

Cortical thinning and connectivity in TLE

PhD candidacy exam presentation
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outline

1. Background

- ▶ TLE: Neuropathology and MRI-based volumetry
- ▶ MRI-based cortical thickness measurements

2. Purpose of the proposal

3. Projects

- ▶ Mapping cortical thinning and mesiotemporal connectivity in TLE
(Bernhardt et al., NeuroImage, 2008)
- ▶ Mapping progressive cortical thinning in TLE
(Bernhardt et al., under revision in Neurology)
- ▶ The role of the thalamus in the network of TLE
- ▶ Disruptions of the underlying white matter in TLE

Background

Epilepsies

- ▶ Seizure disorders
- ▶ Focal and generalized epilepsies
- ▶ ~1% of world population is affected

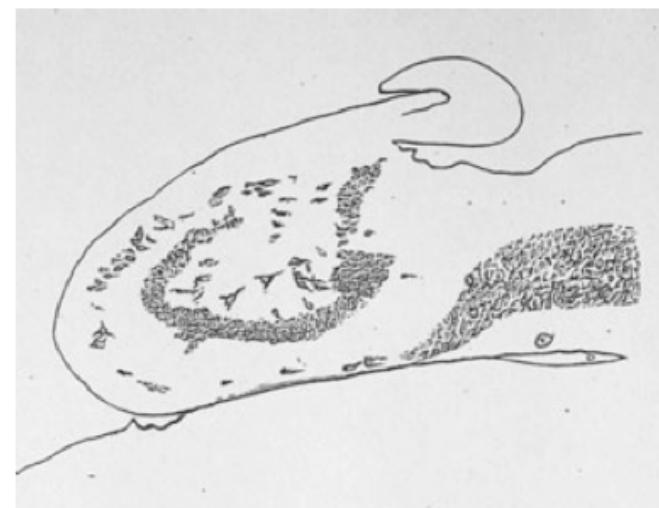
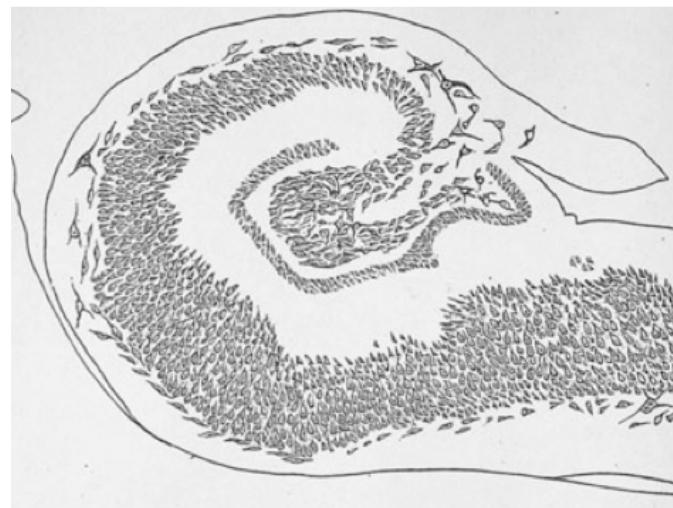
Temporal lobe epilepsy (TLE)

- ▶ Most common focal epilepsy
- ▶ Seizures originate in the temporal lobes
- ▶ Semiology includes
 - ▶ Epigastric sensations, déjà-vu, olfactory hallucinations;
 - ▶ Oro-alimentary and motor automatisms
 - ▶ Potential secondary tonic-clonic generalization
- ▶ Most intractable epilepsy, ~30% drug-resistant
- ▶ These patients may undergo surgery, ~30% failure rates

Histopathological findings in TLE: Hippocampal sclerosis

TLE associated with hippocampal sclerosis, ~70% prevalence

(Cavanagh and Meyer, 1956, Brit J Med)



(Bratz, 1899, Arch Psych Nervenk)

Histopathological findings in TLE: Limbic cell loss

- ▶ Neuronal loss in other limbic regions
 - ▶ Layer 3 of the medial entorhinal cortex
(Du et al., 1993, Epilepsy Res; Du et al., 1995, J Neurosci)
 - ▶ Amygdala (Cavanagh and Meyer, 1956, Brit Med J)
 - ▶ Temporal neocortex (Bothwell et al., 2001, J Neurosci)
 - ▶ Thalamus (Margerison and Corsellis, 1966, Brain)

Histopathological analysis: pros and cons

Pros:

- ▶ Direct measurement of pathological changes
- ▶ High resolution (microscope)

Cons:

- ▶ No insights about abnormalities *in vivo*
- ▶ Difficult to acquire, low *n*
- ▶ Limited to ipsilateral temporal lobe of TLE patients *ex vivo*
- ▶ Limited to *postmortem* studies in controls and extra-temporal TLE pathology
- ▶ Influence of time / stain / angle on measurement

The value of MRI: volumetry detects hippocampal sclerosis

Hippocampal sclerosis is associated with hippocampal atrophy



(Cascino et al. 1991, Ann Neurol)

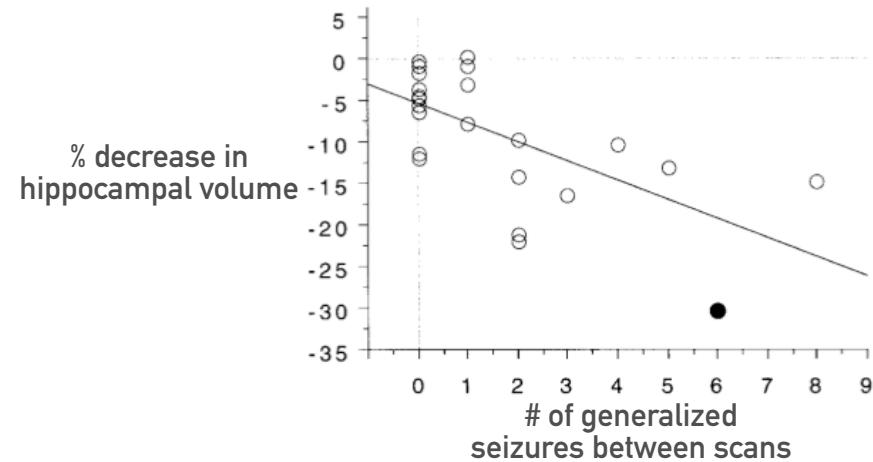
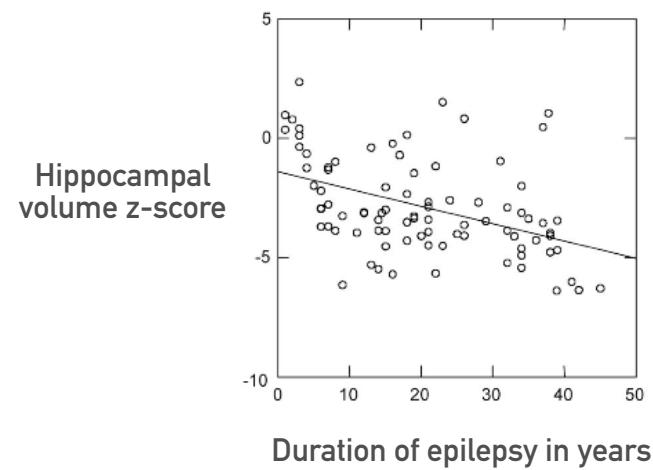
Extrahippocampal volumetry in TLE: limbic atrophy

- ▶ GM volume reduction in
 - ▶ Entorhinal cortex
(Bernasconi et al. 2000, Neurology; Bernasconi et al. 2003, Brain)
 - ▶ Amygdala (Bernasconi et al. 2003, Brain; Cendes et al. 1994, Brain)
 - ▶ Temporopolar region (Sankar et al. 2007, Hum Brain Map)
 - ▶ Thalamus (Natsume et al., 2000, Neurology)

Insights into pathogenesis

Progressive atrophy in ipsilateral mesiotemporal lobe region

(Bernaconi et al. 2005, Neurology; Briellmann, 2002, Ann Neurol)



Volumetry: pros and cons

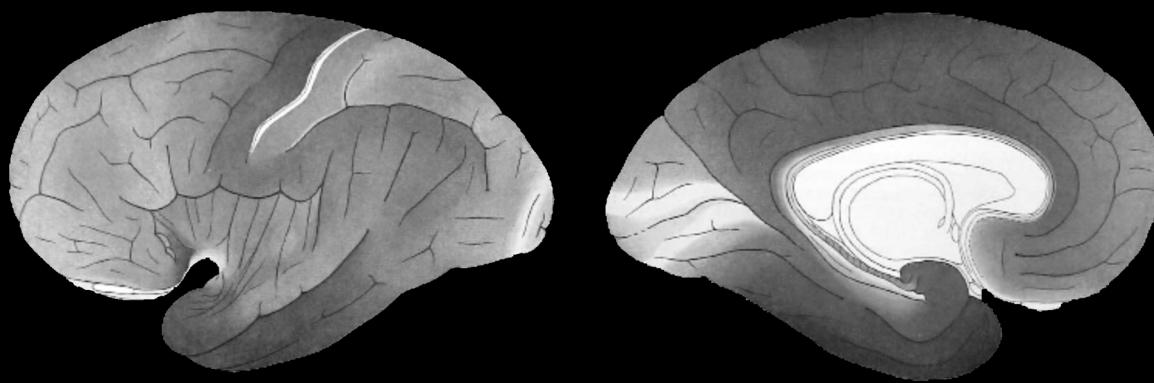
Pros:

- ▶ Non-invasive quantification of atrophy that parallels histopathology
- ▶ Thus: may help to investigate pathogenesis *in vivo*

Cons:

