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Aging Effect, Reproducibility, and Test–Retest Reliability of a New Cerebral Amyloid Angiopathy MRI Severity Marker—Cerebrovascular Reactivity to Visual Stimulation

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Background: Decreased cerebrovascular reactivity, measured as changes in blood-oxygen-level-dependent (BOLD) signal, is a potential new cerebral amyloid angiopathy (CAA) severity marker. Before clinical application, the effect of aging on BOLD parameters, and reproducibility and test–retest reliability of these parameters should be assessed.

Purpose: Assess the effect of healthy aging on cerebrovascular reactivity (BOLD amplitude, time to peak, and time to baseline). And determine reproducibility and test–retest reliability of these parameters.

Study Type: Prospective-observational.

Population: Eighty-six healthy adults (mean age 56 years, 55% female), 10 presymptomatic D-CAA mutation carriers (mean age 34 years, 70% female), and 10 symptomatic D-CAA mutation carriers (mean age 54 years, 70% female).

Field Strength/Sequence: 3-T, three-dimensional (3D) T1-weighted MRI and gradient echo BOLD fMRI.

Assessment: To assess test–retest reliability of BOLD parameters, i.e. BOLD amplitude, time to peak, and time to baseline, BOLD fMRI scans were repeated three times immediately after each other, in both controls and mutation carriers. To assess reproducibility, BOLD fMRI scans were repeated with a 3-week interval for each subject.

Statistical Tests: Linear regression analyses and two-way mixed absolute agreement intra-class correlation approach.

Results: Healthy aging was associated with decreased BOLD amplitude ($\beta = -0.711$) and prolonged time to baseline ($\beta = 0.236$) in the visual cortex after visual stimulation. Reproducibility of BOLD amplitude was excellent (ICC 0.940) in the subgroup of healthy adults. Test–retest reliability for BOLD amplitude was excellent in healthy adults (ICC 0.856–0.910) and presymptomatic D-CAA mutation carriers (ICC 0.959–0.981). In symptomatic D-CAA mutation carriers, test–retest reliability was poor for all parameters (ICCs < 0.5).

Data Conclusion: Healthy aging is associated with decreased cerebrovascular reactivity, measured by changes in BOLD response to visual stimulation. The BOLD amplitude appears to be a robust measurement in healthy adults and presymptomatic D-CAA mutation carriers, but not in symptomatic D-CAA mutation carriers.

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Introduction

Cerebral amyloid angiopathy (CAA) is a subtype of small vessel disease characterized by amyloid beta peptide deposits within cerebral small to medium-sized blood vessels and leptomeningeal arteries.¹ Specifically, CAA is an important cause of spontaneous lobar intracerebral hemorrhages, cognitive decline, and transient focal neurologic symptoms.^{1,2} Moreover, CAA is a common and often asymptomatic finding among the elderly and its prevalence increases with age.^{1,3} Population-based autopsy data indicate a prevalence of 20%–40% in non-demented elderly populations, which increases to 50%–60% in demented elderly populations.³ CAA often accompanies other brain pathologies, such as Alzheimer's disease in which it is observed in up to 98% of the cases.^{3–5}

The imaging-based modified Boston Criteria facilitate a diagnosis of “probable CAA” in living patients, based on the location and presence of (small) hemorrhagic lesions in the brain.⁶ Recently, decreased cerebrovascular reactivity, measured as changes in the blood-oxygen-level-dependent (BOLD) signal in the occipital cortex to visual stimulation using a checkerboard, has been put forward as a new possible CAA severity marker.⁷ The advantage of using visual stimulation instead of the more common hypercapnic challenge to assess cerebrovascular reactivity is that this method is very patient friendly, easy in application and accessible in a wide range of patients, such as patients with dementia, but also easily useable for application in clinical trials and the clinic. It was previously described that non-demented sporadic CAA patients demonstrated altered cerebrovascular reactivity parameters in the occipital cortex after visual stimulation, i.e. decreased BOLD amplitude, prolonged time to peak, and prolonged time to baseline when compared to controls.⁷ Similar findings were observed in young, presymptomatic patients with a hereditary form of CAA referred to as Dutch-type CAA (D-CAA).⁸ Since D-CAA is a hereditary form of CAA, all mutation carriers do develop symptoms usually before the age of 60 years. When mutation carriers do not demonstrate clinical symptoms yet, these persons are usually referred to as being presymptomatic. Moreover, a recent study showed that presymptomatic D-CAA mutation carriers had a lower BOLD amplitude and a prolonged time to peak over a 4-year period, without an increase of hemorrhagic lesions in the brain.⁹ This might indicate that cerebrovascular reactivity, measured by changes in BOLD response to visual stimulation using a checkerboard, can be regarded as an early sensitive marker for disease severity in CAA.⁹

