Changes in Brain Structure in Parkinson‘s Disease

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Neuropathological changes in sporadic Parkinson's Disease (sPD) have been found in the substantia nigra, brain stem nuclei, the cerebral cortex and basal ganglia. Braak et al. [1,2] postulated a six-stage model for the propagation of sPD related pathology in the brain based on the distribution of the α-synuclein aggregates, which were found in Lewy-bodies in postmortem brains. Deviating findings in another neuropathological study [3], however, challenged the hypothesis of an association between the α-synuclein distribution and the symptomatology of sPD.

The present longitudinal study aimed to quantify individual, local volume changes in in-vivo MR-images of sPD patients and healthy control subjects in order to separate structural changes in sPD from those of normal ageing, and to characterize specific pathophysiological changes. In addition, associations of these changes with progredient motor and cognitive impairments were examined.

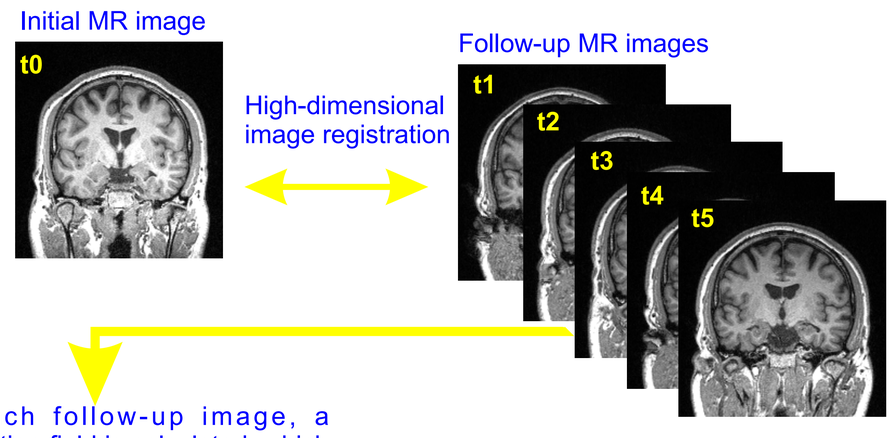
Subjects

PD	N = 38 (m/f = 24/14, age 53 ± 13 years)
Controls	N = 27 (m/f = 12/15 age 60 ± years)

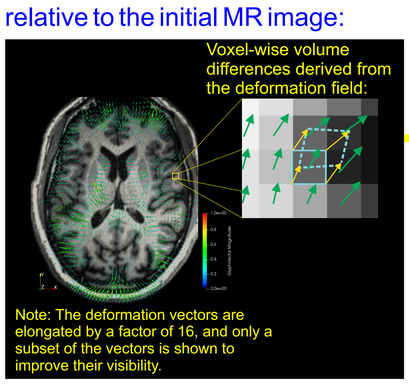
Mean number of examination time points (per subject): 8 ± 4
Mean observation period: 3.9 ± 2.4 years (maximum: 8.8 years).

Image acquisition and analysis

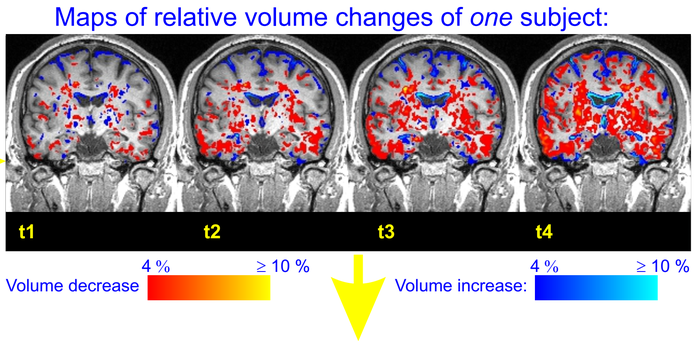
T1-weighted magnetic resonance (MR) images of subjects were acquired on a Siemens 3T Trio scanner (voxel size: 1x1x1 mm^3). Individual series of MR images were analysed by **Longitudinal deformation-based morphometry (DBM)** [4]: The follow-up images of each subject were non-linearly registered with his initial MR image, in order to measure the local volume changes relative to the first time point. The JuBrain atlas [5] was transformed onto each subject's initial MR image in order to compute the volume changes of specific neuroanatomical regions.



