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Cognitive reserve and brain volumes in pediatric acute lymphoblastic leukemia

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Abstract

Acute lymphoblastic leukemia (ALL) is associated with long-term, progressive cognitive deficits and white matter injury. We measured global and regional white and gray matter as well as cognitive function and examined relationships between these variables and cognitive reserve, as indicated by maternal education level, in 28 young survivors of ALL and 31 healthy controls. Results indicated significantly reduced white matter volumes and cognitive testing scores in the ALL group compared to controls. Maternal education was inversely related to both global and regional white matter and directly related to gray matter in ALL and was directly related to both gray and white matter in controls, consistent with the cognitive reserve hypothesis. Cognitive performance was associated with different brain regions in ALL compared to controls. Maternal education was significantly positively correlated with working and verbal memory in ALL as well as processing speed and verbal memory in controls, improving models of cognitive outcome over medical and/or demographic predictors. Our findings suggest that cognitive reserve may be an important factor in brain injury and cognitive outcome in ALL. Additionally, children with ALL may experience some neural reorganization related to cognitive outcome.

Keywords

Leukemia; Neuroimaging; MRI; Brain volumetrics; Cognitive reserve; Maternal education

Introduction

Survivors of acute lymphoblastic leukemia (ALL), the most common childhood cancer, are at increased risk for long-term and potentially progressive cognitive impairments (Buizer et al. 2009; Campbell et al. 2009; Harila et al. 2009; Janzen and Spiegler 2008; Lofstad et al. 2009; Moleski 2000; Peterson et al. 2008). Increasing incidence and survival rates in ALL

make this a large and rapidly growing cohort of cognitively affected individuals. Previous studies indicate that younger age at diagnosis, female gender, cranial radiation, time since treatment and increased treatment intensity may be associated with cognitive impairments in survivors of ALL (Buizer et al. 2009; Mantadakis et al. 2005). Neuroimaging studies have consistently shown brain injury in the form of white matter changes associated with ALL (Dellani et al. 2008; Ficek et al. 2010; Porto et al. 2008; Reddick et al. 2009) and white matter damage may be associated with increased treatment intensity (Reddick et al. 2009). Gray matter volumes have also been shown to be affected by ALL (Porto et al. 2008), though this appears to be a less frequent finding. Abnormal white matter, including hyperintensities, reduced volume and lower fractional anisotropy, have been associated with cognitive deficits in ALL (Aukema et al. 2009; Carey et al. 2008; Paakko et al. 2000; Reddick et al. 2006).

Cognitive reserve is an important and heretofore neglected potential moderator of individual outcome in ALL. It has been suggested that children with ALL have reduced cognitive reserve due to anti-cancer treatments (Jansen et al. 2008; Spiegler et al. 2006), though no specific investigations of cognitive reserve in this population have been conducted to date. The cognitive reserve hypothesis proposes that individual cognitive outcome following brain injury or illness stems from individual variation in brain resources (e.g. size, efficiency, flexibility). Those with greater brain resources will cope better than those with lower brain resources even when the injury magnitude is similar (Sachdev and Valenzuela 2009; Stern 2009). Higher cognitive reserve is associated with higher cognitive performance in both adults and children (Farmer et al. 2002; Fay et al. 2010; Kaplan et al. 2009; van Hooren et al. 2007). Reserve is also positively correlated with brain volumes in typically developing individuals (Haut et al. 2007; Sole-Padulles et al. 2009). However, reserve tends to be inversely correlated with brain volumes in individuals who have experienced a neurologic insult of similar severity because individuals with higher cognitive reserve can sustain a greater degree of brain pathology before deficits are manifest (Kesler et al. 2003; Perneckzy et al. 2007; Sole-Padulles et al. 2009; Stern 2009).

Education level is one of the most frequently used cognitive reserve proxies in adults (Sachdev and Valenzuela 2009; Stern 2009) but is not appropriate in children since most have yet to reach their educational potentials. We instead examined maternal education level as a proxy for cognitive reserve in this study. Maternal education level has been shown to be one of the best predictors of cognitive outcome in children (Gale and Prigatano 2010; Hack et al. 2005; Hammer et al. 2010; Kesler et al. 2008; Majnemer et al. 2006; Vernon-Feagans et al. 2008; Wetherington et al. 2009). The relationship between maternal education level and child cognitive outcome appears to stem from several factors including the strong relationship between education level and IQ (Gray and Thompson 2004), the high correlation between parent and child IQ (Brant et al. 2009; Deary et al. 2009) and the association between maternal education, socioeconomic status and home environment (Desai and Alva 1998; Magnuson 2007). Socioeconomic status moderates genetic influences on cognitive ability (Turkheimer et al. 2003). Additionally, parents with higher levels of education tend to provide their children with more learning-related activities (Davis-Kean 2005); a more enriched environment that has been linked to higher cognitive reserve (Nithianantharajah and Hannan 2009; Petrosini et al. 2009). Therefore, higher maternal education level represents a unique combination of increased genetic endowment and environmental enrichment.

