Diffusion Tensor Imaging in Schizophrenia

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Schizophrenia

- One of the top 10 causes of disability worldwide (WHO 2001)
- Typical Onset in Late Adolescence and Early Adulthood
- Positive Symptoms
  - Delusions
  - Hallucinations
  - Disorganized Speech and Behavior
- Negative Symptoms
  - Flattened Affect
  - Alogia - lack of speech
  - Anhedonia - inability to feel pleasure
  - Avolition - lack of energy, spontaneity and initiative
Oligodendroglia and White Matter

- Oligodendroglia produce myelin in the CNS
- One oligodendroglia myelinates several axons
- Multiple oligodendroglia can myelinate one axon
- Neighboring sections of myelin may come from different oligodendroglia

http://homepage.psy.utexas.edu/homepage/class/Psy332/Salinas/Cells/Cells.html
Myelin and Schizophrenia

Downregulation of Myelin related genes in chronic schizophrenia (Hakak et al., 2001)

<table>
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<th>Table 1. Genes differentially expressed in chronic schizophrenia</th>
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<td><strong>Fold change</strong></td>
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Genes with altered expression levels in schizophrenia samples in comparison with control samples. Genes are clustered into groups by biological function. Genes not classified are also listed. The mean fold-change of each gene in schizophrenia samples relative to control samples, as well as the P value and GeneBank accession number are indicated. Genes with decreases in expression levels are highlighted in red.
Myelin and Schizophrenia

- Decrease in the number and health of oligodendroglia in correlation with an increase in neuronal density in prefrontal, occipital and temporal cortex and deep white matter in patients with schizophrenia. (Davis et al., 2003)

- Whole brain white matter reduction in a metaanalysis of 58 MRI studies on schizophrenia (Wright et al., 2000)
Myelin and Schizophrenia

- **Regional Reductions in White Matter on MRI**
  - Prefrontal Cortex (Brier et al., 1992; Buchanan et al., 1998; Sanfilipo et al., 1992; Sigmundsson et al., 2001)
  - Cingulate (Paillère-Martinot et al., 2001)
  - Internal Capsule (Paillère-Martinot et al., 2001; Zhou et al., 2003)
  - Combined Dorsolateral Frontal, Temporal and Occipital Lobes (Mitelman et al., 2003)
**Diffusion Tensor MRI**

- Measures the diffusion of water with a measure known as anisotropy

![Diffusion Tensor MRI Diagram]

- Due to the shape of axons and the barrier to water diffusion provided by the myelin sheath, anisotropy can be used as a measure of white matter confluence.

- **Low Anisotropy** - Unorganized, Crossing or Unhealthy Axons
- **High Anisotropy** - Highly Organized Healthy Axon Bundles

(Adapted from Lim et al., 1999)
Anisotropy

Fig. 754.—Diagram showing principal systems of association fibers in the cerebrum.
Anisotropy

High Anisotropy

Low Anisotropy
Diffusion Tensor MRI

Anisotropy represented by grey level

Normal 26 y.o. Male
Diffusion Tensor MRI and Schizophrenia

- **General Decrease in Anisotropy in Cortical White Matter**
  - Lim et al., 1999; Minami et al., 2003

- **Regional Decreases in Anisotropy**
  - Prefrontal Cortex
    - Buchsbaum et al., 1998
  - Uncuate Fasciculus
    - Burns et al., 2003; Kubicki et al., 2003
  - Arcuate Fasciculus
    - Burns et al., 2003
  - Corpus Callosum
    - Agartz et al. 2001; Ardekani et al., 2003; Foong et al. 2000
  - Cingulum
    - Sun et al., 2003
  - Subcortical White Matter in Temporal and Occipital Lobes
    - Ardekani et al., 2003

- **Decreased Anisotropy in Frontal White Matter Correlates With Severity of Negative Symptoms**
  - Wolkin et al., 2003
Subjects

Total = 119

Patients w/ Schizophrenia = 63

Normal Controls = 55
Subjects – Sex & Age

Controls

- Male = 32
- Female = 23
- Mean Age = 42.4
- SD = 19.7
- Range = 18-80

Patients

- Male = 44
- Female = 19
- Mean Age = 41.7
- SD = 12.5
- Range = 20-73

Neither Age nor Sex Differences were Statistically Significant Between Groups
Subjects – Handedness

