ICCTF
International Cognition and Cancer Task Force Conference
March 15-17th, 2012
PARIS - FRANCE

This event is supported by:

[Logos of sponsors: GSK, Janssen, Novartis, Pfizer, Roche, Sanofi Aventis]
Longitudinal assessment of chemotherapy-induced structural changes in cerebral WM and its correlation with impaired cognitive functioning in breast cancer patients

S. Deprez, F. Amant, J. Verhoeven, A. Smeets, M-R. Christiaens, A. Leemans, R. Peeters, W. Vanhecke, J. Vandenberghe, M. Vandenbulcke, and S. Sunaert
Breast cancer incidence in Western countries is 1 in 8

Survival rate is increasing

10-40% suffer mild cognitive impairment after systemic adjuvant treatment
  - Impact on quality of life

The pathophysiology is still unclear
Candidate Mechanisms

Immune dysregulation

Induced hormonal changes

Genetic predisposition
  (APOE E4 allele?)

Changes in:
  - cognition
  - brain structure
  - function

Direct neurotoxicity

Oxidative stress and DNA damage

TA Ahles and AJ Saykin, 2007
Possible WM injury?

Changes in WM microstructure measurable with MR Diffusion Tensor Imaging (DTI)?

Potential mechanism = direct neurotoxicity
Based on the measurement of diffusion of water molecules in the brain.

**Diffusion tensor imaging**

Visualisation AND quantification of white matter

\[ D \text{ is equal in all directions} \rightarrow \text{isotropic diffusion} \]

Courtesy Van Hecke W.
Diffusion tensor imaging
Visualisation AND quantification of white matter

Biological tissue: hindered diffusion
- Cell membranes
- Myelin sheaths
- Subcellular structures
  (Hajnal et al., 1991)

D is not equal in all directions

anisotropic diffusion

$D = \begin{pmatrix}
\lambda_1 \\
\lambda_2 \\
\lambda_3 
\end{pmatrix}$
Diffusion tensor imaging
Visualisation AND quantification of white matter

Fractional Anisotropy

\[ FA = \sqrt{\frac{3}{2}} \sqrt{\frac{(\lambda_1 - \bar{\lambda})^2 + (\lambda_2 - \bar{\lambda})^2 + (\lambda_3 - \bar{\lambda})^2}{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}} \]

↑ anisotropy
Diffusion tensor imaging
Visualisation AND quantification of white matter

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Courtesy Van Hecke W.
Evaluate possible changes in WM structure and link with cognitive functioning

- Attention / Concentration
- Processing speed
- Memory
- Executive functioning

Are there changes in WM structure PRE vs POS?

Aim of present LONGITUDINAL study

Self-rated subjective questionnaires
- Cognitive functioning
- Depression
- Anxiety
Subjects

Subjects (age:35-50y)
- 34 C+ breast cancer patients
- 16 C- breast cancer patients
- 19 matched healthy controls

9 months

- Surgery
- t1
- Chemotherapy
- t2

- DTI imaging
  - 3T Intera Philips
  - 45 gradient
  - b=800 s/mm²
- Cognitive testing

- DTI imaging
  - 3T Intera Philips
  - 45 gradient
  - b=800 s/mm²
- Cognitive testing
### Subjects

<table>
<thead>
<tr>
<th></th>
<th>C+ Patients (n=34)</th>
<th>C- Patients (n=16)</th>
<th>Healthy controls (n=19)</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MEAN</td>
<td>SD</td>
<td>MEAN</td>
<td>SD</td>
</tr>
<tr>
<td>Age (years)</td>
<td>44.4</td>
<td>5.6</td>
<td>41.9</td>
<td>5.8</td>
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<tr>
<td>Depression BDI</td>
<td>7.3</td>
<td>5.2</td>
<td>5.3</td>
<td>3.4</td>
</tr>
<tr>
<td>Anxiety STAI</td>
<td>34.4</td>
<td>9.2</td>
<td>35.9</td>
<td>6.2</td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>114.5</td>
<td>9.1</td>
<td>112.4</td>
<td>7.1</td>
</tr>
</tbody>
</table>

- No significant differences in age, IQ, anxiety
- Significant difference in depression score
  
  Include as covariate in statistical analysis
1. Motion and eddy-current correction
2. B-matrix rotation
3. Tensor estimation (iterative, non-linear)
4. Affine + VF Non-rig registration
5. Tensor reorientation (PPD)

FA map
Registered FA map
Smoothed FA map

6. Anisotropic Smoothing

Population-based Atlas
Assessment of changes in FA

Pre processed FA maps at t1

Pre processed FA maps at t2

SPM8 Voxel-based PAIRED t test with BDI and IQ as cov of no interest

Statistical thresholding at p<0.001
Significant decreased FA at t2 vs t1 in C+
**Significant decreased FA:**
Results in control groups

**NO significant differences between t1 and t2**
For BOTH control groups C- and HC
Neuropsychological tests covering:

- **Attention** (Bourdon-Wiersma, Every Day Attention (TEA), Digit span, CORSI block span)
- **Psychomotor speed** (WAIS digit symbol, 9 hole Pegboard test (9HPT))
- **Memory** (AVLT, RVLT)
- **Executive function** (Stroop, Trail Making Test, COWAT)
- **Verbal IQ**

