Altered cerebrovascular reactivity velocity in mild cognitive impairment and Alzheimer disease

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Abstract

Inter-individual variation in neurovascular reserve and its relationship with cognitive performance is not well understood in imaging in neurodegeneration. We assessed the neurovascular reserve in amnestic mild cognitive impairment (aMCI) and Alzheimer's dementia (AD).
28 healthy controls (HC), 15 aMCI and 20 AD patients underwent blood-oxygen level dependent (BOLD) imaging for 9 minutes, breathing alternatively air and 7% CO_2 mixture. The data was parcellated into 88 anatomical regions, and CO_2 regressors accounting for different wash-in and wash-out velocities were fitted to regional average BOLD signals. Velocity of cerebrovascular reactivity (CVR) was analyzed and correlated with cognitive scores. aMCI and AD patients had significantly slower response than HC (mean time to reach 90% of peak: HC 33 seconds, aMCI and AD 59 seconds). CVR velocity correlated with mini mental state examination (MMSE) in 35 out of 88 brain regions ($p=0.019$, corrected for multiple comparisons), including several regions of the default-mode network, an effect modulated by age.
This easily applicable protocol yielded a practical assessment of CVR in cognitive decline.

Keywords: mild cognitive impairment; Alzheimer; cognitive decline; MRI; perfusion; carbon dioxide; vasoreactivity

Abbreviations

AAL: automated anatomical labeling (atlas)
AD: Alzheimer's disease
aMCI: amnestic mild cognitive impairment
ANOVA: analysis of variance
BOLD: blood-oxygen level dependent
CVR: cerebrovascular reactivity
CO_2: carbon dioxyde
DARTEL: diffeomorphic anatomical registration using exponentiated Lie algebra
DMN: default mode network
EPI: echo-planar imaging
FDR: false discovery rate
FLAIR: fluid-attenuated inversion recovery
fMRI: functional magnetic resonance imaging
FWER: familywise error rate
ICBM: international consortium of brain mapping
MCI: mild cognitive impairment
MNI: Montreal neurological institute
MMSE: mini mental state examination
MRI: magnetic resonance imaging
PET: positron emisison tomography
T1w: T1-weighted image
T2*: T2*-weighted image
T2w: Tw-weighted image
TE: echo time
TR: repetition time
VBM: voxel-based morphometry

1. Introduction

Vascular alterations are present in several dementias, including Alzheimer disease, and can appear at an early stage (Claassen et al., 2009). Through neurovascular coupling, vascular alterations can cause changes in cognitive performance (Novak and Hajjar, 2010). This interaction is made more complex by inter-individual variation in cognitive reserve (Stern, 2012), which modulates the relationship between cognitive function and structural damage (MRI) or impaired metabolism (PET) (Fotenos et al., 2008, Garibotto et al., 2008). In order to shed light on the complex interplay between cognitive performance and neurovascular reserve, a better understanding of the link between cognitive deficits and brain pathology in the transition from healthy controls (HC) to amnestic mild cognitive impairment (aMCI) to AD could be provided by determining if alterations in cerebrovascular reserve, which can be assessed via a measurement of cerebrovascular reactivity (CVR), are linked to alterations in cognition.

The application of carbon dioxide (CO_2) induces vasodilation, which can be assessed in the entire brain parenchyma using blood-oxygen level dependent (BOLD) MRI (Cohen et al., 2002, Kassner and Roberts, 2004, Ziyeh et al., 2005, Haller et al., 2006, Haller et al., 2008a, Mutch et al., 2012). Beyond changes in CVR amplitude, one previous fMRI study (Cantin et al., 2011) observed that a different slope of response to hypercapnia was found in MCI and AD patients than in controls, suggesting that the temporal dynamics of CVR may differ. In that study, however, the spatial distribution of these changes in timing was not studied, and no relationship between cognition and velocity was established. Other studies suggest that changes in the amplitude of CVR in AD is widely distributed across the brain: Impaired CVR in frontal, parietal and temporal lobes has been found using CT (Oishi et al., 1999), and BOLD-MRI studies (Cantin et al., 2011, Yezhuvath et al., 2012) showing that large-scale vascular changes are occurring with the disease. Coherently, resting-state BOLD fMRI investigations also demonstrated large-scale functional network alterations in dementia (Greicius et al., 2004), suggesting that studying regional changes across the whole brain yields additional insights into the spatial localization of differences between patients and controls. An additional motivation for studying changes at the regional level is that, in healthy controls at least, CVR is very regionally specific (Rostrup et al., 2000).

The current investigation tested the hypothesis that aMCI and AD patients exhibit abnormal vascular CVR dynamics, and that these abnormalities are related to cognition. To this end, we assessed the velocity of the regional CVR during a CO_2 challenge in aMCI and AD compared to healthy controls.

