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Hypothalamic atrophy correlates with onset of disease-defining symptoms in patients with ALS

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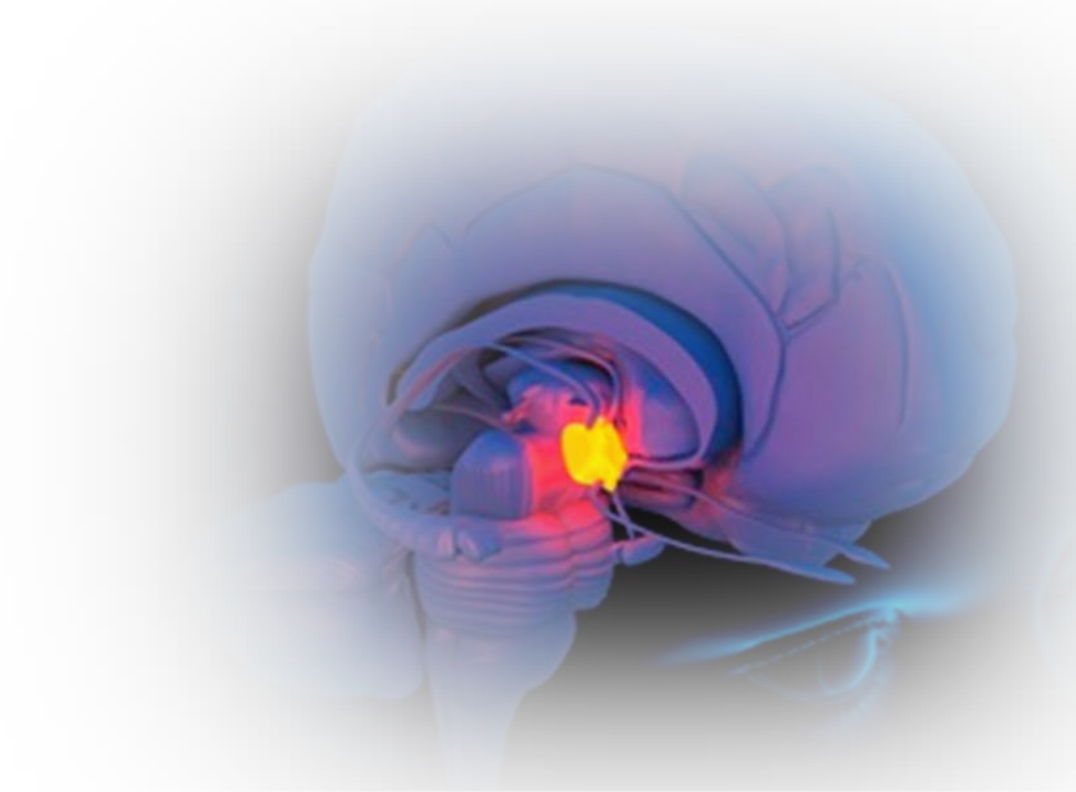
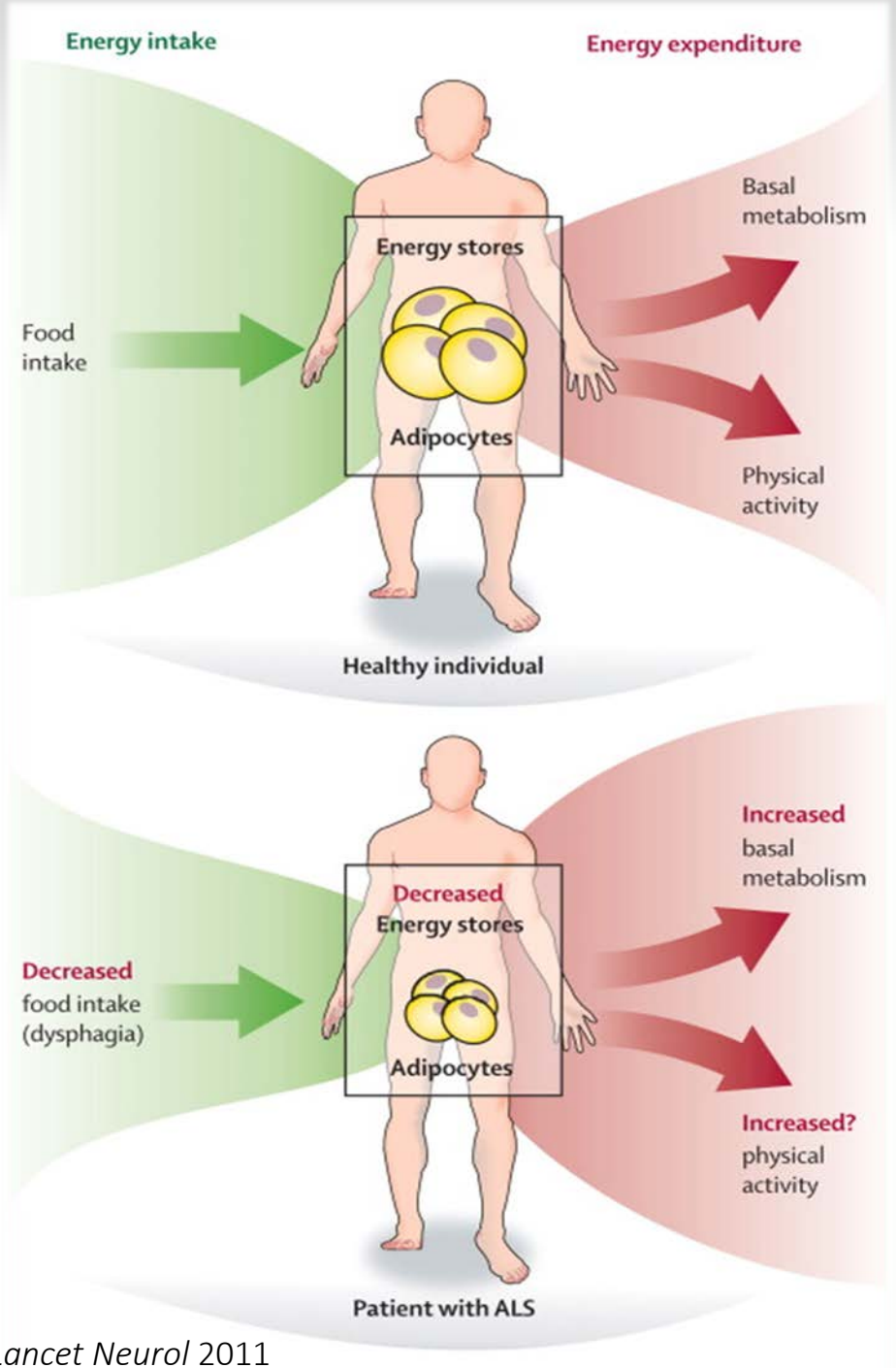
ENCALS 2017



Energy metabolism in ALS

- A strong relationship between metabolism and neurodegeneration has been suggested (Procaccini et al., *Metabolism* 2016)



