Brain Connectivity

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Brain network connectivity and executive function in long-term survivors of childhood acute lymphoblastic leukemia

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Abstract

Chemotherapeutic agents used to treat acute lymphoblastic leukemia (ALL), the most common cancer affecting young children, have been associated with long-term cognitive impairments that reduce quality of life. Executive dysfunction is one of the most consistently observed deficits and can have substantial and pervasive effects on academic success, occupational achievement, psychosocial function and psychiatric status. We examined the neural mechanisms of executive dysfunction by measuring structural and functional connectomes in 161 long-term survivors of pediatric ALL age 8-21 years who were treated on a single contemporary chemotherapy–only protocol for standard/high or low risk disease. Lower global efficiency, a measure of information exchange and network integration, of both structural and functional connectomes was found in survivors with executive dysfunction compared to those without dysfunction ($p < 0.046$). Patients with standard/high versus low risk disease and those who received greater number of intrathecal treatments containing methotrexate had the lowest network efficiencies. Patients with executive dysfunction also showed hyper-connectivity in sensorimotor, visual and auditory processing regions ($p = 0.037$) and poor separation between sensorimotor, executive/attention, salience and default mode networks ($p < 0.0001$). Connectome disruption was consistent with a pattern of delayed neurodevelopment that may be associated with reduced resilience, adaptability and flexibility of the brain network. These findings highlight the need for interventions that will prevent or manage cognitive impairment in survivors of pediatric acute lymphoblastic leukemia.

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1. Introduction

We previously showed that survivors of pediatric acute lymphoblastic leukemia (ALL) treated only with chemotherapy have significant impairments in memory, processing speed and executive function (Cheung et al., 2016; Kesler et al., 2014; Krull et al., 2016). These deficits persist decades beyond treatment cessation and negatively impact educational and occupational functioning as well as health-related behaviors (Krull et al., 2011; Krull et al., 2013; Schuitema et al., 2013). Widespread injury to brain structure and function has been observed following treatment for pediatric ALL (Edelmann et al., 2014; ElAlfy et al., 2014; Kesler et al., 2014; Tamnes et al., 2015; Zeller et al., 2013). Many of these studies show correlations between neuroimaging metrics and cognitive outcomes but few if any have examined differences in neurobiologic status between cognitively impaired versus non-impaired.

Additionally, few studies have examined interactions between brain regions within affected neural networks that subserve cognitive functions. Connectomics is a method for evaluating brain networks based on graph theory, the study of objects and their connections. Connectomes are frequently constructed from neuroimaging data including diffusion tensor imaging (DTI) for structural connectivity and resting state functional MRI (fMRI) for functional connectivity. We previously demonstrated alterations in connectome organization in small samples of young survivors of ALL compared to typically developing controls (Hosseini et al., 2012; Kesler et al., 2016).

In the present study, we compared connectome organization between ALL survivors with or without executive dysfunction at long-term follow-up. Deficits in executive function are among the most common impairments in these patients (Cheung et al., 2016; Kesler et al., 2014; Krull et al., 2016). Executive function refers to a set of cognitive skills, critical for goal-oriented behaviors, adaptive function, and self-regulation. Executive function is associated with health behavior trajectories and longevity among non-cancer populations (Hall and Fong, 2013; Williams and Thayer, 2009). We hypothesized that patients with executive dysfunction would demonstrate lower functional and structural connectome organization compared to those without executive

dysfunction. We also examined the effects of age at diagnosis, sex and chemotherapy exposure on connectome organization.

2. Materials and Methods

2.1. Participants

From 2000 to 2010, 408 children with ALL were treated at St. Jude Children's Research Hospital on the Total Therapy XV protocol (ClinicalTrials.gov, NCT00137111). Survivors who were receiving pediatric follow-up care at SJCRH, were at least five years from diagnosis and at least eight years of age were eligible to participate. Survivors were excluded for the following reasons: death prior to long-term follow-up (n=35); treatment with cranial radiation for CNS relapse or bone marrow transplantation (n=30); neurodevelopmental condition, genetic disorder, or brain injury unrelated to cancer but associated with cognitive impairment (n=22); lack of proficiency in English (n=1); not eligible for follow-up (e.g., discharged from pediatric follow-up care [n=13], under foster care [n=4] or in prison [n=1]). Of the 302 eligible survivors, 218 participated in neurocognitive testing beginning on January 1, 2010. Thirty-eight survivors refused brain imaging studies, 12 had imaging contraindications (e.g. orthodontia), and seven produced non-evaluable data (i.e. excessive movement, technical complications), resulting in 161 survivors with neurocognitive and imaging studies. This study was approved by the institutional review board and conducted at St. Jude Children's Research Hospital. Informed consent/assent was obtained from parents and/or participants, as appropriate.

2.2. Chemotherapy Exposure

We recorded the number of intrathecal treatments containing methotrexate, hydrocortisone and cytarabine that each patient received as well as exposure to high dose intravenous methotrexate. Blood samples were drawn before methotrexate and at 6, 23, and 42 hours following the start of each course. Exposure was quantified as area under the curve (AUC).