Self-rated subjective questionnaires:

- **Cognitive Failure Questionnaire** (CFQ)
- **Spielberger State-Trait Anxiety Inventory** (STAY)
- **Beck Depression Inventory** (BDI)
NP assessment
PAIRED T-test t1 vs t2

**C+**

**Performance Sign ↓**

- **t2 vs t1**
  - Attention and concentration
    - WAIS letter number sequencing (p=0.01)
  - Psychomotor speed
    - 9PEG (p=0.03 and p=0.007); WAIS digit/symbol (p=0.04)
  - Verbal memory
    - AVLT (p=0.02 and p=0.04)

**C-**

**Performance Sign ↑**

- **t2 vs t1**
  - Attention and concentration
    - Bourdon Wiersma (p=0.01); Every day attention (p=0.04)
  - Memory
    - Verbal memory (p=0.004); Visual memory (p=0.01)

**HC**

**Performance Sign ↑**

- **t2 vs t1**
  - Attention and concentration
    - WAIS digit span (p=0.01); Every day attention (p=0.001)
  - Psychomotor speed
    - 9PEG (p=0.4)
  - Verbal memory
    - AVLT (p=0.006)
## Correlation analysis in C+

### Pearson Correlation

<table>
<thead>
<tr>
<th>Region</th>
<th>WM tract</th>
<th>Test</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cluster 1 Parietal</td>
<td>Cluster covering corona radiata, corpus callosum</td>
<td>Attention Digit span</td>
<td>0.006</td>
</tr>
<tr>
<td>Cluster 2 Parietal</td>
<td>Superior longitudinal fasciculus</td>
<td>Attention Digit span</td>
<td>0.01</td>
</tr>
<tr>
<td>Cluster 3 Frontal</td>
<td>Superior longitudinal fasciculus</td>
<td>Verbal Memory AVLT learning</td>
<td>0.02</td>
</tr>
<tr>
<td>Cluster 4 Occipital</td>
<td>Forceps major</td>
<td>Verbal Memory AVLT learning</td>
<td>0.04</td>
</tr>
</tbody>
</table>

$\Delta FA$ (t2 - t1) in the 4 identified clusters

$\Delta$ test scores (t2 – t1)

* Corrected for multiple comparisons
Correlation analysis in C+
Subjective cognitive complaints

Correlation changes self-report and NP test performance:

- $\Delta$ CFQ distraction and $\Delta$ attention test, verbal memory ($p<0.05$)
- $\Delta$ CFQ name and word finding and $\Delta$ COWAT ($p=0.02$)
Summary

<table>
<thead>
<tr>
<th>C+</th>
<th>C-</th>
<th>HC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DTI FA analysis</strong></td>
<td><strong>FA Sign ↓</strong></td>
<td><strong>No sign ≠</strong></td>
</tr>
<tr>
<td><strong>NP analysis</strong></td>
<td><strong>Performance Sign ↓ or =</strong></td>
<td><strong>Performance Sign ↑ or =</strong></td>
</tr>
<tr>
<td><strong>Self evaluation</strong></td>
<td><strong>Cognitive complaints Sign ↑</strong></td>
<td><strong>Cognitive complaints =</strong></td>
</tr>
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</table>

Correlation between ∆ FA and ∆ performance for C+
Chemotherapy seems to affect WM microstructure

This decrease in FA could be correlated with a decrease in performance on memory and attention tests

DTI WM parameters seem to have the required sensitivity to quantify chemotherapy-induced changes

Deprez et al, Journal of Clinical Oncology 2012
Thanks!!
Cross-sectional DTI study

- C+ lower FA in Frontal, Temporal WM then controls
- C+ lower MD in Frontal WM then controls

Deprez et al, Human Brain Mapping, 2011

+ Significant correlations of FA and NP

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Assessment of changes in FA

- 4 regions where FA significantly > at t1 vs t2

<table>
<thead>
<tr>
<th>Region</th>
<th>Cluster p FWE</th>
<th>Cluster size</th>
<th>WM tract</th>
<th>T value</th>
<th>Mean FA C+ POS</th>
<th>Mean FA C PRE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parietal</td>
<td>0.002</td>
<td>146</td>
<td>Cluster covering corona radiata, corpus callosum</td>
<td>6.44</td>
<td>0.336</td>
<td>0.350</td>
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<tr>
<td>Parietal</td>
<td>&lt; 0.001</td>
<td>197</td>
<td>Superior longitudinal fasciculus</td>
<td>5.52</td>
<td>0.206</td>
<td>0.217</td>
</tr>
<tr>
<td>Frontal</td>
<td>0.021</td>
<td>91</td>
<td>Superior longitudinal fasciculus</td>
<td>5.15</td>
<td>0.297</td>
<td>0.311</td>
</tr>
<tr>
<td>Occipital</td>
<td>0.017</td>
<td>96</td>
<td>Forceps major</td>
<td>4.78</td>
<td>0.268</td>
<td>0.280</td>
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</tbody>
</table>
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