VISUAL WORKING MEMORY AND VISUAL SELECTIVE ATTENTION AMONG SURVIVORS OF PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

A Dissertation

Presented to

The Faculty of the Department of Psychology

University of Houston

In Partial Fulfillment

Of the Requirements for the Degree of

Doctor of Philosophy

By

Melissa Treviño

August, 2016

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ABSTRACT

The present study investigated the relationship between visual working memory (VWM) and visual selective attention in survivors of pediatric acute lymphoblastic leukemia (ALL) either at high-risk or low-risk for neurocognitive impairments based on their treatment regimen and non-cancer controls. Previous investigations of neurocognitive impairments in survivors of pediatric ALL have employed broad-based measures of functioning whereas the present study utilized standard experimental measures that are sensitive to specific spatial and feature-based aspects of VWM and visual selective attention. A dual-task paradigm, combining a VWM task and a flanker task, assessing visual selective attention, was used. Participants ran in 6 dual-task conditions that varied in VWM feature/task (color, shape, location) and of the flanker feature/task (color, shape). Participants also ran in 3 single-task VWM control conditions and 2 single-task flanker conditions. Results reveal maintenance of information in VWM is susceptible to interference from the concurrent visual selective attention task for all three groups. VWM storage estimates, *k,* were shown to decrease when a VWM task was preceded by a visual selective attention task compared to a single VWM task. These interference effects were also found to be feature specific for all groups. For the visual selective attention tasks, both high and low-risk groups had lower performances on flanker tasks than non-cancer controls when collapsing across condition (single-task vs. dual-task). Only the low-risk group appeared to be susceptible to interference from a concurrent VWM task, with flanker effects (difference between incongruent and congruent reaction times) varying across conditions (single-task vs. dual-task). Thus, survivors of pediatric ALL are comparable with non-cancer controls in how visual selective interferes with WVM; however, visual selective attention for only the low-risk group was affected by VWM.

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I would like to express my sincere gratitude to my advisor, Dr. Bruno G. Breitmeyer, for his continuous guidance and support in this work. I am thankful to Dr. Kimberly Raghubar for providing indispensible advice, help and generously forgoing countless Saturdays that enabled me to collect data. In addition, I am most grateful to The Duncan Foundation for financially supporting this research and to both Texas Children's Hospital and the Cognitive Development Lab at the University of Houston for allowing me to recruit and conduct this research at their facilities.

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Visual Working Memory and Visual Selective Attention among Survivors of Pediatric Acute Lymphoblastic Leukemia (ALL)

Acute lymphoblastic leukemia (ALL) is the most commonly diagnosed cancer among children and adolescents. An approximated 2,900 new cases are diagnosed each year, which accounts for 25% of all cancers among children under the age of 20 (Dores et al., 2012; Howlader et al., 2012; Ries et al., 1999). Historically, the prognosis of pediatric ALL has been poor with high mortality rates compounded with low 5-year relative survival rates. Today, there has been considerable improvement in both mortality rates and the 5-year relative survival rates; approximately 75% of patients diagnosed with pediatric ALL are expected to be long-term, event-free survivors (Moghrabi et al., 2007; Moricke et al., 2008; Salzer et al., 2010). These improvements in survival have been attributed to advances in treatment protocols (Smith et al., 1996).

Treatment Protocols

Pediatric ALL is a cancer of the blood and bone marrow, where the bone marrow produces too many lymphocytes, i.e., a type of white blood cell. ALL is comprised of several leukemia subtypes that are molecularly distinct, respond differently to treatment, and have various risks of relapse, i.e., cancer returning after treatment and after a period of improvement (Pui & Evans, 1998). Due to the heterogeneous nature of pediatric ALL, current treatment protocols follow a risk-based treatment assignment that modifies the intensity of treatment based on the patient's risk of relapse (Smith et al., 1996). Risk of relapse is influenced by both clinical and biological factors of the patient. The National Cancer Institute (NCI) determines the risk-based assignment groups according to the age and white blood cell count (WBC) of the patient. Patients with a high-risk of relapse are children

aged 10 or older and have a WBC of 50 x 10^9/L or greater and patients with a standard-risk of relapse are children from the ages of 1 to 9 years and that have a WBC less than 50 x 10^9/L (Smith et al., 1996). Risk-based treatment assignment allows for patients that have a standard-risk for relapse to avoid an intensive and a more toxic treatment typically reserved for patients with a high-risk of relapse (Pui & Evans, 1998; Silverman et al., 2001).

Treatment for both standard-risk and high-risk ALL is typically done in three phases. The first phase, remission induction, leukemia cells are destroyed in the blood and bone marrow in order for the cancer to go into remission, i.e., when bone marrow samples contain fewer than 5% of leukemia cells and blood counts become normal (Lee et al., 2011). After 1 month of induction, at least 95% of patients enter remission (Lee et al., 20111). Consolidation or intensification is the second phase of treatment that targets the leukemia cells that still remain in the body and lasts about 1 to 2 months. Consolidation is followed by the maintenance phase, also called the continuation therapy phase, where any leukemia cells that may regrow are eradicated. Typically, treatment protocols that include the remission induction, consolidation, and maintenance phases will last 2 to 3 years (Lee et al., 2011).

Treatment phases involve systemic and intrathecal chemotherapy and central nervous system (CNS)-prophylaxis, i.e., preventative chemotherapy treatment that includes either intrathecal or intravenous chemotherapy. Cranial radiation therapy was once a standard inclusion of CNS-prophylaxis, however, due to the effects on growth and brain development associated with cranial radiation, it is now only administered for those at highest risk for relapse (Bleyer, 1988; Pui, Robinson & Look, 2008). In many current treatment protocols, patients of high-risk ALL are given more anticancer drugs and at higher doses, especially during the consolidation phase, than patients of standard-risk ALL.

Late Effects of Treatment Protocols

The development of risk-based treatment assignment and the introduction of CNS-prophylaxis have led to significant improvements in survival rates. Patients are now living longer but there has been increasing concern over adverse late effects associated with treatment. Treatment protocols of pediatric cancer have been investigated since the 1970s and have long been acknowledged as a primary cause of neurocognitive decline (Danoff et al., 1982). Neurocognitive deficits are classified as late effects as they become apparent years after the start of treatment (Costa, 2010; Cousens et al., 1988; Jankovic et al., 1994; Mulhern, Fairclough & Ochs, 1991; Rubenstein, Varni & Katz, 1990; Schatz et al., 2000).

Risk Stratification. A risk stratification system for neurocognitive impairments has been introduced that is based on the intensity of treatment, age at diagnosis, and gender. Patients treated with higher dosages of chemotherapy agents and/or cranial radiation therapy have a higher risk for neurcognitive impairments after the completion of treatment (Buizer et al., 2005; Langer et al., 2002; Spiegler et al., 2006). Girls and children younger than or equal to 6 years old at diagnosis also have an increased risk for neurocognitive impairments (Buizer et al., 2005; Langer et al., 2002; Von der Weid, et al., 2003). Low-risk for neurocognitive impairments affects boys, patients who had received lower doses of chemotherapy agents, and children older than 6 years old at the time of diagnosis (Buizer et al., 2005; Langer et al., 2002; Von der Weid, et al., 2003).

Cranial Radiation. Previous research has established a strong link between treatment protocols of pediatric ALL that incorporate cranial radiation therapy and subsequent neurocognitive impairments. Historically, significant decreases in IQ scores, the standard method in evaluating neurocognitive impairments, have been reported in association with the

usage of cranial radiation therapy (Butler et al., 2006; Fletcher & Copeland, 1988; Grill et al., 2004; Kieffer-Renaux et al., 2000; Mulhern et al., 1998, 2004; Packer et al., 1989; Watanabe et al., 2011). Today, neurocognitive deficits can be classified as either core or secondary deficits. Core deficits commonly reported among pediatric ALL survivors who have undergone cranial radiation therapy include impairments in attention, memory, processing speed, executive functions (failure in planning and organizing behavior), verbal function, and complex visual spatial problem solving (Hill et al., 1997; Reddick et al., 2006; Schatz et al., 2000). Secondary deficits include low IQ scores and poor academic achievement, which are speculated to be the outcome of impairments in core abilities (Mulhern et al., 1998). Learning disabilities are also reported among pediatric ALL survivors who received cranial radiation therapy (Gamis & Nesbit, 1991; Kaemingk et al., 2004; Roman & Sperduto, 1995; Von der Weid et al., 2003).

Current Treatment. Within the literature of current chemotherapy-only protocols, there are inconsistencies whether survivors of pediatric ALL have neurocognitive impairments following treatment. Memory functioning, attention, and processing speed have been reported to be intact among survivors of pediatric ALL (Hill et al., 2004; Spiegler et al., 2006). Hill et al. (2004) evaluated long-term memory on the Wide Range Assessment of Memory and Learning (WRAML) and visual-spatial memory on the Rey-Osterrieth Complex Figure and found no differences between survivors and non-cancer controls on measures. Additionally, Spiegler et al. (2006) compared working memory measured with the Children's Memory Scale and the Wechsler Memory Scale-III along with processing speed on the Wechsler Intelligence Scale for Children-III [WISC-III] or with the Wechsler Adult Intelligence Scale-III [WAIS-III] and sustained attention on the Gordon Diagnostic System.