Dupuis et al., *Lancet Neurol* 2011

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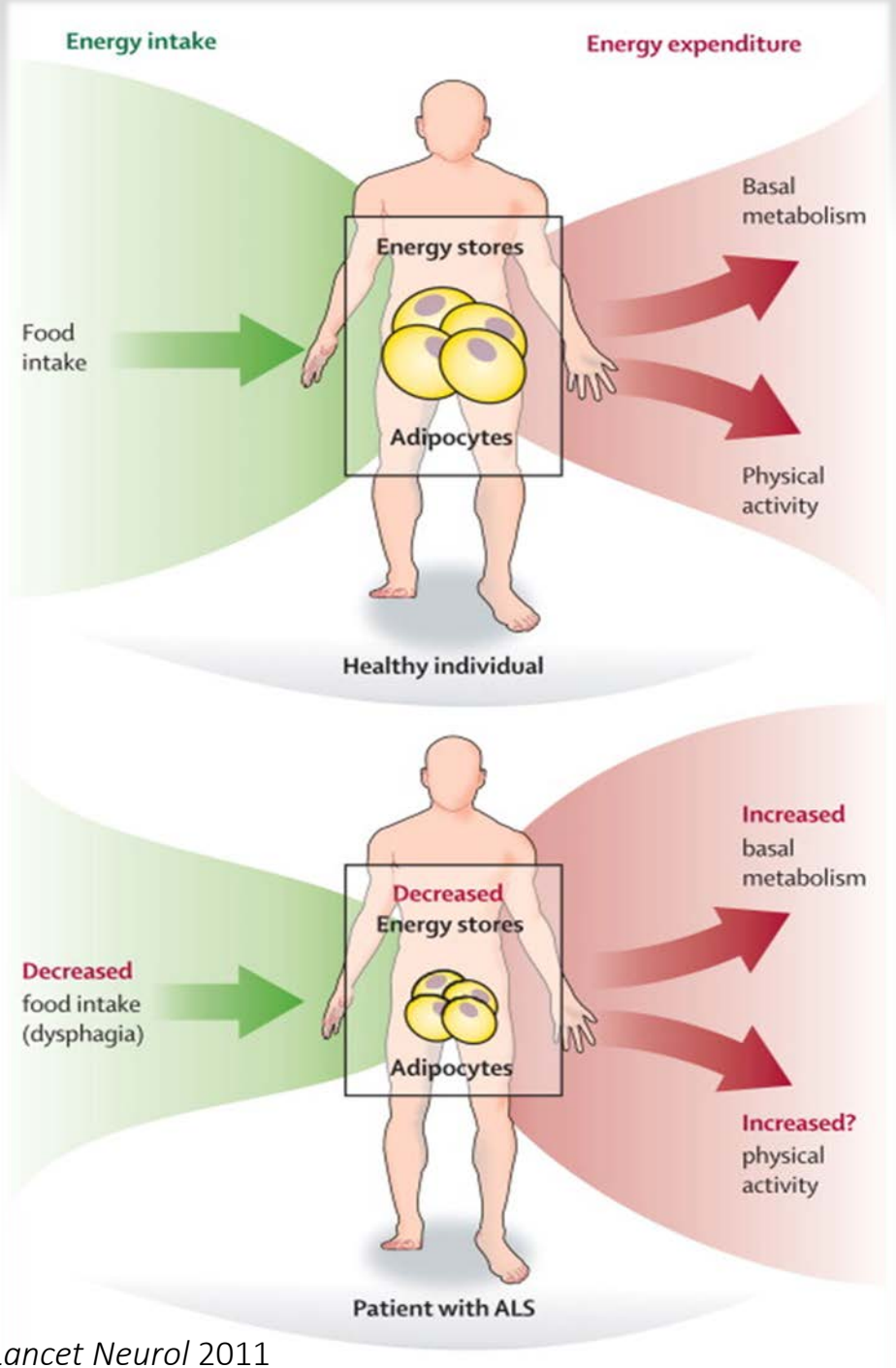

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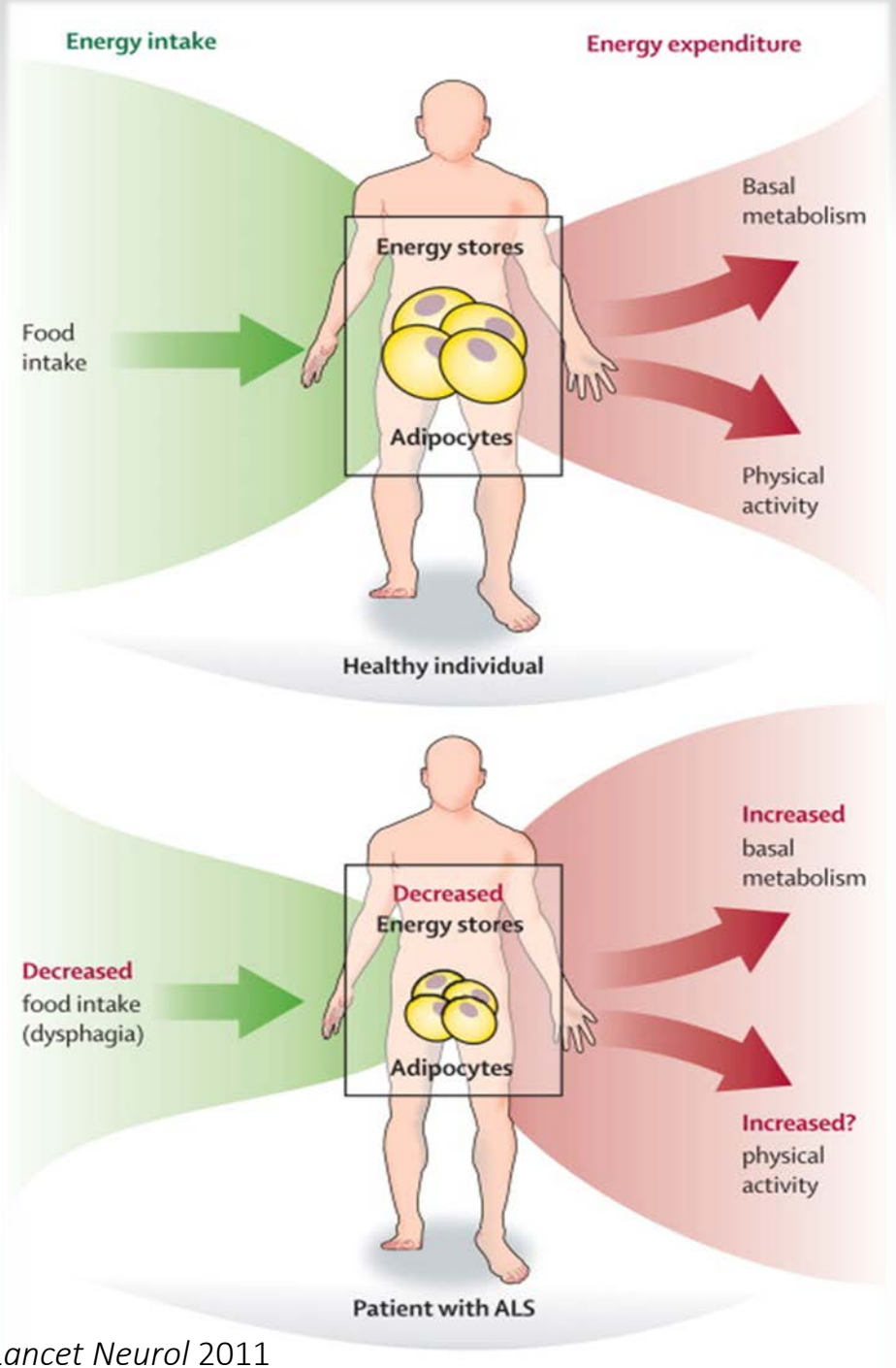

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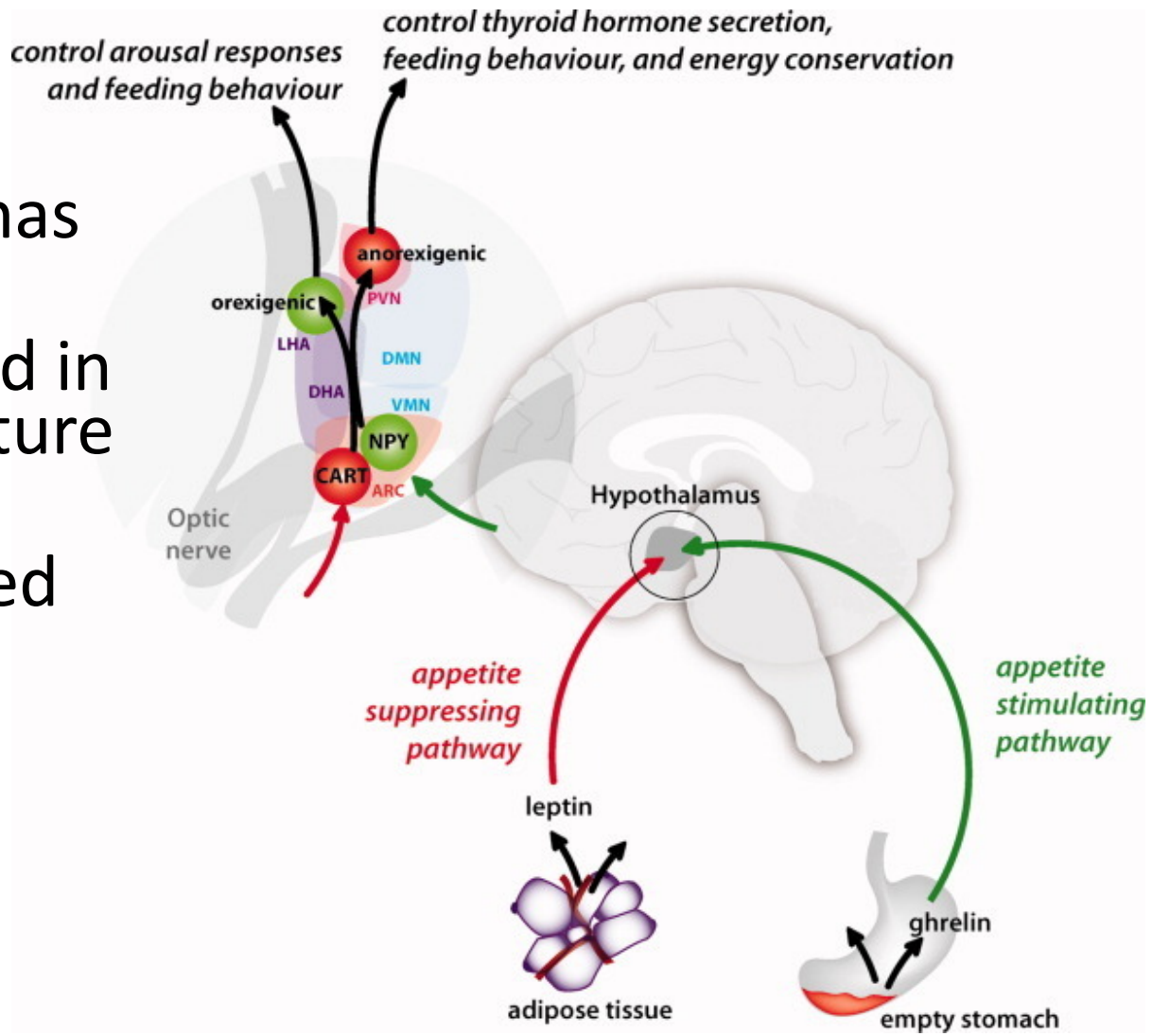

