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NEUROCOGNITIVE OUTCOMES IN CHILDREN EXPERIENCING SEIZURES DURING
TREATMENT FOR ACUTE LYMPHOBLASTIC LEUKEMIA

A Dissertation
presented in fulfillment of requirements
for the degree of Doctor of Philosophy
in the Department of Psychology
The University of Mississippi

by

STEPHANIE L. NASSAR

July 2014

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ABSTRACT

There is a growing literature for cognitive late effects among childhood cancer survivors, yet little empirical information is known regarding specific neurocognitive outcomes of children who experience seizures while treated for acute lymphoblastic leukemia. This study examined prevalence of on-protocol seizures, seizure risk factors, and neurocognitive change in children with therapy-related seizures in comparison to the normative sample and a matched cohort of children without on-protocol seizures. Participants included children enrolled on the St. Jude frontline leukemia treatment protocol, Total Therapy 15 (TOTXV) - the first systematic investigation of intensified chemotherapy agents plus optimal intrathecal therapy without irradiation. Out of 498 children, 19 experienced therapy-related seizures. To increase the statistical power of comparisons, the 19 children were matched on relevant variables to two children without on-protocol seizures. Neuropsychological assessment and magnetic resonance imaging each occurred across three treatment time-points. Results revealed a 3.82% two-year incidence of seizures during TOTXV with over 50 percent of seizures during induction and consolidation phases. No demographic or clinical factors were predictive of seizures; although, a trend for standard/high treatment intensity was observed. When the neuropsychological performance of the seizure group was compared to normative scores, patterns of differences emerged and maintained across time-points for domains of attention, working memory, and processing speed significantly elevated for the seizure group. Similar patterns also emerged across time-points between the seizure group and the non-seizure cohort. At therapy completion,

the seizure group performed significantly worse for attention and working memory tasks than the cohort, and these deficits persisted two years later with the addition of processing speed deficits and significantly worse intellectual functioning. Imaging findings indicated that children with therapy-related seizures experienced more significant early neurotoxicity (i.e., leukoencephalopathy) than non-seizure cohorts. Based on these preliminary findings, it appears that children who experience treatment-related seizures are at greater neurocognitive risk when compared to counterparts who do not. Findings point to a relationship between on-therapy seizures, leukoencephalopathy, and deficits in neuropsychological performance, specifically attention, working memory, and processing speed skills, which may lead to overall declines in intellectual functioning. Further research is needed to identify changes in neurocognitive status that indicate risk for long-term CNS effect in the hope of providing greater comprehension on how to earlier treat and prevent cognitive late effects.

DEDICATION

This dissertation is dedicated to my family and my little bug, Chewie.

LIST OF ABBREVIATIONS

ALL	Acute Lymphoblastic Leukemia
CNS	Central Nervous System
CRT	Cranial Radiation Therapy
DEX	Dexamethasone
HDMTX	High Dose Methotrexate
ITHMA	Intrathecal Hydrocortisone, Methotrexate, and Ara-C
TOTXV	Total 15 Protocol
MRI	Magnetic Resonance Imaging
DTI	Diffusion Tensor Imaging
AED	Antiepileptic Drug
GABA	Gamma-Aminobutyric-Acid
EQ	Estimated Intellectual Quotient
FSIQ	Full-Scale Intellectual Quotient
WIAT	Wechsler Individual Achievement Test
FFD	Freedom from Distractibility
DS	Digit Span
PSI	Processing Speed Index
CPT	Conners' Continuous Performance Test
CPRS	Conners' Parent Rating Scale

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INTRODUCTION

The American Epilepsy Society (2006) defines a seizure as “the clinical manifestation of a hyperexcitable neuronal network, in which the electrical balance underlying normal neuronal activity is pathologically altered—excitation predominates over inhibition.” (p. 6). A diversity of medical health conditions engenders brain damage and abnormal electroencephalogram (EEG) activity which predispose patients to seizures. Seizures may also result as a side effect of treatment and medications. Several medical populations that are susceptible to seizures include those suffering with encephalitis, meningitis, Huntington’s disease, acquired immunodeficiency syndrome (AIDS), dementia, multiple sclerosis, stroke, traumatic brain injury, brain tumors, and other infections of the brain. One particular medical population that is at elevated risk for seizure experience due to the nature of treatment, and is the focus of this paper, is children treated for acute lymphoblastic leukemia (ALL).

In order to understand the impact of seizure experience as an indicator of brain damage within this specific cancer population, it is helpful to first discuss seizure prevalence, etiology, classification, and clinical management within healthy child populations. It is also useful to examine the neuropsychological and neuroimaging correlates of seizures within healthy child populations. Next, this paper considers the neuropsychological consequences that occur within the context of leukemia treatment, including seizures. Comparisons between healthy children and children with cancer will aid in parsing out neuropsychological deficits related to leukemia treatment versus deficits related to seizure experience, with added appreciation for potential confounding factors or synergistic effects, when changes are observed.

Seizures in Healthy Children

Prevalence

Seizures are among the most common, emergent pediatric neurologic problems (Friedman & Sharieff, 2006; Patel, Walsh, & Garg, n.d.), with approximately three to five percent of children in the United States experiencing a febrile seizure by age five (Reuter & Brownstein, 2002) and approximately 4 to 10 percent experiencing a seizure by age 16 (McAbee & Wark, 2000). Epidemiological research suggests that each year about 150,000 children in the United States experience a first unprovoked seizure, with 30,000 of those developing epilepsy (Hauser, 1994).

Developing countries appear to be at two to three times higher risk for first onset seizure and epilepsy compared to incidence rates of Western, industrialized countries (Banerjee & Hauser, 2008). A review of studies suggests that males are at higher risk than females for unprovoked seizures even after controlling for risk factors such as head injury, as well as individuals from lower socioeconomic levels than those from high socioeconomic status even after controlling for race (Banerjee & Hauser, 2008). According to the International Classification of Epileptic Seizures, partial seizures appear the most common seizure type, accounting for just more than 50 percent of classified cases (Banerjee & Hauser, 2008; Commission on Classification and Terminology of the International League Against Epilepsy [ILAE], 1989).

Etiology and Seizure Classification

Seizures have distinctive etiologies and are categorized by particular clinical descriptions and electroencephalographic wave patterns (Kaufman, 2001). Classification of seizure etiology

as unprovoked or provoked is important in determining treatment options and prognosis (Chu-Shore & Tseng, 2011). Causes of provoked seizures include head trauma; central nervous system (CNS) infections such as meningitis, encephalitis, and subdural empyema; metabolic abnormalities in glucose, sodium, or calcium levels; and cerebral structural abnormalities such as congenital malformations, stroke, or mass lesions (Chu-Shore & Tseng, 2011). Prenatal drug exposure and drug withdrawal must also be considered when identifying possible causes (Reuter & Brownstein, 2002). The most commonly identified cause of seizures in Western, industrialized countries is cerebrovascular disease, accounting for 12 percent of new onset cases; whereas, in South America, the most frequently identified cause is CNS infection (Banerjee & Hauser, 2008).

Classification of seizure type and ruling out epileptogenic syndromes is also informative for treatment options and prognosis. The most frequently employed taxonomy is the ILAE's *International Classification of Epileptic Seizures*, which was recently reorganized (Berg et al., 2010). The two major seizure classifications include *focal* (previously *partial*), where network involvement is within just one hemisphere where abnormal activity is discretely localized or widely distributed, and *generalized*, where network involvement emerges within and engages bilateral hemispheres (Berg et al., 2010; Berg & Scheffer, 2011). Within the nomenclature of *focal*, it is important to categorize the seizure as either 1) without impairment in consciousness (*simple partial*) or 2) with impairment in consciousness, dyscognitive (*complex partial*). Simple partial seizures may be further characterized by one or more features: motoric, autonomic, or sensory/psychic aura aspects. Focal seizures typically last less than two minutes. It is important to note that focal seizures may evolve into bilateral, convulsive seizures. *Generalized* seizures include several categories: *tonic-clonic* (*grand mal*), *absence* (*petit mal*), *tonic*, *clonic*, *atonic*,

and *myoclonic*. The *tonic-clonic* seizure typically lasts for three to five minutes. They are often preceded by an aura, followed by loss of consciousness with skeletal muscle tension (tonic) causing the person to fall if standing, followed by muscle convulsions that can range from twitching to violent, rapid movements of the tensed extremities (clonic), with often eyes rolled back or closed and tongue bruised by jaw contractions. *Absence* seizures are brief, usually lasting less than 20 seconds and involve impairment of consciousness with generalized spike-and-slow wave EEG discharges. Absence seizures are divided into two types: *typical* and *atypical*. Typical absence seizures are clinically identified as staring spells with impaired responsiveness or awareness and characterized by fast >2.5 Hz generalized spike-wave EEG discharges. Atypical absence seizures (<2.5 Hz spike and slow wave) may allow some responsiveness and be accompanied by eye blinking or twitching of the lips. *Atonic* seizures, or drop attacks, typically last less than 15 seconds and involve loss of muscle tone, causing the eyelids to suddenly drop as well as the body to drop if in standing position. *Myoclonic* seizures are very brief (less than two seconds) and involve rapid jerking or twitching of a muscle or muscle groups.

Classification is based on a thorough history of clinical symptoms, description of the seizure event, and the identification of seizure antecedents, such as trauma, fever, or underlying medical conditions (Reuter & Brownstein, 2002; Williams & Sharp, 2000). While no routine laboratory procedures exist for first-onset seizures, a physical examination with vitals, supplemented by blood glucose levels is a good place to start (Reuter & Brownstein, 2002). The electroencephalogram (EEG) is the preferred laboratory assessment as the presence of abnormal epileptiform discharges is diagnostic of seizure; however, a normal EEG does not rule out the possibility of seizures (Williams & Sharp, 2000). Ictal EEG recordings, while ideal, are rare to capture within the hospital setting and EEG recordings should be scheduled several days to

weeks after the first seizure to avoid residual generalized slowing usually seen in the postictal phase (Reuter & Brownstein, 2002).

Computed tomography or magnetic resonance imaging (CT or MRI) in the acute care setting is recommended when seizure duration is prolonged beyond 15 minutes, the postictal phase prevents clinical treatment, or high risk factors would indicate a positive scan of newly identified neuronal anomalies. Risk factors for positive imaging results include age 6 months or younger, first-onset focal neurological deficits, and high risk conditions such as a recent CSF shunt revision, closed head trauma, neurocutaneous disease, and malignancies (Reuter & Brownstein, 2002).

Clinical Management of Seizures

The gold standard treatment for seizures and epilepsy is antiepileptic drugs or AEDs (Kaufman, 2001). Given seizures are clinical manifestations of a hyperexcitable neuronal network, the most successful anticonvulsants combat excitatory neuronal processes and enhance inhibitory neuronal processes (American Epilepsy Society, 2008). The most important CNS inhibitory neurotransmitter is gamma-aminobutyric-acid (GABA) and several anticonvulsants are known to enhance the inhibitory GABA system, such as clonazepam (Klonopin), tiagabine (Gabatril), pregabalin (Lyrica), and phenobarbital. The most important excitatory neurotransmitter is glutamate. Glutamate receptor antagonists as novel AEDs are appealing given their promising prevention of neuronal damage post-stroke and post-status epilepticus in addition to traditional seizure prevention (American Epilepsy Society, 2008).

Treatments for acute seizures, including status epilepticus, typically include benzodiazepines (e.g., diazepam, lorazepam, and midazolam), which disrupt and calm the whole system. Barbiturates (e.g., pentobarbital, phenobarbital, primidone, thiopental) are also

commonly used. Both benzodiazepines and barbiturates have direct influence on the important inhibitory GABA system.

While excessive AED dose concentration generally causes cognitive impairment including memory and attention difficulties (Kaufman, 2001), there is evidence that typical administration of anticonvulsants may have deleterious effects on cognitive outcomes. Management of seizures via AEDs is a matching game of sorts as the individual may be best treated by an AED other than the one with the best statistical cognitive-behavioral profile in controlled clinical studies (Devinsky, 1995). Phenytoin has been shown to impair memory and cognition, which resolves after drug withdrawal (Gallassi et al., 1988). Two other drug withdrawal studies of children successfully treated for epilepsy with carbamazepine (CBZ), phenytoin (PHT), valproate (VPA) monotherapy revealed improved cognitive functioning for measures of psychomotor speed (Aldenkamp et al., 1993, Blennow et al., 1990). In one study, children who were seizure-free for a year withdrew from AEDs for three months with neuropsychological re-evaluation after complete withdrawal at three to four months later. Improvement was found on just one neuropsychological measure of psychomotor speed, and children prescribed PHT experienced greater cognitive impairment on measurements of mental and motor speed than those prescribed CBZ (Aldenkamp et al., 1993). In the other study, researchers found that withdrawal from AEDs improved performance on binary choice and visual search tasks, although these findings were similar to the healthy control group (Blennow et al., 1990). Of mention however is that children prescribed CBZ performed most similar to healthy children before and after drug withdrawal, whereas children prescribed PHT performed most poorly. A similar pre- and post-withdrawal poor performance pattern was noted for children prescribed VPA (Blennow et al., 1990).

A recent randomized, double-blind, placebo-controlled study examined the impact of AED discontinuation on measures of attention, reaction time, and information processing speed in 150 patients without seizures for more than two years on monotherapy AEDs mostly consisting of CBZ and VPA (Hessen, Lossius, Reinvang, & Gjerstad, 2006). The main finding was that AED discontinuation significantly improved performance on tasks requiring complex cognitive processing under time pressure when compared to performance of the non-discontinuation group. Attention and reaction time tasks were not significantly different between groups. Similar to Blennow and colleagues' (1990) findings, when examining drug type, discontinuation of CBZ produced significant results parallel to the overall study outcome, whereas VPA discontinuation demonstrated a non-significant trend in the same direction (Hessen et al., 2006). In a randomized, double-blind study, verbal memory has also been shown to improve following CBZ and VPA discontinuation (Hessen, Lossius, & Gjerstad, 2011).

Impact of Seizures on Neuropsychological Outcomes

Until the late 90s, research in the area of cognitive outcomes for children diagnosed with epilepsy focused mostly on overall intellectual functioning and achievement (Williams, Griebel, & Dykman, 1998). While some researchers asserted that intelligence for children with epilepsy followed the normal curve seen in the healthy child population, others reported intelligence findings skewed toward the low average range. Achievement abilities have generally been found to be disrupted within children diagnosed with epilepsy, regardless of seizure type or treatment. While some studies point to a hemisphere lateralization of deficits based on seizure type (i.e., right versus left temporal lobe epilepsy), others do not evidence hemispheric differences when examining verbal and performance abilities, personality, or school problems (Camfield et al., 1984).

The relationship between seizures and cognitive impairment may be an indirect one, where learning problems and disruptions in cognitive development are secondary to a general decreased alertness and inattention stemming from the seizure activity (Sturniolo & Galletti, 1994). Regardless of causal mechanisms, cognitive impairment has been well established in children with epilepsy (Farwell, Dodrill, & Batzel, 1985; Williams & Sharp, 2000), appearing at seizure onset (Fastenau et al., 2009) and possibly even emerging before onset based on the transient cognitive impairment model, in which cognitive disruptions are indicated by epileptiform EEG discharges (Aldenkamp & Arends, 2004).