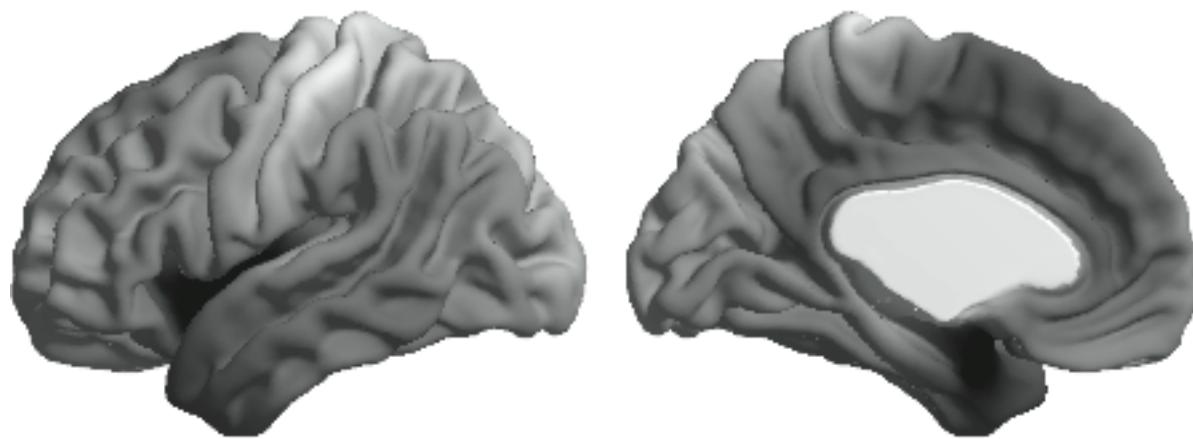
- ▶ Labor-intensive
- ▶ Rater-dependent
- ▶ ROI-based
- ▶ Thus: limited in neocortex

The measurement of cortical thickness

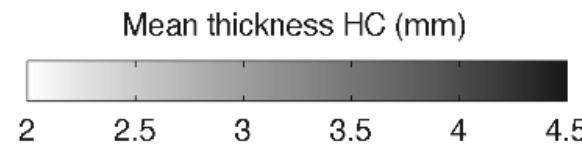


Von Economo and Koskinas, 1925

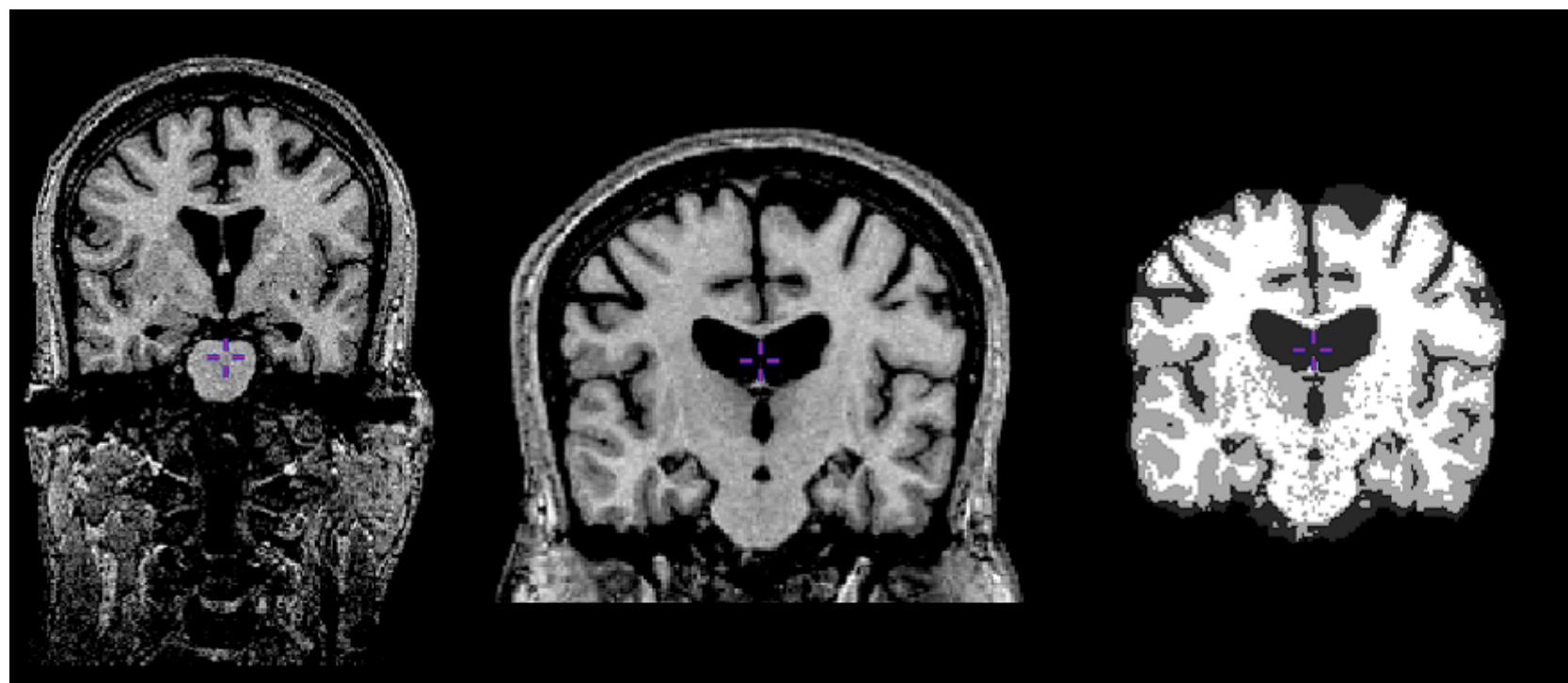
MRI-based cortical thickness measurements