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2.3. Neurocognitive Function

All participants completed neurocognitive testing with certified examiners under the supervision of a board-certified clinical neuropsychologist. Measures of executive function, processing speed, intelligence, attention and memory span were examined (eTable 1). These included selected subtests from the Delis-Kaplan Executive Function System (Delis et al., 2008), Wechsler intelligence and memory scales (Wechsler, 1997; Wechsler, 2003; Wechsler, 2008) and Rey Complex Figure Test (Rey and Osterrieth, 1993). Impairment was defined as an age adjusted score falling below the 10^{th} percentile of national normative data.

2.4. Structural and Functional Connectivity

FMRI was obtained during five minutes of eyes open rest on a 3T scanner (Siemens Trio or Skyra MR; Siemens, Malvern, PA) using a single-shot T2*-weighted EPI pulse sequence (TR = 2.06s, TE = 30ms, FOV = 192mm, matrix = 64x64, slice thickness = 5mm). DTI was obtained on a 1.5T scanner (Siemens Avanto; Siemens, Malvern, PA) using a double spin echo EPI pulse sequence (TR/TE=10000/100ms, b=1000, 3.0X1.8X1.8mm, acquisition time ~1.5 min each) with 4 acquisitions and 12 gradient directions.

Visual artifact inspection resulted in exclusion of five DTIs. There were no significant differences in demographic, treatment or neurocognitive variables between excluded and included participants. DTIs were preprocessed using FMRIB Software Library (FSL) v5.0 as previously described (Kesler et al., 2016; Kesler et al., 2015), including eddy current correction, tensor reconstruction and probabilistic tractography. FMRIs were preprocessed using Statistical Parametric Mapping v8 (SPM8) as previously described (Bruno et al., 2012; Kesler and Blayney, 2016; Kesler et al., 2014; Kesler et al., 2013) including realignment, normalization and smoothing (8mm full width half maximum). Functional volumes were further denoised to reduce motion and signal related artifacts using a wavelet despiking method (Patel et al., 2014). In the non-impaired group, 97 participants had usable DTI, 65 had usable fMRI, and 62 had both. In the impaired group, these numbers were 57, 36 and 32, respectively.

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Functional connectivity matrices were obtained using CONN Toolbox as previously described (Kesler and Blayney, 2016; Kesler et al., 2014; Kesler et al., 2013), including filtering data to the <0.1 Hz range of spontaneous activity (Whitfield-Gabrieli and Ford, 2012) and correction of motion and physiologic/non-neuronal artifacts (Behzadi et al., 2007). Correlation coefficients were calculated between fMRI time courses for each pair of 90 regions of interest (ROIs) (Tzourio-Mazoyer et al., 2002) in standard space. The resulting z-score connectivity matrices were thresholded to minimum connection density and then submitted to graph theoretical analysis (Rubinov and Sporns, 2010).

We determined the number of DTI tractography streamlines connecting each pair of ROIs in native space (Kesler et al., 2016; Kesler et al., 2015). Regions were considered connected if one streamline endpoint terminated within one region and the other endpoint terminated within the other region. A threshold of three streamlines was applied to minimize false positive connections (Kesler et al., 2016; Kesler et al., 2015). We weighted each valid edge using the product of the streamline number and fractional anisotropy divided by average ROI volume. These weighted connectivity matrices were submitted to graph theoretical analysis.

We focused on connectome efficiency of information processing. The connectome is organized in such a manner that most regions are connected to their neighbors and can be reached by every other region via a small number of steps or paths (Latora and Marchiori, 2001). Efficient information processing is assumed to follow the shortest paths between regions (eFigure 1) (Latora and Marchiori, 2001). We previously demonstrated impaired connectome efficiency associated with adult-onset cancer (Kesler et al., 2017b; Kesler et al., 2015).

2.5. Statistical Analyses

Global and local connectome efficiencies were compared between executive function groups (impaired or unimpaired) using ANCOVA with sex, age at diagnosis, maternal education, and treatment (low vs. standard/high risk) as covariates. Age at evaluation also differed between functional groups but was highly collinear with age at diagnosis ($r = 0.93$, $P < 0.001$) so only age at diagnosis was included in our models. To

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further evaluate the effect of age at diagnosis and sex on connectome efficiency, we tested differences in global efficiency between four age at diagnosis groups defined arbitrarily using quantiles and in a data-driven manner using K-means clustering. Age groups were evaluated across the entire sample and within females and males separately using omnibus ANCOVA followed by pairwise t-tests, controlled for multiple comparisons with false discovery rate (FDR) (Benjamini and Yekutieli, 2001). These analyses were conducted in the R Statistical Package v3.3.2 (R Foundation). Hypothesis tests were two-sided and considered significant when p values were < 0.05.

We used a network-based statistic approach to determine the specific regional profile of structural and functional connectivity differences between the executive function groups. This method identifies connected substructures, or components, within the larger network. Permutation testing with 5000 permutations was then used to determine group differences in components controlling for multiple comparisons using family-wise error (FWE) (Zalesky et al., 2010). Covariates as described above were included in these models. We also examined network modularity, which involves decomposing the brain into non-overlapping groups of regions (modules) that have maximal within-group connections and minimal between-group connections.(Sporns and Betzel, 2016) Modularity was compared between groups using permutation testing with 1000 permutations (Pereira et al., 2016; Zalesky et al., 2010).