We hypothesized that white matter volumes and cognitive performance would be significantly reduced in survivors of ALL compared to healthy controls and that lower white matter volumes would be correlated with lower cognitive test scores. We expected that maternal education would show an inverse relationship with white matter volume in ALL

but a direct correlation in controls, consistent with previous studies of reserve. We also examined the relationships between cognitive reserve and uninjured brain volumes in both groups with the expectation that these would be directly correlated. We hypothesized that higher maternal education level would be associated with higher cognitive function in survivors of ALL as well as controls, accounting for more of the variance in cognitive outcome than medical or demographic variables. We defined cognitive reserve as maternal education level, brain injury as reduced brain volume (compared to typical development), healthy brain volumes as those not different between groups and cognitive outcome as cognitive testing scores.

Methods

Participants

We recruited 28 children and adolescents with a history of ALL age 5.0–19.8 years (mean=12.0±4.6) who had completed all anti-cancer treatments for at least 6 months (mean=50.3±30.6, range=6–126 months). Participants with ALL were recruited through physician referrals at local hospitals and clinics. We also recruited 31 healthy controls age 4.1–18.4 (mean=12.3±3.8) from the same zip codes as the participants with ALL to reduce differences in socioeconomic status. Control participants were recruited through community advertisements. Participants with ALL were excluded for cranial radiation, bone marrow transplant and any history of neurologic, medical and/or psychiatric condition known to affect cognitive function that preceded or was determined to be unrelated to ALL by their oncologist. Control participants were excluded for any neurologic, medical and/or psychiatric condition known to affect cognitive function. All participants were excluded for MRI contraindications (e.g. certain orthodontia, non-MRI safe metallic implants). The two groups were frequency matched for age, gender, maternal education level and minority status (Table 1).

All participants with ALL were treated with intrathecal methotrexate (MTX). Specific treatment regimens included COG/POG protocols 9404 ($N=1$), 9405 ($N=3$), 9605 ($N=1$), 9904 ($N=6$), 9905 ($N=10$), AALL0232 ($N=3$), AALL0331 ($N=3$) and ALL2003 ($N=1$). In terms of treatment intensity, previously defined as intermediate versus high dose MTX (Buizer et al. 2005), 15 participants with ALL had intermediate dose while 13 had high dose MTX. Although protocol 9605 involved intermediate dose MTX, we classified this participant as being in the high intensity treatment group given that this protocol involved cumulative intrathecal MTX intensification, which has been associated with increased cognitive dysfunction (Montour-Proulx et al. 2005). Participants with ALL were excluded for CNS involvement or relapse during therapy. Participants with ALL did not have any gross neuropathologies (e.g. leukomalacia, ventriculomegaly). This study was approved by Stanford University's Institutional Review Board and the Stanford Cancer Center's Scientific Review Board. Informed consent was obtained from adult participants or from the parent/legal guardian of minor participants and assent was obtained from participants age 8 years and older per Stanford University's regulations.

Cognitive outcome measurement

Selected subtests of the Wechsler Preschool and Primary Scale of Intelligence 3rd Edition (Wechsler 2002) (for children younger than 6 years of age, $N=3$), the Wechsler Intelligence Scale for Children 4th Edition (Wechsler 2003) (for those age 6–16) and the Wechsler Adult Intelligence Scale 3rd Edition (for participants 17 and older) were administered. Specifically, the Vocabulary subtest was used as a measure of verbal comprehension, Letter-Number Sequencing for working memory (age 6 and older only), Symbol Search for processing speed and Matrix Reasoning for perceptual reasoning. Executive function was

assessed using the Children's Category Test (age 16 or younger) (Allen et al. 2006) or Category Test (age 17 and older) (Allen et al. 2007). Verbal and visual declarative memory were measured for all participants using the Verbal Learning and Picture Memory subtests of the Wide Range Assessment of Learning and Memory 2nd Edition (Sheslow and Adams 2005). Visual-spatial processing was assessed with the Motor-Free Visual Perceptual Test 3rd Edition (Colarusso and Hammill 2003) and visual attention was measured using the Cancellation subtest of the Woodcock-Johnson Tests of Cognitive Abilities 3rd Edition (Woodcock et al. 2001) for all participants. Tests with strong psychometric properties for the sample age range were chosen to cover major cognitive domains with a priority on limiting administration time in order to increase participant compliance and minimize fatigue.

MRI acquisition

High resolution, 3D spoiled gradient recall MR images were obtained using a 3 Tesla GE Signa whole body scanner (GE Medical Systems, Milwaukee, WI) with the following parameters: repetition time=6.436 msec, echo time=2.064 msec, flip angle=15°, number of excitation=3, matrix size=256×256 voxels, field of view=220, slice thickness=1.5 mm, 124 contiguous slices. MRI scans and cognitive assessments were completed on the same day for every participant.

Brain volume measurement

Voxel-based morphometry (VBM) analyses were conducted in Statistical Parametric Mapping 8 (SPM8) (Friston et al. 2007) using the VBM8 Toolbox (<http://dbm.neuro.uni-jena.de/vbm/>). We utilized the optimized VBM process (Good et al. 2001) which included 1) segmentation and extraction of the brain in native space, 2) normalization of the images to a standard space using a customized pediatric template, created via Template-O-Matic software (Wilke et al. 2008) using images from all subjects, 3) segmentation and extraction of the normalized brain (extraction is repeated to ensure that no non-brain tissues remain), 4) modulation of the normalized images to correct for tissue volume differences due to the normalization procedure, and 5) smoothing of the normalized, segmented, modulated images using a 8 mm FWHM kernel to reduce the effects of noise. Resulting images were visually inspected by expert raters blinded to group assignment for quality, guided by boxplots and covariance matrices output by the VBM8 toolbox. Two scans from the ALL group and two from the control group were excluded due to overall covariance below 2 standard deviations and visually identifiable excessive motion artifact. These participants' data were excluded from the brain volume analyses but included in cognitive analyses. Raters also utilized SPM8 tools to ensure proper registration of individual images to the template.

