Magnetic Resonance Imaging (MRI): Providing Clues in Understanding Dementia

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Outline

• Why use MRI
• How does MRI work
• Alzheimer’s Disease
• Biomarker
• MRI and Alzheimer’s Disease
• Guessing game?
Why Magnetic Resonance Imaging?

- Expensive
- Abysmal Signal/Noise
Why Magnetic Resonance Imaging?

- Expensive
- Abysmal Signal/Noise
- Experiments often a pain to perform
- Images difficult to interpret
Because

Mouse brain

Bright area shows a stroke

Detects changes inside the body non-invasively

First seen by MOSELEY MRM 1990

Figure from van der Weerd Experimental Neurology, 2005
Because

How does MRI work?
Highest Field Strength MRI Scanner in Canada (NRC Winnipeg)
The stronger the magnetic field of the MRI scanner, the higher the frequency of the note sung.

\[ \vec{\omega} = -\gamma \vec{B} \]
How do you make an image?

scanner
Model of an MRI image

Back (High Frequency)

Left (Phase lagged)

Front (Low Frequency)

Right (Phase advanced)
k-space $\rightarrow$ FT $\rightarrow$ r-space
Why is some of the Image Dark and some of the Image Light?

This is called contrast.
What Makes the Contrast?
What Makes the Contrast?
Artificial Contrast
Chemical Shift Artifacts

Water molecules $\text{H}_2\text{O}$

Fat molecules $\text{CH}_3 - \text{CH}_2 - \text{CH}_3$

500 MHz

Great for chemists!

Expected image

Fat molecules $\text{CH}_3 - \text{CH}_2 - \text{CH}_3$

499.99825 MHz

Bad for imagers!

Actual image
Magnetic Resonance Imaging Physics at University of Winnipeg

- **Prof. Chris Bidinosti**
  - Low field MRI (3 mT)
  - Human lung airspace
  - Hyperpolarized noble gases

- **Prof. Melanie Martin**
  - High field MRI ($\geq 7$ T)
  - Brain and spinal cord
  - Animal models

physics.uwinnipeg.ca and mri.uwinnipeg.ca
Clinical MRI resolution ~ mm

Single cell resolution ~ microns

$^{1}H$ MRI water (~constant proton density) signal ~ volume
$mm^3 \rightarrow (10 \text{ micron})^3$ ... signal down ~ $10^6$

Image time $\sim 1/\Delta x^6$ ... time up $\sim 10^{36}$
Alterations to make μMR imaging feasible:

- $B_0$: 1 $\rightarrow$ 10 T, $S/N$ increase $10^3$
- Electronics: m $\rightarrow$ mm, $10^3$
- Sample: m $\rightarrow$ mm, 10
- Protocol: micro-specific, 10
In Vivo Experimental Animal Magnetic Resonance Microscopy Centre

- Recently upgraded through two CFI/MRIF grants (UW and UM) > $1 million
- 7 T scanner (300 MHz \(^1\)H)
How Strong is 7 T?
Diagnostic Imaging

• Anatomical imaging is often used to diagnose diseases and determine the stage of the disease

• My focus has been on imaging states of central nervous system diseases
  - Alzheimer’s Disease
Alzheimer’s toll may rank with cancer, heart disease

By Matt Smith, CNN
Updated 4:03 PM EST, Wed March 5, 2014

6 ways to keep the brain young

STORY HIGHLIGHTS
A new study suggests Alzheimer’s may be the third-leading U.S. cause of death.
Current figures are “a gross undercount,” Alzheimer’s Association says.
The study followed 3,500 people for 8 years; 400 died of Alzheimer’s.
Advocates hope the findings will build support for more research.

(CNN) — Alzheimer’s disease ravages the brain, robbing its victims not only of their memories but often their ability to do things as basic as swallowing.

Now, a study of aging patients suggests its true toll may top half a million lives a year — a figure that would put Alzheimer’s just below heart disease and cancer on the list of America’s top killers.

The incurable, degenerative brain disease was blamed for 83,000-plus U.S. fatalities in 2010, making it the sixth-leading cause of death that year.