We computed two-tailed partial correlations controlling for sex, age at diagnosis, treatment and maternal education between connectome efficiencies and executive function test scores. Efficiencies included global and local efficiency as well as regional efficiency (i.e. mean efficiency of significant network components). Correlations were FDR corrected and only those that survived correction for global/local efficiencies were examined for regional efficiency. We also calculated partial correlations between connectome efficiencies and chemotherapy exposure variables.

We predicted functional connectivity from structural connectivity by generating simulated functional connectivity matrices based on network communication measures (path transitivity, search information and shortest path length) derived from structural

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connectivity and then computing the correlation between the simulated and observed matrices for each participant (Goñi et al., 2014; Honey et al., 2009). Between group difference in these correlations was measured using ANCOVA as described above.

3. Results

3.1. Participants

We included 161 participants, of whom 61 (37.9%) were impaired on measures of executive function. On average participants in both groups were 14 years old at the time of data collection, and between six and seven years old at the time of their ALL diagnosis. 64% of the impaired group were male compared to 41% of the non-impaired group. Demographic and medical data for the Non-impaired and Impaired groups are displayed in Table 1.

3.2. Functional Connectome

All participants demonstrated expected small-world connectome organization as indicated by small-worldness index greater than one (Humphries and Gurney, 2008). Global efficiency was significantly lower ($F = 4.09$, $P = 0.046$) while local efficiency was moderately higher ($F = 3.42$, $P = 0.068$) in survivors with executive dysfunction (Table 2). Sex was a significant covariate in both models ($P < 0.04$) as more males had executive dysfunction. Treatment group was also a significant covariate in both models ($P < 0.05$) indicating that standard/high risk patients had lower global and higher local efficiency than low risk patients. Age at diagnosis did not contribute to the models ($P > 0.25$) and age group analyses were not significant ($P > 0.46$).

Lower global efficiency was associated with higher number of intrathecal methotrexate treatments ($r = - 0.21$, $P = 0.036$) but was not significantly correlated with methotrexate AUC ($r = 0.09$, $P = 0.416$). Local efficiency was not correlated with either treatment variable ($P > 0.45$). The effect of treatment group on connectome efficiencies was likely driven in part by number of intrathecal treatments, which was significantly higher in standard/high compared to low risk patients ($t = 10.70$, $P < 0.0001$).

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Regional analysis indicated hyper-connectivity of a mesial-lateral-posterior network in survivors with executive dysfunction ($P = 0.037$, FWE corrected, Figure 1). Modularity was lower in the impaired group ($P < 0.0001$). Non-impaired participants showed a typical profile of modules consistent with distinct salience, sensorimotor, default mode and attention/executive networks. The impaired group demonstrated poor separation between sensorimotor and attention/executive, default mode and attention/executive, and salience and sensorimotor networks (Figure 2).

Partial correlations demonstrated direct relationships between global efficiency and executive function test scores ($P < 0.006$) and negative correlations between local/regional efficiencies ($P < 0.005$) and executive function test scores (eTable 2).

3.3. Structural Connectome

All participants demonstrated expected small-world connectome organization as indicated by small-worldness index greater than one.(Humphries and Gurney, 2008) Both global ($F = 5.02$, $P = 0.027$) and local ($F = 5.31$, $P = 0.023$) efficiencies were lower in the executive dysfunction group (Table 2). Age at diagnosis was the only significant covariate in these models ($P < 0.004$). The quantile based age at diagnosis group analyses was significant ($P < 0.0001$) and indicated that children diagnosed at approximately age five years or younger tend to be the most vulnerable to alterations of structural brain network efficiency. A similar finding was observed using K-means clustering (Figure 3). There did not appear to be a sex interaction given that both younger females and younger males demonstrated lower efficiency compared to older children. There were no differences in efficiency between sexes within each age group and no differences in sex between the age groups or clusters ($P > 0.507$).

There were no significant differences between the groups in terms of regional structural connectivity or modularity.

None of the partial correlations between efficiencies and executive function test scores survived correction (eTable 3). There were no significant correlations between efficiencies and chemotherapy exposure variables.

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3.4. Relationship Between Structure and Function

Structural connectivity significantly predicted functional connectivity in all participants (mean r = 0.28 (0.05), range = 0.18-0.41, $P < 0.0001$) but there was no between group difference (P = 0.876).

4. Discussion

We examined neural mechanisms underlying cognitive impairment in adolescent and young adult survivors of pediatric ALL by measuring structural and functional connectome properties in survivors with and without executive dysfunction. Global efficiency of information exchange, a measure of brain network integration and capacity for parallel information processing, was significantly lower in survivors with executive function impairment compared to those without impairment. This finding was observed in both functional and structural connectomes. Global efficiency was lowest for survivors who were younger at diagnosis, had a history of standard/high treatment with higher dose of dexamethasone, and a higher number of intrathecal methotrexate injections. Additionally, we noted direct correlations between global efficiency and performance on several executive function tests including those measuring abstract reasoning, verbal fluency and shifting attention. Global efficiency deficits have been observed in several other pediatric conditions that are associated with cognitive impairment (Rudie et al., 2012; Thompson et al., 2016; Yuan et al., 2015).