Statistical analysis

Analyses of brain volumes were performed on two levels: 1) analysis of global gray and white matter volumes and 2) regional, voxel-by-voxel analyses. Global brain volumes were obtained for gray and white matter by calculating the raw volumes in native space using the VBM8 Toolbox after segmentation and brain extraction. Regional analyses were performed on a voxel-wise basis after normalization and smoothing. Both approaches were utilized to examine potentially unique relationships between global versus regional volumes, cognitive reserve and cognitive function.

Global brain volumes between groups—Differences in total brain volume were measured between groups using a general linear model in PASW 18.0 (<http://www.spss.com>). Global gray and white matter were evaluated between groups using a multivariate general linear model. Although groups were matched for age and gender,

gender was included as a fixed effect and age as a covariate given the significant effects of these variables on neurodevelopment (Giedd et al. 2009). Total brain volume was included as a covariate when evaluating tissue specific volumes.

Regional brain volumes between groups—Regional differences between groups were measured using voxel-wise analyses with the general linear model framework in SPM8 to obtain probability maps indicating voxels characterized as gray or white matter. A two-sample t-test model was employed, controlling for age and gender. Absolute threshold masking (threshold = .20) was used to minimize brain/non-brain boundary effects and implicit masking was used to disregard voxels with zero values. The statistics for VBM analyses were normalized to T scores.

Cognitive reserve and injured global brain volumes—Principal component analysis (PCA) using Kaiser normalization and Scree function was used to create a composite of previous predictors for the ALL group. This included age at diagnosis, treatment intensity (coded as $-.50$ for high and $.50$ for low), gender (coded as $-.50$ for female and $.50$ for male) and time since treatment in months. The single component extracted accounted for 98.6% percent of the common variance among these predictors. A separate PCA was conducted resulting in a single extracted component (comprising 54.5% of the variance) that was used to create a global composite cognitive testing score. Because only one factor was extracted for each of the PCA analyses, the solutions were not rotated.

To examine the relationships between cognitive reserve and injured global volumes, multiple regression analyses were performed in PASW 18.0 using maternal education in years as the independent variable and corrected tissue-specific volume (global tissue specific volume to total brain volume ratio) that was significantly different between groups as the dependent variable. This analysis was conducted to test our hypothesis that maternal education would be inversely correlated with injured global volumes in ALL but directly correlated in controls. The regression analyses in the ALL group included the previous predictors composite (PPC) as an independent variable to control for cognitive impairment risk factors in an effort to homogenize our ALL sample as much as possible in terms of ALL-related brain injury. The regression analysis for controls included age and gender.

The regression analyses also included the global cognitive testing composite as an independent variable to control for global cognitive function (Sole-Padulles et al. 2009). Cognitive function is controlled for in these analyses because the cognitive reserve hypothesis posits that individuals with higher reserve will show greater brain damage when clinical effects are manifest. Because not all participants show the same level of clinical effect (i.e. cognitive dysfunction), this must be controlled for when examining the relationship between brain status and cognitive reserve.

Cognitive reserve and uninjured global brain volumes—We also conducted the regression analyses described above using corrected global tissue volumes that were not significantly different between groups. These analyses were conducted to explore potentially unique or distinguishable relationships between cognitive reserve and global tissue volumes that were not defined as injured and should therefore show patterns of association similar to controls (i.e. be directly correlated).

Cognitive reserve and injured regional brain volumes—For the ALL group, we examined relationships between injured regional brain volumes with cognitive reserve. This analysis was accomplished using voxel-wise regression analysis in SPM8 that was constrained to the regions of significant between group difference by external masking and

was expected to show inverse correlations with maternal education. Controls were not included in this analysis as they were not expected to have regional brain injury.

Cognitive reserve and uninjured regional brain volumes—We also examined the relationships between maternal education and healthy regional volumes in ALL by conducting voxel-wise regression analysis in SPM8 on all regions outside the injured regions. A binary mask was created such that voxels inside the injured regions were set to 0 and those outside were set to 1. This binary mask was then multiplied with a mean tissue-specific volume consisting of the volume from each participant in the ALL group. This multiplication converted all voxels in the mean volume that were within the injured regions to 0 and thus excluded these from the analyses. These analyses were expected to show direct correlations with maternal education. For controls, we conducted regression analyses without external masking because controls were not expected to have regions of injured tissue. Analyses were controlled for PPC (ALL group) or gender and age (controls) and cognitive testing composite.

Cognitive test performance between groups—Cognitive testing scores were compared between groups using a multivariate general linear model with group and gender as fixed effects and age as a covariate. A multivariate model was used given the known intercorrelations between the individual cognitive measures. Tests of between subject effects were corrected for multiple comparisons using Bonferroni alpha criterion.

