performance in an exploratory manner, however, two components demonstrated significant negative relationships; greater disengagement of the DMN was correlated with better performance on this challenging task. This likely reflects healthy individuals' need to minimize DMN-directed mind-wandering and internal processing in order to successfully navigate highly demanding cognitive tasks.

Although most controls were limited by ceiling effects of the 0-back task, d' scores were still negatively correlated with engagement of the frontal pole component while that task was underway, perhaps indicating that those participants who did not need to exert remarkable cognitive effort on this simple task tended to perform better, whereas greater engagement was required by those who struggled to attend to the task. However, at the more challenging 2-back level, task-based engagement of this network was positively correlated with working memory performance outside the scanner, suggesting that those who utilized this network in the scanner were also able to engage effectively to perform outside the scanner as well. The positive

relationship observed in exploratory analyses between 3-back component recruitment and task performance for another ECN component further supports the prior literature that indicates relationships between task-positive functional connectivity and working memory task performance (Liang et al., 2016).

Controls' engagement of an executive control network component during the basic attention task in the scanner was also negatively correlated with fine motor abilities in the same hand with which they used the button box for the scanner task. It may be that more engagement of this network when completing a simple task reflects a display of increased effort in responding, which is related to poorer fine motor abilities in general. However, given that this component also included negative clusters, the peak of which was in the ventromedial prefrontal cortex, the relationship may also be driven by the engagement of these DMN regions involved in self-referential thinking (Andrews-Hanna et al., 2010); healthy individuals who are more attentive to their own thoughts and behaviors over the task may demonstrate a similar lack of engagement in a cognitively simple finger-tapping task, resulting in poorer performance.

Overall, general trends were observed in which healthy controls engaged task-positive networks and disengaged task-negative default mode and sensory networks in response to increasingly challenging tasks. Some degree of trade-off among these networks may reflect the balance of internally- and externally-focused attention and differences in top-down and bottom-up processing. Correlational trends indicate the possibility of relationships between degree of networks' task-related recruitment and healthy controls' performance on attention and working memory tasks.

4.1.2 Task-Relatedness of Functional Connectivity in Low Grade Tumor Survivors

Low grade survivors' cognitive and neurological function echoed that of their healthy peers in many ways but demonstrated some discrepancies, specifically with respect to the degree of default mode network component recruitment that that may function in a compensatory manner. One potential latent resource was also identified. Of note, the limited sample size of 9 low grade survivors may have prevented some trends from reaching significance.

With respect to DMN component engagement during tasks, load and group effects were observed across four DMN components. All showed negative task relatedness overall throughout the task and differences between LG survivors and their peers. In two instances, LG survivors demonstrated less disengagement of these components than their healthy peers, similar to Reichert and colleagues' (2017) findings in a sample of long-term survivors of childhood low grade posterior fossa tumors. On the other hand, with another DMN component, LG survivors showed greater disengagement than their healthy peers, and with yet a fourth DMN component, LG survivors disengaged to a greater degree than both their healthy and high grade survivor peer groups. All four of these components covered different areas of the DMN; peaks in the components where LG survivors showed less disengagement were located in the somatosensory cortex and medial prefrontal cortex, respectively, while peaks in the components where LG survivors showed more disengagement were in the right inferior temporal gyrus and motor cortex. Results may speak broadly to LG survivors' specific suppression of inferior temporal lobe components in the face of cognitive challenges, while the mPFC component may play a different role in LG survivors, particularly given its relationship to working memory (Barker et al,. 2007). Recent rat studies have indicated demonstrate the importance of the top-down input from the mPFC within working memory processes (Jayachandran et al., 2019), and it is possible

that instead of disengaging these regions as part of default mode functioning, LG survivors are utilizing these regions more within these processes to support working memory networks that may otherwise be compromised due to tumor and resection (Ravizza et al,. 2006).