Appreciating risk factors and specific causes for neurocognitive deficits is crucial in prompt intervention for common cognitive and academic difficulties. Given this, there has been a recent shift from measuring global cognitive abilities to measuring more specific cognitive abilities. Neuropsychological assessments often include performance measures of memory, attention, processing speed, language, fine motor skills, executive function, visual motor integration, and parental report of behavior.

Healthy children with seizures experience adverse effects for specific cognitive outcomes, including decreased short-term memory, visual spatial difficulties, and poorer concentration, when compared to same-age peers (Blennow et al., 1990; Dam, 1990). The most consistent finding across studies in children with seizures is the disruption of attentional skills (Williams & Sharp, 2000).

Fastenau and colleagues (2009) examined outcomes for four factors of neuropsychological performance (factor 1: attention/executive/construction; factor 2: language; factor 3: processing speed; factor 4: verbal memory and learning) and academic achievement for 282 children with first onset seizure in comparison to a healthy sibling group ($n=147$).

Neuropsychological deficit was operationalized as 1.3 SD below the healthy sibling norm on the 4 factors, corresponding with the 10th percentile or upper range of borderline intellect. While there was no difference between groups in academic achievement, children with seizures performed worse on all measures of neuropsychological functioning when compared to healthy siblings, particularly for the factor of attention/executive/construction (Fastenau et al., 2009). Children with seizures also displayed significantly higher odds ratio for neuropsychological deficits in at least one neuropsychological domain, by important clinical risk factor than the sibling group (27.4 percent versus 18.2 percent, respectively, $\chi^2 p = .04$), with nearly twice as many in the seizure group demonstrating deficits for factors of language, verbal memory and learning, and attention/construction/executive functioning, (13.9 percent versus 7.7 percent for each factor). The proportion for processing speed was somewhat narrower (13.5 versus 8.4). Antiepileptic drug (AED) use was related to neuropsychological deficiencies on all four factors. A second seizure, even in non-medicated children, was found to be related to deficits in attention/construction/executive functioning. The authors assert that this finding adds to the conceptualization of deleterious effects of seizures, which are not limited to children with frequent seizures, generalized symptomatic epilepsy, high AED usage, or extremely early onset (Fastenau et al., 2009).

Newer research indicates that abnormalities in neuropsychological function, brain structures, and behavior are present even at, or near, the time of new seizure diagnosis (Hermann et al., 2012). Thorough clinical histories suggest that neurologic problems and behavioral difficulties even exist before the first seizure. Within the literature on seizures and epilepsy, the cause and development of *neurobehavioral comorbidities* (a broad term which includes cognitive status, psychiatric status, and social-adaptive behaviors) is covered by Hermann and colleagues

(2012) in hope of providing greater knowledge and comprehension on how to treat and prevent these difficulties.

Three items of evidence are provided by the authors in support of neurodevelopmental influence of seizures (Hermann et al., 2012). The first piece of evidence includes data revealing that individuals with earlier age at onset of recurrent seizures suffer more adverse consequences for cognitive function (Hermann et al., 2002; Kaaden & Helmstaedter, 2009). The second piece of evidence comes from 30-year-long or longer controlled community and population-based studies following those with childhood-onset epilepsy, showing that it effects essential quality of life factors including marriage, employment, income, social involvement, independent living, psychiatric condition, and other major lifespan outcomes, even in those with intact intelligence and those in remission without AED assistance (Hermann et al., 2012). Unfavorable lifespan outcomes have been found to be related to *neurobehavioral comorbidities* such as early history of psychiatric or cognitive/learning problems (e.g., Attention-Deficit/Hyperactivity Disorder, ADHD). The third and final piece of evidence includes population-based and clinical care center investigations of neurobehavioral comorbidities in children with epilepsy, which indicate reduced performance in overall cognitive abilities, language abilities, executive function, academics, mood, nonverbal reasoning, verbal memory, motor functioning, and psychosocial function (Hermann et al., 2012).

It appears that a number of factors are related to these neuropsychological deficits, such as age at seizure onset, seizure frequency and recurring seizures, epilepsy type, length of illness, EEG results, and AED usage. There is some caution, however, in using these variables as sole predictors given their inconsistency across studies and findings of other factors influencing

declines in neuropsychological performance, such as pre-existing neuropsychological impairment, learning difficulties, psychopathology, and family factors (Jones et al., 2010).

Neuroimaging Correlates of Seizures

Although the neuroimaging findings among children with seizures are limited in comparison to the cognitive impact of seizures literature, it serves as a promising companion to understanding the neuropsychological consequence and sequelae of seizures. Childhood seizure onset has been shown to be related to reductions in whole brain volume among individuals with complicated febrile convulsion (Theodore et al., 2003), abnormal white and gray matter volumes (Hermann, 2002; Kaaden et al., 2011; Riley et al., 2010), altered volumes of the corpus callosum (Hermann et al., 2003; Weber et al., 2007), and disruptions in white matter connectivity among individuals with chronic partial epilepsy (Herman et al., 2003).

Children with Acute Lymphoblastic Leukemia (ALL)

Prevalence of ALL

Leukemia is the most common type of childhood cancer, with acute lymphoblastic leukemia (ALL) accounting for three out of four cases of childhood leukemia. The American Cancer Society (2012) estimated approximately 6,050 new cases of ALL in the United States for 2012. For reasons unknown, the incidence of ALL across race is notably higher in Caucasian children than in African American children, although highest in Hispanic children (National Cancer Institute, 2012).

Treatment of ALL

Survival rates. Survival rates for children with ALL have improved dramatically over the past several decades from less than 10 percent to nearly 90 percent (Pui et al., 2009).

Increases in survivorship were initially related to prophylactic treatment of the CNS to reduce

secondary malignancies, particularly once-standard cranial irradiation treatment. With the advent of chemotherapy, prophylactic treatment has improved in its specificity and sensitivity, and in turn, enhanced survival rates. Although survival has increased, 20 percent of treatment protocols still employ radiation, with radiation-related cognitive late effects observed in more than two-thirds of survivors (Pui, 2004). Cognitive late effects are defined as neurocognitive deficits (e.g., executive function, memory, attention, processing speed) and learning difficulties observed at two to five years after treatment (National Cancer Institute, 2012). Therefore, great efforts have been made to intensify systemic and intrathecal chemotherapy in order to offset potential risks of removing cranial irradiation therapy from ALL treatment.

A recent study including more than 21,000 children with ALL (more than half of the United States' patients) that took part in the Children's Oncology Group 1990 to 2005 clinical trials revealed a higher 5-year survival rate of 90.4 percent for children diagnosed between 2000 and 2005 compared to 83.7 percent for those diagnosed from 1990 to 1994 (Hunger et al., 2012). Children aged 1 to 9 years are more likely to experience disease-free survival than infants and children aged 10 or older (Möricke et al., 2005; Schrappe et al., 2000; Smith et al., 1996).

Although prognosis is favorable, childhood cancer survivors are still at risk for significant acute and long-term sequelae related to disease and treatment, with 60 percent experiencing at least one long-term treatment-related side effect (Fulbright et al., 2011; Kopp et al., 2012; Oeffinger & Hudson, 2004). There is increased focus on the effect of chemotherapy on psychosocial and quality of life issues, including neurobehavioral outcomes (Phipps et al., 2012). Most often studied indicators of neurotoxicity include global intellectual and academic performance, although there has been a recent focus on specific neurocognitive processes (Butler

& Haser, 2006; Phipps et al., 2012). Research data on cognitive late effects of childhood leukemia support the conceptualization that it is a chronic illness in need of continued care for its expanding survivorship population (Phipps et al., 2012).

Impact of Chemotherapy Alone on Cognitive Outcomes of ALL Survivors

While the elimination of cranial radiation therapy (CRT) from leukemia treatment has reduced overall neuropsychological impairment in ALL survivors, neurocognitive problems (predominately working memory and attention deficits) still exist among the population in subtle yet significant ways that impact daily life (Ashford et al., 2010; Conklin et al., 2012). Reviews and meta-analyses of the neurocognitive effects of central nervous system (CNS-directed) chemotherapy in ALL survivors suggest an adverse impact on several domains of neuropsychological functioning (Anderson & Kunin-Batson, 2009; Buizer et al., 2005, 2009; Campbell et al., 2007; Moore, 2004, Nathan et al., 2007; National Cancer Institute, 2012; Peterson et al., 2008). Cognitive impairments include deficits in intellectual and academic functioning (particularly arithmetic skills), verbal and nonverbal memory, verbal comprehension, attention, processing speed, complex fine motor skills, visual-motor integration, visual-spatial skills, and facets of executive function (Brown et al., 1992; Halsey et al., 2011; Jansen et al., 2008; Mennes et al., 2005; Moleski, 2000; Peterson et al., 2008). Risk factors that account for worse cognitive outcomes include younger age at diagnosis, female gender, greater time since treatment, and higher treatment intensity (Buizer et a., 2005; Buizer et al., 2009; Cohen & Duffner, 1991; Conklin et al., 2012; National Cancer Institute, 2012; Peterson et al., 2008; Phipps et al., 2012; von der Weid, 2003).

Leukemia treatment specialists have made a case for refined measurement of cognitive deficits in particular neuropsychological functions, namely central processing skills, as they

appear to account for overall intellectual and academic declines, as well as nearly 50 percent of age-related developmental improvements (Fry & Hale, 1996; Phipps et al., 2012). Central processing is a mid-level term that includes a subset of performance-based cognitive skills such as attention to stimuli, speed of processing information, recall of information, and other executive functions such as working memory, or holding information “online” (Phipps et al., 2012). Meta-analyses have suggested that ALL survivors experience significant decrements in these areas (Campbell et al., 2007; Peterson et al., 2008).

Of the central processing skills, deficits in processing speed and working memory skills appear particularly important in relation to the emergence of cognitive late effects. Of the two, working memory measurements seem most useful in detecting treatment-related change, as they are sensitive to cognitive declines even in non-irradiated, chemotherapy-only samples where treatment intensity is based on risk (e.g., low and standard/high). Increased chemotherapy dosing of intravenous methotrexate worsens cognitive deficits, specifically declines in attention, (Buizer et al., 2005) and attentional deficits in ALL survivors have been linked to smaller and abnormal cerebral white matter volumes (Ashford et al., 2010; Reddick et al., 2006).

Central processing skills as a mediator in cognitive late effects of CNS-directed therapy is substantiated by the temporal-spatial sequence of neurobehavioral declines in relation to chemotherapy and temporal-spatial coherence between cognitive declines and decreased cerebral white matter volumes (Schatz et al., 2000). Ashford and colleagues (2010) also discovered that working memory performance scores, which identified cognitive deficits overlooked by estimated intelligence scores, predicted overall intelligence scores. Detecting performance declines in these specific, purported mediating neuropsychological processes (e.g., working memory, attention) adversely affected by chemotherapy is necessary to develop targeted, cost-

and time-effective interventions. It will also assist in the discovery and confirmation of neural pathways hypothesized to be directly related to these neurobehavioral deficits (Phipps et al., 2012).

Impact of Chemotherapy on Behavioral and Psychological Functioning of ALL Survivors

Surprisingly, children with cancer cope relatively well, often reporting similar or even lower levels of psychological distress (e.g., depression and anxiety) than healthy peers (Phipps, 2007). Reviews reveal that both self- and other-reports of psychological distress suggest lower levels of distress in cancer survivors, relative to children with other chronic illnesses (Eiser, Hill, & Vance, 2000; Lavigne & Faier-Routman, 1992; Noll et al., 1997; Patenaude & Kupst, 2005; Phipps & Srivastava, 1997).

The lack of maladjustment findings has created skepticism for some researchers who argue that traditional symptom measures are unable to portray difficulties unique and specific to the childhood cancer population. As a result, the past decade's pediatric cancer coping research has focused on symptomatology of post-traumatic stress disorder (PTSD), particularly subclinical levels of post-traumatic stress symptoms (PTSS) given null findings of significant PTSD within the pediatric cancer population (Bruce, 2006). Yet significant differences in PTSS have not emerged in the few studies comparing pediatric cancer samples to healthy controls (Barakat et al., 1997; Schwartz & Drotar, 2006).

Research conducted at St. Jude Children's Research Hospital suggests that adaptive style plays a more prominent role than history of health condition in contributing to PTSS (Phipps, Jurbergs, & Long, 2009; Phipps, Larson, Long, & Rai, 2006). Adaptive style, or individual disposition to perceived threats, was measured by self-reported defensiveness and trait anxiety, allowing researchers to categorize children's adaptive style into four groups: repressor, low

anxiety, high anxiety, and defensive high anxious. Children categorized as low anxious or repressive adaptive style (low anxiety, high defensiveness) endorsed lower levels of PTSS than children categorized as high anxious. High anxious adaptive style was associated with a greater probability of arousal, avoidance, numbing, intrusive thoughts, and re-experiencing of events (Phipps et al., 2006). In a following study with an added healthy child control group, the adaptive style findings were replicated regardless of health condition and there was a lack of significant group differences for PTSS (Phipps et al., 2009). Relapse was the only cancer-related variable correlated with elevated PTSS. While children with cancer endorsed greater numbing and avoidance than healthy children, they also endorsed fewer intrusive thoughts and trauma re-experience. Other research findings and reviews have also questioned the conceptualization of childhood cancer experience as a traumatic event, offering alternative conceptual models such as “psychosocial transition” (Cordova & Andrykowski, 2003; Deimling et al., 2002) and “post-traumatic growth” (Barakat, Alderfer, & Kazak, 2006).

Impact of Chemotherapy on Neuroimaging Outcomes

While CRT with and without chemotherapy (primarily methotrexate) has been strongly linked to intracranial white matter changes, vascular damage, and other serious neuropsychological and neuroendocrine issues (Cohen & Duffner, 1991; Packer et al., 1987), chemotherapy alone has also been considered by some investigators to result in comparable neurocognitive side effects (Buizer et al., 2009). Consequences of chemotherapeutic drugs include brain atrophy, vascular injury, and white matter damage; the latter termed leukoencephalopathy or reversible acute methotrexate neurotoxicity (Anderson & Kunin-Batson, 2009; Paakko et al., 2000; Reddick et al., 2006; Wilson et al., 1991). Leukoencephalopathy

prevalence, measured by MRI, is as high as 86 percent after seven intravenous high-dose methotrexate (MTX) rounds, with a reduced 40 percent at treatment completion (Reddick et al, 2005). If methotrexate neurotoxicity has not reversed at end of therapy, it is thought to resolve within a year or so after (Haykin et al., 2006; Wilson et al., 1991; Ziereisen et al., 2006). However, using single-photon emission computed tomography (SPECT), Paakko and colleagues (2000) discovered small brain perfusion defects at up to eight years post-treatment, which were missed by perfusion MRI.