2. Materials & Methods

2.1. Subjects

The local ethical committee approved this prospective study; all participants gave written informed consent prior to inclusion. From our memory clinic, 63 subjects were prospectively included, including 20 AD patients, 15 aMCI patients, as well as 28 HC from the Basel Study on the Elderly (Monsch and Kressig, 2010). Groups were relatively well balanced for sex and age (Table 1), showing no significant differences. AD patients had lower mini mental state examination (MMSE) scores, but generally were minimally impaired. The subjects were examined according to standard diagnostic procedures (Monsch and Kressig, 2010), including brain MRI without contrast agents. The diagnosis criteria for AD were based on the NINCDS-ADRDA criteria (McKhann et al., 1984). The diagnosis criteria for aMCI were based on (Winblad et al., 2004).

Table 1: Demographic information

	HC	aMCI	AD
Number of subjects	28	15	20
Number of women (percentage)[a]	18 (64)	9 (60)	10 (50)
Average age [y] ± SD[b]	73±7	71±10	76±7
Mean MMSE score [a.u.] ± SD[c]	29±1	28±2	25±3
Median Fazekas score [a.u.] (range)[d]	1 (0-3)	1 (0-3)	1 (0-3)

Notes: SD: standard deviation
[a]: no significant difference between groups (χ^2=1.0, p=0.61)
[b]: no significant difference between groups (F=1.9, p=0.16)
[c]: significant difference between groups (F=31.9, $p<10^{-9}$), no diff. between HC and aMCI.
[d]: no significant difference between groups (χ^2=0.12, p=0.94).
Continuous measures are compared between groups using a one-way ANOVA. Dichotomous variables: χ^2 test. Ordinal measures: Kruskal-Wallis test.

2.2. MR Imaging

Imaging was performed on a 3T clinical whole-body MRI scanner (Verio, Siemens Medical Systems, Erlangen, Germany). Standard routine clinical imaging included a 3D T1w ($1mm^3$ isotropic, 256x256x176 matrix). Additional sequences (T1w, T2w, T2*, FLAIR) were acquired and analyzed to exclude brain pathology such as ischemic stroke, subdural hematomas or space-occupying lesions and determine white matter lesion severity (Fazekas et al., 1987), Table 1.
The 9 min CO_2 challenge consisted of CO_2 administered via a nasal canula in a concentration of 7% mixed in synthetic air, with the sequence 1 min OFF, 2 min ON, 2 min OFF, 2 min ON, 2 min OFF (details below). Subjects were asked to breathe normally through the nose. Simultaneous multi-echo echo-planar imaging (EPI) covering the entire brain was acquired with the following parameters: 64 x 48 matrix, 34 slices, voxel size 3.44 x 3.44 x 3.5 mm^3, TEs of 12.3, 29.5, 46.8 and 64ms, TR 2970ms, 180 repetitions.

We deliberately chose a very simple experimental setup, consisting of a gas-bottle with a ready for use mix of 7% CO2 and synthetic air. This gas bottle was outside the MRI in the control room, and connected via a simple silicone tube to a standard nasal canula in the MRI room. The technician manually started and stopped the CO2 application at 8 l/min using a standard clinical flow meter. Note that much more sophisticated setups exist including automatic synchronization with the MRI sequence and use of tight face masks to segregate inflow and outflow with the ability to measure expiratory CO2 concentration. Such a setup is in our experience most appropriate for a research setting in younger individuals, as for example tight face masks are oftentimes not well tolerated by elderly individuals.

2.3. Preprocessing

Data was preprocessed using SPM8 (version 5236, http://fil.ion.ucl.ac.uk/spm/). For BOLD analysis, the second echo of the EPI sequence was used. Functional images were motion-corrected (realignment to the mean image). The T1w structural image was segmented and normalized ("new segment" algorithm). Functional images were coregistered to the normalized T1w structural image. The structural images were parcellated into 90 cortical and subcortical gray matter regions using the AAL atlas (Tzourio-Mazoyer et al., 2002). The bilateral globus pallidus was removed from the data due to characteristic segmentation issues related to its small size in the atlas, leaving 88 regions. EPI data were averaged within each atlas region, yielding 88 regionally averaged time-series per subject with improved signal-to-noise ratio compared to individual voxel-wise data. Each time series was rescaled by the grand mean computed over all atlas regions of the corresponding subject, and linearly detrended. The 6 translation and rotation parameters from the realignment procedure were regressed out. Lastly, each time-course was Winsorized to the 5th and 95th percentile to minimize the effect of any remaining intensity spikes.
For voxel-based morphometry (VBM) analysis, the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm/) was used. T1w images were normalized to MNI space (DARTEL warping, default ICBM template). The resulting normalized gray matter segments were modulated to account for spatial normalization. The data were smoothed by convolution with a 8 mm-FWHM Gaussian kernel.