Mean cortical thickness maps in 48 healthy controls



MRI-based cortical thickness measurements: processing pipeline

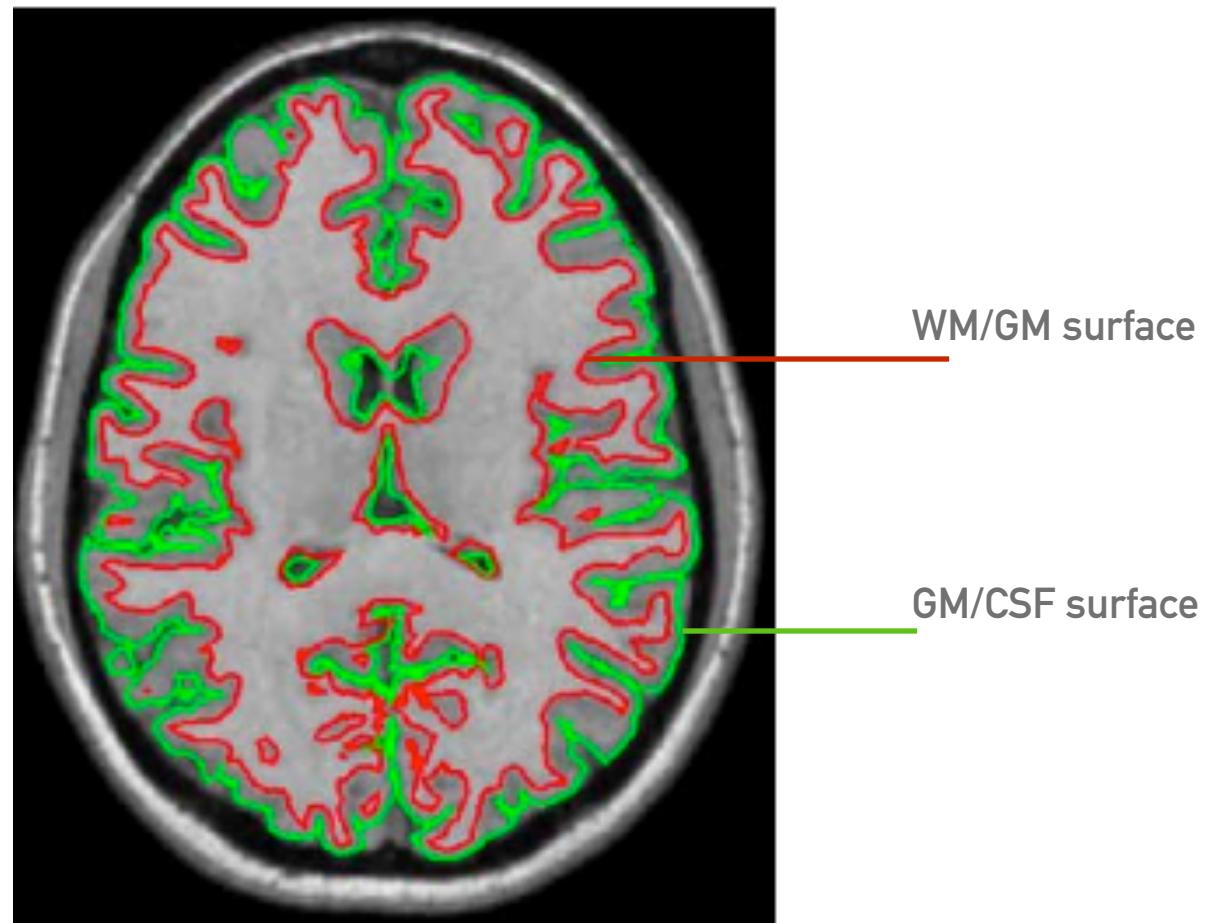


a) native space MRI

b) registered and NUC MRI

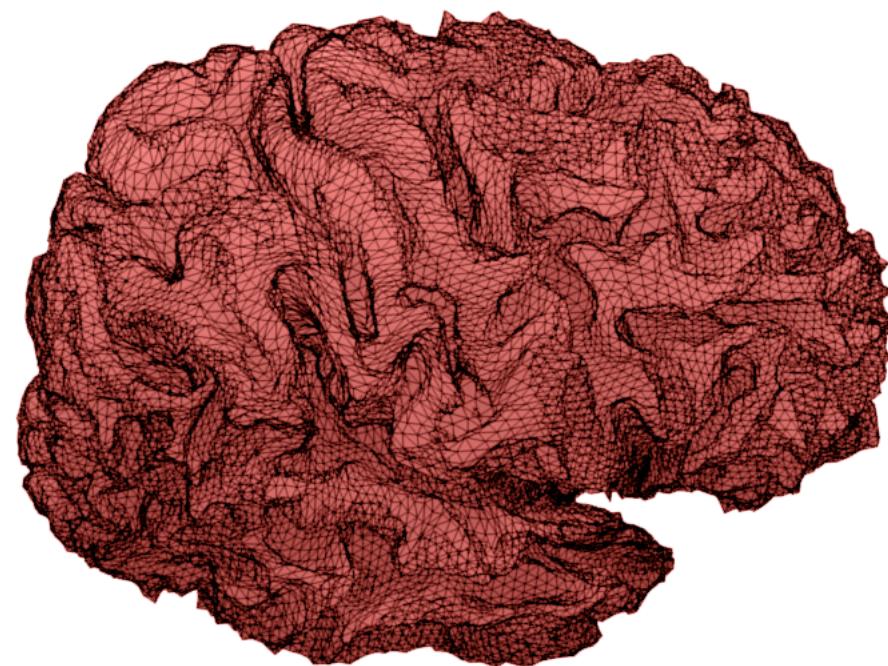
c) classified MRI

MRI-based cortical thickness measurements: processing pipeline



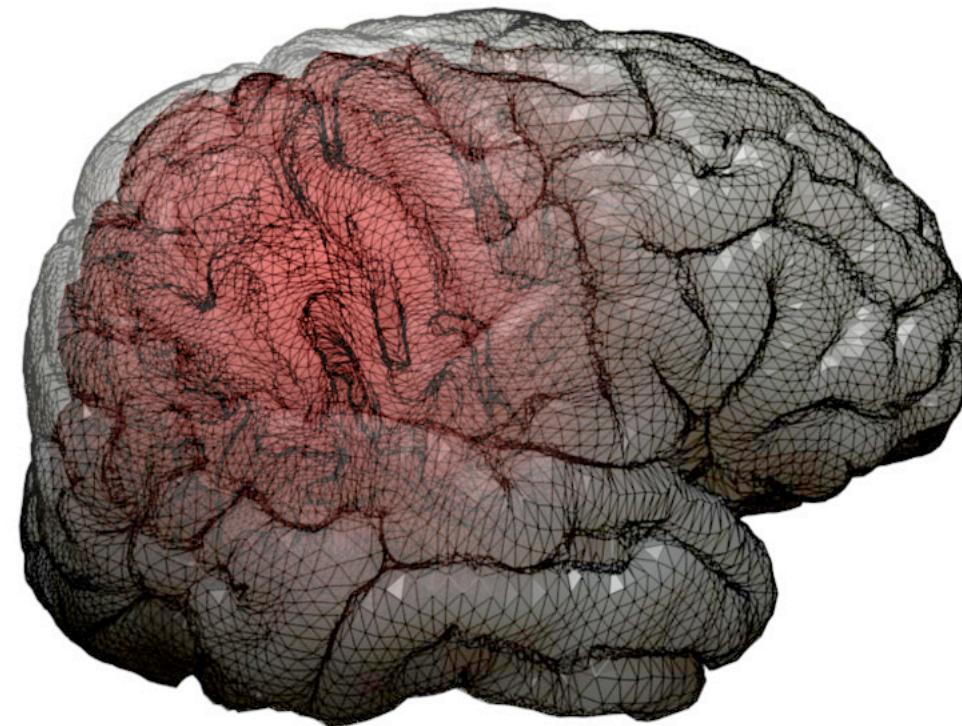
Kim et al. 2005, NeuroImage

MRI-based cortical thickness measurements: processing pipeline



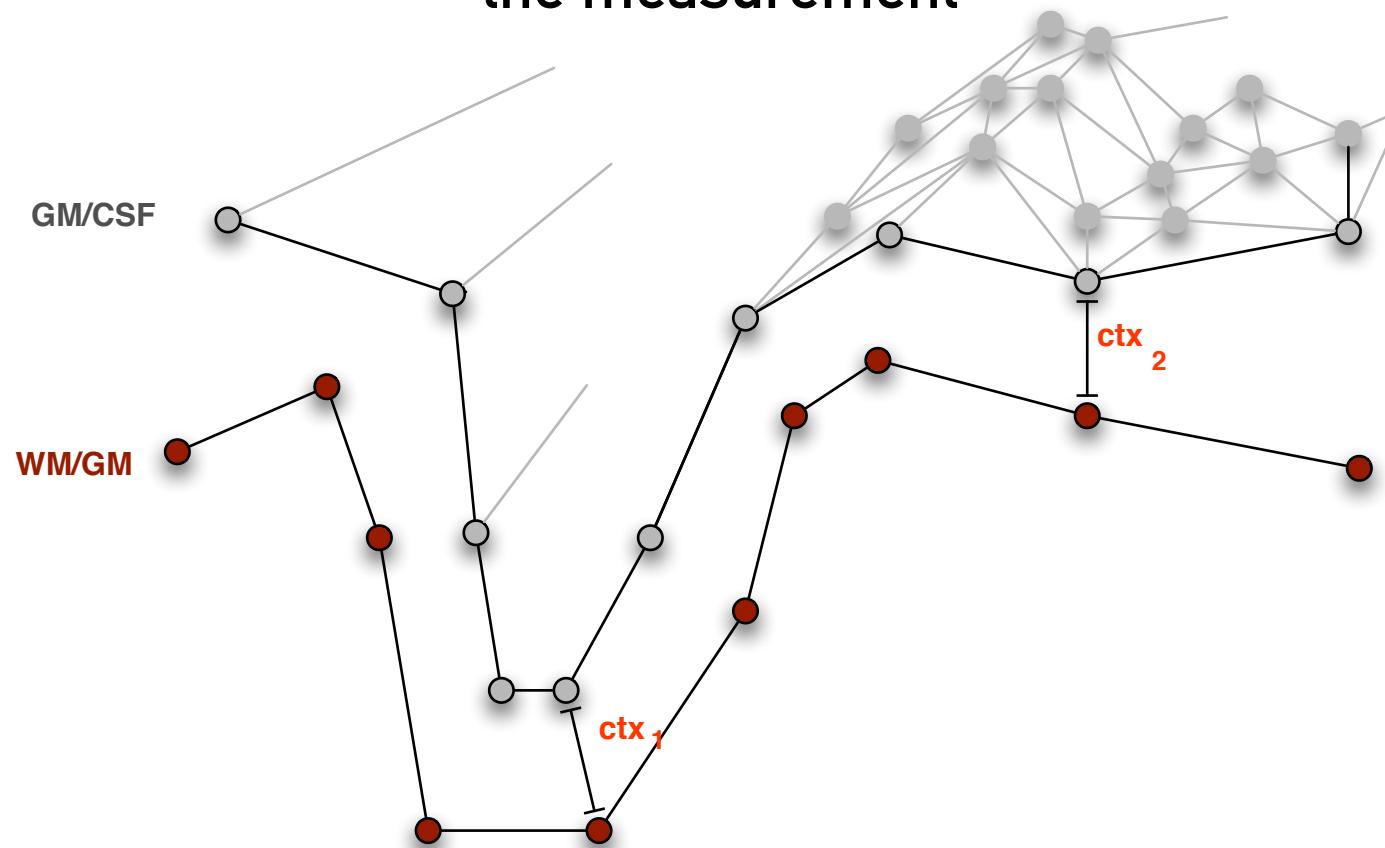
WM/GM surface

MRI-based cortical thickness measurements: processing pipeline



GM/CSF surface

MRI-based cortical thickness measurements: the measurement



MRI-based cortical thickness measurements: pros and cons

Pros:

- ▶ Non-invasive *in vivo*
- ▶ Automated
- ▶ Whole-cortex
- ▶ Continuous, respecting topology
- ▶ Biological meaning

Cons:

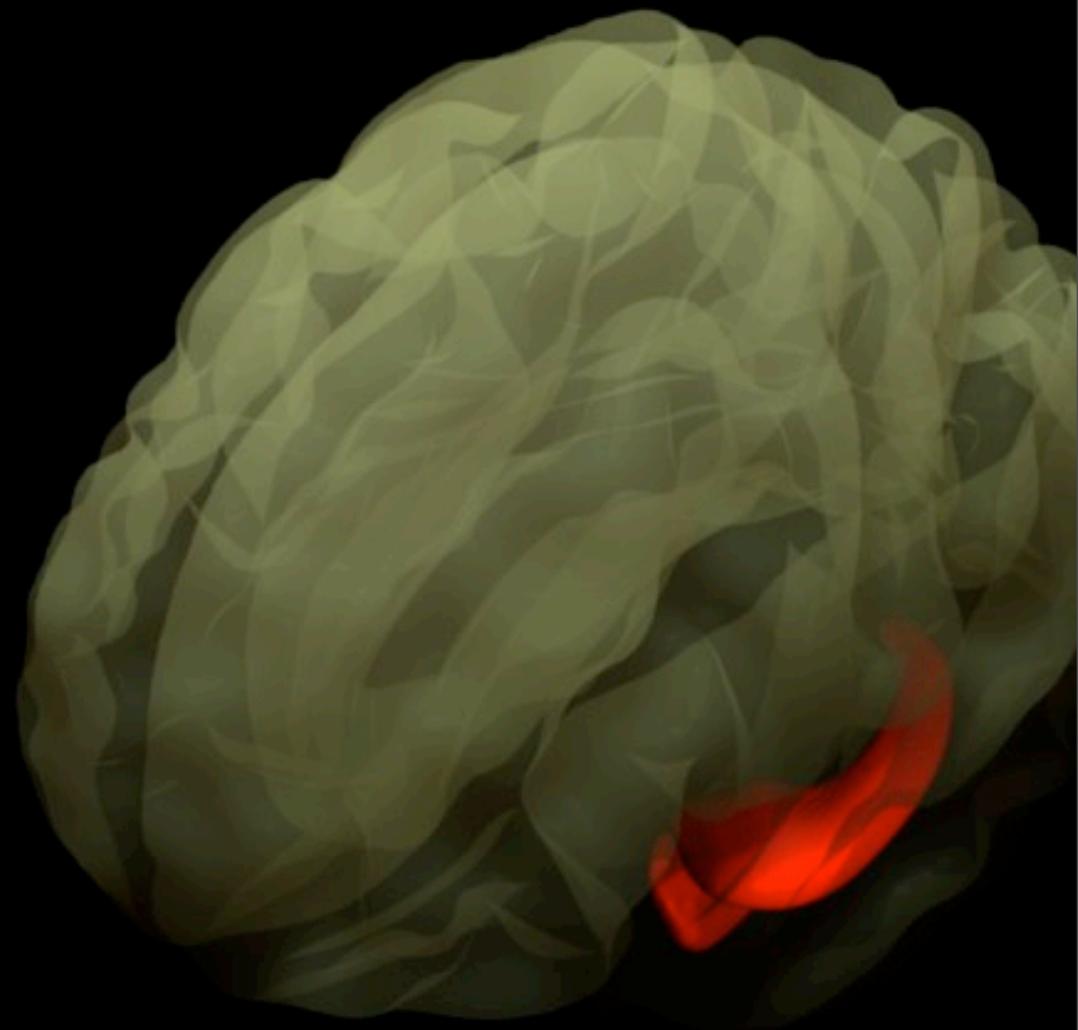
- ▶ Subcortical structures / WM need different measure
- ▶ Dependent on tissue classification results

