

# Brain volume and cognitive function in adult survivors of childhood acute lymphoblastic leukemia

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**Abstract:** The survival rate for childhood acute lymphoblastic leukemia (ALL) is greater than 80%. However, many of these survivors develop long-term chronic health conditions, with a relatively common late effect being neurocognitive dysfunction. Although neurocognitive impairments have decreased in frequency and severity as treatment has evolved, there is a subset of survivors in the current treatment era that are especially vulnerable to the neurotoxic effects of ALL and its treatment. Additionally, little is known about long-term brain development as survivors mature into adulthood. A recent study by Zeller *et al.* compared neurocognitive function and brain volume in 130 adult survivors of childhood ALL to 130 healthy adults matched on age and sex. They identified the caudate as particularly sensitive to the neurotoxic effects of chemotherapy. We discuss the implications and limitations of this study, including how their findings support the concept of individual vulnerability to ALL and its treatment.

**Keywords:** Magnetic resonance imaging (MRI); neurocognitive; chemotherapy; acute lymphoblastic leukemia (ALL); late outcomes

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The 5-year survival rate for childhood acute lymphoblastic leukemia (ALL) has improved from 5% in the 1960s to more than 80% today (1). A significant part of this improved survival is due to prophylactic treatment of the central nervous system (CNS). However, survival following this treatment has a cost, namely in contributing to long-term chronic health conditions. Recently, this has become readily apparent in long-term adult survivors of childhood ALL. Adult survivors of childhood leukemia have a fourfold relative risk for having a severe or life-threatening health condition when compared to siblings of cancer survivors (2). Survivors of ALL appear to be at greatest risk for cardiac, endocrine, metabolic, and neurocognitive dysfunction (3). These consequences have decreased in frequency and severity as prophylactic treatment of the CNS has moved from radiation therapy to intrathecal (IT) chemotherapy. However, neurocognitive impairment is still estimated to occur in 20-40% of survivors of childhood ALL treated

with chemotherapy only (4). Difficulties in processing speed, attention, and working memory have been identified as particular weaknesses (5). Poor neurocognitive outcomes have been found in survivors treated with IT or high-dose intravenous methotrexate (HD-IV) as well as dexamethasone (6,7).

Chemotherapy treatment for childhood ALL is associated with neuroanatomical abnormalities. Reddick and colleagues used magnetic resonance imaging (MRI) of the brain to prospectively examine the prevalence of abnormal white matter in children undergoing chemotherapy for ALL. The rate of abnormal white matter was 86% shortly after treatment with IT and HD-IV methotrexate. By the end of therapy, the rate of abnormal white matter was reduced to 30% suggesting some white matter abnormalities are transient whereas others are persistent (8). Five-year survivors of ALL treated only with chemotherapy had smaller white matter volumes when compared to matched

healthy controls. These neuroanatomical differences appear to have functional consequences as the volume of white matter in ALL survivors was correlated to performance on sustained attention tasks (9). A similar study found that over 30% of long-term survivors of childhood ALL treated only with chemotherapy had abnormal MRI findings suggestive of brain atrophy (10). Although one small study found reduced white matter volume in ten young adult survivors of childhood ALL treated only with chemotherapy (11), it is largely unclear what happens in the brains of these survivors as they age into latter adulthood.

In the *Journal of Clinical Oncology*, Zeller and colleagues (12) compare neurocognitive function and brain volumes of 130 adult survivors of childhood ALL to 130 healthy adults matched on age and sex. The survivors were diagnosed at Oslo University Hospital, Norway, over a span of 30 years [1970–2002]. The large span of treatment era resulted in a heterogeneous group with about 15% of survivors having a history of relapse, 14% receiving cranial radiation therapy, 2% with transplanted stem-cells, and a wide variation in the administered dose of methotrexate and anthracycline. The healthy comparison group was recruited from two ongoing studies at the Center for the Study of Human Cognition at the University of Oslo. Study participants underwent neurocognitive assessment and brain MRI.

