

Effects of Treatment on Neurocognitive and Psychosocial Development in Adolescent Brain
Tumor Survivors

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ABSTRACT

Research on the cognitive and psychosocial effects of treatment for childhood brain tumors has consistently found deficits in these areas. However, the connections between these deficits, as well as their biological basis, are largely unidentified. This study used cognitive tests, parent questionnaires, and functional neuroimaging to further examine possible deficits in these areas of functioning. Brain tumor survivors had increased levels of neurocognitive and psychosocial problems, as well as decreased brain activation during working memory tasks as compared with healthy controls. Additionally, brain activation and social problems were found to be the best predictors of internalizing problems. These results further clarify the deficits observed in brain tumor survivors and support the hypothesis that brain tumor treatment is associated with inhibited brain activation.

INTRODUCTION

Among adolescents, brain and central nervous system (CNS) tumors are the second most common malignancy and the most common type of solid tumors (Butler, 2006). Brain tumors represent 20-25% of all malignancies among children under age 15 and are also one of the most devastating illnesses, ranking as the second leading cause of disease death among children under the age of 20 (Panigraphy et al., 2009).

Both the high level of occurrence, as well as the harsh course of the disease and its treatment, has led to a rapid growth in research of the disease and methods of treatment. As a result of significant advances in treatment, survival for childhood brain tumor patients is over 60% (Ness et al., 2007). As survival rates have increased, treatment has been able to transform the diagnosis of a brain or CNS tumor in a child from a situation in which the sole focus was survival of the patient, to one that is now much more complicated and encompasses the consequences of treatment 5 or 10 years later. Rather than focusing exclusively on overcoming the main obstacle of surviving the tumor, research with these patients and their healthcare providers is now examining more in depth the long-term results of the disease and treatment.

The standard of care for newly diagnosed brain tumor patients currently consists of a combination of surgery, chemotherapy, and cranial radiation (Khasraw et al., 2010). In spite of significant advances in survival rates, the results of this treatment are often times achieved at a high cost. There has been growing evidence that patients who have undergone this treatment protocol have cognitive, social, physical, and psychological deficits beyond those of their peers (Ness et al., 2007). The current study looked to build on these findings and examine the psychosocial and cognitive effects of brain tumor treatment through the use of psychological

testing. In addition, brain activation, as measured by functional magnetic resonance imaging (fMRI), will be examined to begin to create a better picture of the possible neurobiological factors related to these cognitive and psychosocial effects.

Regarding the long-term cognitive effects faced by childhood brain tumor survivors, there is increasing evidence that the brain tumor treatment can lead to negative effects in overall cognitive functioning and full-scale intelligence quotient (FSIQ). Spiegler et al. (2007) examined subjects ranging from baseline (0-5 years off treatment) to 15 years off treatment and found that there was a significant, exponential decrease in IQ score among the brain tumor population when compared to normative data. These findings were further supported by a study conducted by Merchant and colleagues that also found a significant decrease in IQ following brain tumor treatment, although the data was fit to a linear model (Merchant et al., 2009). Perhaps the most convincing evidence of the cognitive declines seen in childhood brain tumor survivors is a recent meta-analysis that reviewed the literature to create a sample of 1318 subjects. Robinson et al. (2010) found that patients who had undergone treatment for a brain tumor during adolescence scored almost a full standard deviation below the normal level for their overall cognitive ability. These findings were important in moving beyond the identification of cognitive deficits to evaluate the severity of the effects of treatment (Robinson et al., 2010).

In addition to declines in overall cognitive functioning and FSIQ, childhood brain tumor survivors have been found to show deficits in executive functioning. Executive functioning involves higher order thinking and is related to the ability to synthesize stimuli, form goals and aspiration, preparation, attention, verification, and inhibition (Anderson, 2002). As executive functioning develops throughout adolescence, it plays an increasingly important role on cognitive functioning, behavior, emotion, and social interactions (Anderson, 2002). The broad-

reaching role of executive functioning makes this a critical area of development and one in which deficits are costly. Such deficits have been identified in brain tumor patients, who have been found to have lower processing speeds and executive functioning following treatment (Kesler et al., 2011). Based on such findings, it is not surprising that brain tumor survivors have also been shown to have deficits in sustained attention and attention flexibility, aspects of cognitive function that are closely associated with executive functions (Butler et al., 2009). Similarly, childhood leukemia survivors exhibited deficits in various attention switching and shifting tasks, both between immediate stimuli and between local and global stimuli (Butler et al., 2006). Glauser et al. (1991) also found deficits among brain tumor patients in visual and perceptual abilities.

When examining such results, it is important to keep in mind the potential practical effects of declines in these different cognitive areas. One major outcome among children and adolescent populations is decreased performance in school. Testing children years after diagnosis, Mabbott and colleagues found that reading, spelling, and mathematics performance was lower in children who had received treatment for medulloblastomas and ependymomas (Mabbott et al., 2005). This decrease was extrapolated to fit a quadratic pattern of decline and was found not only through direct cognitive testing, but also through parent and teacher ratings of school performance- both of which decreased following diagnosis and treatment (Mabbott et al., 2005).

Just as important as the cognitive deficits faced by survivors of childhood brain tumors are the psychosocial effects. As previously described, cognitive and social or behavioral effects are often interconnected and may be the outcome of a common impairment (Anderson, 2002). Children spend a large portion of their time in highly social environments such as school or day care, where they are expected to interact with one another (Bonner et al, 2008). Such interactions

and sociability are crucial in the normal development of a child and many negative effects, both short and long-term, can arise if a child has difficulties in this area (Brenghden et al., 2002).

One of the leading studies regarding both the cognitive and social effects of cancer treatment, including that of brain tumors, is the Childhood Cancer Survivor Study (CCSS). Incorporating 26 sites and over 14,000 cancer patients, the study represents the most comprehensive database of childhood cancer survivorship outcomes. Using this data, Hudson and colleagues analyzed the psychological functioning of over 9000 pairs of survivors and siblings, finding that cancer survivors were significantly more likely to report mental health problems than their non-cancer siblings (Hudson et al., 2003). More specifically, survivors were found to be 1.5 times more likely to show depressive/anxiety symptoms and 1.7 times more likely to have antisocial problems when compared to their non-cancer siblings (Schultz et al., 2007).

The high variability of the measured social and behavioral effects of adolescent cancer treatment has led to a somewhat conflicting picture of the challenges facing this population. Although Schultz and colleagues (2007) found that brain tumor patients showed significantly higher levels of internalizing problems, a meta-analysis conducted to assess the social, emotional, and behavioral outcomes in childhood brain tumor patients found little conclusive evidence that this population experienced increased internalizing or externalizing problems (Fuemmeler et al., 2002). However, there was significant evidence that these patients demonstrated lower social competence when compared to normative data and healthy controls (Fuemmeler et al., 2002). Additional studies involving teacher and parent evaluation of school-age brain tumor patients did not endorse an increase in internalizing or externalizing problems at baseline or over time (Mabbott et al., 2005). However, once again, social problems did appear to

increase over time through an estimated increase in CBCL and teacher rating scores (Mabbott et al., 2005).