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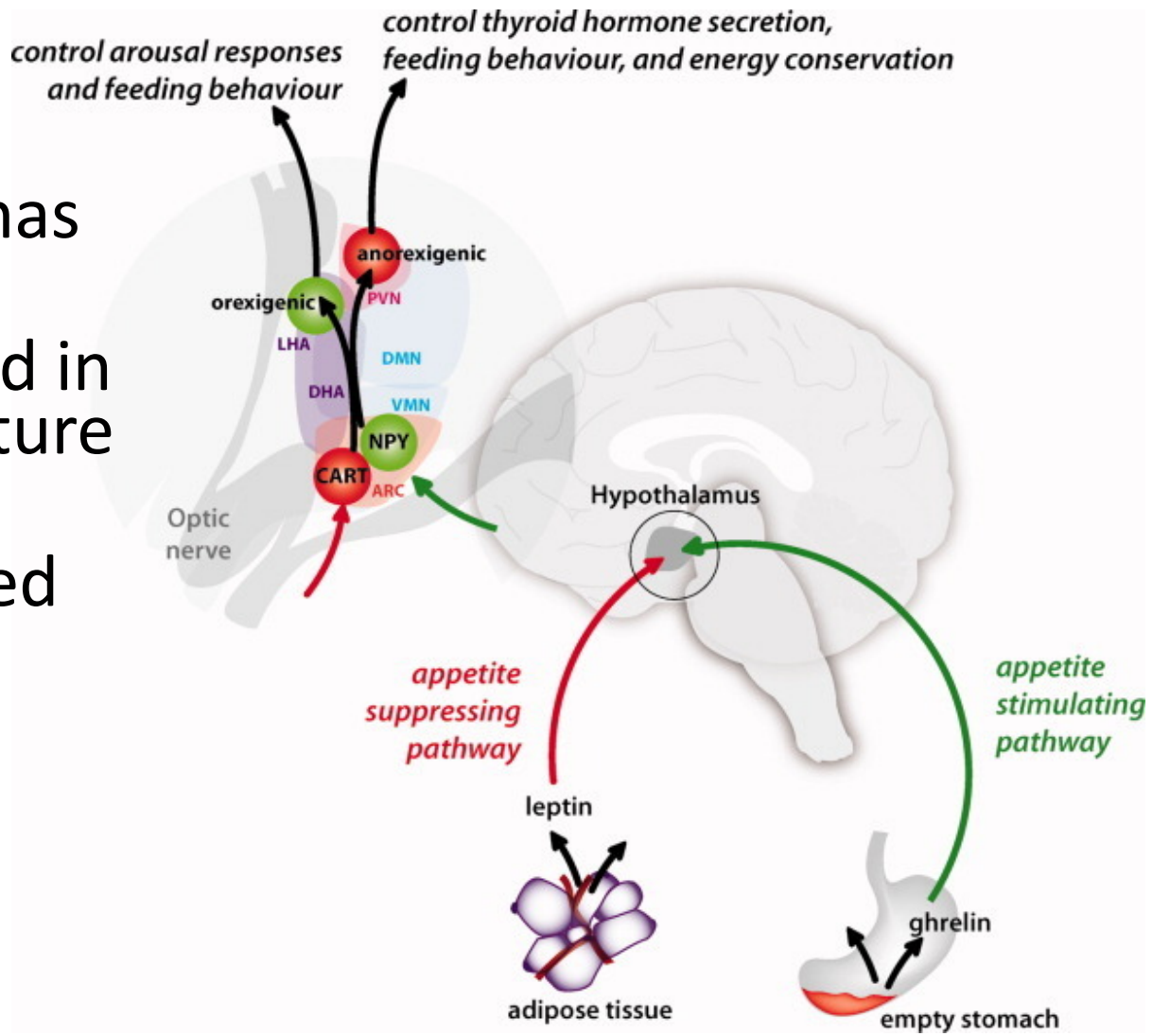
- A strong relationship between metabolism and neurodegeneration has been suggested (Procaccini et al., *Metabolism* 2016)
- Energy metabolism is severely altered in ALS: Hypermetabolism is an early feature of ALS (Dupuis et al., *Lancet Neurol* 2011)
- The hypothalamus is critically involved in regulating energy metabolism
- Hypothalamic alterations have been recently described in an ALS animal model (Vercruysse et al., *Brain* 2016)



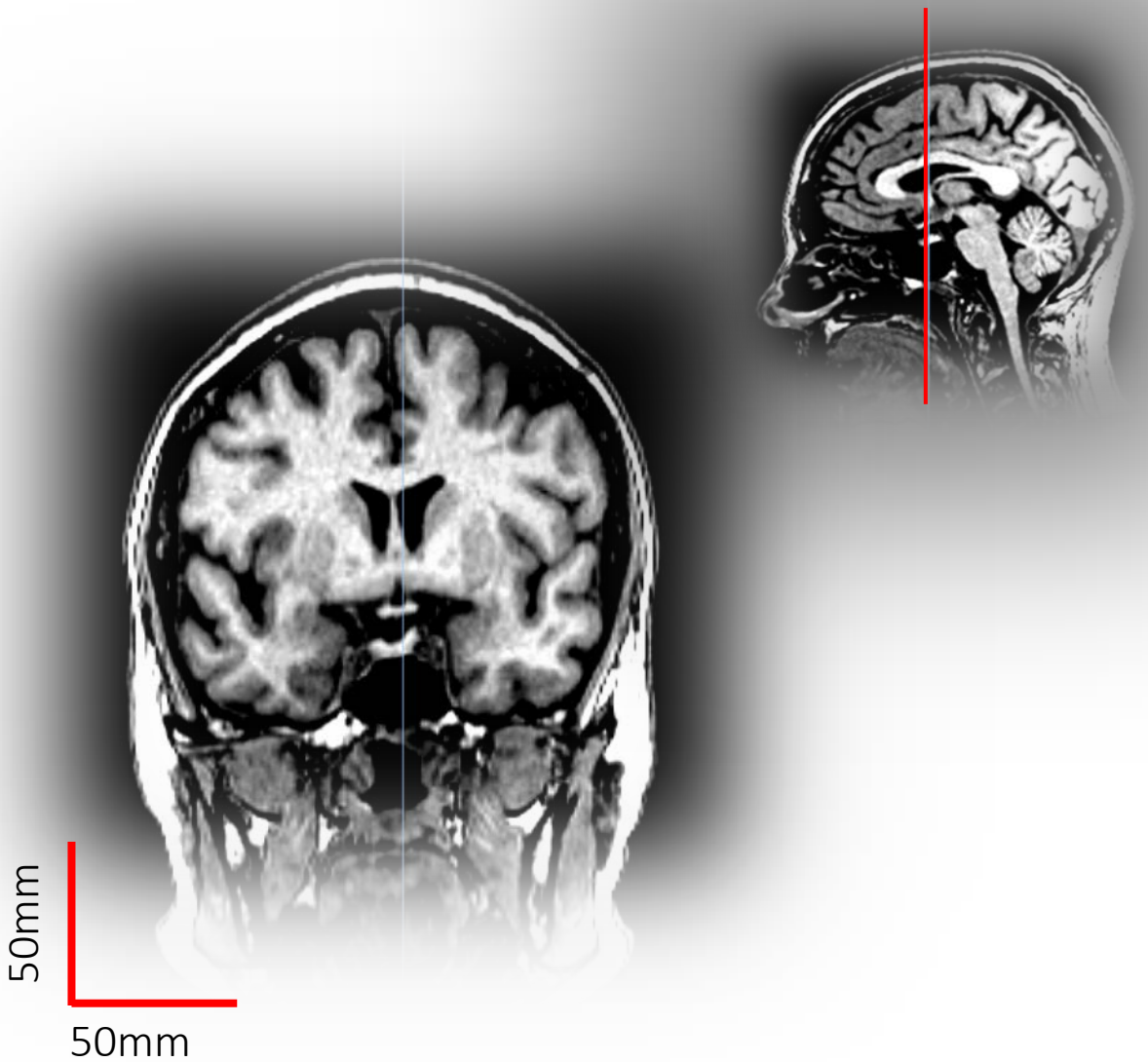
Objective / Cohorts

- To investigate structural alterations in the hypothalamus and correlate the hypothalamic volume with functional measures (metabolic indices, disease progression)