Although there was no difference in global intelligence (i.e., IQ), survivors performed worse than the comparison group in processing speed, executive functioning, and verbal learning/memory tasks. When interpreting these results, there are several issues worth considering. The comparison group had a median of 15 years of education and performed above the norm for each neurocognitive measure suggesting that they might be higher functioning than the general population. Survivors also demonstrated an average estimated IQ that was almost one standard deviation (SD) above the norm. Although the survivors had lower scores than the comparison group in multiple domains, the median score for those measures was no more than a third of a SD below the norm, suggesting relatively mild weaknesses. Their performance in processing speed, executive function, and memory were comparable to levels found in a large study by Krull *et al.* examining adult survivors of ALL treated only with chemotherapy (13). Within that large study by Krull *et al.* (N=567), as well as the Zeller *et al.* study, there was a large amount of variability in neurocognitive performance among survivors. For example, the Zeller study found that the processing speed of some survivors was severely impaired (more than 5 SDs below

the norm) while other survivors performed above average (more than 1.5 SD above the norm) (12). Although the percent of survivors clinically impaired were not reported in the Zeller study, Krull *et al.* (13) found that adult survivors of ALL treated only with chemotherapy performed at impaired rates of about 17% in processing speed, 16% in executive functioning, and 13% in memory as compared to the expected rate of 2% based on an impairment threshold of  $\geq 2$  SDs below the population mean. Results from both studies suggest that some survivors of ALL are at much greater risk for developing neurocognitive late effects, while many other survivors who were treated in a similar manner remain neurologically intact.

Variability in global neurocognitive outcomes after treatment for ALL has been documented for some time. A prospective study conducted in 1991 found that 28% of patients treated only with chemotherapy had clinically significant ( $\geq 1$  SD) declines in verbal and performance intelligence between the beginning of treatment and three years post-treatment (4). A more recent study has found similar variability where about 33% of survivors had a clinically significant decline in performance intelligence, whereas, about 40% of survivors remained stable or even improved (14). Some well-recognized factors that appear to contribute to individual vulnerability include: cumulative dose and intensity of cancer therapy; age at diagnosis; years since diagnosis; and gender (15). The contributions of other factors are beginning to emerge. Polymorphisms related to drug metabolism and oxidative stress have been associated with neurocognitive outcomes in survivors of ALL (16,17). Disrupted sleep and fatigue are known to promote neurocognitive sequelae and about half of long-term survivors of ALL report sleep problems (18). Disrupted sleep in cancer survivors has been associated with polymorphisms that influence inflammatory cytokine expression (19). The association between genetics, disrupted sleep, and neurocognitive late effects suggests that many of the factors contributing to individual vulnerability are a result of complex interactions between the environment, treatment, and inherent patient characteristics. Identifying the factors contributing to these individual vulnerabilities will be critical for understanding the pathophysiology of neurocognitive late effects and should inform future interventions.

In the Zeller *et al.* study (12), adult survivors of ALL had reduced volume of cortical gray and white matter, caudate nucleus, amygdala, and hippocampus when compared to healthy controls. These neuroanatomical volume