Brain injury and associated cognitive deficits following pediatric ALL is believed to stem in part from direct and indirect effects of chemotherapy. Methotrexate is an antimetabolite agent that targets the folate pathway and is administered throughout the entire treatment of ALL, generally two or more years in duration (Cooper and Brown, 2015). Methotrexate is also administered intrathecally to treat and/or prevent CNS disease. Methotrexate has been associated with several neuropathologic effects including glial progenitor cell death, suppression of neurogenesis, microvascular damage, and leukoencephalopathy, among others (Monje and Dietrich, 2012; Seigers et al., 2009; Seigers et al., 2010; Shuper et al., 2002). Accordingly, we demonstrated that higher

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number of intrathecal injections containing methotrexate was associated with lower functional global efficiency.

Patients with standard/high risk disease also received 50% higher cumulative dosage of dexamethasone compared to low-risk patients. The cytotoxic action of dexamethasone and other glucocorticoids involves binding of glucocorticoid receptors (Inaba and Pui, 2010). These receptors have been shown to play important roles in cognition, particularly memory functions (Barsegyan et al., 2010; Meir Drexler and Wolf, 2016). Previous studies involving survivors of pediatric ALL have shown associations between dexamethasone treatment and brain function (Edelmann et al., 2013; Waber et al., 2013). Previous studies investigating the steroid-induced long-term neurocognitive outcomes have not found significant differences between prednisone and dexamethasone (Warris et al., 2014). However, these previous studies have been confounded by the inclusion of survivors treated with cranial radiation therapy. For example, in one trial, the investigators did not adjust for radiation dose or check for radiation/corticoid steroid interactions, thus any differences between prednisone and dexamethasone may have been confounded by radiation therapy. Another trial did find that the dexamethasone group used more special education services and this intervention may have ameliorated some of the neurocognitive late-effects. Finally, all three trials that have previously compared prednisone and dexamethasone outcomes, have used intrathecal hydrocortisone, which when combined with intrathecal methotrexate would produce the same proposed injury as dexamethasone and methotrexate (Warris et al., 2014).

Patients treated on standard/high risk ALL regimens showed lower functional global efficiency compared to those treated on low risk regimens. Since patients were treated with risk-adapted therapy, those with higher risk disease received more aggressive therapy regimens (Cooper and Brown, 2015). However, leukemia itself likely has an independent effect on brain structure and function. Emerging evidence suggests that, prior to treatment, solid tumors originating outside the CNS are associated with altered structural and functional connectome organization as well as cognitive impairment (Kesler et al., 2017a; Patel et al., 2015). Little is known regarding the direct impact of hematologic cancer cells on CNS integrity and long-term function. However, we have recently

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demonstrated that children diagnosed with ALL have evidence of brain white matter injury prior to initiation of chemotherapy (Cheung et al., 2017). The contribution of disease pathogenesis alone to brain injury and cognitive impairment in ALL has received limited attention and requires further study.

Younger age at diagnosis was another significant risk factor, which has been noted in several previous studies (Kahalley et al., 2013; Kesler et al., 2014; Reddick et al., 2014). Our findings further demonstrated that children diagnosed at approximately age five or younger tend to have the highest risk for impaired connectome efficiency. The number of white matter tracts is established by approximately four years of age and structural connectomes become more integrated over time, i.e. global efficiency increases with age as longer tracts continue to develop (Richmond et al., 2016). Our regional findings also point to neurodevelopmental mechanisms. The impaired group demonstrated regional hyper-connectivity between postcentral gyri and other regions important for somatosensory, auditory and visual functioning. These brain regions are among those that mature earliest and may therefore be preferentially vulnerable to early brain injury (Gogtay and Thompson, 2010). Our group and others have shown that temporal lobe regions are particularly sensitive to early brain injury (Kesler et al., 2006). In the context of lower global efficiency, our regional results suggest that local functional networks may be overly segregated and not well integrated with other processing centers. Accordingly, there were significant negative correlations between functional local efficiency and performance on executive function tests.

It is unclear why age was associated with structural but not functional connectome properties or why sex was associated with functional but not structural metrics. DTI and fMRI measure different neurobiologic properties and therefore tend to have divergent associations with demographic and other data. It is possible that age has a greater effect on white matter development while sex has a larger impact on functional dynamics. Few studies in this population (and others) include examination of multi-modal connectomes and therefore these relationships require further examination.

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Additionally, the impaired group demonstrated significantly fewer modules in the functional connectome compared to the non-impaired group. Previous studies demonstrate that the brain network is decomposable into distinct modules or subnetworks representing known functional components (Chen et al., 2013; Grayson and Fair, 2017). In the impaired group, the executive function/attention network was overly connected to default mode and sensorimotor networks. Modularity is present very early in brain development, although in a primitive form that is dominated by sensorimotor networks. Salience, executive/attention and default mode networks tend to be refined and distinguished over time (Grayson and Fair, 2017). This is consistent with our observation that regions of functional hyper-connectivity largely involved sensory systems and again suggests that ALL and its treatments disrupts normal brain maturation. Lower modularity may result in a brain network that is less adaptable, flexible and resilient (Sporns and Betzel, 2016).

Structural and functional connectomes showed global correspondence but there were also inconsistencies including local efficiency, regional differences, modularity and correlations with chemotherapy exposure variables and executive function performance. Our findings may simply reflect differences in neural properties, network densities, and imaging modalities (Bassett et al., 2011). Cunningham et al. (2017) suggested that differences in structural and functional connectivity may reflect the dynamic nature of functional networks and/or limitations of DTI. It is also probable that structure-function relationships are nonlinear, which was beyond the scope of this study and requires further investigation.

