

Electronic Supplementary Material

Title: Mental speed is associated with the shape irregularity of white matter MRI hyperintensity load

Journal: Brain Imaging and Behavior

Authors: Catharina Lange, Per Suppa, Anja Mäurer, Kerstin Ritter, Uwe Pietrzyk, Elisabeth Steinhagen-Thiessen, Jochen B. Fiebach, Lothar Spies, Ralph Buchert

Corresponding author: Ralph Buchert, Department of Nuclear Medicine, Charité – Universitätsmedizin Berlin, Berlin, Germany, email: ralph.buchert@charite.de, tel.: +49 30–450627059, fax: +49 30–450527912

Online Resource 1. iDSS sample characteristics. Numbers are given as mean±standard deviation [range] (deviant sample size). (AD, Alzheimer’s disease; COSU, confluency sum score; CVD, cerebrovascular disease; MD, mixed etiology; MMSE, mini-mental state examination; TMT, trail making test; WMH, white matter hyperintensities)

| characteristic | non-neurodegenerative (n=15) | AD (n=17) | CVD (n=23) | MD (n=25) | other neurodegenerative than AD (n=7) | all (n=87) | p-value* (ANOVA) |
|------------------------------|------------------------------|-------------------------|---------------------------------|---------------------------------|---------------------------------------|---------------------------------|-------------------------|
| age [years] | 82.13±5.48 | 79.18±3.84 | 80.52±6.20 | 83.60±4.87 | 78.57±3.87 | 81.26±5.33 | .045 ^g |
| sex [females] | 11 / 73.3% | 13 / 76.5% | 13 / 56.5% | 17 / 68.0% | 3 / 42.9% | 57 / 65.5% | .547 |
| education [years] | 10.97±2.74 | 12.41±3.54 | 12.61±3.71 | 12.24±3.35 | 12.21±5.41 | 12.15±3.54 | .505 |
| <i>CERAD-plus [z-scores]</i> | | | | | | | |
| animals | -0.31±0.97 | -1.79±1.13 | -1.50±0.86 | -1.70±0.95 (n=24) | -1.94±1.16 | -1.44±1.10 (n=86) | .000 ^{a,b,c} |
| Boston | 0.19±1.14 | -0.74±1.72 | -0.51±1.14 (n=22) | -0.31±1.28 (n=23) | -0.80±1.22 | -0.40±1.33 (n=84) | .249 |
| MMSE | -2.73±1.74 | -3.99±1.37 | -3.18±1.70 | -3.99±1.38 | -3.60±1.35 | -3.53±1.58 | .038 ^g |
| learning word list | -1.61±1.40 | -3.15±1.71 | -2.22±0.98 | -2.44±1.56 (n=24) | -1.79±1.46 | -2.32±1.48 (n=86) | .026 ^a |
| copy figures | -0.97±1.06 | -1.42±1.04 | -1.10±1.36 (n=22) | -1.57±1.21 (n=23) | -2.57±2.67 | -1.39±1.40 (n=84) | .381 |
| recall word list | -1.46±1.20 | -2.87±0.93 | -1.65±0.96 | -2.26±1.19 (n=23) | -1.13±0.69 | -1.98±1.17 (n=85) | .001 ^{a,d} |
| word list intrusions | -0.81±1.08 | -0.99±1.63 | -0.91±1.41 | -1.17±1.23 (n=24) | -0.39±1.50 | -0.94±1.35 (n=86) | .864 |
| recognition word list | -0.87±1.35 | -1.98±1.73 | -0.47±1.60 | -0.90±1.52 (n=23) | -1.39±1.50 | -1.03±1.61 (n=85) | .029 ^d |
| recall figures | -1.01±1.25 | -2.14±1.13 | -1.70±1.11 (n=22) | -2.00±0.92 (n=23) | -2.23±0.87 | -1.79±1.13 (n=84) | .021 ^a |
| TMT-A | -0.58±1.17 (n=14) | -1.33±1.33 (n=13) | -1.41±0.95 (n=19) | -1.69±0.80 (n=17) | -1.25±0.83 (n=6) | -1.28±1.08 (n=69) | .036 ^c |
| TMT-B | -0.65±0.73 (n=8) | -1.27±0.86 (n=7) | -1.23±1.15 (n=6) | -1.65±0.79 (n=4) | -1.55±0.35 (n=2) | -1.16±0.88 (n=27) | .299 |
| s-word list | -0.03±1.33 | -1.05±1.11 | -1.32±1.03 | -1.41±0.99 (n=23) | -1.53±0.72 (n=6) | -1.08±1.17 (n=84) | .002 ^{b,c} |
| <i>WMH</i> | | | | | | | |
| total volume [ml] | 8.67±7.74 [0.24-21.58] | 9.29±7.60 [0.88-26.31] | 35.47±20.09 [6.91-74.92] (n=22) | 34.29±16.11 [7.70-72.98] (n=22) | 10.24±6.53 [2.04-19.36] | 23.22±19.02 [0.24-74.92] (n=86) | .000 ^{b,c,d,e} |
| COSU | 8.45±4.96 [0.89-21.88] | 10.46±5.57 [3.32-25.48] | 12.08±2.52 [7.73-19.90] (n=22) | 13.47±3.99 [6.69-26.44] | 8.69±1.58 [6.69-11.20] | 11.25±4.45 [0.89- 26.44] (n=86) | .005 ^c |