Controls

- Right: 51
- Left: 4

Patients

- Right: 60
- Left: 3
Subjects – Ethnicity

- Normal Controls
  - 49.1% Caucasian
  - 30.9% African American
  - 14.5% Hispanic

- Patients w/ Schizophrenia
  - 31.8% Caucasian
  - 46.1% African American
  - 22.1% Hispanic
Subjects - Education

Education in Years

- Controls: SD=2.3
- Patients: SD=1.9

$t=7.4, df=116, p<0.05$
Subjects – Marital Status

Controls

- Married: 20
- Unmarried: 35

Patients

- Married: 5
- Unmarried: 59

Chi-square, p<0.001
Patients – Medication

- Atypical Antipsychotics: 59.20%
- Typical Antipsychotics: 17.50%
- Clozapine: 17.50%
- Unmedicated: 4.80%
Patients

- Mean Age of Onset = 23.5 years (SD=6.9)
- Mean Duration of Illness = 18.2 years
  - Duration of < 2 years in 7 Patients
- Positive and Negative Syndrome Scale (PANSS)
  - Mean Positive Subscale Score = 15 (SD=5.9)
  - Mean Negative Subscale Score = 17.3 (SD 5.9)
  - Mean Total = 32.7 (SD=10.2)
Image Acquisition

- **Anatomical**
  - Magnetization Prepared Rapid Gradient Echo (MP-RAGE); 0.82x0.82x0.82mm, TR=2500ms, TE=4.38, T1=1100ms, flip angle=8 degrees

- **Diffusion Tensor**
  - Pulsed Gradient Spin-Echo; 32 3mm thick slices with 12 gradient directions

- **Scan Time ≈ 50 minutes**
Image Processing and Analysis

- Fractional Anisotropy (FA) images created in Matlab
- All images converted to Analyze format
- Anatomical images placed in standard Talairach position and then warped to Montreal Neurological Institute standard brain using nonlinear technique in AIR 5.1 (Automated Image Registration)
- DT images aligned to original anatomical image using rigid body transformation and then warped using anatomical image transformation files in AIR 5.1
- T-tests performed between groups via R
Image Processing and Analysis

Average Anatomical
Average Anisotropy
t-test of Anisotropy Controls v. Patients
t-test Results

- Patients Lower Anisotropy
- Patients Higher Anisotropy
Frontal White Matter

- Lower Anisotropy in Patients
- Similar to Findings in Several Other Studies
- Frontal Lobe is highly involved in planning, decision making, and abstract reasoning, all of which are affected in schizophrenia
Cingulate Gyrus

- Patients Lower Anisotropy
- Patients Higher Anisotropy
Internal Capsule

- Communication the thalamus and frontal lobe
- Decreased in patients with schizophrenia

- Patients Lower Anisotropy
- Patients Higher Anisotropy
Replicated significance maps

1999
Sinai Sample
Red=Sz<Controls
N=11

2004
VA Sample
Red=Sz<Controls
N=72
Overlap w/1999=0

2005
Sinai Conte Sample
Blue=Sz<Controls
N=199
Overlap w/2004≈5
Corpus Collosum

- Interhemispheric communication including between frontal and temporal lobes
- Decreased in patients with schizophrenia

¤ Patients Lower Anisotropy
¤ Patients Higher Anisotropy
Superior Longitudinal Fasciculus

- Communication between Frontal, Parietal and Occipital Lobes
- Decreased in patients with schizophrenia
- Decreased in patients with schizophrenia on the right
- The temporal lobe is responsible for a range of language functions. It is thought to be the area responsible for some of the language problems in schizophrenia.
Future Directions

- Expand the population
  - Unmedicated patients – Drug Effects
  - First Psychotic Break and Longitudinal Follow-ups – Disease Course
  - Currently $\approx 220$ Subjects Have Been Scanned
    - $\approx \frac{1}{2}$ Schizophrenic
Future Directions

- Investigation of Anisotropy by Brodmann Region
Future Directions

- Tract Tracing
Thanks To

- **Neuroscience PET Lab**
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- **Dept of Neuroscience**
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- **NIMH**
  - Brad Buchsbaum, PhD
Anterior areas more affected
Thalamocortical and interhemispheric regions affected

- Anterior Limb
- Internal capsule

Corpus callosum