Tracking ALS progression using neuroimaging

Federica Agosta, M.D., Ph.D.

Neuroimaging of Neurodegenerative Diseases Group,
Institute of Experimental Neurology, Division of Neuroscience,
San Raffaele Scientific Institute, Milan, Italy
Tracking ALS progression

- Do we have MRI biomarkers for ALS?
- Can we track ALS progression using MRI?
- Foreseeing before disease onset
- Network analysis: a new approach to track ALS
Tracking ALS progression

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MRI biomarkers in ALS
MRI biomarkers in ALS

**C-Index ALS vs controls: 0.75**

*Optimal cutoff = 2.42 mm:
Specificity 82%
Sensitivity 84%*
MRI biomarkers in ALS

\[ C\text{-Index ALS vs controls: 0.75} \]

Agosta et al., PlosONE 2012

\[ \text{ALS vs HC} \]

\[ p=0.05 \]

\[ p=0.01 \]

\[ T\text{-value} \]

\[ 0 \]

\[ -1.68 \]

\[ -4 \]

Verstraete et al., JNNP 2012

\[ \text{MND-PLUS vs controls} \]

\[ \text{MND-MOTOR vs controls} \]

\[ \text{MND-PLUS vs MND-MOTOR} \]

Agosta et al., Hum Brain Mapp 2016

\[ \text{Optimal cutoff = 2.42 mm:} \]

\[ \text{Specificity 82\%} \]

\[ \text{Sensitivity 84\%} \]
## MRI biomarkers in ALS

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Agosta et al., Hum Brain Mapp 2013
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Agosta et al., Hum Brain Mapp 2013

CST FA decrease in patients without UMN signs at the time of MRI

Sach et al., Brain 2004
MRI biomarkers in ALS

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Independent predictors of survival:
- ALSFRS deterioration rate  
  \( p=0.01, \text{HR}=2.2, 95\% \text{CI}=1.2-3.9 \)
- CST FA  
  \( p=0.06, \text{HR}=0.94, 95\% \text{CI}=0.89-1.00 \)

Agosta et al., Hum Brain Mapp 2013

Sach et al., Brain 2004

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Agosta et al., Eur J Neurosci 2010
MRI biomarkers in ALS
MRI biomarkers in ALS

Kassubek et al., Brain 2014

ALSFRS-R

Disease duration

C = 0.290
P = 0.0019

C = -0.293
P = 0.0017
MRI biomarkers in ALS
MRI biomarkers in ALS

Diagnostic accuracy

**ALS vs ALS mimic disorders**
- DT MRI values
  - Accuracy = 0.87
- Combined MRI metrics
  - Accuracy = 0.87

**PUMN vs ALS mimic disorders**
- DT MRI values
  - Accuracy = 0.95
- Combined MRI metrics
  - Accuracy = 0.94

Agosta et al., AAN 2017
MRI biomarkers in ALS
MRI biomarkers in ALS

C9orf72 vs sporadic ALS

- Left Cerebellum
- Right Cerebellum
- Left Hippocampus
- Right Hippocampus
- Left Thalamus
- Right Thalamus

Legend:
- HC
- C9orf72
- Sporadic-motor
- Sporadic-cognitive
- Sporadic-early

* indicates statistical significance.
MRI biomarkers in ALS
MRI biomarkers in ALS

Spinal cord

Valsasina et al., JNNP 2007

Carew et al., Neurology 2012
MRI biomarkers in ALS

Peripheral nervous system

Nerve root increased signal

Healthy control

STIR

Nerve root T2 signal vs disease progression: $r = 0.40$

3D T2 VISTA

Supraspinatus muscle edema

Healthy control

T2

STIR

Adipose tissue deposition between trapezius and supraspinatus muscle

T1

Healthy control

Gerevini et al., Radiology 2016
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## Tracking ALS progression

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Menke et al., Neurotherapeutics 2017
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Menke et al., Neurotherapeutics 2017
Tracking ALS progression
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Longitudinal WM damage vs GM atrophy in ALS

Correlates of white and grey matter pathology in ALS

**TBSS:**
- **A:** sagittal
  - $x = 22$
  - $y = -18$
  - $z = 1$

- **B:** coronal
  - $x = -36$
  - $y = -12$
  - $z = 48$
  - $x = -56$
  - $y = -10$
  - $z = 10$