But its true toll may be as much as six times that, said Bryan James, an epidemiologist at the Rush Alzheimer’s Disease Center in Chicago.

"Death certificates are well known to underreport deaths from Alzheimer’s and other types of dementia," said James, the lead author of the study published Wednesday. "The more immediate causes of death, such as pneumonia or heart attack, are usually listed, and the underlying causes of death are usually left off."

The eight-year study, published in the peer-reviewed journal Neurology, followed more than 2,500 people over 85. Of those, nearly a quarter developed Alzheimer’s, and the disease was the cause of death in about 400 people, James said.

Overwhelming burden, cost of Alzheimer's to triple, report

Katy Perry
Pussy Riot
Andrew Garfield
Upskirt

More from CNN Video:
Alzheimer’s Disease

- Affects 4.5 million people world-wide, including half of all people over 85.
- Symptoms include:
  - Memory loss affecting day-to-day function
  - Difficulty performing familiar tasks
  - Problems with language
  - Disorientation of time and place
  - Poor or decreased judgment
  - Problems with abstract thinking
Alzheimer’s disease and other forms of Dementia

• Affect almost 20,000 Manitobans
• If nothing new is done,
  - The number is expected to rise to more than 34,000 by 2038
  - Expected to reach 1.1 million in 2035 for all of Canada
When to Diagnose Alzheimer’s Disease

• Currently: absolute diagnosis comes after death
• PET imaging methods available to make absolute diagnosis before death
  - Most not clinically approved or relevant
• Plaques and signs of Alzheimer’s disease come after brain damage
First Detection Of Plaques Without Contrast Agent

Plaques and signs of Alzheimer’s disease come after brain damage
When to Diagnose Alzheimer’s

- The brain is already damaged by the time the now visible signs of the disease have occurred
- We need an earlier biomarker for Alzheimer’s Disease
- Start treatments earlier
- Obtain better outcomes of the disease
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Biomarker

• Measurable characteristic that reflects the severity or presence of some disease state*

• Anything that can be used as an indicator of a particular disease state*

• Current biomarkers of Alzheimer’s disease come very late in the disease course

*From wikipedia
Today's Biomarkers

- MRI calculated volume of grey matter
  - Used to distinguish between Alzheimer’s and frontotemporal lobar degeneration
  - About as reliable as a lumbar puncture
  - Cheaper than a lumbar puncture
  - Less invasive for the person
  - Borderline cases can be followed up with PET or lumbar puncture
MRI and Alzheimer’s Today

• Typically MRI is used to rule out other causes of memory loss
  - Tumour
  - Blood clot
• Can be used to assist in diagnosis
  - Evaluating for particular patterns of brain atrophy
  - PET evaluates typical patterns of glucose uptake
Early Biomarkers

• If the disease can be detected earlier
  - Treatments can begin earlier
  - Disease progression can be slowed
  - Risk factors can be studied in more detail

• My goal is to use MRI to detect early biomarkers of Alzheimer’s disease
Early Biomarkers

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Earlier Biomarker for Alzheimer’s Disease? - Brain Volume and Shape Changes

• In humans, brains shrink with aging, more so with Alzheimer’s
• Maybe brain shrinkage, or regional brain shrinkage could be an earlier biomarker for the disease
• With a mouse model of this (regional) brain shrinkage we could test new therapies for
  - Halting progress
  - Preventing shrinkage from occurring
Brain Volume and Shape Changes

- In mice, brains grow or stay the same depending on gene mutations.
- Shape changes can also occur if parts of the brain degenerate.
  - Eg CA1 subfield of hippocampus is altered with dementia.
- These changes appear to be species and gene mutation specific.
- We need
  - A mouse model with these brain changes
  - A method to accurately measure brain changes.
Our Study for Volume/Shape

• We removed all non-brain tissue from the images “segmentation”
Brain Volume of APP/PS1 Mice

- Counted voxels (3D pixels) in the image to determine brain volume
- No change in volume from 6-13 months of age
- Note: mice live for ~ 24 months
- First physical changes occur ~ 6 months

Vincent et al. Magnetic Resonance Insights 2010: 4 19-26
Brain Shape Measurements

