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Attention and Functional Connectivity in Survivors of Childhood Brain Tumors

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ATTENTION AND FUNCTIONAL CONNECTIVITY IN SURVIVORS OF CHILDHOOD

BRAIN TUMORS

by

MICHELLE FOX

Under the Direction of Tricia Z. King, PhD

ABSTRACT

To study potential hyperactivity and hyperconnectivity based on the latent resource hypothesis, this study assessed functional connectivity in survivors of childhood brain tumors compared to their healthy peers during an attention task using psychophysiological interaction (PPI) analyses and evaluated for a relationship with performance. Twenty-three survivors and 23 healthy controls completed a letter n-back task in the scanner. An empirically-based seed was placed in the parietal lobe, a theoretical seed was placed in the hippocampus, and a control seed was placed in the occipital lobe. Differences in both performance and functional connectivity networks from each seed emerged between groups, with some findings supporting the latent resource hypothesis and other networks showing compensatory function in survivors. Attention networks, phonological networks, and executive function networks were all found to differ between controls and survivors.

INDEX WORDS: Brain tumors, Attention, Functional connectivity, Long-term outcomes, Neuropsychology

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A Thesis Proposal Submitted in Partial Fulfillment of the Requirements for the Degree of

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DEDICATION

This proposal is dedicated to my parents, brother, and extended family and friends who have provided me ongoing support throughout my education and enabled me to reach this stage.

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1 INTRODUCTION

Improvements in treatment of pediatric brain tumors in recent decades have led to increased survivorship into adulthood (Gurney et al., 2003), resulting in a greater need to study long-term neuropsychological sequelae of the illness. In particular, attention and working memory emerge as areas of weakness among survivors (Dennis et al., 1991; Edelstein et al., 2011; Nagel et al., 2006). To date, only a few studies have examined functional magnetic resonance imaging (fMRI) of working memory in survivors of childhood brain tumors (King, Na, & Mao, 2015; Robinson, Pearson, Cannistraci, Anderson, Kuttesch, Wymer, Smith, & Compas, 2014; Robinson, Pearson, Cannistraci, Anderson, Kuttesch, Wymer, Smith, Park, et al., 2014; Wolfe et al., 2013), and neuroimaging research of attention in this population remains nearly untouched. Studies of blood oxygen level dependent (BOLD) response from fMRI have shown different activation patterns. However, the field is moving toward a conceptualization of the brain as a series of networks as opposed to individually operating regions. Thus, more information is needed to understand correlations in activity between brain regions over the course of a task, particularly within clinical populations such as that of brain tumor survivors.

Working memory, one's ability to maintain, monitor, and manipulate information in the short-term (Goldman-Rakic, 1996), is frequently found to be deficient in pediatric brain tumor survivors using neuropsychological measures (Edelstein et al., 2011; Nagel et al., 2006). However, in order to understand an individuals' working memory capabilities, it is necessary to first consider their level of attention to the information they are expected to maintain, monitor, and manipulate. Evaluating working memory through a letter n-back task, as will be used in the proposed study, requires an understanding of participants' performance—and correlated brain activity and connectivity, in this instance—on a subset of the task that taps attention and

vigilance, the 0-back. In the limited studies available, brain tumor survivors have sometimes shown impaired attention (Derks, Reijneveld, & Douw, 2014; Gehrke et al., 2013; Robinson, Pearson, Cannistraci, Anderson, Kuttesch, Wymer, Smith, Park, et al., 2014), though other studies have not found significant differences (e.g., Robinson, Pearson, Cannistraci, Anderson, Kuttesch, Wymer, Smith, & Compas, 2014). Although imaging research in this field with survivors is limited, studies of healthy individuals have begun to identify networks involved in attention, such as a frontoparietal network (Parks & Madden, 2013). The roles of these networks are being investigated with fMRI and analyses of functional connectivity.

Functional connectivity analyses can be used to illuminate correlational relationships between regions across the brain and implicate their common role during tasks. Specifically, psychophysiological interaction (PPI) analyses assess whether there is an interaction between the correlation in activity across two distal brain areas and some measure, such as certain conditions within a task (O'Reilly et al., 2012). The associated principle is that if two areas increase and decrease in synchrony across conditions, there is a functional association between the regions, potentially indicative of communication regarding a task or support or suppression from one region to the other as it relates to task performance. Since its advent, functional connectivity has been used to investigate correlational activity across the brain during a number of cognitive tasks, including those that utilize attention and working memory. However, to date, it does not appear that research has considered the role of functional connectivity during an attention task in survivors of pediatric brain tumors and how it may compare to that of their healthy peers.

Neuroimaging studies have begun to guide researchers toward an understanding of the specific impact of changes in regional activity and connectivity between healthy and clinical groups. Frequently, groups with attention and working memory deficits such as traumatic brain

injury (TBI) or multiple sclerosis demonstrate greater recruitment or connectivity than their healthy peers, i.e., hyperactivity or hyperconnectivity (Hillary, 2008; Hillary et al., 2014). Medaglia and colleagues (2012) succinctly describe three theories that are used to explain this phenomenon. First, some researchers argue that increased recruitment of certain regions in clinical groups compared to controls reflects reorganization of pathways associated with the task participants are completing. These are believed to be permanent changes that should correlate with improved abilities within the clinical group (Sanchez-Carrion et al., 2008). The second theory is similar, suggesting that hyperactivity and hyperconnectivity are compensatory, i.e., these changes are necessary to make up for other difficulties (Maruishi et al., 2007; Scheibel et al., 2007). The final theory, which the present study aimed to support, is the latent resource hypothesis. The latent resource hypothesis states that as opposed to hyperactivity or hyperconnectivity being a function of compensation, it is a temporary increase in a network in response to specific challenges, working as cognitive reserves when standard function is somehow compromised (Hillary, Genova, Chiaravalloti, Rypma, & DeLuca, 2006; Hillary, 2008). This is supported by the findings of elevated recruitment of brain regions across various clinical populations and the association with poorer performance. We hypothesize that the proposed study will support the latent resource hypothesis using functional connectivity analyses in survivors of childhood brain tumors.

The present study investigated functional connectivity of attention networks in long-term survivors of pediatric brain tumors and their healthy peers, as well as evaluate the relationship between the strength of these connections and participants' performance. Measures were obtained during a functional MRI scan in which participants completed a letter n-back task, and FSL (fMRIB's Software Library, www.fmrib.ox.ac.uk/fsl) was used to conduct

psychophysiological interaction analyses to evaluate functional connectivity during the 0-back task relative to crosshair presentation and its association with performance.

1.1   Pediatric Brain Tumor Survivorship

Each year, more than 4,200 children in the United States are diagnosed with a brain tumor, with the majority of said tumors located in the posterior fossa (CBTRUS, 2012). Recent medical advances have led to a significant increase in long-term survivorship of individuals who suffer from pediatric brain tumors (Armstrong et al., 2009; Gurney et al., 2003; Maher & Raffel, 2004; Porter, McCarthy, Freels, Kim, & Davis, 2010). With so many of these individuals reaching adulthood, professionals across psychology, neurology, and neuropsychology are beginning to conceptualize the long-term impact that these tumors and their related treatments have on survivors' functioning, from the neuronal to the behavioral level. Survivors of pediatric brain tumors frequently present with difficulties across domains ranging from social skills to academic achievement (Eiser, 2004; Gottardo & Gajjar, 2008; Macartney, Harrison, VanDenKerkhof, Stacey, & McCarthy, 2014). Overall, survivors' quality of life is consistently beneath that of their peers (Hudson et al., 2003; Zebrack et al., 2002), and it has been noted that attention is a mediator of pediatric brain tumor survivors' daily living skills (Papazoglou et al., 2008). The specific capabilities of attention pervade many aspects of day-to-day function, and studying individual elements of functioning can bring us closer to informing the development of interventions that can benefit survivors across domains.

1.2   Attention and Working Memory in Brain Tumor Survivors

Working memory is defined as the ability to maintain and manipulate information over a short period of time and contributes elements of moment-to-moment functioning from language comprehension to deductive reasoning (Baddeley, 1992). In 1974, Baddeley and Hitch explained

working memory as a three-part system for storing and manipulating information that is comprised of a "phonological loop" containing a phonological store and articulatory rehearsal system, a "visuospatial sketchpad" that allows for the maintenance and manipulation of visuospatial information, and a "central executive" component that mediates the functions of the other two. This central executive, however, Baddeley went on to argue in 1993, does not involve storage and therefore does not involve memory; thus, it may even be more appropriate to label the entire system as one of "working attention." Ultimately, though, he concludes that although the central executive's primary role is attentional, it is still only part of an important memory system.

Working memory and its underlying component of attention are consistently found to be impaired in survivors of pediatric brain tumors across types of assessment (Dennis, Hetherington, & Spiegler, 1998; Conklin et al., 2012). Dennis and colleagues (1998) draw attention to the particular challenges faced by those who suffer from posterior fossa tumors; attention and memory are theoretically impeded due to the tumor and subsequent lesion's proximity to the brainstem ascending activation system. Survivors' attention and working memory difficulties may be a factor in both social and academic deficits leading to a lower quality of life (Lannering et al., 1998; Moyer et al., 2012; Zebrack et al., 2002).

1.3   Attention, Memory, and the Frontoparietal Network

Functional magnetic resonance imaging (fMRI) first appeared in the literature in the 1990s, and it has been conceived of as a way to obtain location-specific information about how the brain operates during a task. Although many neuropsychological tests that tap into the domain of working memory are available, one of the most widely-applied is the n-back task (Gevins & Cutillo, 1993). In the n-back, participants must indicate whether a letter, shape, or

position of an object presented on the screen in front of them is the same as the one presented n-slides ago. For example, on a letter 2-back task, in the sequence "b, a, B, c, D," a participant would be expected to only indicate "yes" with a button box when the B was presented, as it was the same letter as two letters back, and "no" for all other letters presented.

Numerous reviews indicate an increase in blood oxygenation level dependent (BOLD) signal that occurs in the dorsolateral prefrontal cortex during 2-back and 3-back blocks compared to 0-back and 1-back blocks, as these are considered measures of working memory. In contrast, 0-back and 1-back are generally considered measures of attention and vigilance (Carpenter, Just, & Reichle, 2000; Owen, McMillan, Laird, & Bullmore, 2005; Smith & Jonides, 1998). The right and left hemispheres tend to exhibit differences in activation depending on whether the task is spatial or verbal, respectively, and the concordance of the left hemisphere being more involved in language and the right being more involved in spatial reasoning provides a substantial theory as to why this may be (Wager & Smith, 2003).

Recent research has identified particular frontal and parietal regions as being involved in attention processes. In particular, the intraparietal sulcus (IPS)/superior frontal sulcus (SPL), temporoparietal junction (TPJ), and frontal eye fields (FEF) consistently emerge as areas of activity in attention-based fMRI, PET, and transcranial magnetic stimulation (TMS) studies (Corbetta & Shulman, 2002; Parks & Madden, 2013; Petersen & Posner, 2012). These regions emerge across go/no-go tasks, attention shifting tasks, search tasks, and more. Together, they are thought to comprise a frontoparietal attention network, making them areas of particular interest for the present study. Furthermore, the parietal lobes in particular are often implicated in working memory abilities, thought to play roles in both rehearsal and the storage process (Jonides et al., 1998; Owen et al., 2005). This has been noted across imaging studies (e.g., Wager & Smith,

2003) and lesion studies (e.g., Koenigs, Barbey, Postle, & Grafman, 2009; Smith & Jonides, 1998).