2.4. Statistical analyses

Analyses were performed using Matlab R2012b and the statistics and optimization toolboxes version R2012b (Mathworks, Natick, MA, USA), as well as R 3.0.2 with the stats 3.0.2, nlme 3.1-113, car 2.0-19, multcomp 1.3-1, and effects 2.3 packages (R Foundation for Statistical Computing, Vienna, Austria).

2.4.1. VBM Analysis

For visual quality assurance of the homogeneity of the data, the sample covariance matrix was displayed, as well as one slice per image. A group-level full factorial GLM was created by entering the normalized, modulated individual gray matter volumes as predictors, and a categorical ternary group

membership variable (HC, MCI, or AD) as a covariate. The model parameters were estimated, and pairwise contrasts (HC > MCI, HC > AD, and MCI > AD) were computed. Multiple comparison correction was applied using Family-wide error rate (FWER).

2.4.2. CVR analysis

Studies of hypercapnia typically use end-tidal CO_2 time courses measured in vivo as a regressor for the BOLD signal (Cantin et al., 2011). In our setup, no end-tidal CO_2 levels are monitored, and the regressors are therefore defined analytically. A CO_2 challenge regressor was defined by convolving the CO_2 on-off timing vector with a filter whose frequency response is

$$H(\omega) = \frac{c}{1+(1-c)e^{-\omega}},$$

where c is a constant, leading to an exponential wash-in and wash-out behavior (see Figure 1). c was set to 0.15, to obtain a shape similar to previous work (Stefanovic et al., 2006, Jiang et al., 2010, Rieger S.W. et al., 2012) (see Figure 3 for example fits). Note that in (Jiang et al., 2010) a similar regressor was obtained by convolving the CO2 timing vector with a gamma function, also exhibiting the exponential behavior. We denote this the "nominal" CO_2 regressor, meaning that it represents the expected response in healthy subjects, based on the literature. A second CO_2 regressor with $c = 0.11$ was computed, representing a slower vessel dilation and lower slope during the steady-state phase of hypercapnia (Cantin et al., 2011). This was denoted as the "slow" CO_2 regressor. Linear combinations of these regressors give rise to a flexible family of possible BOLD response time courses, representing the various possible dynamics of the CVR. Regressors were shifted by 1 TR (3 s.) to account for hemodynamic lag. The two regressors were normalized to unit peak-to-peak amplitude, demeaned, and orthogonalized (Figure 1). The principle of using linear combinations of regressors to obtain a more flexible temporal representation is similar to adding temporal derivative to the canonical hemodynamic response function (Friston et al., 1998), except that in our case the effect of adding the “slow” regressor is to modify slopes of the wash-in and wash-out, instead of shifting the basis functions forwards or backwards (note also that the “slow” regressor is not the derivative of the “nominal” regressor).