Younger aged children's developing brains are more vulnerable to therapy-related neurotoxicity, evidenced by measured decreased cerebral white matter volumes and increased oxidative stress in the CNS post-treatment (Rajamani et al., 2000). Females appear to be particularly vulnerable to the effects of CNS-directed therapy as males' neurodevelopmental experience involves greater white matter volume increases in childhood (Maytal et al., 1995). Biomarkers of oxidative stress include increased levels of brain specific proteins. Oxidized fractions of the most prevalent cerebrospinal fluid phospholipid called phosphatidylcholine (PC) measured after induction and consolidation phases of chemotherapy treatment predict executive function decline two years later (Caron et al., 2009).

Impact of therapy medications. Leukemia chemotherapeutic agents commonly include methotrexate (MTX), cytosine arabinoside (Ara-C), L-asparaginase (L-ASP), and vincristine (VCR). Experts have hypothesized how these agents contribute to cognitive late effects, with more recent investigation on MTX. Methotrexate interferes with folate metabolism by inhibiting the enzyme dihydrofolate reductase (DHFR) from converting dihydrofolates into active folate. Folate deficiency results in elevated levels of homocysteine, causing vascular endothelial injury and allowing permeability of the blood brain barrier to chemotherapeutic agents. With more

agents in the central nervous system, homocysteine excitotoxicity and neuronal death occurs, which may clinically present as focal neurological deficits, stroke-like episodes, and/or seizures (Anderson & Kunin-Batson, 2009; Rao et al., 2002). Excess homocysteine may also enhance levels of glutamate, which is found in epileptogenic foci, resulting in calcium influx that similarly causes excitotoxicity and neuronal death. In general, acute MTX neurotoxicity is associated with calcification, hemorrhage, thrombosis, or white matter signal abnormalities (Rao et al., 2002).

Disruptions in the folate and homocysteine systems link to physiological changes in the brain as well as neurocognitive late effects. Active MTX therapy has been associated with abnormal frontal lobe white matter and working memory deficits at end of treatment, yet the long-term effects related to these changes are not clear (Ashford et al., 2010; Khong et al., 2006; Reddick et al., 2005a). Smaller white matter tissue volumes have also been significantly associated with greater decrements in intelligence, academics, and attention (Reddick et al., 2006). Reduced frontal lobe white matter volumes in childhood cancer survivors, when compared to healthy controls, have been linked with deficits in attention, mathematics, mental flexibility, and visual-construction abilities (Carey et al., 2008). Imaging studies employing computed tomography (CT) and magnetic resonance imaging (MRI) have revealed calcifications at neural pathways that involve intellectual, memory, and attentional abilities (i.e., basal ganglia and gray-white matter junctions).

Glucocorticoids, such as dexamethasone and prednisone, are also a part of leukemia treatment. While they demonstrate helpful anti-inflammatory and immunosuppressant functions, they also initiate metabolic changes, which may result in seizure experience. Glutamate excitotoxicity, particularly occurring in the hippocampus, results in neuronal death (Hoschl &

Hajek, 2001), which also is a potential initiating factor of seizure episodes. Dexamethasone, which has a longer half-life than prednisone and other corticosteroids plus more readily infiltrates the CNS, is of particular concern when considering the neurocognitive development of children undergoing ALL treatment (Bostron et al., 2003; Phipps et al., 2012). Children treated with dexamethasone demonstrated a lower mean IQ of 11 points and poorer performance on measures of academic achievement and visual-spatial skills as compared to children treated with prednisone (Waber et al., 2000).

Seizure Occurrence among Children Treated for ALL

Prevalence of Seizures during Leukemia Treatment

Among the neurological complications seen in leukemia therapy, seizures are one of many (e.g., transient ischemic attacks, meningitis, polyneuropathy, transient paresis or paraplegic attacks, transient dysarthria, ataxia, aphasic episodes, acute altered mental states such as disorientation, loss of consciousness, and irritability, and postintrahecal severe headaches). Children with ALL are a specific pediatric cancer population with unique risk factors for and pathophysiologic causes of seizure development, such as toxic-metabolic disturbances (Antunes, 2003). Within the childhood cancer literature, approximately 3 to 13 percent of children treated for acute lymphoblastic leukemia (ALL) experience seizures (Fasano & Bergen, 2009; Goldsby et al., 2010; Kuskonmaz et al., 2006; Mainero et al., 2000; Maytal et al., 1995; Ochs et al., 1984; Skoczen et al., 2004).

Associated Risk Factors for Seizures

Data from a Memorial Sloan-Kettering Cancer Center pediatric oncology database revealed that out of 384 children diagnosed with systemic cancer, 47 were positive for seizures (Atunes, 2003). Out of the 47 children with underlying cancer and seizures, 22 (46.8 percent)

children were diagnosed with leukemia, and more specifically 16 (34 percent) children with ALL. From the sample of 47 children, the age distribution indicated a risk for younger children (aged ≤ 10). The sex distribution indicated a slightly higher occurrence of seizures in males ($n = 27$), particularly those diagnosed with ALL (Atunes, 2003). This is contrary to the finding by Maytal and colleagues (1995) from a sample of 127 children treated for ALL that revealed girls at higher risk for seizures than boys. Higher doses of intrathecal and intravenous MTX have been previously linked to seizure experience (Ochs et al., 1984).

Seizure Onset, Type, and Duration

When treatment-related seizures occur, the onset often takes place during the first six weeks of acute induction and consolidation (Fasano & Bergen, 2009). A majority of seizures occur between weeks three and four of the induction phase (Gerrard, Eden, & Lilleyman, 1986). Consistent with those temporal findings of seizure occurrence in earlier phases of leukemia treatment, a study of 1,395 pediatric patients undergoing therapy for ALL who received triple intrathecal therapy with or without high-dose MTX revealed that one percent (15 patients) experienced seizures: six during induction, four during consolidation, one during interphase, two during intensification, and two during maintenance therapy (Dufourg et al., 2010). In a retrospective study of adult survivors of childhood ALL, roughly 6 percent (249 out of 3,860 patients) reported a seizure disorder and over half of those were classified as late-onset: 5 years post-diagnosis (Goldsby et al., 2010).

Regarding seizure type, Ochs and colleagues (1984) observed a majority of seizures (93/96) to be primary generalized tonic-clonic (grand mal) or focal motor seizures, with severity of seizure classified as status epilepticus for 38 and recurrent for 45. However, these numbers on

seizure type and duration may be reflective of the older, less-refined methods of CNS prophylaxis, including high-doses of intrathecal MTX combined with cranial irradiation.

Pathophysiologic Etiology of Seizures

Among children treated for ALL, Rao and colleagues (2002, p. 1335) noted that the most common etiologies of seizures include “metabolic disturbances, coagulopathy with cerebral infarction or venous sinus thrombosis, intracerebral hemorrhage, CNS infection, fever, meningeal leukemia and drugs (such as MTX and L-asparaginase).” Kuskonmaz and colleagues (2006) noted cerebral thrombosis and ischemic infarction to be the most common etiologies, accounting for 40 percent of seizure presentations. The sample included 20 children treated for ALL that were reported to have neurological complications, with 10 of them experiencing seizures. One possible culprit of intracerebral hemorrhage and thrombosis identified was the chemotherapeutic drug, L-asparaginase (L-ASP). The mechanism of action behind L-ASP is believed to be declines in proteins that are necessary for proper coagulation and fibrinolysis (Kuskonmaz et al., 2006).

Among a sample of children with leukemia, in addition to metabolic factors, arterial hypertension and leukoencephalopathy were observed as common causes of seizures, with leukoencephalopathy believed to be the most common etiology (Antunes, 2003). Other researchers have observed this same relationship between leukoencephalopathy and treatment-related seizures. Abnormal structural brain changes were secondary to vascular-related injuries of leukemia treatment involving high-dose intravenous and intrathecal chemotherapy, specifically white matter damage secondary to methotrexate (Lövlad et al., 1998).

Treatment for Seizures and Prognosis

It is recommended that children with ALL who experience a first seizure during an early treatment phase should undergo brain imaging and coagulation studies (Maytal et al., 1995). If tests show no clear etiology, a complete metabolic work-up and cerebral spinal fluid (CSF) evaluation is advised to rule out electrolyte imbalance, disease relapse, and infection. Children with ALL who have an acute symptomatic seizure without any neuroatypicality or brain lesions should be observed closely *without* AEDs after correction or elimination of etiology of seizure. If neuroatypical results are found or seizures reoccur, AEDs are suggested for one to two years or until leukemia treatment is complete. However, long-term AEDs are cautioned (Relling et al., 2000). Treatment modifications may also be appropriate. Reduced dosing or discontinuation of chemotherapeutic drugs, such as vincristine, L-asparaginase, or intrathecal MTX, is advised (Gerrard et al., 1986). In leukemia treatment protocols with CRT, when feasible, delaying cranial irradiation for one to seven months or omitting cranial prophylaxis altogether has been proposed.

Regarding the prognosis of those who experience treatment-related seizures, Maytal and colleagues (1995) reported that 35 percent (6 out of 17 patients) had recurrent seizures, with 28 percent developing epilepsy (2 out of 17 patients). Dimario and Packer (1990) reported that 13 percent of their sample (4 of 30 patients) developed epilepsy. In a larger sample of 203 ALL patients, Kuskonmaz and colleagues (2006) found that while 5 percent (10 out of 203) experienced seizures and 2.5 percent (5 out of 203) developed epilepsy, there was a 50 percent risk of developing epilepsy after the first seizure (5 out of 10 patients). Out of the 20 patients with neurological complications, 25 percent (5 patients) developed epilepsy.

Cognitive Outcomes Data is Limited

While the rate of therapy-related seizures among children treated for leukemia is established, the cognitive impact of seizures is not well known in this population. Among children with CNS relapse, Mulhern and colleagues (1987) found weak negative correlations between seizures and overall cognitive and academic functioning. However, a significant moderate negative correlation was found between seizures and performance IQ ($r = -0.42, p < .01$). Rao and colleagues (2002) noted that patients experiencing seizures are “at a higher risk for ... recurrent seizures and delayed intellectual development” (p. 1335). However, little is known about the cognitive outcomes and neuropsychological status of ALL survivors that experienced treatment-related seizures.

Behavioral and Psychological Functioning Data is Limited

The data for behavioral and psychosocial outcomes of children who experience seizures while treated for leukemia is also limited. Fasano & Bergen (2009) followed five adults in their mid-late twenties (range = 25-29) who had been diagnosed with ALL before the age seven and later developed intractable epilepsy (defined as at least 1 seizure per month), years after ALL treatment completion. It is important to note that all five were treated with whole-brain irradiation and chemotherapy. Mean years for seizure experience post-treatment was 7.5 years, with mean age of seizure experience at age 10.

Findings indicated that three of the five experienced first seizure during treatment and all five were treated with multiple AEDs (Fasano & Bergen, 2009). While three responded to AEDs for several years, seizures returned. Only two, who experienced seizure onset during middle adolescence, completed high school. All five were cognitively impaired, with one unable to maintain employment, one living at home with parents, and two placed in care facilities. The

specific living circumstances of the other two were not reported; however, they were classified as borderline intellectual functioning and verbally impaired.

Neuroimaging Outcomes Data is Limited

While there is imaging data for children who were treated for leukemia, the data for imaging outcomes of children treated for ALL who experience seizures is limited. Rao and colleagues (2002) investigated the case of a 27-year-old woman with tonic-clonic seizures who was treated with active MTX. MRI revealed enhancement in the meningeal, cortical, and subcortical brain regions, as well as focal white matter hyposignal and cerebrospinal fluid (CSF) infiltration. CT scan revealed white matter signal abnormalities, thrombosis, ischemic stroke, and bilateral parietal hypodensities. CSF exam revealed a slight increase in protein, for which she was treated with phenytoin for three months. A follow-up MRI at 10 days later revealed resolution in aforementioned enhancements. In this specific case, the pattern of brain damage (calcification, hemorrhage, thrombosis, and white matter abnormalities) was classified as acute MTX neurotoxicity (Rao et al., 2002).

Another CT and MRI study examined neuroimaging findings of four children with ALL hospitalized for seizures after treated with high-dose intravenous and intrathecal chemotherapy (Lövlad et al., 1998). In all four children, CT was positive for diffuse periventricular white matter hypodensities and in three of the four children, subcortical hyperdense foci were present. In all four cases, MRI revealed diffuse hyper-intense white matter lesions on T2-weighted images, which was concordantly observed on susceptibility-sensitive FLASH sequences in the CT hyperdense foci as well as T1-weight images of hyperintense foci. Therefore, the authors asserted that the white matter lesions with calcification were related to leukoencephalopathy, namely a pure form of methotrexate encephalopathy, resulting in seizures (Lövlad et al., 1998).

CURRENT STUDY

Purpose of this Study

While the literature reports on the prevalence, onset, prognosis, and treatment of seizures during leukemia treatment, and while there is a whole host of data on cognitive outcomes for childhood cancer survivors indicating cognitive late effects, little empirical information is available regarding specific cognitive outcomes for children treated for ALL who experience therapy-related seizures. We desired this information given the importance of identifying cognitive risk early in treatment with respect to treatment planning, monitoring, and caregiver education. To address this gap in the literature, this study examined the relationship between seizures during leukemia therapy and cognitive outcomes in childhood leukemia survivors in the hope that it improves these aspects of care.

Current Study Objectives and Hypotheses

Our first study objective was to estimate the rate of seizure occurrence in children treated for ALL and identify demographic and clinical factors associated with seizure risk, such as age at diagnosis, gender, race, treatment intensity, and prior history of seizures. We also examined which treatment phases had the highest frequency of seizures. Given the removal of cranial irradiation and overall reduction of therapy intensity in the current study protocol, we estimated that the rate of seizure occurrence in the current sample was within the low range seen in the literature, roughly three to five percent. We predicted that clinical factors of prior history of

seizures and therapy intensity would be associated with seizure risk during leukemia therapy, with a greater number of seizures occurring during induction and consolidation phases.

Our second study objective was to assess neurocognitive change in children with therapy-related seizures by comparing their performance on neuropsychological measures across time points of first assessment, end of therapy, and two years post therapy completion. We predicted that children who experienced treatment-related seizures would significantly worsen in cognitive performance from first assessment to two years post therapy completion.

Our third study objective was to compare the neuropsychological performance of children who experienced therapy-related seizures to the normative sample as well as to the performance of a cohort of similarly treated patients without seizures matched on relevant variables (i.e., gender, age at treatment, risk arm). We predicted that post-treatment cognitive performance among children with treatment-related seizures would be significantly worse compared to the normative sample as well as the performance of the matched cohort of similarly treated patients without seizures.

Our fourth study objective was to compare the rate of leukoencephalopathy (i.e., white matter damage) between children who experienced therapy-related seizures and the matched cohort of similarly treated patients without seizures. We predicted a significantly greater occurrence of leukoencephalopathy among children with treatment-related seizures compared to similarly treated patients without seizures.