In the specific context of a 0-back task, positron emission tomography (PET) study of healthy individuals by Jonides and colleagues (Jonides et al., 1997) showed a relative activation during the 0-back compared to baseline in the left insula but a relative deactivation in the right posterior parietal area and the superior frontal area. More recently, King and colleagues (King, Na, & Mao, 2015) found that increased left parietal region activity was negatively correlated with accuracy on the 0-back task across pediatric brain tumor survivors and healthy controls. The 0-back task is frequently used as a relative control measures such that researchers may evaluate contrasts such as [2-back – 0-back] with the aim of isolating what may be considered functions of working memory. However, before taking that step, particularly with a clinical population, it is necessary to evaluate 0-back related findings, as is our goal with the present study.

Beyond the frontoparietal network, other regions of the brain are known for their involvement in attention and working memory as well. The dorsolateral and ventrolateral prefrontal cortices (dlPFC and vlPFC) have been implicated in numerous elements of working memory including encoding, maintenance and retrieval (Dove, Rowe, & Owen, 2001; Owen et al., 2005; Owen, 1997). The anterior cingulate cortex (ACC) is implicated in working memory tasks such that within healthy populations, its activity tends to increase as task load increases (Botvinick, Cohen, & Carter, 2004). In adolescents with traumatic brain injury, the region appears to be more active than in their healthy peers during a spatial working memory task as well (Cazalis et al., 2011). Beyond their distinct roles in memory, initial studies of functional connectivity suggest that the dlPFC and ACC together also play a role in attention monitoring (Han et al., 2013; Silton et al., 2011).

Connectivity research conducted in healthy populations has also grown steadily over recent years with more and more information coming from task-based analyses, and the dlPFC frequently emerges as part of functionally connected pairs of regions during working memory tasks (Dima, Jogia, & Frangou, 2014; Honey et al., 2002; Narayanan et al., 2005; Sala-Llonch et al., 2012), most consistently showing correlations in activity with the ACC, as well as regions of the parietal lobes. Such findings suggest that it would be reasonable to hypothesize that these regions may functionally interact with regions in the frontoparietal attention network and direct us toward the question of whether differences would emerge between healthy and clinical populations.

1.4   Attention and the Hippocampus

Since H.M.'s infamous bilateral medial temporal lobectomy over half a century ago, research on the hippocampus and surrounding medial temporal cortex has focused on the structure's role in memory. Recent findings suggest that the attentional component of working memory may have some basis in the hippocampus as well, particularly in survivors of pediatric brain tumors. Using the California Verbal Learning Test-Second Edition (CVLT-II), Jayakar and colleagues identified a relationship between hippocampal volume and auditory attention but not between volume and any other memory measure from the task after controlling for attention in survivors (Jayakar, King, Morris, & Na, 2015).

1.5   Hyperactivity, Hyperconnectivity, and the Latent Resource Hypothesis

The occurrence of hyperactivity and, a more recent topic of interest, hyperconnectivity in the brain has brought contemporary researchers to establish three conflicting theories. Hyperactivity tends to present in the cases of various clinical groups, such as those with traumatic brain injury, multiple sclerosis, or HIV, compared to healthy controls (Hillary, 2008).

Despite the distinctly different impacts that these diseases can have on the brain, hyperactivity, particularly in the prefrontal cortex, is a consistent trend. Alone, these findings can be interpreted to support the hypothesis of brain reorganization that occurs following some sort of neurological damage such that a new network develops in order to accomplish certain tasks, and the dlPFC bears more of the responsibility in this newly derived system. Others use such results to bolster the similar hypothesis of neural compensation, that is, the notion that this additional activation or connectivity is necessary for neurological populations to perform a task nearing a level of their healthy peers.

However, findings from additional studies suggest that some amendments to the hypotheses of reorganization and compensation are necessary. Within any given group, be it healthy controls or a clinical population, as task load increases, so does activity throughout the prefrontal cortex (Hillary, 2008; Narayanan et al., 2005). As a task becomes more routinized, PFC activity decreases (Medaglia et al., 2012; Qin et al., 2004). Thus, hyperactivity appears to be a tactic for dealing with situations that require more effort in both clinical and healthy populations. From this notion comes the latent resource or latent support hypothesis (Hillary, 2008; Hillary et al., 2011); certain regions, such as the dlPFC, and networks including them may be available resources for high-effort scenarios. Damage across the brain in individuals with TBI, MS, etc. may not cause complete rewiring as the reorganization hypothesis implies, but it will impact one's functioning such that more effort is required. Thus, humans tend to tap into these latent resources in order to complete the task in front of them, which presents as hyperactivity, particularly in the case of working memory challenges.

The minimal extant literature on functional MRI in pediatric brain tumor survivors follows the trend of hyperactivity as a latent resource as well. Within a subsample of the participants who

will be assessed in the proposed study, King and colleagues (2015) found increased blood-oxygen level dependent (BOLD) signals in survivors' frontal and parietal lobes relative to controls while completing a letter n-back task, and increased BOLD response correlated negatively with 0-back performance as well as performance on tasks of working memory.

1.6   Functional Connectivity

The recent advent of functional connectivity analyses allows us to understand how regions in the brain co-activate over a certain time frame, either a resting state or, in the case of the present study, a task, which therefore illuminates how regions are working in concert to conduct specific behaviors. Unlike fMRI analyses that look strictly at average activation throughout the brain, functional connectivity analyses assess correlations in activity between a seed region and elsewhere in the brain, providing information about similar patterns of activity in response to different elements of a task and elucidating functional networks across the brain. Overall, functional connectivity tends to be stronger within hemispheres than between hemispheres during cognitive tasks such as language or spatial processing (Liu, Stufflebeam, Sepulcre, Hedden, & Buckner, 2009; Wang & Liu, 2014). Motor tasks, however, have been shown to involve more interhemisphere connectivity (Gazzaniga, 2000).

Psychophysiological interaction (PPI) analyses, also known as context-dependent analyses, provide an assessment of one psychological and one physiological variable (Friston et al., 1997). In the case where the analysis being done is of a task in the MRI scanner, the psychological variable is the condition of the task itself, e.g., a 0-back trial compared to a crosshair presentation within an n-back task. The physiological component is the neural activity itself, that is, the BOLD signal from the seed region. An interaction regressor is subsequently generated from these data. The data obtained through this interaction analysis arguably provide

insight into information exchange between brain areas in certain contexts (O'Reilly, Woolrich, Behrens, Smith, & Johansen-Berg, 2012). Subsequent higher-order analyses can contrast these findings between groups, e.g., survivors compared to controls.

In recent years, PPI analyses along with other fMRI-based techniques such as independent component analyses and graph theory have allowed researchers to probe more deeply into the study of functional connectivity of various brain regions. However, as methodology is newer and interpretation remains highly varied, results are not always consistent across studies. For example, a study by Kasahara and colleagues (Kasahara et al., 2011) supported the latent resource hypothesis when looking at simple activation between TBI patients and healthy controls; both used the same regions and demonstrated more activation for more difficult levels of an n-back task, but patients showed relative hyperactivity. However, patients showed less functional connectivity within some networks that were significant in controls and in fact demonstrated more negative connectivity, that is, a stronger inverse relationship between regions, in some networks compared to controls, though only in patients did a correlation between PPI strength and percent correct response emerge. As such, although the study's activation findings support the latent resource hypothesis, the connectivity findings lean toward a theory of compensation.

Within a healthy population, Prado and colleagues (Prado, Carp, & Weissman, 2011) used PPI analyses on a selective attention task. They found that reduced frontal-parietal and intra-frontal functional connectivity correlated with an increased reaction time within the task, although these regions had shown increased individual activation during the task. Other methods of evaluating functional connectivity in healthy individuals have shown increased connectivity of similar networks correlating with improved performance on attention tasks (Wen et al., 2012).

Undeniably, more research is needed to clarify these networks and their role in attentional processes.

A recent meta-analysis by Hillary and colleagues (Hillary et al., 2014) examined 126 studies of resting state connectivity across different neurological populations and found that while connectivity decreased in degenerative diseases like Alzheimer's, individuals with TBI and MS consistently showed hyperconnectivity compared to their healthy peers. Despite the data coming from resting state scans, a relative baseline, the authors suggest that these findings would be expected across varying levels of situational demands. No task-based functional connectivity studies involving survivors of pediatric brain tumors have been conducted as of yet, and, as such, the conflicting findings from the TBI population remain the best model on which to develop hypotheses.

1.7 Aims of This Study

The current study aimed to examine functional connectivity between specific seed regions and the remainder of the cortex and subcortical regions during an attention task across pediatric posterior fossa brain tumor survivors and age- and sex-matched healthy controls. Attention was assessed with a letter n-back task that took place while participants were in the MRI scanner, and analyses compared the 0-back attention condition to the crosshair presentation to specifically evaluate regions involved in vigilance and attention. Attention-based functional connectivity was measured with psychophysiological interaction analyses using seed regions in the left hemisphere.

1.7.1 Specific Aim 1

We aimed to investigate differences in pediatric brain tumor survivors' compared to controls' functional connectivity during the letter n-back task, specifically in the contrast of the

0-back trials to the crosshair. The 0-back task is conceptualized as a measure of attention and vigilance. Cortical and subcortical regions were included in analyses. First-level PPI analyses showed regions that are functionally connected with the seed regions over the contrast, and second-level analyses indicated any significant differences between survivor and control groups. The initial seed region was selected based on results of an analysis of BOLD signal differences between the two groups across the [0-back – crosshair] contrast, with the *a priori* hypothesis that a left parietal region and the hippocampus would emerge as regions of significant difference. It was determined that if no regions in the left hemisphere emerge with significant BOLD differences between groups, the left hippocampus and left Brodmann area 40, which is bounded by the IPS, would be used as seed regions.

Hypotheses:

- A seed at the intraparietal sulcus would be functionally connected to regions within the established dorsal frontoparietal network, e.g., frontal eye fields and superior parietal lobule due to their known roles in attentional processes, and would be functionally connected to regions known for their working memory involvement as well, e.g., the dorsolateral prefrontal cortex and hippocampus.

- A hippocampal seed would be functionally connected to the aforementioned regions as well, along with the intraparietal sulcus.

- Functional connectivity was expected to be more present within the left hemisphere than across hemispheres per findings by Liu and colleagues (Liu et al., 2009) and Wang and Liu (Wang & Liu, 2014) and their theories of the development of the human brain.

- All pairs of functionally connected regions will be more functionally connected in survivors than in healthy controls (hyperconnectivity).

1.7.2   Specific Aim 2

We aimed to investigate the relationship between functional connectivity evaluated in Specific Aim 1 and performance on the attention task. The survivor group and the healthy control group were assessed with separate regression analyses before being compared in a moderation analysis. We also assessed the relationship among connectivity, 0-back performance, and a clinical measure of attention (BRIEF Task Monitor subscale; see Additional Planned Analyses). To show specificity, we ran the same analyses with a clinical measure of presumed non-significance (BRIEF Emotional Control subscale) and the BRIEF Global Executive Composite scores.

Hypotheses:

- Task accuracy, as evaluated by Macmillian & Creelman's (Macmillan & Creelman, 1990) measure of d', would be negatively correlated with functional connectivity between the seed regions and other regions of the brain within each group.

- Connectivity would correlate more strongly with accuracy in survivors due to a greater need to maintain use of this latent resource network, similar to the findings by Kasahara and colleagues (Kasahara et al., 2011) in traumatic brain injury patients.

- Attention as observed in daily life, as measured by the BRIEF Task Monitor subscale, would correlate with 0-back performance and show patterns and relationships similar to said attention task.