Cognitive test performance and brain volumes—To test our hypothesis that injured brain volumes would be associated with lower test scores in ALL, we computed a composite of the three cognitive tests that were significantly different between groups using PCA. This approach reduced the number of correlational tests from 12 to 4 as well as the measurement error associated with each individual test. The single component extracted explained 68.7% of the variance and was used as the dependent variable in multiple regression analysis. For the ALL group, the PPC and injured global or regional volumes were entered as independent variables. We conducted these analyses for controls as well to determine if there were different profiles of brain-cognitive relationships between groups. Mean volume was extracted from regions of between group difference for each subject using the REX Toolbox (<http://web.mit.edu/swg/software.htm>). The extracted volume was then entered as the independent variable in the regression analyses described above.

Cognitive reserve and cognitive outcome—Hierarchical linear regression in PASW 18.0 was used to compare models of cognitive function within each group. For the ALL group, the PPC was entered into the first step with the respective cognitive test score as the dependent variable. Age and gender were entered into the first step for controls. Maternal education was entered into the second step for both groups. Only those cognitive tests that were significantly different between groups were modeled.

Tests of between subjects effects for multivariate models conducted in PASW 18.0 (i.e. tissue specific total volumes, cognitive test scores) were examined only when omnibus F statistics were significant ($p \leq .05$). Independent variables for all regression analyses (in PASW and SPM8) were median-centered to facilitate valid interpretation of regression coefficients and reduce multicollinearity (Kraemer and Blasey 2004). Effect sizes were calculated using Cohen's d or f^2 (Cohen 1998). Significant clusters of volume difference in voxel-wise analyses were determined using a height threshold of $p < .001$ and an extent threshold of 50 voxels, uncorrected, though findings surviving family-wise error (FWE) correction were noted when applicable. Thresholded statistical parametric maps from voxel-wise analyses were overlaid on a mean image of all participants' brain volumes and cluster locations were interpreted using known neuroanatomic landmarks.

Results

Global brain volumes between groups

As shown in Table 2, the groups did not differ in terms of total brain volume ($p=.79$) or gray matter volume ($p=.83$) but the ALL group showed significantly lower white matter ($p=.01$) compared to controls. As is typical, males showed larger brain volumes than females ($p=.004$) but there were no significant group by gender effects ($p=.15$). Both age ($p<.0001$) and total brain volume ($p<.0001$) were significant covariates.

Regional brain volumes between groups

The ALL group showed significantly reduced white matter in the left caudate extending into left corpus callosum, right caudate, bilateral thalamus (anterior thalamic radiation), fornix and bilateral superior fronto-occipital fasciculus compared to controls (Fig. 1). These findings were significant even after FWE correction. Regional gray matter was not significantly different between the groups.

Cognitive reserve and injured global brain volumes

As shown in Fig. 2, in the ALL group, the model of global white matter volume and cognitive reserve was significant ($R^2 = .69$, $p<.0001$, $f^2=2.2$). Only maternal education was a significant predictor, demonstrating the expected inverse relationship with white matter volume ($Beta=-.77$, $p<.0001$). In controls, the white matter model was significant ($R^2 = .72$, $p<.0001$, $f^2=2.6$) with all predictors being significant and maternal education showing the expected direct relationship with white matter volume ($Beta = .56$, $p=.02$).

Cognitive reserve and uninjured global brain volumes

The model for gray matter volume in the ALL group was significant ($R^2=.49$, $p=.008$, $f^2=.96$). Maternal education was the only significant predictor and was positive ($Beta=.65$, $p=.005$). In controls, the gray matter model was also significant ($R^2=.43$, $p=.04$, $f^2=.75$) with both maternal education ($Beta=.60$, $p=.05$) and gender ($Beta=.52$, $p=.03$) being significant.

Cognitive reserve and injured regional brain volumes

Contrary to our hypotheses, the ALL group demonstrated no significant correlations between maternal education and regions of injured white matter at the a priori threshold. At a lowered threshold of .01, there were significant negative correlations with the right corpus callosum extending into left caudate. There were no regions of positive correlation (Fig. 3, Table 3).

Cognitive reserve and uninjured regional brain volumes

Also unexpectedly, there were no significant positive correlations with the white matter regions defined as uninjured among the ALL group. Instead, there were several regions of significant negative correlation with maternal education in the uninjured regions. These included right inferior frontal gyrus, right precentral gyrus, bilateral superior corona radiata, left middle frontal gyrus, right superior fronto-occipital fasciculus and right superior parietal lobe (Fig. 3, Table 3).

Consistent with our hypotheses, the ALL group showed significant positive correlations between maternal education and regions of gray matter including left inferior parietal lobe, left superior frontal gyrus, left hippocampus, left superior temporal gyrus, left inferior frontal gyrus, left precentral gyrus, left middle frontal gyrus, right putamen and left inferior and middle occipital gyri (Fig. 3, Table 3). There were no negative correlations with gray matter.

In controls, maternal education was significantly positively associated with white matter in the left superior frontal gyrus, right internal capsule extending into the right thalamus and the left inferior longitudinal fasciculus extending into the left hippocampus. There were no significant negative correlations with white matter. Maternal education was also significantly positively correlated (FWE corrected) with gray matter in the left anterior cingulate extending into left medial frontal, superior and middle frontal gyri and the right superior temporal gyrus extending into right inferior frontal gyrus (Fig. 3, Table 3). There were no significant negative correlations with gray matter.

Cognitive test performance between groups

As shown in Table 4, after Bonferroni correction, the ALL group demonstrated significantly lower scores on Symbol Search (processing speed, $p < .0001$), Letter-Number Sequencing (working memory, $p = .002$) and Verbal Learning (verbal memory, $p < .0001$). There were no significant gender ($p = .38$) or gender by group effects ($p = .70$) and age was not a significant covariate ($p = .43$).