This study had several limitations. Certain results are difficult to interpret without data from a typically developing comparison group. It is possible that our “non-impaired” group would be impaired relative to healthy, non-cancer controls. However, comparing patient with and without executive dysfunction is a strength of the study and represents an important examination of cognitive deficit that is unique in this field. This comparison provides insight regarding potential neural mechanisms of deficit that are independent of disease and treatment, not just the divergence from typical development. The cross-sectional design prevented evaluation of independent effects of chemotherapy, cancer

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pathogenesis and other factors. Currently, there is no standard definition of cognitive impairment and while ours was consistent with methods used in other studies, alternate definitions of impairment may yield different results. Our DTI acquisition had lower resolution than many similar studies, which may have contributed to the lack of overlap with functional connectome topology. This possibility seems unlikely given that other studies observing inconsistencies between structural and functional connectivity have employed high resolution DTI (Cunningham et al., 2017; Kesler et al., 2017a; Rudie et al., 2012). Our fMRI acquisition was relatively short (5 minutes) and obtained with a different field strength compared to DTI. It is well known that test-retest reliability of connectome properties increases with increased scan time (Andellini et al., 2015). However, studies have noted stable and accurate graph metrics using scans as short as two minutes (Whitlow and Maldjian, 2011). Our imaging sequences had to be completed on clinical scanners and were designed and implemented over 8 years ago and acquired over a five year period, given the relative rarity of childhood leukemia. Efficiency of the protocol with respect to scheduling of clinical scanner time had to be balanced with study goals. Additionally, we demonstrated significant and robust correlations between functional connectome properties and neuropsychological test performance suggesting that our fMRI graph metrics represent important biomarkers of cognitive function in this sample. Further, structural connectivity was highly predictive of functional connectivity despite the difference in scanner field strength, which we have also demonstrated preclinically showing that this correlation discriminates between genetic models (Kesler et al., 2018).

5. Conclusion

Our findings contribute novel insights regarding the cognitive effects of ALL and its treatments as well as the neural mechanisms underlying these effects. The innovative aspects of this study include the comparison between functional groups, the combination of structural and functional imaging, the focus on connectome organization, and measurement of chemotherapy exposure. ALL and/or its treatments appear to disrupt normal brain maturational processes including refinement of functional networks that support higher-order cognitive skills such as executive function, attention and monitoring. Our findings highlight the need for interventional strategies that will help prevent and

manage cognitive impairment and normal brain neural network development in patients with pediatric ALL and assist these patients with maintaining brain health across the lifespan.

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Acronyms Page

ALL: acute lymphoblastic leukemia

DTI: diffusion tensor imaging

FA: fractional anisotropy

FDR: false discovery rate

FWE: family-wise error

fMRI: functional magnetic resonance imaging

ROI: region of interest

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Table 1: Demographic and medical data shown as mean (standard deviation) unless otherwise noted

	Non-Impaired (N = 100)	**Impaired (N = 61)**	**t/Chi Sq.**	**p**
Age at Evaluation (years)	14.87 (4.9)	14.23 (4.4)	0.857	0.393
Age at Diagnosis (years)	7.08 (4.6)	6.47 (4.1)	0.875	0.383
Maternal Education (years)	14.04 (2.5)	12.81 (2.3)	3.10	0.002
Gender (male)	40%	64%	8.68	0.003
Treatment Intensity (standard/high risk)	41%	44%	0.165	0.684
Intrathecal methotrexate	14.43 (4.1)	14.77 (4.0)	0.519	0.605
Methotrexate area under the curve	32.20 (11.3)	33.72 (12.15)	0.779	0.438

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Table 2: Connectome efficiency data shown as mean (standard deviation)

	N	Non-impaired	N	Impaired	F	p
Functional Connectome						
Global Efficiency	65	0.580 (0.005)	36	0.578 (0.007)	4.09	0.046
Local Efficiency	65	0.717 (0.012)	36	0.721 (0.014)	3.42	0.068
Modularity*	65	0.348	36	0.3001	-	< 0.0001
Structural Connectome						
Global Efficiency	97	0.162e-2 (0.12e-3)	57	0.158e-2 (0.13e-3)	5.02	0.027
Local Efficiency	97	0.146e-2 (0.94e-4)	57	0.142e-2 (0.11e-3)	5.31	0.023
Modularity*	97	0.4999	57	0.4990	-	0.458
Relationship Between Structural and Functional Connectivity						
Pearson R	62	0.280 (0.049)	32	0.283 (0.054)	0.025	0.876

Footnote. *p values for modularity are obtained using permutation testing of the mean difference so there is no associated F statistic or standard deviation. The mean difference for functional modularity was 0.0479 with a 95% confidence interval of -0.019 to 0.016. The mean difference for structural modularity was 0.0009 with a 95% confidence interval of -0.014 to 0.014.