METHODOLOGY

Participants

Participants ($N = 498$) included children enrolled on the St. Jude frontline leukemia treatment protocol, Total Therapy 15 (TOTXV), which was the first systematic investigation of intensified chemotherapy agents plus optimal intrathecal therapy, without any prophylactic cranial irradiation (Pui et al., 2009). Out of the 498 children on protocol, 19 experienced therapy-related seizures. Out of those 19 children, two children had a prior history of seizures. To increase the statistical power of comparisons, each of the 19 children who experienced on-therapy seizures were matched to two similarly treated children on protocol without seizure experience ($n = 38$). Matching variables included gender, race, age at treatment, and treatment intensity.

Measures

Measurements included three time points for neuropsychological assessment as well as imaging. Neuropsychological testing was conducted at first assessment (week 6 continuation), end of therapy (week 120 continuation), and two years post therapy completion. Imaging was conducted at the end of 6-week remission induction, week 7 continuation, and end of therapy (week 120 continuation).

Neuropsychological assessment. Neuropsychological measurements included performance-based assessments of overall intellectual functioning, academic achievement,

attention and working memory, as well as parental report of behavioral problems. The assessment battery has been previously described in detail (Conklin et al., 2012).

Intellectual functioning. Overall cognitive functioning was measured using age-appropriate intelligence tests, including the Wechsler Adult Intelligence Scale – Third Edition (WAIS-III; Wechsler, 1997; ages > 16), Wechsler Intelligence Scale for Children – Third Edition (WISC-III; Wechsler, 1991; ages 6-16), Wechsler Preschool and Primary Scale of Intelligence – Revised (WPPSI-R; Wechsler, 1989; ages 3-6), and Bayley Scales of Infant Development – Second Edition, Mental Development Index (BSID-II MDI; Bayley, 1993; ages 1-3). All Wechsler scores and the BSID-II MDI have an age standardized mean of 100 and standard deviation of 15. Estimated Intelligence Quotient (EIQ) scores were obtained at all three assessment time-points; whereas Full Scale Intelligence Quotient (FSIQ) scores were obtained at the second (end of therapy) and third (two years post therapy completion) assessment time-points. EIQ was calculated from the Information, Similarities, and Block Design subtests from the WAIS-III, WISC-III, or WPPSI-R using a formula provided in Sattler (1992), which correlates highly with FSIQs ($r = .93$).

Academic Achievement. Academic achievement was assessed using two subtests from the Wechsler Individual Achievement Test (WIAT; Wechsler, 1992): Word Reading and Math Reasoning. The WIAT is similar to the other Wechsler (IQ) tests in that it employs age-based scores, with a mean of 100 and standard deviation of 15, and was standardized using the same sample as the WISC-III. Internal consistency reliabilities for the two subtests are adequate, within the high .80s to mid .90s (Wechsler, 1992). Criterion-related validity is adequate as moderately high correlations ($r_s = .70s$ to $.80s$) have been observed between the WIAT and previously established individually administered achievement tests, such as the Woodcock-

Johnson Psycho-Educational Battery-Revised, Tests of Achievement ($r_s = .68$ to $.88$), the Wide Range Achievement Test-Revised ($r_s = .69$ to $.87$), the Kaufman Test of Educational Achievement ($r_s = .73$ to $.87$), and the Peabody Picture Vocabulary Test-Revised ($r_s = .68$ to $.75$). Test-retest reliabilities from a sample of 367 students across five grades ranged from the mid .80s to low .90s (Wechsler, 1992).

Attention, working memory, and processing speed. Participants between the ages of 6 and 16 were administered the WISC-III, which allowed Wechsler indices of attention, working memory, and processing speed to be examined. Indices include Freedom from Distractibility (FFD), Digit Span Total (DS), and Processing Speed Index (PSI), respectively. The Conners' Continuous Performance Test (CPT; Conners, 2000a), a computerized measure of selective and sustained attention, was also administered to participants aged 6 and older. During the 14-minute task, children are instructed to press the space bar as quickly and accurately as possible for letters (targets presented at 250ms each), except "X" (non-target, which appears on 10 percent of the 360 trials). Intervals between stimuli vary by lengths of 1, 2, or 4 seconds depending on the trial block. The CPT computes multiple indices and of interest to the current study are indices suggesting inattention or failure to respond to a target (Omission Errors) and processing speed (Reaction Time). Index scores are age standardized, with a percentile score calculated for Omission Errors (mean of 84, standard deviation of 6) and a T-score calculated for Reaction Time (mean of 50, standard deviation of 10). Test-retest reliabilities range from .55 to .84 for a 3-month interval (Conners, 2000a). Construct-related validity is evidenced by differences in performance between children with ADHD diagnoses and those without (Seidel & Joschko, 1990). The CPT has insignificant practice effects for repeat administration, with reliable

classification of children with inattention at roughly 87 percent sensitivity and 74 percent specificity (Conners, 1995).

Parent report of behavioral problems and attention abilities. Behavioral problems and inattention symptoms were assessed using four subscales of the Conners' Parent Rating Scale (CPRS, Conners 2000b): Learning, Psychosomatic, Impulsive-Hyperactive, and Hyperactive. CPRS subscales are age and gender standardized, with a T-score (mean of 50, standard deviation of 10). Internal consistency reliabilities range from the mid .80s to mid .90s, with adequate test-retest reliability. Criterion-related validity is evidenced by significant correlations with the Conners' CPT ($r = .44$; Conners, 1995).

Leukoencephalopathy assessment. MRI exams were classified categorically as either 1) normal appearing white matter or 2) leukoencephalopathy/white matter damage by neuroradiologist, Dr. Fred Laningham, who was blind to neuropsychological assessment. The imaging protocol has been previously described in detail (Ashford et al., 2010). Images were acquired using a 1.5 Tesla Avanto whole-body MRI scanner with a standard circularly polarized volume head coil (Siemens Medical Systems, Iselin, NJ). Leukoencephalopathy, or hyperintensities within white matter, is best imaged with a T-2 weighted sequence preferably with attenuated cerebrospinal fluid.

The current protocol quantified images using an automated hybrid neural network segmentation and classification method (Reddick, Glass, Cook, Elkin, & Deaton, 1997). Image sets included most of the cerebrum, beginning at the apex of the brain, excluding the cerebellum. Imaging was obtained using at minimum 19 oblique 4-mm-thick axial images with 1-mm gap. T-2 weighted images were acquired using a dual spin-echo sequence ($TR/TE1/TE2 =$

3500/17/102ms, 7 echoes). Fluid-attenuated inversion recovery images were acquired with a multi-echo inversion recovery sequence (TR/TE/TI = 9000/119/2470 ms; 11 echoes).

Procedure

Relevant data was extracted from the TOTXV database as well as through retrospective review of medical records for children treated on the TOTXV protocol.

Data Analytic Strategy

Prior to analyses, all values were examined to ensure accuracy of data entry. All data were screened to detect values outside the range of possibility. Mahalanobis distance detected no extreme outliers for exclusion from analyses. An alpha level of .05 was used to assess the significance of all statistical comparisons. To characterize the sample, qualitative analyses of demographic and clinical variables were performed. Demographic and clinical variables were also examined to ensure group equivalence. Cumulative incidence was utilized to estimate the rate of seizure occurrence in children treated on TOTXV and identify demographic or clinical factors associated with seizure risk. For the following analyses, *P* values were not adjusted for multiple comparisons as it will result in fewer errors of interpretation given that the current data being examined are not random numbers but rather actual observations on nature (Rothman, 1990). One-way repeated measures ANOVA was utilized to assess change in the neuropsychological performance of children with therapy-related seizures across three assessment time points. One-sample t-tests were utilized to compare the neuropsychological performance of children with therapy-related seizures at each time point to published normative scores. Mixed Model repeated measures ANOVA was utilized to compare the neuropsychological performance of children with therapy-related seizures to the neuropsychological performance of a matched non-seizure cohort across time points. Fisher's

exact test was utilized to compare the rates of leukoencephalopathy classification at each neuroimaging time point between children with therapy-related seizures and the matched non-seizure cohort.

RESULTS

Group Equivalence for Age, Race, Gender, and Treatment Intensity

Descriptive statistics of relevant demographic and clinical variables (i.e., age, race, gender, and treatment intensity) were derived to ensure group equivalence on these matched variables. Table 1 displays the mean, median, and range of ages for each group at diagnosis. Ages ranged from 2 to 18 years old, with a mean age of 8.2 across groups. A one-way between-groups analysis of variance revealed no statistically significant differences for age across the three groups ($p = .99$). Table 2 displays the remaining relevant variables (i.e., race, gender, and treatment intensity). Using Pearson's Chi-Square Test, no significant differences between the seizure and non-seizure cohort groups existed at diagnosis for race, gender, and treatment intensity ($p = .68$; $p = .99$; $p = .99$, respectively, Table 2).

Sample Incidence Rate of Seizures and Associated Factors

To address the first study objective, the cumulative incidence of children who experienced seizures during TOTXV therapy was calculated relative to the entire TOTXV sample. Grade 3 seizures were defined as altered consciousness. The estimated 1-year and 2-year cumulative incidence rates of Grade 3 and higher seizures were $3.21\% \pm 0.79\%$ and $3.82\% \pm 0.86\%$, respectively (Figure 1).

Cumulative incidence curve and estimates were also utilized to identify whether any of the selected demographic and clinical variables were statistically associated with risk for on-therapy seizures. The cumulative incidence of seizure (i.e., first event) was tested between

groups by using the method described by Gray (1988) and the estimation was produced by using the method described by Kalbfleisch and Prentice (1980). None of the relevant factors of age at diagnosis, race, or gender had a statistically significant effect on seizure development ($p = .15$; $p = .33$; $p = .27$, respectively, Table 3). Treatment intensity was trending toward statistical significance, with Standard/High Risk group having a higher estimated rate than the Low Risk group at 2-year cumulative incidence (5.6 ± 1.6 versus 2.5 ± 0.9 , respectively, $p = .06$, Table 3). There were no significantly different dosings (mg/m^2) of therapeutic agents, which included dexamethasone (DEX, $p = .96$), high dose methotrexate (HDMTX, $p = .25$), and intrathecal therapy (ITHMA: hydrocortisone, methotrexate, and cytarabine/Ara-C, $p = .45$), between children who experienced therapy-related seizures and children who did not (Table 4).

A frequency count of seizure onset during each treatment phase was calculated and totals were transformed into percentages of seizure occurrence by phase (Table 5). The Induction and Consolidation phases were the two most prominent phases for Grade 3 seizures to occur, each accounting for approximately 26 percent of seizures. Fifty-two percent of seizures occurred during these early phases of treatment.

Cognitive Outcomes Comparisons

For the second objective, we conducted a one-way repeated measures ANOVA to assess the neuropsychological performance of children with therapy-related seizures across three time points: first assessment, end of therapy, and two years post therapy completion. The means and standard deviations are presented in Table 6. There was no significant change in estimated intellectual functioning (EIQ) scores across the three time points for children who experienced seizures ($p = .45$). A statistically significant difference was found for basic reading scores from baseline to 2 years post therapy, with a worsening trend (-7.43 points, $p = .01$). There were no

significant differences across measurements of math reasoning, attention, working memory, or processing speed ($p = .39$; $p = .76$; $p = .38$; $p = .82$, respectively). Freedom from Distractibility approached significance for a worsening trend from end of treatment to 2 years post ($p = .06$). Parental report on the Conners' indicated significant improvement in Learning from baseline to 2 years post (-19.56 points, $p = .01$). None of the other Conners' rating scales revealed significant differences, although improvements in Hyperactivity approached significance ($p = .06$).

To address the third study objective, we conducted one-sample t-tests to compare cognitive performance of children who experienced therapy-related seizures to published normative scores at each of the three assessment time points. The means and standard deviations for respective time points are presented in Tables 7, 8, and 9. At first assessment, there was a statistically significant difference for estimated IQ, with the seizure group having a lower mean IQ of 89 compared to normative mean IQ of 100, $p = .01$. There were no significant differences between the seizure group and normative scores for measures of academics, inattention, or processing speed. Lastly, at first assessment, the Conners' Parent Rating Scale revealed significantly more psychosomatic problems in the seizure group ($M = 68.64$) than the norm group ($M = 50$), $p < .01$. In comparison to normative scores at end of therapy (week 120), significant differences for IQ were no longer present; however, the seizure group performed significantly worse on working memory tasks (FFD = 80.14 vs. 100 norm, $p = .02$; DS Total = 6.43 vs. 10 norm, $p = .03$) and their parents reported greater psychosomatic problems (65.00 vs. 50 norm, $p = .02$). At two years post therapy completion, the same pattern was observed for working memory as the seizure group performed significantly worse than the norm (FFD = 79.43 vs. 100 norm, $p = .01$; DS Total = 6.00 vs. 10 norm, $p = .02$) as well as parental report of psychosomatic problems (65.70 vs. 50 norm, $p = .03$).

We conducted a Mixed Model repeated measures ANOVA (between and within subjects factors) to compare cognitive performance of children who experienced treatment-related seizures to the matched cohort of children on protocol without seizures across the three time points (first assessment, end of therapy, and two years post therapy completion). The means and standard deviations for respective time points are presented in Tables 10, 11, and 12. At first assessment, the seizure group demonstrated a significant difference for lower estimated IQ when compared to the non-seizure cohort group (89.33 vs. 100.74, $p = .05$). There were no other significant differences in cognitive functioning or parental report of behavioral problems at first assessment. In comparison to the non-seizure cohort group at end of therapy (week 120), the seizure group performed significantly worse on attention and working memory tasks (FFD = 80.14 vs. 100.74, $p < .01$; DS Total = 6.43 vs. 9.52, $p = .05$). Parents of children who experienced therapy-related seizures reported greater learning problems, impulsivity, and hyperactivity (62.27 vs. 49.69, $p = .04$; 59.36 vs. 48.65, $p = .04$; 57.45 vs. 49.59, $p = .04$, respectively). At two years post in comparison to the non-seizure cohort group, the seizure group performed significantly worse on a measure of overall intelligence (FSIQ = 88.92 vs. 101.00, $p = .04$). The same pattern of the seizure group performing significantly worse than the non-seizure cohort group on measures of attention and working memory was observed (FFD = 79.43 vs. 101.17, $p < .01$; DS Total = 6.00 vs. 10.04, $p = .01$), with additional processing speed deficits in the seizure group (PSI = 88.57 vs. 103.92, $p = .02$). There were no significant elevations on parental report of behavioral problems for the seizure group in comparison to the non-seizure cohort group.

Imaging Comparisons

For the final objective, we used Fisher's exact test to compare the rates of leukoencephalopathy classification between children with treatment-related seizures and similarly treated children without seizures. Results are reported in Table 13. Significant differences on MRI were observed between the seizure and cohort groups at second time point of week 7 continuation (56% vs. 12.9%, $p < .01$) and third time point of end of therapy (week 120: 38% vs. 6%, $p = .01$) but not at the first imaging time point of week 5 remission (15.38% vs. 2.94%, $p = .18$).