Effects of group due to differences in the LG group versus controls were not observed across cognitive or sensory components. Such results, particularly within ECN components, differ from a similar comparison made by Reichert and colleagues (2017) wherein LG posterior fossa tumor survivors did not recruit this task-positive network as effectively as their healthy peers during attention and working memory tasks. In both the Reichert study and the present one, LG survivors did not differ remarkably from their healthy peers on most cognitive domains, though the Reichert LG group demonstrated lower IQ scores than controls; their LG survivors demonstrated generally average IQ scores compared to controls' high average mean, while the IQ of the LG survivors in the present study did not differ significantly from their healthy peers; it is possible that a lower-functioning LG group may have presented differently.

Across all performance measures and an informant report of working memory, LG survivors did not differ from their healthy peers. However, LG survivors showed some unique relationships between network engagement and task performance at uncorrected levels; similar to controls, no correlations remained significant following Benjamini-Hochberg FDR correction. To begin, in two DMN components, LG survivors who showed less disengagement during the 2-back task in the scanner tended to do better on a working memory measure outside of the scanner, though actual in-scanner task performance did not differ. LG survivors did not disengage one of these components as much on average as controls during the 2-back. Thus, it may be that these dorsal DMN components function as a compensatory resource for LG survivors; they are performing at the same level as their healthy peers on tasks overall, and

utilization of these segments of the DMN at a time they might otherwise be disengaged may reflect their role as a resource for those LG survivors who are more successful.

Relationships between cognitive network recruitment and performance unique to LG survivors were observed in one instance; task-related recruitment at the 2-back level was negative correlated with LG survivors' working memory performance outside the scanner. This suggests the possibility of this ECN component functioning as a latent resource; increased recruitment on the moderately challenging 2-back task may reflect increased effort in the LG group among those who struggle but do not find performance benefits as a result. There may be specific demands required by the n-back that differ from digit span tasks that help explain why the same patterns relative to in-scanner performance would not be found (Scharinger et al., 2017), but that ECN recruitment relates to either supports its role in attention and working memory tasks.

A trend also emerged for only LG survivors where recruitment of the primary visual network component during the working memory task in the scanner was positively correlated with performance on the same measure. This result ran counter to any hypotheses but may indicate some reallocation of resources to a unique component of neurological function in survivors compared to healthy controls. Additionally, negative mPFC clusters in this component may function as part of the DMN, demonstrating a possible inverse relationship between more basic, bottom-up processes and functions such as mind-wandering or self-referential thought. Increased utilization of visual networks may also be utilized more strongly for visually-based tasks in this population; as cerebellar-frontal connections are compromised in surgery-only posterior fossa tumor survivors (Ailion et al., 2019; Law et al,. 2015b), potentially impacting

higher cognitive abilities, it may be that greater recruitment of sensory or more basic cognitive networks become more heavily engaged in the process of attending to these tasks.

This study's LG survivors resembled their healthy peers with respect to attention and working memory performance, adding to the mixed corpus of literature on long-term outcomes for this group that often does not require adjuvant treatment (Ris & Beebe, 2008). However, the unique patterns of neural network recruitment observed in this group may be indicative or predictive of functional differences that were either not quantified as part of this assessment, such as fatigue, or not yet observable, such as the premature aging patterns that have been recorded in survivors of acute lymphoblastic leukemia by middle-adulthood (Schuitema et al., 2013). The LG survivor sample in this study consisted of solely older teenagers and young adults, and it will be valuable to track these individuals and others across their lifespan to determine whether the experience of a brain tumor and resection, even often without further deleterious treatment, will ultimately impact cognition and neural function in a manner that has not yet been observed.

4.1.3 Task-Relatedness of Functional Connectivity in High Grade Tumor Survivors

High grade survivors also demonstrated some distinctions from their healthy peers and low grade survivor peers. DMN component recruitment was generally similar to healthy controls, but two group by load interactions in cognitive components appeared to be driven by differences in high grade survivors. Some correlational trends suggest the possibility of compensatory functioning of certain neural components in the years following these survivors' extensive treatment regiment.