*Comparison of numerical characteristics (all except sex) between groups was performed by one-way ANOVA. In case of a significant between groups effect, post hoc multiple comparisons were performed using either Scheffe’s test (assuming equal variance) or Tamhane’s test (unequal variance), depending on the result of Levene’s test for homogeneity of variance. The chi-square test was used to compare the distribution of sex between all groups. In case of a significant between groups effect, the chi square test was applied to all possible pairs of two groups. A significance level of $\alpha = 0.05$ was assumed for between all groups tests as well as for post hoc tests. Between groups testing included all diagnostic groups except ‘other neurodegenerative disease than AD’ which was excluded because of its small sample size.

^a Post-hoc analysis: significant group difference between ‘non-neurodegenerative’ and ‘AD’.

- ^b Post-hoc analysis: significant group difference between 'non-neurodegenerative' and 'CVD'.
- ^c Post-hoc analysis: significant group difference between 'non-neurodegenerative' and 'MD'.
- ^d Post-hoc analysis: significant group difference between 'AD' and 'CVD'.
- ^e Post-hoc analysis: significant group difference between 'AD' and 'MD'.
- ^f Post-hoc analysis: significant group difference between 'CVD' and 'MD'.
- ^g Post-hoc analysis: none of the pairwise post-hoc comparisons reached statistical significance.

Online Resource 2. NACC sample characteristics. Numbers are given as mean±standard deviation [range] (deviant sample size). (AD, Alzheimer’s disease; COSU, confluency sum score; MMSE, mini-mental state examination; NC, normal control; TMT, trail making test; VaD, vascular dementia; WMH, white matter hyperintensities)

| characteristic | AD (n=66) | VaD (n=66) | NC (n=66) | all (n=198) | p-value (ANOVA) |
|------------------------------|---------------------------------------|---------------------------------------|-----------------------------|----------------------------------------|-----------------------|
| age [years] | 79.15±5.95 | 83.63±5.87 | 81.54±5.21 | 81.44±5.95 | .000 ^a |
| sex [females] | 36 / 54.5% | 36 / 54.5% | 41 / 62.1% | 113 / 57.1% | .597 |
| education [years] | 14.44±3.24 | 12.94±4.41 | 15.44±2.93 | 14.27±3.71 | .000 ^c |
| <i>CERAD-plus [z-scores]</i> | | | | | |
| animals | -1.43±0.88 | -0.95±0.90 | -0.07±0.83 (n=65) | -0.82±1.03 (n=197) | .000 ^{a,b,c} |
| Boston | -2.69±2.08 (n=65) | -2.12±1.79 (n=64) | -0.16±0.79 (n=65) | -1.65±1.97 (n=194) | .000 ^{b,c} |
| MMSE | -5.48±2.88 | -3.63±3.37 (n=65) | 0.51±0.96 | -2.86±3.62 (n=197) | .000 ^{a,b,c} |
| TMT-A | -1.69±2.64 | -2.27±2.74 (n=60) | 0.11±0.96 (n=65) | -1.26±2.46 (n=191) | .000 ^{b,c} |
| TMT-B | -2.72±1.74 (n=61) | -2.57±1.56 (n=50) | -0.07±1.00 (n=65) | -1.70±1.91 (n=176) | .000 ^{b,c} |
| <i>WMH</i> | | | | | |
| total volume [ml] | 15.72±16.17 [0.00-69.87] (n=65) | 20.32±17.60 [0.24-74.37] (n=62) | 11.33±12.07 [0.00-49.09] | 15.70±15.76 [0.00-74.37] (n=193) | .010 ^c |
| COSU | 8.64±4.20 [0.00-18.20] (n=65) | 7.97±3.46 [0.98-17.54] (n=62) | 7.47±3.22 [0.00-14.62] | 8.02±3.67 [0.00-18.20] (n=193) | .180 |