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Figure Legends

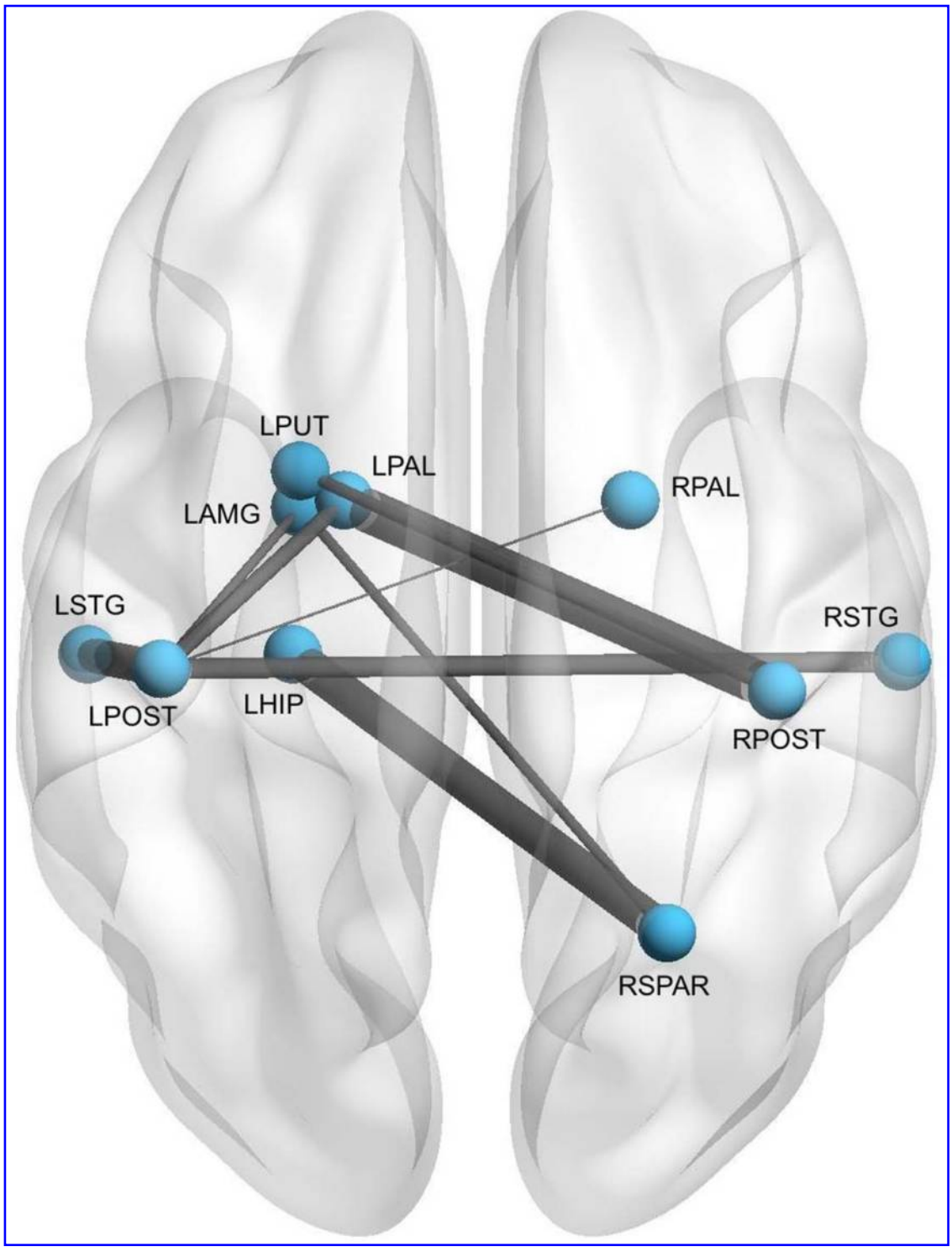

Figure 1. Functional Regional Connectivity. Patients with executive dysfunction demonstrated hyper-connectivity among several regions compared to patients without

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executive dysfunction (*P* = 0.037, corrected). Regions are shown as spheres and their connections as lines, which are weighted by the test statistic for that connection (i.e. thicker line = greater hyper-connectivity). LAMG: left amygdala, LPAL: left palladium, RPAL: right palladium, LPUT: left putamen, RSTG: right superior temporal gyrus, RPOST: right postcentral gyrus, RSPAR: right superior parietal, LHIP: left hippocampus, LPOST: left postcentral gyrus, LSTG: left superior temporal gyrus.