To begin, in one ECN component, at working memory levels, HG survivors demonstrated weaker task-related recruitment than the other groups. Although they resembled

their healthy and LG survivor peers at the less challenging, attention-based levels of the task, they were unable to engage effectively at the more challenging working memory levels. This may be due to being cognitively overwhelmed by these tasks that demand both attending to the task and manipulating information, a challenging combination when these core cognitive abilities are compromised (Palmer, 2013). In a sensorimotor network component in which the general trend was more negative task-relatedness as task load increased, HG survivors did not disengage as effectively as the other groups at the working memory levels, potentially limiting the resources that other groups were utilizing within other cognitive networks.

With respect to task performance, HG survivors performed significantly worse than their peers on all measures of attention, working memory, and fine motor skills except for the 2-back d', indicating persistent long-term deficits in cognitive abilities in this particular subset of brain tumor survivors. As it trended in the predicted direction, the lack of significance in 2-back d' scores may reflect a relative lack of sensitivity of the d' measure and provide insight into why trends observed between network engagement and tasks outside the scanner were more common than between network engagement and 2-back performance, though exploratory assessment of percent correct on the 2-back task garnered similar non-significant differences. It is possible that the relatively small sample size may have resulted in some underpowered findings.

In one DMN component, successful disengagement by HG survivors on the 2-back task was related to better working memory performance outside the scanner. Given the remarkable discrepancy in working memory performance between HG survivors and the other groups, this domain should be targeted for intervention in this population. Improving attention and memory while minimizing mind wandering may help survivors effectively disengage the dorsal DMN and perform better on tasks requiring working memory. Limited pilot studies have begun to

demonstrate effects of "brain training" programs on brain tumor survivors' attention and working memory (Hardy et al., 2011; van't Hooft & Norberg, 2010); these positive results along with the convergent imaging and cognitive findings from the present study suggest that this is worth further pursuit. A randomized control trial assessing impacts of both computerized cognitive training and physical training on neuropsychological and other outcomes in pediatric cancer (CNS and non-CNS) survivors that will also provide additional insight in the coming years (Benzing et al., 2018).

Within the cognitive networks, HG survivors demonstrated only one relationship between component recruitment and performance. For a bilateral ECN component, greater working memory task-relatedness was related to improved performance on said task. This reflects prior studies indicating that increased ECN intranetwork connectivity was related to increased working memory performance in healthy individuals (Liang et al., 2016), but the same trend was not seen in the present study's controls or LG survivors. The greater variability in performance and recruitment in the HG survivors in this particular component may have contributed to these results, though it should be noted that this same relationship emerged to a stronger degree during the 3-back task in HG survivors but still was not observed in other groups. Relationships between task-based ECN functional connectivity and working memory performance have been observed in healthy controls in the literature (Liang et al., 2016), though relationships specifically between task-related recruitment and task performance were not observed in controls or LG survivors in a study that closely resembled the present one (Reichert et al., 2017). Thus, this functional element of the ECN may be uniquely recruited by some HG survivors in a compensatory manner, resulting in better long-term cognitive outcomes.

4.2 Review of Resting State Findings

Components from various default mode, cognitive, and sensory networks were present across combined participant groups. Similar to task findings, dorsal and ventral DMN, ECN, anterior SN, higher visual network, and sensorimotor network components were observed during rest; however, clusters within these networks frequently differed in location. Exceptions were noted among one pair of dDMN components that overlapped in the mPFC as well as five pairs that were adjacent but not overlapping. One ECN pair overlapped in the left dlPFC and two others were composed of adjacent clusters. A language network component was also observed during resting state though not during the task.