Cognitive test performance and brain volumes

There were no significant associations between global or regional brain volumes and cognitive outcome in the ALL group, even when post-hoc analyses were conducted using single cognitive test scores instead of the composite. The PPC also was not a significant predictor of cognitive outcome in ALL. However, in controls, regional white matter volume (the regions of significant between group difference) was significantly associated with cognitive outcome ($R^2 = .29$, $p = .03$, $f^2 = .41$; Beta = .45, $p = .02$). Age and gender were not significant predictors. Global white matter volume was not associated with cognitive outcome in either group.

Cognitive reserve and cognitive outcome

In the ALL group, the addition of maternal education significantly improved the models for Letter-Number Sequencing (significant F change = .008) and Verbal Learning (significant F change = .01). The first step was not significant for any of the models (Table 5).

In controls, maternal education significantly improved the models for Symbol Search (significant F change $< .0001$) and Verbal Learning (significant F change = .01). Maternal education was a significant predictor in both models. The first step was not significant for any of the models although age and gender were significant in the second step for the Symbol Search model (Table 5).

Discussion

Consistent with previous studies (Carey et al. 2008; Chu et al. 2003; Paakko et al. 2000; Reddick et al. 2009), we demonstrated white matter injury in pediatric survivors of ALL. Our findings were irrespective of age, gender and total brain volume and included both global and regional white matter volumes. Regional analyses indicated significantly reduced white matter in the bilateral caudate, left corpus callosum, bilateral thalamus (anterior thalamic radiation), fornix and bilateral superior fronto-occipital fasciculus in children with ALL. Our regional findings are highly consistent with previous VBM as well as diffusion tensor imaging studies (Aukema et al. 2009; Porto et al. 2008; Reddick et al. 2009).

Cognitive reserve, as indicated by maternal education level, was inversely associated with global white matter volumes in the ALL group but directly related in the control group, consistent with previous studies of the cognitive reserve hypothesis (Haut et al. 2007; Sole-Padulles et al. 2009). This same pattern was noted for regional white matter—the ALL group

showed non-significant but only negative correlations with injured white matter regions whereas controls showed significant and only positive correlations with regional white matter. These findings suggest that, in children with higher cognitive reserve, greater white matter involvement is required before cognitive effects of ALL are manifest. Our study is consistent with the passive model of cognitive reserve, which suggests that a critical threshold of brain damage must be reached before clinical symptoms of the condition become evident. Impairment will putatively appear in all patients who have reached this threshold (Stern 2009).

The positive relationship between white and gray matter volumes and cognitive reserve in healthy individuals demonstrated here and previously provides evidence that individuals with higher cognitive reserve have larger brain volumes prior to a neurologic injury or illness. Thus, more damage is required for these individuals to reach the critical threshold for impairment. For ALL survivors, this threshold might be a specific loss of white matter volume and/or microstructural integrity, for example. A longitudinal study design that could provide a measure of the change in white matter from pre- to post-treatment and examine the correlation between white matter delta and cognitive status would be necessary to further test this hypothesis. Global and regional gray matter volumes were positively related to maternal education in ALL, consistent with healthy controls. Such direct relationships between brain measures and cognitive reserve proxies appear to represent uninjured or healthy neurobiologic status (Haut et al. 2007; Sole-Padulles et al. 2009). This is consistent with gray matter being relatively intact in ALL.

Accordingly, we also expected the white matter regions we defined as uninjured (i.e. regions not significantly different from controls) in the ALL group to be directly related to cognitive reserve. However, contrary to our hypotheses, we found only negative correlations with “uninjured” white matter regions in ALL. These findings may indicate that the morphometric analyses we employed were not sufficiently sensitive to other possible mechanisms of white matter injury in ALL. The “healthy” white matter regions we identified as having significant negative correlations with maternal education in the ALL group could have non-morphologic deviations from typical neurodevelopment such as metabolic, physiologic and/or micro-structural alterations. In fact, these regions included frontal and parietal areas, which have been shown to have abnormalities in ALL patients detected by other imaging techniques including perfusion MRI (Paakko et al. 2003), MR spectroscopy (Chu et al. 2003; Ficek et al. 2010) and diffusion tensor imaging (Aukema et al. 2009). We did demonstrate global reduction in white matter volume in the ALL group which may include other regions of white matter injury that were not detected by our regional white matter analysis due to factors such as low statistical power.

The specific gray and white matter regions that were positively correlated with cognitive reserve across both groups included prefrontal cortex, thalamus, superior temporal gyrus and hippocampus. These regions are highly consistent with those identified in cognitive reserve studies of adults and are postulated to comprise a neural compensatory network (Bartres-Faz et al. 2009; Sole-Padulles et al. 2009; Stern et al. 2005). Individuals with lower cognitive reserve may show reduced ability to optimally or efficiently activate these regions during certain cognitive tasks and/or in response to increased task difficulty (Scarmeas et al. 2003; Sole-Padulles et al. 2009). Our findings suggest that this network is associated with cognitive reserve in young children and adolescents as well.