All neurocognitive measures were reported to be unaffected in survivors relative to normative population means (Spiegler et al., 2006) (See Appendix A).

In contrast, other studies have observed survivors showing neurocognitive impairments following current chemotherapy-only protocols. Robinson et al. (2010) identified impairments of memory, processing speed, and executive functioning among survivors relative to non-cancer controls, using the Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV) to measure processing speed, the Delis-Kaplan Executive Function System (D-KEFS), and a visual N-back task to assess working memory. Attention and working memory functions have also been assessed using the Digit Span Forward subtest and the Digit Span backward subtest with survivors showing impairments on both tasks compared to normative ranges (Ashford et al., 2010). Impairments of sustained attention have been reported among survivors of ALL treated with chemotherapy-only protocols relative to normative samples (Ashford, et al., 2010; Conklin et al., 2012; Krull et al., 2013). The Conners' Continuous Performance Test (CPT) is a popular measure that has been used to assess sustained attention and has yielded impairments among survivors (Conklin et al., 2012; Krull et al., 2013) (See Appendix A).

Neuroanatomical Abnormalities. Structural and functional neuroimaging studies demonstrate there may be several underlying mechanisms for the neurocognitive deficits that have been reported among survivors of pediatric ALL. Survivors who received both chemotherapy and cranial radiation therapy are reported to have reduced volumes of cortical gray matter, cerebral white matter, amygdala, caudate, hippocampus, and thalamus compared to non-cancer controls (Zeller et al., 2013). The strongest effect size was found for the caudate, which is known to support executive functions such as planning and problem

solving (Mendez et al., 1989; Zeller et al., 2013). Survivors who received only chemotherapy are reported to have reduced white-matter volumes of corpus callosum, frontal and temporal lobes (Edelmann et al., 2014; Reddick et al., 2005; Reddick et al., 2006). Robinson el al. (2010) assessed working memory, using a visual N-back task, in survivors who received only chemotherapy and found during an increased working memory demand, survivors had greater activation and required more oxygenated blood to both the dorsolateral and ventrolateral prefrontal cortex, areas commonly associated with working memory (Robinson et al., 2010). Indicating, more energy is required for survivors to perform the working memory task relative to non-cancer controls. Regarding the integrity of white matter tracts, studies show survivors treated only with chemotherapy have lower fractional anisotropy[1] in frontal white matter tracks relative to non-cancer controls (Schuitema et al., 2013). However, recently higher fractional anisotropy has been found among survivors treated only with chemotherapy in multiple fiber tracts within the right hemisphere (Edelmann et al., 2014). Areas with low fractional anisotropy and abnormally high fractional anisotropy have been indicative of microstructural abnormalities (Budde et al., 2011; Kumar et al., 2009; Pierpaoli & Basser, 1996; Schuitema et al., 2013; Sidaros et al., 2008; Wilde et al., 2008).

Studies have also demonstrated neural abnormalities found among survivors correlate with reported neurocognitive deficits. White matter abnormalities, i.e., reduced white matter volumes, among survivors who received only chemotherapy, have been correlated with sustained attention deficits and impaired immediate memory (Armstrong et al., 2013; Reddick et al., 2006). Additionally, deficits in memory performance have also been associated with reduced temporal white matter and thinner parietal and frontal cortices (Armstrong et al., 2013). In contrast, Kingma et al. (2001) reported neural abnormalities, i.e.,

atrophy and calcifications, among survivors treated only with chemotherapy were not correlated with deficits found in memory. Hippocampal volume has also been found to not differ among survivors who received chemotherapy only and non-cancer controls, as well survivors and controls were comparable among measures of long-term memory and no correlations were found between volumetric and neurocognitive measures (Hill et al., 2004).

Attention and Visual Working Memory

As outlined above, research examining neurocognitive deficits following current treatment protocols that include only chemotherapy has yielded inconsistent results whether survivors demonstrate neurocognitive difficulties. To further examine this population, we investigated survivors that were classified as having a low-risk for neurocognitive deficits due to receiving only chemotherapy at low dosages, survivors having a high-risk for neurocognitive deficits as a result of receiving chemotherapy at high dosages and/or radiation therapy, and non-cancer controls. We assessed the neurocognitive functions of attention and memory, specifically visual attention and visual working memory, as there is not a cohesive consensus that impairments in these areas are present. The present study seeks to further investigate these processes by using standard experimental measures to assess visual attention and visual working memory separately, as well as the dynamic relationship between the two. Fully understanding the extent of impairments of attention and working memory is crucial because they are not only fundamental neurocognitive processes but also essential for higher-level neurocognitive functions, such as reading (Casco, Tressoldi & Dellantonio, 1998; Conway et al., 2005), language comprehension (Daneman & Merikle, 1996), academic success (Alloway & Alloway, 2010), arithmetical attainment (McLean & Hitch, 1999) and decision making (Curtis & Lee, 2010; Zizlsperger, Sauvigny & Haarmeier, 2012).

Attention and VWM in Non-Clinical Population. Visual working memory (VWM) is a specialized store within working memory that maintains visual information in the absence of sensory input (Baddeley, 2003; Jonides et al., 2008). Among healthy adults, there is evidence for the fractionation of VWM based on visual spatial information and visual object information, however, it is unclear whether objects are stored as a whole or by feature dimensions (e.g., surface features: colors, textures; or contour features: orientation, curvature) (Alvarez & Cavanagh, 2008; Courtney et al., 1996; Fougnie, Asplund & Marois, 2010; Harrison & Tong, 2009; Morgan et al., 2010; Olson & Jiang, 2002; Smith et al., 1995; Tresch, Sinnamon & Seamon, 1993; Wheeler & Treisman, 2002). These different types of information are processed in separate VWM stores (Fougnie, Asplund & Marois, 2010; Olson & Jiang, 2002; Smith et al., 1995). Visual attention is the selective processing of visual information (Chun, Golomb & Turk-Browne, 2011). Similar to the different types of VWM, theoretical and empirical evidence suggest there are separate, functionally dissociated mechanisms for visual attention (Brefczynski & DeYoe, 1999; Gandhi, Heeger & Boynton, 1999; Pasupathy & Connor, 1999; Rossi & Paradiso, 1995; Saenz, Buracas & Boynton, 2002; Scholl, 2001; Somers et al., 1999). These include visual spatial attention, in which attention is focused on a target location (Brefczynski & DeYoe, 1999; Gandhi, Heeger & Boynton, 1999; Somers et al., 1999), visual object-based attention in which attention is focused on an object as a whole (Olson, 2001; Somers et al., 1999), and feature-based attention, which is when attention is focused on specific aspects of objects (e.g., surface features such as color or texture; or contour features such as orientation or curvature) (Carrasco, 2011; Pasupathy & Connor 1999; Saenz, Buracas & Boynton, 2002). Traditionally, VWM and visual attention have been viewed and investigated independently.

Recently, however, there has been an increasing interest on the relation between VWM and visual attention (de Fockert et al., 2001; Downing, 2000; Gazzaley & Nobre, 2012; Lavie & de Fockert, 2005; Oberauer, 2003; Olivers, et al., 2011).

There are two major areas of research investigating the relationship between VWM and visual attention. One focus is on how attention influences working memory at multiple processing stages. Visual attention selects not only which information will enter VWM (encoding stage), but also selects which information can be held within VWM (maintenance) (Awh & Jonides, 2001; Gazzaley & Nobre, 2012; Oberauer, 2003; Olivers, et al., 2011). The second area focuses on the influence of VWM on visual attention, specifically visual selective attention. Visual selective attention involves the selective concentration of target-relevant information while inhibiting distracting or non-target relevant information (Desimone & Duncan, 1995). Studies reporting that VWM plays a major role in visual selective attention utilized a dual-task paradigm, in which participants had to retain several items (e.g., a series of digits, letters) in VWM while performing a visual selective attention task that required identification of a target stimulus while inhibiting distractor stimuli (Ahmed & de Fockert, 2012; de Fockert et al., 2001; Downing, 2000; Lavie & de Fockert, 2005; Lavie et al., 2004). The number of items that had to be retained either well exceeded VWM capacity of four (± 1) items (e.g., 7 items) or was well within this limit (e.g., 1 item). The role of visual selective attention has been implemented in several dual-task paradigms in which one of the two tasks was a Stroop task, a traditional flanker task, and a visual search task. When VWM exceeded capacity, there was greater impairment in participants' performance in the visual selective attention task compared to when VWM capacity was low. Thus, these studies concluded that when cognitive resources are devoted to encoding and

storing items in VWM the allocation of resources to visual selective attention was reduced, thus impairing the focusing on relevant-target information (Ahmed & de Fockert et al., 2012; de Fockert et al., 2001; Downing, 2000; Lavie & de Fockert, 2005; Lavie et al., 2004; Pratt, Willoughby & Swick, 2011).