The null results observed in resting state functional network connectivity analyses may have been a result of various factors. Most remarkably, both the relatively short resting state scan and the relatively small sample size limited the power of the analyses. Additionally, use of ICA-AROMA fit with best practices in much of current neuroimaging, but removal of motion to such a strong degree may have removed variance that could have been due to factors such as group, potentially contributing to null results in group comparisons. It may be that one set of classifiers does not fit all included data sets, and alternatives may include using FMRIB's ICA-based Xnoiseify (FIX; Griffanti et al,. 2014; Salimi-Khorshidi et al., 2014) and developing one's own classifiers. Future studies may also consider employing methods that remove physiological noise such as RVTMBPM, which appears to maintain both sensitivity to and specificity between functional connections and local white matter fluctuations during resting state scans (Krishnamurthy et al., 2018).

4.3 Limitations and Strengths

Current findings should be considered in light of some limitations. To begin, both survivor and control groups were self-selected, and selection bias may therefore limit generalizability of the study. It is possible that our sample is lower functioning and chose to participate because of ongoing concerns around their health or well-being, while those with fewer concerns may have felt the study was irrelevant to them. On the other hand, it appears more likely that our survivor sample is a generally higher functioning group than average posterior fossa brain tumor survivors; they are individuals who had time to participate in the study and find transportation to the study site, and full scale IQ scores across both the low and high grade tumor survivor groups were within the average range. The present study's initial exclusionary criteria (no tumor progression or recurrence; no developmental disorders) may also result in a more highly functioning group than would be observed across survivors on average. While it was initially posited that additional exclusions could further result in a higher functioning group overall, preliminary results suggest that our exclusion of individuals who were not scanned at CABI or whose scans were unusable due to an inability to complete the full 3-back task or excessive motion or artifact does not heavily skew our group; those with usable scans (M=98.39, SD=13.47) and 26 of the 28 without usable scans (M=90.81, SD=20.26) did not demonstrate significantly different FSIQ scores on average (p=0.126). However, it does appear that the excluded group trends in the direction of lower functioning, a frequent occurrence throughout the neuroimaging literature (Greene et al., 2016). Two potential participants who were excluded did not have FSIQ scores (one due to administrator error, one due to visual impairment); however, all participants considered for the study had Scales of Independent Behavior-Revised (SIB-R; Bruininks, 1996), and included (M_z=-0.16, SD_z=2.00) and excluded

(M_z=-0.66, SD_z=2.16) groups did not differ significantly in SIB-R Broad Independent Living Skills (p=0.404).

The study is also inherently limited by its cross-sectional methodology. While all survivor participants are long-term survivors of childhood brain tumors, the present data are from a single time point, meaning results, particularly those regarding brain-behavior relationships, reflect correlation as opposed to causation. The use of an age- and sex-matched control group allowed us to draw inferences about the long-term effects of tumors and treatment; however, confounds persist, particularly with respect to treatment. All survivors underwent neurosurgery, a process which differentiates them from healthy controls beyond their survivorship status, and all high grade tumor survivors underwent chemotherapy and/or radiation. As a result, it is not possible to disentangle the effects specific to a high grade tumor and those specific to adjuvant treatments within the present study, though current findings may be considered an accurate picture of high grade tumor survivor functioning given the frequency of this treatment regimen in this population.

With regard to psychometric properties of measures, n-back performance tends to show skewness and kurtosis due to the relative ease of the task (Haatveit et al., 2010). Although d' is used as a metric of task performance over percentage correct due to its slightly more normal distribution, the 0-back d' measurement is significantly negatively skewed across participants due to the ease of the task. This reinforces the utility of incorporating additional neuropsychological measures; although the BRIEF, Digit Span, and Finger Tapping Test are administered outside of the scanner and functional connectivity is therefore not measured during completion of these tasks, our intent is to use these well-normed measures to evaluate possible relationships between neurological function during a basic, fMRI-appropriate task and a task

assessing a similar construct. Furthermore, while Digit Span is an auditory task and the scanner n-back task is a visual task, the use of the letter n-back in particular likely utilizes the same neurological networks due to humans' tendency toward subvocalizations in such attention and memory tasks within the phonological loop (Baddeley & Hitch, 1974; Buchsbaum & D'Esposito, 2008). Implications of the cerebellum's role in verbal working memory supports the importance of these analyses in survivors of posterior fossa brain tumors in particular (Ben-Yehudah et al., 2007).