2   METHODS

2.1   Procedures

2.1.1   Participant Recruitment and Screening

Brain tumor survivor participants were recruited through a combination of referrals from Children's Healthcare of Atlanta and mailings sent to participants in a previous study, and all were at least five years out from their initial diagnosis of medulloblastoma, astrocytoma, or PNET. Participants' tumors were located in the general posterior fossa area so as to maintain as much uniformity as possible for analyses of cortical regions. The control sample was recruited through Georgia State University's research pool and fliers and advertisements throughout the Atlanta community. All participants signed consent forms. The control sample was age- and gender-matched with the survivor sample (Table 1). Controls had no history of neurological or psychological disorder and were administered the SCID-II (First, Spitzer, Gibbon, & Williams, 1997) to ensure of no present or past psychological disorders or substance abuse. All participants underwent screening to confirm that they were safe to enter the magnetic resonance imaging (MRI) scanner. Survivors' medical history was obtained through self-report and confirmed with medical chart review by graduate students. Participants were excluded from analyses due to excessive motion, scanner problems or use of a different MRI scanner, tumor recurrence, sensorineural deficits, and developmental disorders (Figure 1). Pre-processing showed clean scans from 23 survivors and 23 matched controls during the task.

Table 1. Survivor and control participant information

	Controls	Survivors
N (Number of Participants)	23	23
Number of Females (%)	15 (65%)	15 (65%)
Race	15 Caucasian, 5 African-American, 2 Asian, 1 Not Reported	18 Caucasian, 1 African-American, 1 Asian, 1 Hispanic, 2 Biracial
Age at Examination: Mean Years (SD)	23.42 (4.17)	23.65 (5.49)
Years of Education: Mean Years (SD)	14.91 (1.70)	14.00 (2.76)
Wechsler Abbreviated Scale of Intelligence Score: Mean Score (SD)	112.13 (9.02)	98.39 (13.47)
Tumor Type	-	12 medulloblastoma, 10 astrocytoma, 1 PNET
Specific Tumor Location	-	12 posterior fossa, 10 cerebellum, 1 medulla
Age at Diagnosis: Mean Years (SD)	-	8.83 (5.14)
Hydrocephalus		74% Yes
Radiation Treatment	-	61% Yes
Chemotherapy Treatment	-	57% Yes
Neurosurgery	-	100% Yes
Seizure Disorder	-	0% Yes
Hormone Deficiency	-	61% Yes
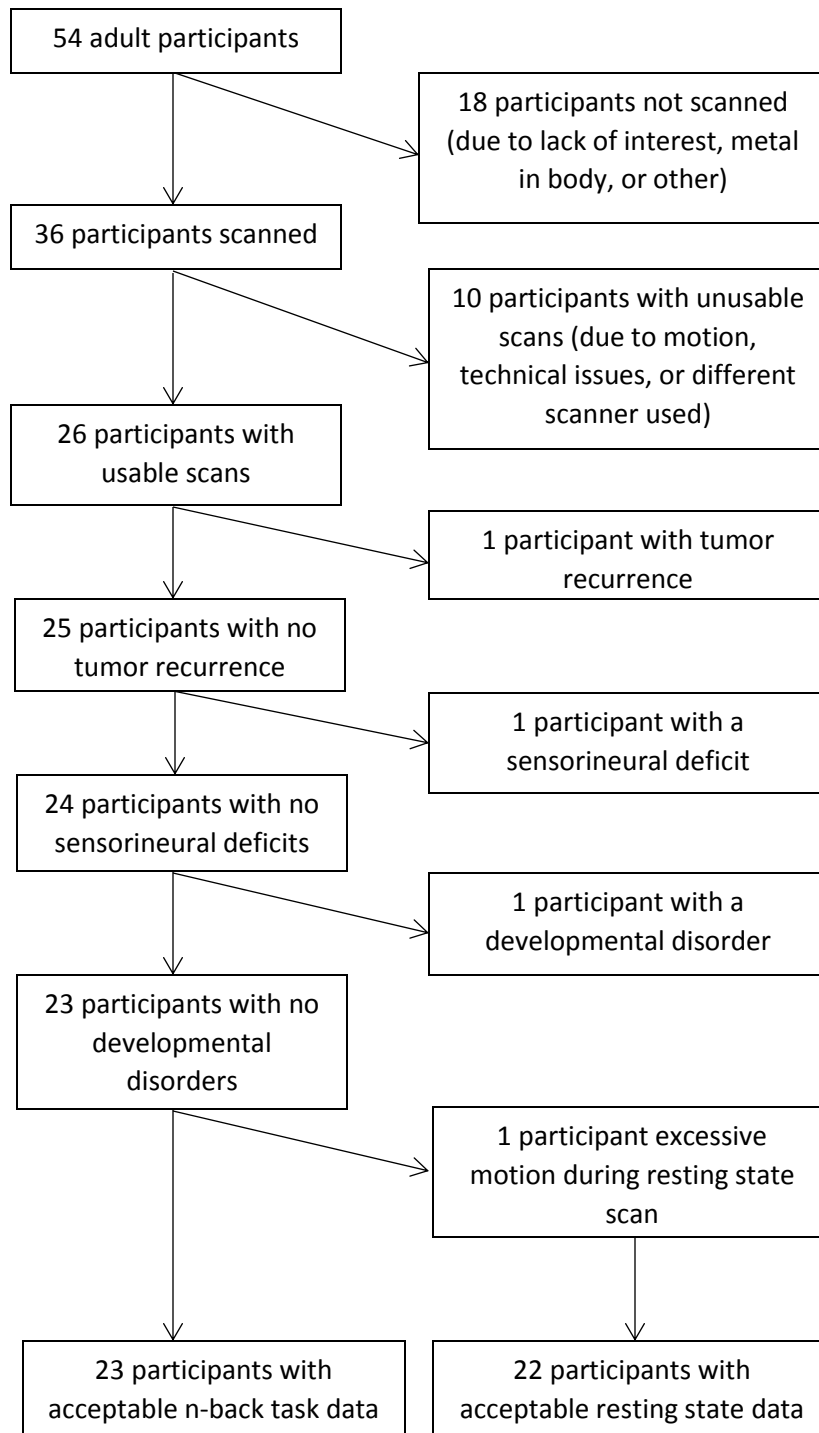
Figure 1. Survivor participant exclusion tree

2.1.2 Letter n-Back Task

At the GSU/GaTech Joint Center for Advanced Brain Imaging, both survivors and

healthy controls completed the n-back task (Gevins & Cutillo, 1993), a well-established working

memory task, in the MRI scanner. In the n-back, participants must indicate whether a letter

presented on the screen in front of them is the same as the one presented n letters ago. To

evaluate attention and set a basis for later evaluations of working memory, we analyzed the 0-

back data. 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. Specifically, analyses used a [0-back – crosshair] contrast in

attempt to discount any connectivity that was based in elements of the task not involving

attention, such as visual processing of the stimulus or other sensory processing that naturally

occurs during an MRI scan. 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.

Participants were in the scanner for approximately 45 minutes.

The task was set up as a block design with five total runs, each comprised of a fixation

period and five blocks (a crosshair block and 0-, 1-, 2-, and 3-back blocks). Each block lasted

approximately four minutes, making the entire task last approximately 20 minutes. Blocks were

counterbalanced. 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 d' (i.e., "d prime"; Haatveit et al., 2010; Macmillan & Creelman, 1990) index that

includes evaluation of hits, misses, false alarms, and correct recognition of non-targets (i.e., pressing the "no" button at the appropriate time).

2.1.3   Additional Neuropsychological Measures

All participants were administered the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 2009) and the Behavior Rating Inventory of Executive Function (BRIEF; Gioia et al., 2000) self- and informant-report forms as part of a larger neuropsychological test battery. Participants 18 years and older completed the Adult version and, and an informant completed the Adult Informant form. Participants who were 17 years old completed the Child version and a parent completed the Parent Informant form. Questions varied slightly between versions, but all scales utilized were the same. The Informant BRIEF Task Monitor subscale, which contains statements such as "makes careless errors when completing tasks" and "has problems completing his or her work," was used as a proxy for a clinical measure of attention in analyses. To evaluate specificity in any relationships identified between the BRIEF Task Monitor subscale and functional connectivity, the BRIEF Emotion Regulation subscale scales were also analyzed with respect to functional connectivity. The BRIEF Global Executive Composite (GEC) scale scores were evaluated as well. Higher BRIEF scores indicate greater impairment, and $T{\geq}65/z{\geq}1.5$ indicates significant impairment.

2.1.4   Imaging Parameters

Imaging data was acquired using a 3T Siemens Trio MRI scanner. A total of 620 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)=204 mm and flip angle = 90 degrees). The imaging sequence was acquired as 40 axial slices, 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=$3.0\times3.0\times3.0$ mm^3. The

scan time was 275 s, with a total of 129 volumes recorded.

2.1.5   Imaging Analysis

fMRI data analyses were conducted using FEAT (fMRI Expert Analysis Tool) Version

5.98, which is part of FSL (fMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). The first five

volumes were removed from the beginning of the fixation period that started each run to allow

for T1 equilibrium effects. For individual pre-processing, FEAT was used for the following:

motion correction using MCFLIRT, slice-timing correction using Fourier-space time-series

phase-shifting, brain extraction using BET, spatial smoothing using a Gaussian kernel of FWHM

5mm, and highpass temporal filtering (Gaussian-weighted least-squares straight line

fitting, sigma = 50.0s). Further, FEAT was used to register individuals' preprocessed functional

data to their unique T1 MPRAGE images, at which point all was registered to MNI space.

The AFNI software package (Cox, 1996) was utilized for resting state analyses.

Preprocessing was conducted using uber_subject.py, the graphical interface to afni_proc.py.

Similar to the functional runs, the first five volumes were removed from the beginning of the

fixation period that started each run to allow for T1 equilibrium effects. Spatial smoothing used a

kernel of FWHM 5mm and the motion censor limit was set to 0.3mm per TR. One survivor

participant was dropped from resting state analyses due to excessive motion beyond 0.3mm per TR in one direction, although this subject's n-back task imaging data were acceptable and therefore utilized. Images were set to register to the MNI152 template.

2.2 Analyses

2.2.1 Analyses for Specific Aim 1

2.2.1.1 BOLD Analyses

First level analyses were conducted using a general linear model (GLM) in FSL's FEAT; an unpaired two-group difference model was used to assess the between-subjects effect of group and within-subjects effect of load (i.e., 0-back or crosshair). Z-statistic images were thresholded at $z > 1.96$ with a corrected cluster significance threshold of $p < 0.05$, and a mask of the MNI brain was utilized to minimize extraneous motion findings outside of the brain. To assess whether hyperactivity in survivors aligned with the latent resource hypothesis, we ran correlational analyses between percent signal change of the left parietal region of interest that emerged (see Results section for additional detail) and participants' 0-back d' value. Percent signal change was calculated using FSL's FEATQuery tool. Correlations were run among percent signal change for the identified parietal cluster and a priori hippocampal cluster and behavioral variables (d', BRIEF Task Monitor, BRIEF Emotional Control, and BRIEF Global Executive Composite).

2.2.1.2 Psychophysiological Interaction Analysis

Our first region of interest was established at the local maximum of greatest significance that was at least three millimeters in from the edge of the MNI template brain in the survivors-controls [0-back – crosshair] contrast, which was in the left parietal lobe at (-30, -76, 44). A

3mm-radius sphere was created at this point on the MNI 2mm template brain using the fslmaths feature of FSL before being warped into individual subjects' functional space and visually inspected to ensure that the sphere was within each subject's brain.

As no significant local maxima were identified in the left hippocampus, a seed was centered at (-28, -18, -18), the voxel of highest probability of hippocampal placement per the Harvard-Oxford Subcortical Structural Atlas. A 3mm-radius sphere was created and checked here using the same procedure as with the parietal seed described above.