Cohort (monocentric data from Ulm, Germany)

sALS	fALS	healthy controls
(*N*=251)	(*N*=19)	(*N*=112)

MRI-based segmentation of the hypothalamus



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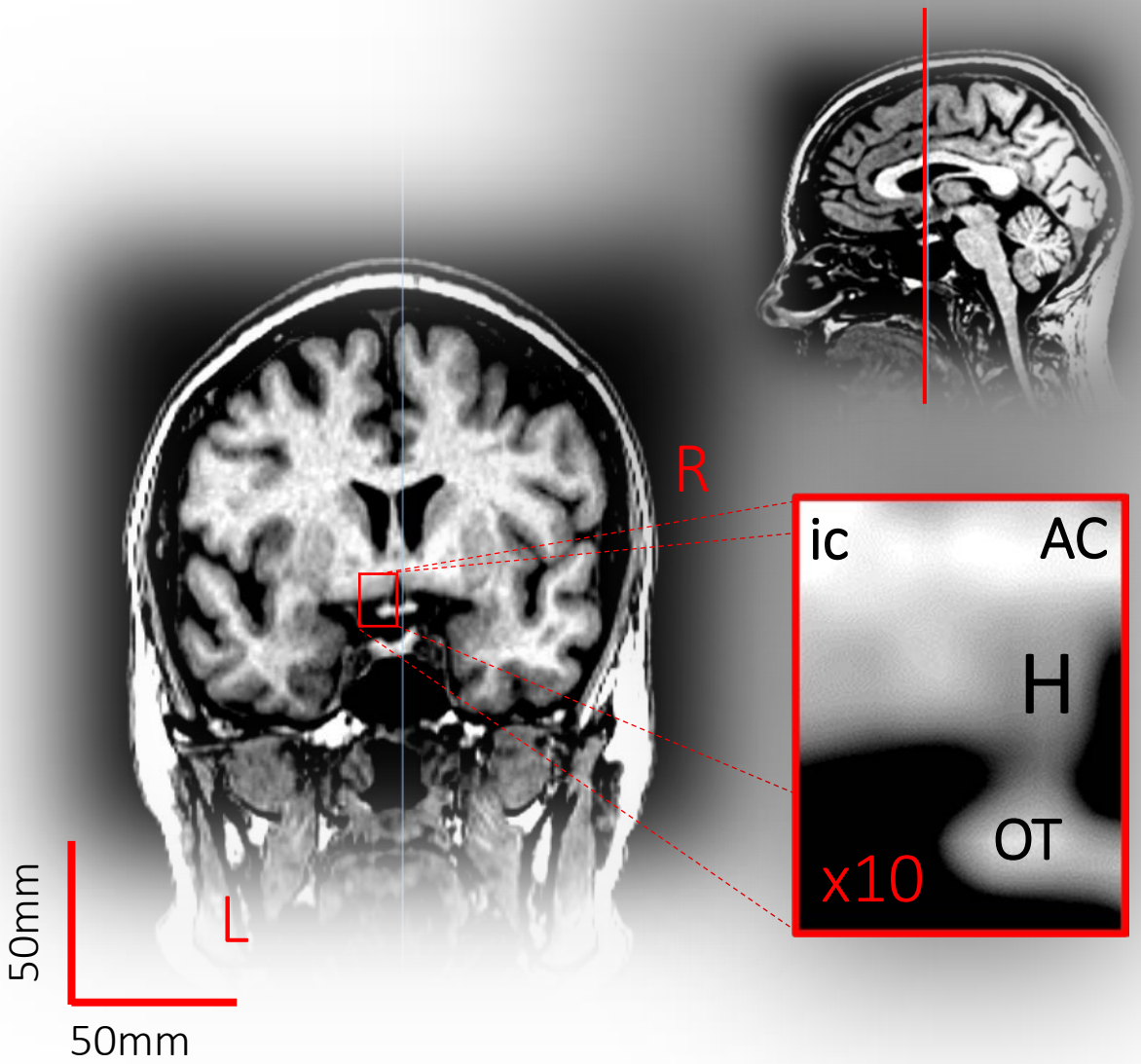

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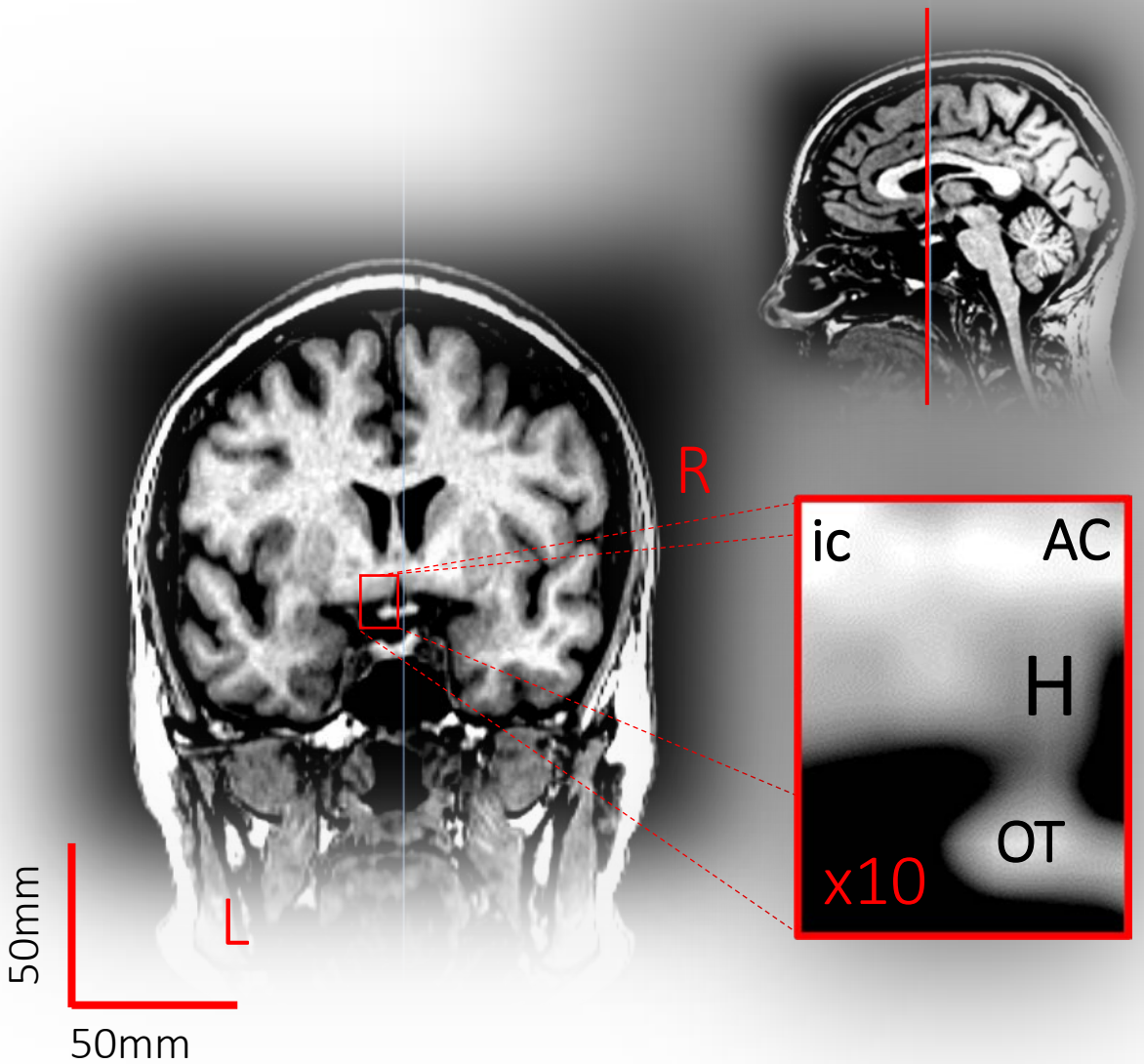