*Comparison of numerical characteristics (all except sex) between the three groups was performed by one-way ANOVA. In case of a significant between groups effect, post hoc multiple comparisons were performed using either Scheffe’s test (assuming equal variance) or Tamhane’s test (unequal variance), depending on the result of Levene’s test for homogeneity of variance. The chi-square test was used to compare the distribution of sex between the three groups. In case of a significant between groups effect, the chi square test was applied to all possible pairs of two groups. A significance level of $\alpha = 0.05$ was assumed for between all groups tests as well as for post hoc tests.

^a Post-hoc analysis: significant group difference between ‘AD’ and ‘VaD’.

^b Post-hoc analysis: significant group difference between ‘AD’ and ‘NC’.

^c Post-hoc analysis: significant group difference between ‘VaD’ and ‘NC’.

Online Resource 3. Correlation between the performance in the CERAD-plus subtests (z-scores) and the COSU after the effect of overall cognitive performance (MMSE) or the effect of the etiology of cognitive impairment (with neurodegenerative disease versus without neurodegenerative disease) or the effect of ApoE genotype (number of E4 alleles) was removed. The value given is the partial correlation coefficient. Statistical significance is indicated by an asterisk (*p-value \leq 0.05; **p-value \leq 0.01). (COSU, confluency sum score; MMSE, mini-mental state examination; N/A, not available; TMT, trail making test; WMH, white matter hyperintensities)

| CERAD-plus [z-scores] | MMSE | | etiology | | ApoE genotype | |
|-----------------------|--------|--------|----------|--------|---------------|---------|
| | iDSS | NACC | iDSS | NACC | iDSS | NACC |
| animals | .098 | -.183 | .065 | -.117 | .018 | -.313* |
| Boston | .027 | .081 | -.004 | .072 | -.019 | -.146 |
| MMSE | - | - | -.069 | -.070 | -.092 | -.290* |
| learning word list | .129 | N/A | .067 | N/A | .054 | N/A |
| copy figures | -.087 | N/A | -.097 | N/A | -.088 | N/A |
| recall word list | -.055 | N/A | -.081 | N/A | -.124 | N/A |
| wordlist intrusions | .100 | N/A | .092 | N/A | .088 | N/A |
| recognition word list | -.016 | N/A | -.040 | N/A | -.053 | N/A |
| recall figures | -.118 | N/A | -.139 | N/A | -.149 | N/A |
| TMT-A | -.381* | -.240* | -.369* | -.255* | -.365* | -.333** |
| TMT-B | .061 | -.291* | .180 | -.228 | .205 | -.378** |
| s-word list | .025 | N/A | .002 | N/A | -.064 | N/A |

Online Resource 4. Correlation between the performance in the CERAD-plus subtests (z-scores) and the COSU or the total WMH volume in the NACC sample after either the effect of the time delay between MR acquisition and cognitive testing, or the effect of the magnetic field strength (1.5 T versus 3 T), or the effect of the voxel volume in T2 FLAIR MRI was removed. The value given is the Spearman correlation coefficient rho. Statistical significance is indicated by an asterix (*p-value \leq 0.05; **p-value \leq 0.01). (COSU, confluency sum score; MMSE, mini-mental state examination; N/A, not available; TMT, trail making test; WMH, white matter hyperintensities)

| CERAD-plus [z-scores] | time difference (MRI / CERAD) | | magnetic field strength | | FLAIR voxel volume | |
|-----------------------|-------------------------------|---------|-------------------------|---------|----------------------|---------|
| | total volume [ml] | COSU | total volume [ml] | COSU | total volume [ml] | COSU |
| animals | -.270* | -.240* | -.300* | -.234 | -.296* | -.276* |
| Boston | -.110 | -.031 | -.142 | -.075 | -.146 | -.081 |
| MMSE | -.083 | -.233 | -.133 | -.209 | -.155 | -.227 |
| TMT-A | -.082 | -.271* | -.105 | -.292* | -.101 | -.306** |
| TMT-B | .026 | -.336** | -.035 | -.337** | -.039 | -.357** |