Purpose

Purpose of the proposed research

- ▶ To map cortical thinning in drug-resistant TLE *in vivo*
- ▶ To assess
 - ▶ Its relationship to MTL connectivity (*project 1*)
 - ▶ Progressive neocortical changes (*project 2*)
 - ▶ The involvement of the thalamus (*project 3*)
 - ▶ Its relationship to disruptions of the underlying WM (*project 4*)

Project 1: Mapping neocortical thinning and mesiotemporal connectivity



Project 1: Rationale

1. Tendency for limbic pathology in TLE
 - ▶ Anatomical connectivity may determine sites of atrophy
 - ▶ This has not been tested in the neocortex
2. Connections can be mapped using morphometric correlations
(Lerch et al. 2006, *NeuroImage*)

Project 1: Rationale

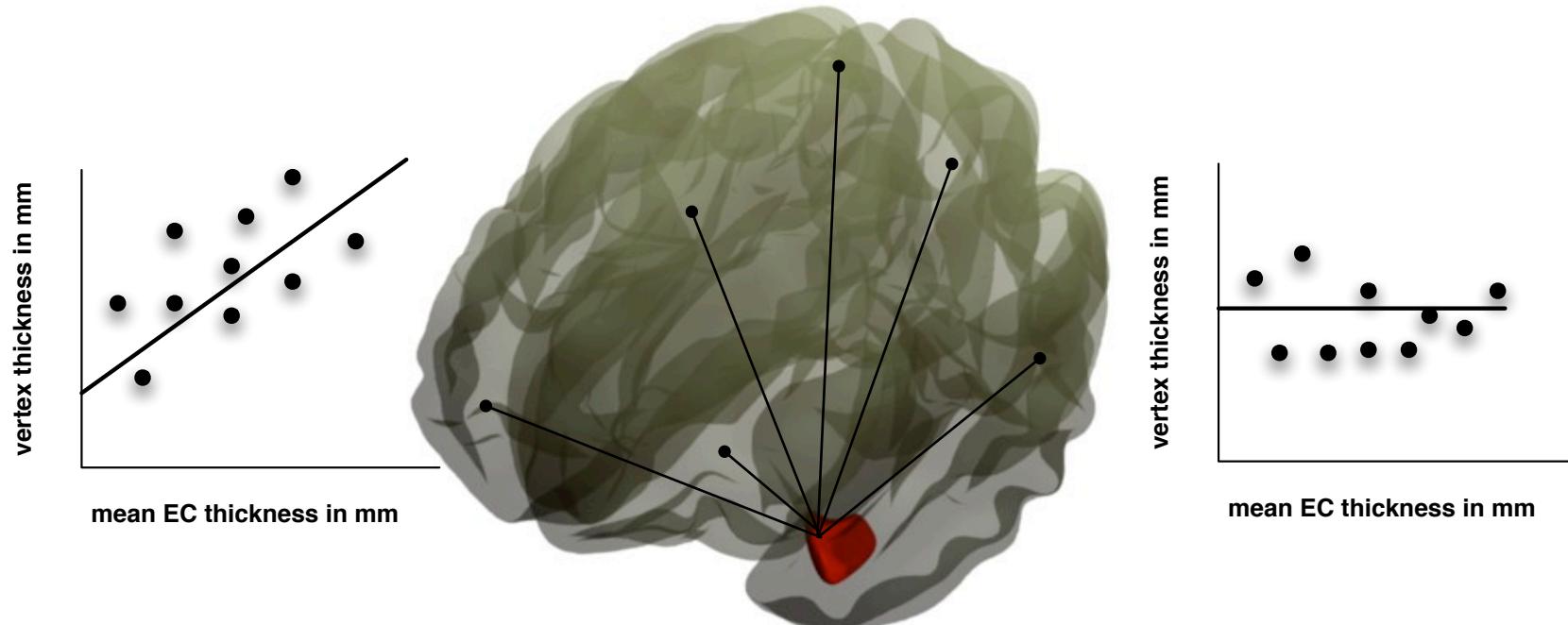
3. In TLE, entorhinal cortex is a very suitable seed region

▶ Hub between the hippocampus and the neocortex

(Insausti, 1987, J Comp Neurol)

▶ Pivotal role in the epileptic network

(Bernasconi et al., 2001, Neurology; Bartolomei et al., 2005, Epilepsia)

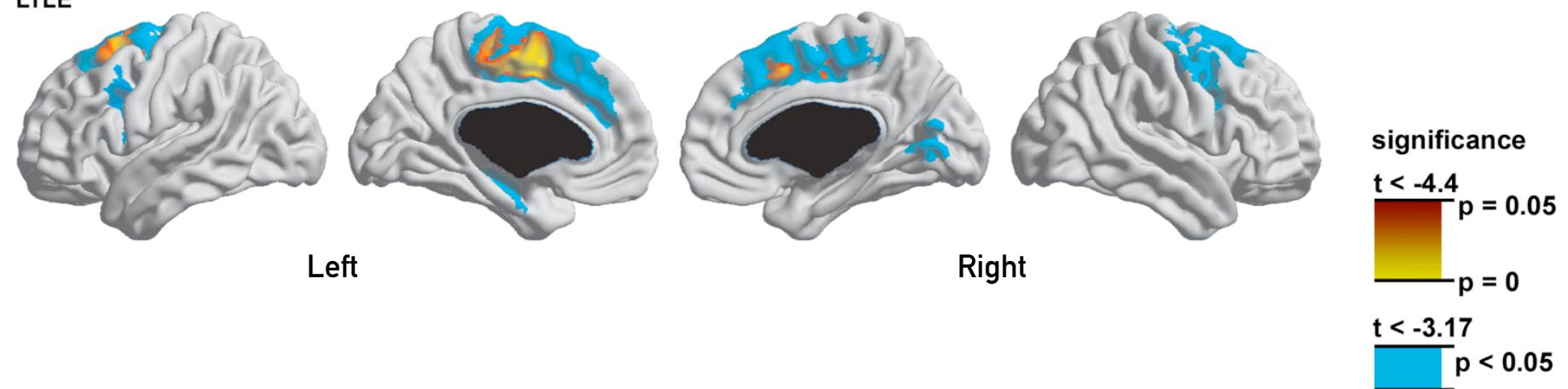


Project 1: Purpose

1. Mapping cortical thinning
2. Mapping mesiotemporal connectivity using thickness correlations
3. Determine their relationship