differences remained significant even when comparing a subset of survivors who did not receive CRT ( $n=112$ ). When interpreting the neuroimaging data, there are two main points to consider. First of all, survivors of ALL had a smaller intracranial volume (ICV) than the comparison group and ICV is an index of the global brain volume attained following development. After adjusting for ICV, the difference in volume of the caudate nucleus was the only region that remained significantly different between groups. Although it is unclear whether the caudate is particularly vulnerable to cancer treatment, it is one of the areas undergoing the most intense myelination during childhood (20). The caudate seems to play a role in many cognitive processes, including: executive function; attention; learning; and memory (21). However, the difference in ICV makes it challenging to clearly interpret whether other brain regions are differentially affected or whether there is simply mild global differences in brain volume. Evidence suggests that some brain regions might be more susceptible to ALL and its treatment. Previous studies have found that brain regions have temporally distinct maturational trajectories. It appears that higher-order association areas, such as the prefrontal and temporal cortices, only mature after lower-order sensorimotor regions (22). Additionally, imaging conducted in adolescent survivors of ALL found more white matter abnormalities in the frontal regions, suggesting white matter tracts within the frontal lobe may be more susceptible to insults during ALL and its treatment (23). To further investigate potential regional differences, it would be interesting to compare the ratio between a brain region of interest and ICV. The second point that needs consideration is the difficulty in determining the clinical relevance of these neuroanatomical findings. Without adjusting for ICV, there were only very weak ( $r_s < 0.25$ ) correlations between structural changes and neurocognitive performance. This lack of correspondence might, in part, be due to the complexity of the neurocognitive tasks and the large heterogeneous brain regions being correlated. Emerging evidence suggests that how the cortical thickness develops over time is more predictive of functional characteristics than absolute cortical thickness in adulthood (24). Recent advances in imaging, such as diffusion tensor imaging, also provide more sensitive ways to investigate functional consequences of volume differences by measuring integrity of white matter in various networks. Future research using longitudinal data and advanced technology may shed more light onto the functional significance of volume differences.

Although Zeller and colleagues began with the aim of examining associations between cancer treatment and brain volume, it is still unclear how various aspects of the cancer experience contribute to neuroanatomical group differences. No correlations were found between specific drug treatment and brain regions with reduced volume in survivors. To better understand if cancer treatment alters brain structure; it would be important to examine drug-specific contributions to volume differences after adjusting for other treatment variables. As the authors point out, neurotoxic treatment has direct effects on brain volume by killing cells leading to atrophy of gray matter and/or demyelination of white matter (25). However, treatment with multiple agents may also indirectly influence brain structure. Adult survivors of childhood cancer are at risk for many chronic late effects, including: cardiac, pulmonary, and endocrine dysfunction (3). Dysfunction in these organ systems have been linked to neurocognitive difficulties. For example, Hodgkin lymphoma survivors who received thoracic radiation, but no known neurotoxic treatment, were more likely to have impairments in attention, memory, and executive function compared to normative data. Survivors who received  $\geq 30$  Gy of chest radiation were more likely to have white matter abnormalities compared to survivors who received  $< 30$  Gy which suggests that damage to cardiopulmonary systems may in turn damage brain cells. In addition, survivors with cardiac dysfunction were more likely to display poor working memory and efficiency, while survivors with pulmonary dysfunction were more likely to display attention problems (26). Future research is needed to better understand how cancer treatment might disrupt brain integrity and neurocognitive function by promoting chronic disease. This becomes more imperative as the survivor continues to age into adulthood. As the authors point out, there are other factors that may help explain brain volume differences, such as: prolonged periods of reduced health during cancer treatment or long-lasting stress. Adult survivors of ALL report about a fourfold greater risk for post-traumatic stress symptoms when compared to siblings (27). Adolescent survivors of childhood ALL were also more likely to report symptoms of depression and anxiety when compared to siblings (28). Posttraumatic stress disorder and major depression have been reported to have smaller gray matter volume, particularly within frontal and temporal regions, when compared to controls (29). Future research is needed to determine whether cancer survivors reporting higher levels of chronic stress or depression have reduced brain volume.

In conclusion, neurocognitive late effects in survivors of ALL have decreased in frequency and severity as treatment has evolved. Emerging evidence suggests that there is a subset of survivors in the modern treatment era that are particularly vulnerable to the neurotoxic effects of ALL and its treatment. The study by Zeller *et al.* substantially contributes to this notion and suggests that the caudate is particularly vulnerable to the neurotoxic effects of chemotherapy. This study has some limitations to consider but helps inform future research directions. Research is needed to determine the functional consequences of brain volume differences, how ALL and its treatment shapes neurological differences, and why certain individuals are more vulnerable to neurotoxicity.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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