Despite the mixed evidence regarding the specific problems manifested by childhood brain tumor survivors, it is becoming increasingly clear that this population does indeed suffer social deficits. These effects are not only present during the disease and treatment, but long after these patients have recovered. Comparing self, teacher, and parent scores on the Revised Class Play and the Liking Scale (Masten et al., 1985), children were matched to others in their class based on gender, age, and other socioeconomic factors. Children who had been diagnosed with brain tumors received fewer friend nominations from the other children in the class and were also reported as more socially isolated, sick, fatigued, and absent by self, teacher, and parent ratings (Vannatta et al., 1998). Such findings highlight the manifestations of the psychological and social deficits faced by these children into everyday situations. These deficits not only affect the survivors on a personal level, but also on an outwardly noticeable level, evident to both teachers and parents.

When examining these deficits, it is important to not only view them on the larger scale of everyday implications and outwardly evident effects, but also to look at the more basic underpinnings that possibly lead to the larger effects. Facial expressions are a crucial component of effective communication and social functioning because of their role as one of the “complex and varied social cues” that add information beyond what is directly said (Bonner et al., 2008). Therefore, it follows that deficiencies in interpreting facial cues and expressions would lead to larger social consequences. In fact, when compared to children suffering from rheumatoid arthritis, and, after being controlled for IQ levels, childhood brain tumor survivors had a significantly impaired ability to identify and interpret adult facial expressions (Bonner et al.,

2008). Thus, it would be reasonable to extrapolate the possibility of such a deficit to play a role in some of the larger-scale deficiencies, such as those seen in the classroom setting.

Although many of the cognitive, psychological, and social effects of adolescent brain tumor treatment have begun to be identified, there has been a clear lack of progress in understanding the neurobiological basis and causes of these deficits. The current study not only measured the social, psychological, and cognitive deficits related to brain tumor treatment, but also evaluates the underlying processes that create deficiencies in these different areas and how they relate to brain activation. In order to test the neurobiological effects of the stress faced by adolescent brain tumor survivors, as well as the direct neurobiological effects of the treatment they undergo, the current study used fMRI methods. In the past decade, fMRI has emerged as the leading way to measure and monitor brain activity at the neuronal level. fMRI measures neuronal activity through “metabolic and hemodynamic responses” that correspond to changes in neuronal activity in the brain (Zou et al., 2004). For example, Zou and colleagues (2005) were able to demonstrate that fMRI was an effective measurement for brain activation in cancer populations. These researchers assessed the brain activation of subjects when shown a visual stimulus and found that brain activity that is “qualitatively similar, but quantitatively different” between cancer patients and healthy controls (Zou et al., 2005).

In addition to ascertaining that there is an observable, neurological response to stress and that the measurement is effective in the population of interest, it is also essential to be able to map the variables of interest (i.e., social and cognitive deficits) onto brain activity observed via fMRI. Brain activation as measured by fMRI has been found to correlate well with psychological testing scores and cognitive functioning (Kesler et al., 2011). For example, increased processing speed, cognitive flexibility, and verbal/visual declarative memory scores were shown to be

associated with increased pre-frontal cortex activation (Kesler et al., 2011). In a similar study involving survivors of adolescent lymphocytic leukemia, fMRI was used to test brain activation during an N-back task testing working memory (Robinson et al., 2010). Like the Kesler study, this study utilized both fMRI and psychological tests (i.e. WISC, D-KEFS) to measure the cognitive levels of the participants. However, unlike the Kesler et al. study, Robinson and colleagues compared the neuronal activity of the ALL group to a group of healthy controls (Robinson et al., 2010). This study found that the ALL group underperformed on higher level tasks and displayed significantly greater activation in the areas underlying working memory and error monitoring when compared to the controls (Robinson et al., 2010). Both of these studies support the conclusion that the brain activation and neurocognitive performance are correlated.

However, there has been much inconsistency in the findings regarding the neurocognitive underpinnings of cognitive deficits in adolescents who have suffered from cancer. As mentioned, Robinson et al. (2010) found that lower scores on measures of cognitive output and executive functioning were associated with increased neuronal activation in the prefrontal cortex of the pediatric ALL survivors. This is in contrast to the findings of the Kesler group in which activation increased with *improved* cognitive performance. Both the Wisconsin Card Sorting Task used by Kesler et al. and the N-back task used by Robinson et al. are designed to test executive function and thus a similar relationship between performance and neuronal activity would be expected. The current study further addressed the relationship between brain activation in the prefrontal cortex and performance on cognitive tasks.

Although the link between cognitive performance and brain activation has begun to be more heavily documented, the mapping of specific brain areas that correspond to social cues is a recent discovery (Masten et al., 2009). For example, when participating in a social exclusion task

during fMRI, adolescents displayed insular and prefrontal activity that was related to self-reported distress (Masten et al., 2009). Overall, adolescents with higher self-reported and parent-reported distress levels showed “greater neuronal evidence of emotional distress” (Masten et al., 2009). These findings are crucial in establishing the ability to track social functioning effects through fMRI measurement.

The current study examined neurobiological correlates of not only cognitive functioning, but also social functioning. fMRI has been used in cancer populations mainly to examine cognitive deficits. However, based on previous findings that deficits in executive functioning and cognitive ability are correlated with increased behavioral and social problems in ALL and maternal depression populations (Campbell et al., 2009), it could be expected that these results can be extrapolated to the brain tumor group. However, no research has directly compared executive function levels to brain activation during socialization tasks. The current study also serves as one of the first studies using fMRI to examine cognitive function in childhood brain tumor survivors. Although MRI has been used to diagnose brain tumors and evaluate treatment for over 25 years, studies have examined the broader range of adolescent cancer patients, adolescent lymphocytic leukemia patients, and healthy children (Panigraphy et al., 2009). However, as shown by the Spiegler et al. and Merchant et al. studies, brain tumor patients show high levels of cognitive deficits following treatment and are thus an important group to monitor (Spiegler et al., 2003, Merchant et al., 2010). A more fundamental and in depth understanding of the biological processes underlying detrimental cognitive and social effects is crucial for the brain tumor population.

The goals of this study were to examine differences in executive functioning, anxious/depressive symptoms, and social functioning between brain tumor survivors and healthy

controls using neuropsychological assessment and BOLD signal activation during fMRI. The following hypotheses were tested:

Hypothesis 1. Brain tumor survivors will perform more poorly than matched healthy controls on measures of executive function, cognitive flexibility and inhibition, measures of social problems, as well as measures of anxious and depressive symptoms.