For each follow-up image, a deformation field is calculated, which encodes the structural differences relative to the initial MR image:



Maps of relative volume changes of *one* subject:

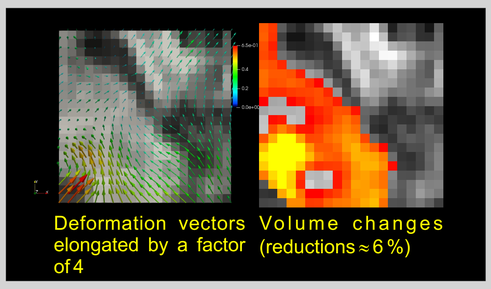


Transformation of brain atlases (e.g. JuBrain [5]) onto the initial MR image of a given subject enables the calculation of region-based volume changes → facilitates direct **comparisons between subjects or groups** (examples see on the right).

Method of longitudinal DBM:

- Deformations (=changes of brain structure) which occur in normal ageing or Parkinson‘s disease over observation periods up to ≈ 6 years are usually less than the resolution of MR images
- Noise and inhomogeneity artifacts further degrade image information

→ Minimization of a dissimilarity metric by a **regularized gradient descent optimization** procecure



Dissimilarity metric *M*:

- Local cross-correlation metric
- evaluated separately in each voxel over a spherical neighbourhood with diameter 13 voxels

Regularization *R*:

- Modelling the deformation of a visco-elastic medium to avoid too strong local distortions
- Derived from physical equation of motion → System of partial differential equations (PDE) in the components of the deformation vector field

Objective function:

$$F = M + \alpha R$$

- Minimization with respect to the components of the deformation field, i.e. about 40 millions degrees of freedom
- The PDE system which is induced by the regularizer is solved by a multigrid solver.

Implementation:

- Running on JURECA [6]
- Parallelized by OpenMP and by CUDA to run on GPUs

Statistical procedures

Linear mixed models were applied to analyse the relative volume changes of brain regions.

Group comparison between PD patients and healthy controls:

$$\log(\Delta V_{rel}) = X\beta + Z\gamma + \varepsilon$$

with: ΔV_{rel} = relative volume change, β = fixed effects (group effects),
γ = random effects (individual deviations from group effects)

References
[1] Braak, H., et al., Mov. Disord. 21, (2006): p. 2042-2051
[2] Braak, H., et al., Neurobiol Aging 24, (2003): p. 197-211
[3] Parkkinen, L., Pirttilä, Tuula, and I. Alafuzoff, Acta Neuropathol, 115, (2008): p. 399-407.
[4] Pieperhoff, P., et al., Neuroimage. 43, (2008): p. 269-287.
[5] Amunts, K. and K. Zilles, Neuron. 88, (2015): p. 1086-107.
[6] Krause, D., Jülich Supercomputing Centre (2016) JLSRF 2, A62

