DBM in a German multicenter SCA14 cohort reveals structural changes in cerebellum and forebrain

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Introduction:

Since its genetic definition in 2003, the rare autosomal dominant spinocerebellar ataxia type 14 (SCA14), a late onset progressive disorder caused by mutations in protein kinase C gamma gene (PKCγ), is increasingly recognized among patients with hitherto undefined Spinocerebellar Ataxias in Germany. Patients mostly present with a slowly progressive cerebellar ataxia, but reports on additional symptoms (cognitive decline, hyperreflexia, myoclonus, dystonia) could indicate extracerebellar alterations. Previous case series based on the retrospective analysis of routine clinical MR images reported mild to severe atrophy of the cerebellum (in particular in its medial zone) and sometimes also in the brainstem and forebrain. The present study, however, examined prospectively the up to now largest sample of SCA14 patients in comparison to matched controls to detect group differences in brain structure, and to elucidate associations with clinical outcomes. This study was part of a cross-sectional German multi-centre study investigating the phenotype in SCA14, coordinated by the Research Centre Jülich and Charité Berlin.

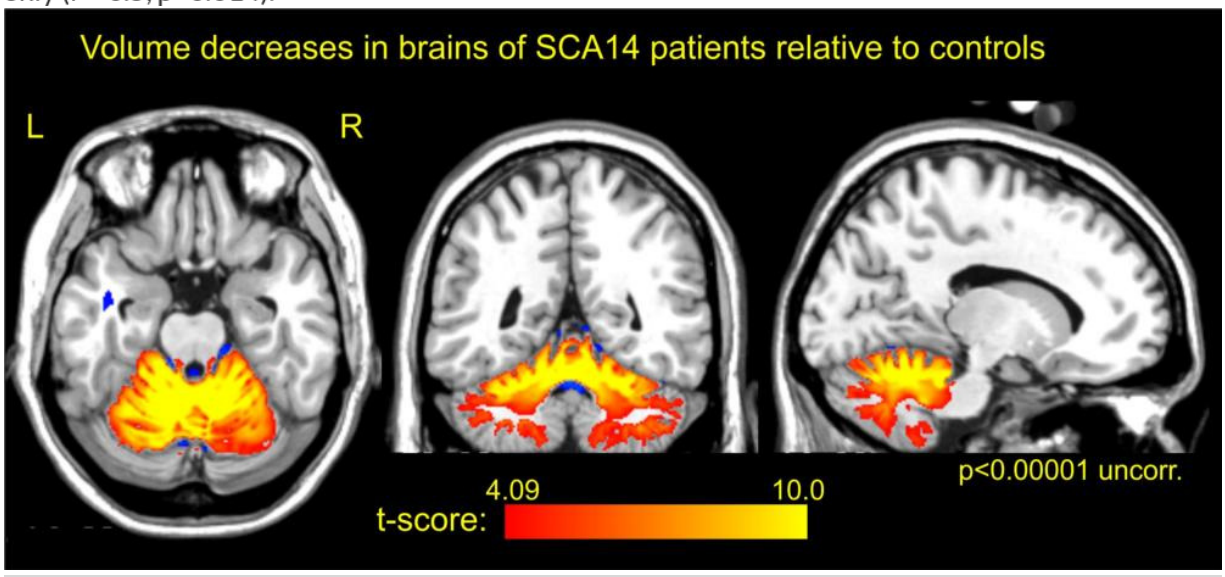
Methods:

Twenty-two clinically well-characterized and genetically heterogeneous SCA14-patients from 14 different families (m/f 9/13, age 49.8 ± 12.3 years, disease duration 17.8 ± 13.0 years) and matched

healthy controls were examined. T1-weighted magnetic resonance images (3T, MPRAGE sequence, voxel-size: 1x1x1 mm^3) of all subjects were analysed by Deformation-based morphometry (DBM)(Pieperhoff et al. 2008): Each subject's brain image (=source image) was non-linearly registered with a reference brain (MNI single subject template(Holmes et al. 1998)), yielding a 3D-deformation field that encodes the structural differences between source and reference brain. Maps of voxel-wise volume differences between each source and reference brain were computed and statistically analysed in each voxel and in anatomical regions as defined by the JuBrain atlas (Amunts and Zilles 2015; available through the HBP Human Brain Atlas; https://www.humanbrainproject.eu/en/explore-the-brain/), and the SUIT atlas of the cerebellum (Diedrichsen 2006) in order to detect local volume differences between both groups and associations between volumes of anatomical regions and ataxia severity scores.

