Quantitative In-vivo Imaging of the Impact of Cancer Therapy on the Normal Pediatric Brain

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The Clinical Problem

- **Acute lymphoblastic leukemia (ALL) is the most common childhood cancer**
  - Affecting 2,400 children annually in the US
  - Young age at diagnosis and high survival rate

- **Brain Tumors are the most common solid tumors of childhood**
  - Affecting 3,110 children annually in the US
  - Most common cause of cancer related death in children
  - High rate of severe morbidity

Source: CBTRUS and SEER
Increasing Importance of Neurotoxicity

% survival

1930 1950 1970 1990

ALL

CNS

Source: CBTRUS and SEER

RJ Gilbertson
Independent Research Program
Probing Substrates of Neurotoxicity

**Basic Research Focus:** Development of innovative algorithms and methods to quantify the structure and integrity of cerebral white matter *in vivo*

**Clinical Research Focus:** Use non-invasive imaging technology to quantify neurostructural changes resulting from radiological or pharmacological insult

**Ultimate Goal:** To assist in the development of therapy that would prevent, mediate, or intervene to minimize impact of neurotoxicity in survivors of pediatric cancer
Translational Imaging Research

- **Basic Research**
  - Image Registration and Fusion
  - RF Correction
  - Segmentation
  - Volume of Interest Analyses
  - Diffusion and Perfusion

- **Clinical Research (BT)**
  - Historical Background
  - Most Recent Results
  - Ongoing Studies

- **Clinical Research (ALL)**
  - Most Recent Results
  - Ongoing Studies
3D Affine Registration

Within an examination

Between examinations
Fusion of RT Dose with Segmented MR
Bias Field Correction (in plane)

(Ji et al. MRM [in prep], 2005)
Bias Field Correction (between planes)

Bias Field Correction (between planes)

PD Intensity (a.u.)

Section Number

0 5 10 15 20

Pre

Post
Kohonen Self-Organizing Map (Segmentation)

Learning Algorithm

\[ \Delta \text{weight}_{i,j} = \left( \text{neigh}(\text{iter}) \right)^2 \left[ \text{input}_j - \text{weight}_{i,j} \right] \]

\[ \text{neigh}(\text{iter}) = \eta \exp \left[ -\frac{\left( x^2 + y^2 \right)}{2 \sigma^2} \right] \]

\[ \eta = 0.005 \frac{\text{iter}}{\text{iter}_{\text{max}}} \]

\[ \sigma = 3 \left( 0.4 \frac{\text{iter}}{\text{iter}_{\text{max}}} \right) \]

(Reddick et al. *IEEE-TMI*, 1997)
SOM of Normal Examination

Intra-class correlations for N = 14

White matter \( r_i = 0.91 \) (\( p < 0.01 \))
Gray matter \( r_i = 0.95 \) (\( p < 0.01 \))
CSF \( r_i = 0.98 \) (\( p < 0.01 \))

(Reddick et al. *MRM*, 2002)
SOM of Abnormal Examination

T1  T2  PD  FLAIR

(Som et al. MRM, 2002)
Additional Refinements

<table>
<thead>
<tr>
<th>FLAIR</th>
<th>SOM-02</th>
<th>SOM-03</th>
<th>SOM-04</th>
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<tbody>
<tr>
<td>Obs 1</td>
<td>0.651</td>
<td>0.653</td>
<td>0.744</td>
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<tr>
<td>Obs 2</td>
<td>0.602</td>
<td>0.615</td>
<td>0.699</td>
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</table>

Kappa measure of agreement (N = 15)

(Glass et al. MRM, 2004)
Index vs Expanded Sampling
Expand Coverage
3D Visualization

Regional Analysis

Prefrontal
Frontal
Parietal / Mid-Temporal
Parietal / Occipital

(Mulhern et al. JINS, 2004)
Quantifying White Matter Integrity

FLAIR  SOM  ADC  FA
Quantifying White Matter Perfusion
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Why Normal-Appearing White Matter?