In addition to reduced global and regional white matter, our sample of children with ALL demonstrated significantly lower scores compared to controls on measures of memory and executive function, including processing speed, working memory and verbal learning. We expected that lower test scores would be directly correlated with altered morphology as

previous studies involving ALL have shown such associations (Paakko et al. 2000; Reddick et al. 2006). The white matter regions that were significantly reduced in our ALL group included the bilateral caudate, left corpus callosum, bilateral thalamus, fornix and bilateral superior fronto-occipital fasciculus. These regions have been shown to be associated with memory and executive functions (Chiang et al. 2009; Grahn et al. 2008; Kesler et al. 2001). However, while controls showed significant associations between these regions and measures of memory and executive function, the ALL group did not.

As discussed above, the definition of brain injury is limited by the imaging technique employed and possibly misses other types of injury that may explain more of the variance in cognitive outcome. Additionally, the ALL group may utilize alternate brain regions to bypass the area of supposed injury resulting in relatively intact but less efficient function compared to healthy peers. Consistent with this hypothesis, mean test scores in the ALL group were still within what is considered the “average” range (T scores between 44–56) (Spreeen et al. 2006), although they were significantly lower than that of typically developing controls. Such compensatory neural or functional reorganization is frequently seen in traumatic brain injury (Bosnell et al. 2008; Draganski and May 2008; Raymont and Grafman 2006).

To explore the possibility of neural compensation or functional re-organization, we conducted a post-hoc linear interaction model in SPM8 to determine if there were brain regions where the correlation with cognitive outcome differed for the ALL group compared to controls. We used group as the factor and the PCA-based composite of Symbol Search, Letter-Number Sequencing and Verbal Learning as a covariate. This allowed us to identify brain regions where the cognitive outcome regression slope differed in the ALL group compared to controls. Results indicated significantly different profiles of white and gray matter correlations with cognitive outcome between the groups (Table 6). The regions of higher correlation in ALL included dorsolateral prefrontal areas, which are known to be involved in executive and memory function (Leh et al. 2009) while controls showed higher correlations in mesial temporal regions, particularly the hippocampus. The hippocampus is critical for memory function but also interacts with frontostriatal and other systems to integrate and coordinate executive functions (Leh et al. 2009).

The ALL group showed significantly higher positive correlations with cognitive function only in prefrontal regions that were not identified as reduced compared to controls or negatively correlated with cognitive reserve. Interestingly, they showed higher correlations with cognitive function in prefrontal regions contralateral to those that were negatively correlated with cognitive reserve. These findings are reminiscent of what is seen in traumatic brain injury where contralateral regions take over for injured areas (Strangman et al. 2005) and may suggest that the ALL group re-routed cognitive functions to other, uninjured regions. This may indicate some degree of neural reorganization and compensation in response to cancer-related brain injury among children with ALL.

Consistent with our hypothesis, maternal education level was significantly positively correlated with verbal memory in both groups as well as working memory in ALL and processing speed in controls. Maternal education level was a more significant predictor compared to medical and demographic variables in both groups. Treatment-related and demographic variables were not correlated with cognitive outcome measures in our ALL group as in previous studies (Buizer et al. 2005). Our sample size was relatively small and thus these analyses may have been underpowered. We also utilized different cognitive tests than other studies. Like several previous studies (Buizer et al. 2009, 2005; Precourt et al. 2002), we showed that predictors were associated with some cognitive measures but not others. This variability highlights the importance of utilizing comprehensive assessment of

multiple cognitive domains as well as continued examination of alternate potential predictors of cognitive outcome in ALL.

Cognitive reserve has received less attention in children and adolescents than in adults. Education level or occupational attainment cannot be used as proxies in children and adolescents. IQ is another commonly used proxy of cognitive reserve in adults (Stern 2009). The use of IQ as a cognitive reserve proxy is somewhat challenging given that IQ is often also considered a measure of brain injury outcome. This is particularly important in the case of ALL given that IQ scores tend to decline over time in these children (Brown et al. 1992; Harila et al. 2009; Nathan et al. 2009). Also, although IQ is a common proxy of reserve, it has been shown that environmental factors can contribute to reserve separately from innate intelligence (Stern 2009). Our study suggests that maternal education level may be an appropriate proxy of cognitive reserve, representing a combination of genetic and environmental endowment.

Cognitive reserve is important for studies of outcome in all individuals with neurologic injury or disease as cognitive reserve can putatively be increased through simple lifestyle changes such as physical exercise and cognitive stimulation (Fritsch et al. 2007; Scarmeas and Stern 2003; Valenzuela 2008; Xiong and Doraiswamy 2009) and thus represents a potential preventative intervention. Despite having some genetic substrates (Lee 2003), cognitive reserve is not fixed (Stern 2006) and thus can putatively be increased to protect individuals from future or further effects of brain injury. Just as activities that increase cognitive reserve may prevent or ameliorate cognitive decline associated with aging or dementia (Fritsch et al. 2007; Hall et al. 2009; Valenzuela 2008), it may be possible to prevent or lessen continuing cognitive decline in survivors with ALL using physical and mental exercise. In fact, a recent study demonstrated the efficaciousness of cognitive remediation for improving attention deficits in young survivors of ALL or brain tumor (Butler et al. 2008).