With respect to imaging methods, the present study is also limited by the lack of "gold standards" for elements of processing in the context of ICA, e.g., the number of components to be estimated. However, use of ICA should be regarded as a strength of this study, as it provides an understanding of functional connectivity in both task and resting state settings without requiring the biased action of seed selection. This is particularly relevant in neurological populations when regions within expected networks may be impacted by the incident or disease or by subsequent treatment. ICA's utility across both task-based and resting state scans further strengthens its applicability across populations. In the case of the present study, a longer resting state scan may have provided even more information about independent components and their functional inter- and intra-network connectivity.

Additionally, the cerebellum and brainstem were masked out of analyses so as to only capture cortical changes that resulted from of survivors' tumors in these regions and to minimize interference of the lesions in the imaging analysis process. While this allowed us to specifically investigate functional connectivity within the cortex, some of the FIND Lab network templates utilized included cerebellar clusters. Our processing methodologies may have made it

statistically less likely for components to be sorted as belonging to those templates; however, this was likely rectified by visual inspection of each component and recategorization when necessary.

This study is strengthened by its sample. Survivor participants are at least 5 years past their diagnosis, providing an in-depth look into long-term survivorship, and all participants' tumors were in the same general location. The delineation of participants by tumor type allows for deeper analysis into the effects of malignancy and adjuvant treatments on long-term outcomes in this population and into the effects observed in the low grade tumor group who is rarely followed for extended periods of time. Despite its cross-sectional nature, this study's use of a demographically matched control sample provides insight into differences in both neurological and cognitive functioning in this vulnerable, understudied population. Results of this study may lead to a better understanding of long-term survivorship and provide a basis for future longitudinal and interventional studies.

4.4 Conclusions and Future Directions

The brain is a series of spatially distributed but functionally connected regions that engage in synchrony in order to effectively process information and complete tasks. Both task-positive and task-negative components were observable across attention and working memory tasks and resting state scans among healthy controls and long-term survivors of childhood brain tumors of the posterior fossa. Healthy controls generally demonstrated effective disengagement of default mode components and sensory components as task difficulty increased as well as greater recruitment of cognitive components. Survivors' task-relatedness of components often trended in the same direction, but distinctions were still observed.

Low grade survivors who rarely underwent treatment beyond neurosurgery, and although they tended to resemble their healthy peers in terms of task performance scores, differences in

some patterns of neurological function and recruitment were still observed. Differences in the degree of DMN component disengagement during tasks may be a result of neural plasticity following a treatment protocol that, while less neurotoxic than the chemoradiation protocols undergone by their high grade peers, still results in structural and apparently functional changes to our low grade survivors' brains (Ailion et al., 2017, 2019). That less disengagement of some of these components trended with better working memory performance outside the scanner is indicative of a pattern of compensatory neural changes following tumor and treatment. Increased recruitment of a task-positive network was also correlated at trend level with poorer working memory performance outside the scanner in low grade survivors, a pattern that was not observed in healthy controls.

High grade tumor survivors, most of whom underwent significant adjuvant treatment around the time of their diagnoses and tumor resection, struggled to both engage an executive control network component and disengage a sensorimotor network component at working memory task levels relative to their peers. In some cases, high grade survivors' limited DMN disengagement showed a trend in which it was related to poorer task performance, insinuating a relationship between survivors' ability to inhibit internal processing for the sake of task completion and actual attention span or working memory abilities. The relationship between ECN recruitment and task performance varied in this group, with one component resembling a potential compensatory mechanism as greater recruitment during the working memory task was correlated with better performance on that task.