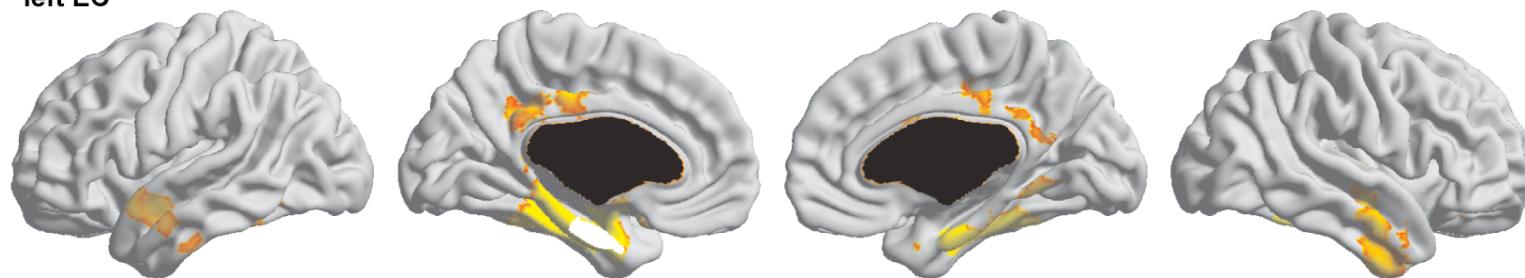
Project 1: Cortical thinning

a) Significant atrophy in TLE
LTLE

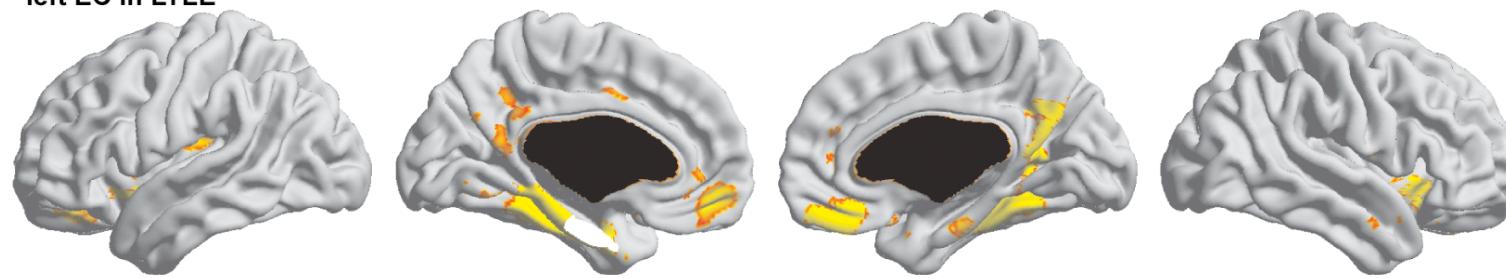


Project 1: Mesiotemporal connectivity

a) EC connectivity in controls
left EC

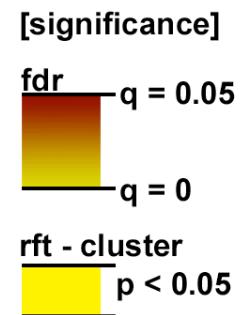


b) EC connectivity in TLE
left EC in LTLE

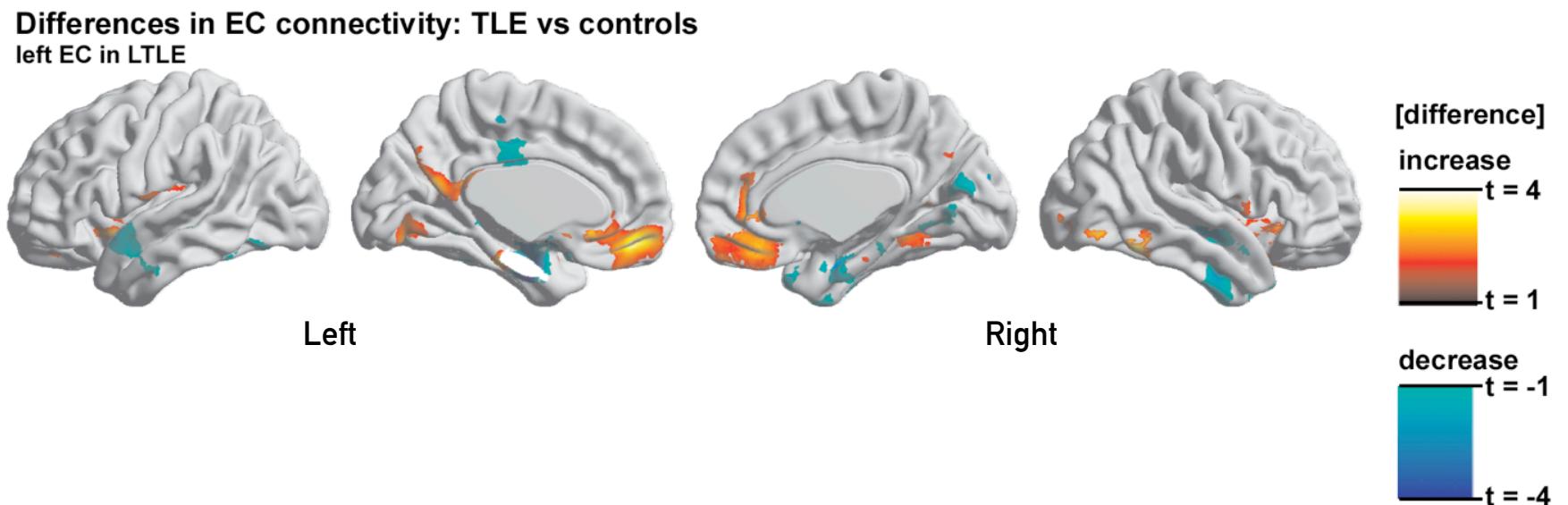


Left

Right



Project 1: Mesiotemporal connectivity

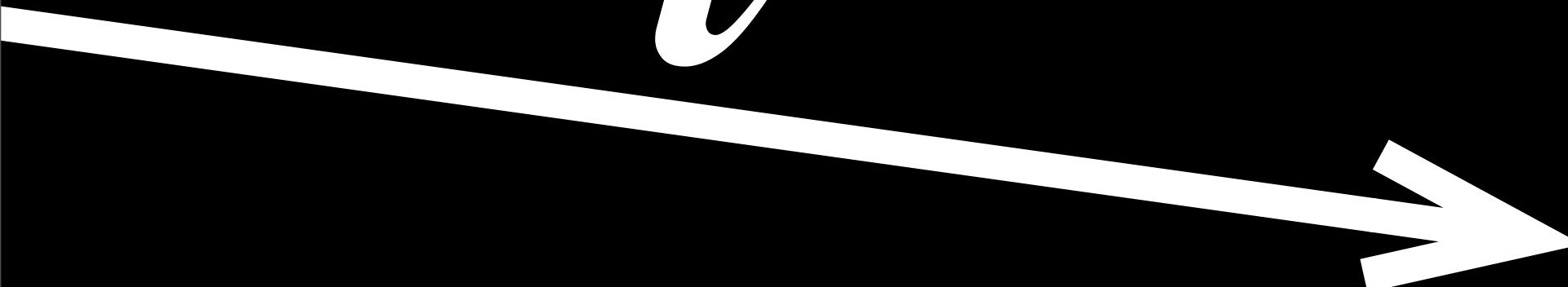


Project 1: Conclusions

1. No clear relationship between thinning and EC connectivity
 - ▶ Thinning in limbic AND fronto-central regions
 - ▶ Role of seizure propagation?
2. Correlation analysis suitable to infer EC connectivity
3. Altered connectivity of the EC in TLE may reflect
 - ▶ (↓) Structural disconnection within the temporal lobe ?
 - ▶ (↑) Correlated tissue loss, seizure-spread to frontal lobes ?

Project 2: Mapping progressive neocortical thinning in TLE

t



Project 2: Rationale

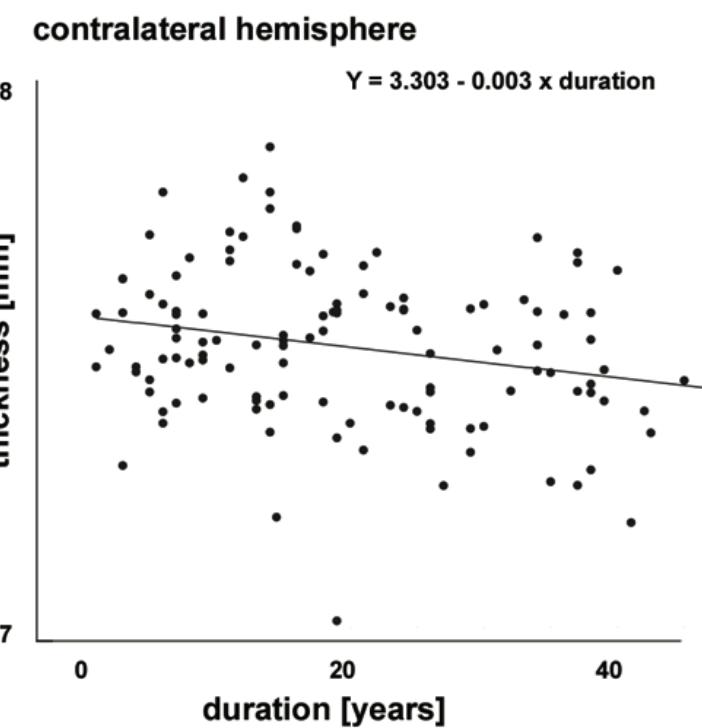
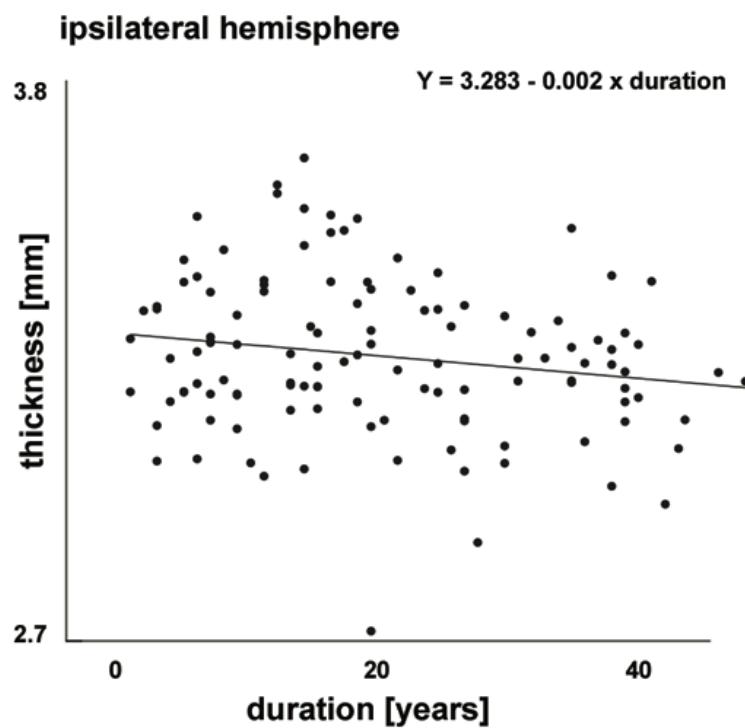
- ▶ *Project 1: seizure propagation as potential pathogenic mechanism*
- ▶ Progression over time
- ▶ Cross-sectional studies in TLE demonstrated progressive mesiotemporal atrophy (Bernasconi et al. 2005, Neurology)
- ▶ Cortical findings are unclear (Liu et al. 2003, Annals of Neurology)
- ▶ Sensitivity to detect changes may increase cortical thickness measurements

Project 2: Purpose

- ▶ The purpose of this study was to assess progressive neocortical thinning in TLE
 - 1. Cross-sectional correlation with duration
 - 2. Longitudinal analysis of progressive change
 - 3. Cross-sectional comparison of aging effects