Attention and VWM in Clinical Populations. In order to comprehend the nature of neurocognitive processes in VWM and visual selective attention among survivors of pediatric ALL, we examined whether this relationship is impaired by pediatric ALL and subsequent treatments. We utilized a behavioral dual-task paradigm, consistent with previous research, in which participants had to retain several items in VWM while performing a visual selective attention task that required processing of a target stimulus while inhibiting the processing of distractor stimuli (Ahmed & de Fockert et al., 2012; de Fockert et al., 2001; Downing, 2000; Lavie & de Fockert, 2005; Lavie et al., 2004; Pratt, Willoughby & Swick, 2011). However, previous studies have utilized complex stimuli (e.g., faces, words), overtly familiar stimuli (e.g., digits, letters) and naturalistic scenes (e.g., houses) (Ahmed & de Fockert et al., 2012; de Fockert et al., 2001; Downing, 2000; Lavie & de Fockert, 2005; Lavie et al., 2004; Pratt, Willoughby & Swick, 2011). The current study used basic spatial and feature-based stimuli in order to examine how, among survivors of pediatric ALL, these basic information categories encoded and stored in VWM relate to visual selective attention devoted to a target stimulus in a flanker task. Given, as noted above that encoding and maintenance of information in VWM relies on visual attention (Awh & Jonides, 2001; Gazzaley & Nobre, 2012; Oberauer, 2003; Olivers, et al., 2011), and therefore that the encoding and maintenance of information in VWM and a separate visual attention task tap

into common cognitive resources, we can consider the following hypotheses. In a dual-task paradigm,

- H1: a visual selective attention task can unidirectionally interfere with the VWM task.
- H2: conversely a VWM task can interfere unidirectionally with the visual selective attention task.
- H3: the interference can be bidirectional in that both tasks can mutually interfere with each other.
- H4: the degree to which there is (unidirectional or bidirectional) interference in concurrent VWM and visual selective attention tasks depends directly on the degree to which the two tasks have to access the same source of cognitive resources.

Additionally, we investigated whether these four general hypotheses related to the severity of treatment by assessing survivors of pediatric ALL that differed by their severity of treatment, with low-risk survivors receiving low dosages of chemotherapy, high-risk survivors receiving high dosages of chemotherapy and/or radiation therapy, and non-cancer control children who were not diagnosed with cancer. On the assumption that the VWM and the visual selective attention tasks can share common cognitive resources, it is reasonable to expect that the degree of interference in a dual-task depends directly on the degree to which the common resources, or access to them, are compromised. Specifically, relative to the common cognitive resources available to non-cancer controls, the degree to which these resources are compromised is higher in low-risk pediatric and adolescent survivors who were treated for ALL with low dosages of chemotherapy, and highest in high-risk pediatric and adolescent survivors who were treated with high dosages of chemotherapy and/or radiation

therapy. On that basis we consider the following additional hypothesis. Regardless of the directionally of interference,

- H5: Relative to the least interference in concurrent VWM and visual selective attention tasks found in non-cancer controls, the degree of interference in concurrent VWM and visual selective attention tasks should be higher in low-risk children and adolescents who were treated for ALL with low dosages of chemotherapy, and highest in high-risk children and adolescents who are treated with high dosages of chemotherapy and/or radiation therapy.

METHOD

Participants

Thirty-nine survivors of pediatric ALL and 18 non-cancer controls participated in the current study. Seventeen of the ALL survivors were deemed to be at a high-risk for neurocognitive impairments based on the intensity of their treatment protocol, i.e., high dosage of chemotherapy and/or radiation therapy. The high-risk group consisted of children/adolescents treated on protocols involving a dosage of methotrexate equal to or exceeding 5000 mg/m^2. Nine out of the 17 high-risk survivors were also treated with radiation therapy (avg. 12 Gy) in addition to the high dosage of chemotherapy. Of the nine high-risk survivors, seven received cranial radiation therapy, one received cranial and spinal radiation therapy, and one received mediastinal radiation therapy. Twenty-two participants were deemed to have a low-risk for neurocognitive impairments due to receiving a low dosage of chemotherapy. The low-risk group consisted of children/adolescents receiving doses of methotrexate lower than 5000 mg/m^2. All survivors of pediatric ALL were recruited

through the Texas Children's Cancer Center Long-Term Survivor (LTS) Program. The non-cancer controls were recruited from the University of Houston. Informed consent was obtained from all participants and their parental guardians.

Participant ranged in age from 10-18 years old. Overall, participants' age was 13.68 (± SD = 2.28) years, with an average 13.3 (± SD = 2.16) years for the low-risk survivors, 14.3 (± SD = 1.92) years for the high-risk survivors, and 13.55 (± SD = 2.7) years for the non-cancer controls. There was no significant difference between the three groups in age as determined by a one-way analysis of variance (ANOVA) ($F(2,54) = .914$, $p = .407$, $\eta^2 = .03$). Age at diagnosis for ALL survivors ranged from 11 months to 10 years old, with an average of 3.92 (± SD = 2.41) years for all survivors, 3.91 (± SD = 1.97) years for low-risk survivors, and 3.94 (± SD = 2.97) years for high-risk survivors. Length of treatment for all survivors was 2.44 (± SD = 0.56) years with a range of 1 to 3 years. Low-risk survivors had treatment length of 2.57 (± SD = 0.51) years and 2.25 (± SD = 0.62) years for high-risk survivors. Pediatric ALL survivors were off treatment and disease-free for at least 2 years with an average of 6.39 (± SD = 3.132) years, 6.0 (± SD = 2.76) years for low-risk survivors, and 6.87 (± SD = 3.61) years for high-risk survivors. Years off treatment ranged from 2 years to 12 years for ALL survivors.

Categorized by ethnicity, the majority of the 57 participants were Hispanic (n=31, 52.6%); 18 were Caucasian (31.5%), four were multi-ethnic (7.0%), three were Asian (5.2%), while one was African American (1.7%); and according to sex, 34 (59.64%) were male and 23 (40.35%) were female. For low-risk survivors of pediatric ALL, the majority of participants were Caucasian (n=11, 50.0%), eight were Hispanic (36.3%), two were Asian (9.0%), while one was multi-ethnic (4.5%). As to sex, there were 15 (68.18%) males and 7

(31.81%) females. For the high-risk survivors of pediatric ALL a majority consisted of Hispanic participants (n=12, 70.5%); four of the participants were Caucasian (23.5%), and one was multi-ethnic (5.8%). As to sex, there were 10 (58.82%) males and 7 (41.17%) females. For the non-cancer controls, the majority of participants were Hispanic (n= 11, 61.1%); three were Caucasian (16.7%), two were multi-ethnic (11.1%), one participant was African American (5.6%) and one participant was Asian (5.6%). As to sex, there were 9 (50.0%) males and 9 (50.07%) females.

Apparatus and Stimuli

E-Prime software version 2.0 (Psychology Software Tools, Inc.) was used and stimuli were presented at a frame rate of 60Hz on a Mac Book Pro, 1024 x 768 Pixel, color monitor, operated by Windows 2000 Professional software. Viewing distance was approximately 65cm. The VWM stimuli were centered on a notional circle (with a radius of 3.1°) that in turn was centered at fixation. There was a total of 9 possible locations on the circle where the stimuli could be presented. Stimuli for the visual selective attention (i.e., the flanker task) were positioned above fixation on a second notional circle that was twice the size of the notional circle of the VWM task (with a radius of 6.2°), in order to ensure against spatial overlap of the two tasks. The stimuli for the visual selective attention task were twice the size of the VWM stimuli in order to account for cortical magnification. Three types of visual information were used in the VWM task: (1) colors, (2) shapes, and (3) locations. For the color VWM task, the stimuli consisted of three colored discs randomly selected from a set of nine colors: yellow, red, blue, green, white, violet, teal, pink, and brown; for the shape VWM task, three solid black geometric shapes were randomly selected from a set of nine shapes: U-shape, heart, triangle, pentagon, star, arrow, bowtie, rhombus, and square; and for

the locations VWM task, three solid black discs were placed randomly at the nine possible locations. The color black was not utilized in the color VWM task because black was the designated color for shape and location VWM tasks. Also, the circle was not used in the shape VWM task because the circle was the designated shape used in the color and location VWM tasks. Two types of visual information categories were used in the visual selective attention task: (1) colors (2) shapes. Although the VWM and selective attention tasks sampled from the same set of nine colors or shapes, on any trial there was no overlap of the two colors or shapes used in the flanker task and the remaining seven colors or shapes used in VWM task. For example, a red circle or a (black) triangle presented in the color or shape VWM task was not selected as a possible color or shape to be presented in the visual selective attention task.

Experimental Design

The dual-task paradigm consisted of a VWM task and a visual selective attention task. The VWM task (see Figure 1) is a version of the change-detection paradigm utilized by

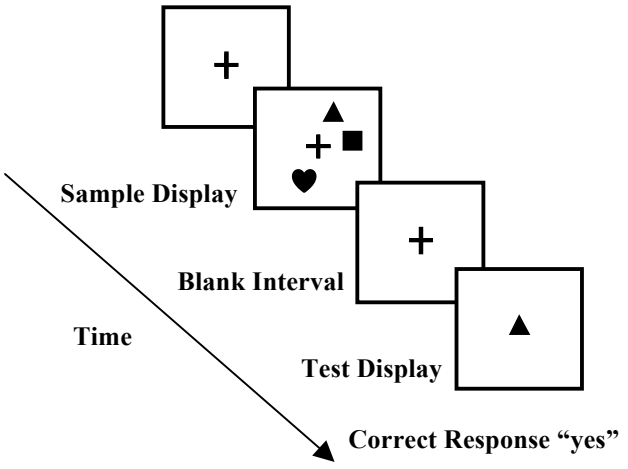

Figure 1. The display sequence of a VWM task.