- **C:** axial
  - $x = -24$
  - $y = -14$
  - $z = 11$

**VBM:**
- **D:** coronal
  - $x = -50$
  - $y = 10$
  - $z = 8$

*Menke et al., Brain 2014*
Tracking ALS progression
Tracking ALS progression

Longitudinal WM damage vs GM atrophy in ALS

No longitudinal GM changes

Cardenas-Blanco et al., NeuroImage: Clinical 2016
Tracking ALS progression
Tracking ALS progression

Longitudinal WM damage vs GM atrophy in ALS

No longitudinal GM changes

de Albuquerque et al., NeuroImage: Clinical 2017
Tracking ALS progression
Tracking ALS progression

Longitudinal WM damage vs GM atrophy in ALS

6 month follow-up

9 month follow-up

12 month follow-up

Overall progression

Ferraro et al., AAN 2017
Tracking ALS progression
Tracking ALS progression

Longitudinal WM damage vs GM atrophy in ALS

Baseline: ALS vs HC

9-month vs baseline

12-month vs baseline

FA

radD

Ferraro et al., AAN 2017
Tracking ALS progression
Tracking ALS progression

Van der Graaff et al., Brain 2011

PMA vs controls

PMA – 6 month follow up
Tracking ALS progression
### Spinal cord MRI

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<th>Follow-up</th>
<th>p Value*</th>
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<td><strong>Cord cross-sectional area (mm³)</strong></td>
<td>Mean (SD) 71.1 (6.2)</td>
<td>69.4 (5.6)</td>
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<td></td>
<td>Range 59.3 to 83.4</td>
<td>57.8 to 78.6</td>
<td></td>
</tr>
<tr>
<td><strong>Cord average MD (×10⁻³ mm² s⁻¹)</strong></td>
<td>Mean (SD) 0.89 (0.06)</td>
<td>0.95 (0.08)</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>Range 0.78 to 0.99</td>
<td>0.81 to 1.07</td>
<td></td>
</tr>
<tr>
<td><strong>Cord average FA</strong></td>
<td>Mean (SD) 0.48 (0.03)</td>
<td>0.45 (0.04)</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>Range 0.42 to 0.53</td>
<td>0.39 to 0.54</td>
<td></td>
</tr>
<tr>
<td><strong>Brain CST average MD (×10⁻³ mm² s⁻¹)</strong></td>
<td>Mean (SD) 0.80 (0.03)</td>
<td>0.79 (0.03)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Range 0.74 to 0.87</td>
<td>0.73 to 0.84</td>
<td></td>
</tr>
<tr>
<td><strong>Brain CST FA</strong></td>
<td>Mean (SD) 0.56 (0.03)</td>
<td>0.56 (0.02)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Range 0.50 to 0.60</td>
<td>0.52 to 0.60</td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for follow-up duration. See the text for further details.

CST, corticospinal tract; FA, fractional anisotropy; MD, mean diffusivity; NS, not significant.

---

**Tracking ALS progression**

---

**Additional Information**

- Agosta et al., JNNP 2009
- de Albuquerque et al., NeuroImage: Clinical 2017
Tracking ALS progression
Tracking ALS progression

Peroneal and tibial nerve DTI

<table>
<thead>
<tr>
<th></th>
<th>ΔALSFRS-R</th>
<th>ΔMRCSS-LL</th>
<th>ΔCMAP</th>
<th>ΔMUNE</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔFA peroneal</td>
<td>-0.11 (0.53)</td>
<td>-0.06 (0.75)</td>
<td>-0.01 (0.94)</td>
<td>0.01 (0.97)</td>
</tr>
<tr>
<td>ΔFA tibial</td>
<td>0.05 (0.77)</td>
<td>-0.40 (0.02)</td>
<td>-0.13 (0.94)</td>
<td>0.13 (0.45)</td>
</tr>
<tr>
<td>ΔAD peroneal</td>
<td>0.22 (0.21)</td>
<td>0.21 (0.22)</td>
<td>0.05 (0.76)</td>
<td>0.20 (0.26)</td>
</tr>
<tr>
<td>ΔAD tibial</td>
<td>0.38 (0.03)</td>
<td>-0.23 (0.20)</td>
<td>0.02 (0.91)</td>
<td>0.18 (0.32)</td>
</tr>
</tbody>
</table>

