Imaging in “Healthy” Aging & Dementia: A Bigger Sand Box

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Failed Clinical Trials in Early AD

APOE ε4 Carriers

- Reduction
- CSF P-tau 181P
- Mean (+/-SE) Change From Baseline (pg/mL)

- Placebo (n=85)
- Bap 0.5 mg/kg (n=127)

- Bap 0.5 mg/kg p=0.005

APOE ε4 Non-Carriers

- Reduction
- CSF p-tau 181P
- Mean (+/-SE) Change From Baseline (pg/mL)

- Placebo (n=77)
- Bap 0.5 mg/kg (n=47)
- Bap 1.0 mg/kg (n=54)

- Bap 0.5 mg/kg p=0.984
- Bap 1.0 mg/kg p=0.009

Fox, CTAD presentation, 2012
Staging of Alzheimer’s Disease

Sperling et al., Alzheimer’s & Dementia, 2011
The German National Cohort Study
https://www.helmholtz.de/en/research_infrastructure/national_cohort_study/

- The goal is development of new strategies for risk assessment, early detection and prevention of common widespread diseases, focusing on emergence of important chronic diseases (e.g., neurodegenerative diseases), their sub-clinical pre-stages, and functional changes.
- 200,000 study participants aging between 20 and 69 years old in 18 different study centers, with 30,000 having MRI scans.
- MRI images listed are T1-weighted (1 mm$^3$), FLAIR (.9 X .9 X 4 mm), and resting-state BOLD (3.1 mm$^3$, TR=2 s)
The Rhineland Study

https://www.dzne.de/en/research/research-areas/population-health-sciences/rhineland-study.html/

- The goals are identifying modifiable and non-modifiable causes of neurodegenerative or neuropsychiatric diseases, investigating biomarkers to identify individuals at risk of neurodegenerative or neuropsychiatric diseases who would benefit from preventive measures, and understanding the normal and pathological brain structure and function over the adult life course.
- 30,000 participants ≥ 30 years old at 7 centers.
- Core protocol includes T1-weighted, T2-weighted, multi-echo T2*-weighted, functional MRI, and spin-echo EPI diffusion weighted MRI. Additionally, each participant will undergo at least 1 of the following: ASL, body-fat evaluation, metabolic imaging (CSI), quantitative imaging (T1 and T2), magnetization transfer quantification, and zoomed high resolution imaging (<0.5mm) in target ROIs such as the hippocampus or the locus coeruleus, task-related fMRI.
The UK Biobank Study
http://imaging.ukbiobank.ac.uk/

- Medical imaging has enormous potential for early disease prediction, but is impeded by the difficulty and expense of acquiring datasets prior to symptom onset. UK Biobank aims to address this problem directly by acquiring high quality, consistently acquired imaging data from 100,000 predominantly healthy participants, with health outcomes tracked over coming decades.

- 100,000 participants 40 – 69 years old. Within the imaged cohort, 1800 participants are expected to develop Alzheimer’s disease by 2022.

- MRI images listed are T1, T2 FLAIR, susceptibility weighted MRI, Resting fMRI, Task fMRI, and Diffusion MRI.
Age X Disease Interaction (with disease burden held constant)

Based on Crosson et al., *Frontiers in Human Neuroscience*, 2015
Neuroimaging Measures for EHAS

- CSF
- Endothelial Dysfunction
- Cerebral Metabolic Rate for Oxygen
- Structural Changes
- Blood-Blood-Barrier Compromise
- Neuromelanin
- Functional Connectivity
- GABA & Glutamate Concentrations
- White Matter Integrity
- Cognition
- Lifestyle
HAS Neuroimaging Pilot Study (Phase 1)

- MCI Aβ+ N=30
- Asym Old Aβ+ N=30
- Asym Old Aβ- N=30
- Young Aβ- N=30

Neuroimaging Measures (2 Sessions)
- T1-MRI
- FLAIR
- DWI
- ASL
- QSM
- CVR
- Neuromelanin
- rs-fcMRI
- CMRO$_2$
- GABA MRS
- Myelin H$_2$O
- Neuro-inflammation
- DSC

HAS N=1,000 (Phase 2)
Neuroimaging Protocols for Healthy Aging
GABA MRS

Courtesy of Lisa Krishnamurthy
In pre-SMA, GABA concentration (corrected for creatine concentration), accounts for 46% of the variance in aging. Considering that fitness probably also accounts for some of the aging variance, as does a gender X age interaction, this is a very strong GABA signal. It also implies reliability.