Luck and Vogel (1997; see also Phillips, 1974; Vogel, Woodman & Luck, 2001). The task is initiated by a sample display, which presents the stimuli to be stored in VWM. After a brief post-stimulus time interval, a memory test display is presented. The participant then indicates whether the VWM test probe presented in the memory test display matched or did not match one of the items in the sample display. On half of the trials, the test probe matches and the other half of the trials the test probe does not match one of the items in the sample display. The visual selective attention task that was used is a modified version of the flanker task (Eriksen & Eriksen, 1974; Tapia, Breitmeyer & Broyles, 2011). As illustrated in Figure 2, in the initial display, two flankers (distractors) are presented followed by a brief blank interval, which in turn, is followed by a target display. The target is always positioned halfway in between the locations of the prior flankers, and participants are required to identity the flanker as rapidly and accurately as possible. The VWM and visual selective attention tasks were performed concurrently in order to examine if and how maintaining information in VWM affected visual selective attention and, conversely, if and how a visual selective attention task affected maintenance of information in VWM.

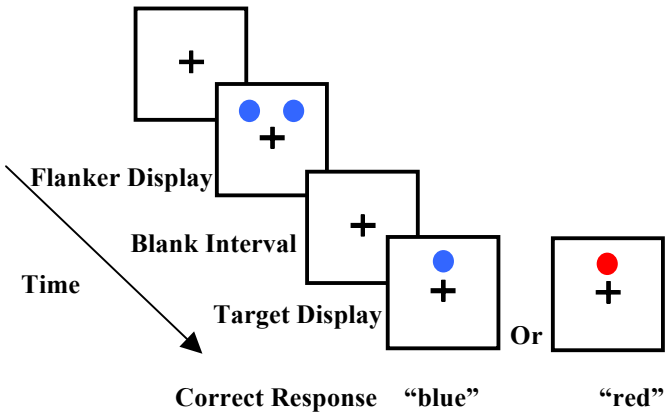

Figure 2. Example of the temporal display sequence in the color flanker task when targets are congruent (blue) and incongruent (red) with the flanker. Similar sequence was used in the shape flanker task.

Each trial of the dual-task consisted of the following sequence (for an example, see Figure 3): a blank display was presented for 800 ms, followed by a 500 ms VWM sample display that contained three items that the participant had to hold in VWM. After the VWM sample display, a blank display was presented for 1000 ms, followed by the flanker task. A flanker display was presented for 33 ms, followed by a blank display for 67 ms, followed in turn by the 50-ms target display. The duration of the flankers, blank display, and target displays were selected to ensure the target display would be presented 67 ms after the onset of the flankers display, as previous flanker studies showed that interference effects are present maximally when flankers precede the target by 50-100 ms (Eriksen & Eriksen, 1974; Eriksen & Schultz, 1979; Flowers & Wilcox, 1982; Tapia, Breitmeyer & Broyles, 2011). Participants then were required to identify the target by pressing one of two designated keys

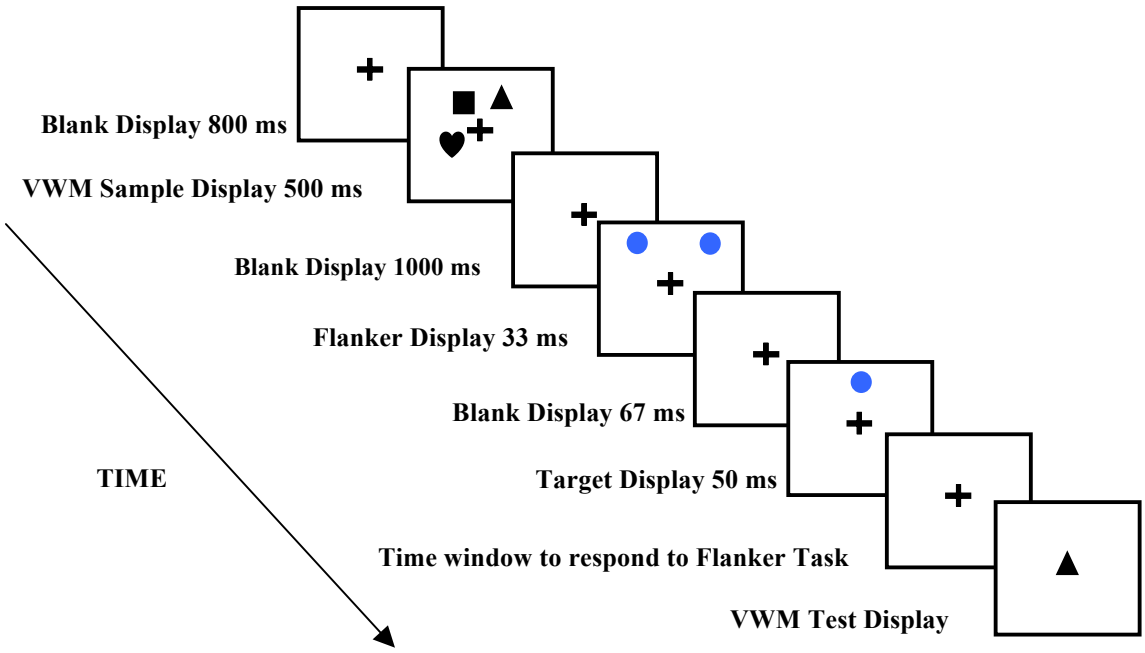

Figure 3. Example of the temporal display sequence of the dual-task. Here a between-category condition with a shapes VWM task and a colors flanker task is illustrated. Similar sequence is used in the other three conditions (within-category: shape-shape, color-color; and between-category: color-shape, location-color, location-shape).

on a keyboard as quickly and accurately as possible. On half of the trials the flankers and target were congruent and the other half of the trials they were incongruent. After a response to the flanker task, a VWM test probe was presented until the participant's response. Here, participants were required to indicate whether or not the test probe matched an item in the initial VWM display by pressing one of two designated keys on a keyboard. No time pressure was imposed on the response in the VWM task.

Six conditions were used to assess different information categories (see Figure 4). All six conditions were implemented in the dual-task paradigm. There were two conditions where the information category being maintained in VWM was the same as the information category being processed in the flanker task. Condition 1 had a color VWM task combined with a color flanker task and Condition 2 had a shape VWM task combined with a shape flanker task. There were four conditions where the information category being maintained in VWM was different from the information category being processed in the flanker task. That is, Condition 3 contained a color VWM task combined with a shape flanker task. Condition 4

	VWM Task	**Flanker Task**
Cond. 1	Color	Color
Cond. 2	Shape	Shape
Cond. 3	Color	Shape
Cond. 4	Shape	Color
Cond. 5	Location	Color
Cond. 6	Location	Shape

Figure 4. The six dual-task conditions.

had a shape VWM task combined with a color flanker task. Condition 5 had a location VWM task combined with a color flanker task. Condition 6 included a location VWM task combined with a shape flanker task. Each condition was composed of 4 types of trials. This is

because the VWM task was composed of 'yes' and 'no' trials. A 'yes' trial is when the VWM test probe matched an item of the VWM sample display and a 'no' trial is when the VWM test probe did not match any item in the VWM sample display. The flanker task, requiring the participants to identify the target, was composed of 'congruent' and 'incongruent' trials. A 'congruent' trial was when the target was the same as the flankers and a 'incongruent' trial occurred when the target and flankers differed. Thus, resulting in four types of trials: (1) a 'yes' trial in the VWM task and an 'incongruent' trial in the flanker task, (2) a 'yes' trial in the VWM task and a 'congruent' trial in the flanker task, (3) a 'no' trial in the VWM task and an 'incongruent' trial in the flanker task, (3) a 'no' trial in the VWM task and a 'congruent' trial in the flanker task. These trials ensured that all possible combinations of the VWM task and flanker task were tested. Participants also ran in three corresponding single-task (color, shape, location) VWM control conditions and two single-task (color, shape) flanker conditions. All eleven conditions were counterbalanced across participants to ensure against order effects.

Procedure

Pediatric ALL survivors were recruited through the Texas Children's Cancer Center Long-Term Survivor (LTS) Program. The non-cancer controls were recruited through the Cognitive Development Lab at the University of Houston. There was a total of nine measures that the pediatric ALL survivors completed including the experimental dual-task paradigm. The additional eight measures were part of a broader study investigating working memory and attention on math outcomes in survivors of ALL. The non-cancer controls only completed the experimental dual-task paradigm. Parents/guardians of both the pediatric survivors of ALL and non-cancer controls were asked to complete a questionnaire that

collected key demographic information. At the end of the session, the pediatric survivors of ALL were compensated with a $100 gift card to Amazon and the non-cancer controls were compensated with a $5 gift card to Target.