To enable the development of treatment strategies for CAA, the assessment of cerebrovascular reactivity seems important as the decrease of cerebrovascular reactivity is seen already in the presymptomatic phase of the disease.^{8,9} However, before cerebrovascular reactivity can be applied as a severity marker in clinical trials, the effect of aging on the BOLD parameters, and reproducibility and test–retest

reliability of these parameters should be established. First, as CAA is an age-related disease and its prevalence increases with age,^{1,3} the effect of aging on the parameters of cerebrovascular reactivity in response to visual stimulation needs to be established. It is expected that there will be an age-dependent effect on the parameters, since previous studies described that the hemodynamic response function is lowered in older adults.^{10,11} Second, for clinical use, determination of reproducibility and test–retest reliability is essential. At present, no such data are available, neither in healthy subjects nor in CAA patients.

Therefore, the aim of the present study was to assess in a group of healthy adults the effect of aging on the BOLD amplitude, time to peak, and time to baseline determined by BOLD functional MRI (fMRI) during a visual checkerboard stimulus. Moreover, we aimed to determine the reproducibility of the cerebrovascular reactivity parameters and test–retest reliability in healthy adults, as well as in a group of presymptomatic and symptomatic D-CAA mutation carriers.

Materials and Methods

The local medical ethics committee (institutional review board), approved this study and written informed consent was obtained from all participants. The procedures followed were in accordance with institutional guidelines.

Participants

For this prospective observational study, we included 86 healthy adults between 20 and 86 years (mean age \pm standard deviation [SD]: 55.8 \pm 16.0 years, 39 males and 47 females) and 20 D-CAA mutation carriers, of which 10 were presymptomatic mutation carriers (mean age \pm SD: 34.1 \pm 12.1 years, 3 males and 7 females) and 10 were symptomatic mutation carriers (mean age \pm SD: 54.3 \pm 4.8 years, 3 males and 7 females). To study reproducibility of the visually stimulated BOLD measurements, 11 participants were randomly selected from the healthy adult group (mean age \pm SD: 41.0 \pm 11.3 years, 9 males and 2 females). D-CAA mutation carriers were included via the D-CAA patient association and the outpatient clinic of the department of neurology. Subjects were considered symptomatic when they had experienced signs of the disease reported to a general practitioner. Healthy adults were selected from individuals at risk for D-CAA, but who tested genetically negative and were derived from the database at the radiology department and various advertisements. All controls were ascertained to be both stroke-free as well as negative genetic tested. Inclusion criteria were based on diagnosis as described above. Exclusion criteria were MRI contra-indications, specific contraindications to fMRI (seizure within prior year and noncorrectable visual impairment), incapacitated to give informed consent, and age above 90 (enrollment period May 2012–October 2013 and September 2019–December 2021).

Study Design

All participants were screened for neurological and cerebrovascular diseases and for cognitive complaints/dysfunction by neuropsychological assessment. For the visual stimulation task during MRI, visual

functional status was checked, and if necessary corrected for by glasses in the MRI. In case of severe visual impairment participants would be excluded, however this was in none of the participants the case. For this study, medical history, blood pressure measurement, and global cognitive functioning using the mini-mental state examination¹² were assessed, and an MRI of the brain was performed. To assess reproducibility, BOLD fMRI scans were repeated with a 3-week interval in the same subject at the same time of the day in 11 randomly selected healthy controls. To assess test–retest reliability, BOLD fMRI scans were repeated three times immediately after each other in all study participants, while participants did not leave the MR scanner in-between the three measurements.