As stated above, the cognitive reserve hypothesis attempts to explain the discontinuity between the magnitude of brain damage and the clinical outcome. Specifically, individuals with the same type of brain injury can demonstrate very different levels of cognitive function (Stern 2009). Our ALL sample demonstrated lower cognitive function compared to controls on average but showed a large range of cognitive performance. The mean range across cognitive measures was 41 points, ranging from scores that are clinically classified as “impaired” (T score ≤ 30 , ≤ 2 nd percentile) to “very superior” (T score ≥ 80 , ≥ 98 th percentile) (Spren et al. 2006). Thus, our sample demonstrated marked variance in cognitive outcome despite having the same mechanism of brain insult, namely, ALL. We attempted to homogenize our ALL sample as much as possible in terms of ALL-related brain injury through inclusion/exclusion criteria and the use of statistical covariates. For example, we controlled for differences in disease severity by including treatment intensity in our models of cognitive reserve given that sicker patients tend to receive more intense treatment regimens. However, there is much that is currently unknown in terms of factors that influence the presence and severity of brain injury in ALL. Further research is required to increase our understanding regarding brain injury and cognitive outcome in ALL.

There are several limitations of our study including the use of composite scores which can lead to different results depending on the PCA methods employed (DiStefano et al. 2009) and did not allow for examination of specific relationships between previous predictors, cognitive reserve, cognitive function or brain volumes. Our sample of patients with ALL was not enrolled consecutively but restricted by exclusion criteria to a subgroup whose neurodevelopmental and cognitive outcomes may not generalize to the larger population of ALL survivors. The correlation between maternal education and regions of white matter

defined as injured in the ALL group seemed to be underpowered and most of our voxel-wise regression analyses did not survive family-wise error correction, likely due to small sample size. We were also not able to examine other factors that may potentially contribute to neurobiologic status in ALL such as corticosteroids, folinate rescue, chemotherapies used in addition to intrathecal methotrexate, specific treatment protocols, cytokine levels and genetic variants due to small sample sizes. The cross-sectional design of this study limits definitions and interpretations of brain injury and potential recovery. Longitudinal studies are necessary to more specifically examine neurobiologic changes and their associated impact on cognitive development in ALL. However, our findings suggest that cognitive reserve may be an important factor to consider as research involving cognitive outcomes in ALL moves forward.

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Fig. 1.

Axial overlays of significant between group regional white matter differences. The ALL group showed significantly reduced white matter compared to controls in the left caudate (peak MNI: -12, 3, 20) extending into left corpus callosum, right caudate, bilateral thalamus (anterior thalamic radiation), fornix and bilateral superior fronto-occipital fasciculus ($p < .0001$ FWE corrected/50 voxels, $T=5.03$, number of voxels=2434). The color bar represents T score

Fig. 2.

Scatterplots of relationships between maternal education level and adjusted tissue-specific global volumes in the ALL (**a**) and control (**b**) groups. Beta and p values for maternal education in the regression model are shown for each plot. Maternal education (years) for this illustration is the unstandardized residual after removing the variance due to covariates in the model. The residual was normalized by adding the mean maternal education. Adjusted global volumes represent the ratio of white or gray matter to total brain volume in cubic centimeters

Fig. 3.

Axial overlays of significant correlations between maternal education and gray or white matter regions. Controls demonstrated significant positive correlations with white matter in the left superior frontal gyrus, right internal capsule extending into the right thalamus and the left inferior longitudinal fasciculus extending into the left hippocampus (**a**). The ALL group showed significant negative correlations with white matter in the right inferior frontal gyrus, right precentral gyrus, bilateral superior corona radiata, left middle frontal gyrus, right superior fronto-occipital fasciculus and right superior parietal lobe (**b**). Controls showed significant positive correlations with gray matter in the left anterior cingulate extending into left medial frontal, superior and middle frontal gyri and the right superior temporal gyrus extending into right inferior frontal gyrus (**c**). The ALL group demonstrated significant positive correlations with gray matter in the left inferior parietal lobe, left superior frontal gyrus, left hippocampus, left superior temporal gyrus, left inferior frontal gyrus, left precentral gyrus, left middle frontal gyrus, right putamen and left inferior and middle occipital gyri (**d**). Color bars represent T score ($p < .0001/50$ voxels uncorrected)

Demographic data for study participants shown as mean (standard deviation) unless otherwise indicated

Table 1

	ALL N=28	Controls N=31	F/Chi Sq	p
Age	12.0 (4.6) range: 5.0–19.8	12.5 (3.8) range: 4.1–18.4	.16	.69
Maternal education (yrs)	16.3 (2.6) range: 10–20	15.9 (2.9) range: 12–24	.24	.63
Male	56%	52%	.09	.76
Minority status ^a	30%	32%	.05	.83

^a minority groups included Black, Asian, Hispanic and Mixed-race

Table 2

Brain volumes in cubic centimeters (cc) for participants with ALL and controls shown as marginal mean (standard deviation)

Volumes	ALL N=26 ^a	Controls N=29 ^a	F	p	d
Total brain	1398 (128)	1408 (129)	.07	.79	.10
White matter	466 (44)	499 (44)	7.0	.01	.75
Gray matter	708 (55)	711 (55)	.05	.83	.05

^aTwo participants from each group were excluded from these analyses due to unusable MRI data

Table 3

Regional brain volumes significantly correlated with maternal education in the ALL and control groups. "Uninjured" regions were defined as those not differing significantly between groups. There were no significant correlations between regions defined as injured and maternal education in the ALL group