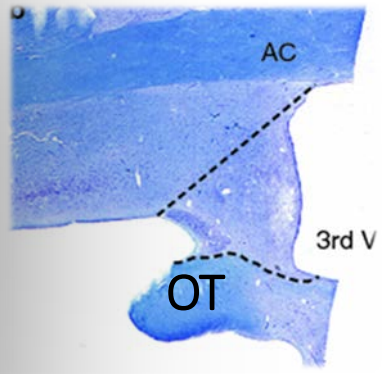

Gabery et al., *Acta Neuropathol* 2010

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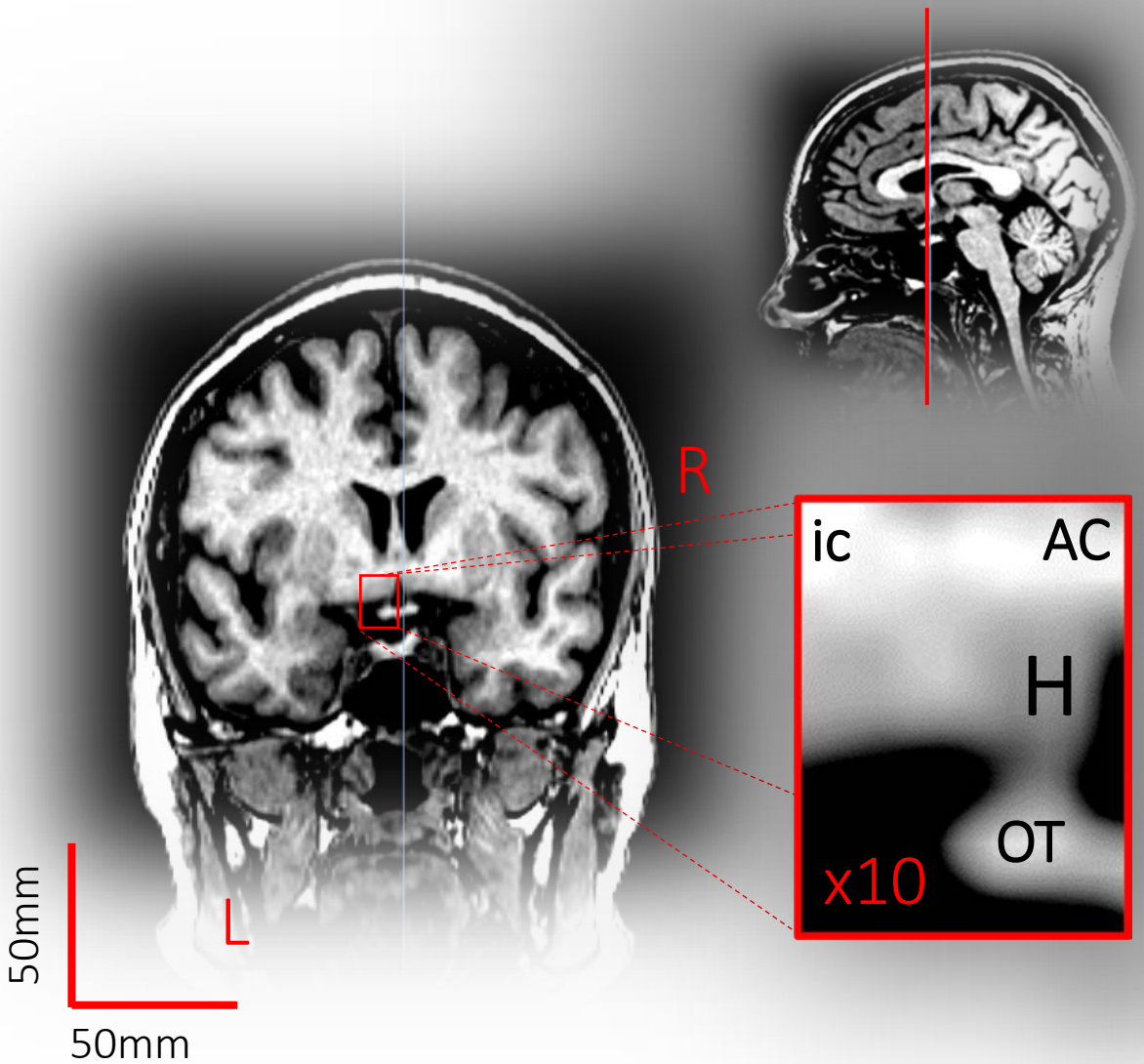

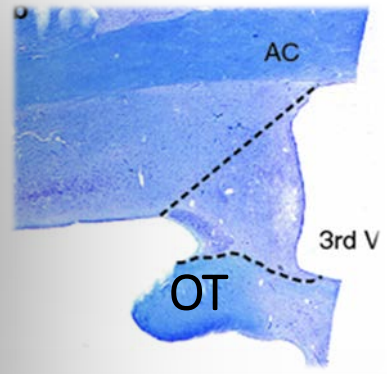

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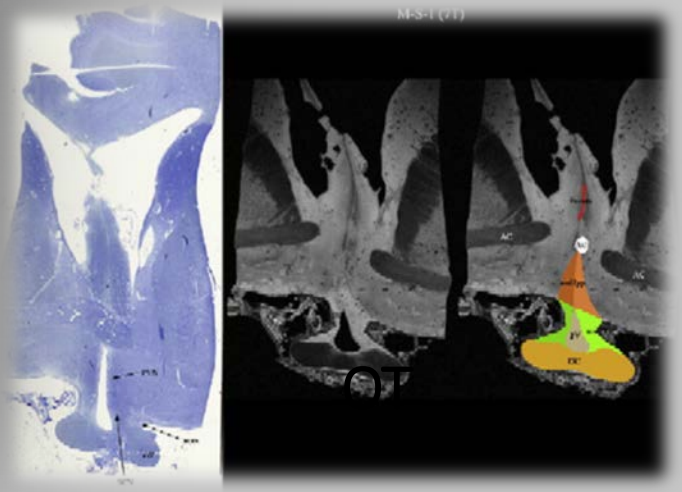