Hypothesis 2. Following findings that support a strong connection between early social difficulties and anxious/depressive problems (Hymel et al., 2008), it is expected that differences in social problems will account for differences in anxious/depressive symptoms between the brain tumor survivors and healthy controls. In addition, these differences in social problems will explain the expected correlation between cognitive performance and anxious/depressive symptoms.

Hypothesis 3. Brain tumor survivors will perform more poorly than healthy controls on the N-back task during the scan as compared to healthy controls and there will be differences in prefrontal brain BOLD activation between the two groups during this task. Findings in this area have been mixed, and thus this question is more exploratory in nature. However, it is possible to expect a lower level of activation in the prefrontal cortex of the brain tumor survivors when compared to healthy controls because of the demyelination and necrosis of white matter following brain tumor treatment (Burger and Bokyo, 1991). Additionally, it is expected that BOLD activation may play a role in the differences in neurocognitive functioning between the two groups.

METHODS

Participants

The sample included 20 adolescents (12 male) who have been treated for a brain tumor and 20 (9 male) healthy control participants. The brain tumor participants were recruited from the Monroe Carell Children's Hospital Pediatric Oncology Clinic and the healthy controls were recruited from the Vanderbilt University Study Finder program. Upon enrollment in the study, brain tumor survivors were an average of 12.15 years old ($SD = 2.72$) and healthy controls were 12.4 years old ($SD = 2.98$). 18 brain tumor survivors and 12 healthy controls self-identified as Caucasian and then next most represented ethnicity was Black or African American with one brain tumor survivor and six healthy controls self-identifying. One participant in each group self-identified as Asian or Pacific Islander and one healthy control self-identified as Latino. Demographic information for participants can be found in Table 1. Between groups *t*-tests and chi-square analyses were conducted to examine potential differences between the two populations. These analyses found that brain tumor survivors and healthy controls were similar regarding age ($t = .277, p = .783$), gender ($\chi^2 = .91, p = .342$), race ($\chi^2 = 5.77, p = .123$), parent/main caregiver ($\chi^2 = 3.24, p = .072$), and household income ($\chi^2 = 1.059, p = .589$). However, there was a significant difference in the education level of the parents of brain tumor survivors when compared to healthy controls ($\chi^2 = 4.44, p = .035$). Despite this difference, the results indicate that survivors and healthy controls were adequately matched and did not differ significantly in terms of demographic characteristics.

Procedure

Letters were sent to the parents or guardians of pediatric brain tumor patients through the Monroe Carell Jr. Children's Hospital hematology/oncology department. Healthy controls were recruited using the Vanderbilt University StudyFinder website. The families were then contacted by the research coordinator for this project who conducted a phone screen to determine if the

participants met the inclusion criteria. An appointment was then set up for the functional neuroimaging and psychological testing components of the study. The family could either arrange to do this all in one full day or divide it between two half days.

Study participation included a neurocognitive assessment battery, completion of questionnaire measures, and a neuroimaging session. On the scheduled appointment day, the participant completed the battery of neurocognitive testing administered by a psychologist or trained graduate student. These tests included measures of overall cognitive functioning, memory, and executive function. Additionally, parents and children completed several questionnaire measures assessing various domains of functioning, including psychosocial, emotional, and behavioral problems, and executive function.

All imaging was conducted on a 3Tesla MR scanner (Philips Medical Systems, The Netherlands) dedicated for research. The functional neuroimaging session began with an introduction to the memory task (N-back) and social task (Cyberball) during which the examiner explained how to answer and respond to the different tasks. The child was given a chance to run through one full cycle of the N-back on a computer screen for practice to insure they understood the task. The child was then shown a mock scanner to become accustomed to the environment of the actual scan. The child was also introduced to the headset and response pad need for the N-back tasks during the mock scanner session. After any additional questions were answered, the child was taken back to the scanner and was put into the scanner by a certified technician. The response pad was given to the child, a pulse oximeter was attached to the participant's index finger to record heart rate, and a respiration belt was placed over the participant's diaphragm to record respiration rate.

The imaging protocol was then followed, with the N-back task controlled via a computer in the adjacent room. Participants were able to respond to questions using buttons on the response pad, and they were able to communicate with study personnel throughout the scan via headphones and a microphone. The entire protocol of anatomic and functional scans took 60-80 minutes. Following the scan, the child was debriefed and the session was formally concluded.

Measures

Neurocognitive Functioning. The Delis-Kaplan Executive Function System (D-KEFS) was used to evaluate executive functioning (PsychCorp, San Antonio, TX.). This test has both high reliability and validity and is normalized based on a sample of 1,750. This included the Color-Word Interference Test, which tests verbal inhibition and cognitive flexibility, both of which have been shown to be affected in cancer populations (McCoy, 2009; Butler et al., 2009)). The Color-Word Interference test is based off of the Stroop Task and contains four conditions. The first two, color naming and word naming, test basic component functions and involve presenting the participant with a page either containing a series of red, blue, and green squares or the words “red,” “blue,” and “green.” The subject is then asked to say the color in the box or read the word on the page as quickly as possible. The last two tasks, inhibition and inhibition/switching, require an inhibition of the natural response and mental flexibility (McCoy, 2009). In the inhibition trial, the participant is presented with a series of the words “red,” “green,” and “blue” written incongruently in red, green, or blue ink. The participant is asked to say the color of the written word, not the ink. This condition is most closely related to the Stroop Task. The final condition, inhibition/switching, is similar to inhibition, with the addition of boxes around half the words. For these boxed words, the participant must say the name of the color of the ink as opposed to the word itself. Thus, the participant is switching between two sets of instructions throughout the task (Lippa & Davis, 2009).

The Behavior Rating of Executing Functioning was also used to measure executive functioning of both the brain tumor survivors and healthy controls. The BRIEF is a questionnaire filled out by the parents of the survivors and healthy controls that has demonstrated both high internal consistency ($\alpha = .80-.98$) and test-retest reliability ($r_s = .82$) (PAR Inc., Lutz, FL.). The BRIEF consist of 86 items that form eight clinical scales. Of particular interest for this study are the behavioral regulation scale, which involves emotional control, inhibition, and shift, and the shift scale, which measures the ability to change from one task to another.

Emotional and Behavioral Problems. Parents provided information about the emotional and social problems of survivors and healthy controls by completing the Child Behavior Checklist (CBCL; Achenback & Rescorla, 2001). This test measures symptoms of anxiety problems, internalizing symptoms, and social problems among others. These scales have strong test-retest reliability and criterion validity. In the following analyses, social problems and anxious/depressive symptoms will be assessed using the Social Problems, Anxiety Problems, and Internalizing Symptoms scales.