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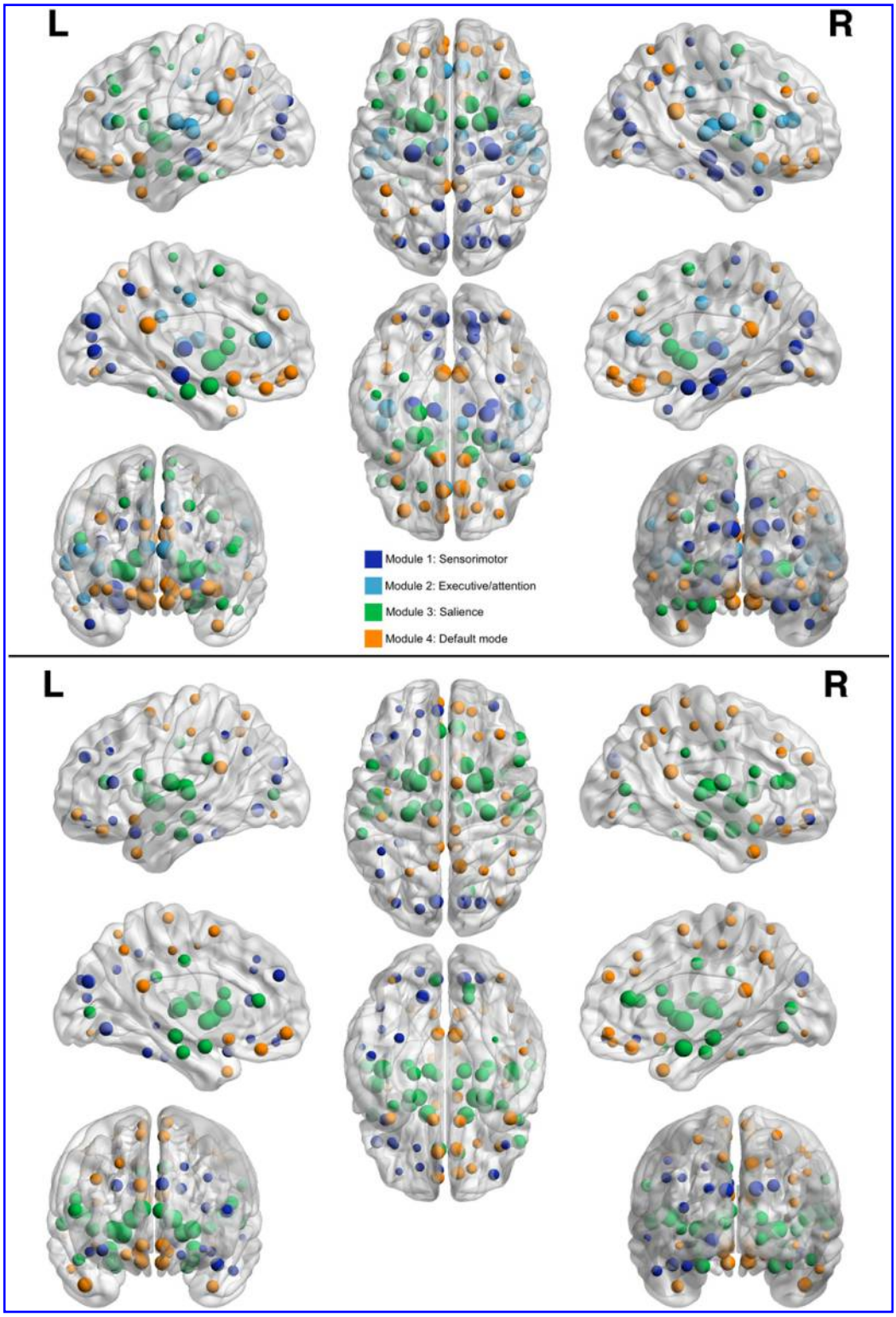

Figure 2. Functional Network Modules. Patients with executive dysfunction demonstrated lower modularity ($P < 0.001$) compared to patients without executive dysfunction

indicating lower separation among networks, consistent with hyper-connectivity. Non-impaired patients (top) showed distinct salience, sensorimotor, default mode and executive/attention networks while the impaired group (bottom) demonstrated overlap between sensorimotor and attention/executive, default mode and attention/executive, and salience and sensorimotor. Regions are show as spheres colored by module membership.

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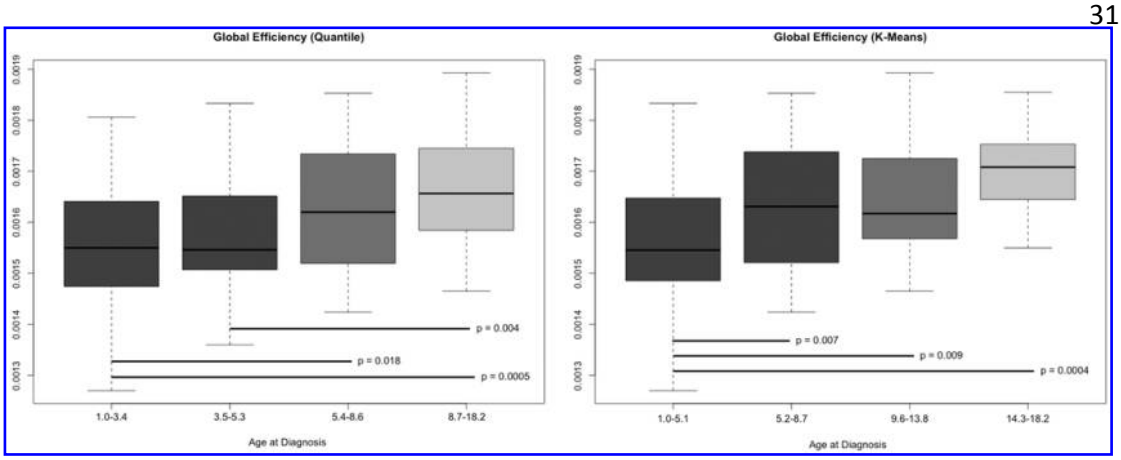

Figure 3. Structural Network Efficiency by Age at Diagnosis Groups. Dividing the sample by age at diagnosis into quantiles or K-means clusters suggested that children approximately age 5 and younger at diagnosis demonstrated the greatest vulnerability to disruption of brain network efficiency. P values are FDR corrected.

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eTable 1. Neurocognitive testing z-scores. Data are shown as mean (standard deviation).