Results:

The DBM analysis revealed pronounced symmetrical volume reductions in the patients' brains relative to controls in almost all lobules of the cerebellum ($p<0.0001$). Largest reductions were in lobules I to IV and X of the hemispheres, where the difference exceeded 30 %, whereas the volumes of cerebellar nuclei were reduced by 16 to 23 %. In the forebrain less pronounced volume reductions were found e.g. in the frontal pole, but also volume increases in the white matter of the parietal and temporal lobes of patients' brains (about 3-5 %, $p < 0.05$). Volume reductions in the brainstem potentially affected the medial lemniscus (ML, $p < 0.002$).
The disease severity score of upper limbs ataxia was negatively correlated with the volumes of cerebellar lobules V, VI and X (r between -0.4 and -0.6, $p < 0.05$ whereas dysarthria was correlated with lobule IV only ($r=-0.5$, $p=0.014$).



·Local volume differences between SCA14 patients and controls

Conclusions:

Pronounced volume deficits found in the cerebellar cortex are in line with the reported high expression of PKCγ in Purkinje cells. Bilateral affection in particular of the anterior lobe and cerebellar nuclei agrees well with the clinical finding of prominent ataxia of gait and stance. PKCγ is also expressed in the dorsal column nuclei (Hughes et al. 2008) from where the ML originates. This may be related to both, the sensory deficits reported by SCA14 patients and the structural changes observed along the ML. The observed volume increases in the white matter of the cerebrum potentially reflect compensatory changes.

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Disorders of the Nervous System:

Parkinson's Disease and Movement Disorders [1]

Imaging Methods:

Anatomical MRI [2]

Modeling and Analysis Methods:

Image Registration and Computational Anatomy

Keywords:

Cerebellar Syndromes
Cerebellum
Degenerative Disease
Morphometrics
Movement Disorder

[1|2]Indicates the priority used for review

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No

Please indicate below if your study was a "resting state" or "task-activation" study.

Other

Healthy subjects only or patients (note that patient studies may also involve healthy subjects):

Patients

Was any human subjects research approved by the relevant Institutional Review Board or ethics panel? NOTE: Any human subjects studies without IRB approval will be automatically rejected.

Yes

Was any animal research approved by the relevant IACUC or other animal research panel? NOTE: Any animal studies without IACUC approval will be automatically rejected.

Not applicable

Please indicate which methods were used in your research:

Structural MRI
Neuropsychological testing

For human MRI, what field strength scanner do you use?

3.0T

Which processing packages did you use for your study?

SPM
FSL

Provide references using author date format

Amunts, K. and K. Zilles (2015). "Architectonic Mapping of the Human Brain beyond Brodmann." Neuron 88(6): 1086-1107.

Diedrichsen, J. (2006). "A spatially unbiased atlas template of the human cerebellum." NeuroImage 33(1): 127-138.

Holmes, C. J., R. Hoge, L. Collins, R. Woods, A. W. Toga and A. C. Evans (1998). "Enhancement of MR images using registration for signal averaging." J Comput Assist Tomogr 22(2): 324-333.

Hughes, A. S., S. Averill, V. R. King, C. Molander and P. J. Shortland (2008). "Neurochemical characterization of neuronal populations expressing protein kinase C gamma isoform in the spinal cord and gracile nucleus of the rat." Neuroscience 153(2): 507-517.

Pieperhoff, P., L. Hömke, F. Schneider, U. Habel, N. J. Shah, K. Zilles and K. Amunts (2008). "Deformation field morphometry reveals age-related structural differences between the brains of adults up to 51 years." J Neurosci 28(4): 828-842.