RESULTS AND DISCUSSION

VWM Tasks: Storage Estimates

In subsequent analyses of the VWM tasks, only trials that were correct for the flanker task were included and where reaction times (RTs) in the flanker task were below 100 ms or exceeded 1550 ms were excluded. Hit and false alarm rates (*h* and *f*) were obtained from each participant to compute his/her estimates of VWM storage, *k.* According to Rouder et al. (2011) and Cowan et al. (2013), storage estimates based on probe-appropriate formulae were used. Cowan's (2001) *k* estimate, appropriate for VWM tasks that contain a location probe, i.e., a single test item displayed at one of the randomly selected locations of the VWM sample display, was used to compute storage estimates for the location VWM tasks. Cowan et al.'s (2013) *k* formula was used to estimate storage for color and shape VWM tasks as they both contained a center probe, a single test item displayed at central fixation. Assuming that *N* is the VWM load, i.e., the number of items in a VWM sample display that are to be encoded and stored in VWM, the following are the probe-appropriate formulae used to compute the estimates of *k*:

(1) $k = N(h-f)$, appropriate for location probes, according to Cowan (2001);

(2) $k= N(h-f)/h$, appropriate for center probes, according to Cowan et al.(2013).

Correlational analyses were used to examine the relationship between the age of participants and their *k* estimates to determine if a repeated measures ANOVA was the

appropriate procedure to evaluate statistical effects on *k* estimates. Results indicated there was no significant correlation between age and *k* estimates for all participants (one-tailed, r (55) = .17, p >.108) and separately there was no significant correlation between age and each of the groups: low-risk survivors (one-tailed, r (20) = .09, p >.346), high-risk survivors (one-tailed, r (15) = -.001, p >.498), and non-cancer controls (one-tailed, r (16) = .34, p >.083). Since, significant correlations between age and VWM *k* estimates were not obtained, a

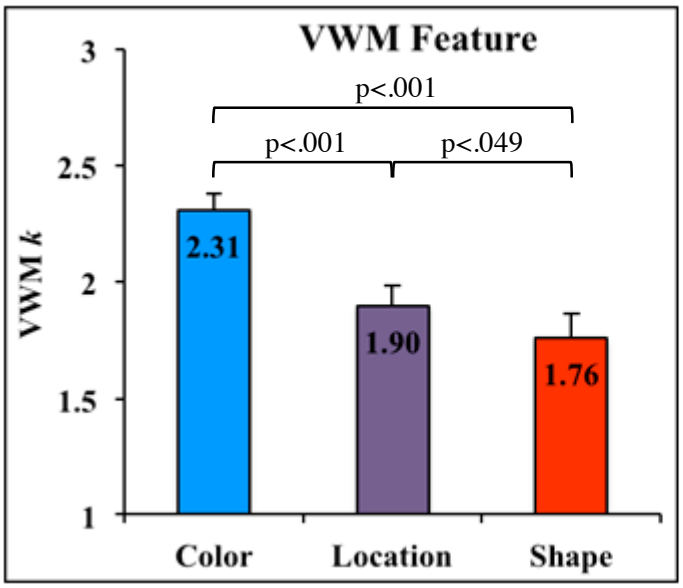

Figure 5. VWM storage estimates (*k*) as a function of VWM feature (color, location, shape).

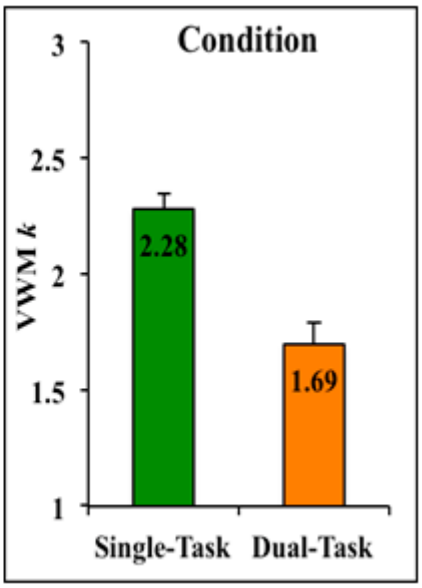

Figure 6. VWM storage estimates (*k*) obtained as a function of task condition (single-task, dual-task).

repeated-measures ANOVA was performed on *k* estimates, with group (non-cancer controls, low-risk, high-risk) as the between-subjects factor and VWM feature (color, location, shape), task condition (single-task, dual-task), and flanker feature (color, shape) as within-subjects factors. The ANOVA revealed significant main effects of VWM feature ($F(2,108) = 29.91$, $p < .001$, $\eta^2 = .12$) and task condition ($F(1,54) = 85.95$, $p < .001$, $\eta^2 = .19$; see Figure 6). For the main effect of VWM feature (see Figure 5), the highest *k* value was obtained for color VWM (2.31), followed in order by location VWM (1.90) and shape VWM (1.76). Follow up

paired-comparison t-tests revealed significant differences between mean *k* values for all three comparisons: obtained for color - location (one-tailed $t(56) = -7.42$, $p < .001$), color - shape (one-tailed $t(56) = -7.13$, $p < .001$), and location - shape VWM (one-tailed $t(56) = -1.69$, $p < .049$).

The two-way interaction between VWM feature and flanker feature ($F(2,108) = 6.80$, $p < .003$, $\eta^2 = .01$), as well as the three-way interaction between task condition, VWM feature, and flanker feature ($F(2,108) = 6.80$, $p < .003$, $\eta^2 = .01$) were significant. Illustrated in Figure 7, is the significant three-way interaction between task condition, VWM feature and flanker feature. As expected, VWM performance was generally superior in the single-task than in the dual-task condition. Moreover, follow up paired-comparison t-tests on the interaction between mean *k* values obtained for color and shape flanker tasks when color items are being maintained in VWM, reveal there is a significant difference between *k* values, with lower estimates for a concurrent color flanker task compared to a shape flanker

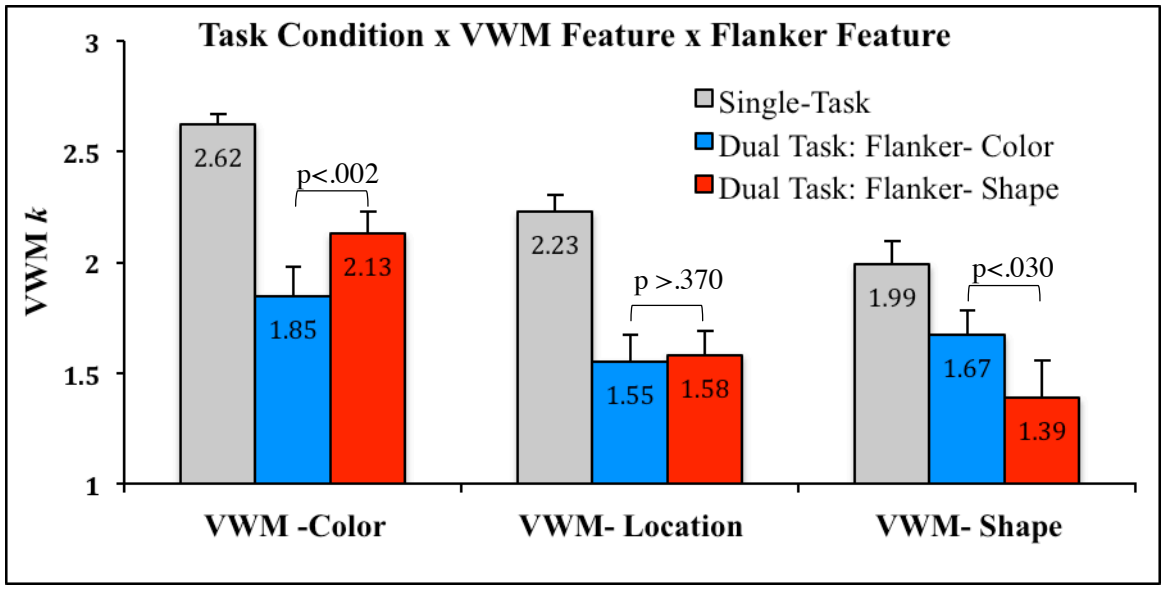

Figure 7. VWM storage estimates (*k*) obtained as a function of task condition for color VWM (left panel), for location VWM (middle panel), and for shape VWM (right panel).

task (one-tailed $t(56) = 3.22$, $p < .002$). A similar, but reverse effect is also demonstrated when shape items are maintained in VWM; here *k* estimates are lower when a concurrent shape flanker task is being performed compared to a color flanker task (one-tailed $t(56) = -2.07$, $p < .030$). However, when location information is being maintained in VWM, VWM *k* is not differentially affected by the shape or color flanker task (one-tailed $t(56) = 0.34$, $p > .370$). According to hypothesis H1 attention to a flanker task can, and here does, interfere with a concurrent VWM task but only as long as according to hypothesis H4 the concurrent VWM and flanker tasks access a common source of cognitive resources. More specifically, the above results indicate, as is reasonably expected by hypotheses H1 and H4, a) that attention to a given (color or shape) feature in the flanker task interferes more strongly with retention of the same (color or shape) feature than with retention of a different (shape or color) feature in VWM, and b) that attention to a (color or shape) feature in the flanker task does not interfere differentially with retention of the VWM location since both flanker features differ from the VWM location feature.