Distinctions between both survivor groups and their healthy peers clearly indicates changes to cortical functioning following posterior fossa tumor and resection. While we were unable to distinguish between the effects of a higher grade tumor and the presence of

chemoradiation within the present study's sample, it is likely that both a faster growing, malignant tumor and more substantial adjuvant treatments contribute to unique cognitive and neurological changes in our high grade survivor group in the face of attention and working memory tasks. Damage to the cerebellum impacts cerebellar-frontal white matter tracts that support these cognitive abilities (King et al., 2015a; Law et al,. 2015b; Ravizza et al., 2006;). Verbal working memory, an ability required by both the out-of-scanner Digit Span and in-scanner letter n-back due to expected subvocalizations, requires engagement of the phonological loop (Buchsbaum & D'Esposito, 2008). Recent fMRI studies implicate the involvement of brain regions such as the prefrontal cortex, fusiform gyrus, parietal cortex, and cerebellum relative to greater load on such tasks (Emch et al., 2019). Such findings align with our components with mPFC clusters and their recruitment patterns by task load. Emch and colleagues' (2019) findings also lend credence to the present results wherein our survivor groups who likely experienced different patterns of atrophy, demyelination, and other neurological damage demonstrated different cognitive abilities and differential recruitment patterns with more complex tasks.

Results of this study indicate that along with their high grade survivor peers, low grade survivors of childhood brain tumors experience neurological changes that persist for many years past their treatment. At five or more years past their diagnosis, high grade tumor survivors are demonstrating persistent attention and working memory difficulties that may preclude them from gaining the independence in activities of daily living that is expected in their healthy peers by this point in their young adult lives (Chevignard et al., 2017). Similar to prior literature, the present data suggest that these survivors will experience lifelong challenges and neurological differences (King et al., 2017; Ris & Noll, 1994); however, new treatment protocols may be able to limit neurotoxic exposure while still destroying the tumor, and new research should

investigate whether survivors who have undergone these treatments exhibit similar deficits to our survivors, some of whom were treated as early as the 1980s. Recent studies assessing how host genome single nucleotide polymorphisms (SNPs) predict cognitive outcomes (Kautiainen et al., 2020; Siegel et al., 2019) have laid the groundwork for the possibility of genome mapping upon diagnosis in order to individualize treatment to maximize long-term functioning.

While surveillance recommendations for low grade tumor survivors in the years and decades following their tumor and brief treatment remain unstandardized (Zaazoue et al., 2020), these findings suggest that it will be invaluable for this group to be monitored long-term, potentially including functional neuroimaging when possible. Although cognitive task performance did not differ between low grade survivors and their healthy peers, differing patterns of neural network recruitment may result in cognitive fatigue or, although effects may not be measurable as survivors are young adults, these differences in neurological function may result in survivors experiencing premature cognitive aging. In order to best inform prognosis, it should be a priority of providers to maintain contact with low grade tumor survivors in the same manner they track high grade tumor survivors who demonstrate more noticeable impairment. In particular, future studies of all brain tumor survivors may consider evaluating functional connectivity alongside structural neuroimaging analyses such as white matter tractography, cortical thickness measurements, and lesion mapping in the interest of establishing additional biomarkers for and correlations with future impairment, premature aging, or maintenance of cognitive reserve.

In the interest of maximizing quality of life, it will be necessary to establish more survivorship clinics tailored toward supporting all brain tumor survivors in their transition into and through adulthood. Interventions such as a cognitive remediation summer program can help

older children and teens increase independence and improve adaptive functioning skills in hopes of easing this transition of care (Murdaugh et al., 2019). Guidelines for working with this unique but growing group such as those set forth by Janss and colleagues (2019) will be invaluable to medical and other professionals as chances of these patients' long-term survival continue to improve.