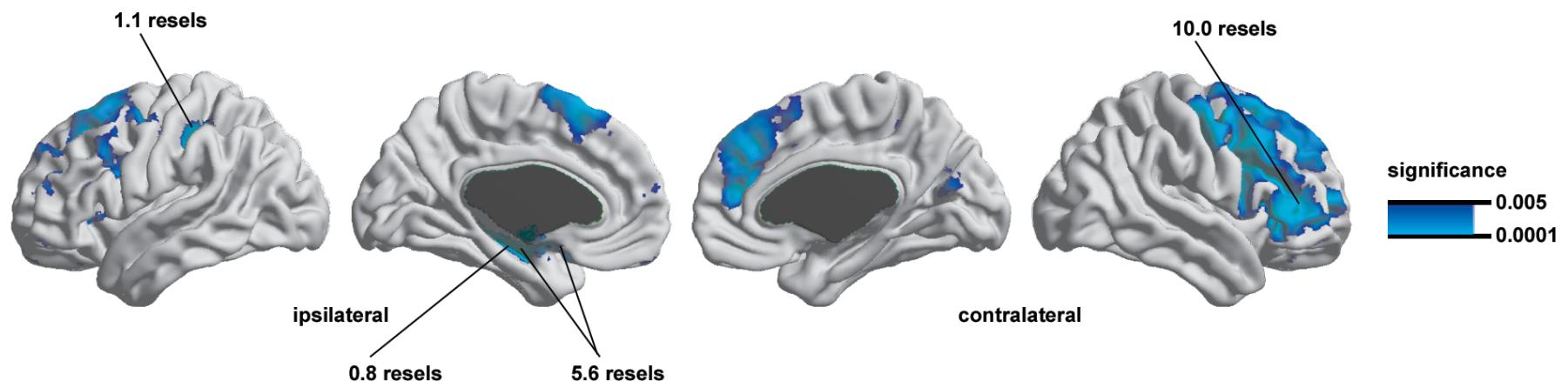
Project 2: Duration effects

A) Mean cortical thickness



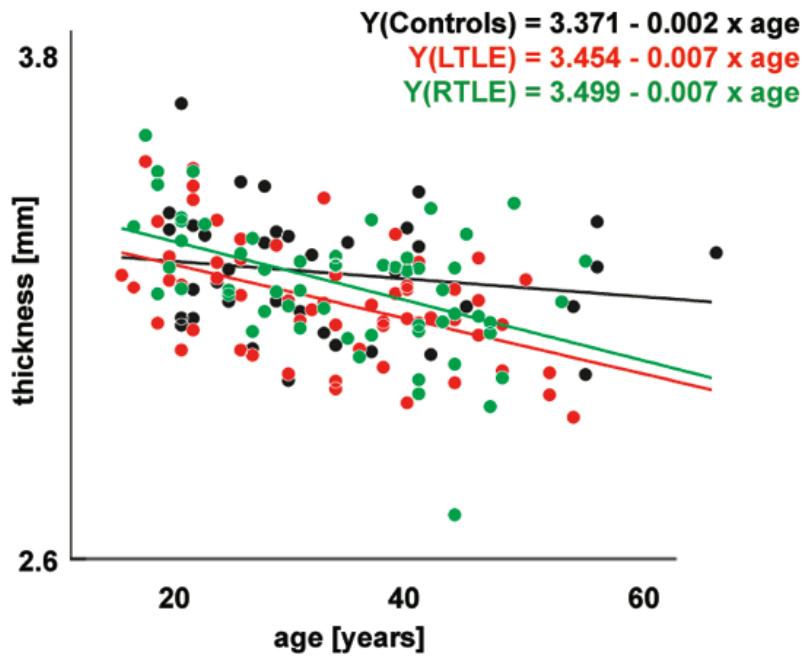
Project 2: Duration effects

B) Cortical thickness at each vertex

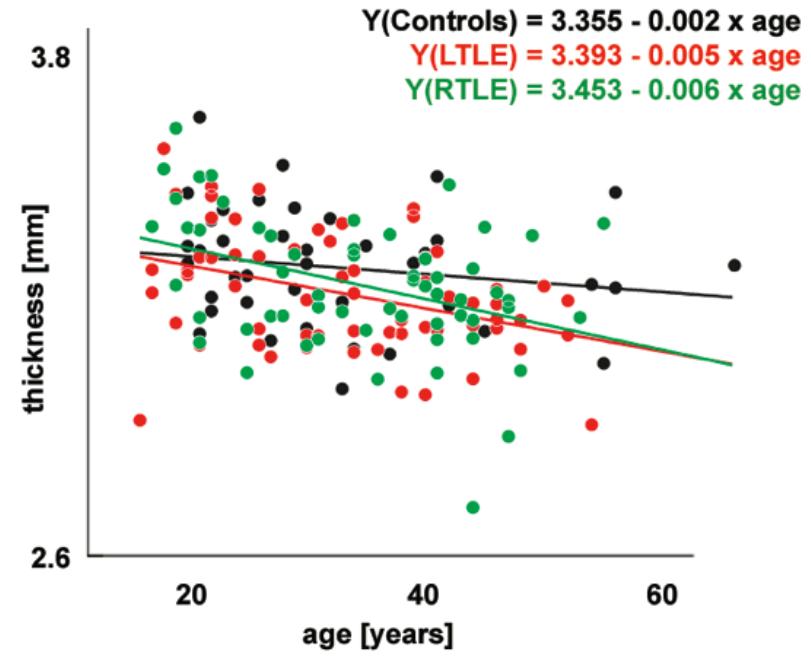


Project 2: Comparison of aging effects

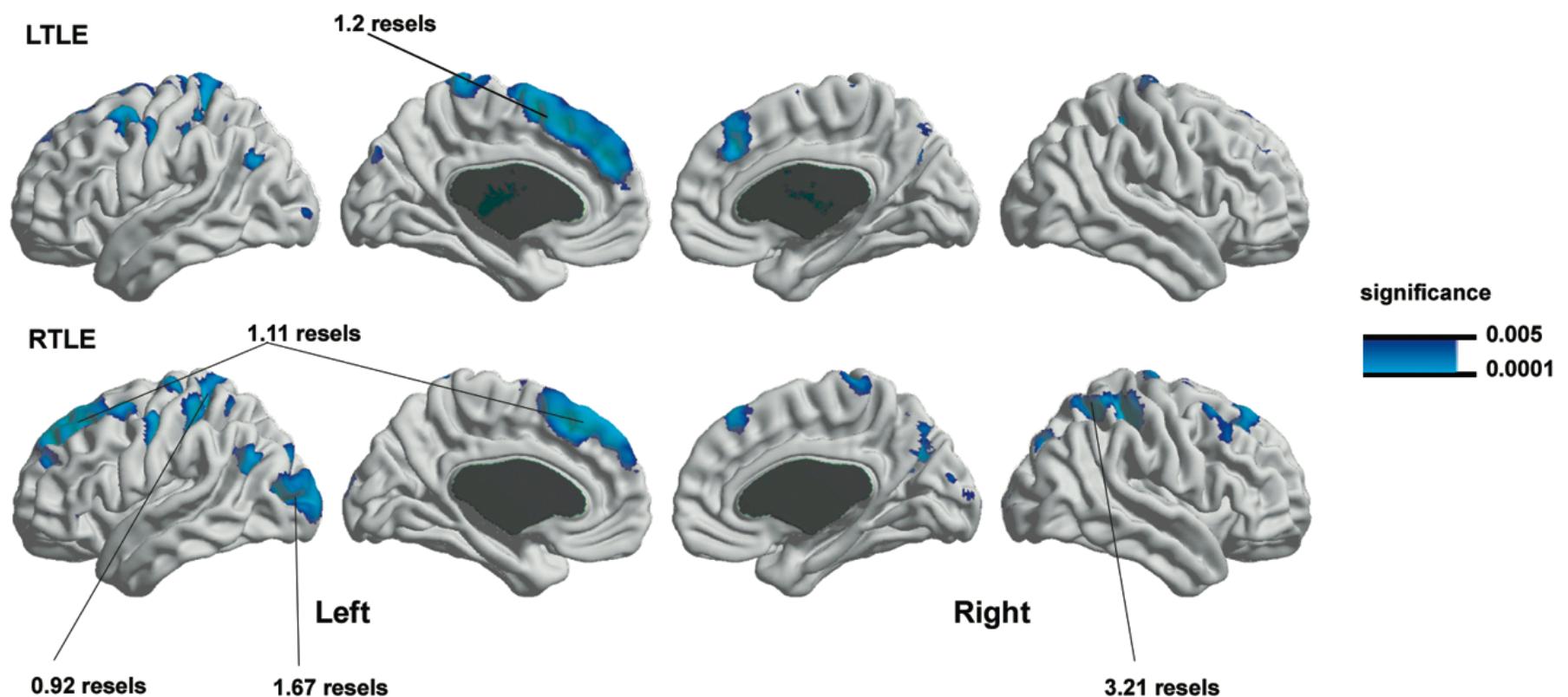
left hemisphere



right hemisphere



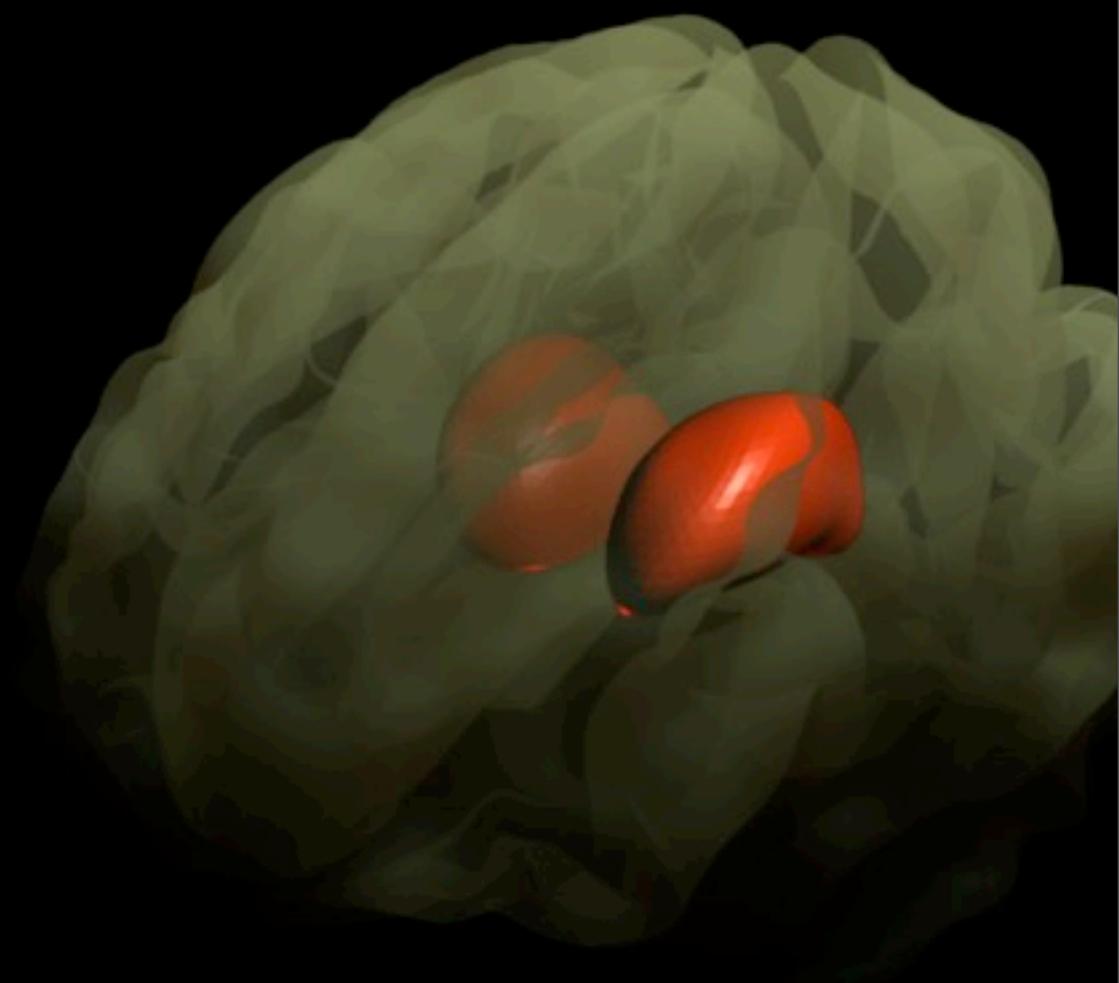
Project 2: Comparison of aging effects



Project 2: Conclusions

- ▶ Progressive multilobar thinning in intractable TLE
- ▶ More pronounced than healthy aging
- ▶ May represent seizure-induced damage
- ▶ Importance of early effective treatment in TLE