Flanker Tasks: Flanker Effect & Proportion Correct

For analyses of flanker effects, only trials that were both correct for the VWM task and flanker task were included and flanker trials that were below 100 ms or exceeded 1550 ms were excluded. Flanker effects were computed as the difference between incongruent RTs and congruent RTs. Correlational analyses were used to examine the relationship between the age of participants and flanker effects and whether a repeated-measures ANCOVA was an appropriate method to assess flanker effects. No correlation was found between age and flanker effects for all participants (one-tailed, $r(55) = -0.16$, $p > .119$), low-risk survivors (one-tailed, $r(20) = -0.10$, $p > .331$), high-risk survivors (one-tailed, $r(15) = -0.10$, $p > .344$),

and for non-cancer controls (one-tailed, r (16) = -0.25, p >.157). Since, no significant correlations were found between age and flanker effects, a repeated-measures ANOVA was performed on flanker effects, with group (non-cancer controls, low-risk, high-risk) as the between-subjects factor and task condition (single-task, dual-task), VWM feature (color,

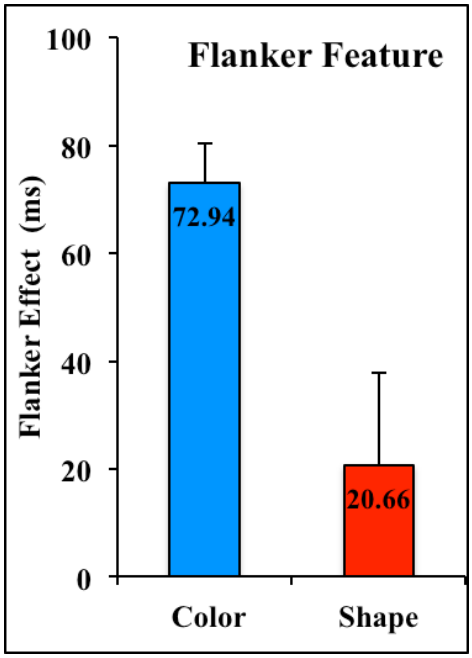

Figure 8. Flanker effects as a function of flanker feature (color,

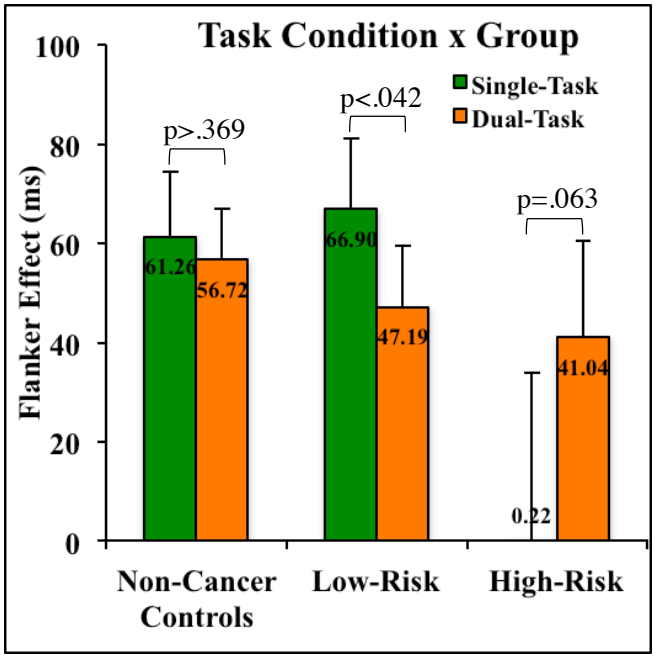

Figure 9. Flanker effects as a function of flanker tasks (single, dual) for non-cancer controls (left panel), low-risk ALL survivors (middle panel), and high-risk ALL survivors (right panel).

location, shape), and flanker feature (color, shape) as within-subjects factors. Only the main effect of flanker feature ($F(1,54) = 8.75$, $p < .006$, $\eta^2 = .05$) and the two-way interaction between task condition and group was significant ($F(2,112) = 3.46$, $p < .039$, $\eta^2 = .01$). Figure 8 and Figure 9 depict, respectively, the main effect of flanker feature and the interaction between task condition and group. For the two-way interaction between task condition and group, follow up paired-comparison t-tests were performed between mean flanker effects of single-task and dual-tasks for each group: for non-cancer controls the slightly higher flanker effect for single task than the dual tasks did not differ significantly

(one-tailed t(17) = -0.33, p > .369); but as expected from hypothesis H5, for the low-risk survivors flanker effects were significantly higher for the single task than the dual tasks (one-tailed t(21) = -1.81, p < .042); and for the high-risk group an unexpected *lower* flanker effect in the single task than the dual tasks approached statistical significance (one-tailed t(21) = -1.81 (one-tailed t(16) = 1.60, p = .063).

In the following analyses of the proportion of correct responses in the flanker tasks, only trials that were correct for the VWM task and for which RTs were between 100 ms and 1550 ms were included. Correlational analyses were used to examine the relationship between the age of participants and the arcsine transforms of the proportions of correct responses for the flanker tasks, as well as the appropriateness of using a repeated measures ANOVA to analyze the arcsine transforms. Results indicated there was no correlation between age and proportion correct for all participants (one-tailed, r (55) = -0.06, p >.324), low-risk survivors (one-tailed, r (20) = -0.03, p >.439), high-risk survivors (one-tailed, r (15) = -0.28, p >.136), and for non-cancer controls (one-tailed, r (16) = 0.03, p >.446). Since, no significant correlations were obtained between age and the arcsine transforms of the proportions of correct responses, a repeated-measures ANOVA was performed on the arcsine transforms for the flanker tasks, with group (non-cancer controls, low-risk, high-risk) as the between-subjects factor and task condition (single-task, dual-task), VWM feature (color, location, shape), and flanker feature (color, shape) as within-subjects factors. The ANOVA revealed a main effect of VWM feature ($F(2,108) = 4.75$, $p < .010$, $\eta^2 = .01$) and the interaction between task condition and VWM feature ($F(2,108) = 4.75$, $p < .010$, $\eta^2 = .01$) was significant. Figure 10 depicts the main effect of VWM feature on the obtained proportion correct responses in the flanker task. For this main effect, follow-up paired-

comparison t-tests between mean proportion correct values obtained for the three VWM tasks revealed: a larger proportion correct when location information is being maintained in VWM compared to when either color information (one-tailed $t(56) = 2.73$, $p < .005$) or shape information (one-tailed $t(56) = -3.37$, $p < .001$) is being maintained; but no difference in proportions correct when shape or color items were held in VWM (one-tailed $t(56) = -0.10$, $p > .460$). These results are in agreement with hypothesis H2, stating that a VWM task can interfere with the visual selective attention task, and with hypothesis H4, according to which interference is less if the two tasks do not share a common source of cognitive resources.

The group effect was also significant ($F(2,54) = 3.76$, $p < .031$, $\eta^2 = .12$) (see Figure 11). For the significant group effect, follow up independent-samples t-tests were performed between mean proportion correct values of the three groups: as would be expected from hypothesis H5, the non-cancer controls had a significantly higher flanker proportion correct than both the low-risk (one-tailed $t(38) = 2.618$, $p < .007$) and high-risk group (one-tailed

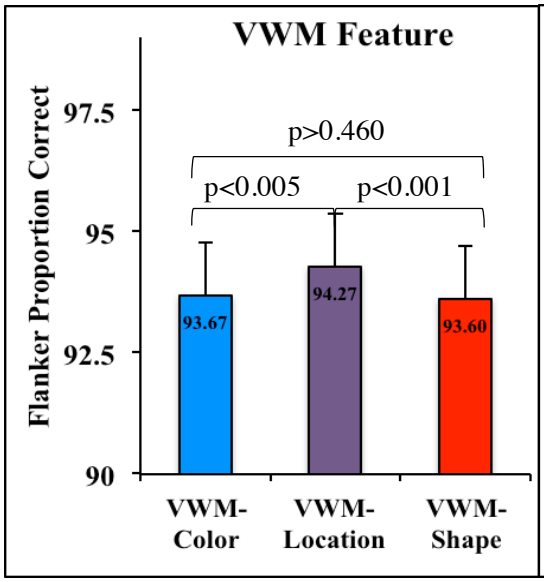

Figure 10. Proportion correct in the flanker task as a function of VWM feature.

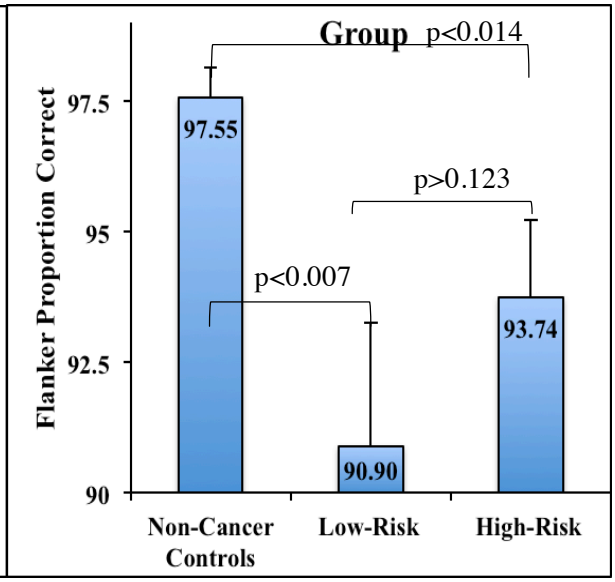

Figure 11. Proportion correct in the flanker task as a function of participant group.

t(33) = 2.32, p < .014); and the unexpected higher flanker proportions correct for the high-risk group did not differ significantly from the lower proportions correct obtained by the low-risk group (one-tailed t(37) = -0.71, p > .123).