DISCUSSION

Results from this study revealed that two-year incidence of therapy-related seizures for children treated on the TOTXV protocol was 3.82%, which is a relatively positive outcome given that it falls within the lower range of 3 to 13 percent seizure incidence found in the literature. This lowered incident rate, in comparison to the larger literature, is likely reflective of the lessened neurotoxic effect of chemotherapy-only protocols on neurodevelopment and cognitive late effects. Contrary to *a priori* hypotheses, demographic or clinical factors such as prior seizure history or intensity of chemotherapy were not statistically significant predictors of seizure development. Although, a trend for standard/high treatment intensity was observed for seizure risk ($p = .06$). Over 50 percent of seizures observed in this study occurred during the induction and consolidation phases, consistent with historical findings of seizures during early phases of treatment in which chemotherapy doses are typically at its highest.

Of particular interest is the notable lack of significant change in neuropsychological performance for children with therapy-related seizures when compared to themselves across treatment time points. Measures of overall intellectual functioning, math reasoning, attention, working memory, and processing speed did not significantly differ from first assessment to two years post therapy completion. The only exception was performance on a measure of basic reading, which significantly worsened from first assessment to two years post therapy. One potential explanation for this contrary finding is that first assessment was not a true baseline, as four doses of high dose methotrexate (HDMTX) were administered prior to first

neuropsychological assessment. It is possible that intensified chemotherapy agents were already influencing cognitive performance at first assessment. This ‘artifact baseline’ hypothesis may also explain parents’ reports on the CPRS of significantly reduced learning problems from first assessment to two years post therapy completion. Parents of children with treatment-related seizures may have already been observing learning problems at first assessment, which they acclimated to two years post therapy. Another plausible explanation, given that end of therapy corresponded with school re-entry for many children, is that learning problems may have been particularly notable for parents at therapy completion (second assessment). School accommodations and reintegration into the social learning environment may have lessened these issues over time.

Although there was a broad lack of neuropsychological change within the seizure group across time, when the neuropsychological performance of the seizure group was compared to normative sample scores, patterns of differences emerged and maintained across assessment time points. Significant differences were observed in domains of attention, working memory, processing speed, and parental report of psychosomatic problems for children with therapy-related seizures. This finding is consistent with previous literature that supports cognitive late effects, namely impaired attention and working memory abilities, in children treated for ALL (Ashford et al., 2010; Conklin et al., 2012; Phipps et al., 2012).

Similar patterns for attention, working memory, and processing speed also emerged during comparisons of neuropsychological performance across assessments between the seizure group and the non-seizure cohort. At leukemia therapy completion, children with therapy-related seizures performed significantly worse for attention and working memory tasks than the matched cohort, and these deficits persisted two years later with the addition of processing speed deficits.

Results also revealed that children with treatment-related seizures performed significantly worse on a measure of estimated intelligence at first assessment and also on a full-scale measure of intelligence (FSIQ) at two years post therapy completion when compared to the matched cohort. The ‘artifact baseline’ hypothesis likely also explains significant differences for estimated intellectual functioning at first assessment. However, the finding for decreased overall intelligence at two years post therapy alongside problems in attention, working memory, and processing speed deficits is of particular interest. Given these concurrent findings, it is possible that early cognitive late effects of attention and working memory problems among children who experienced on-therapy seizures may precede later declines observed in overall IQ. It is important to also mention that at therapy completion, the seizure group parents reported significantly more problems with learning, impulsivity, and hyperactivity than parents of non-seizure cohorts, but these differences become insignificant by two years post therapy completion as group scores are nearly the same. As aforementioned, end of therapy corresponds with school-reentry for many children, such that learning and behavioral problems may be even more salient for parents of children with treatment-related seizures, which lessen over time with school accommodations.

This study’s imaging findings indicated that children with therapy-related seizures experienced more significant early neurotoxicity (i.e., leukoencephalopathy as indicated by white matter hyperintensities on MRI) than non-seizure cohorts, which likely contributes to higher levels of cognitive late effects observed among children with on-therapy seizures. Further supporting the early cognitive late effect hypothesis, significant differences in treatment-induced leukoencephalopathy between the seizure group and cohort group were observed concurrently with significantly worse neuropsychological performance for the seizure group in comparison to

the cohort group on measures of estimated intellectual functioning, attention, and work memory. This observation is consistent with previous empirical findings of decreased abilities on attention and working memory tasks to be associated with treatment-related neuroanatomical changes such as smaller and abnormal cerebral white matter volumes (Ashford et al., 2010; Khong et al., 2006; Reddick et al., 2005a; Reddick et al., 2006). Smaller white matter tissue volumes have also been related to larger declines in intelligence and academics (Reddick et al., 2006).

Rates of leukoencephalopathy prevalence for this study were also consistent with previous literature indicating a rise in white matter lesions after several intravenous HDMTX rounds, followed by reductions in white matter damage at therapy completion (Reddick et al., 2005). Therefore, the observed abnormal structural brain changes in cerebral white matter are likely subsequent to on-therapy vascular-related injuries, namely a form of HDMTX encephalopathy (Lövlad et al., 1998). While metabolic factors and arterial hypertension undoubtedly play a role in seizure risk, leukoencephalopathy is a probable common etiology of treatment-related seizures in this study.

A major implication of these neurocognitive findings for children who experienced therapy-related seizures while treated for ALL is the provision of preliminary yet promising information that may assist with treatment planning, monitoring of cognitive outcomes, and caregiver education, all with the ultimate end goal of improving quality of life for this growing group of survivors. Based on this study's observations, it appears that children who experienced treatment-related seizures are at greater neurocognitive risk when compared to matched cohorts without seizures. The task then presented is to detect *how* and *when* we can best identify significant changes in neurocognitive status that indicate risk for long-term CNS effects. Performance-based and imaging-based measures have demonstrated to be sensitive and specific

indicators of neurotoxicity. Utilizing these methods as appropriate in the early phases of chemotherapy, coupled with sophisticated clinical observation (e.g., seizure occurrence as treatment intensifies), is likely to lead to earlier detection of children at risk for CNS effects. Earlier detection would allow for earlier interventions and treatment modifications that may mitigate the neurotoxic effects of high-dose chemotherapy on the neurodevelopment of childhood cancer survivors.

Domain-specific neuropsychological testing combined with more advanced neuroimaging such as magnetic resonance diffusion tensor imaging (DTI) may help in the early identification of subtle cerebral white matter damage. The earliest identification of even subtle changes in neurocognitive status could make the utmost difference for medical researchers and physicians developing more effective therapies that result in fewer cognitive late effects and mitigate other side effects such as leukoencephalopathy and seizures. Identification would better inform each patients' treatment plan with enhanced physician insight on when regimen-related accommodations are needed, such as modifying the timing or dosing of chemotherapy administrations to minimize white matter damage or seizure risk without sacrificing a favorable prognosis. Identification would also allow healthcare professionals to develop patient-centric medical regimens that not only implement therapeutic interventions targeted at domain-specific cognitive rehabilitation, but enact preventative therapy that may serve as a cognitive protective factor against lasting therapy-related CNS impairments. For patients and their caregivers, early identification of treatment-related neurocognitive deficits would allow them to develop compensatory and remedial strategies to minimize therapy-related impairments, which is likely to result in improved prognosis and reintegration into classroom and social settings.

Recent empirical findings for neurocognitive interventions that lessen cognitive late effects appear promising for the expanding cancer survivorship population. These interventions comprise pharmacologic and non-pharmacologic methods that rely heavily on the cognitive rehabilitation literature for traumatic brain injury, childhood ADHD, and dementia (Davis et al., 2013; Phipps et al., 2012). Psychostimulant medication used to mitigate attention deficits in children diagnosed with ADHD, specifically methylphenidate (MPH), has demonstrated similar positive attentional benefits in childhood cancer survivors (Conklin et al., 2007; Davis et al., 2013; Mulhern et al., 2004; Thompson et al., 2001). Medications used to treat mild to moderate dementia, such as donepezil, have also been under examination and preliminary results suggest improvement in cognitive function as well as mood and health-related quality of life (Castellino et al., 2012; Shaw et al., 2006). There is also a movement towards using pharmacological interventions as neuroprotective agents during treatment, such as the anti-Alzheimer drug memantine to prevent cognitive decline related to oxidative stress in the CNS (Brown et al., 2012). However, medication side effects, parental disapproval, and medical contraindications may interfere with the feasibility pharmacological interventions. Non-pharmacological interventions such as the Cognitive Remediation Program (CRP, Butler & Copeland, 2002) and CogMed© Working Memory Training (Klingberg et al., 2002; Klingberg et al., 2005) have developed as an alternative to medication. Butler and colleagues (2008) multicenter, randomized clinical trial of CRP produced promising results for 167 childhood cancer survivors, including modest effect size within the .5 range, parental report of significant improvements in attention, and gains on measures of academic abilities in language and mathematics. CogMed's well-demonstrated efficacy for remediation of attention deficits in children diagnosed with ADHD has encouraged researchers to begin exploring this targeted working memory program in childhood

cancer survivors (Conklin et al., 2013; Hardy, Carlson-Green, & Conklin, 2012; Hardy, Willard, Allen, & Bonner, 2012). While a computer-based treatment is favored due to its portable nature and limited staffing needs, research continues to investigate the feasibility, generalizability, and continuation of benefits following computerized intervention. The Pediatric Cancer Genome Project, led by St. Jude Children's Research Hospital and Washington University School of Medicine, also offers hope of identifying genetic markers of greater risk for cognitive late effects in those diagnosed with ALL.

Limitations and Future Directions

The current findings should be interpreted within the context of study limitations. One limitation of this study is its retrospective nature. A prospective, longitudinal study would allow for a more systematic investigation of the emergence of cognitive late effects, including potential mechanisms of change. Efforts are directed toward conducting earlier baseline assessments, yet this is difficult due to children being sick, needing immediate medical treatment, and receiving high-dose steroids. None of which are positive factors for valid and reliable estimates of cognitive function. Future studies would also benefit from timing neuropsychological assessments to correspond with neuroimaging assessments for more exact comparisons. Likewise, for this study, an additional imaging time point at two years post therapy would have been helpful in examining whether hypothesized declines in leukoencephalopathy, which were observed at end of treatment in our sample, continue beyond therapy completion.

In regard to study measures, although EIQ is highly correlated with FSIQ, the use of an estimated intelligence measure at first assessment likely limited sensitivity to detect neurocognitive changes in overall intellectual functioning. It also made comparisons to later assessments of full-scale intellectual functioning less appropriate. Careful replication of the

finding for declines in overall intelligence with sensitive measures throughout is warranted. It was also difficult to interpret CPRS findings as they were often inconsistent with neurocognitive performance scores. The lack of correlation between parent report and performance-based measures may be one of the unfortunate yet expected drawbacks of subjective rater measures, which have previously been shown to exhibit low rates of sensitivity and specificity for performance-based changes in childhood cancer populations (Howarth et al., 2013). While it could be that problematic child behaviors such as learning difficulties and hyperactive-impulsivity significantly alleviated post-treatment, it may also be that parents are relatively limited to gross assessments of behavioral changes, relying on salient factors such as grades in school or misconduct within the school and home environments.

In recent years, neuroimaging methods have advanced from basic structural MRI to more sophisticated techniques, such as magnetic resonance spectroscopy, volumetrics, and diffusion tensor imaging (DTI). Future studies will benefit from DTI specifically as it enables the examination of location, orientation, and anisotropy of white matter pathways associated with neuroanatomical models of attention and memory, such as the prefrontal cortex, in relation to chemotherapy-induced cognitive late effects. Preliminary findings of DTI studies indicate greater frontal white matter changes after chemotherapy than before treatment in children treated for hematological malignancies, such as ALL (Morioka et al., 2013). Decreased white matter diffusion anisotropy observed after cancer treatment has also been associated with significant negative effects on IQ (Khong et al., 2006). A recent review of DTI within the context of chemotherapy-induced neurocognitive impairment, drawing from longitudinal and cross-sectional data, indicates that current studies confirm the relationship between abnormal cerebral

white matter and impaired cognitive performance (Deprez, Billiet, Sunaert, & Leemans, 2013). Therefore, assessment of white matter pathways via DTI is likely to be a valuable clinical tool for measurement of treatment-induced neurotoxicity in childhood cancer survivors.

Conclusions

There has been growing empirical evidence of cognitive late effects for survivors of acute lymphoblastic leukemia. While demographic and clinical factors have been associated with greater likelihood of cognitive late effects in leukemia therapy (i.e., younger age at diagnosis, female gender, higher treatment intensity, and greater time since treatment), this study's aim was to understand the impact of treatment-related seizures as an indicator of neurotoxicity with associated cognitive decline and subsequent cognitive late effects.

Despite this study's limitations, the current findings point to a relationship between on-therapy seizures, leukoencephalopathy, and deficits in neuropsychological functioning, specifically attention, working memory, and processing speed skills, which may lead to overall declines in intellectual functioning. However, these findings also raise questions about the neurobehavioral mechanisms, including neuroanatomical pathways, involved in cognitive late effects associated with seizures. Future research on theoretically driven neurobehavioral processes is necessary to unravel these mechanisms within the context of leukemia therapy so that we may improve caregiver education, treatment planning, and treatment monitoring for as many children as possible.