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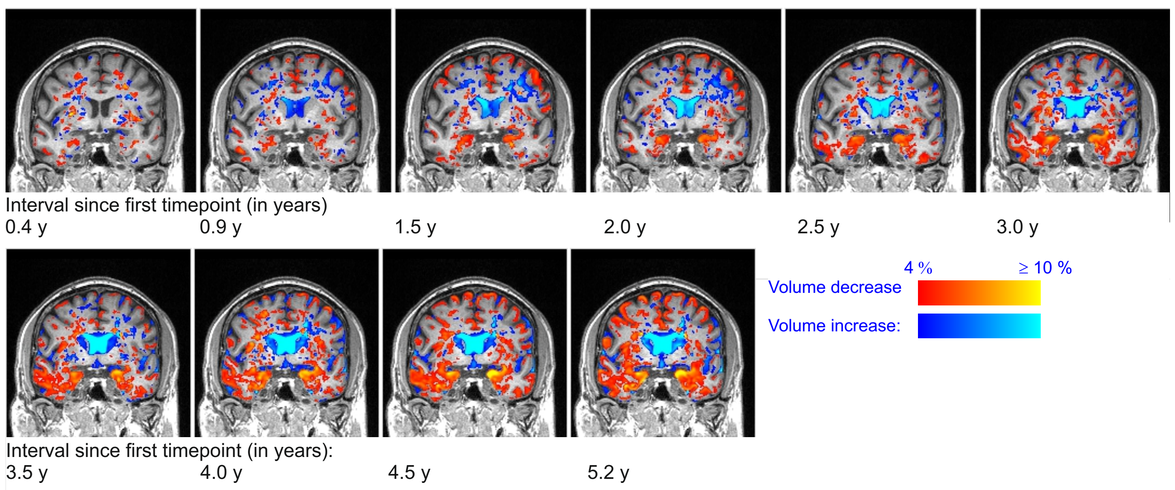
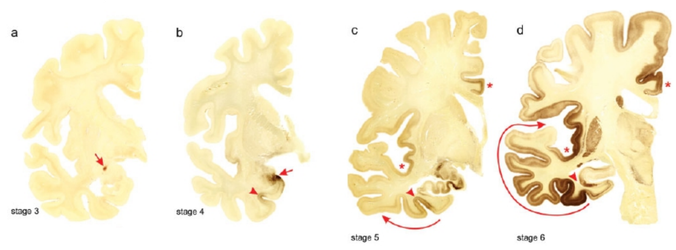
Results

Volume changes in the brain of an *individual* PD patient (male, age 69 y, disease duration 3.3 y)



→ Volume decrease suggesting tissue atrophy mainly in the **Amygdala, temporal cortex, insula,** and from there spreading to **frontal and cingulate cortex.**

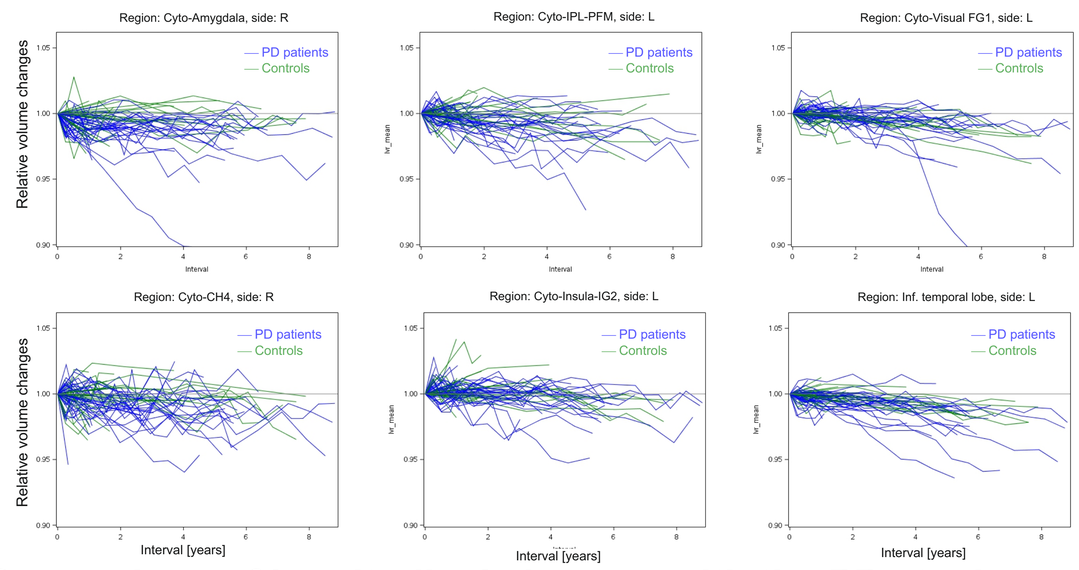
These changes should be compared with the propagation of α-synuclein aggregats, that was described by H. Braak et al.[1,2] in post-mortem brains of PD patients.