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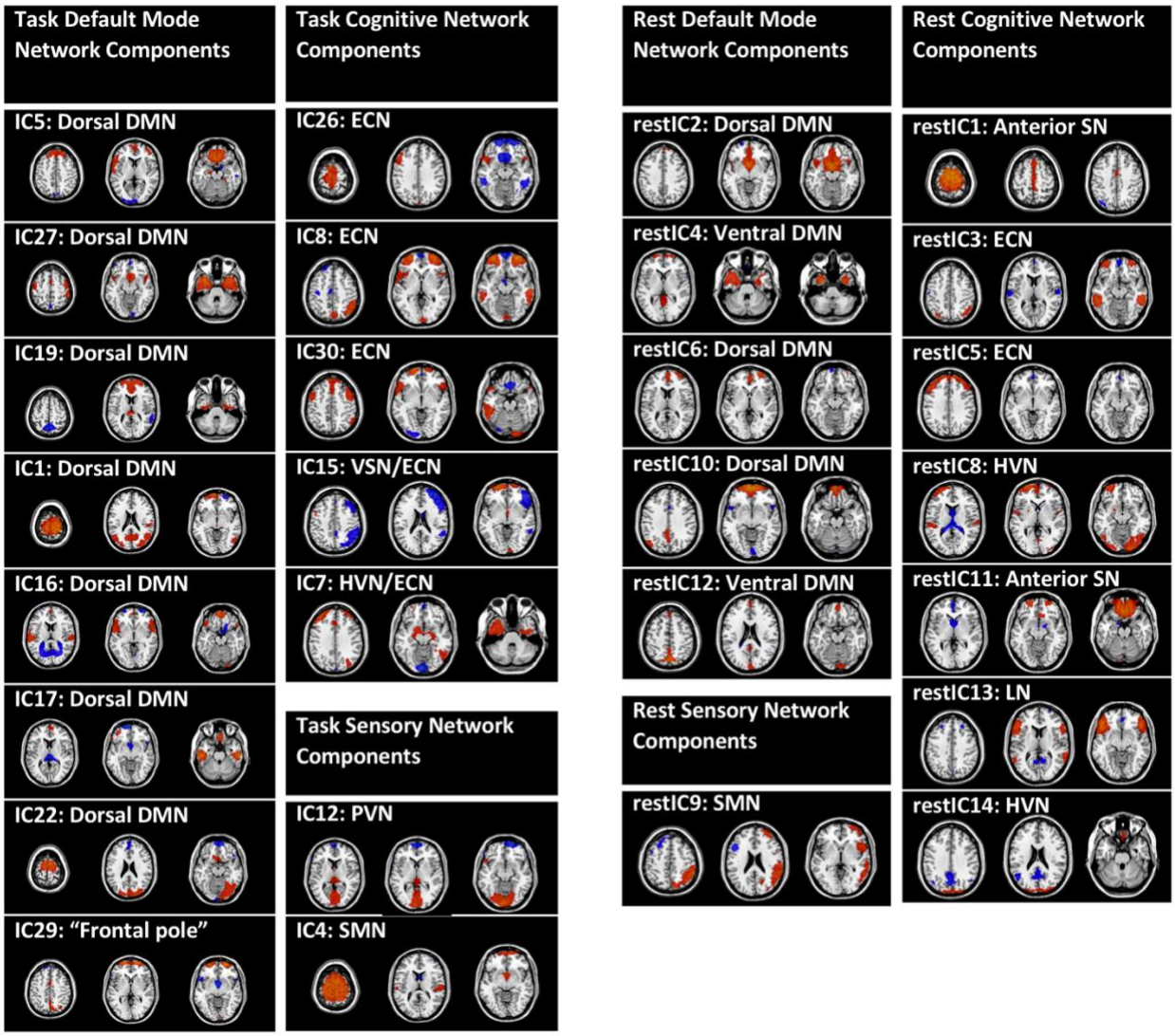
APPENDICES

Appendix A



Select axial slices from analyzed components. Warm colors indicate positively related regions; cool colors indicate negatively related regions.

DMN=default mode network; ECN=executive control network; HVN=higher visual network; LN=language network; PVN=primary visual network; SMN=sensorimotor network; SN=salience network; VSN=visuospatial network