Gao et al., *NeuroImage*, 2013
iSP seems to be driven by GABA_B mechanisms. For example, it is enhanced by baclofen, a GABA_B agonist, enhances iSP.

McGregor et al. (2011) showed that iSP was reduced in sedentary older (65-80) adults relative to both young (18-37) adults and physically active older adults. Active older adults show reduced iSP relative to young adults.

McGregor et al. (2012, 2013) showed that iSP was reduced in sedentary middle-aged (41-60) adults relative to both young (18-37) adults and physically fit middle-aged adults. There is no difference in iSP length between young and fit middle-aged adults. There was no iSP difference between fit and sedentary young adults.
3-Month Aerobic Exercise Program Increases iSP

**TABLE 5** | TMS change measures after interventions.

<table>
<thead>
<tr>
<th>Metric</th>
<th>Spin</th>
<th>Balance</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RMT change</td>
<td>-6.60 (4.1)</td>
<td>-7.18 (5.98)</td>
<td>0.54</td>
</tr>
<tr>
<td>iSP change</td>
<td>2.22 (2.96)</td>
<td>-0.41 (2.75)</td>
<td>0.05</td>
</tr>
<tr>
<td>pplHI change</td>
<td>-0.01 (0.38)</td>
<td>0.04 (0.11)</td>
<td>0.72</td>
</tr>
</tbody>
</table>

*RMT, Resting motor threshold; iSP, ipsilateral silent period; IHl, paired pulse interhemispheric inhibition. iSP is measured in ms, while IHl is percentage change from baseline pulse to preconditioned pulse. BOLD denotes statistical significance below p = 0.05.*

McGregor et al., *Frontiers in Aging Neuroscience*, 2018
Negative Activity during Picture Naming in Young Adults Converts to Positive Activity in Old Adults

Wierenga et al., *Neurobiology of Aging*, 2008
1. GABA MRS

Increases in BOLD Activity for Older Adults Also Confirmed For Semantic Fluency and Are Negatively Correlated with Accuracy

Meinzer et al., *Journal of Cognitive Neuroscience*, 2009

Meinzer et al., *Neurobiology of Aging*, 2012
Aerobic Exercise decreases BOLD activity during Semantic Fluency

Decrease in BOLD activity during semantic fluency for Aerobic vs Control Intervention

Regression of VO₂ max change on change in BOLD activity change for semantic fluency

Nocera et al., *Neural Plasticity*, 2017
2. Neuroinflammation with MRS

Lower glutamate levels in AD may indicate neuroinflammation

Table 3 Metabolite abnormalities in selected brain regions evaluated in degenerative brain disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Metabolite Abnormalities</th>
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<tbody>
<tr>
<td>Alzheimer’s disease</td>
<td>↑ MI or MI/tCr in Parietal (GM &gt; WM) and temporoparietal region; ↓ NAA and NAA/tCr in Parietal GM &gt; WM; ↓ NAA/tCr in hippocampus and anterior temporal lobe (correlated with MMSE, CDR, and clock drawing test)</td>
</tr>
</tbody>
</table>

Chang et al., *Journal of Neuroimmune Pharmacology*, 2013
3. Cerebral Metabolic Rate for Oxygen (CMRO\(_2\))

There is paradoxical increase of CMRO\(_2\) with age (\(P = 0.0101\)). Average CMRO\(_2\) of typical 20-year-old subjects is approximately 164.1 \(\mu\)mol/100 g/min, and it increases with age at a rate of 2.6 \(\mu\)mol/100 g/min per decade.