A control seed was created in the left occipital lobe after visual verification that the region was not found to present with significant percent signal change in the [0-back – crosshair] for survivors, controls, or the difference between the two groups. A 3mm-radius sphere was created at (-10, -100, -6) and checked using the same procedure as described above.

The timecourse of each seed was extracted using FSL's fslmeants before setting up a GLM in FEAT. All EVs from the original BOLD activation analyses were maintained, and three additional EVs were created. Our psychological regressor was the task regressor, a text file of [0-back – crosshair] convolved with a hemodynamic response function. Our physiological regressor was the timecourse of the given seed region, and the psychophysiological interaction regressor was generated by the interaction feature of the FEAT GUI. A contrast consisting of the mean of each of these regressors as well as the negative mean of the interaction were generated by FEAT. This process was completed for each seed in each individual subject without corrections, and an unpaired two-group group-level analysis was conducted for each seed. A mask created in FSLView that included all cortical and subcortical regions from the MNI template but excluded the brainstem, cerebellum, and ventricles was used to generate a t-map of significance in each group and differences between the survivors and controls. Results were z-maps of the brain

indicating which regions' activity in the 0-back (but not crosshair) significantly correlate with that of the seed region in our contrast, i.e., have significant beta weights thresholded at $p < 0.001$ and uncorrected for multiple comparisons, and clusters with 10 or more voxels were considered significant (Harding et al., 2012). Within a given network of the seed and another region, one group could show greater functional connectivity than the other, the two groups could not differ at all, or one group could show more "negative" connectivity, that is, an anticorrelation between the seed and other region during the task or increased connectivity during rest compared to the task. As per the latent resource hypothesis, we expected that survivors, being more in need of this latent support for a challenging task, will show greater functional connectivity than controls. We expected positively correlated networks to emerge between the parietal lobe and the frontal eye fields, within the parietal lobe (e.g., between the intraparietal sulcus and superior parietal lobule), and between the hippocampus and regions of this dorsal frontoparietal network, all regions known to be involved in attention, memory, and/or task-positive behavior.

The trial type itself (i.e., 0-back or crosshair) was inherently modeled out as a covariate of no interest as it is the task regressor in the PPI, but participants' accuracy as assessed by our d' variable was not controlled for in these initial connectivity analyses. Holding constant the effect of performance at this first pass may suppress trends of interest, as it would have been possible to see correlations between performance and connectivity. According to the latent resource hypothesis, additional connectivity would be utilized when participants' brain function is otherwise compromised but would not necessarily improve performance; however, various discrepancies in performance were still possible and would each contribute to the corpus of knowledge about connectivity. Thus, we chose to investigate these relationships in Specific Aim

2. This plan of analysis was modeled after that of Kasahara and colleagues (Kasahara et al., 2011).

2.2.2 *Analyses for Specific Aim 2*

Beta weights for the positive interaction were extracted at the peak of each significant cluster using FEATQuery. Both grouping together and separating the controls and survivors, we performed correlational analyses between our [0-back – crosshair] PPI strength for each cluster of significance and performance on the n-back as assessed by the d' scores on the 0-back. In the cases where any set of participants showed significant relationships between d' and connectivity, an interaction model was also set up to explicitly evaluate the relationship between connectivity and performance between the survivor and control groups.

Correlations and some subsequent moderation models were also run between 0-back behavioral measure and the BRIEF Task Monitor and Emotion Regulation subscale scores and Global Executive Composite score. BRIEF scores were subsequently analyzed with respect to connectivity beta weights in the same manner as the 0-back performance values. The use of an emotional control measure followed a model set forth by King and colleagues (King, Smith, & Ivanisevic, 2015), as it is an executive skill that is not expected to be disrupted in survivors.

Due to ceiling effects of the 0-back task, performance data for both survivors and controls showed noticeable negative skewness. Following suggestions by Tabachnick and Fidell (Tabachnick & Fidell, 2001) and Howell (Howell, 2007), we attempted log-transforming these data with the following equation in SPSS: NEWX = LG10(K-X), where K is a constant from which each score is subtracted so that the smallest score is 1. Square root transformations and inverse transformations were also considered but elected to use the log transformation as it minimized skew and kurtosis.

As detailed by Hillary and colleagues (Hillary et al., 2006) and later supported by findings of Medaglia and colleagues (Medaglia et al., 2012) with TBI patients, we expected that connectivity would correlate more strongly with decreased 0-back accuracy in survivors. Such results would provide support for the latent resource hypothesis, as survivors who are challenged by the 0-back task would be recruiting this network, even though it would not bring them up to par with their healthy peers, as noted by d' values. A hyperconnected network in survivors that is not at all correlated with performance despite showing a significant relationship in controls could also be indicative of said network being a latent resource; such a network might be recruited in response to a challenge and may be an indication of increased effort without any improvement in performance.

3 RESULTS

3.1 Foreword to the Results and Discussion

PPI imaging analyses were conducted with an uncorrected voxel threshold of $p<0.001$, and clusters were identified as "significant" when composed of 10 or more of these surviving voxels, a traditional thresholding process in the literature first set forth by Harding and colleagues (2012) and commonly used with PPI analyses (e.g., Kasahara et al., 2011). However, the publication of a recent paper (Eklund et al., 2016) has clearly indicated to the neuroimaging community that more stringent voxel-wise corrections must be conducted in order to control for family-wise error and be confident that a study is not rife with false positive results. Thus, all results from the present study must be interpreted with caution. Future analyses will include stricter voxel-wise thresholding before any attempts at publication of these data are made. Additional information is detailed in the Discussion section.

3.2   Specific Aim 1

3.2.1   *Behavioral Analyses*

Behavioral analyses identified a difference in performance on the 0-back between

survivors and controls such that controls performed better on this measure of attention as

measured by d' ($M_{survivors}$=3.568, $SD_{survivors}$=0.775 while $M_{controls}$=3.946, $SD_{controls}$=0.244, t=-2.23,

p<0.05). As both groups demonstrated notable negative skew (t=-2.992, SE=0.350) and kurtosis

(t=10.386, SE=0.688), d' values were log-transformed as suggested by Tabachnick and Fidell

(Tabachnick & Fidell, 2001) and Howell (Howell, 2007), reversing the direction of the skew

(t=1.963, *SE*=0.350) and shrinking both the skew and kurtosis (t=3.821, SE=0.688) such that

skew was less than ±2 and the kurtosis was less than ±5 as suggested by (Tabachnick & Fidell,

2001). All following analyses were conducted with both d' and d' log-transformed values, but

due to success of the transformation, only those with the log-transformed d' values are reported.

A lower d' log-transformed value reflects better performance, e.g., $M_{survivors}$=0.140,

$SD_{survivors}$=0.173 while $M_{controls}$=0.046, $SD_{controls}$=0.080 (t=2.371, p<0.05). A non-parametric

Mann-Whitney U test was also run to confirm group differences and also indicated that

performance was significantly better in controls than survivors (U=173.500, p=0.043). When

both groups were evaluated together, four survivors' log-transformed scores remained outliers,

while no controls' scores were outliers.

Although the healthy controls were age- and sex-matched with the survivor sample, the

controls' mean IQ (*M*=112.13, *SD*=9.02) was significantly higher than that of the survivors

(*M*=98.39, *SD*=13.47; t(44)=4.07, p<0.001). This relationship was consistent across all subtests

of the WASI. We did not control for IQ based on concerns raised by Dennis and colleagues

(Dennis, Francis, Cirino, Barnes, & Fletcher, 2011); controlling for IQ in analyses has been

found to overcorrect impairments in more specific domains, potentially eliminating relevant effects.

3.2.2 BOLD Activation Analyses

First level analyses indicated numerous significant areas of activation (per cluster-wise thresholding) in the control and subject groups in the [0-back – crosshair] contrast, e.g., the middle frontal gyrus, insulae, right cerebellum, and parietal lobes in both groups, the left precentral gyrus in survivors, and the left dlPFC and postcentral gyrus in controls (see Figures 2a & 2b).
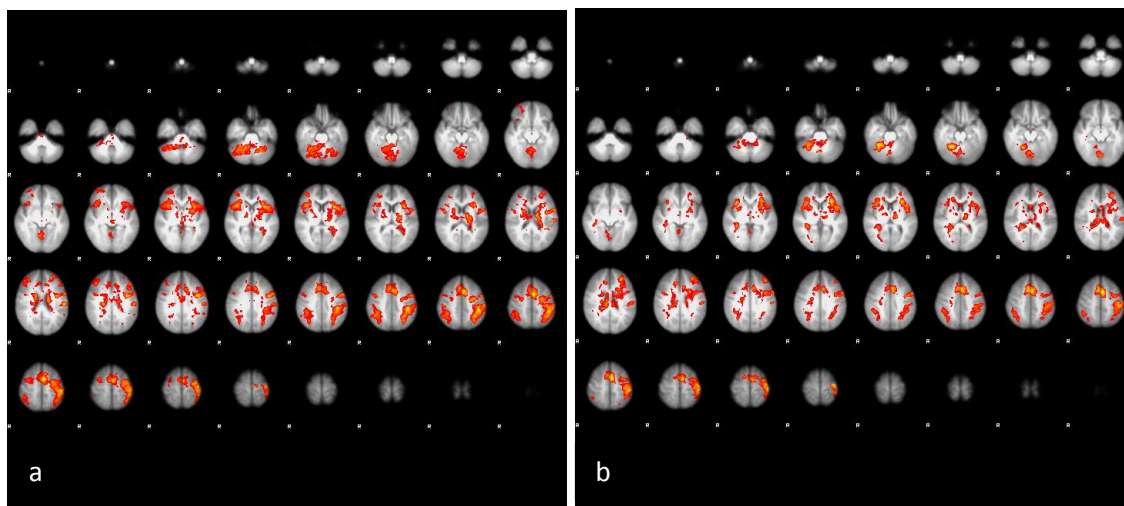
Figure 2. a) [0-back – crosshair] survivor BOLD contrast; b) [0-back – crosshair] control BOLD contrast. Red-yellow regions indicate BOLD activity surpassing the $z>1.95$, cluster $p<0.05$ threshold with brighter colors indicating a greater percent signal change.

A single cluster emerged from the unpaired two-group difference model when $z>1.96$; survivors showed greater activation in the left parietal lobe, BA 19, than survivors (see Figure 3).
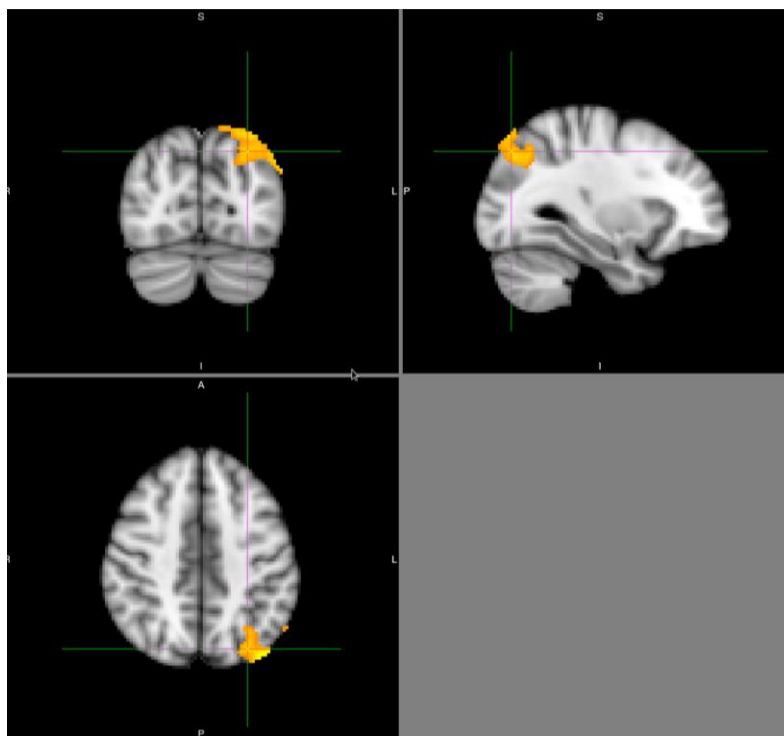
Figure 3. Survivors show greater BOLD signal than controls in the left parietal lobe in the [0-back – crosshair] contrast. Orange-yellow indicates a difference in BOLD activity between the two groups surpassing the $z>1.96$, cluster $p<0.05$ threshold. The crosshair indicates the location at which the PPI seed was centered (30, -76, 44).