Functional Neuroimaging. During their first functional scan, participants completed the N-back task, which is designed to assess working memory. A letter version of the visual N-back task (Barch, Sheline, Csernansky, & Snyder, 2003) has been developed, and involves sequences of uppercase consonants. In the 0-back condition, participants were instructed to respond to a single target (i.e., V). In the 1-back condition, participants were instructed to respond only when the consonant was identical to the one preceding it (e.g., M, M). In the 2-back condition, participants responded only when the consonant was identical to the one presented two trials prior (e.g., M, T, M), and in the 3-back condition, participants responded when the consonant was identical to the one presented three trials prior (e.g., M, T, F, M). Each condition was presented three times in order of increasing difficulty, for a total of 12 blocks. Each block contained 15 consonants, and 3 of these

consonants required a response, for a total maximum accuracy score of 45. This task has been used effectively with children in this age group with no adverse effects (Robinson, Livesay, et al., 2010). N-back task performance data were extracted using ePrime software (Psychology Software Tools Inc., Pittsburgh, PA). Accuracy was calculated for each participant at each level of N-back difficulty.

Preparation of Imaging Data for Analysis. Imaging produced 33 oblique axial slices parallel to the AC-PC plane (Anterior Commissure, Posterior Commissure). All of the data from the functional neuroimaging sessions were analyzed using Brain Voyager QX software (Brain Innovation B. V., Maastricht). The images were first analyzed for motion and if motion exceeded the threshold of 3mm, the data from the corresponding N-back condition was removed. Next, the functional imaging was imposed onto the patient's anatomical scan that was then adjusted to fit a standardized space known as Talairach. Talairach transformation allows spatial comparisons in brain activation to be constant across different participants despite variability in brain morphology. Thus, activation in voxel 12 of brain A will correspond to the same structural area as voxel 12 of brain B, even if the brains are of varying sizes and morphologies. Following Talairach transformation, clusters of interest were identified based on the level of brain activation in that area. If 6 or more functional voxels within a cluster were activated, the region became labeled as a cluster of interest and was examined during data analysis.

Design

Study hypotheses were analyzed as follows:

Hypothesis 1. Independent-samples t-tests were conducted to examine whether brain tumor survivors performed more poorly than healthy controls on measures of executive function, measures of social problems, and measures of anxious and depressive symptoms. Measures included the DKEFS, BRIEF, N-back, and CBCL.

Hypothesis 2. Linear regression models were conducted to determine the relationships between social problems, anxious/depressive symptoms, and neurocognitive functioning. Measures included the DKEFS and CBCL.

Hypothesis 3. An independent-samples t-test was conducted to examine whether brain tumor survivors differed from healthy controls in prefrontal BOLD activation during the N-back task. BOLD activation was also included in the linear regression models to determine if it best accounted for the variance found between brain tumor survivors and healthy controls on measurements of social problems. .

RESULTS

Hypothesis 1

It was predicted that brain tumor survivors would perform more poorly on measures of executive function, social problems, and anxious/depressive symptoms. Means and standard deviations for measures of executive function, social problems, and anxious/depressive symptoms are reported in Table 2. On both measures of executive function taken from the BRIEF, the mean *T* scores of the brain tumor survivors fell above that of the normative population, with the mean score on the Behavioral Regulation scale (58.75) lying almost a full standard deviation above the normative mean (higher scores indicate more problems in executive function). In contrast, the mean *T* score for the healthy controls for each of these measures were approximately equal to that of the normative population. Comparisons between the brain tumor survivors and healthy controls, calculated using independent samples *t*-tests, found that the two groups differed significantly on both of these measures (Shift Scale: $t = 3.01, p = .005$; Behavioral Regulation Scale: $t = 2.60, p = .013$). Similar results were indicated by the tests of executive function on the DKEFS. The brain tumor survivors' mean scaled scores were below

the normative mean for both tests, whereas the mean scaled scores of the healthy controls were slightly above the normative mean for both tests (higher scores indicate better executive function). Independent samples t-tests were again used to compare the two groups and found that the scaled score means of the two populations differed significantly on the inhibition/switching task ($t = -.387, p = .000$), but not on the word reading task ($t = -1.90, p = .065$).

In regards to social problems, the brain tumor survivors mean T score on the social problems scale of the CBCL was over a full standard deviation above the normative mean (higher scores indicate more problems). The mean T score of the healthy controls on this scale was also above that of the normative sample; however, when an independent-samples t-test was used to examine differences between the two groups, the mean T score of the brain tumor population was still found to be significantly higher than that of the healthy controls ($t = 3.22, p = .003$). Brain tumor survivors were also found to differ significantly from healthy controls on the internalizing ($t = 2.80, p = .008$) and anxiety problems ($t = 2.18, p = .035$) scales of the CBCL. The brain tumor population had a mean T score approximately one standard deviation above average for each of the scales, in contrast to the healthy controls in which the mean T score was significantly closer to the average.

Taken together, these scores indicate that brain tumors performed more poorly than healthy controls on measures of executive function, social problems, and anxious/depressive symptoms.

Hypothesis 2

Social problems were hypothesized to account for the variance between brain tumor survivors and healthy controls in anxious/depressive symptoms and serve as an intermediate between cognitive performance and anxious/depressive symptoms. Pearson correlations were

used to measure the connection between social difficulties and anxious/depressive symptoms, as well as the association between neurocognitive performance and anxious/depressive symptoms. The Pearson correlation values are reported in Table 3. From these analyses, it was found that social problems were significantly correlated with anxious/depressive symptoms, as measured by the *T* scores for the internalizing and anxiety problems scales (internalizing: $r = .53, p < .001$; anxiety problems: $r = .63, p < .001$). In both cases, the correlation was positive, indicating a direct relationship between social problems and anxious/depressive symptoms.

Regarding the relationship between neurocognitive performance and anxious/depressive symptoms, these two variables were found to be significantly correlated based on multiple measures. Both the executive function scales of the BRIEF and DKEFS correlated significantly with the anxiety problems scale of the CBCL. Both scales from the BRIEF were positively correlated to anxiety problems (shift: $r = .73, p < .001$; behavioral regulation: $r = .78, p = .001$) and both scales from the DKEFS were negatively correlated to anxiety problems (word reading: $r = -.48, p = .002$; inhibition/switching: $r = -.37, p = .018$). It is important to remember that higher scores on the BRIEF correspond to increased deficits in executive function. Thus, both the positive correlations between BRIEF scores and anxiety problems, and the negative correlations between DKEFS scores and anxiety problems both correspond to an inverse relationship between executive function performance and anxiety problems. This inverse relationship holds true for executive function and anxious/depressive problems as well. As executive function increases, anxious/depressive symptoms tend to decrease as demonstrated by the negative correlation between the internalizing *T* score on the CBCL and the scaled score on the DKEFS CW reading task ($r = -.41, p = .008$). However, unexpectedly, the inverse correlation between executive function and anxious/depressive symptoms only approached significance for the relationship

between the DKEFS CW inhibition/switching score and internalizing problems ($r = -.29, p = .07$). Despite this, overall these correlations support previous findings of a direct relationship between social difficulties anxious/depressive symptoms (Hymel et al., 2008), as well as supporting a direct relationship between cognitive performance and anxious/depressive symptoms.