Makris et al., *Neuroimage* 2016

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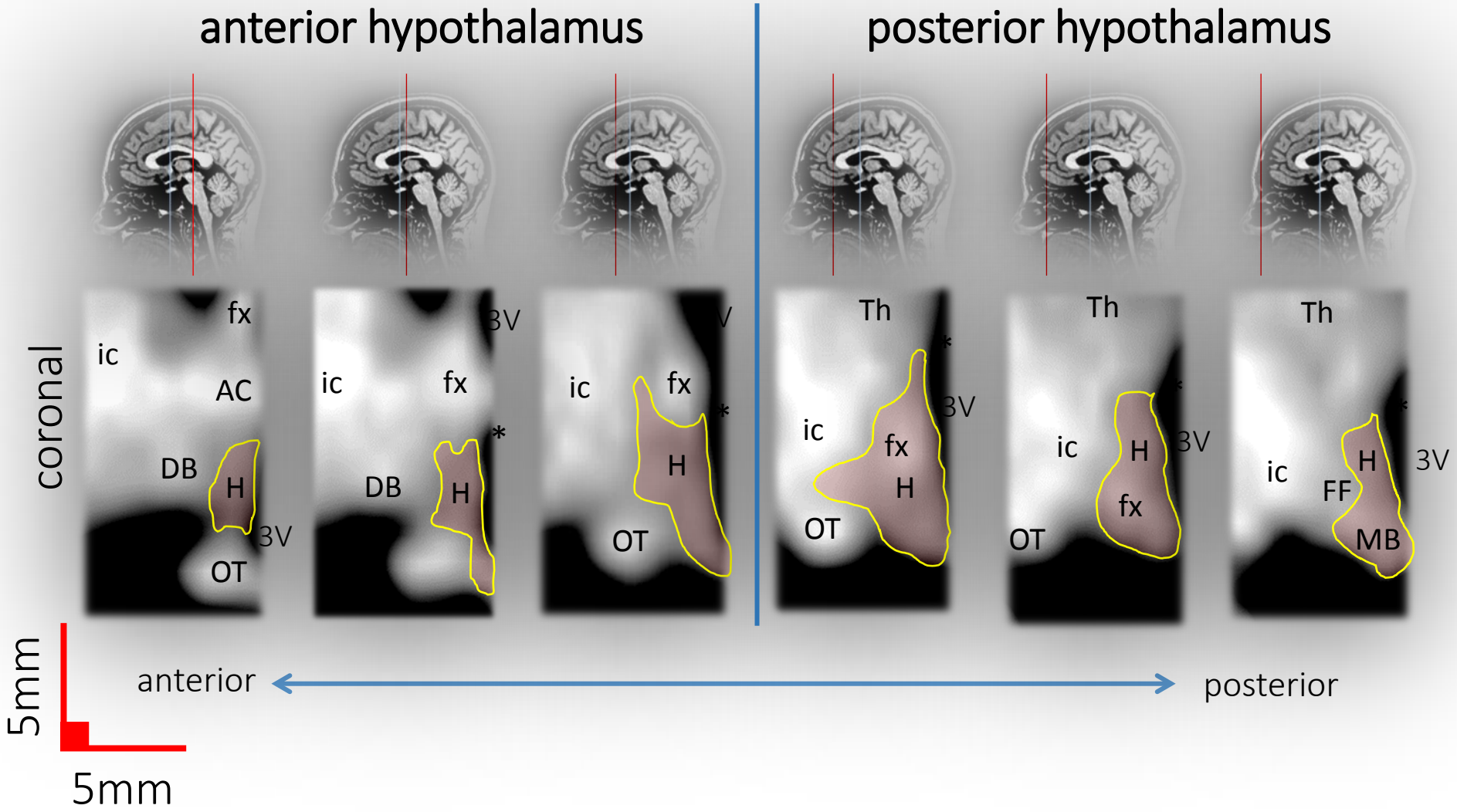
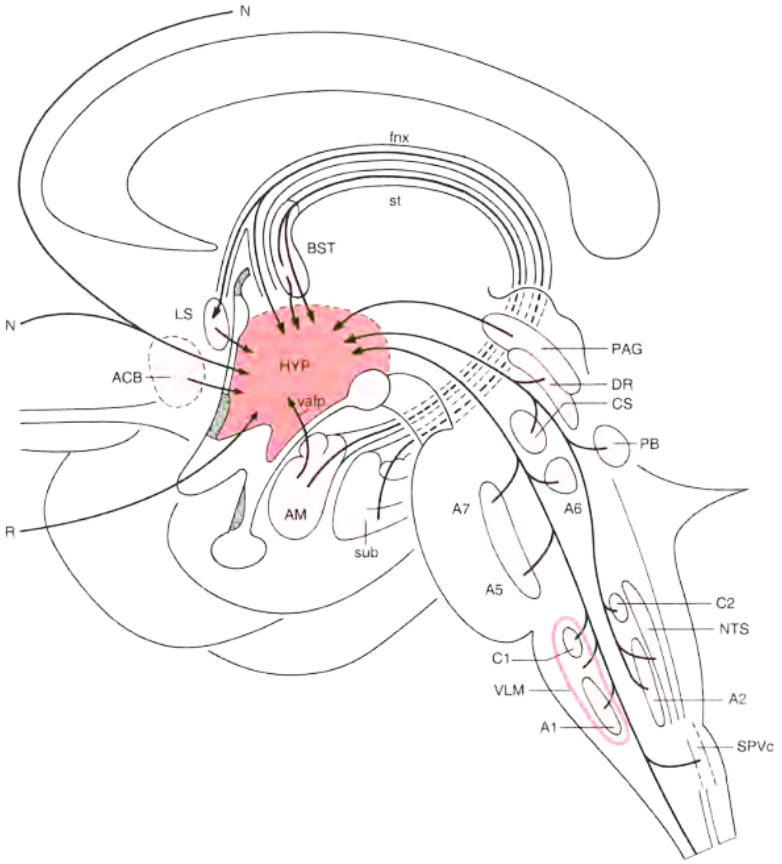
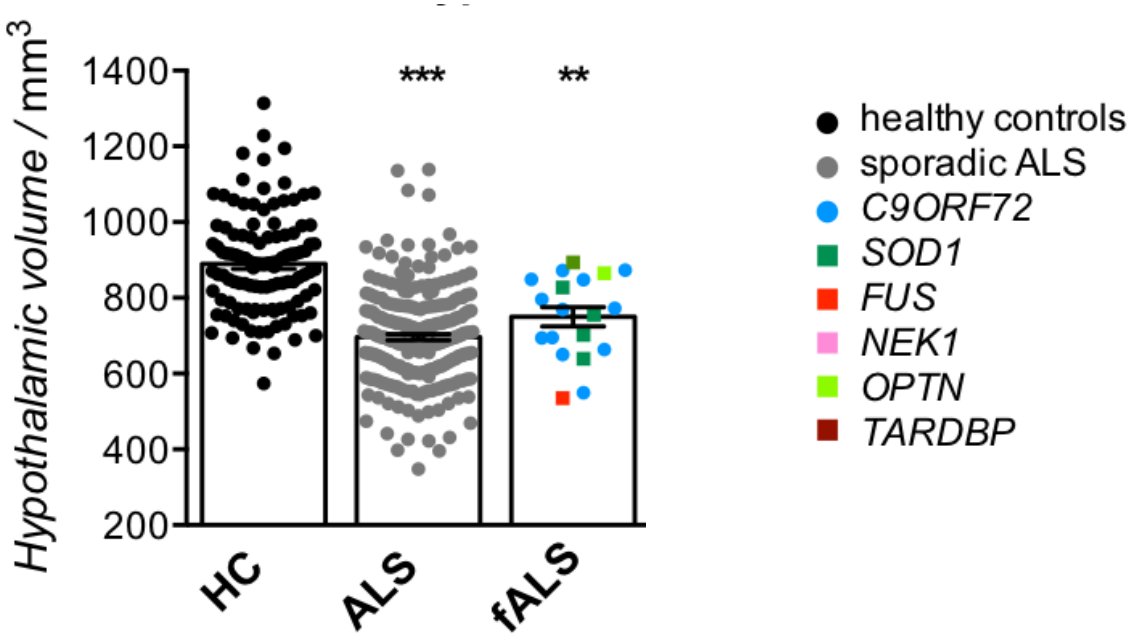


Data analysis

- data were shuffled prior to the analysis
- both raters were blinded to any clinical demographic or genetic information
- inter and intra-rater reliability has been demonstrated (CV<4%, ICC>0.9)
- Quantified volumes were corrected for
  - intracranial volume
  - gender
  - age