The peak voxel of this cluster was located at (-40, -82, 42) where $z=3.95$ but was not selected as the center of the seed region due to its nearness to the edge of the example functional template brain. The voxel of greatest activation that was at least 3 voxels away from the edge of the brain, (30, -76, 44), $z=2.96$, was selected to best ensure that the 3mm seed ROI that was to be created for the PPI analyses would be located within each subject's brain.

There was a significant positive correlation between percent signal change of the selected parietal seed and log-transformed d' when all subjects were grouped together, $R=0.350$, $p=0.017$, though such a significant trend did not emerge in either group alone (survivors' $p=0.270$, controls' $p=0.125$). This is despite regression analyses indicating that survivors ($B=0.089$) had a more positive slope than either controls ($B=0.043$) or both groups combined ($B=0.083$; see

Figure 4). Note that a higher log-transformed d' score indicates poorer performance. Percent

signal change of the parietal seed did not correlate with any BRIEF scores. Percent signal change

of the structurally defined hippocampus seed did not correlate with any behavioral measures.
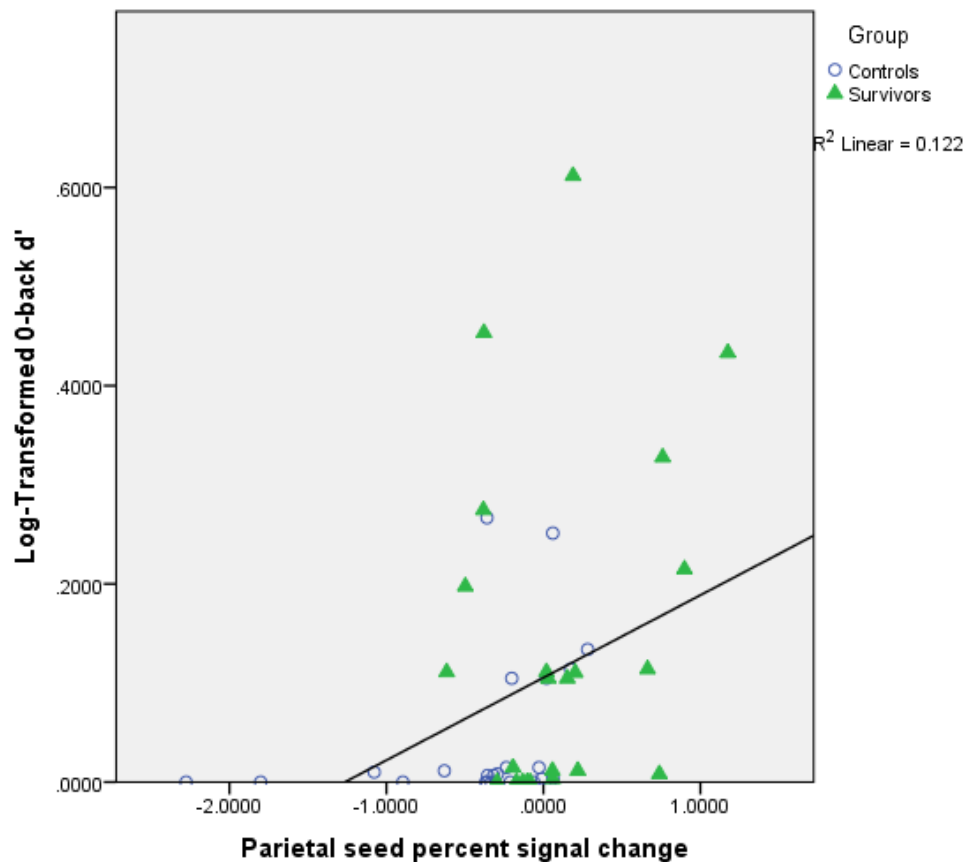
Figure 4. Correlation between parietal seed's BOLD percent signal change in [0-back – crosshair] contrast and log-transformed 0-back d' scores by group.

3.2.3 Functional Connectivity Analyses

All significant PPI findings are outlined in Table 2. At a threshold of $p<0.001$,

uncorrected for multiple comparisons, no significant clusters emerged from the positive

interaction between the [0-back – crosshair] task contrast and the extracted parietal seed's

timecourse for the survivors, the controls, or the difference between the two. However, in the

case of the negative interaction, in survivors only, the left parietal seed interacted with the right superior parietal lobe (BA 7, peak voxel (10, -70, 48) z=3.588, p<0.001; see Figure 5). In controls only, the left parietal seed negatively interacted with the right dorsomedial occipital lobe (BA 19; peak voxel (8, -84, 38) z=3.573, p<0.001; see Figure 6a) and medial prefrontal cortex, (BA 9; peak voxel (0, 60, 10) z=3.573, p<0.001; see Figure 6b).
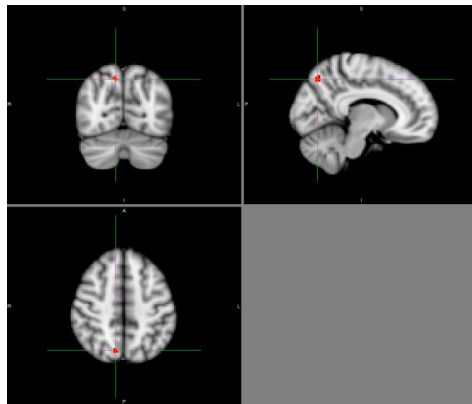
Figure 5. Right superior parietal cluster that negatively interacts with the left parietal seed in survivors across the [0-back – crosshair] contrast overlaid on the MNI152 template at the uncorrected voxel threshold of p<0.001; crosshair at peak voxel (10, -70, 48).
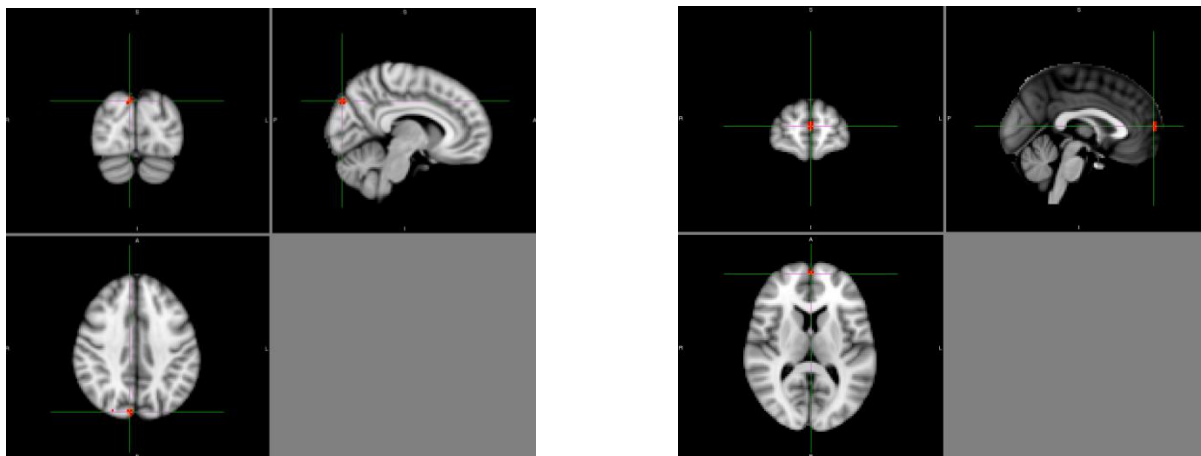
Figure 6. Clusters that negatively interact with the left parietal seed in controls across the [0-back – crosshair] contrast overlaid on the MNI152 template at the uncorrected voxel threshold of p<0.001. a) A right superior parietal cluster, crosshair at peak voxel (8, -84, 38); b) a medial prefrontal cortex cluster, crosshair at peak voxel (0, 60, 10).

At a threshold of $p<0.001$ uncorrected for multiple comparisons, the difference between survivors' and controls' positive interaction between the left hippocampal seed and the left temporal fusiform gyrus over the [0-back – crosshair] task contrast was significant, with the peak voxel in the fusiform gyrus cluster at (-24, -40, -20), $z=3.539$. As expected, this same cluster emerged as negatively correlated with the controls minus survivors contrast with all values remaining the same.

Furthermore, for survivors alone, the left hippocampal seed region negatively interacted with two clusters in the right postcentral gyrus (peak voxels (62, -12, 20), (54, -12, 34); $z=3.658$, 3.975, respectively) and one cluster in the left postcentral gyrus (peak voxel (-34, -30, 54); $z=3.572$). It also negatively interacted with the left dorsolateral prefrontal cortex (peak voxel (-24, 58, 24); $z=3.530$), three clusters in the left precentral gyrus (peak voxels (-28, -40, 58), (-56, 6, 36), (-46, -12, 38); $z=3.462$, 3.488, 3.491, respectively), and two clusters in the supramarginal gyrus of the left parietal lobe (peak voxels (-54, -30, 38), (-44, -34, 40); $z=3.644$, 3.429, respectively). Controls alone showed a positive interaction between the left seed region and the left inferior temporal gyrus (peak voxel (-56, -24, -22), $z=3.440$).

Interactions from the left occipital control seed region were seen in difference scores and among survivor and control groups separately, but no overlap was seen between the regions functionally connected to the control seed or the regions functionally connected to either hypothesized seed.

Table 2. Summary of results of PPI analyses from all seeds.

Interaction	Group/ Contrast	Peak Voxel z	x	y	z	BA	Region
				Coordinates			
Negative PPI from L parietal seed	Survivors	3.588	10	-70	48	7	R medial parietal lobe
	Controls	3.594	8	-84	38	19	R medial parietal lobe
		3.573	0	60	10	10	medial PFC
Positive PPI from L hippocampal seed	Survivors> Controls	3.539	-24	-40	-20	20	L temporal fusiform gyrus
Negative PPI from L hippocampal seed	Controls> Survivors	3.539	-24	-40	-20	20	L temporal fusiform gyrus
	Survivors	3.975	54	-12	34	3	R lateral postcentral gyrus
		3.658	62	-12	20	4	R lateral postcentral gyrus
		3.644	-54	-30	38	40	L supramarginal gyrus
		3.572	-34	-30	54	40	L postcentral gyrus
		3.530	-24	58	24	9	L dorsolateral PFC
		3.491	-46	-12	38	3	L lateral precentral gyrus
		3.488	-56	6	36	6	L lateral precentral gyrus
		3.462	-28	-40	58	7	L medial postcentral gyrus
		3.429	-44	-34	40	40	L lateral parietal
	Controls	3.440	-56	-24	-22	20	L inferior temporal gyrus
Positive PPI from L occipital seed	Controls> Survivors	3.650	-26	26	32	9	L middle frontal gyrus
		3.644	-52	6	36	6	L precentral gyrus
Negative PPI from L occipital seed	Survivors> Controls	3.650	-26	26	32	9	L middle frontal gyrus
		3.644	-52	6	36	6	L precentral gyrus
	Survivors	3.797	-26	26	32	8/9	L middle frontal gyrus
		3.700	24	-100	-6	17	R occipital pole
		3.618	-32	-64	-22	19	L temporal occipital fusiform cortex
		3.616	20	-90	22	18	R medial occipital lobe
		3.549	-8	-82	-12	18	L medial inferior occipital lobe
		3.478	-26	-88	26	19	L lateral occipital lobe
		3.450	-2	-86	0	18	L medial occipital lobe
	Controls	3.622	28	-66	-12	18	R occipital fusiform gyrus
		3.461	36	28	-8	47	R ventrolateral PFC

False discovery rate (FDR) corrected values of $q<0.05$ were used as initial significance thresholds when evaluating the AFNI resting state functional connectivity data. No significant clusters emerged as functionally connected with any seed at $q<0.05$ for the contrast between survivors and controls. However, numerous voxels survived even at $q<0.001$ for each seed within the separate survivor and control groups. Consistently, the areas around the seed region

and their bilateral counterparts were significant (e.g., left parietal-right parietal). In survivors, following the cluster surrounding the left parietal seed itself (723 voxels), the next largest cluster of voxels functionally connected to the left parietal seed was 306 voxels large and located in the right parietal lobe with the peak at (36, -60, 44), $z=6.69$, $q<0.001$. In controls, the cluster surrounding the left parietal seed itself was largest (2060 voxels), and the third largest cluster of voxels functionally connected to the left parietal seed was a right parietal cluster of 521 voxels with the peak at (44, -66, 38), $z=6.39$, $q<0.001$. The connectivity between the left and right parietal lobes seen in each group is one of the only networks that also emerged from the PPI analysis.