In order to examine the role of social problems in accounting for the differences in scores between brain tumor survivors and healthy controls on anxious/depressive symptoms and determine if they explain the correlation between cognitive performance and anxious/depressive symptoms, a linear regression was used. The *beta* and *R*-squared values for the four step model are presented in Table 4 and the model is outlined in Figure 1. When executive function was added to the model, it better predicted differences in anxiety problems than group and the beta value approached significance ($t = -1.9, p = .07$). However, when social problems were added they better accounted for the variance in anxiety problems than group, executive functioning, or BOLD activation ($t = 4.05, p < .001$). Social problems remained the best predictor of anxious/depressive symptoms when the internalizing scale ($t = 2.53, p = .017$) of the CBCL was used instead of the anxiety problems scale of the CBCL. A second linear model was created to determine what factor best accounted for the variance found between healthy controls and brain tumor survivors on the social problems scale of the CBCL. The *beta* and *R*-squared values for the three-step model are presented in Table 5 and the model is outlined in Figure 2. Contrary to the hypothesis that neurocognitive performance would account for the variance in social problems, supporting the idea that social problems serve as an intermediate step between cognitive performance and anxious/depressive symptoms, the variance in social problems was best accounted for by BOLD activation in the prefrontal cortex. Thus, these results supported the hypothesis that social problems would best account for the variance in anxious/depressive

symptoms, but contradicted the hypothesis that social problems are an intermediate step between cognitive performance and anxious/depressive symptoms.

Hypothesis 3

Regarding functional neuroimaging, brain tumor survivors were expected to perform more poorly on the N-back task during the scan as compared to healthy controls and to show decreased BOLD activation while completing the task. Additionally, BOLD activation was expected to play a role in predicting the variability in the scores on the social problems scale of the CBCL. The means and standard deviations for the total accuracy for both brain tumor survivors and healthy controls on each of the three N-back levels are reported in Table 2. Independent-samples *t*-tests were run to evaluate the differences in accuracy between the two groups. These tests indicated that, although brain tumor survivors and healthy controls did not differ in total accuracy on the 0-back, 1-back, or 2-back conditions, brain tumor survivors performed significantly more poorly on the 3-back condition. It was only during the most difficult portion of the task that the two groups differed significantly. The means and standard deviations for the BOLD activation of each group while performing the 3-back task are also recorded in table 2. The area analyzed, Brodmann's area (BA) 32, corresponds to the dorsal anterior cingulate cortex (D-ACC), located in the prefrontal cortex. The prefrontal cortex is recruited during complex tasks that require skills such as working memory, and more specifically, BA 32 has been found to be activated during executive function tasks (Robinson et al., 2010). Consistent with the hypothesis, the results of an independent samples *t*-test indicated that the healthy controls had significantly higher activation in BA 32 during the 3-back task when compared to brain tumor survivors.

Lastly, a linear regression model was run to determine which factor best predicts the variance seen between healthy controls and brain tumor survivors on scores of social problems. The 3-step model included group, CW inhibition/switching, and BA 32 BOLD activation as independent variables, and social problems (CBCL) as the dependent variable. The *beta* and *R*-squared value for this regression are listed in Table 5 and the model is outlined in Figure 2. To test the hypothesis that BOLD activation in BA 32 would best predict variance in neurocognitive performance, a linear regression model was run with CW inhibition/switching as the dependent variable. This test indicated that the variance in neurocognitive performance was best accounted for by group ($t = 2.31, p = .029$), contradicting the original hypothesis. However, as described during the results of hypothesis 2, BOLD activation in BA 32 was found to be the best predictor of social problems. In order to further test this connection, a linear regression model was created with BOLD activation in BA 32 as the dependent variable and measures of executive function and group as the independent variables. This test indicated that BOLD activation in BA 32 is best predicted by group status (brain tumor survivors vs. healthy controls). From these analyses, a theoretical model can be created in which group predicts BOLD activation, which in turn predicts social problems, which lastly predicts anxious/depressive symptoms (Figure 3).

DISCUSSION

The increased effectiveness of cancer treatments, including surgery, chemotherapy, and radiation, has led to momentous gains in survival rates for cancer patients, including those who have suffered from childhood brain tumors. However, these treatments carry potentially heavy adverse consequences. This study sought to examine some of these deficits in cognitive and psychosocial functioning in the largely understudied group of pediatric brain tumor survivors.

Through the use of parent questionnaires and standardized testing, the executive function performance of both the healthy controls and brain tumor survivors were measured. Executive function is an essential development in cognitive capabilities that involves a more complex level of thinking and understanding crucial for mental control and self-regulation (Anderson, 2002). Previous research indicates that brain tumor patients show significant decreases in executive function following treatment (Kesler et al., 2011). Based on these findings, it was expected that brain tumor survivors would show lower levels of executive function when compared to healthy controls. Indeed, the brain tumor patients tested in this study were found to have decreased executive performance when compared to healthy controls, both based on parent questionnaires as well as on scores from a complex task involving cognitive flexibility and inhibition. These findings reemphasize the presence of consistent deficits in neurocognitive function for survivors of childhood cancer, and more specifically in regards to brain tumor survivors. It is essential to identify the specific deficits facing these populations in order to move closer to potentially alleviating them.

In addition to neurocognitive functioning, differences in psychosocial functioning were also examined. Although somewhat mixed, there have been a substantial number of findings that indicate large social deficits arising in brain tumor and other cancer populations (e.g., Schultz et al., 2007; Mabbott et al., 2005). Consistent with findings that cancer survivors display lower social competency levels, it was hypothesized that brain tumor survivors would have higher levels of social problems when compared to healthy controls. Additionally, based on data supporting connections between early social problems and the development of anxious/depressive symptoms (Hymel et al., 2008), brain tumor survivors were expected to show increased anxious/depressive symptoms when compared to healthy controls. Comparisons

between the two groups on self-report scales of social problems, internalizing symptoms, and anxiety problems supported these hypotheses. Brain tumor survivors were much more likely to show both social problems and anxious/depressive symptoms as measured by parent reports. Such findings are essential in clarifying the picture of the specific social deficits faced by brain tumor survivors and, coupled with the deficits seen in neurocognitive function, emphasizing the harsh reality of the consequences of cancer treatment.

