Robustness of MRI-based volumetry for the prediction of short-term conversion from mild cognitive impairment to Alzheimer´s dementia

Oliver Peters, MD[1], Per Suppa[2,3], Brigitte Haas, PhD[1], Ralph Buchert, PhD[3], Lothar Spies, PhD[2], Isabella Heuser, MD, PhD[1]

(1) Department of Psychiatry, Charité, Berlin, Germany
(2) jung diagnostics GmbH, Hamburg, Germany
(3) Department of Nuclear Medicine, Charité Berlin, Germany

Background

Magnet resonance imaging (MRI)-based hippocampus volumetry (HV) appears to be useful for enriching AD trials that test the efficacy of disease modifying drugs.

Problems of HV, especially in clinical routine exams, are slightly differing MRI acquisition protocols. The Alzheimer's Disease Neuroimaging Initiative (ADNI) has therefore suggested harmonization procedures of image acquisition protocols across scanner platforms.

Aim

- to investigate the power of MRI-based HV for the prediction of conversion from mild cognitive impairment (MCI) to AD in a large-scale multi-center study of the German Dementia Competence Network (DCN) in comparison to the ADNI study, whereas the DCN study allowed for considerably more variability of the MRI acquisition protocols between the different sites.

Subjects

In the ADNI cohort, MR scans were acquired with either a Siemens, Philips or GE 1.5 T MRI system using a sagittal 3-dimensional magnetization prepared rapid gradient echo (3D-MPRAGE) sequence with an approximate TR=2400 ms, minimum full TE, approximate TI=1000 ms and a flip angle of approximately 8°. Scans were collected with a 24 cm field-of-view and an acquisition matrix of 192x192x166 to yield a standard voxel size of 1.25x1.25x1.2 mm^3. Images were then reconstructed to give a 256x256x166 matrix and voxel size of approximately 1x1x1.2 mm^3. Images were downloaded from the ADNI repository as "unpreprocessed" (no gradwarp, B1 non-uniformity or N3 correction). In total, 134 subjects from the ADNI1 study were included: 32 MCI subjects who had converted to AD within a period of 12 months (MCI-to-AD converters) and 102 MCI subjects who had remained stable over a period of 36 months (MCI-stable subjects).

In the DCN study, MR scans were acquired with a Siemens or a Philips 1.5 T MRI system at multiple participating sites with much less stringent harmonization of acquisition protocols. 106 MCI subjects from the DCN study were included: 33 MCI-to-AD converter who had converted to AD within a period of 12 months and 73 MCI-stable subjects who had remained stable over a period of 36 months.

Table 1. Demographic data and volumes of DCN and ADNI subgroups. TIV = total intracranial volume, FIRST-HV = (unadjusted) hippocampal volume, FIRST-HVad = (age and TIV adjusted) hippocampal volume.

cohorts	N	Age	TIV	FIRST-HV	FIRST-HVad
ADNI_m12_converter	32	74.68 +/- 6.45#	1436 +/- 131.81	5.96 +/- 0.80*	6.38 +/- 0.69*
ADNI_m36_stable	102	75.10 +/- 7.12#~	1468.6 +/- 139.91	6.94 +/- 1.04+	7.28 +/- 1.02
DCN_m12_converter	33	70.75 +/- 8.18#	1444.3 +/- 178.97	6.25 +/- 1.03*	6.55 +/- 0.80*
DCN_m36_stable	73	63.70 +/- 8.44~	1469.3 +/- 143.02	7.36 +/- 0.89	7.40 +/- 0.83

* p<0.05 (Tamhane-T2) vs. ADNI_m36_stable and DCN_m36_stable
+p<0.05 (Scheffé) vs. ADNI_m12_converter and DCN_m12_converter & DCN_m36_stable
# p<0.05 (Scheffé) vs. DCN_m36_stable
~p<0.05 (Scheffé) vs. DCN_m12_converter

Hippocampal volumetry

All MR scans, both from ADNI and from DCN, were converted into nifti-format using MRIConvert and subsequently were transformed into a common coordinate system. SPM12-rigid body co-registration to a whole brain template in MNI space was used for this preprocessing step. Hippocampus segmentation was performed using the FIRST module of the FMRIBs software package. The "run_first_all" routine was applied with slight modifications as described elsewhere (Hibar et al., 2011). Total hippocampus volume (FIRST-HV) was obtained by summing the volume in the left and right hemisphere.