In both survivors and controls, the left parietal seed was also functionally connected with the left frontal lobe during rest. Controls' second largest cluster following that surrounding the left parietal seed was a 682-voxel cluster that stretched through the left lateral prefrontal cortex with a peak at (-46, 54, 0), $z=6.34$, $q<0.001$. Smaller clusters survived similar thresholding in the left PFC survivors (e.g., a 37-voxel cluster in the dlPFC, peak (-48, 18, 44), $z=5.27$, $q<0.001$). In controls, smaller clusters also survived the threshold of $q<0.001$ in the right frontal lobe.

From the left hippocampal seed, at $q<0.001$, survivors only showed functional connectivity surrounding the seed, though controls demonstrated both that and a 51-voxel cluster of bilateral connectivity in the right hippocampus (peak (30, -16, -18), $z=6.68$, $q<0.001$). At a slightly more lax threshold of $q<0.01$, both survivors and controls showed resting state functional connectivity with the medial prefrontal cortex as well as some occipital clusters. Survivors also showed connectivity between the hippocampus and the temporal lobes, while controls showed connectivity between the hippocampus and bilateral dorsolateral prefrontal cortices as well as the subgenual posterior cingulate cortex. From the occipital seed, survivors showed connectivity

with the right parietal lobe (peak (6, -72, 50), z=5.81, q<0.001) while controls showed no significant clusters other than that surrounding the seed region at q<0.001. At q<0.01, both survivors and controls demonstrated connectivity to the left occipital seed throughout the frontal, temporal, and parietal lobes as well as the insula.

3.3   Specific Aim 2

Of regions that were functionally connected to the left parietal seed in either group, one demonstrated a relationship to performance. The beta weights (i.e., strength) of the interaction with the right BA 19 cluster almost bilateral to the seed region were within normal ranges of skew (t=-0.438, SE=0.350) and kurtosis (t=0.027, SE=0.688) and were positively correlated with only the survivor group's log-transformed d' scores (R=0.452, p=0.030) such that greater connectivity strength predicted better performance (see Figure 7). To further probe this relationship, a hierarchical regression analysis was conducted to evaluate any interaction among variables.
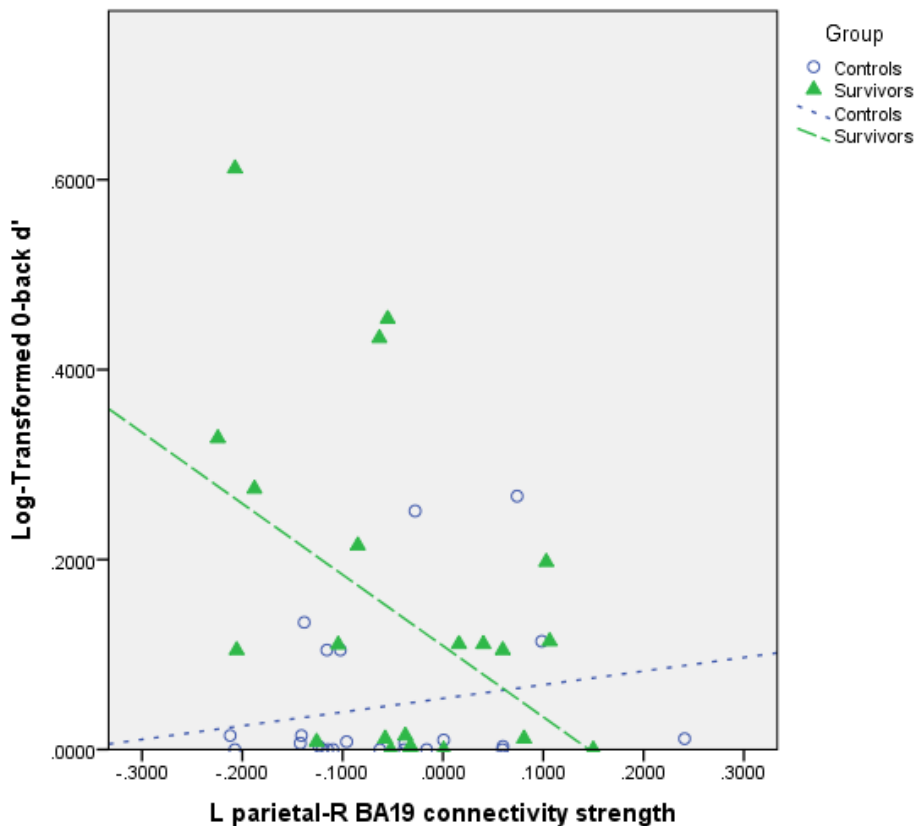
Figure 7. Left parietal-right parietal functional connectivity strength predicting performance by group.

Within the regression model, one's group, survivors or controls, predicted performance as measured by log-transformed d' ($r=0.337$, $p=0.011$). Strength of the positive PPI between the left parietal seed and the right BA 19 cluster did not predict performance ($r=0.192$, p=n.s.). There was also not a significant relationship between group and PPI strength ($r=-0.069$, p=n.s.). In the hierarchical regression, the dependent variable was the log-transformed d', and Step 1 included the mean centered predictor variable of PPI strength and the moderator variable of group. Step 2 included the aforementioned variables and the interaction term between PPI strength and group. Group and PPI strength alone contributed 12% of the variance in performance, $F(2, 43)=4.084$, adjusted $R^2=0.121$, $p=0.024$. In the second step of the model, the association between PPI

strength and d' was significantly moderated by group, B=0.893, t=2.504, p=0.016. When the interaction variable was included in the model, 22% of the variance in d' was accounted for, F(3, 42)=5.147, adjusted R^2=0.217, p=0.004.

Of regions that were functionally connected to the left hippocampal seed in either group, only the left dorsolateral prefrontal cortex (dlPFC), a region functionally connected to the hippocampus in survivors, demonstrated a relationship to performance and did so only in controls. Beta weights demonstrated an acceptable amount of skewness at t=-1.450, SE=0.350, but were strongly kurtotic at t=5.856, SE=0.688. The beta weights of the positive interaction between the left hippocampus and the left dlPFC cluster (-24, 58, 24) was positively correlated with controls' log-transformed d' scores (R=0.458, p=0.028) such that greater connectivity between these regions predicted worse performance (see Figure 8). Interaction analyses among PPI strength, group, and d' were conducted, but no significant effects emerged.
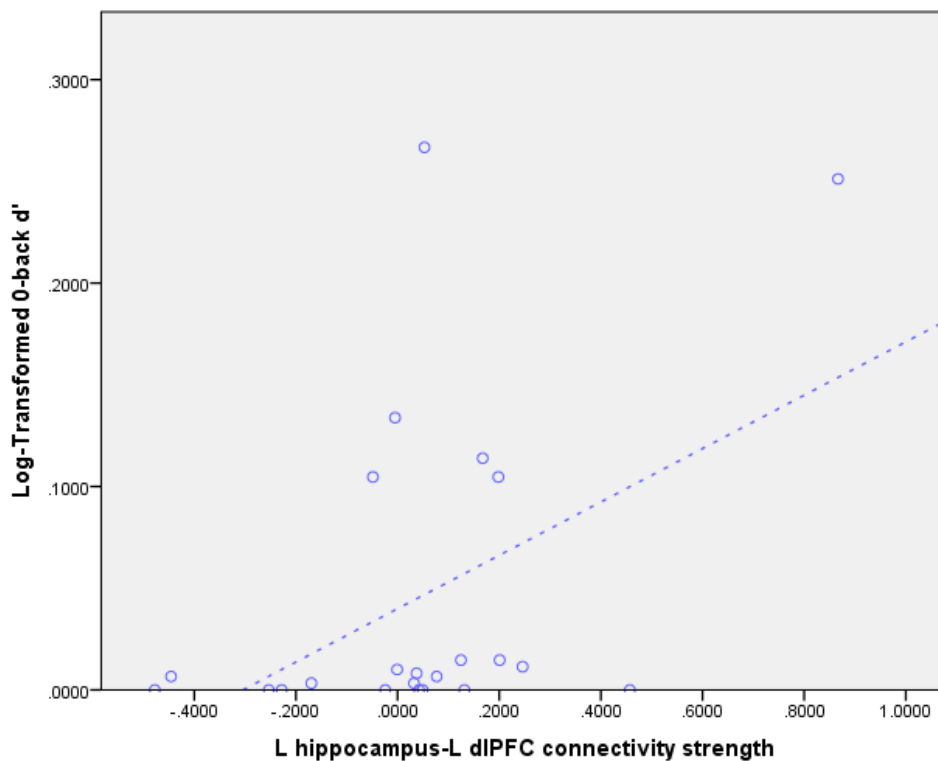
Figure 8. Left parietal-left dlPFC functional connectivity strength predicting performance in controls.

Though it did not predict performance, strength of the connectivity between the left hippocampal seed and left lateral precentral gyrus (-46, -12, 38) showed distinct trends in each group. In controls, PPI strength linearly predicted BRIEF Emotional Control subscale scores such that increased connectivity predicted worse emotional control (R=0.424, p=0.044). In survivors, PPI strength inversely predicted BRIEF Task Monitor subscale scores such that increased connectivity predicted improved task monitoring. Interaction analyses among PPI strength, group, and d' were conducted for each set of measures, but no significant effects emerged.

0-back log-transformed d' scores were not significantly correlated with the BRIEF Task Monitor subscale, Emotional Control subscale, or Global Executive Composite score. No controls demonstrated clinically significant impairment in any of the domains evaluated.

However, four survivors showed clinically elevated Task Monitoring subscale scores. Of these four, one survivor also had an elevated Global Executive Composite score, and one also had both an elevated Emotional Control subscale score an elevated Global Executive Composite score. Two survivors had clinically elevated Emotional Control subscale scores only. BRIEF scores did not predict seed regions' percent signal change.