Analysis	p value	No. of voxels	T Score	Peak location (MNI)			Location description	
				x	y	z		
ALL								
“Uninjured” White Matter (negative correlation)	<.0001	137	8.62	22	42	-9	Right inferior frontal gyrus	
	<.0001	132	6.50	21	-18	60	Right precentral gyrus	
	<.0001	82	5.16	-18	-28	39	Left superior corona radiata	
	<.0001	53	5.07	-15	42	-8	Left middle frontal gyrus	
	<.0001	403	4.64	18	20	14	Right superior fronto-occipital fasciculus	
	<.0001	63	4.55	30	-42	40	Right superior parietal lobe	
	<.0001	81	4.26	16	-20	38	Right superior corona radiata	
	<.0001	109	6.04	-44	-34	26	Left inferior parietal lobe	
	<.0001	57	5.91	-16	33	39	Left superior frontal gyrus	
	<.0001	323	5.46	-34	-20	-16	Left hippocampus	
“Uninjured” Gray Matter (positive correlation)	<.0001	71	5.28	-45	-22	2	Left superior temporal gyrus	
	<.0001	130	4.95	-50	12	21	Left inferior frontal gyrus	
	<.0001	52	4.62	-12	52	21	Left superior and middle frontal gyri	
	<.0001	53	4.62	-28	45	12	Left middle frontal gyrus	
	<.0001	108	4.60	34	-20	-3	Right putamen	
	<.0001	50	4.44	-42	-76	-12	Left inferior and middle occipital gyri	
	<.0001	54	4.35	-56	-4	-2	Left superior temporal gyrus	
	Controls							
	White Matter (positive correlation)	<.0001	206	6.39	-21	42	15	Left superior frontal gyrus
		<.0001	619	5.92	28	-28	8	Right internal capsule extending into Right thalamus
Gray Matter (positive correlation)	<.0001	104	5.72	-48	-33	-16	Left inferior longitudinal fasciculus extending into left hippocampus	
	<.0001 ^a	2524	6.24	-8	21	40	Left anterior cingulate extending into left medial, superior and middle frontal gyri	
	<.0001 ^a	637	5.83	42	-34	15	Right superior temporal gyrus extending into right inferior frontal gyrus	

α FWE corrected

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Table 4
T scores for cognitive testing data shown as marginal mean (standard deviation)

Test	ALL N=28	Controls N=31	F	p	d
Symbol search ^a	49 (12)	60 (12)	23.3	>.0001	.92
LNS ^{ab}	51 (15)	60 (14)	10.9	.002	.62
Verbal learning ^a	45 (12)	56 (11)	25.1	>.0001	.96
Category test	45 (15)	53 (14)	8.1	.007	.55
Cancellation	47 (13)	53 (12)	4.8	.03	.48
Picture memory	45 (13)	48 (12)	1.8	.18	.24
MVPT	52 (18)	58 (16)	2.6	.12	.35
Vocabulary	55 (17)	64 (16)	7.6	.008	.55
Matrix reasoning	52 (16)	60 (14)	7.0	.01	.53

LNS Letter-number sequencing; MVPT Motor-free Visual Perception Test

^aOnly these tests were significant after Bonferroni correction

^b2 children with ALL and 1 control were under 6 years of age and thus did not receive this test

Summary of hierarchical regression analysis results predicting cognitive outcome. Beta values for independent variables are shown as standardized coefficients. Beta values significant at $p \leq .05$ are denoted with (*) and (**) for $p \leq .01$. Only the model with the highest adjusted R^2 is displayed. The Model p value refers to the significance of the model shown. A Change p value $\leq .05$ indicates that the addition of maternal education at the second step resulted in a significantly improved model

Table 5

Equation		Adjusted R^2	Model p	Model f^2	Change p
ALL					
Symbol Search	49 + .11(PPC)	-.02	.59	.01	.43
LNS ^a	51 + .28(PPC) + .50(MED)**	.33	.005	.62	.008
Verbal Learning	24 - .04(PPC) + .49(MED)**	.17	.04	.31	.01
Control					
Symbol Search	60 + .61(AGE)* - .53(GEN)* + 1.3(MED)**	.63	.001	2.3	<.0001
LNS ^a	58 - .37(AGE) + .17(GEN)	.10	.15	.22	.15
Verbal Learning	39 - .12(AGE) - .02(GEN) + .52(MED)**	.24	.02	.48	.01

PPC previous predictors composite, MED maternal education, GEN gender

^a 2 children with ALL and 1 control were under 6 years of age and thus did not receive this test

Results of post-hoc analysis showing brain regions where the correlation with cognitive outcome differed for the ALL group compared to controls. Cognitive outcome was defined as the composite of processing speed, working memory and verbal learning performance, which were significantly reduced in the ALL group compared to controls

Table 6

<i>p</i> value uncorrected	No. of voxels	T score	Peak location (MNI)			Location description
			x	y	z	
White matter: ALL>Con						
<.0001	162	3.68	-36	12	24	Left superior longitudinal fasciculus and left inferior frontal gyrus
<.0001	179	3.58	26	50	2	Right middle frontal gyrus
White Matter: Controls>ALL=not significant						
Gray Matter: ALL>Controls						
<.0001	127	3.18	4	-87	15	Right cuneus
Gray Matter: Controls>ALL						
<.0001 ^a	7633	4.67	22	-40	-15	Right parahippocampal gyrus extending into hippocampus, fusiform gyrus, cerebellar culmen and declive

^aFWE corrected