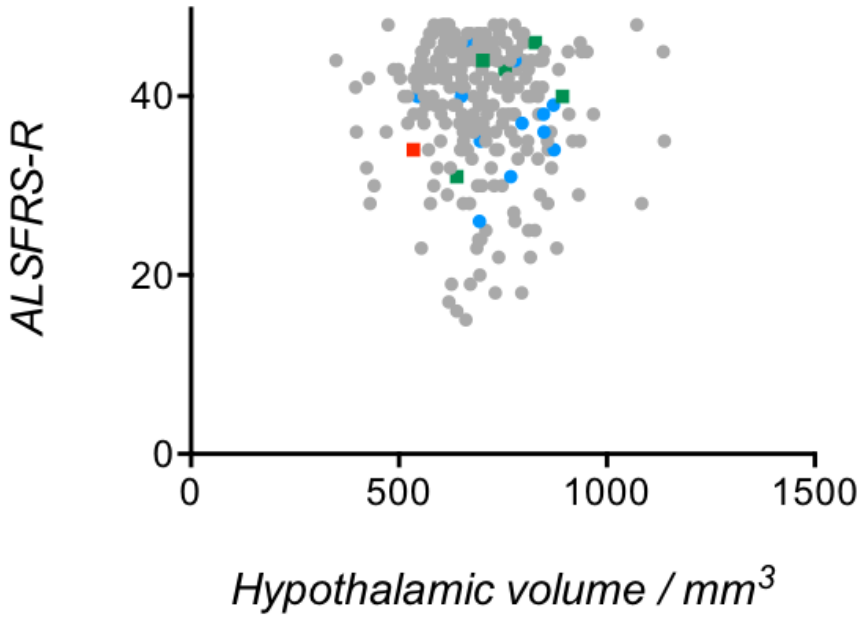


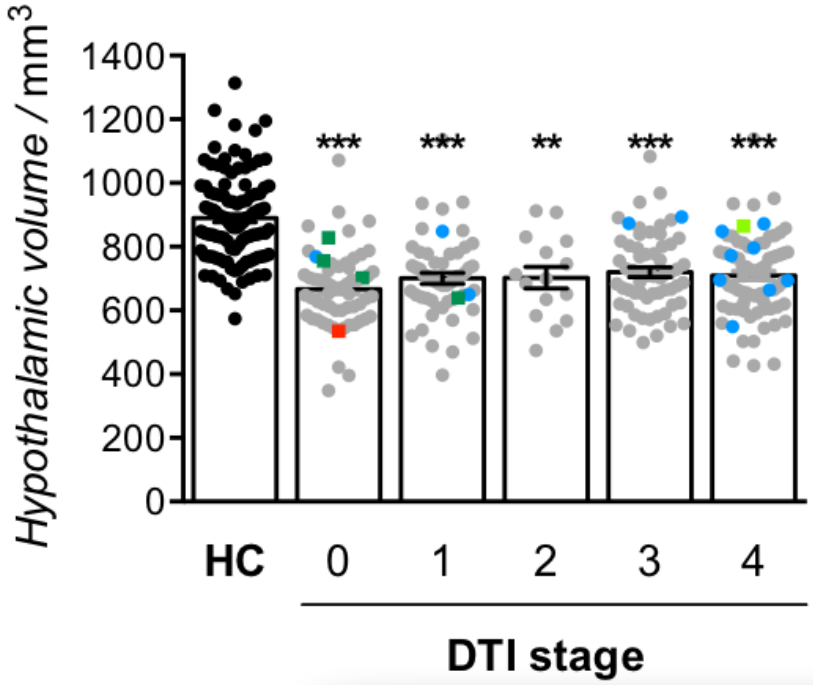
Results: Hypothalamic atrophy



→ Atrophy of the hypothalamus in ALS patients

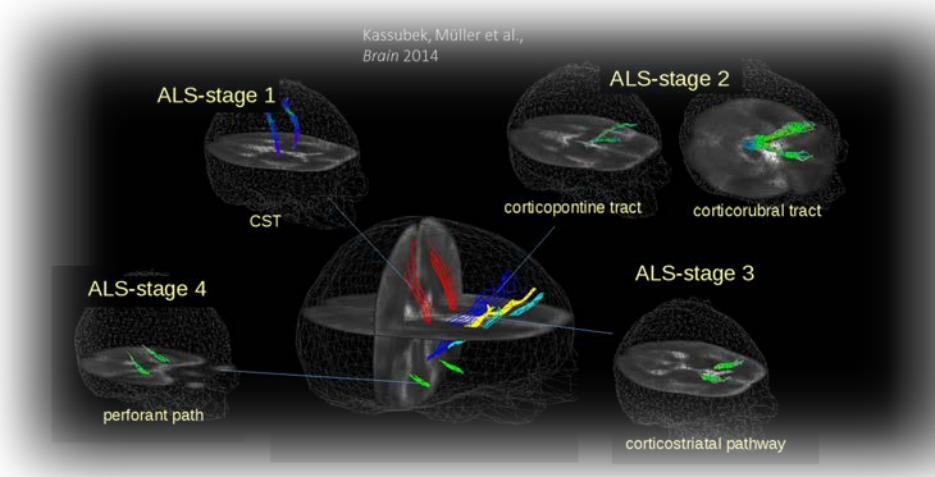
Correlations with ALSFRS-R / DTI-Staging



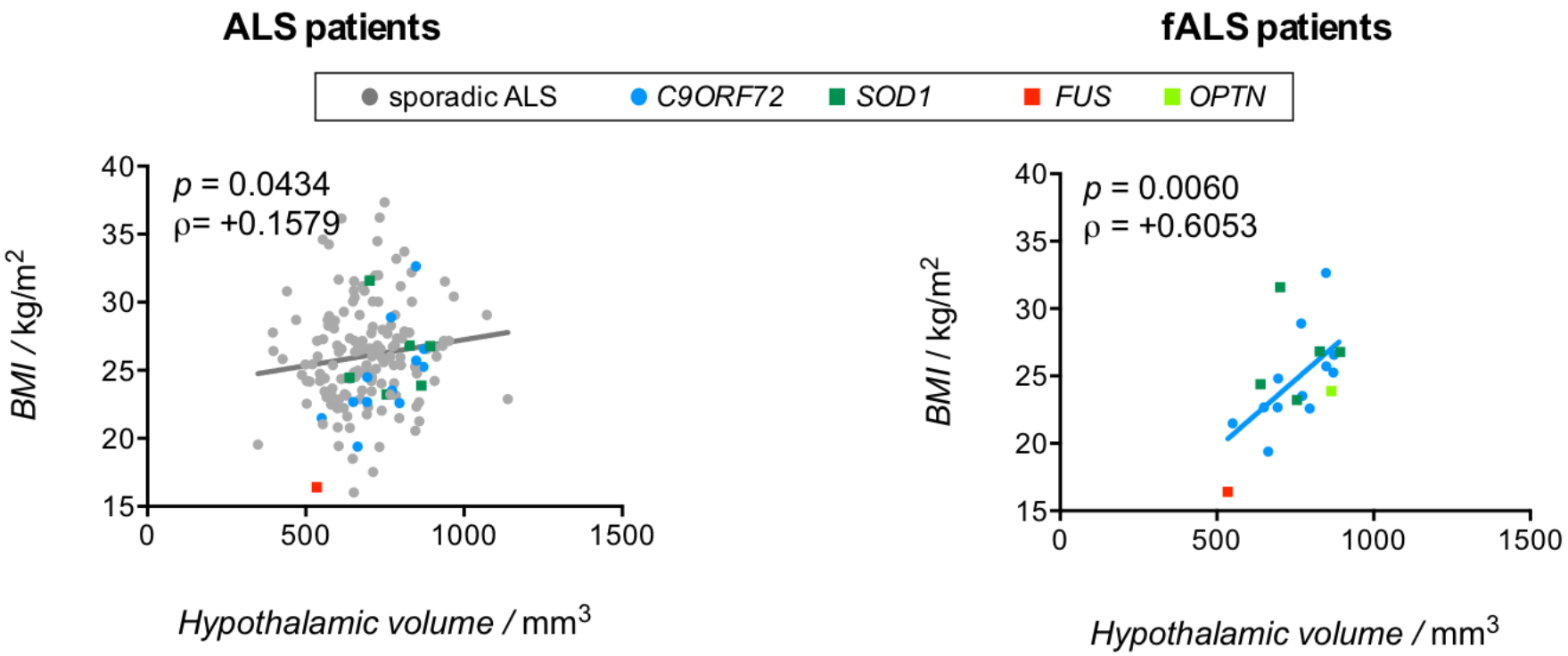


- healthy controls
- sporadic ALS
- *C9ORF72*
- *SOD1*
- *FUS*
- *NEK1*
- *OPTN*
- *TARDBP*