Project 3: Mapping the role of the thalamus in the network of TLE



Project 3: Rationale

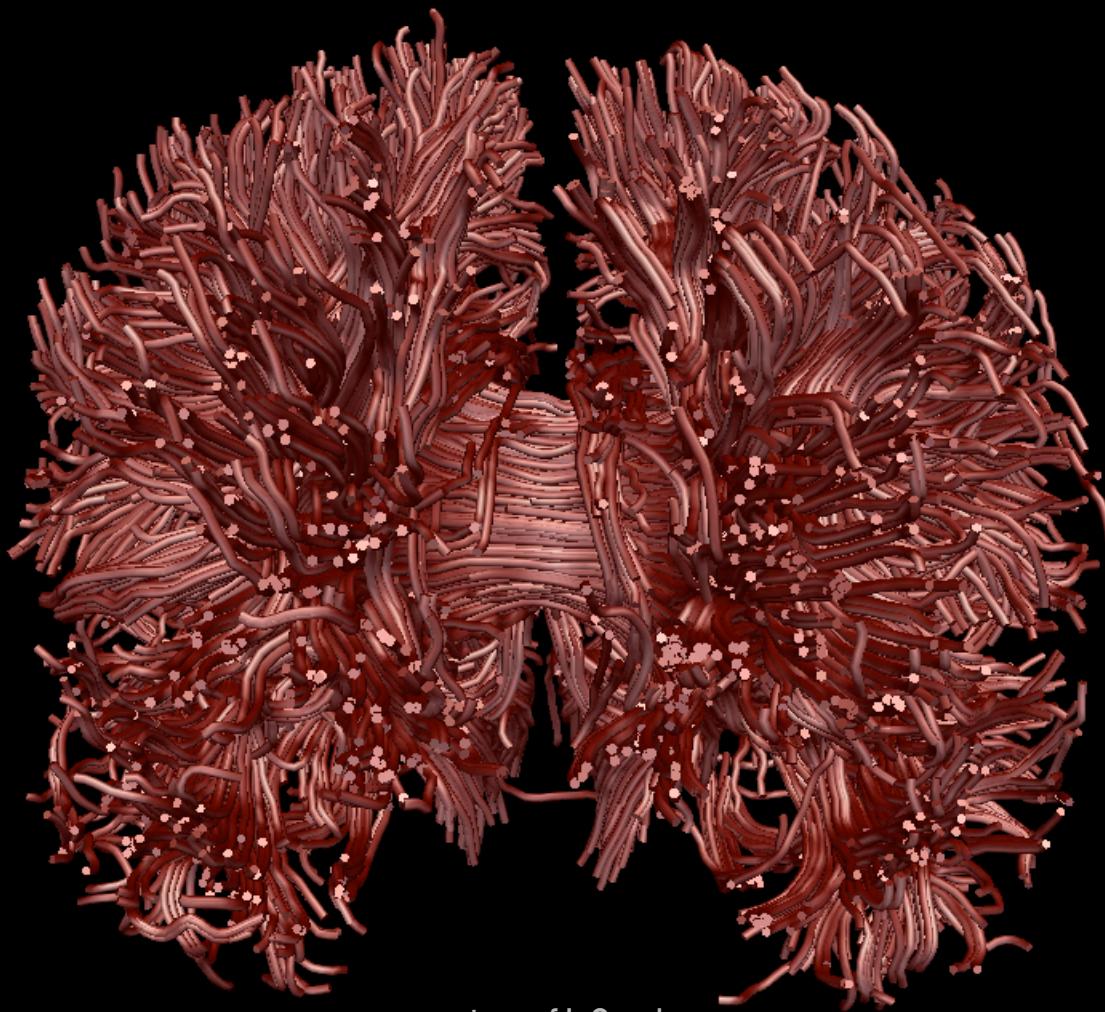
- ▶ Seizure spread may be a crucial mechanism of cortical pathology
 - ▶ *Project 1* : thinning not only in regions connected to MTL
 - ▶ *Project 2*: atrophy also progressive in these regions
- ▶ Does the thalamus have a role in neocortical pathology?
 - ▶ Connected to MTL and to fronto-central neocortical regions
 - ▶ Participates in the seizure network of TLE
 - ▶ Global atrophy in TLE (Natsume et al., 2001, Neurology)

Project 3: Purpose

Assessment of thalamic abnormalities using surface-based deformation mapping techniques (Styner et al., 2006, MICCAI)

1. Mapping local thalamic deformations
2. Mapping the effects of clinical parameters
3. Mapping the connectivity between the MTL, thalamus, and the neocortex through morphometric correlations

Project 4: Mapping the relationship between cortical atrophy and white matter disruptions



courtesy of L.Concha

Project 4: Rationale

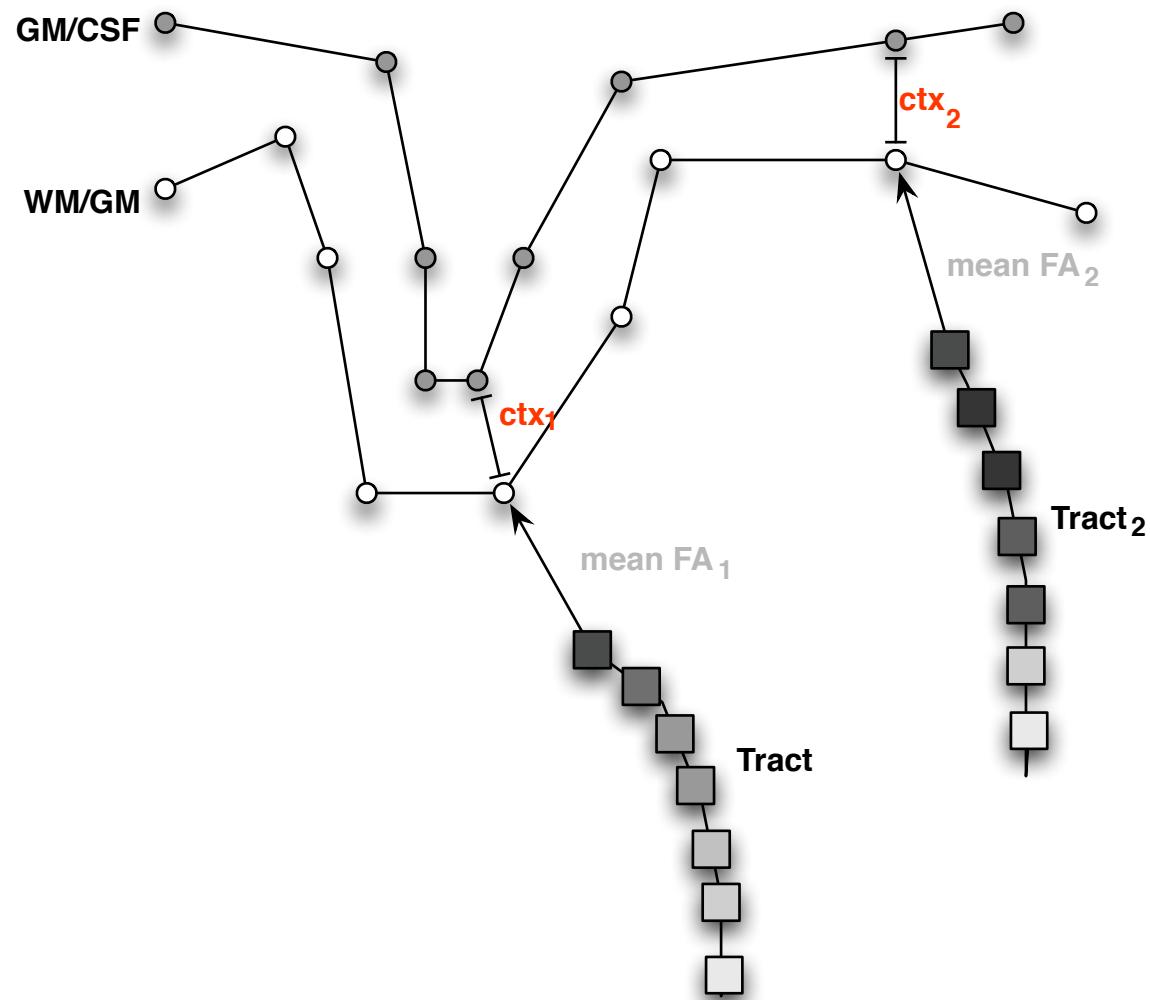
- ▶ *Project 1 : changed (functional) MTL-cortical connectivity*
- ▶ Pathological increase in WM density in TLE (Thom et al. 2001, Brain)
- ▶ Diffusion Tensor Imaging (DTI) allows:
 - ▶ Mapping of WM microstructural integrity
 - ▶ Tracing of WM fiber tracts using tractography
- ▶ In TLE, previous DTI tractography studies demonstrated disrupted axonal integrity in fornix and cingulum
(Concha, 2005, Annals of Neurology)
- ▶ Is axonal degeneration related to neocortical thinning?