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LIST OF APPENDICES

Table 1

Means, Standard Deviations, Medians, and Ranges of Ages Across Groups at Diagnosis

	Total	Seizure Group	Cohort 1	Cohort 2	<i>p</i> -value
N	57	19	19	19	0.99 ^A
Mean (SD)	8.26 (4.72)	8.27 (4.80)	8.26 (4.81)	8.23 (4.82)	
Median	7.66	7.21	8.00	7.66	
Range	2.07-18.73	2.07-18.73	2.09-17.12	2.14-18.73	

^A Analysis of Variance

Table 2

Race, Gender, and Treatment Intensity Across Groups at Diagnosis

	Total	Seizure Group	Cohort 1	Cohort 2	<i>p</i> -value
N	57	19	19	19	
Race [n (%)]					0.68 ^P
White	42 (73.7)	14 (73.7)	13 (68.4)	15 (78.9)	
Black	14 (24.6)	5 (26.3)	5 (26.3)	4 (21.1)	
Other	1 (1.8)	0 (0)	1 (5.3)	0 (0)	
Gender [n (%)]					0.99 ^P
Male	39 (68.4)	13 (68.4)	13 (68.4)	13 (68.4)	
Female	18 (31.6)	6 (31.6)	6 (31.6)	6 (31.6)	
Treatment Intensity [n (%)]					0.99 ^P
Low	21 (36.8)	7 (36.8)	7 (36.8)	7 (36.8)	
Stand/High	36 (63.2)	12 (63.2)	12 (63.2)	12 (63.2)	

^P Pearson's Chi-Square Test

Figure 1

Cumulative Incidence of \geq Grade 3 Seizures on TOTXV

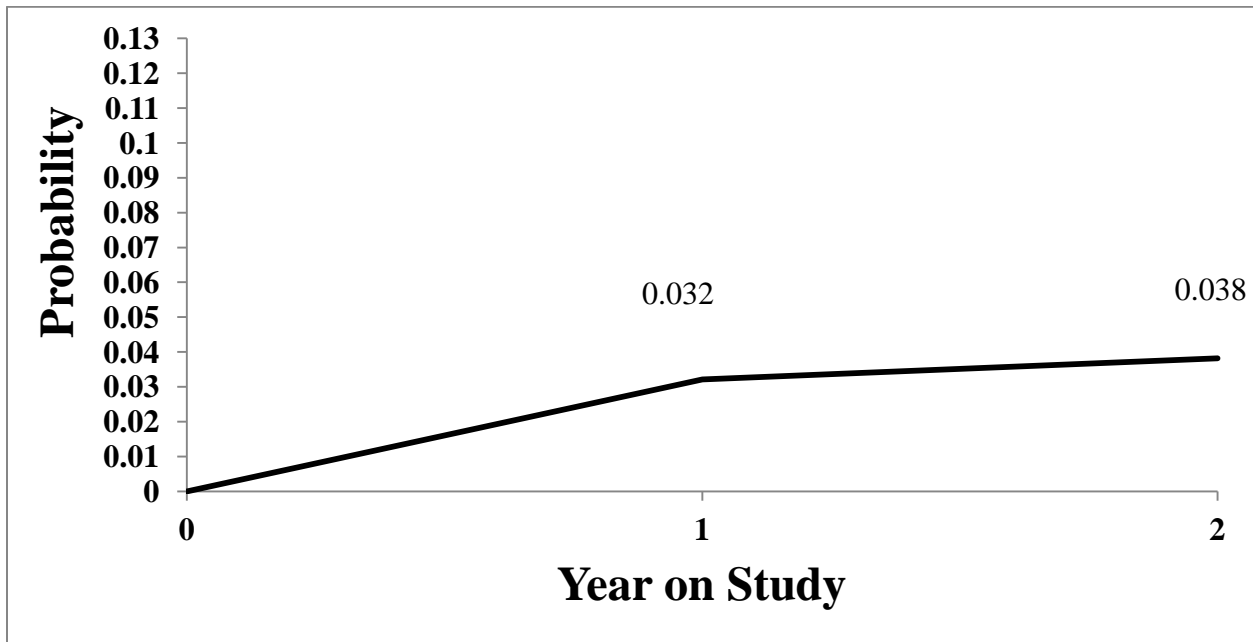


Table 3

Cumulative Incidence of Seizures by Relevant Factors

Factors	N	Year 1	Year 2	p-value
Age at Diagnosis				0.15 ^G
<5 Yrs	235	1.3 ± 0.7	2.6 ± 1.0	
Others	263	4.9 ± 1.3	4.9 ± 1.3	
Race				0.33 ^G
White	402	2.7 ± 0.8	3.5 ± 0.9	
Black	79	6.3 ± 2.8	6.3 ± 2.8	
Other	17	0	0	
Gender				0.27 ^G
Male	279	3.9 ± 1.2	4.7 ± 1.3	
Female	219	2.3 ± 1.0	2.7 ± 1.1	
Treatment Intensity				0.06 ^G
Low	284	1.4 ± 0.7	2.5 ± 0.9	
Stand/High	214	5.6 ± 1.6	5.6 ± 1.6	

^GGray's Test

Table 4

Total Dose of Drug (mg/m²) Received Before First Seizure Event Across Groups

	Total (n=57)	Seizure Group (n=19)	Cohorts (n = 38)	<i>p</i> -value
DEX				0.96
Mean (SD)	151.37 (232.34)	149.36 (234.15)	152.38 (234.58)	
Max	866.62	858.17	866.62	
HDMTX				0.25
Mean (SD)	11070.73 (8780.95)	9193.60 (7840.70)	120009.29 (9169.41)	
Max	32263.77	26401.27	32263.77	
ITHMA				0.45
Mean (SD)	69.64 (47.33)	62.94 (46.09)	73.00 (48.19)	
Max	144.00	132.00	144.00	

Table 5

Frequency Count and Percent of Seizure Onset Across Treatment Phases

	Frequency	Percent
Pre-Treatment	1	5.26%
Induction	5	26.32%
Consolidation	5	26.32%
Continuation Weeks 1-6	1	5.26%
Continuation Weeks 10-16	3	15.79%
Continuation Weeks 48-95	1	5.26%
LR Continuation Weeks 20-47	2	10.53%
LR Continuation Weeks 21-47	1	5.26%

Table 6

Means and Standard Deviations on Cognitive Measures for Seizure Group Across Time Points

	First Assess (Wk 6)	End Therapy (Wk 120)	2 Yrs Post	<i>p</i> -value
Wechsler EIQ	89.33 (10.10)	90.73 (19.82)	94.33 (18.84)	0.45
Wechsler FSIQ	--	88.20 (21.29)	88.92 (18.35)	--
FFD	--	80.14 (17.86)	79.43 (15.11)	0.06
PSI	--	86.29 (24.31)	88.57 (18.04)	0.82
DS Total	--	6.43 (3.60)	6.00 (4.00)	0.38
WIAT				
Basic Reading	93.33 (7.39)	90.80 (22.38)	86.56 (22.26)	0.01*
Math Reasoning	91.83 (16.79)	87.00 (19.30)	89.67 (22.47)	0.39
Conners' CPT				
Omissions	86.15 (21.79)	89.43 (12.69)	83.04 (21.33)	0.76
Hit RT	51.04 (9.69)	50.84 (13.81)	53.27 (15.59)	0.92
CPRS				
Learning	63.27 (23.43)	62.27 (18.66)	44.00 (9.21)	0.01*
Psychosomatic	68.64 (17.29)	65.00 (19.54)	65.70 (20.39)	0.74
Impulse-Hyper	56.36 (15.36)	57.45 (11.47)	50.50 (9.81)	0.28
Hyperactive	59.73 (20.56)	59.36 (17.03)	46.60 (9.34)	0.06

Table 7

Comparisons on Cognitive Measures Between Seizure Group and Normative Sample at First Assessment (Week 6)

	Seizure Group	Normative Sample	<i>p</i> -value
Wechsler EIQ	89.33 (3.37)	100 (15)	0.01*
WIAT			
Basic Reading	93.33 (3.02)	100 (15)	0.07
Math Reasoning	91.83 (6.61)	100 (15)	0.27
Conners' CPT			
Omissions	86.15 (9.75)	84 (6)	0.83
Hit RT	51.04 (4.33)	50 (10)	0.82
CPRS			
Learning	63.27 (7.06)	50 (10)	0.08
Psychosomatic	68.64 (5.21)	50 (10)	< 0.01*
Impulse-Hyper	56.36 (4.63)	50 (10)	0.19
Hyperactive	59.73 (6.20)	50 (10)	0.14

Table 8

Comparisons on Cognitive Measures Between Seizure Group and Normative Sample at End of Therapy (Week 120)

	Seizure Group	Normative Sample	<i>p</i> -value
Wechsler EIQ	90.73 (5.98)	100 (15)	0.15
Wechsler FSIQ	88.20 (6.73)	100 (15)	0.11
FFD	80.14 (6.75)	100 (15)	0.02*
PSI	86.29 (9.19)	100 (15)	0.18
DS Total	6.43 (1.36)	10 (3)	0.03*
WIAT			
Basic Reading	90.80 (7.08)	100 (15)	0.22
Math Reasoning	87.00 (6.10)	100 (15)	0.06
Conners' CPT			
Omissions	89.43 (4.23)	84 (6)	0.23
Hit RT	50.84 (4.60)	50 (10)	0.85
CPRS			
Learning	62.27 (5.62)	50 (10)	0.05*
Psychosomatic	65.00 (5.89)	50 (10)	0.02*
Impulse-Hyper	57.45 (3.46)	50 (10)	0.05*
Hyperactive	59.36 (5.14)	50 (10)	0.09

Table 9

Comparisons on Cognitive Measures Between Seizure Group and Normative Sample at Two Years Post-Therapy

	Seizure Group	Normative Sample	<i>p</i> -value
Wechsler EIQ	94.33 (5.44)	100 (15)	0.31
Wechsler FSIQ	88.92 (5.30)	100 (15)	0.06
FFD	79.43 (5.71)	100 (15)	0.01*
PSI	88.57 (6.82)	100 (15)	0.14
DS Total	6.00 (1.41)	10 (3)	0.02*
WIAT			
Basic Reading	86.56 (7.42)	100 (15)	0.10
Math Reasoning	89.76 (7.49)	100 (15)	0.20
Conners' CPT			
Omissions	83.04 (6.43)	84 (6)	0.88
Hit RT	53.27 (4.70)	50 (10)	0.50
CPRS			
Learning	44.00 (2.91)	50 (10)	0.06
Psychosomatic	65.70 (6.45)	50 (10)	0.03*
Impulse-Hyper	50.30 (3.10)	50 (10)	0.92
Hyperactive	46.60 (2.95)	50 (10)	0.27

Table 10

Comparisons on Cognitive Measures Between Seizure Group and Matched Cohort at First Assessment (Week 6)

	Seizure Group	Cohort Group	<i>p</i> -value
Wechsler EIQ	89.33 (3.37)	100.74 (3.18)	0.05*
WIAT			
Basic Reading	93.33 (3.02)	102.45 (3.09)	0.10
Math Reasoning	91.83 (6.61)	104.65 (3.28)	0.08
Conners' CPT			
Omissions	86.15 (9.75)	72.49 (6.86)	0.22
Hit RT	51.04 (4.33)	44.42 (3.31)	0.37
CPRS			
Learning	63.27 (7.06)	50.03 (1.71)	0.19
Psychosomatic	68.64 (5.21)	67.17 (3.30)	0.74
Impulse-Hyper	56.36 (4.63)	50.23 (1.73)	0.22
Hyperactive	59.73 (6.20)	49.13 (1.57)	0.17

Table 11

Comparisons on Cognitive Measures Between Seizure Group and Matched Cohort at End of Therapy (Week 120)

	Seizure Group	Cohort Group	<i>p</i> -value
Wechsler EIQ	90.73 (5.98)	100.41 (2.81)	0.14
Wechsler FSIQ	88.20 (6.73)	97.61 (2.29)	0.21
FFD	80.14 (6.75)	100.74 (2.67)	< 0.01*
PSI	86.29 (9.19)	100.74 (3.37)	0.14
DS Total	6.43 (1.36)	9.52 (0.50)	0.05*
WIAT			
Basic Reading	90.80 (7.08)	102.04 (2.62)	0.22
Math Reasoning	87.00 (6.10)	100.46 (2.45)	0.07
Conners' CPT			
Omissions	89.43 (4.23)	84.42 (3.26)	0.51
Hit RT	50.84 (4.60)	47.42 (1.90)	0.50
CPRS			
Learning	62.27 (5.62)	49.69 (2.35)	0.04*
Psychosomatic	65.00 (5.89)	56.41 (3.19)	0.16
Impulse-Hyper	57.45 (3.46)	49.59 (2.08)	0.04*
Hyperactive	59.36 (5.14)	48.66 (2.03)	0.04*

Table 12

Comparisons on Cognitive Measures Between Seizure Group and Matched Cohort at Two Years Post-Therapy

	Seizure Group	Cohort Group	<i>p</i> -value
Wechsler EIQ	94.33 (5.44)	101.64 (2.87)	0.29
Wechsler FSIQ	88.92 (5.30)	101.00 (2.77)	0.04*
FFD	79.43 (5.71)	101.17 (3.58)	< 0.01*
PSI	88.57 (6.82)	103.92 (2.59)	0.02*
DS Total	6.00 (1.41)	10.04 (0.68)	0.01*
WIAT			
Basic Reading	86.56 (7.42)	101.53 (2.79)	0.07
Math Reasoning	89.76 (7.49)	100.20 (2.65)	0.22
Conners' CPT			
Omissions	83.04 (6.43)	78.32 (3.18)	0.19
Hit RT	53.27 (4.70)	52.52 (1.97)	0.61
CPRS			
Learning	44.00 (2.91)	46.71 (2.76)	0.37
Psychosomatic	65.70 (6.45)	68.71 (3.94)	0.48
Impulse-Hyper	50.30 (3.10)	47.00 (2.66)	0.35
Hyperactive	46.60 (2.95)	47.47 (3.35)	0.70

Table 13

Comparisons of Leukoencephalopathy on MRI Between Seizure Group and Matched Cohort Across Time Points

	Seizure Group	Cohort Group	<i>p</i> -value
Baseline [n (%)]			0.18
Leuko	2 (15.38)	1 (2.94)	
Normal	11 (84.62)	33 (97.06)	
Week Post-First Assessment [n (%)]			< 0.01*
Leuko	9 (56.25)	4 (12.90)	
Normal	7 (43.75)	27 (87.10)	
End of Therapy [n (%)]			0.01*
Leuko	5 (38.46)	2 (6.06)	
Normal	8 (61.54)	31 (93.94)	

VITA

STEPHANIE L. NASSAR

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Citizenship: USA

Education

- 2014** **Doctor of Philosophy, Clinical Psychology**
The University of Mississippi, University, MS
Doctoral Dissertation: *Neurocognitive Outcomes in Children Experiencing Seizures During Treatment for Acute Lymphoblastic Leukemia*
Advisors: Kelly G. Wilson, Ph.D.; Heather M. Conklin, Ph.D.
- 2014-2013** **APA Approved Pre-Doctoral Internship, Clinical Medical/Health Psychology**
The University of Florida, Health Science Center, Gainesville, FL
Director of Internship Training: Dr. Lori B. Waxenberg, Ph.D., ABPP
- 2011** **Master of Arts, Clinical Psychology**
The University of Mississippi, University, MS
Master's Thesis: *Discriminating Emotions and Engaging Difficult Emotional Material: Implications for Process and Outcome in Written Disclosure*
Advisor: Kelly G. Wilson, Ph.D.
- 2004** **Bachelor of Science, Magna Cum Laude**
Spring Hill College, Mobile, AL
Major: Psychology
Minor: Philosophy
Senior Thesis: *The Effects of Personality Type on Procrastination in College Students*
Advisor: Lisa D. Hager, Ph.D.

Research Experience

2013-2011 *Principal Investigator*

Cognitive Outcomes in Children Experiencing Seizures during Treatment for Acute Lymphoblastic Leukemia (XPD11-032)

St. Jude Children's Research Hospital, Memphis, TN

- conducted a retrospective study to explore neuropsychological outcomes and neuroimaging findings in children experiencing seizures during leukemia treatment

Supervisor: Heather M. Conklin, Ph.D.

2012-2010 *Clinical Research Assistant* to Heather M. Conklin, Ph.D.

Computerized Intervention for Amelioration of Cognitive Late Effects Among Childhood Cancer Survivors (COGTRN)

St. Jude Children's Research Hospital, Memphis, TN

- *ClinicalTrials.gov Identifier:* NCT01217996
- conducted archival data collection, electronic database searches, data entry and manipulation, quality assurance checks, literature searches, recruitment calls, eligibility checklists, participant scheduling, neuropsychological testing (cognitive, achievement, memory, attention, executive functioning), protocol scoring and interpretation

Supervisor: Heather M. Conklin, Ph.D.