The second major topic examined in this study was the relationships between psychosocial functioning, cognitive performance, and anxious/depressive symptoms. As expected, there was a strong correlation between cognitive performance and anxious/depressive symptoms. In addition, the variation in anxious/depressive symptoms was better accounted for by executive function performance than group status alone. When social problems were added to the model, they best predicted anxious/depressive symptoms, supporting the hypothesis that they may be an intermediate step between executive function and anxious/depressive symptoms. However, when a regression model was run to determine the best predictor of social problems, it was not found to be executive function, but rather BOLD activation in the prefrontal cortex, a relationship that will be addressed further shortly.

The third major topic addressed by this study was the identification of potential neurobiological differences between brain tumor survivors and healthy controls using functional neuroimaging and a verbal memory task. Following previous research regarding cognitive deficits in brain tumor populations, it was hypothesized that these declines would hold true for performance on a working memory task conducted within the scanner as well. Indeed, brain tumor survivors performed significantly more poorly on the most complex level of the N-back working memory task when compared to healthy controls. In addition to documenting the

presence of such deficits, this study served as one of the first to examine the potential brain activation response underlying these negative neurocognitive effects. Although little research has been done regarding brain activation during working memory tasks for brain tumor survivors, there have been multiple studies examining this response in Acute Lymphocytic Leukemia survivors. However, the results of such studies have been mixed. Some of these studies have found that ALL survivors show increased levels of brain activation than healthy controls when completing an equally difficult task, indicating a compensatory mechanism (Robinson et al., 2010). In contrast, other studies have found that cancer survivors perform more poorly on executive function tasks and this corresponds to decreases in brain activation (Kesler et al., 2011). It was predicted that the brain tumor survivors in this study would show decreased brain activation when compared to healthy controls because of the demyelination effect and necrosis of white matter that often results from the radiation therapy included in brain tumor treatment (Burger & Bokyo, 1991). The findings of this study supported this hypothesis and differ from the results found in ALL survivors by Robinson et al. (2010), with brain tumor survivors showing decreased activation in the prefrontal cortex compared to healthy controls. Additionally, increased BOLD activation in the prefrontal cortex correlated significantly with better executive function performance, decreased internalizing symptoms, and decreased social and anxiety problems. These findings offer strong support for the theory that the neuronal damage caused by radiation therapy may lead to decreases in brain activation that are both cognitively and psychosocially detrimental.

More specifically, the area in which these differences in activation occurred was BA 32, which corresponds to the dorsal anterior cingulate cortex (D-ACC). The D-ACC is one of the primary brain regions underlying working memory and is involved in task evaluation,

monitoring, and error detection (Robinson et al., 2010). The D-ACC is also fundamental to circuits responsible for cognitive processing and tasks that require target assessment and attention to language (Staffen et al., 2005). Robinson et al. (2010) found differences in activation of the D-ACC between healthy controls and ALL survivors, and this study further supported these findings and the theory that the D-ACC is one of the brain regions that may be most affected by cancer treatment.

fMRI was also used to examine potential brain activation differences corresponding to the variance in social functioning and neurocognitive performance observed between groups. It was hypothesized that BOLD activation would serve as a strong predictor of executive function performance based on the known functions of the D-ACC and prefrontal cortex. However, BOLD activation in the D-ACC did not better predict executive function performance than group status. The lack of a connection between BOLD activation and executive function performance was also evidenced by the largely non-significant correlations found between the two variables. However, although BOLD activation did not strongly predict executive function performance, differences in BOLD activation were found to be the best predictor of the variance in social problems.

These results indicate a hypothesized model in which neuronal differences found in brain tumor patients, most likely as a result of radiation therapy and treatment, lead to an impaired ability to function socially. It is then a short, and well documented, step to increased levels of anxious and depressive symptoms. Such a model supports the conclusion that social problems are not solely a social phenomenon, but have a biological basis as well. Noticeably missing in this model is executive function performance. Although executive function deficits were found to correlate significantly with social problems, they did not best account for the variance

observed in social problems nor were they best predicted by BOLD activation in the prefrontal cortex as would be expected if they served as an intermediate step between BOLD activation and social problems. Although it is possible that neurocognitive performance is not best accounted for by BOLD activation in the prefrontal cortex, prior research in this area has indicated otherwise, and it may instead be due to the relatively small sample size examined in this study.

The findings from executive function performance differences, both within and outside of the scanner, bring to light another interesting relationship --- group differences in performance as a function of task. As mentioned previously, the differences in activation in the D-ACC were seen for the 3-back level of the N-back task. This level is the most complex level of the task, containing the most letters between the two target stimuli, thus requiring the participant to cognitively capture and manipulate the largest amount of information. When the scores of brain tumor survivors were compared to those of healthy controls for the progressively less complex 2-back, 1-back, and 0-back conditions, no significant difference in performance was observed. Thus, as has been found in prior research with ALL survivors, these deficits in working memory were seen only with the most complex tasks (Robinson et al., 2010). This relationship was further supported by comparison of the performance of brain tumor survivors and healthy controls on the DKEFS color-word interference subscales. On the word reading task, during which the participant is only responsible for reading the name of a color written in black ink, brain tumors performed no differently than healthy controls. However, on the inhibition/switching task, the most complex subscale of the color-word interference task, involving both cognitive inhibition and flexibility, brain tumor survivors performed significantly more poorly than healthy controls. Just as with the N-back task, the neurocognitive deficits of the brain tumor survivors only became apparent during the most complex tasks. Based on these

results, it can be speculated that the damage caused by the treatment of cancers either selectively affects the circuitry responsible for these most complex tasks, or affects both complex and simple circuits, but in a way that the detrimental effects to the simple circuits can be overcome by neuronal plasticity and other recovery mechanisms.

The results of this study allow for a better, and more complete, understanding of the cognitive and social deficits faced by the brain tumor population and, just as importantly, an improved understanding the underlying biological basis of these problems. This study is one of the first to use neuroimaging to observe both the neurobiological basis of executive function as well as differences in the neurobiological processes of brain tumor survivors as compared to healthy controls. The multiple measures of neurocognitive and social functioning provide conclusive evidence of the significant differences seen in these areas between brain tumor survivors and healthy participants. Such knowledge could prove useful in designing more effective and less detrimental brain tumor treatment options, in addition to beginning to search for methods to alleviate some of these problems.