- New technique to study brain shape
- Aligned all images “registration”
- Looked at how much stretching “scaling” was done
Brain Shape of APP/PS1 Mice

- No significant changes in any direction
- Need a better mouse model

Vincent et al, Magnetic Resonance Insights, 2010 4 19-26
Earlier Biomarker for Alzheimer’s Disease? – Hippocampus Volume

- Hippocampus
  - Part of brain involved with memory
  - One of the most affected regions of the brain in Alzheimer’s disease

- In 2008 it was found that
  - The hippocampus was one third smaller in people with Alzheimer’s disease
  - 19% smaller in people with impairments but not yet diagnosed with Alzheimer’s
Earlier Diagnosis of Alzheimer’s Disease - Hippocampus Volume

Hayes et al, Journal of Neuroscience Methods, 2014
Hippocampus Volumes of Different Mice

• Single transgenic mice (PS1 or APP) were used to “calibrate” method
• Significant differences were found between hippocampus volumes of mice
• Indicates need for longitudinal studies in live mouse for comparisons of volumes within a mouse itself
Why Are They Different?

Size of hippocampus could depend on the weight of the mouse.
Propagation of an action potential in an unmyelinated (top) and myelinated (bottom) nerve

Diffusion Tensor

• From all 7 diffusion-weighted images, a 3D mathematical representation of diffusion can be calculated - the diffusion tensor.

\[ D = \begin{pmatrix}
D_{xx} & D_{xy} & D_{xz} \\
D_{yx} & D_{yy} & D_{yz} \\
D_{zx} & D_{zy} & D_{zz}
\end{pmatrix} \]

\[ D = \begin{pmatrix}
\lambda_1 & 0 & 0 \\
0 & \lambda_2 & 0 \\
0 & 0 & \lambda_3
\end{pmatrix} \]
Earlier Diagnosis of Alzheimer’s Disease - Hippocampus Substructure

Thiessen et al, ISMRM 2013
Earlier Biomarker - Axon Diameter Changes

Herrera et al, ISMRM 2013
Herrera et al, ISMRM Diffusion Workshop 2013
Herrera et al, ISMRM 2014
Understanding Disease - White Matter Changes

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Katyak-Ibrahim et al, Magnetic Resonance Imaging, 2013
Cuprizone Mouse Model

- Cuprizone-fed mice makes a toxic model of demyelination, causing cell death of oligodendrocytes followed by extensive demyelination.
- Mice were fed 0.4% (w/w) cuprizone starting at 8 weeks of age.
- 5 control mice and 5 cuprizone-fed mice were imaged in vivo at 0, 1, 2, 3, 4, 5, and 6 weeks after start of treatment.
- After 6 weeks of treatment, mice were perfused with PBS/saline. To reduce the effects of fixation on the MR parameters, each ex vivo brain was imaged overnight immediately after perfusion. After ex vivo imaging, brains were fixed in 2% glutaraldehyde + 2% PFA prior to electron microscopy.
Cuprizone Data from Six Week Study

Thiessen, et al, NMR in Biomedicine, 2013
Change in $T_2$-Weighted Signal

* Normalized to signal in CSF (3$^{rd}$ ventricle)

Thiessen et al, NMR Biomed, 2013
Change in Magnetization Transfer Ratio (MTR)

Thiessen et al, NMR Biomed, 2013
MTR peaks at 5 weeks

T₂ peaks at 4 weeks

Thiessen et al, NMR Biomed, 2013
Physical Meaning of MR Metrics

- While magnetization transfer (MT) and $T_2$ and Diffusion metrics all indicate myelin damage, each are influenced by different characteristics.
Summary Alzheimer’s Disease

- Able to measure (regional) brain size and shape
- Able to measure behavioural effects
- Able to perform pharmaceutical testing
- Looking for earlier biomarkers
- MRI methods available
- Mouse models needed
Conclusion

• Magnetic Resonance Imaging can be used for understanding brain disorders
• Physicists are needed to make better imaging methods
• We need to push the resolution limits
• We need to optimize contrast
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Guessing game?