MR Image Acquisition

All participants underwent MRI of the brain on a 3-Tesla scanner (3T Achieva Philips Medical Systems, Eindhoven, the Netherlands) using a standard 32-channel head coil. For each participant, three-dimensional (3D) T1-weighted images (echo time [TE] 3.5 to 4.6 msec, repetition time [TR] 7.9 to 9 msec, flip angle 8°, field of view [FOV] = 224 mm × 177 mm × 168 mm). In the reproducibility study ($2 \times n = 11$), a slightly different FOV for the 3D T1-weighted scan was used (250 mm × 199 mm × 170 mm) in the second scan. Unfortunately, this scan was accidentally copied from a different scan exam card. We do not expect registration differences between the two scans. In all cases, similar visually stimulated BOLD fMRI scans (TE/TR: 31 msec/1499 msec, flip angle 75°, FOV 220 × 220 mm, matrix 80 × 80 mm, slices 25, slice thickness 3 mm, 130 dynamics, scan duration 201 sec) were acquired. The visual stimulation task was presented on a screen which was visualized via a mirror on the head coil. The visual angle was 0°, and the distance from head coil to the screen was 123 cm. The visual stimulus consisted of 16 blocks of an 8 Hz flashing radial black and white checkerboard pattern for 20 sec alternated with 28 sec of gray screen.⁷ A fixation dot was presented during both the checkerboard pattern as well as the gray screen. This fixation dot changed color (light red to dark red) and the participants were asked to press a button every time a color change was seen. Correct responses were monitored in order to check if attention was focused on the task.

Cerebrovascular Reactivity Data Analysis

Cerebrovascular reactivity was determined as described previously.¹³ All scans in this entire study were analyzed similarly. To extract BOLD time series, a region of interest (ROI) was data-driven created for each participant based on the results of an initial subject-level analysis. During this subject-level analysis, brain regions were identified that reacted to the stimulus train using the general linear modeling approach implemented in FEAT for FSL (version 6.0.10; FMRIB's Software Library, <https://fsl.fmrib.ox.ac.uk/>).¹⁴ Specifically, FEAT is a software tool for high-quality model-based fMRI data analysis as part of FSL.

The degree to which each voxel responded to the stimulus was expressed in a Z-statistic map. To obtain the functional ROI for each participant, a binary mask was constructed by taking the top 10% most activated voxels from this Z-statistic activation map. Using this mask, an average BOLD time series was calculated for each participant by averaging across all masked voxels. The resulting time series was cut up into blocks that each contained a stimulus

period (20 sec) and a subsequent rest period (28 sec). Subsequently, time series of each block were expressed as percentage BOLD change using the mean value of all blocks. Based on the method previously described by Dumas et al,⁷ a trapezoidal function was fitted to the cerebrovascular reactivity response (i.e. percentage BOLD signal change) in the average BOLD time series, which was done to extract the time to peak, time to baseline, and amplitude of the BOLD response. The time to peak was calculated from the beginning of the block at $t = 0$ sec to the onset of the trapezoid ceiling. The time to baseline is defined as the duration from the end of the stimulus at $t = 20$ sec to baseline. The BOLD amplitude was defined as the distance from baseline to the peak response. The entire algorithm described above was implemented in R (The R foundation for Statistical Computing, Vienna, Austria, version 1.2.5033, <https://www.r-project.org/>). The full source code, along with additional mathematical details, has been published on GitHub (<https://github.com/jjhbw/TrapFit/>).

Statistical Analysis

All statistical analyses were performed with the Statistical Package of Social Sciences SPSS (version 25.0; IBM Corp., Armonk, NY, USA). To test for an association between age and any of the BOLD parameters (i.e. BOLD amplitude, time to peak, and time to baseline) in healthy adults, we performed linear regression analyses, which were adjusted for sex. Reproducibility and test–retest reliability were assessed in all separate groups using a 2-way mixed absolute agreement intraclass correlation (ICC) approach. ICCs were interpreted as follows: poor (<0.5), moderate (0.5–0.75), good (0.75–0.9), and excellent (>0.9).¹⁵ A negative ICC is interpreted as a reliability of zero. Bland–Altman plots were used to visualize the agreement between the two measurements with a 3-week interval (reproducibility). A P -value < 0.05 was considered statistically significant.

Results

Participants

Table 1 shows the demographic characteristics of the participants. None of the healthy adults reported any neurological symptoms. Figure 1 shows a typical example of the BOLD activation map superimposed on an anatomical image and the BOLD time course and fit results for a control, presymptomatic and symptomatic D-CAA mutation carrier.