Two age-matched groups treated for brain tumors of the Posterior Fossa

<table>
<thead>
<tr>
<th>Variable</th>
<th>MB (N=18)</th>
<th>LGA (N=18)</th>
<th>Significance</th>
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<tbody>
<tr>
<td>FSIQ</td>
<td>82.0 ± 10.9</td>
<td>92.9 ± 15.7</td>
<td>P=0.026</td>
</tr>
<tr>
<td>ICV</td>
<td>82.5 ± 5.4</td>
<td>85.2 ± 6.0</td>
<td>NS</td>
</tr>
<tr>
<td>White</td>
<td>21.4 ± 4.4</td>
<td>24.7 ± 5.7</td>
<td>P=0.008</td>
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<tr>
<td>Gray</td>
<td>52.6 ± 5.1</td>
<td>54.3 ± 6.1</td>
<td>NS</td>
</tr>
<tr>
<td>CSF</td>
<td>8.1 ± 4.0</td>
<td>6.1 ± 4.5</td>
<td>NS</td>
</tr>
</tbody>
</table>

(Reddick et al. *MRI*, 1998)
A New Understanding of Decreasing IQ

(Palmer et al. JCO, 2001)
Linking Therapy & Neurocognitive Deficits

Cross sectional study of Medulloblastoma survivors (N=42)

Age at irradiation significantly associated with FSIQ
($R^2 = 0.170; P = 0.006$; controlled for time since irradiation)

Mediational model: ~70% of association explained by Normal Appearing White Matter

(Mulhern et al. JCO, 2001)
Model explains: ~ 60% of variance in reading
~ 60% of variance in spelling
~ 80% of variance in math

Most Recent Results

- Longitudinal study of 324 MR exams from 52 subjects treated for Medulloblastoma
  - All received 36 Gy CSI
  - 19 had shunts placed
  - Median age @ irradiation 8.3 yrs (3.4 to 20.0 yrs)
  - Median time since irradiation 2.5 yrs (-0.2 to 7.9 yrs)

- Cross-sectional study of a subset of 19 patients age similar to controls and without shunts
  - Single most recent MR
  - Age at examination 13.0 ± 3.1 yrs

- 26 healthy sibling controls imaged once
  - Age at examination 12.6 ± 3.4 yrs

A Gajjar
Longitudinal Brain Volume Development

Younger at RT

Older at RT

(Reedick et al. *Neuro Onc*, 2005)
Longitudinal Brain Volume Development

**Younger at RT**

**Older at RT**

(Reddick et al. Neuro Onc, 2005)
Longitudinal Brain Volume Development

Longitudinal Brain Volume Development (Reddick et al. Neuro Onc, 2005)

p<0.001
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Most Recent Results

Longitudinal study of 164 MR exams from 45 subjects treated for ALL on Total 14

<table>
<thead>
<tr>
<th></th>
<th>Low Risk</th>
<th>Standard / High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Subjects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post 1 IV-MTX</td>
<td>21</td>
<td>23</td>
</tr>
<tr>
<td>Post 4 IV-MTX</td>
<td>20</td>
<td>21</td>
</tr>
<tr>
<td>Post 7 IV-MTX</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>End of Therapy</td>
<td>20</td>
<td>17</td>
</tr>
<tr>
<td>Gender</td>
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</tr>
<tr>
<td>Male</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Female</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Age at Diagnosis (years)</td>
<td>5.0 ± 2.7</td>
<td>9.2 ± 4.8</td>
</tr>
</tbody>
</table>
Prevalence of LE

Standard / High-Risk
Low-Risk

(Reddick et al. AJNR [in press], 2005)
Transient vs. Persistent

Week 5  20  45  132  240

KJ Helton
Proportion WM affected

- 35% (p = 0.002)
- 30% (p = 0.046)
- 25% (p = 0.010)
- 20%
- 15%
- 10%
- 5%
- 0%

Week on Protocol:
- 5
- 20
- 45
- 132

Standard / High-Risk
Low-Risk

(Reddick et al. AJNR [in review], 2005)
Intensity of LE

Standard / High-Risk
Low-Risk

(Reddick et al. AJNR [in review], 2005)
Relationship Between Intensity Measures

(Reddick et al. AJNR [in review], 2005)
Translational Imaging Research Summary

Basic Research

- Developed essential novel image processing capabilities which were optimized for specialized clinical research applications
- Continue to develop innovative algorithms and methods to quantify the structure and integrity of cerebral white matter *in vivo*

Clinical Research

- Used non-invasive imaging technology to quantify neurostructural changes resulting from radiological or pharmacological insult and related these changes to neurocognitive performance
Translational Imaging Research Summary

Building on extensive experience with MB

- New studies designed to combine radiation dosimetry maps with MR imaging measures of perfusion and diffusion
- Investigate the integrity of white matter microvasculature and axonal myelin
- Changes in these measures is hypothesized to precede more global changes in cerebral white matter volume
- 120 subjects with 1560 MR exams
Building on preliminary experience with ALL

- Ongoing ALL study designed to test hypotheses that early changes in MR imaging measures are:
  - predictive of later white matter changes
  - proportionate to exposure to HDMTX
  - related to CSF and plasma homocysteine
  - predictive of treatment-induced neurocognitive deficits and diminished quality of life in survivors
  - 300 subjects with 1200 MR examinations
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