Test Name	Non-Impaired (N = 100)	Impaired (N = 61)	Test Reference
20Q Abstraction	0.057 (1.001)	-0.546 (0.901)	1
20Q Achievement	0.060 (0.862)	-0.322 (0.951)	1
Color-Word Inhibition Switching	0.104 (0.869)	-0.546 (0.963)	1
Trails Number-Letter Switching	0.170 (0.604)	-1.508 (1.131)	1
Letter Fluency	0.060 (0.800)	-1.055 (0.775)	1
Rey Complex Figure Copy	-1.494 (1.899)	-3.585 (2.474)	2
Block Design	0.025 (0.857)	-0.680 (0.986)	3,4
Digits Back	-0.040 (0.942)	-0.628 (1.006)	3,4
Digits Forward	-0.150 (1.048)	-0.678 (0.839)	3,4
Digit Symbol	-0.047 (0.908)	-0.792 (0.895)	3,4
Spatial Span Forward	0.097 (0.898)	-0.590 (0.787)	3,4

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eTable 2. Partial correlations between functional connectome efficiencies and executive function tests

Global Efficiency	R	p	Local Efficiency	R	p	Regional Efficiency	R	p
20Q Abstraction	0.29	0.004*	20Q Abstraction	-0.28	0.005*	20Q Abstraction	-0.15	0.151
20Q Achievement	0.23	0.023	20Q Achievement	-0.2	0.051	20Q Achievement		
Color-Word Inhibition Switching	0.04	0.722	Color-Word Inhibition Switching	-0.02	0.814	Color-Word Inhibition Switching		
Trails Number-Letter Switching	0.1	0.33	Trails Number-Letter Switching	-0.07	0.523	Trails Number-Letter Switching		
Letter Fluency	0.28	0.006*	Letter Fluency	-0.3	0.003*	Letter Fluency	-0.18	0.073
Rey Complex Figure Copy	0.19	0.059	Rey Complex Figure Copy	-0.1	0.326	Rey Complex Figure Copy		
Block Design	0.15	0.15	Block Design	-0.13	0.187	Block Design		
Digits Back	0.18	0.083	Digits Back	-0.05	0.642	Digits Back		
Digits Forward	0.31	0.002*	Digits Forward	-0.31	0.002*	Digits Forward	-0.4	< 0.0001*
Digit Symbol	0.11	0.29	Digit Symbol	-0.11	0.3	Digit Symbol		
Spatial Span Forward	0.1	0.32	Spatial Span Forward	-0.06	0.529	Spatial Span Forward		

Footnote. *p value survives correction for multiple comparisons

eTable 3. Partial correlations between structural connectome efficiencies and executive function tests

Global Efficiency:	R	p	Local Efficiency	R	p
20Q Abstraction	-0.03	0.683		-0.05	0.552
20Q Achievement	-0.1	0.231		-0.167	0.039
Color-Word Inhibition Switching	0.153	0.061		0.19	0.021
Trails Number-Letter Switching	0.01	0.876		0.04	0.667
Letter Fluency	0.04	0.656		0.08	0.328
Rey Complex Figure Copy	-0.05	0.552		-0.03	0.726
Block Design	-0.19	0.02		-0.15	0.063
Digits Back	-0.04	0.648		0.02	0.784
Digits Forward	0.06	0.432		0.07	0.413
Digit Symbol	0.06	0.445		0.11	0.165
Spatial Span Forward	0.03	0.746		0.15	0.062

Footnote. No p values survived correction for multiple comparisons

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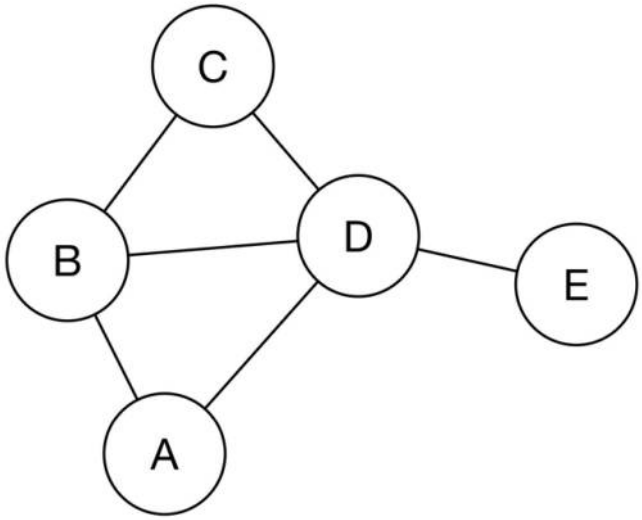
Online-Only Supplements

eFigure1. Network Efficiency.



$$E_{glob} = {}^{1}/_{n(n-1)\sum_{i,j} d(v_i, v_j)}$$

$$E_{loc} = {}^{1}/_{n}\sum E(G_i)$$

Efficient information exchange between brain regions is assumed to follow the shortest path between those regions. As illustrated here, there are several possible paths or routes from region A to region E with A→D→E being the shortest or most efficient. Global efficiency (E_{glob}) of a network is defined as the average inverse shortest path length across all regions in the network where n is the number of regions and $d(v_i, v_j)$ is the length of the shortest path between regions i and j. Local efficiency is the average efficiency (E) of the local subgraphs (G_i).