Aging

In healthy adults, we found a significant association between age and BOLD amplitude ($\beta = -0.711$), i.e. an increase in age was associated with a decrease of BOLD amplitude (Fig. 2a). We also found a significant, but smaller association between age and time to baseline ($\beta = 0.236$), i.e. increasing age was associated with a longer time to baseline (Fig. 2b). No significant association between age and time to peak ($\beta = -0.115$, $P = 0.299$) was found (Fig. 2c).

Table 1. Demographic Characteristics of the Participants

| | Healthy Adults (<i>n</i> = 86) | Subgroup Healthy Adults (<i>n</i> = 11) | Presymptomatic D-CAA Mutation Carriers (<i>n</i> = 10) | Symptomatic D-CAA Mutation Carriers (<i>n</i> = 10) |
|---|------------------------------------|---|---|--|
| Age, mean (SD; range) | 55.8 (16.0; 20–86) | 41.0 (11.3; 26–60) | 34.1 (12.1; 20–51) | 54.3 (4.8; 45–62) |
| Female, <i>n</i> (%) | 47 (54.7%) | 2 (18.2%) | 7 (70%) | 7 (70%) |
| Education—Verhage score, median (range) | 6 (3–7) | - | 6 (4–7) | 5 (3–6) |
| MMSE score, median (range) | 29 (26–30) | 30 (29–30) | 30 (29–30) | 27.5 (16–30) |
| Systolic blood pressure, mean (SD; range) | 138.9 (25.9; 83–204) | 134.3 (13.8; 115–164) | 126.0 (14.9; 106–155) | 141.8 (22.8; 115–175) |
| Diastolic blood pressure, mean (SD; range) | 85.2 (13.3; 58–120) | 85.4 (12.5; 73–116) | 81.8 (7.3; 72–92) | 86.6 (10.5; 72–103) |
| Mean arterial pressure, mean (SD; range) | 103.1 (16.5; 70.3–139.7) | 101.7 (12.6; 88.3–132.0) | 96.5 (7.9; 84.0–109.7) | 105.0 (14.0; 86.3–127.0) |
| Pulse pressure, mean (SD; range) | 53.6 (17.5; 19–98) | 48.9 (6.5; 39–58) | 44.2 (14.5; 29–69) | 55.2 (15.1; 38–85) |
| Hypertension, <i>n</i> (%) | 11 (12.8%) | 0 (0%) | 0 (0%) | 1 (10%) |
| Hyperlipidemia, <i>n</i> (%) | 8 (9.3%) | 0 (0%) | 0 (0%) | 1 (10%) |
| Diabetes mellitus, <i>n</i> (%) | 2 (2.3%) | 0 (0%) | 2 (20%) | 1 (10%) |
| Cardiovascular disease—other than CAA, <i>n</i> (%) | 10 (11.6%) | 0 (0%) | 0 (0%) | 1 (10%) |
| BOLD amplitude (%), mean (SD; range) | 1.4 (0.4; 0.7–2.6) | 1.7 (0.4; 1.0–2.6) | 1.4 (0.7; 0.2–2.2) | 0.3 (0.1; 0.2–0.5) |
| Time to peak (s), mean (SD; range) | 5.8 (1.4; 2.2–10.2) | 5.7 (1.9; 3.2–10.2) | 6.1 (1.3; 4.0–8.3) | 4.8 (0.9; 3.2–5.8) |
| Time to baseline (s), mean (SD; range) | 8.0 (1.8; 5.1–12.7) | 7.3 (1.7; 5.9–11.6) | 8.3 (2.9; 5.0–15.2) | 6.8 (2.9; 2.4–12.4) |

SD = standard deviation; MMSE = mini-mental state examination; D-CAA = Dutch-type cerebral amyloid angiopathy; BOLD = blood-oxygen-level-dependent.