4   DISCUSSION

4.1   Behavioral Findings

Behavioral analyses demonstrated a difference in performance on the 0-back task between groups such that controls performed significantly better than survivors when taking into account hits, misses, false positives, and correct recognition of non-targets. As our survivor sample excluded inherently lower-functioning survivors (i.e., those unable to remain still in the scanner or understand the n-back task), the difference may still be an underestimation of the difference in performance between survivor and control populations. Due to the low difficulty of the task for neurotypical individuals, there was a ceiling effect in the control group, but the difference in performance between the two groups demonstrated that it maintained a degree of sensitivity not seen elsewhere. Thus, despite its negative skew, it was selected as an attention task of interest to compare to the subjects' crosshair exposure while in the scanner and log-transformed. Following the transformation, four survivors' scores remained outliers in the direction of poorer performance, and no controls' scores were outliers due to the clustering at the ceiling.

The 0-back d' was not correlated with the BRIEF Task Monitor subscale, BRIEF Emotional Control subscale, or BRIEF GEC in either group or in both groups combined.

Survivors showed no significant impairment as a group on any of the three scales. There were four survivors whose Task Monitor scores were in the clinically significant range, one of whom was also an outlier with regard to extremely poor 0-back performance. The lack of relationship between performance on an attention task and an informant report of task monitoring was contrary to our hypotheses but may instead suggest that 0-back performance is a more subtle measure of individuals' attention than ratings made by a family member or close friend.

4.2   BOLD Findings

Again, we begin the discussion of imaging data with the caveat that none of these findings have yet passed stringent whole-brain corrections. In keeping with prior literature and our planned analyses, BOLD findings reported were those that survived z-statistic thresholding at z>1.96 with a corrected cluster significance threshold of $p<0.05$ (King et al., 2015), and PPI findings reported were those that survived our pre-planned voxel uncorrected threshold of $p<0.001$ and cluster size $K_E>10$ (Harding et al., 2012, Kasahara et al., 2011). However, without more extensive thresholding, these results may still be susceptible to inflation (Eklund et al., 2016) and should be interpreted with caution.

Both survivors and controls demonstrated numerous clusters of activation throughout the brain in the [0-back – crosshair] contrast. Activity throughout the parietal lobes, insulae, and medial frontal gyrus were noted in both groups, indicating involvement of the attention network and motor planning regions in the 0-back task, during which participants had to remain engaged and ready to press a button, compared to the crosshair presentation, during which participants were instructed to simply lay still and fixate on the crosshair.

The only region that showed significant differences in activation over the [0-back – crosshair] contrast was in the left parietal lobe, where survivors showed greater activation than

controls. This finding lends support to the hyperactivity component of the latent resource hypothesis; survivors were recruiting that region—known to be involved in attention networks— more during a task. However, this brain activity was not compensatory; overall, survivors performed worse on the 0-back task as evaluated by the d' measure, and at trend level, those with greater activation in fact performed more poorly.

When all 46 subjects were included in the analysis, the percent signal change of the 3mm seed in this parietal region was negatively correlated with 0-back performance such that greater activation was correlated with worse performance, further indicating that this increased activation is not "compensatory" but an attempt at recruitment of a region that has potential involvement in the attention process. It may be the case that without recruitment of this region, individuals who were challenged by the task would have performed even more poorly. Such correlational results with performance were not identified within either the survivor or control group alone, but the survivors alone had a greater negative slope than either the controls alone or all subjects together, suggesting that size of the group may have played a role.

Neither the BRIEF Task Monitor subscale scores nor the BRIEF Emotional Control subscale scores were predicted by left parietal percent signal change, and there was no relationship between participants' GEC and percent signal change either. Although the Task Monitor subscale was hypothesized to be a representation of day-to-day attention and therefore show similar patterns as 0-back performance, these differences likely reflect that the 0-back is a more specific, subtle measure of attention-based performance. The BRIEF scores utilized in this study were garnered from an informant whereas the 0-back data reflects actual performance. It may be that the 0-back is a more subtle, specific measure of these individuals' cognitive capabilities, and the informant may not be aware of what is subtly challenging for the individual.

4.3   Functional Connectivity Findings

As many findings from the psychophysiological interaction analyses were negative interactions, it should first be clarified as to how this may be interpreted. First, a negative interaction between a seed region and connected cluster in the context of the [0-back – crosshair] contrast could indicate more synchronization in the two regions' activity during crosshair exposure (i.e., rest) than 0-back (i.e., the task); see Figures 9a & 9b for a visual representation. Second, it may be that the two regions are not particularly correlated during rest but are in fact anticorrelated in their activity during the task; see Figures 9c & 9d for a visual representation. Concurrent assessment of resting state data will be utilized to provide basis for either interpretation and will be indicated in each instance. Additionally, prior research by other groups indicates whether certain networks are more likely to be correlated during rest versus anticorrelated during a task.
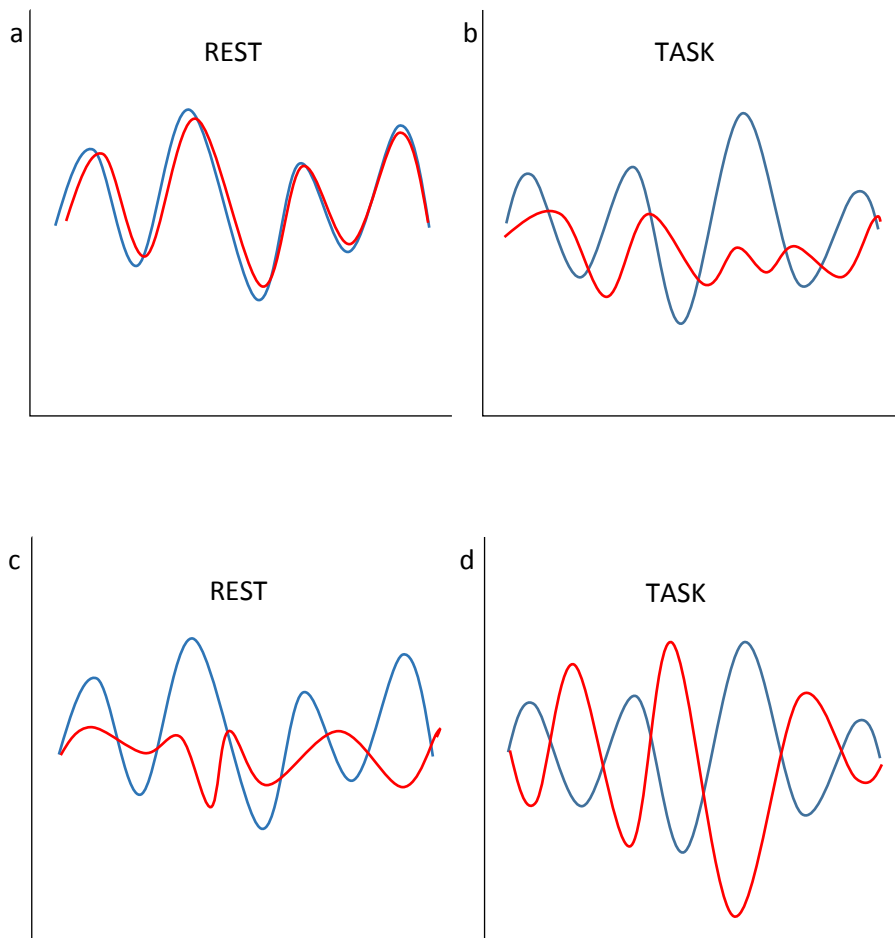
**Figure 9. Potential interpretations of a negative psychophysiological interaction.
a-b) The seed and other region show synchronized activity during rest but no relation in
activity during the task. c-d) The seed and other region show no relation in activity during
rest but show inverse patterns in activity over the course of the task.**

Planned analyses include assessing functional connectivity during resting state scans

using the same seed regions that were utilized in the task-based functional imaging analyses.

Initial considerations included mathematically centering PPI values around resting state data, but

due to software capabilities and additional conceptual understanding of PPI, this plan was

substituted for cluster inspection at traditional FDR-corrected thresholds and qualitative

comparison of resting and task findings. Specifically, FSL does not have a function which allows

for straightforward evaluation of resting state functional connectivity; thus, AFNI was selected

for these analyses. As the preprocessing and analysis steps differ slightly, the output from the

rest and task analyses could not be effectively compared at this stage. However, the inherent centering of PPI around a baseline eliminated the need to mathematically control for resting state connectivity regardless.

At an FDR-corrected threshold of $q<0.05$, none of the three seed regions showed resting state connectivity with clusters of significant difference between survivors and controls. However, when groups were analyzed separately, numerous clusters emerged as functionally connected with each seed during rest, and to more specifically identify said clusters, the threshold of significance was raised to $q<0.001$ for cluster-wise inspection. The region around the seed and the region precisely bilateral to the seed consistently emerged for both groups across all seeds. Almost no networks that were identified by the PPI analysis were also identified as functionally connected networks during resting state, with the exception of the connections between the left and right parietal lobes. All other networks were distinct and provide direction for future studies of resting state networks in survivors of childhood brain tumors.

4.3.1 Parietal Seed

While survivors showed more activity overall than controls at the selected left parietal seed, functional connectivity between that seed and any other brain regions during the attention task did not differ significantly between the groups, nor did it differ significantly during rest. However, distinct presentations in negative psychophysiological interaction between the seed region and elsewhere in the brain for the [0-back – crosshair] contrast for each group indicate use of distinct networks to maintain attention. A negative interaction may indicate that the synchronization between the seed and connected region is stronger during crosshair exposure (rest) than the task. This interpretation was supported by the fact that during rest, both groups showed great connectivity within the left parietal lobe and, as seen in the negative PPI, between

the left parietal seed and the right parietal lobe. Thus, it is likely that this particular negative interaction presents due to increased correlation during rest and lack of correlation during the task rather than anticorrelated connectivity that is specific to the attention task.

Bilateral posterior parietal cortical connectivity is implicated in early stages of visual processing (Ma et al., 2013). Although both groups showed negative connectivity between the left parietal seed and some distinct right medial parieto-occipital cluster, the nearness of the clusters suggests a possibility for minute changes in this bilateral network following tumor and treatment, likely, as noted above, during rest as opposed to during a task. Brain tumors and treatment such as radiation are understood to alter white matter volume (Reddick et al., 2014), and it is possible that such disruptions to the physical networks have ramifications regarding functional networks as well, altering them subtly.

While the negative connectivity between the left parietal seed and the right cluster in Brodmann area 19 was present only in controls, there was a group by positive connectivity interaction predicting performance on the attention task such that survivors' positive connectivity between the regions predicted performance but controls' showed no relationship. Although controls, who performed significantly better on the task overall to the extent of a ceiling effect, were more likely to disengage this network when moving from rest to task, it was the survivors who engaged it more during the task who tended to perform better. Contrary to hypotheses, this may be some sort of compensatory network for survivors. The pair of regions was identified because of its function in controls, but it is utilized in a different manner by survivors; it appears to be recruited following insult in order to provide additional support on an attention task, and it may in fact increase their performance. Instead of resembling their healthy peers, the most successful survivors have developed alternate networks on which to rely.

Controls demonstrated a negative interaction between the left parietal seed and the medial prefrontal cortex (mPFC). The mPFC is understood to be part of the default mode network, a series of regions active during rest and thought to be involved in self-monitoring and other internal states (Raichle et al., 2001), and a disengagement of connectivity between part of the DMN and the attention network during an attention task is a function of a healthy, typical brain (Carbonell et al., 2014; Fox et al., 2005). Although s difference between survivors' and controls' connectivity in this network was not found, the fact that it did not emerge as negative in survivors indicates a potential disruption of a healthy disengagement. Hyperactivity and hyperconnectivity of the DMN during tasks and hyperconnectivity between the DMN and other networks has been identified in individuals with ADHD (Metin et al., 2015), and while the connectivity strength was not correlated with performance in either group, future studies may consider investigating behavioral outcomes related to DMN-task-positive network abnormalities such as ADHD symptomatology. Furthermore, it must be noted that we are interpreting this finding as disengagement was more pronounced during a task than at rest, though prior studies (e.g., Carbonell et al., 2014; Fox et al., 2005) found anticorrelations between the DMN and attention networks during rest, indicating a need for further dissection of each network and their interconnections.