Total intracranial volume (TIV) was estimated using the method described in (Malone et al., 2015). FIRST-HV values were adjusted for TIV and age using a bilinear regression approach. Regression coefficients were estimated by using a subset of 137 ADNI-Normal subjects who were documented as stable throughout a period of 36 months.

ROC analysis was performed for the discrimination of MCI-to-AD converters and MCI-stable subjects by adjusted FIRST-HV in the ADNI sample. The Youden index was used to determine the optimal cutoff value. This cutoff value derived from the ADNI sample was then used to classify DCN MCI patients.

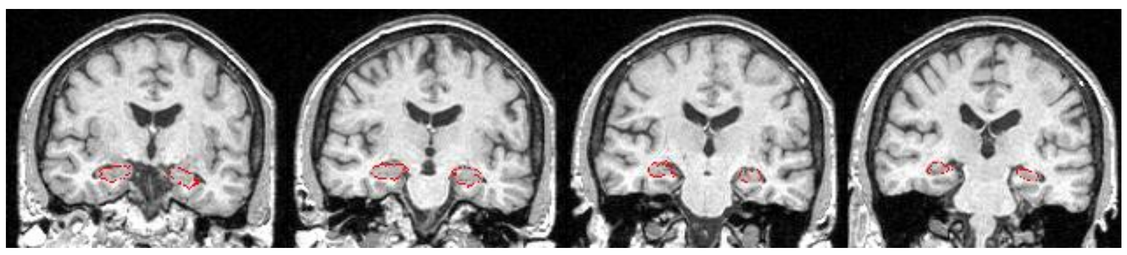

Figure 1. Typical result of FSL-HV segmentation (contour in red color) of a DCN-MCI subject shown on coronarl slices of 3D-MPRAGE image data.

Results

MR images from the DCN study showed a considerably larger variability of slice thickness: 1.39 ± 0.46 mm (range 1.0 mm to 2.4 mm) and 1.20 ± 0.00 mm for DCN and ADNI, respectively. The difference of the variance was highly significant according to Levene's test for homogeneity of variance ($p < 0.001$).

The AUC of adjusted FIRST-HV for the discrimination of MCI-to-ADsubjects from MCI-stable individuals in the ADNI cohort was 0.79. The Youden cut-off (adjusted FIRST-HV = 6.24 ml) provided an accuracy of 76% (sensitivity = 72%, specificity = 77%).

Using the same cut-off in the DCN sample resulted in an accuracy of 77% (sensitivity = 75%, specificity = 77%).

Table 2. Area (AUC) under the ROC curve, cut-off value on FIRST-HVad determined by the maximum Youden index, accuracy measures, sensitivity and specificity for prediction of MCI-to-ADD converter. Accuracy, sensitivity and specificity were cross-validated by 100 repeats of 20-fold cross-validation.

			cross validated		
	AUC	FIRST-HVad cutoff [ml]	accuracy	sensitivity	specificity
ADNI	0.77	6.24	0.76	0.72	0.77
DCN	---	6.24	0.77	0.75	0.77

Conclusion

Despite its considerably larger variability in slice thickness, the DCN cohort had similar 12-months prognostic power as the ADNI sample. This suggests that MRI-based hippocampal volumetry with FSL-FIRST is a rather robust protocol with regard to variations as they might occur in routine clinical practice.

References

Hibar D, et al. (2011). Enigma Consortium First Protocol. ttp://enigma.loni.ucla.edu/protocols/imaging-protocols/first-protocol.
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