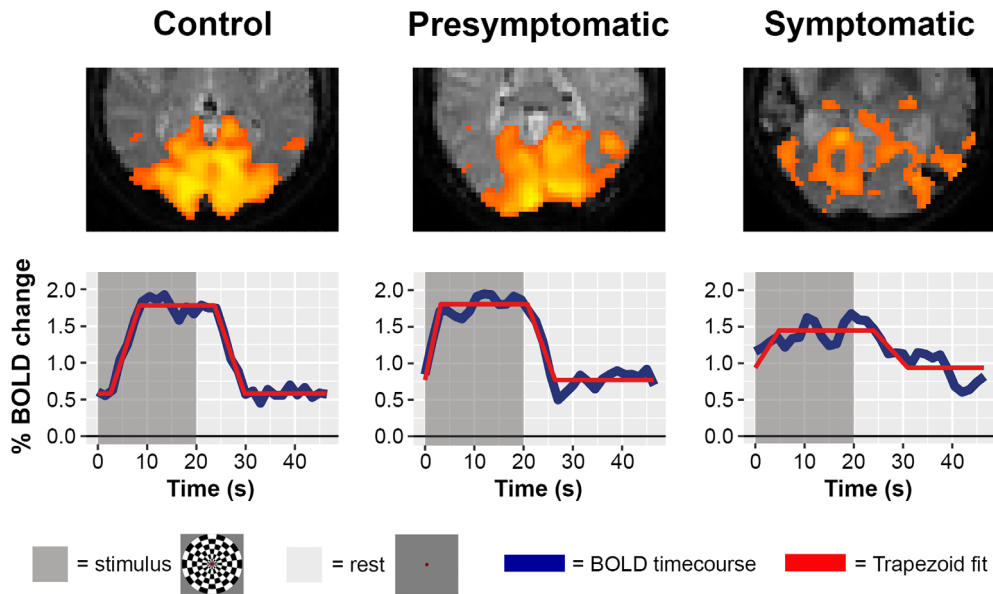


Figure 1: A typical example of the blood-oxygen-level-dependent (BOLD) activation map superimposed on an anatomical image and the BOLD time course and fit results for a control, presymptomatic, and symptomatic D-CAA mutation carrier.

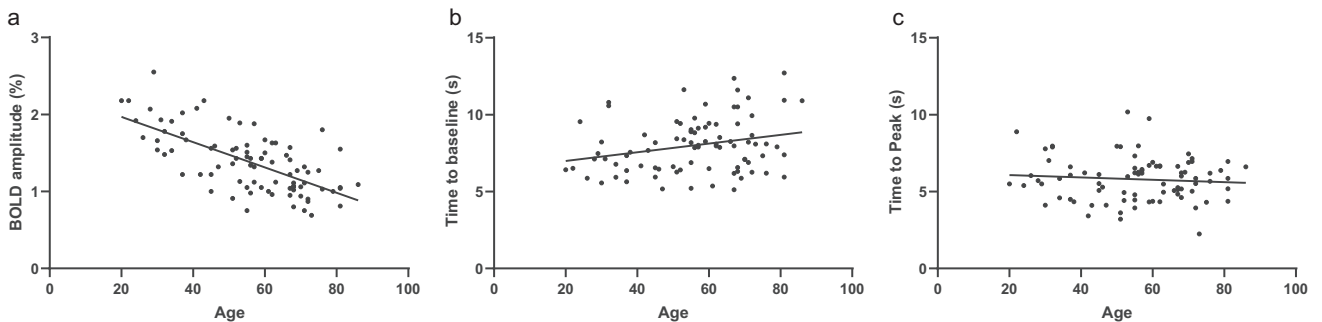


Figure 2: The associations between the cerebrovascular reactivity parameters on the y-axis, i.e. blood-oxygen-level-dependent amplitude (a), time to baseline (b), and time to peak (c), and age on the x-axis in healthy adults.