2011-2009 *Principal Investigator*

Investigating the Expressive Writing Paradigm

The University of Mississippi, University, MS

- investigated the effects of writing about emotionally traumatic events vs. writing about personal values on psychological processes and outcomes

Supervisor: Kelly G. Wilson, Ph.D.

2009 *Co-Investigator*

Mindfulness for Two: Manipulating the Therapist and Context

The Psychological Services Center, University of Mississippi, University, MS

- investigated the effects of therapist and contextual manipulations on interviewers' and interviewees' personal experiences (e.g., mood, physical sensations, quality of interaction)

Supervisor: Kelly G. Wilson, Ph.D.

2009 *Research Assistant* to Catherine H. Adams, M. A.

Perspective-Taking Among People with Intellectual Disabilities

The Baddour Center, Senatobia, MS

- trained adults with developmental disabilities in deictic framing and perspective taking for Theory of Mind tasks and social skills interactions

Supervisor: Kelly G. Wilson, Ph.D.

- 2008** *Co-Investigator*
An Examination of the Stability of Implicit Relational Assessment Procedure (IRAP) Performance over Repeated Administrations
The University of Mississippi, University, MS
- examined the reliability, validity, and procedural integrity the IRAP, a computerized measure of implicit cognition
- Supervisor: Kelly G. Wilson, Ph.D.
- 2008** *Applied Behavior Analysis Trainer*
Acceptance and Commitment Training (ACT) to Address Burnout and Stress in Staff Working with People with Intellectual Disabilities
North Mississippi Regional Center (NMRC), Oxford, MS
- trained NMRC staff in ABA techniques across three weeks
 - collected pre- & post-data
- Supervisor: Kelly G. Wilson, Ph.D.
- 2008** *Co-Investigator*
Psychological Struggle and Flexibility
The University of Mississippi, University, MS
- conducted survey research investigating the relationships across measures of psychological flexibility, valued living, mindfulness, body image, eating behaviors, academic procrastination, and established measures of psychological distress/outcome
- Supervisor: Kelly G. Wilson, Ph.D.
- 2007** *ACT Luckyday Scholars Group Facilitator*
The University of Mississippi, University, MS
- facilitated group discussions with undergraduate Luckyday Scholars having academic difficulties utilizing various Acceptance and Commitment Training exercises; collected time-series data
- Supervisor: Kelly G. Wilson, Ph.D.
- 2006-2005** *Co-Investigator*
Investigating the Emotional Writing Paradigm: An Analysis of Experimenter Interaction and Individual Experience of Emotion
The University of Mississippi, University, MS
- investigated the effects of therapist manipulations on individuals' experiences of emotion and psychological outcome
 - coded, entered, and analyzed written narratives into Linguistic Inquiry Word Count (LIWC) Program Software
- Supervisor: Kelly G. Wilson, Ph.D., Leslie J. Rogers, M.A.

- 2005-2004** *Research Assistant* to Kelly G. Wilson, Ph.D.
The University of Mississippi, University, MS
Part-time position
- aided in revising Clinic IRB application
 - assisted in data collection and running studies for senior lab members' thesis & dissertation projects

- 2004** *Principal Investigator*
Spring Hill College, Mobile, AL
- investigated the effects of personality type on measures of academic procrastination and task completion
- Supervisor: Lisa D. Hager, Ph.D.

Teaching and Administrative Experience

- Sprg 2010** *Co-Instructor, PSY 420: Special Topics in Psychology*
The University of Mississippi, University, MS
- assisted students in gaining research experience beyond their laboratory class with a special emphasis in clinical psychophysiology
 - aided students in preparing materials for graduate school applications
- Supervisor: Scott A. Gustafson, Ph.D.

- Fall 2010** *Guest Lecturer, Introductory Psychology, Social Psychology Module*
The University of Mississippi, University, MS

- 2010-2008** *Assistant Director*
Part-time position
The Psychological Services Center, University of Mississippi, University, MS
- assisted Director with daily management of clinic
 - provided quality assurance reviews of clinic records
 - marketed and advertised services; increased community relations
 - organized and monitored clinic duties and emergency cell phone duties
 - organized and tracked individual supervision team's client flow
 - oriented and trained incoming graduate therapists on clinic protocol
 - revised clinic manual and streamlined procedures
 - surveyed experts for treatment manuals to be included in the resource library
- Supervisor: Scott A. Gustafson, Ph.D.

- 2010-2008** *Executive Team Leader*
The Psychological Services Center, University of Mississippi, University, MS
- improved quality of clinical training, services, and clinic facilities
 - recorded client activity to assist with triage
 - brainstormed and implemented marketing and advertising ideas
- Supervisor: Scott A. Gustafson, Ph.D.

2008-2007 *Senator, Graduate Student Council*

The University of Mississippi, University, MS

- served as liaison between psychology department and graduate school

2008-2007 *Clinic Administrative Group Member, Feng Shui*

The Psychological Services Center, University of Mississippi, University, MS

- served as liaison between clinic group and supervision team
- kept records of client activity
- managed funds to update clinic equipment and decor

Supervisor: D. Scotty Hargrove, Ph.D.

2007 *Seminar on College Teaching*

The University of Mississippi, University, MS

- joined and contributed to the Society for the Teaching of Psychology listserv
- created a syllabus for a 15 wk course in Abnormal Psychology
- prepared and delivered an Abnormal Psychology lecture to a small number of students (n=25) which incorporated explicit learning objectives, active learning techniques, outcome measures, and exam questions in which all levels of learning were assessed
- provided peer reviews for colleagues' lectures and received peer reviews
- created a teaching portfolio with statement of Teaching Philosophy

Supervisor: Kenneth J. Sufka, Ph.D.

2004 *Teaching Assistant* to Kelly G. Wilson, Ph.D.

The University of Mississippi, University, MS

Part-time fall position

- administered and graded examinations and extra credit for an undergraduate Abnormal Psychology class
- created class study guides for test preparation purposes

Clinical Experience

2014-2013 *Clinical Medical/Health Psychology Intern*

The University of Florida, Health Science Center, Gainesville, FL

- conducted semi-structured diagnostic assessments, primary caregiver interviews, neuropsychological testing, brief and long-term evidence-based treatments, with a variety of inpatient and outpatient medical populations, as well as ongoing supportive psychosocial services for families, across the following rotations:
 - *Transplant Psychology, Acute Adult Neurotrauma, Psycho-Oncology, Chronic Pain/GI/Primary Care, Women's Health, Rehabilitation Health, Adult Neuropsychology, Behavioral Sleep Medicine, and Child Health*

- authored integrated neuropsychosocial reports and EPIC medical records
- Supervisors: Glenn S. Ashkanazi, Ph.D.; Robert T. Guenther, Ph.D., ABPP (RP); Deidre Pereira, Ph.D.; Lori B. Waxenberg, Ph.D., ABPP; Patricia E. Durning, Ph.D.; Thomas R. Kerkhoff, Ph.D., ABPP (RP); Nicole E. Whitehead, Ph.D.; Duane A. Dede, Ph.D.; David Janicke, Ph.D.; Christina S. McCrae, Ph.D.

Pres-2004 *ACT Treatment Development Group (ACTTDG)*

The University of Mississippi, University, MS

- developing expertise in the ACT model of assessment, case conceptualization, and treatment
- co-developing a training model that mixes didactic and experiential components
- observing, consulting, and supervising peer therapists

Supervisor: Kelly G. Wilson, Ph.D.

2013-2012 *Provisionally Certified Mental Health Therapist*

Batesville Crisis Stabilization Unit, Batesville, MS

- conducted intakes, individual therapy, and group therapy sessions with an adult acute inpatient population presenting with active psychosis, suicidal and homicidal ideation
- completed intake paperwork including DSM-IV-TR diagnoses, targeted behaviors of change, and elaborated behavioral treatment plans
- authored individual and group therapy notes

Supervisors: Julie Garner, M.Ed., L.P.C., Director; Scott A. Gustafson, Ph.D.

2013-2005 *Graduate Student Therapist*

The Psychological Services Center, University of Mississippi, University, MS

- conducted screening, intake, and therapy sessions with clients
- authored therapy notes and completed other psychological documents
- trained in Acceptance and Commitment Therapy (ACT) and Cognitive Behavioral Therapy (CBT)

Supervisors: Kelly G. Wilson, Ph.D. (2005-Present); Laura R. Johnson, Ph.D. (2006-2007; 2008-2009); Alan M. Gross, Ph.D. (2007-2008); Todd A. Smitherman, Ph.D. (2010-2011); Scott A. Gustafson, Ph.D. (2011-2012); Tom Lombardo, Ph.D. (2012-2013)

2010 *Group Facilitator, Coping With College Life*

The Psychological Services Center, University of Mississippi, University, MS

- facilitated five one-hour group meetings for college students adjusting to college life/stressors
- utilized Acceptance and Commitment Training Model
- incorporated present moment, mindfulness, cognitive defusion, and values-centered exercises

Supervisor: Kelly G. Wilson, Ph.D.

2010-2009 Behavioral Consultant

Behavior, Attention, and Developmental Disabilities Consultants, LLC
Clarksdale Municipal School District, Clarksdale, MS

- conducted psychological assessments with children and adolescents, and authored detailed psychological reports
- conducted psychological/behavioral consultations and functional behavior analysis consultations for numerous elementary, middle, and high schools within Coahoma County
- conducted client history reviews, multiple-setting client observations, structured interviews with teachers, parents, and client, analyzed functions of client behavior, made recommendations, and wrote formal reports detailing consultation

Supervisor: Emily Thomas Johnson, Ph.D.

2010-2009 Mental Health Consultant

ICS, MS Head Start Centers

- conducted classroom observations of teacher-student interactions
- conducted individual child behavioral observations and assessments
- developed and implemented behavioral intervention plans for children
- engaged in classroom consultation with teachers, aides, and parent consultation

Supervisor: Alan M. Gross, Ph.D.

2009-2008 Cultural Connections Ambassador

The Counseling Center, The University of Mississippi, University, MS

- facilitated a weekly two hour group comprised of American and international students
- assisted international students with acculturation process

Supervisor: Laura R. Johnson, Ph.D.

2009-2008 Behavioral Consultant

Part-time position

Desoto County School System, Olive Branch, MS

- conducted psychological assessments with children and adolescents, and authored detailed psychological reports
- conducted psychological/behavioral consultations and functional behavior analysis consultations for numerous elementary, middle, and high schools within Desoto County
- conducted client history reviews, multiple-setting client observations, structured interviews with teachers, parents, and client, analyzed functions of client behavior, made recommendations, and wrote formal reports detailing consultation

Supervisors: Sheila Williamson, Ph.D.; Emily Thomas Johnson, Ph.D.

2008-2007 *Neurohealthrehabilitative Psychology Intern*

Behavioral Health Center, North Mississippi Medical Center, Tupelo, MS

Part-time position

- conducted pain evaluations, competency and dementia evaluations, adolescent drug overdose evaluations, personality assessments, and neuropsychological assessments with adults and geriatric population
- authored and dictated neuropsychosocial reports
- conducted psychosocial intakes, individual therapy sessions, and group therapy sessions with inpatients on Acute A, Acute B, Geriatric, and Chemical Dependency Units

Supervisors: Mike Oliver, Ph.D.; Thomas E. Witty, Ph.D.; Brian Thomas, Psy.D.

2007 *Summer Graduate Student Therapist*

The Psychological Services Center, University of Mississippi, University, MS

Quarter-time position

- conducted screening, intake, and therapy sessions with clients
- authored therapy notes and completed other psychological documents

Supervisor: D. Scotty Hargrove, Ph.D.

2007-2006 *Neuropsychological Examiner*

Center for Pediatric Neuropsychology, Le Bonheur Children's Hospital, Memphis, TN

Part-time position

- conducted over 50 neuropsychological assessments with infants, toddlers, children, adolescents, and a few adults
- conducted evaluations within the Epilepsy Monitoring Unit (EMU) and Spina Bifida Clinic
- authored over 50 detailed neuropsychological reports including DSM-IV-TR diagnoses and recommendations

Supervisor: Vickie R. Brewer, Ph.D.

2006-2005 *Community Home Graduate Student Psychologist*

North Mississippi Regional Center, Oxford, MS

Part-time position

- conducted cognitive and adaptive functioning assessments, weekly counseling sessions, and data collection with MR community clients
- authored behavioral programs and psychological reports

Supervisors: Kimberly Sallis, Ph.D.; Doug Buglewicz, M.Ed.

2004-2003 *Behavioral Specialist*

BayPointe Hospital, Mobile, AL

Part-time position

- supervised behaviorally and emotionally disturbed female adolescents
- therapeutically assisted adolescents with daily living skills

Supervisor: Angela Ferrera, M.S., L.P.C., Coordinator of Clinical Services

2003 ***Psychology Intern***
Therapy Associates, Mobile, AL
Part-time position

- assisted with scheduling clients and clinical filing, observed and participated in therapy sessions, and created an anger management game for children

Supervisors: Dodie Ward, M.S., L.P.T.; Kim Zweifler, Ph.D.

2003-2000 ***Physical Therapist Aide***
Providence Hospital, Mobile, AL
Part-time position

- scheduled and transported patients; aided in wound care dressing removal and application, aided in gait training and therapeutic exercises
- utilized hospital software MediServe and Invision; retrieved medical records, lab results, supplies, and medications

Supervisors: Loverette Vaughn, Office Coordinator; Kathy Mignone, P.T.A.

Professional Training

2010 ACT Summer Institute at the University of Nevada, Reno
2009 Vincent Carbone's Verbal Behavior Therapy at Hernando Elementary School, Hernando, MS
2008 ACT Summer Institute at the Illinois Institute of Technology, Chicago, IL
2007-2006 Center for Pediatric Neuropsychology Rounds at Le Bonheur Children's Medical Center, Memphis, TN
2006 ACT Advanced Practice Workshop at The University of Mississippi, University, MS
2005 ACT Experiential Workshop at Camp Hopewell, Oxford, MS
2004 ACT Summer Institute and Introductory Experiential Workshop at the University of Nevada, Reno

Grants

Gustafson, S., & Nassar, S. L. (2010). Clinical Training: Creation of a Service Consortium. *United States Department of Health and Human Services, Health Resources and Service Administration* (\$377,123.00, unfunded)

Publications

Nassar, S. L., Berkout, O. V., & Wilson, K. G. (in preparation). Preliminary Psychometric Properties of the Valued Living Questionnaire-II: An Expanded Measure of Values and Committed Action.