GENERAL DISCUSSION

The current study examined if and how visual selective attention (i.e., flanker task) and VWM tasks might influence each other, and how these influences might differ among pediatric ALL survivors at low and high-risk for neurocognitive impairments based on their treatment protocols and non-cancer controls. Based on a reasonable assumption of limited cognitive resources, we entertained three global hypotheses of how the two tasks might influence each other: 1) a visual attention task should interfere with a concurrent VWM task; 2) a VWM task should interfere with a concurrent visual attention task; 3) the two tasks mutually interfere with each other; 4) the degree of interference depends on the degree to which the two tasks share cognitive resources. Moreover, we hypothesized that if there is some sort of interference, 5) it should be strongest in pediatric ALL survivors that have a high-risk for neurocognitive deficits, weaker in survivors having a low-risk for neurocognitive deficits, and weakest in non-cancer controls. Below we first address hypothesis H1-H4 before we address hypothesis H5.

Overall VWM and Visual Selective Attention Task Effects

Averaged across groups, overall VWM storage estimates, *k*, reveal maintenance of information in VWM is susceptible to interference from a concurrent flanker task. This is reflected in the significant main effect of task condition, which shows a lower VWM *k* estimate when both a VWM task and a flanker task are performed concurrently as compared

to a single VWM task (see Figure 6). This finding could be consistent with either hypothesis H1, according to which the flanker task unidirectionally interferes with a concurrent VWM task or H3, according to which the flanker and concurrent VWM task mutually or and bidirectionally interfere with each other. These interference effects were also found to be feature specific, as evidenced by the significant three-way interaction between task condition, VWM feature, and flanker feature (see Figure 7). This demonstrates that when concurrent VWM and selective-attention tasks are processing information from the same visual information category (i.e., color or shape) and thus maximally share common limited cognitive resources a decrease in VWM *k* values is found compared to VWM *k* values obtained when information from different categories are being processed, thus minimally sharing common cognitive resources. This finding would be consistent with either of the above two hypotheses H1 and H3 in combination with hypothesis H4, according to which storing and attending to information from the same visual information category taps into common limited cognitive resources available for that particular category, whereas storing and attending to information from different visual information categories taps into separate limited cognitive resources. This conclusion in turn is consistent with the findings showing that VWM maintenance of spatial location and spatial selective attention in healthy adults shares the same neural pathways (Awh & Jonides, 2001; Chun, Golomb & Turk-Browne, 2011; Gazzaley & Nobre, 2012; Ikkai & Curtis, 2011; Mayer et al., 2007; Silk et al., 2010). A reasonable extrapolation of these findings could thus generalize to neural pathways being shared between visual attentional and VWM tasks when color or shape is the relevant shared feature to be processed in the two tasks.

Overall, feature-specific effects were found, with color VWM tasks yielding the highest *k* values, followed by lower *k* values in location VWM tasks, and the lowest *k* values in shape VWM tasks (see Figure 5). This color-superiority effect, well documented with healthy adults, is characterized by a significant superior VWM performance for colored items as compared to shape items (Alvarez & Cavanagh, 2004; Awh, Barton & Vogel, 2007; Eng, Chen & Jiang, 2005; Song & Jiang, 2006; Woodman & Vogel, 2008). This may be due to the fact that shape stimuli used in the current and previous studies are more complex than color stimuli and thus carry a higher information load (Alavarez & Cavanagh, 2004).

Conversely, to assess hypotheses H2, according to which a VWM task can unidirectionally interfere with a concurrent visual attention task, and H3, according to which the interference is bidirectional or mutual, we also investigated the effect of VWM maintenance on visual selective attention allocated to the flanker task. Collapsed across groups, the overall flanker effect and proportion correct revealed that a VWM task did not interfere with a concurrent visual selective attention task as variation of task condition overall did not significantly affect the magnitude of flanker effect ($F(1,54) = 0.31$, $p > .580$, $\eta^2 = .00$) and the arcsine transforms of the proportions of correct responses ($F(1,54) = 0.01$, $p > .936$, $\eta^2 = .00$). This could be taken as evidence that hypothesis H2 and by extension hypothesis H3 are disconfirmed (but see below).

Regarding visual selective attention allocated to the flanker task, the significant main effect of flanker feature on flanker effects revealed a larger flanker effect for colors than for shapes (see Figure 8). This again might relate to the color-superiority effect. Here, two possible factors may singly or in combination contribute to this finding: 1) processing of color, being a simple feature and easy to encode, is more susceptible to the incongruency

effects in the flanker task and thus yields a greater flanker effect than does the processing of shape, which is less susceptible to inconguency effects; or 2) overall higher RTs, in this case for shape, are correlated with lower flanker effects. Regarding the latter possible factor, a correlation analysis was performed on the differences between RTs for the shape and color stimuli and corresponding differences between flanker effects. We based this approach of the following rationale: higher differences between shape and color RTs should correlate negatively with lower differences in corresponding flanker effects. Results indicate that although the correlation was negative as expected, it was not significantly different from zero (one-tailed, $r(55) = -0.14$, $p > .141$). Thus, failing to support a significant contribution of the second factor and leaving the hypothesis that the color feature is easier to encode and consequently the major contributor to stronger incongruency effects for colors than for shapes.

In contrast to the lack of evidence in support of hypothesis H2 provided by analysis of flanker effects, a more extensive analysis of proportion correct responses in the flanker task in terms of feature-specific − rather than overall (see above) − effects does support hypothesis H2 and by extension hypothesis H3. Investigating further possible effects of a VWM task on a concurrent selective-attention task, the main effect of VWM feature on proportion correct responses in the flanker task demonstrates there indeed were feature-specific effects of a VWM task on the concurrent flanker task (see Figure 10). An overall higher proportion correct was found for flanker tasks performed concurrently with a location VWM task compared to being performed with either a concurrent color or shape VWM task. Thus, the results indicate, as expected, that in comparison to maintaining color or shape information in VWM, maintaining location information in VWM interferes less with color or

shape attentional processing. This finding does support hypotheses H2 or H3. However, the contradictory inferences drawn in relation to hypotheses H2 or H3 when looking jointly at analysis of proportion correct responses and the above analysis of flanker effects awaits future study to resolve the apparent inconsistency one way or the other.

Group Effects on VWM and Visual Selective Attention Tasks

Maintenance of information in VWM was found to be equally susceptible to interference from visual selective attention, regardless of group. This is supported by the fact that the group factor failed to interact significantly with any other factor or combination of factors. In contrast, analyses of flanker effects and proportion correct response in the flanker tasks revealed that VWM tasks affected concurrent visual selective attention tasks differently across groups. The significant two-way interaction of task condition and group on flanker effects demonstrates that only the low-risk group was significantly vulnerable to interference from a concurrent VWM task, whereas the high-risk group unexpectedly benefitted, via a nearly significant enhancement of flanker effects, from a concurrent VWM task (see Figure 9, middle and right panels). Why this was so is not clear, since on the basis of hypothesis H5 one might have expected that the high-risk group of subjects would be most vulnerable to interference, rather than enjoy a beneficial enhancement, from a concurrent VWM task. The significant group effect on proportion correct values of flanker tasks reveal non-cancer controls obtained a higher proportion correct compared to both low-and high-risk groups that in turn did not differ from each other (see Figure 11). Accordingly, only for the low-risk group did both a VWM task and a visual selective attention task mutually interfere with each other, whereas for both the high-risk group and the non-cancer controls a visual selective attention task interfered with a concurrent VWM task but not vice versa.

Implications for Future Studies

Both VWM maintenance and visual selective attention process information distinctively along spatial, object-based, or feature-based lines (Brefczynski & DeYoe, 1999; Fougnie, Asplund & Marois, 2010; Gandhi, Heeger & Boynton, 1999; Olson & Jiang, 2002; Pasupathy & Connor, 1999; Rossi & Paradiso, 1995; Saenz, Buracas & Boynton, 2002; Scholl, 2001; Smith et al., 1995; Somers et al., 1999). According to Treisman's (1980) theory of feature integration, simple features or visual primitives, e.g., color, orientation, spatial frequency, brightness, direction of movement, are first processed pre-attentively followed by the attention-demanding integration of features that lead to the perception of whole objects. The current study used spatial information (location), simple feature-based information (color), and object- or shape-based information, i.e., conjunctions of simple orientation features or curvature features, to be processed in both VWM and visual selective attention. Future studies can use different combinations of spatial, object-, and feature- based information to provide a more thorough understanding of how information categories affect the relationship between VWM and visual selective attention. For example, how object-based information that is a combination of color and orientation and simple feature-based information of brightness could be used to study how visual selective attention and VWM tasks interact. Additionally, the current study did not use spatial selective attention; whereas future studies can implement a visual search task, which contains a spatial processing component (Treisman & Gelade, 1980). Figure 12 illustrates a possible future study utilizing, as examples, color and orientation object-based information, feature-based brightness information, and spatial location in nine possible dual-task combinations of spatial, object-, and feature- based information categories. Of the possible combinations, the highest degree

of interference is expected between the same information categories processed in both VWM and visual selective attention (see the shaded entries: e.g., a spatial VWM task performed currently with a search task relying on spatial selective attention). Such research might first be conducted on typically developing participants to obtain "baseline" results, and then also used in studies of survivors of pediatric ALL, as this paradigm would be sensitive to measure highly specific aspects of attention and working memory.