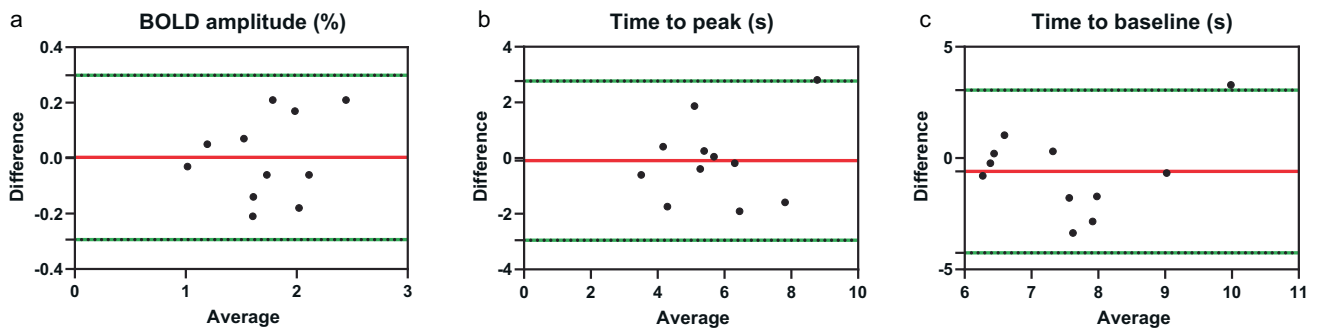


Figure 3: Bland-Altman plots of the reproducibility of blood-oxygen-level-dependent amplitude (a), time to peak (b), and time to baseline (c), showing the difference and mean of the raw scores. The difference between the two measurements (two timepoints) was plotted on the y-axis. The mean of the two measurements (two timepoints) was plotted on the x-axis. The red line represents the group mean difference, and the green lines show the 95% upper and lower limits of agreement (mean difference $\pm 1.96 \times SD$).

Reproducibility

The reproducibility (3-week interval) in a subgroup of 11 healthy adults for BOLD amplitude was excellent (ICC 0.940, 95% confidence interval [CI]: 0.793–0.984). Reproducibility was

moderate for time to peak (ICC 0.666, 95% CI: 0.121–0.899) and poor for time to baseline (ICC 0.219, 95% CI: –0.385 to 0.702). Bland-Altman plots are shown in Fig. 3a–c.

Test–Retest Reliability

Table 2 shows the test–retest reliability (three subsequent measurements) for healthy adults, presymptomatic D-CAA mutation carriers, and symptomatic D-CAA mutation carriers. The overall ICC reflects the reliability of the BOLD parameters over the three fMRI scans together (run1—run2—run3). Test–retest reliability of run1 vs. run2 and run2 vs. run3 are shown separately (Table 2).

HEALTHY ADULTS. Test–retest reliability in healthy adults was good to excellent for BOLD amplitude (ICC 0.856–0.910). Reliability was poor to moderate for time to peak (ICC 0.355–0.556) and poor for time to baseline (ICC 0.097–0.191).

PRESYMPTOMATIC D-CAA MUTATION CARRIERS. Test–retest reliability in presymptomatic D-CAA mutation carriers was excellent for BOLD amplitude (ICC 0.959–0.981). Reliability measurements for time to peak showed a large variation ranging from poor (ICC –0.166) to good (ICC 0.814). A poor to moderate reliability was found for time to baseline (ICC 0.423–0.571).

SYMPTOMATIC D-CAA MUTATION CARRIERS. In symptomatic D-CAA mutation carriers, test–retest reliability was poor for all parameters: mean ICC BOLD amplitude 0.485, mean ICC time to peak –0.382, mean ICC time to baseline –0.102.

Discussion

Our data may show that healthy aging affects cerebrovascular reactivity, measured by changes in BOLD response to visual stimulation using a checkboard. Especially BOLD amplitude decreased with aging and time to baseline was prolonged with aging. Decreased amplitude and prolonged time to baseline mean a two-fold effect on BOLD signal increase rate (slope of the BOLD signal), both findings reducing the signal increase with time. No significant association was found between healthy aging and time to peak. Our findings of an aging effect on cerebrovascular reactivity are in line with previous studies that found a reduced BOLD amplitude in the occipital regions in older subjects compared to younger subjects.^{10,11} Our finding of a reduced BOLD amplitude presumably reflects the normal aging processes, as aging can change the structural and functional integrity of the cerebral vasculature which can alter the BOLD signal.¹⁶ It has been previously described that the number of voxels with no significant activation is higher in elderly versus young participants and that the elderly have a lower signal-to-noise ratio (more noise per voxel) compared to younger participants.¹⁰ This could relate to a distorted view of the changes in the BOLD response. Therefore, in our currently used method only the top 10% of most activated voxels were used in the analysis to select voxels with the highest significance level and exclude non-responding voxels. The finding that in addition to age affects in the BOLD amplitude, time to baseline is prolonged