However, there are also several limitations that must be taken into consideration when interpreting the results of this study. First and foremost, the sample size used in the study was relatively small. With 20 participants in both the brain tumor survivor and healthy control group, data analyses was limited and the extrapolation of these findings to the larger population of brain tumor survivors must be done with caution. In addition, the brain tumor survivor group represents a highly heterogeneous sample in regards to brain tumor location and type and the treatment received- factors that most likely play a significant role in predicting cognitive and social impairments. Regarding the measures used during the study, only a portion of the scales for executive function and social deficits were analyzed. In addition, BOLD activation was

reported and analyzed here for only one cluster. Such limited analyses may have created a skewed or incomplete picture of the challenges facing brain tumor survivors. Lastly, the relationships described between the CBCL measures of social problems and anxious/depressive symptoms, as well as the executive function measures of the BRIEF, may have been influenced by shared method variance. All of these measures were questionnaires completed by the parent and, in the case of the CBCL, the two sub-scores were based off of the same overall measure.

The results of this study suggest many opportunities for continuation and expansion. The label of “brain tumor survivor” encompasses a large variety of diagnoses, each corresponding to varying locations in the brain, types of cells involved, as well as differing symptoms and prognoses. Including all of these diagnoses in one large analysis may overlook distinct differences in the cognitive and social implications of each. Much work has been done examining the possible factor that contribute to the social and cognitive challenges faced by brain tumor survivors, and from this, it has been found that treatment type and tumor location have significant influence on the long-term outcomes of brain tumor treatment.

Regarding treatment type, radiation is perhaps the most damaging treatment method. Radiation therapy has been found to be associated with increased anxious/depressive symptoms, attention problems, and antisocial behaviors (Schultz et al., 2007). In addition, radiation dosage has been found to correlate positively with the slope of IQ decrease following treatment (Merchant et al., 2009). The location of the tumor has been shown to be comparably important in predicting outcome, with the level of cognitive and social deficits faced by brain tumor survivors being potentially related to the location of the tumor within the brain (Glauser et al., 1991). Thus, it would be beneficial to examine cognitive and social deficits with a more homogenous brain tumor population, separated based on treatment type, tumor location, or a combination of both.

Perhaps most importantly, a solid identification of the social and cognitive deficits faced by brain tumor survivors allows for the possibility of a targeted and effective intervention aimed at lessening the detrimental effects. Understanding the specific areas affected most by brain tumor treatment allows an intervention to be created to focus on these specific areas. In addition, an understanding of the relationships between deficits in these different areas (i.e. social, cognitive, and psychological) can lead to an intervention that, through targeting one facet, can lead to improvements in multiple domains. In fact, prior studies have shown that training working memory can lead to changes in tasks and skills outside of those trained (Buschkuhl et al., 2011). Based on these findings and the results from the current study, two general approaches to intervention models can be created. The first would involve a bottom-up approach, in which the intervention would target working memory in hopes of also improving more complex social and behavioral outcomes that are related to working memory performance. The second would be a top-down approach in which social and behavioral skills would be targeted in hopes of also improving cognitive performance.

In conclusion, this study supports prior research indicating the presences of increased levels of social, cognitive, and psychological deficits in brain tumor survivors. In addition, the study allowed for a greater understanding of the neurobiological basis for such deficits and a potential model of how they are related. These findings promise to not only serve as the basis for more focused studies involving specific predictive factors in the future, but also for potential interventions that will necessarily rely on a basic understanding of the deficits, their connections, and their underlying causes. At the core of the current study and these potential future directions lies the ultimate goal of improving cancer patient health and prognosis.

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Table I. Demographics of Brain Tumor Survivors and Healthy Controls

Variables	BT (n=20)	HC (n=20)	χ^2 (p)/ t(p)
Sex			
Female	8 (40%)	11 (55%)	.91
Male	12 (60.00%)	9 (45.00%)	
Age			
Mean (SD)	12.15 (2.72)	12.4 (2.98)	.28
Race/ethnicity (n, %)			
White/Caucasian	18 (90.00%)	12 (60.00%)	5.77
Black/African American	1 (5.00%)	6 (30.00%)	
Latino	0 (0.00%)	1 (5.00%)	
Asian or Pacific Islander	1 (5.00%)	1 (5.00%)	
Main Caregiver (n, %)			
Biological Mother	17 (85.00%)	20 (100%)	3.24 (.072)
Biological Father	3 (15.00%)	0 (0.00%)	
Parent Education (n, %)			
High School or Less	4 (20.00%)	0 (0.00%)	4.44*
Education Beyond High School	16 (80.00%)	20 (76.60%)	
Household Income			
<\$50,000/year	8 (40.00%)	9 (45.00%)	1.06
≥\$50,000/year	11 (65.00%)	11 (55.00%)	
Rather Not Say	1 (5.00%)	0 (0.00%)	

Chi-squares are reported for all variables with the exception of age, for which a t-test was performed

*p≤ .05, **p< .01, ***p< .001

Table II. Mean Scaled Scores and Standard Deviations for Executive Functioning, Social Problems, and Anxiety/Depression Variables

	Brain Tumor		Healthy Control		t (p)
	Mean	SD	Mean	SD	
BRIEF Shift Scale T Score	54.00	11.07	49.25	11.36	3.01**
BRIEF Behavioral Regulation T Score	58.75	10.09	49.60	12.08	2.60*
DKEFS CW Word Reading Scaled Score	9.30	3.56	11.10	2.13	-1.94 (.059)
DKEFS CW Inhibition/Switching Scaled Score	7.70	3.64	11.30	2.00	-3.87***
CBCL Social Problems T Score	61.75	7.00	54.35	7.53	3.22***
CBCL Internalizing T Score	60.60	10.61	51.10	10.82	2.80**
CBCL Anxiety Problems T Score	59.35	7.77	54.00	7.73	2.18*
3v0-back Cluster 19-BA32	0.02	0.22	.21	.18	-2.71*
Total Accuracy 0-back	43.56	2.73	44.47	1.94	-1.14
Total Accuracy 1-back	43.33	2.83	44.59	1.46	-1.63
Total Accuracy 2-back	41.5	2.55	42.35	3.02	-.90
Total Accuracy 3-back	37.50	2.60	40.41	2.37	-3.46**

*p \leq .05, **p $<$.01, ***p $<$.001

Table III. Correlations Among Executive Function, Social Problems, and Anxiety/Depression Scores

	1.	2.	3.	4.	5.	6.	7.	8.
1. BRIEF Shift Scale T Score	--							
2. BRIEF Behavioral Regulation Index Scale T Score	.80***	--						
3. DKEFS CW Word Reading Scaled Score	-.62***	.37*	--					
4. DKEFS CW Inhibition/ Switching Scaled Score	-.54***	-.32*	.72***	--				
5. CBCL Social Problems T Score	.69***	.66***	-.34*	-.34*	--			
6. CBCL Internalizing T Score	.69***	.70***	-.41**	-.29	.53***	--		
7. CBCL DSM Anxiety Problems T Score	.73***	.78***	-.48**	-.37*	.63***	.63***	--	
8. 3v0-back Cluster 19- BA 32	-.36*	-.28	.16	.23	-.50**	-.25	-.15	--