The reasoning underlying the possible research scheme shown in Figure 12 highlights the important role of what information categories are available to VWM and concurrent visual-attention tasks. It also cautions future (and past) research to be (have been) mindful of the information categories being implemented. For example, Hollingworth and Maxcey-Richard (2013) reported that, in healthy adults, attention is not required for selectively

	Spatial VWM	**Object VWM**	**Feature VWM**
Spatial Attention	VWM: Spatial Locations Attention: Search Task	VWM: Orientation&Color Attention: Search Task	VWM: Brightness Attention: Search Task
Object Attention	VWM: Spatial Locations Attention: Orientation/Color	VWM: Orientation&Color Attention: Orientation&Color	VWM: Brightness Attention: Orientation&Color
Feature Attention	VWM: Spatial Locations Attention: Brightness	VWM: Orientation&Color Attention: Brightness	VWM: Brightness Attention: Brightness

Figure 12. Possible combinations of visual selective attention and VWM tasks based on object-, feature-, or spatial features. Shaded regions denote expected highest degree of interference.

maintaining information in VWM, since they found that maintaining non-spatial information (i.e., color) in VWM while concurrently performing a visual search task relying on spatial attention produced no interference effects. However, in their study the VWM task required maintaining color information in VWM, which therefore taxed the cognitive resources of non-spatial VWM. Consequently this task, according to the above rationale, did not interfere

with the spatial information processing required during the visual search task. One could therefore conjecture that selective maintenance of non-spatial (i.e., color) VWM might not depend on spatial attention; whereas, the selective maintenance of spatial information in VWM may depend on spatial attention. Recently, Treviño, Breitmeyer, and Jacobs (2016) tested this conjecture and found that maintaining spatial information in VWM is impaired by a concurrent visual search task, but only when the VWM probe that was used forced participants to rely on spatial information being stored in VWM. Treviño, Breitmeyer, and Jacobs's (2016) study, as well as the current study emphasize the important influence information categories can have on the relationship between VWM and visual selective attention.

APPENDIX A

Hill et al. (2004) evaluated visual and verbal long-term memory in ten survivors of pediatric ALL that ranged in age from 7-14 years at the time of testing and ten matched-controls (matched on age, gender, handedness, school grade, and SES). During treatment, survivors received the following chemotherapy agents: cytosine arabinoside, hydrocortisone, and intrathecal methotrexate. The Wide Range Assessment of Memory and Learning (WRAML), a standardized psychometric measure, was used to assess memory functioning with the following subtests: Delayed Recall of Story Memory, Verbal Learning, and Visual Learning. The Rey-Osterrieth Complex Figure was administered to assess visual-spatial memory and organization. No differences were reported between survivors and matched-controls on all measures (Hill et al., 2004). Thus, memory functioning (long-term memory and visual-spatial memory) was found to be intact among survivors of pediatric ALL.

The neurocognitive functions of processing speed, working memory, and sustained attention are reported to be unaffected following chemotherapy-only treatment protocols (Spiegler, et al., 2006). These functions were assessed in 54 survivors of ALL. Survivors were classified into two groups that differed on the dose of methotrexate they received during treatment. Thirty-two participants (average age at testing: 13.3 ± 2.7) received a high-dose of intravenous methotrexate (8 g/m^2 x 3 doses) and 22 participants (average age at testing: 13.8 ± 3.2) received a very-high dose of intravenous methotrexate (33.6 g/m^2 x 3 doses). Participants completed tests of intelligence (Wechsler Intelligence Scale for Children-III [WISC-III], Wechsler Adult Intelligence Scale-III [WAIS-III]), academic achievement (Wide Range Achievement Test, 3rd Edition), attention (Gordon Diagnostic System) and memory (Children's memory Scale, Wechsler Memory Scale-III). There were no differences on any

measure between children treated with a high-dose or a very high-dose of intravenous methotrexate. Additionally, there were no differences between the combined group of high-dose and very high-dose relative to normative population means (Spiegler et al., 2006).

In contrast, other studies have observed survivors showing neurocognitive impairments following current protocols that comprise of only chemotherapy. Robinson et al. (2010) identified impairments of memory and executive functioning among survivors. Eight survivors of pediatric ALL (average age: 14.07 ± 2.32 years) had received an average dose of 174.9 mg of intrathecal methotrexate and an average dose of 70.0 mg of intrathecal Ara-C. Survivors and seven controls, matched for age and gender, completed the Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV) to measure overall neurocognitive functioning, including general intelligence, working memory, and processing speed. The Delis-Kaplan Executive Function System (D-KEFS) was administered to assess verbal and nonverbal executive functions and a visual N-back task was used to measure working memory. Survivors were found to perform more poorly on measures of overall neurocognitive functioning, working memory, processing speed, and subtests of the D-KEFS (Color Word Interference Test that measures the ability to inhibit a dominant and automatic verbal response and the Sorting Test subtest that measures concept-formation skills, modality-specific problem-solving skills (verbal/nonverbal), and the ability to explain sorting concepts abstractly) compared to controls. However, there were no differences between groups on the N-back task assessing working memory in terms of accuracy and RT.

Impairments of sustained attention have been reported among survivors of ALL treated with chemotherapy-only protocols (Ashford, et al., 2010; Conklin et al., 2012; Krull et al., 2013). Krull et al. (2013) assessed 243 survivors (average age at testing: 20.9 ± 5.5

years) that were assigned to either a low-risk (n=126) or a standard/high-risk (n=117) treatment protocol. Low-risk treatment protocols included 13-18 intrathecal treatments with methotrexate, hydrocortisone, and cytarabine. Additionally, low-risk survivors received intravenous methotrexate (2.5 gm/m^2 x 4 doses) and dexamethasone (8mg/m^2 for 5 days). Standard/high-risk treatment protocols included 16 to 25 intrathecal injections, intravenous methotrexate (5.0 gm/m2 x 4 doses) and dexamethasone (12mg/m2 for 5 days). Survivors were assessed on general intelligence (WISC-III, WAIS-III), processing speed (processing speed index from WISC-III or WAIS-III), working memory (Freedom from Distractibility Index from WISC-III or WAIS-III), and sustained attention (Conners' Continuous Performance Test [CPT]). Impairments were only found within sustained attention when compared with national norms. Survivors were reported to be more inattentive, had a slower response speed, and had higher variability on the Conners' CPT (Krull et al., 2013).

Conklin et al. (2012) evaluated 243 survivors (average age at testing: 8.86 ± 4.39) on measures of general intelligence (Wechsler Preschool and Primary Scale of Intelligence-Revised, WISC-III, WAIS-III), attention, processing speed (Freedom from Distractibility and Processing indices from WISC-III), sustained attention (Conners' CPT), learning, and memory (California Verbal Learning Test [CVLT-Child, CVLT-Adult]). One hundred and twenty-six of the 243 participants were classified as receiving a low-risk treatment protocol that consisted of 13 to 18 treatments and lower doses the chemotherapy agents of methotrexate (11.68 g/m^2) and dexamethasone (10008.18 mg/m^2). One hundred and seventeen of the 243 participants were classified as receiving a standard/high-risk treatment protocol that consisted of 16 to 25 treatments and higher doses of chemotherapy agents of methotrexate (18.61 g/m^2) and dexamethasone (1212.61 mg/m^2). Low-risk patients

performed better than standard/high risk patients on general intelligence and processing speed measures (Full Scale Intelligence Quotient [FSIQ], Freedom from Distractibility Index [FDI], and the Processing Speed Index [PSI]). Both groups showed impairments on sustained attention when compared to normative expectations (Conklin et al., 2002).

Attention and working memory functions were assessed following current chemotherapy-only protocols among 97 survivors (average age at testing: 10.84 ± 3.93) (Ashford et al., 2010). Survivors were classified as either having received a low-risk treatment protocol (n=48) or a standard/high risk treatment protocol (n=49). A low-risk protocol included 13 to 18 treatments that included lower doses of methotrexate (2.5 g/m^2 x 4 doses) and dexamethasone (8 mg/m^2) compared to the standard-high risk protocol of 16 to 25 treatments of methotrexate (5.0 g/m^2 x 4 doses) and dexamethasone (12 mg/m^2). Participants were administered an age appropriate Wechsler Intelligence Scale (WISC-III, WAIS-III) to assess general intelligence, the Digit Span Forward subtest to measure attention and immediate recall, and the Digit Span backward subtest for verbal working memory. The standard/high-risk group showed impairments on the Digit Span Forward subtest compared to the normative population. Both the low-risk and standard/high-risk group performed poorly on the Digit Span Backward subtest as compared to the normative population, consequently illustrating that working memory (as measured by DSB) might be vulnerable following current chemotherapy-only protocols.

FOOTNOTES

[1] Fractional anisotropy is a measure of directional connectivity in the brain; the degree of directionality of diffusion of water molecules along fiber tracts. Its values range from 0 (no directional dependence of the diffusion) to 1 (diffusion along a single direction) (Schimrigk et al., 2007).

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