- Nassar, S. L., Conklin, H. M., Ashford, J. M., Reddick, W. E., Glass, J. O., Jeha, S., Zhou, Y., Cheng, C., & Pui, C-H. (in preparation). Cognitive outcomes in children experiencing seizures during treatment for Acute Lymphoblastic Leukemia.
- Gustafson, S. A., Nassar, S. L., & Waddell, D. E. (in preparation). Neurotherapy of neurally mediated syncope: A single case design. *Journal of Neurotherapy*.
- Bethay, J. S., Wilson, K. G., Schnetzer, L. W., Nassar, S. L., & Bordieri, M. J. (2012). A controlled pilot evaluation of Acceptance and Commitment Training for intellectual disability staff. *Mindfulness, Online First*. doi: 10.1007/s12671-012-0103-8
- Wilson, K. G., Flynn, M. K., Bordieri, M., Nassar S. L., Lucas, N. N., & Whiteman. K. C. (2011). Acceptance and Cognitive Behavior Therapy. In W. O'Donohue & J. E. Fisher (Eds.) *Cognitive Behavior Therapy: Core Principles for Practice*. Hoboken, NJ: Wiley.
- Waddell, D. E., Nassar, S. L., & Gustafson, S. A. (2011). Single-case design in psychophysiological research. Part II: Statistical analytic approaches. *Journal of Neurotherapy, 15*(2), 160-169.
- Gustafson, S. A., Nassar, S. L., & Waddell, D. E. (2011). Single-case design in psychophysiological research. Part I: Context, structure, and techniques. *Journal of Neurotherapy, 15*(1), 18-34.
- Nassar, S. L. (2010). A measure of interest to logotherapy researchers: The Death Depression Scale. *The International Forum for Logotherapy, 33*(1), 56-57.
- Nassar, S. L. (2009). A measure of interest to logotherapy researchers: The Valued Living Questionnaire. *The International Forum for Logotherapy, 32*(2), 121-122.
- Nassar, S. L. (2009). A measure of interest to logotherapy researchers: The Meaningful Life Measure. *The International Forum for Logotherapy, 32*(1), 56-57.
- Nassar, S. L. (2008). A measure of interest to logotherapy researchers: The Satisfaction With Life Scale. *The International Forum for Logotherapy, 31*(2), 114-115.
- Nassar, S. L. (2008). A measure of interest to logotherapy researchers: The Hope Scale. *The International Forum for Logotherapy, 31*(1), 55-56.
- Nassar, S. L. (2007). Movies of interest to logotherapists. *The International Forum for Logotherapy, 30*(2), 112-115.
- Nassar, S. L. (2007). A measure of interest to logotherapy researchers: The Humor Styles Questionnaire. *The International Forum for Logotherapy, 30*(1), 48-50.

Nassar, S. L. (2006). A measure of interest to logotherapy researchers: The Love Attitudes Scale. *The International Forum for Logotherapy*, 29(2), 119-121.

Schulenberg, S. E., & Nassar, S. L. (2006, April 5). Meaningful cinema: Logotherapy and Finding Neverland [Review of the motion picture *Finding Neverland*]. *PsycCRITIQUES-Contemporary Psychology: APA Review of Books*, 51 (No. 14), Article 17. Retrieved April 5, 2006, from the *PsycCRITIQUES* database.

Presentations

Nassar, S. L. (2012, December). Acceptance and Commitment Therapy: An experiential walk around the Hexaflex. Invited talk presented at Vanderbilt University, Nashville, TN.

Gustafson, S. A., & Nassar, S. L. (2012, October). Time Series Design in Clinical Neuropsychophysiology. Invited lecture presented at the University of Alabama, Tuscaloosa, AL.

Nassar, S. L., Wilson, K. G., Kellum, K. K. (2012, July). Defusion as a core ACT process: Conceptual definitions, current empirical literature, and future directions for exploration. In H. Bolderston (Chair), *Cognitive fusion: Conceptualization and empirical findings*. Symposium presented at the 10th Annual World Conference of the Association for Contextual Behavioral Science, Washington, D.C.

Nassar, S. L., Conklin, H., M., Ashford, J. M., Zhou, Y., Cheng, C., Reddick, W. E., Glass, J. O., Jeha, S., & Pui, C-H. (2012, April). Cognitive Outcomes in Children Experiencing Seizures during Treatment for Acute Lymphoblastic Leukemia. In K. Tercyak & C. J. Heckman (Chairs), *Pediatric Oncology: Survivorship and Prevention*. Paper session presented at the 33rd Annual Meeting & Scientific Sessions of the Society of Behavioral Medicine, New Orleans, LA.

Nassar, S. L. & Wilson, K. G. (2011, June). Adapting the Expressive Writing Paradigm as a Values-Based Intervention. In S. L. Nassar (Chair), *New Directions in Values Assessment and Intervention*. Symposium presented at the 9th Annual World Conference of the Association for Contextual Behavioral Science, Parma, Italy.

Parman, M., Nassar, S. L., Kellum, K. K., & Wilson, K. G. (2011, May). Adapting the Expressive Writing Paradigm as a Values-Based Intervention. In A. Branstetter-Rost (Chair), *The Potential Utility of Expressive Writing in Acceptance and Commitment Therapy: Moving Behavior in Valued Directions*. Symposium presented at the 37th Annual Convention for the Association for Behavior Analysis International, Denver, CO.

- Nassar, S. L., Wilson, K. G., & Kellum, K. K. (2010, June). Update on Values-Centered Adaption of the Expressive Writing Paradigm. In S. L. Nassar (Chair), *Research and Therapeutic Application in the Context of Valued Living*. Symposium presented at the 8th Annual World Conference of the Association for Contextual Behavioral Science, Reno, NV.
- Flynn, M. K., Wilson, K. G., & Kellum, K. K., Nassar, S. L., Slater, R. M., Lucas, N. N., Bordieri, M., Bethay, S., Kolivas, E., & Kirkland, K. (June, 2010). Exploring the Use of the Hexaflex Functional Dimensional Experiential Interview. Paper presented at the 8th Annual World Conference of the Association for Contextual Behavioral Science, Reno, NV.
- Nassar, S. L., Wilson, K. G., & Kellum, K. K. (2010, May). Update on Values-Centered Adaption of the Expressive Writing Paradigm. In S. L. Nassar (Chair), *Research and Application in the Context of Valued Living*. Symposium presented at the 36th Annual Convention for the Association for Behavior Analysis International, San Antonio, TX.
- Flynn, M. K., Wilson, K. G., Kellum, K. K., Nassar, S. L., Slater, R. M., Lucas, N., Bordieri, M., Bethay, S. (2010, May). Exploring the Use of the Hexaflex Functional Dimensional Experiential Interview. In S. L. Nassar (Chair), *Research and Application in the Context of Valued Living*. Symposium presented at the 36th Annual Convention for the Association for Behavior Analysis International, San Antonio, TX.
- Williamson, S., Nassar, S. L., & Johnson, C. (2009, October). Elementary and Middle School Interventions. In E. T. Johnson (Chair), *Tutorial: Clinical Strategies within the Classroom for Children with Autism*. Symposium presented at the 60th Annual Conference of the Mississippi Psychological Association, Gulfport, MS.
- Nassar, S. L., Flynn, M. K., Slater, R. M., Kellum, K. K., & Wilson, K. G. (2009, June). Values-Centered Interventions. In R. M. Slater (Chair), *Values in Acceptance and Commitment Therapy: Conceptualization, Clinical Exercises, and Assessment*. Symposium presented at the Third Annual World Conference of the Association for Contextual Behavioral Science, Enschede, The Netherlands.
- Slater, R. M., Nassar S. L., Flynn, M. K., Kellum, K. K., & Wilson, K. G. (2009, June). What are Values? Unpacking Values as Conceptualized in Acceptance and Commitment Therapy. In R. M. Slater (Chair), *Values in Acceptance and Commitment Therapy: Conceptualization, Clinical Exercises, and Assessment*. Symposium presented at the Third Annual World Conference of the Association for Contextual Behavioral Science, Enschede, The Netherlands.

- Flynn, M. K., Nassar, S. L., Slater, R. M., Kellum, K. K., & Wilson, K. G. (2009, June). An Improved Measure of Valued Living: The Valued Living Questionnaire-II (VLQ-2). In R. M. Slater (Chair), *Values in Acceptance and Commitment Therapy: Conceptualization, Clinical Exercises, and Assessment*. Symposium presented at the Third Annual World Conference of the Association for Contextual Behavioral Science, Enschede, The Netherlands.
- Nassar, S. L., Wilson, K. G., Kellum, K. K., & Sandoz, E. K. (2009, May). Mindfulness for Two (Part II): The Effects of Therapist Disclosure. In J. Weinstein (Chair), *Mindfulness for Two (Part II): Manipulating the Therapist*. Symposium presented at the 35th Annual Convention of the Association for Behavior Analysis International, Phoenix, AZ.
- Nassar, S. L., Wilson, K. G., Kellum, K. K., & Flynn, M. K. (2009, May). Values-Centered Writing: Explorations Within The Expressive Writing Paradigm. In S. L. Nassar (Chair), *Research and Treatment in the Context of Valued Living*. Symposium presented at the 35th Annual Convention of the Association for Behavior Analysis International, Phoenix, AZ.
- Howard, R. C., Nassar, S. L., Martin, L., Slater, R. M., Sandoz, E. K., Kellum, K. K., & Wilson, K. G. (2009, May). The Permanent Solution: Suicidal Behavior and Experiential Avoidance. In R. M. Slater (Chair), *Psychological Flexibility and Difficult Clinical Presentations*. Symposium presented at the 35th Annual Convention of the Association for Behavior Analysis International, Phoenix, AZ.
- Davis, D., Hamblin, B., Hankton, U. N., Nassar, S. L., Ofili, P., Weinstein, J., & Johnson, L. R. (2009, April). *Updates on Outreach: Expanding Cultural Competence in our Services and Ourselves*. Diversity Colloquium presented at the University of Mississippi, University, MS.
- Nassar, S., Tucker, C., & Ambrose, C. (June, 2008). *Workplace Violence*. Presentation given at the Medical Ethics Committee meeting at North Mississippi Medical Center, Tupelo, MS.
- Nassar, S. L., Drake, C., & Wilson, K. G. (2008, May). One More Time: An Examination of the Stability of IRAP Performance over Repeated Administrations. In S. L. Nassar (Chair), *How Words Measure Up: An Investigation of the Reliability, Validity, and Procedural Integrity of the Implicit Relational Assessment Procedure*. Symposium presented at the 34th Annual Convention of the Association for Behavior Analysis International, Chicago, IL.
- Bethay, S., Wilson, K. G., Lucas, N., Moyer, K., & Nassar, S. L. (2008, May). Acceptance and Commitment Training (ACT) to address burnout in staff caring for clients with intellectual disabilities (ID). In R. Slater (Chair), *ACT Outside the Clinic: Application of Acceptance and Commitment Therapy to Non-clinical Populations*. Symposium

presented at the 34th Annual Convention of the Association for Behavior Analysis International, Chicago, IL.

Hankton, U. N., Hirschel, M., Nassar, S. L., Tracy, J., & Johnson, L. R. (2007, May). *Reaching Out to International Students: Some Strategies and Lessons Learned*. Diversity Colloquium presented at the University of Mississippi, University, MS.

Posters

Gustafson, S. A., Nassar, S. L., Waddell, D. E. (2012, April). *Treatment of Neurally Mediated Syncope Using Spectral EEG Neurotherapy: A Single Case Design*. Poster presented at the 33rd Annual Meeting & Scientific Sessions of the Society of Behavioral Medicine, New Orleans, LA.

Howard, R. C., Slater, R., Sandoz, E. K., Nassar, S. L., & Wilson, K. G. (2008, May). *The Permanent Solution: Parasuicidality and Experiential Avoidance*. Poster presented at the 34th Annual Convention of the Association for Behavior Analysis International, Chicago, IL.

Nassar, S. L., & Hager, L. D. (2004, May). *The Effects of Personality Type on Procrastination in College Students*. Poster presented at Spring Hill College, Mobile, AL.

Interviews

Morris, M. G. (2008, February 1). Sweat out the small stuff ... or not: Intense exercise, gentle meditative movement play key role in beating back unhealthy stress. *Daily Journal*, pp. 1C, 3C.

Morris, M. G. (2007, September 28). Putting the pieces back together: Young adults in transition particularly vulnerable to mental health issues. *Daily Journal*, pp. 1C, 6C.

Workshops

Nassar, S. L., & Waxenberg, L. B. (2014, May). *Introduction to Acceptance and Commitment Therapy (ACT): An Interactive Workshop*. Case Conference Series presented at the University of Florida College of Public Health and Health Professions, Department of Clinical and Health Psychology, Gainesville, FL.

Wilson, K. G., Flynn, M. K., Bordieri, M. J., Slater, R. M., Nassar, S. L., Whiteman, K., & Schnetzer, L. W. (July, 2011). *Treating Addiction with Co-Occurring Anxiety and Depression*. Workshop presented at the 9th Annual Conference of the Association for Contextual Behavioral Science, Parma, Italy.

- Wilson, K. G., Schnetzer, L. W., Flynn, M. K., Bordieri, M. J., Nassar, S. L., & Whiteman, K. (July, 2011). *Mindfulness and Values Interviewing in Acceptance and Commitment Therapy*. Workshop presented at the 9th Annual Conference of the Association for Contextual Behavioral Science, Parma, Italy.
- Wilson, K. G., Sandoz, E. K., Flynn, M. K., Slater, R. M., Lucas, N. N., & Nassar, S. L. (June, 2009). *Learning Hexaflex Processes Using Mindfulness for Two Videos*. Workshop presented at the Third Annual Conference of the Association for Contextual Behavioral Science, Enschede, Netherlands.
- Sandoz, E. K., & Nassar, S. L. (June, 2009). *Know Thyself, Choose Thyself: Exploring Flexibility with Self and Valued Living*. Workshop presented at the Third Annual World Conference of the Association for Contextual Behavioral Science, Enschede, The Netherlands.
- Wilson, K. G., Sandoz, E. K., Nassar, S. L., Lucas, N., Slater, R. M., Martin, L. (May, 2008). *Advanced Experiential Case Conceptualization Workshop*. Workshop presented at the 4th Association for Contextual Behavioral Science Summer Institute, Chicago, IL.
- Nassar, S. L., Melton, A. M., & Schulenberg, S. E. (2006). *Life Purpose Workshop*. Workshop presented at the Psychological Services Center, University, MS.

Editorial Positions

Guest Reviewer for *Behaviour Research and Therapy* (2013)

Membership in Professional Associations

Society of Behavioral Medicine, Student Member, 2012
Mississippi Psychological Association, Student Affiliate, 2009
Gamma Beta Phi Society, Student Member, 2008
Association for Behavior Analysis, Student Affiliate, 2008
American Psychological Association, Student Affiliate, 2007
Association for Contextual Behavioral Science, Charter Member, 2006
Alpha Sigma Nu, Jesuit Honor Society, Student Member, 2004
Psi Chi, National Honor Society in Psychology, Student Member, 2002

Honors and Awards

- 2009 Wolfe Award Nominee
- 2009 Cambridge Who's Who Honors
- 2008 Gamma Beta Phi Society
- 2008-2004 Graduate Honors Fellowship
- 2004 Alpha Sigma Nu
- 2004-1999 SouthTrust Bank Corporate Scholarship
- 2004-1999 Spring Hill College Faculty Honors Scholarship
- 2004-1999 Mobile Metropolitan Service Award
- 2004-1999 Dean's List, Spring Hill College
- 2002 Psi Chi
- 2002 Outstanding Tutor of the Foley Community Service Center

Professional Recommendations

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