→ no significant correlations

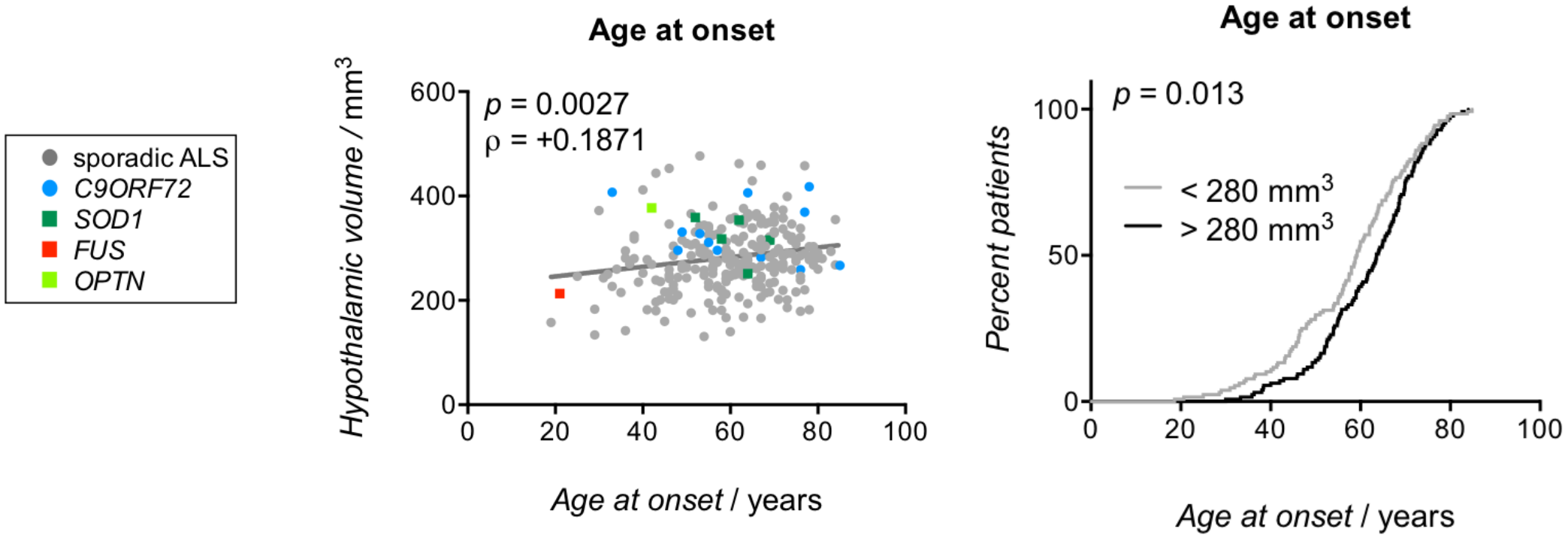


Correlations with BMI



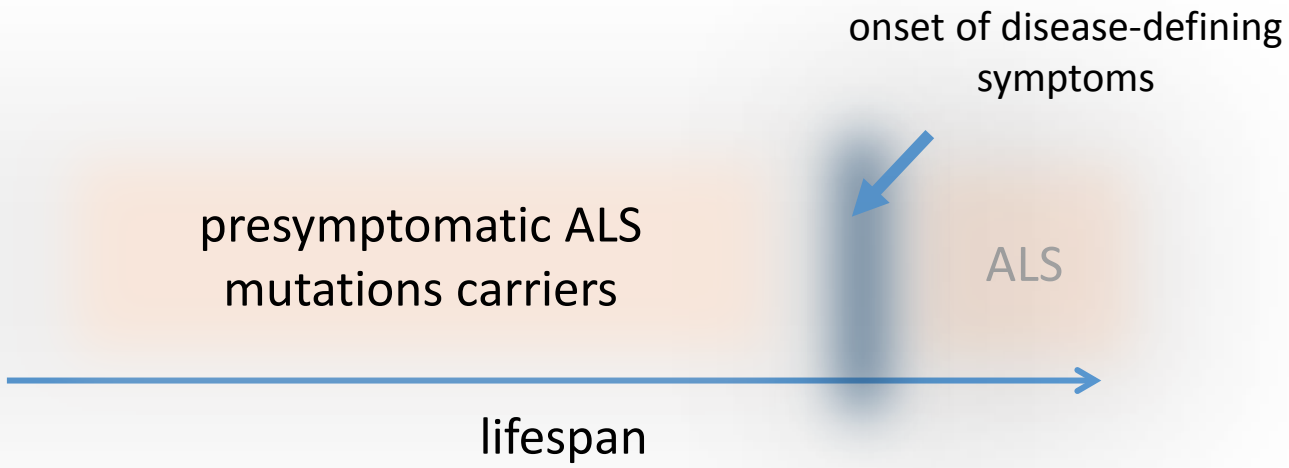
→ significant correlation with BMI

Correlations with age at disease onset



→ hypothalamic atrophy predicts age at disease onset

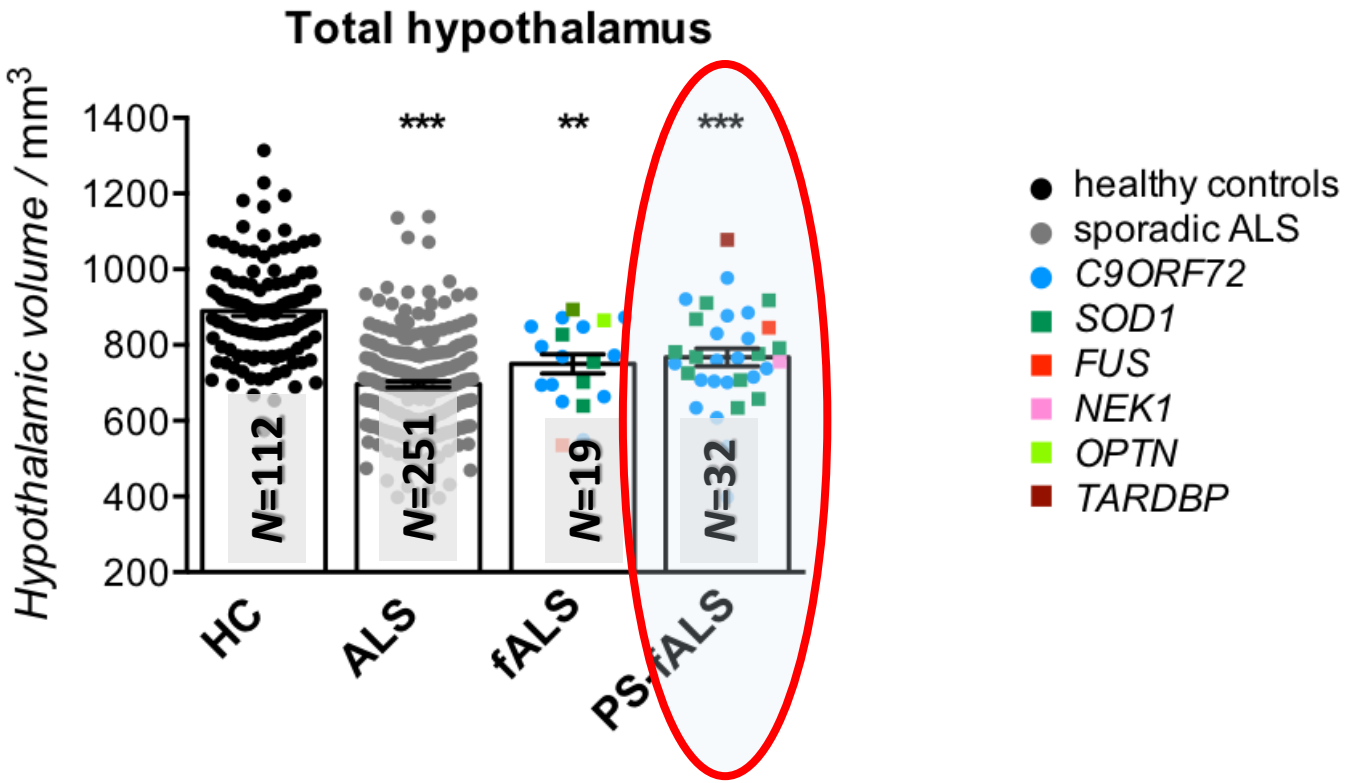
Hypothalamic atrophy prior to disease-defining symptoms?



Mutation carrier cohort
(monocentric data from Ulm, Germany)

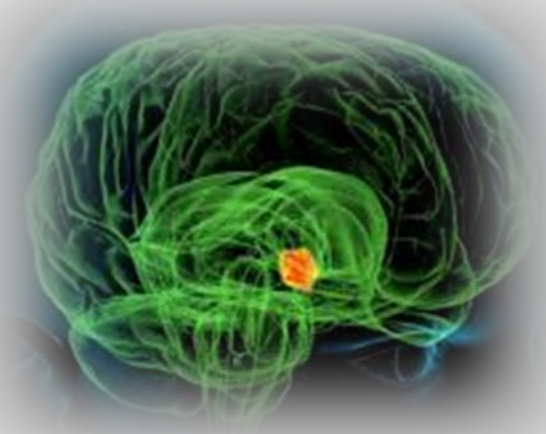
presymptomatic ALS mutation carriers (*N*=32)

Results: Hypothalamic volume in presymptomatic ALS mutation carriers



→ Atrophy of the hypothalamus also in presymptomatic ALS mutation carriers

Summary



- The hypothalamus is substantially atrophied in
  - manifest ALS patients (sporadic + genetic forms)
  - presymptomatic ALS mutation carriers

  → the volume loss occurs before motor symptoms
- BMI is correlated with hypothalamic volume in ALS
- Hypothalamic volume is uncorrelated with clinical data
- Age at onset is predicted by the hypothalamic volume
- *Prospective:* Functional tests of the hypothalamus?

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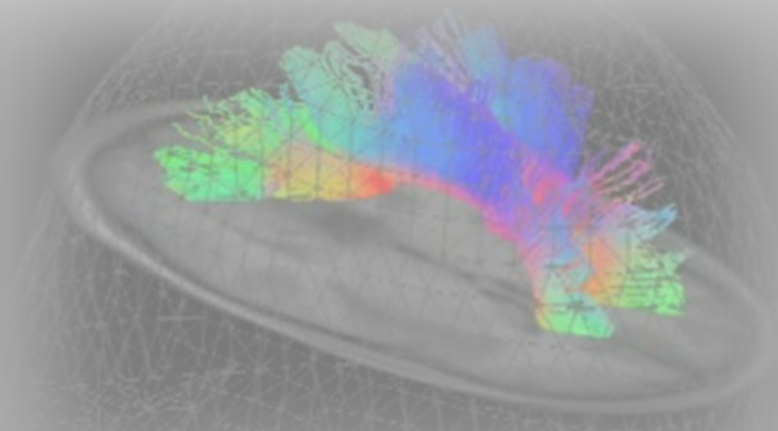
Team

Martin **Gorges** (Ulm) **and**
Pauline **Vercruysse** (Strassbourg)
Hans-Peter **Müller** (Ulm)
Hans-Jürgen **Huppertz** (Zürich)
Angela **Rosenbohm** (Ulm)
Gabriele **Nagel** (Ulm)
Patrick **Weydt** (Ulm/Bonn)
Åsa **Petersén** (Lund)
Albert C. **Ludolph** (Ulm)
Jan **Kassubek** (Ulm) **and**
Luc **Dupuis** (Strassbourg)



Strassbourg

Lund

Zürich

Ulm

BMJ Journals

Journal of Neurology, Neurosurgery & Psychiatry

Martin Gorges[1]*, Pauline Vercruysse[1,2,3]*, Hans-Peter Müller[1], Hans-Jürgen Huppertz[4], Angela Rosenbohm[1], Gabriele Nagel[5], Patrick Weydt[1], Åsa Petersén[6], Albert C. Ludolph[3], Jan Kassubek[1#] & Luc Dupuis[2,3#]:
“Hypothalamic atrophy is related to age at onset in amyotrophic lateral sclerosis”, *JNNP (in press)*