Simons et al J Neurol 2017
• Do we have MRI biomarkers for ALS?
• Can we track ALS progression using MRI?
• **Foreseeing before disease onset**
• Network analysis: a new approach to track ALS
Foreseeing before disease onset
Foreseeing before disease onset

**GM atrophy**

- Cingulate
- Frontal
- Temporal
- Insula
- Occipital
- Parietal

Estimated years from expected symptoms onset

Rohrer et al., Lancet Neurol 2015

**WM damage**

Lee et al., NeuroImage: Clinical 2017

15 presymptomatic carriers (*C9orf72*)

**WM damage**

39 presymptomatic carriers

(28 *PGRN*, 11 *MAPT*)

Dopper et al., Neurology 2014
Foreseeing before disease onset
Foreseeing before disease onset

Altered functional connectivity

15 presymptomatic carriers (C9orf72)

Lee et al., NeuroImage: Clinical 2017

12 presymptomatic carriers (SOD1, C9orf72)

Menke et al., JNNP 2016
Do we have MRI biomarkers for ALS?
Can we track ALS progression using MRI?
Foreseeing before disease onset

Network analysis: a new approach to track ALS
<table>
<thead>
<tr>
<th>Disease</th>
<th>Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer disease</td>
<td>Tau</td>
</tr>
<tr>
<td>Parkinson disease</td>
<td>(\alpha)-synuclein</td>
</tr>
<tr>
<td>Amyotrophic lateral sclerosis</td>
<td>TDP-43</td>
</tr>
<tr>
<td>Frontotemporal dementia</td>
<td>TDP-43</td>
</tr>
</tbody>
</table>
The Network-based Degeneration Hypothesis

Alzheimer disease: Tau

Parkinson disease: α-synuclein

Amyotrophic lateral sclerosis: TDP-43

Frontotemporal dementia: TDP-43
The Network-based Degeneration Hypothesis
The Network-based Degeneration Hypothesis

Neuron-to-neuron spreading

- Normal protein
- Pathological misfolded protein fibrillar ultrastructure
- Aggregate
- Fragmentation into further seeds
- Release
- Uptake
- Extracellular space
- Neighbouring neuron or glial cell
- Further seeded aggregation
- Seeded aggregation
- Cell-to-cell spreading

Brettschneider et al., Nature Reviews 2015
The Network-based Degeneration Hypothesis

Neuron-to-neuron spreading

Normal protein → Misfolding
Pathological misfolded protein fibrillar ultrastructure → Aggregate
Seeded aggregation
Fragmentation into further seeds
Release
Neighbouring neuron or glial cell
Extracellular space
Uptake
Cell-to-cell spreading
Further seeded aggregation

Brettschneider et al., Nature Reviews 2015

Aguzzi & Rajendran, Neuron 2009
Aguzzi & Lakkaraju, Trends Cell Biol 2016
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Neuron-to-neuron spreading

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Brettschneider et al., Nature Reviews 2015

Hypothetical model of microglia role in AD

Aguzzii & Rajendran, Neuron 2009

Aguzzii & Lakkaraju, Trends Cell Biol 2016 1

Agosta et al., Ann Neurol 2014
The Network-based Degeneration Hypothesis

Neuron-to-neuron spreading

Misfolding

Seeded aggregation

Neuron-to-neuron transmission along network connections and across synapses is the most likely mechanism for the nonrandom pattern of pathological spread in neurodegenerative diseases

Brettschneider et al., Nature Reviews 2015

Aguzzi & Lakkaraju, Trends Cell Biol 2016

Agosta et al., Ann Neurol 2014

Bajendra, Neuron 2009

Neuron-to-neuron transmission along network connections and across synapses is the most likely mechanism for the nonrandom pattern of pathological spread in neurodegenerative diseases
The Human Connectome: An innovative paradigm
The Human Connectome: An innovative paradigm
The Human Connectome: An innovative paradigm

The human connectome

- Shortest path length
- Highest degree
- Connector hub
- Highest clustering coefficient (its neighbors are all neighbors of each other)
The Human Connectome in FTD & ALS

