Aging Effects in the Fornix of the Brain

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Scientific Question

Symptoms of aging are easily recognized

BUT what happens during aging in brains?

27 year-old  87 year-old
Essential Facts

- No general decrease in number of neurons detected with normal aging [Peters et al., Cereb. Cortex 8 (1998)]
- Myelinated axons decrease in number [Peters et al., J. Comp. Neurol. 518 (2010)]
  - Little decrease in white matter volume
  - Myelin degeneration increases with age [Bowley et al., J. Comp. Neurol. 518 (2010)]

Myelin sheath = insulator
- Higher conduction velocity
- Energy efficiency
Fornix of the Brain

Why is fornix interesting?

Fornix (Latin: arch)

- C-shaped bundle of nerve fibers going same direction
- Carries signals from the Hippocampus
- Crucial in cognitive functions (memory formation and recall)

Scientific Question:

Differences in the fornix between young and old subjects?
Subjects

25 rhesus monkeys
14 males & 11 females
ages from 3.8 to 33.1 years old
(1 monkey year \approx 3 human years)
328 electron micrographs (EM)
Results

1. Axon Recognition Algorithm
2. Macroscopic Changes with Age
3. Morphological Changes with Age
4. Structural Changes with Age
5. Feature Selection
6. Myelin Sheath
Axon Recognition Algorithm


Recognition via contrast between convex light region (axon) surrounded by dark region (myelin sheath)

Young subject EM image

Old subject EM image

Myelin Sheath (green)

Axon (red)
Recognition Rates

Positive Predictive Value (or precision): fraction of recognized axons that are actual axons

\[
\frac{TP}{TP + FP}
\]

TP – True Positives
FP – False Positives

- The recognition rates are similar for all age groups
The overlap ratios for the algorithm are similar to the overlap ratios between 2 humans.
Results

1. Axon Recognition Algorithm

2. Macroscopic Changes with Age
   a) Axon Density

3. Morphological Changes with Age

4. Structural Changes with Age

5. Feature Selection

6. Myelin Sheath
Myelinated Axon Density

- Axon density decreases with age
- Myelinated axons lost with age
Results

1. Axon Recognition Algorithm
2. Macroscopic Changes with Age
3. Morphological Changes with Age
   a) Axon Area
4. Structural Changes with Age
5. Feature Selection
6. Myelin Sheath
Axon Area Distribution

- Same axon area distribution for young and old
- Myelinated axons lost independently of their areas
Axon Area Distribution

- Axon area distribution is heavy-tailed
  - Matches a Log-Normal distribution
- Hypothesis: stochastic geometric growth of axons?
Results

1. Axon Recognition Algorithm
2. Macroscopic Changes with Age
3. Morphological Changes with Age
4. Structural Changes with Age
   a) Axon Area Correlations
5. Feature Selection
6. Myelin Sheath
Axon Area Autocorrelation

Measure similarity of axon areas in function of distance:

- Autocorrelation $> 0 \rightarrow$ axon areas are similar
- Autocorrelation $< 0 \rightarrow$ axons have different areas
Axon Area Autocorrelation

(i) young subjects

Axons with similar areas are clustered
Axon Area Autocorrelation

(ii) old subjects

lower peak compared to young plot

no long-range correlation

No clustering of axons with similar areas
Results

1. Axon Recognition Algorithm
2. Macroscopic Changes with Age
3. Morphological Changes with Age
4. Structural Changes with Age
5. Feature Selection
6. Myelin Sheath
Feature Selection


Effective local density around axons (measured from nearest neighbor distances)

Taking ONLY these 2 features:
90% accuracy of images
Effective Local Density

- Effective Local Density is a better age discriminant than the actual axon density

\[ \rho = 0.50 \]

\[ \rho_{eff} = 0.49 \]

\[ \rho = 0.50 \]

\[ \rho_{eff} = 0.55 \]
Results

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6. Myelin Sheath
Myelin Sheath

\[ g\text{-}\text{ratio} = \frac{\text{axon diameter}}{\text{fiber diameter}} \]

- The distribution of g-ratio values is relatively identical for each image of a particular subject.
G-ratio dependence with age

- G-ratio depends on sex & age
Conclusions

- Myelinated axons are lost with age
  - This process happens independently of the axons area
- Myelinated axons in fornix have regularity
  - Older subjects have a more disordered fornix
- Simple random axon loss does not explain age differences
- The g-ratio (axon to fiber diameter) depends on the sex of the subjects
Current Work

1) Myelin Sheath properties with age

2) Expansion of feature selection to include myelin data
   - determine which parameters that, *taken together*, can better separate the two age groups

3) Model of aging process
   - compare to random cases
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Questions?
Conduction in Axons

- Axons are projections of neurons conducting electrical signals
  - Signals travel in unmyelinated axons through action potentials

In myelinated axons, the conduction occurs through saltatory conduction
Conduction in Axons

- Myelin sheath advantages:
  - Higher conduction velocity
  - Energy efficiency
• Myelin sheath thickness increases with age