Lu et al., *Cerebral Cortex*, 2011
CMRO$_2$ is reduced by 11% in aMCI compared to normal controls

aMCI: $113.6 \pm 15.7 \, \mu$mol/100 g/min

normal controls: $127.1 \pm 17.1 \, \mu$mol/100 g/min

Liu et al., *Alzheimer’s Disease & Dementia*, 2014
3. Cerebral Metabolic Rate for Oxygen (CMRO$_2$)

Intrasession CoV = 3.84% ± 1.44
Intersession CoV = 6.59% ± 1.56

R = 0.67
Intrasession

Liu et al., *Magnetic Resonance in Medicine*, 2013)
4. Voxel Based Morphometry (VBM) on T1-weighted Images

Medial Temporal Atrophy before Conversion from aMCI to AD

Whitewell et al., *Brain*, 2007
Involvement of Locus Coeruleus in Early AD (Ross et al., *Neurobiology of Stress*, 2015)

Chen et al., *Magnetic Resonance Imaging*, 2014

Clewett et al., *Neurobiology of Aging*, 2016
6. Diffusion Weighted Imaging (DWI)

Measures derived from DWI have varied in predicting AD or prodromal AD.

Fig 2. Accuracies for MCI-Aβ42+ versus HC and the different variance reduction approaches.

Dyrba et al., *Journal of Neuroimaging*, 2015
Leukoaraiosis explains working memory performance
After 3% involvement and visuoconstructional impairment after 14% involvement
8. Myelin Water Fraction (MWF)

8. Myelin Water Fraction

High levels of Amyloid Precursor Protein are associated with decline in MWF in cognitively normal older adults

Figure 2. Regional White Matter Myelin Content, as Measured by Myelin Water Fraction (MWF), Associated With Soluble Amyloid Precursor Protein/\(\beta\)-Amyloid 42 (sAPP\(\beta\)/A\(\beta\)42)

Dean et al., *JAMA Neurology*, 2017
Higher levels of phosphorylated tau lead to increased decline in MWF with increasing age.

Figure 4. Levels of Phosphorylated Tau (Ptau181)/β-Amyloid 42 (Aβ42) Moderate Age-Related Changes of Myelin Water Fraction (MWF)

Dean et al., JAMA Neurology, 2017
Significant differences in Permutation Entropy: Control vs Early MCI vs Late MCI vs AD

Wang et al., Frontiers in Aging Neuroscience, 2017
Permutation Entropy distinguishes AD from Controls, Early MCI, and Late MCI

Wang et al., *Frontiers in Aging Neuroscience*, 2017
10. Arterial Spin Labeling (ASL)

ASL correlates with FDG PET in AD

Wolk & Detre, *Current Opinion in Neurology*, 2012
10. Arterial Spin Labeling (ASL)

Older persons show decreased CBF especially in frontal cortex

Young

Old

Courtesy of Lisa Krishnamurthy
One recent study showed no difference in CVR between aMCI and controls.

Thomas et al., *Journal of Cerebral Blood Flow & Metabolism*, 2017
Correcting for CVR Differences in Aging Studies

11. Cerebrovascular Reactivity (CVR)

Liu et al., *NeuroImage*, 2013
12. Dynamic Susceptibility Contrast (DSC)

Blood–Brain Barrier

Fig 1. Schematic of the NVU. The NVU comprises the cerebral microvascular endothelium (shown in red), its basement membrane, and associated pericytes (yellow) and astrocytes (orange). The perivascular space exists between the endothelium and astrocytic endfeet. The endothelium provides the structural and functional basis for the blood–brain barrier (BBB), while astrocytes and pericytes control barrier induction and maintenance[7]. Junctional proteins exist between endothelial cells and astrocytes (glia limitans) to help regulate entrance into the CNS parenchyma. Image credit: Gareth R. John & Benjamin M. Laitman.
12. Dynamic Susceptibility Contrast (DSC)

Blood-Brain Barrier breakdown occurs early in aging
13. Quantitative Susceptibility Mapping (QSM)

QSM can be used to assess microbleeds

Cronin et al., *NeuroImage*, 2017
But, QSM also can be used to measure tissue iron concentrations after removing large microbleeds and vessels.

Ayton et al., *Brain*, 2017