Healthy controls

- ACC
- MCC
- Prec
- Cal
- MOG
- Cun
- ITG
- Lin
- MTG

bvFTD

- ACC
- MCC
- Prec
- Cal
- MOG
- Cun
- ITG
- Lin
- MTG

Healthy controls

- ACC
- MCC
- Prec
- Cal
- MOG
- Cun
- ITG
- Lin
- MTG

right

Semantic PPA

- SMA
- PreCG
- MFG
- THA
- IFGtr
- MTG
- STG
- ITG
- InfOFC

- ACC
- MCC
- Prec
- Cal
- MOG
- Cun
- ITG
- Lin
- MTG

Agosta et al., Neurology 2013

Agosta et al., Neurobiol Aging 2014
The Human Connectome in FTD & ALS

Verstraete et al., Hum Brain Mapp 2013

Affected subnetwork after 6 months

baseline (T=1)

potential longitudinal connectivity changes (T=2)

A: progressive impairment of initially impaired structural connections

B: expanding subnetwork of impaired connectivity

A + B

C: impairment of distant structural connections

Verstraete et al., Hum Brain Mapp 2013
The Human Connectome in FTD & ALS

Semantic PPA

Patterson et al.
Nat Rev Neurosci 2007

Collins et al., Brain 2017
The Human Connectome in FTD & ALS

Semantic PPA

Patterson et al.
Nat Rev Neurosci 2007

ALS

Schmidt et al., NeuroImage 2016

Collins et al., Brain 2017
Tracking longitudinal changes (NeuroTRACK)
Tracking longitudinal changes (NeuroTRACK)

Pathological aggregates

Shortest path
Tracking longitudinal changes (NeuroTRACK)

Pathological aggregates

Shortest path
Tracking longitudinal changes (NeuroTRACK)

Pathological aggregates

Shortest path

Connection strength
Tracking longitudinal changes (NeuroTRACK)

- Pathological aggregates
- Shortest path
- Connection strength
- Connector hub
The Human Connectome in FTD & ALS

**ALS vs HC**

<table>
<thead>
<tr>
<th>ALS stage</th>
<th>Number of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALS stage 1</td>
<td>8</td>
</tr>
<tr>
<td>ALS stage 2</td>
<td>10</td>
</tr>
<tr>
<td>ALS stage 3</td>
<td>6</td>
</tr>
<tr>
<td>ALS stage 4</td>
<td>14</td>
</tr>
<tr>
<td>Σ</td>
<td>38</td>
</tr>
</tbody>
</table>

FA

Principal connected component

Other affected components

MD

p<0.01

Permuted t test

\( \varphi = 0.36 \) p=0.03

Basaia et al., AAN 2017

The Human Connectome in FTD & ALS
The Human Connectome in FTD & ALS
The Human Connectome in FTD & ALS

Basaia et al., AAN 2017

Fractional anisotropy

Mean topological distance

\( \varrho = 0.23 \ p < 0.001 \)

\( \varrho = 0.08 \ p = 0.22 \)
Conclusions

FROM A DISEASE **BURDEN**...

- “**Young**” onset (40-65 years)
- *Treatments in development*
- *Lack of reliable outcome measures*
- High healthcare **costs**
Conclusions

FROM A DISEASE BURDEN...

• “Young” onset (40-65 years)
• Treatments in development
• Lack of reliable outcome measures
• High healthcare costs

...TO A HIGH GAIN

• Novel, reliable markers for neurodegeneration prediction and monitoring
• (Preclinical) protein-based network degeneration patterns
• Personalized therapies
• Investigations into other proteinopathies (Alzheimer’s and Parkinson’s Diseases)
Neuroimaging Research Unit & Neurodegenerative Disease Group

M. Filippi
S. Basaia
E. Canu
M. Copetti
P.M. Ferraro
S. Galantucci
F. Imperiale
E. Sarasso
E.G. Spinelli

Department of Neurology
N. Riva, G. Comi

Experimental Neuropathology Unit
A. Quattrini, N. Riva, D. Teuta

Department of Neuroradiology
A. Falini, S. Gerevini

A. Chiò, A. Calvo, C. Moglia, Torino
V. Silani, N. Ticozzi, B. Poletti, Milano
G. Tedeschi, F. Trojsi, Napoli

NISALS
The network-based degeneration hypothesis
The network-based degeneration hypothesis

Alzheimer disease: Tau

Parkinson disease: α-synuclein

Amyotrophic lateral sclerosis: TDP-43