Table 2. Test–Retest Reliability (Three Subsequent Measurements) of Cerebrovascular Reactivity Parameters

| | Healthy Adults (<i>n</i> = 86) | Presymptomatic D-CAA Mutation Carriers (<i>n</i> = 10) | Symptomatic D-CAA Mutation Carriers (<i>n</i> = 10) |
|-------------------------|---------------------------------|---|--|
| BOLD amplitude | | | |
| Overall | 0.877 (0.829 to 0.914) | 0.976 (0.933 to 0.993) | 0.485 (0.078 to 0.842) |
| Run 1 vs. run 2 | 0.910 (0.865 to 0.941) | 0.981 (0.926 to 0.995) | 0.441 (–0.149 to 0.829) |
| Run 2 vs. run 3 | 0.856 (0.787 to 0.90) | 0.959 (0.847 to 0.990) | 0.175 (–0.321 to 0.691) |
| Time to peak | | | |
| Overall | 0.525 (0.399 to 0.642) | 0.146 (–0.169 to 0.595) | –0.382 (–0.522 to 0.054) |
| Run 1 vs. run 2 | 0.556 (0.387 to 0.688) | 0.814 (0.410 to 0.950) | –0.213 (–0.888 to 0.531) |
| Run 2 vs. run 3 | 0.355 (0.158 to 0.527) | –0.166 (–0.619 to 0.452) | –0.753 (–1.107 to –0.004) |
| Time to baseline | | | |
| Overall | 0.118 (–0.008 to 0.263) | 0.510 (0.141 to 0.822) | –0.102 (–0.266 to 0.509) |
| Run 1 vs. run 2 | 0.191 (–0.016 to 0.386) | 0.571 (0.016 to 0.869) | –0.137 (–0.837 to 0.647) |
| Run 2 vs. run 3 | 0.097 (–0.124 to 0.308) | 0.423 (–0.114 to 0.804) | 0.155 (–0.181 to 0.651) |

Data are expressed as Intra Class Coefficient (95% confidence interval). D-CAA = Dutch-type cerebral amyloid angiopathy; BOLD = blood-oxygen-level-dependent.

with age may also point at decreased functioning of these small vessels due to changes of the structural and functional integrity. This can lead to stiffening of the vessel walls and alter the BOLD response. Unfortunately, no current literature is available addressing this issue. Taken together, our findings may suggest that the entire cascade of neurovascular responses is affected with increasing age. Therefore, we advise to adjust for age when analyzing findings of the BOLD parameters and to include an age-matched control group in longitudinal research.

Measurements of the BOLD amplitude showed excellent reproducibility in a subgroup of healthy adults and excellent test–retest reliability in both healthy adults and presymptomatic D-CAA mutation carriers. In symptomatic D-CAA mutation carriers, test–retest reliability of the BOLD amplitude was much lower. Time to peak and time to baseline showed an overall lower reproducibility and test–retest reliability in all investigated groups. Assessing the reproducibility and test–retest reliability is essential before cerebrovascular reactivity can be applied as a severity marker in clinical trials for treatment of CAA. Previous studies indicated that BOLD amplitude to visual stimulation can be regarded as an early sensitive marker for disease severity in CAA.^{7–9} Our current findings could add to the potential of this severity marker in the presymptomatic phase of the disease. As time to peak and time to baseline showed much lower and inconsistent reproducibility and test–retest reliability, applying these markers in clinical trials would be suboptimal. Moreover, in symptomatic D-CAA patients all neurovascular parameters show poor test–retest reliability. The use of this marker as a severity marker in advanced stages of CAA seems therefore less suited. We found no differences in test–retest reliability between the different runs for the BOLD amplitude parameters. Therefore, we think that a single BOLD session is, from a practical point of view for use in a clinical trial setting, favorable over three sessions as was performed in this study.

Limitations

In our study, reproducibility was only assessed in a small sample of healthy middle-aged adults. Therefore, generalizability of this finding to sporadic CAA, which occurs in older individuals, has to be considered with caution. Moreover, we also had a relatively small number of subjects in the patient groups testing test–retest reliability. Moreover, we did not assess between-scanner reproducibility.

Conclusion

Our findings may indicate the potential of cerebrovascular reactivity, measured by the BOLD response to visual

stimulation using a checkboard, as a robust and sensitive marker for disease severity in CAA, especially in the early stages of the disease. The use of cerebrovascular reactivity as severity marker in advanced stages of CAA seems less suited. Of the three cerebrovascular reactivity parameters, BOLD amplitude appears to be the most robust.

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