*p \leq .05, **p $<$.01, ***p $<$.001

Table IV. Regression Equation Testing Factors of Anxiety Problems as Dependent Variable

Step	Predictors	β	t(p)	R²	R²- Change	F- Change
Step 1: Group	Group	-.35	-2.01*	.09	.12	4.06*
Step 2: CW Inhibition/Switching	Group	-.19	-1.04	.16	.10	3.61
	Inhibition/Switching	-.35	-1.90 (.07)			
Step 3: Social Problems	Group	.04	.23	.41	.25	13.14**
	Inhibition/Switching	-.23	-1.46			
	Social Problems	.59	3.63**			
Step 4: 3v0-back BA 32 BOLD	Group	-.033	-.20	.44	.046	2.54
	Inhibition/Switching	-.22	-1.43			
	Social Problems	.68	4.05***			
	3v0-back	.26	1.60			

*p \leq .05, **p $<$.01, ***p $<$.001

Table V. Regression Equation Testing Factors of Social Problems as Dependent Variable

Step	Predictors	β	t(p)	R²	R²- Change	F- Change
Step 1: Group	Group	-.48	- 3.01**	.21	.23	9.08**
Step 2: CW Inhibition/Switching	Group	-.39	-2.20*	.22	.03	1.32
	Inhibition/Switching	-.20	-1.15			
Step 3: 3v0-back BA 32 BOLD	Group	-.24	-1.33	.29	.1	4.23*
	Inhibition/Switching	-.19	-1.13			
	3v0-back	.35	2.06*			

*p \leq .05, **p $<$.01, ***p $<$.001

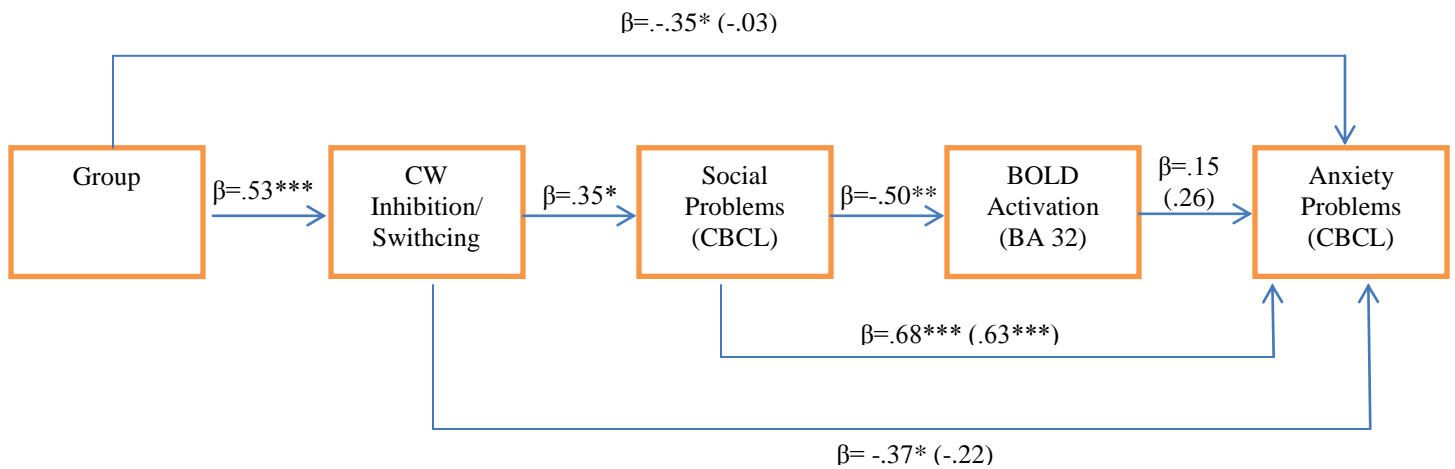


Figure 1. Linear Regression Model with Anxiety Problems as Dependent Variable
 Beta values outside of parenthesis are with two variables only. Beta values inside of parenthesis represent value after final step of regression.
 * $p \leq .05$, ** $p < .01$, *** $p < .001$

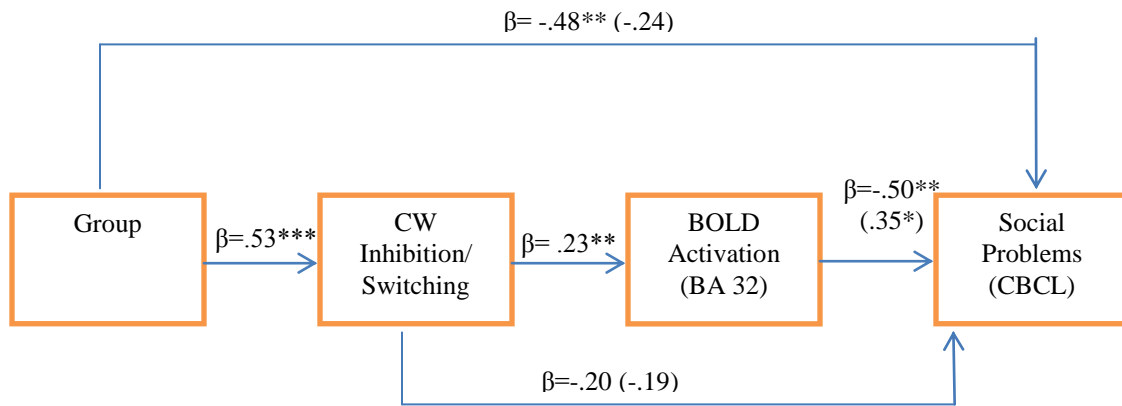


Figure 2. Linear Regression Model with Social as Dependent Variable

Beta values outside of parenthesis are with two variables only. Beta values inside of parenthesis represent value after final step of regression.

* $p \leq .05$, ** $p < .01$, *** $p < .001$

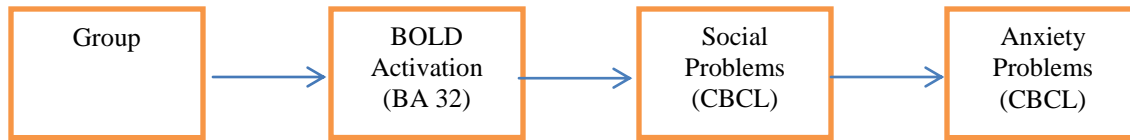


Figure 3. Theoretical model representing possible connections between factors contributing to anxiety problems.