Project 4: Purpose

To assess the relationship between cortical thinning and disrupted microstructure of underlying WM tracts

1. Acquire DTI/MRI data of TLE patients
2. Utilize probabilistic tractography, provided by the FSL toolbox
(Behrens et al. 2002, Nat Neurosci)
3. Map fiber tracts close to the neocortex / between neocortex and MTL / between thalamus and neocortex
4. Relate DTI parameters of these tracts to cortical thickness measurements

Project 4: Methods



Merci

Andrea Bernasconi
Neda Bernasconi
Keith Worsley
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Luis Concha
Hosung Kim
Pierre Besson
Jun Natsume
Alan Evans
Oliver Lyttelton
Uicheul Yoon

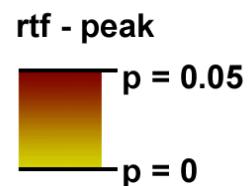
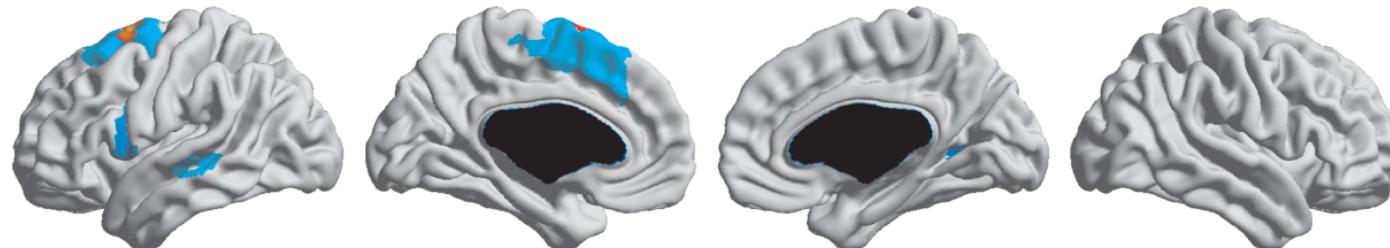
Further avenues

The effects of hippocampal atrophy

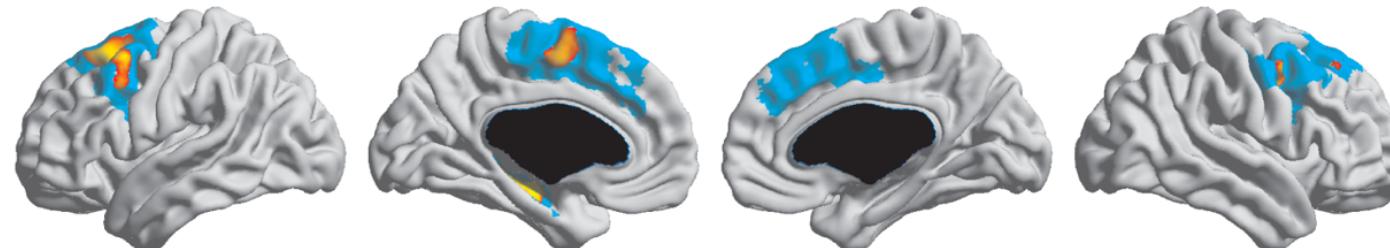
On cortical thinning

Atrophy in TLE

a) LTLE-NV



b) LTLE-HA



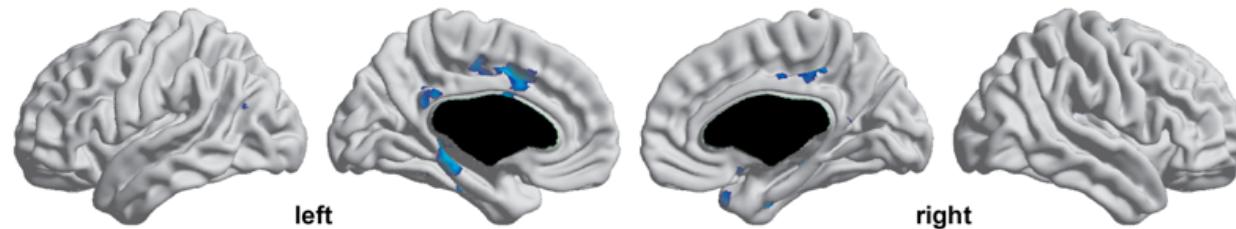
(Bernaconi and Bernhardt 2008, AES)

The effects of hippocampal atrophy

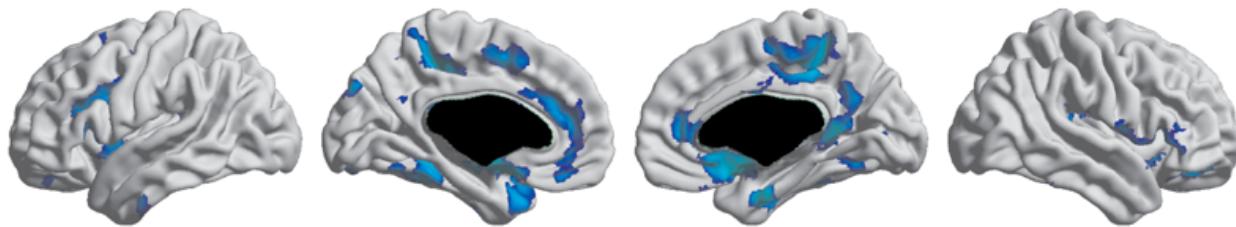
On hippocampal connectivity

Hippocampal connectivity

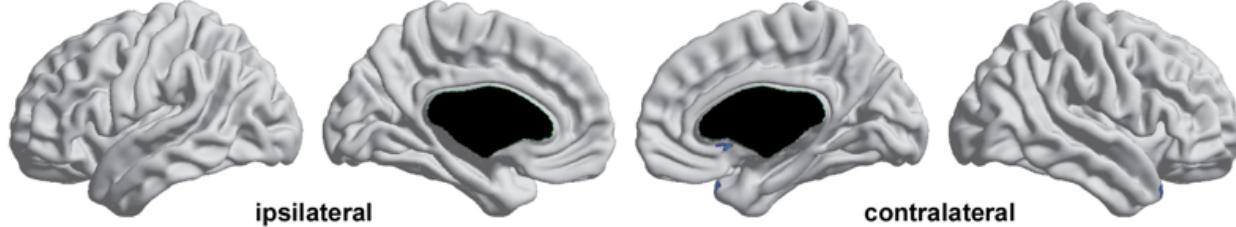
a) Healthy controls



b) TLE-NV

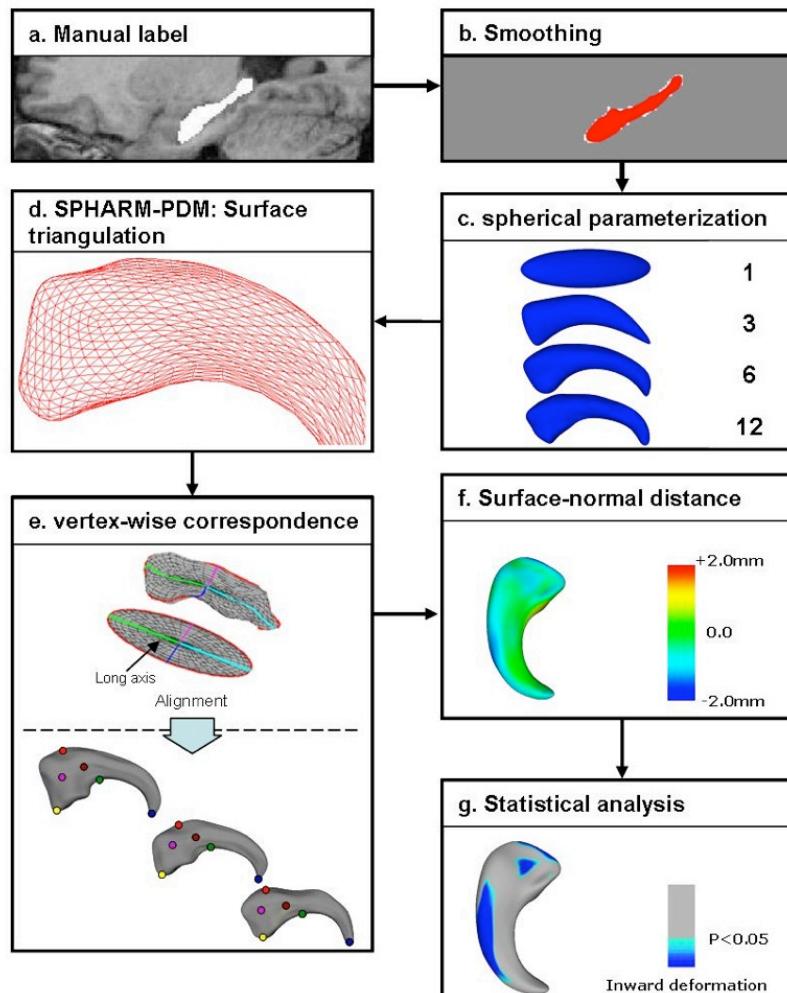


c) TLE-HA



$p = 0.005$
 $p = 0$

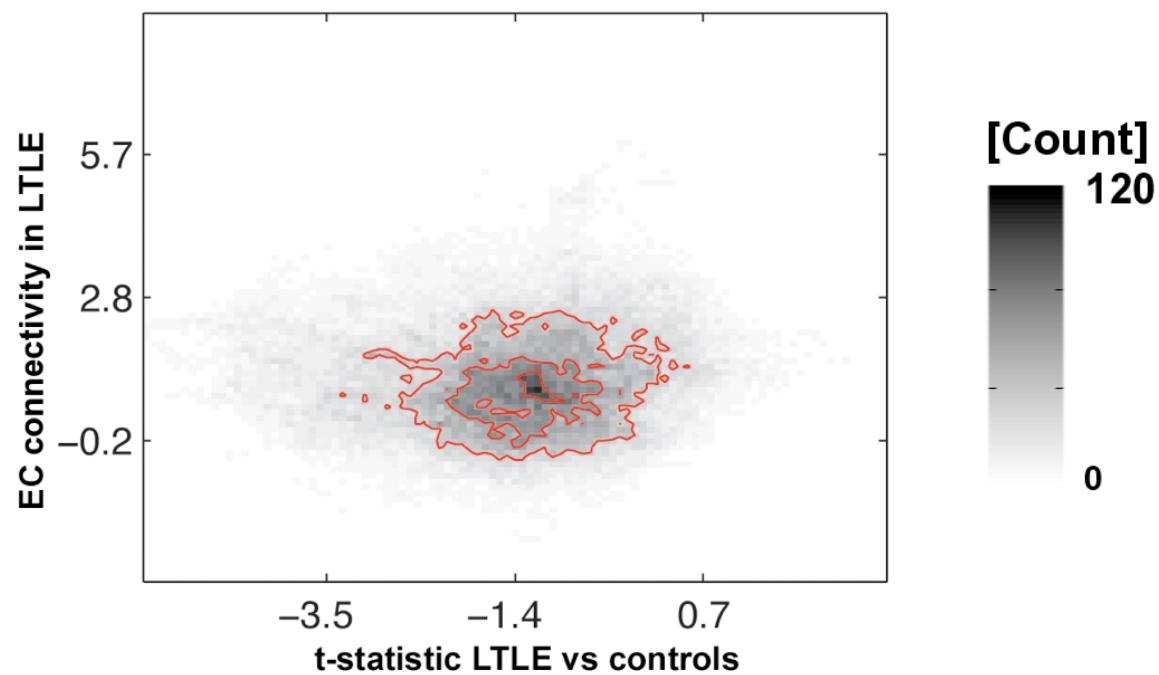
SPHARM shape description



(Courtesy of H.Kim)

Project 1: The relationship between cortical thinning and mesiotemporal connectivity

a) EC connectivity vs atrophy in LTLE



Project 3: Preliminary data

Group analysis: thalamic atrophy in RTLE