Importantly, the parietal seed utilized in these analyses was chosen due to differences in BOLD signal between the two groups. Had a specifically intraparietal sulcus seed been manually generated, other networks understood to play a role in attention may have emerged as functionally connected during the task. Differences in patterns of activity will not necessarily correlate with differences in functional connectivity, hence our subsequent decision to create a seed region in the hippocampus despite a lack of BOLD findings. Additionally, none of the

regions that were functionally connected to the parietal seed in either group were formally ipsilateral, opposing our hypotheses. It should be considered that these findings might differ were an intraparietal sulcus seed used.

4.3.2   *Hippocampal Seed*

Although differences in groups' BOLD signal in the hippocampus were not seen in preliminary analyses, a left hippocampal seed was placed due to its hypothesized role in attention in survivors of childhood brain tumors based on research by Jayakar and colleagues (2015). Notably, the regions that were functionally connected to left hippocampus seed during rest showed minimal overlap with those that emerged from the PPI analysis. Therefore, the PPI outcomes from this seed may more closely reflect correlation and anticorrelation among networks that are specific to the attention task.

The difference between survivors' and controls' left hippocampal seed activity positively correlated with activity in the left temporal fusiform gyrus during the task. The temporal fusiform gyrus plays a role in recognition and is considered the visual word form area (Dehaene & Cohen, 2011; McCandliss et al., 2003), thus likely playing a role in letter recognition and identification as is required in the 0-back letter n-back task. Although it is meant to be a clean measure of attention, letter n-back tasks inherently incorporate reading of letters that will be processed both visually and verbally. Thus, it is likely to incorporate components of Baddeley and Hitch's (1974) working memory system, specifically the "phonological loop" containing a phonological store and articulatory rehearsal system. In the 0-back task, participants were required to hold the target letter in their memory while other letters were presented and read those, making the incorporation of this network inevitable. Identified anatomical correlates of

this process include the hippocampus, angular gyrus, and fusiform gyrus (McGettigan et al., 2011).

Cohen and colleagues (2008) also specifically noted the fusiform gyrus' role in prelexical processing, and as participants were identifying letters as opposed to words in the task, such connectivity, though not predicted, aligns with prior research. Minimal research has been conducted on connectivity specifically between the hippocampus and fusiform gyrus, but the understood role of the hippocampus in encoding of information to create memories (Schacter & Wagner, 1999) and the aforementioned roles of the fusiform gyrus insinuate a reasonable connection between the two during a letter-based attention task. Hyperconnectivity between the regions in survivors compared to controls insinuates that a new role is being taken on by this network following tumor, treatment, or both. Connectivity strength was not correlated with our performance measure or informant-based attention measure, suggesting that it is not a compensatory network.

In survivors alone, there was a negative interaction between the hippocampus seed and the left dorsolateral prefrontal cortex (dlPFC) in the context of the task. As no such patterns emerged during resting state, this may be attributed to a lack of connectivity during the task and an anticorrelation in activity between the regions during the task. The strength of the interaction did not show any relationship to performance in the survivor group; however, in controls, increased positive connectivity strength (i.e., more correlated activity during the task) predicted poorer performance. The dlPFC and surrounding regions are implicated in inhibition (Miller & Cummings, 2007), an important facet of executive functioning. As the difference in connectivity did not impact survivors' ultimate functioning on the task, the change in network behavior cannot be considered compensatory but may instead be attempted recruitment of a latent

resource. As those healthy controls who showed correlated task-based activity tended to perform worse, the data suggest that a lack of correlation or a trend of anticorrelation may be the healthiest relationship between the regions, though such changes do not ultimately bring survivors' performance up to that of their peers.

Survivors' hippocampal seeds also negatively interacted with a number of regions throughout the pre- and post-central gyri. As such connections were not seen in the resting state connectivity analyses, it may be that significant patterns of anticorrelation emerge between the hippocampus and these regions during the attention task. In a review, Corbetta and Shulman (2002) highlight the role of the postcentral sulcus in top-down visual attention, though the studies they analyzed did not involve processing the content presented and instead focused on motion or location. Our finding of a negative interaction so consistently implies some distinct pattern of activity throughout these gyri, and their relationship with hippocampal activity should be further probed in future studies. Remarkably, while nine individual clusters emerged as negatively functionally connected to the hippocampus in survivors with our thresholds, only one was functionally connected in controls. This may reflect a lack of effort needed by controls in this basic task compared to rest. Bilateral appearance of these clusters contradicts hypotheses that networks would be lateralized, but that these networks were primarily anticorrelated warrants further investigation into the role of contralateral connectivity.

Of the networks between the hippocampus and pre- and post-central gyri clusters, one demonstrated behavioral correlates. Survivors showed a negative interaction between the hippocampal seed and a left lateral precentral gyrus cluster during the task, likely due to increased anticorrelated activity during the task. Survivors who showed a stronger positive interaction between the regions were rated as better at task monitoring, indicating that those

whose connectivity looks distinct from rest of their group may have better "real-world" attention skills.

Controls' hippocampal seeds only negatively interacted with the left inferior temporal gyrus during the task. The ITG's primary roles are understood to be visual processing and object recognition, and while the task required participants to process letters, as more letters were non-targets, there may be a sophisticated interplay between the encoding performed by the hippocampus and the recognition performed by the ITG that is present in healthy individuals but lacking in survivors, although neither group showed any relationship between this network's connectivity and performance.

4.3.3   Occipital Seed

The left occipital seed was used as a control seed to confirm that no regions found to be functionally connected with either of the other seeds were spuriously doing so. As overlap between regions connected to the primary seeds did not overlap with those functionally connected with the occipital lobe, it may be concluded that the connectivity identified is unique to each seed.

4.4   Limitations and Strengths

Selection bias should be noted as an unavoidable limitation of this study, as both survivor and control groups were self-selected. It may be that survivors who chose to participate may be more impaired than their peers and participated due to a desire for increased health care provider contact. However, it is equally likely that this sample is skewed in the other direction such that survivors who were capable of participating are those with better adaptive functioning skills or greater cognitive capacity. Those participants who had to be excluded due to motion may also

have skewed our data toward higher-functioning participants, as those who struggled to keep still may also have struggled to successfully engage in attention-based tasks.

Due to the current nature of functional neuroimaging, it was necessary to utilize different software packages for the PPI analyses and resting state functional connectivity, preventing us from quantitatively comparing individuals and groups across states. Additionally, contrary to our predictions, a lack of correlation between 0-back performance and the BRIEF Task Monitor subscale may indicate an inability to generalize subtle task performance to informant ratings of general day-to-day attention.

Importantly, this study investigated networks of functional connectivity in a population that had been minimally studied in this fashion previously. That data from 23 survivors of childhood brain tumors at least five years past diagnosis was obtained and usable is a significant step above some samples of the same population. While this is a large sample size for a study of this small population who is difficult to recruit and scan, an ideal study would have at least 40 participants per power analyses. As we continue to conceptualize the brain as more of a series of networks than individually functioning regions, techniques such as psychophysiological interaction analyses will be increasingly important in guiding our understanding the functional neurological underpinnings of various disorders and identifying systems on which to focus intervention.

4.5   Future Directions

The outcomes of the present study lay the groundwork for many potential investigations. Future studies should consider more thoroughly examining the differences in resting state connectivity within both task-based networks and the default mode network in survivors of childhood brain tumors compared to their healthy peers. By utilizing only one software package,

such as AFNI, for all types of analyses, more quantitatively-based comparisons may allow

researchers to draw more specific conclusions about trends in connectivity by setting.

Additionally, the relationship between gray matter volume of a seed region and its

connectivity, especially when the seed is located in a distinct structure such as the hippocampus,

should be further investigated, as Jayakar and colleagues (2015) found a correlation between

hippocampal volume and attention. Whole brain volume may also be considered as a covariate in

such studies to further solidify inconclusive findings about brain volume and connectivity. Other

imaging techniques such as transcranial magnetic stimulation and diffusion weighted imaging

may offer insight into effective connectivity and structural connectivity of the identified

networks, respectively, and more functional imaging with a more narrow focus, e.g.,

investigations into relationships between two small seeds or a seed and one specific lobe or

region, will provide more insight as to how the brains of survivors function.

In the present study, the regions identified in the PPI were those that showed a change

specifically in the 0-back compared to the crosshair presentation and not during the higher loads.

As both 0- and 1-back n-back trials can be considered tests of attention and vigilance, future

studies may consider collapsing across both types of runs. Utilizing more timepoints across both

0- and 1-back may increase power and identify functionally connected regions that did not

emerge in the present study's analyses. The present study and potential incorporation of the 1-

back in studies of attention also lays the groundwork for future investigations of functional

connectivity during the 2- and 3-back trials that are understood to employ working memory

networks (Owen et al., 2005).

Since the time this study was proposed, a meta-analysis has demonstrated the high

incidence of false positive results when only $K_E > 10$ cluster thresholding is utilized in functional

neuroimaging data (Eklund et al., 2016). Though the current study utilized FSL's FLAME1, the software package that was shown by the meta-analysis to have the least family-wise error (FWE), future studies must incorporate voxel-wise correction to best minimize FWE and generate valid results.

With our present data, we are able to see trends from which future studies will hopefully be able to build a more conclusive model for which we are currently underpowered. Power analyses utilizing NeuroPower (Durnez et al., 2016) indicated that our parietal seed findings and our control-based hippocampal seed findings may not be reproducible in a manner that would survive a stricter cluster-wise correction. In those data that might be reproducible (i.e., survivors' negative PPI analyses with the hippocampal seed), achieving a power level of 0.8 (per Mumford, 2012) would require sample sizes of 41 uncorrected, 104 with random field theory correction, and 183 with the stringent Bonferroni correction. Random field theory and Bonferroni correction both attempt to control the FWE rate described above. No sample size could reach a power level of 0.8 following Benjamini-Hochberg False Discovery Rate (FDR) correction. Future investigations must include more stringent motion correction as well as potentially a broader range of task data, creating more timepoints, and this may increase the ability to identify significant findings in this sample.

4.6   Conclusions

The field of brain mapping has transitioned over recent decades from a focus on localization to one on functional integration of brain regions (Friston, 2011), and the present study attempted to elucidate how these networks emerge in survivors of childhood brain tumors when faced with an attention task. With our selected thresholds, differences emerged in functionally connected networks between typical individuals and survivors. A region of

hyperactivity in the left parietal lobe identified in survivors supports the concept of activity of a certain region being a latent resource in a clinical population, but frequent negative interactions between a task-rest contrast and specific networks make it more challenging to specifically address the role of hyperconnectivity in this population. Some networks, such as the one between bilateral parietal regions, may be recruited in a compensatory manner in survivors, while others like the hippocampus-dlPFC network may be utilized by survivors as a latent resource that does not lead to improved performance. Anticorrelations suggest that these networks identified by our analyses may play some combination of roles, including information exchange during rest or suppression or monitoring of distal activity across the brain.

The specificity of the presence of networks detected, be they correlated or anticorrelated during a task, provides directions for future research within this population. Depending on their likely role in an attention, executive function, or phonological network, different networks showed varying types of relationships that must be further probed. The current dearth of information regarding long-term outcomes of survivors of childhood brain tumors necessitates more investigation, and the present study opens these doors for further exploration of the cognitive and neurobiological outcomes of pediatric brain tumors and their treatment.

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