(H. Braak et al. (2006) Movement Disorders, 21)

Individual courses of volume changes of brain regions

Differences between PD patients and healthy controls in the rates of volume changes were significant at $p < 0.05$. Most of the anatomical regions were defined by cytoarchitectonic maps in the JuBrain atlas [5].

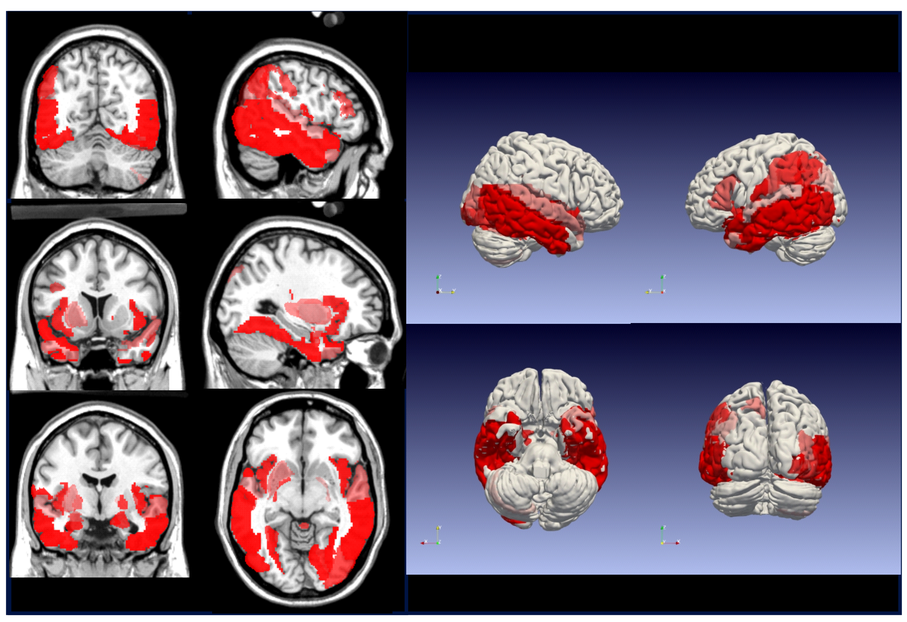


Comparison of longitudinal changes with the PD staging scheme by Braak et al.

Overview of brain regions, which differed significantly between PD patients and healthy controls in the rates of volume changes. The saturation of the red colouring indicates the significance.

p-level 0.05 ≤ 0.01

PD staging scheme based on the occurence of α-synuclein aggregates, postulated by H. Braak et al. (Neurobiol Aging (2003) 24)



Striking similarity of effects in longitudinal morphometry and PD staging scheme: Regions in which the most pronounced differences between PD patients and controls were found (Amygdala, Temporal and Inferior parietal lobe) resemble those regions, which are affected by α-synuclein pathology in PD stages III - IV for the first time. On the other hand, PD symptoms begin to become manifest in stage III [1,2].

Conclusions

- Longitudinal DBM reveals accelerated volume decreases in PD patients as compared to healthy controls, which are associated with the PD staging scheme by Braak et al.
- Strongest longitudinal changes were found in those regions, which are affected by α-synuclein in Braak PD stages III - VI
- Structural changes can be investigated both on the individual but also on the group level

➔ Longitudinal DBM is a complementary in-vivo technique to post-mortem studies.