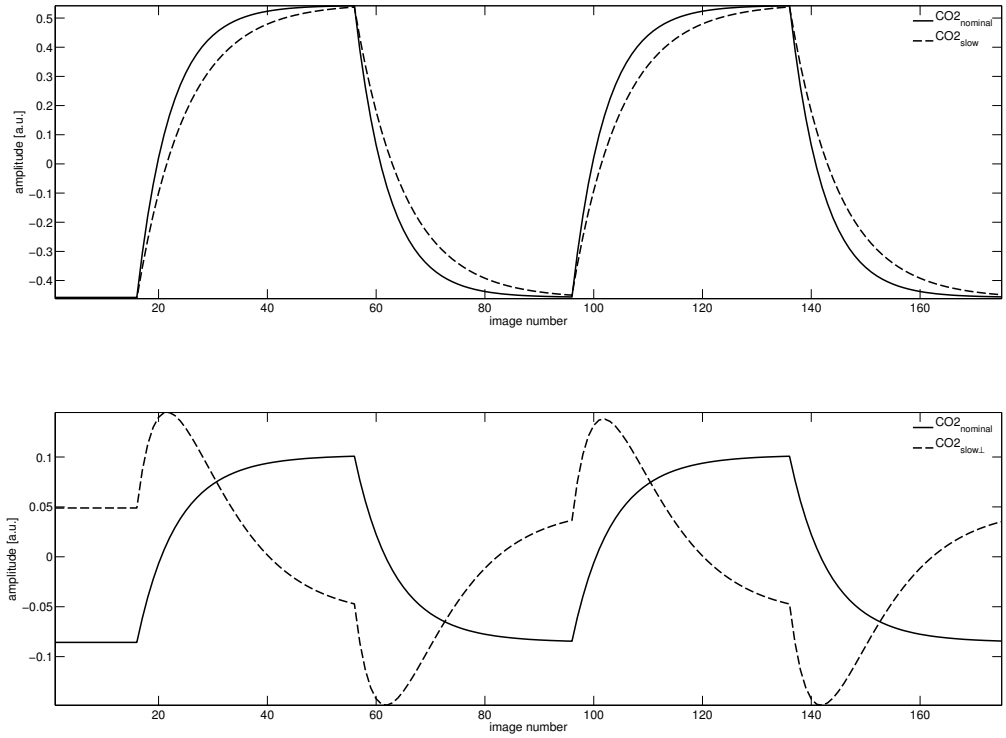


Figure 1:Model regressors for CO_2 challenge
Time courses of the "nominal" (continuous line) and "slow" (dashed line) CO_2 challenge regressors. The top panel shows the regressors prior to orthogonalisation, while the bottom panel shows them as entered in the design matrix.

Two CO_2 regression coefficients (denoted β_1,β_2) were estimated per region (88 per subject) using constrained least-squares fitting (Matlab function lsqlin), imposing positivity of the β_1 coefficient to ensure physiological plausibility of the linear combination of regressors. A negative β_2 value corresponds to a slower response than modeled by the nominal regressor, while a positive β_2 value corresponds to a faster response. Thus, β_2 models CVR velocity (representing the rate of vasodilation or vasoconstriction, and controlling the initial slope of the wash-in and wash-out periods), while β_1 models amplitude. Showing a correspondence with the sigmoid conceptual model relating blood flow change to partial pressure of CO_2 (Sobczyk et al., 2014), a Gompertz sigmoid function can be fit to our linear combination of regressors with very high goodness of fit (R^2 around 0.99), and the β_2 parameter has a clear influence on the Gompertz growth rate parameter. Each region was subsequently represented by its β_1 or β_2 CVR coefficient value in second-level analyses. Model fit was assessed by an F-test.

Four main analyses were performed: 1) overall effect, 2) lobe level, 3) regional level, and finally 4) relationship between CVR parameters and cognitive scores. For the overall analysis, a three-way mixed-effects ANOVA with diagnostic group and lobe as main effects, subject as random effect, and subject nested in group, was conducted on the β_1 and β_2 values, via a linear mixed model. Comparisons on group effect were performed, using the Benjamini-Hochberg step-down procedure (FDR) to adjust the reported p-value for multiple comparisons (Benjamini and Hochberg, 1995). In lobe-

level analysis, to yield insights into the spatial location of differences and enable comparison with the literature (Cantin et al., 2011), brain regions were grouped into 7 lobes (Tzourio-Mazoyer et al., 2002), and the data for each lobe was modeled using a separate linear mixed-effect model, with group as main effect, subject as random effect, and subject nested in group. Tukey contrasts (HC>aMCI, HC>AD, aMCI>AD) were computed for the main effect of group in each model. Within each pairwise contrast, the uncorrected p-values were compared to a significance threshold FDR-adjusted for the number of lobes. For the region-level analysis, pairwise contrasts were computed between diagnostic groups for all 88 regions, using a one-sided two-sample t-test assuming unequal variance, and results were FDR-corrected. In addition, a receiver operating characteristic (ROC) analysis was performed for each region, using 1000 bootstrap replicates to compute a confidence interval on the area under curve (AUC). The relationship between CVR coefficients and any residual motion was tested by a linear mixed model regressing the CVR velocity or amplitude coefficient on 12 summary motion parameters (average and maximum x,y,z translations, and pitch, roll, yaw rotations for each subject), with subject as random effect, and subject nested in group. The relationship between CVR coefficients and global gray matter atrophy was tested by a linear mixed model regressing the CVR velocity or amplitude coefficient on gray matter volume (obtained from VBM analysis), with subject as random effect, and subject nested in group. We also tested the relationship between CVR coefficients and microangiopathy by performing the same analysis as for gray matter volume, but with Fazekas scores.

Finally, the relationship between CVR coefficients and cognitive scores was modeled at the regional level by the full cognitive model $\beta_2 = 1 + gender + age + MMSE + age{:}MMSE$. A baseline model $\beta_2 = 1 + gender + age$ was also used for comparison. Model fit was assessed by F-test. Effect plots were computed (R *effects* package).

3. Results

3.1. Structural voxelwise analysis

No subjects were excluded after quality assurance. VBM analysis showed no significant difference between HC and aMCI groups (α=0.05, family-wise error rate (FWER)-corrected) in gray matter density. The AD group showed a few locations with significant gray matter reductions ($p<0.05$ FWER, peak T-value 8.62) including the hippocampal formation, as well as in the right medial temporal gyrus, right superior temporal gyrus, and left uncus and left amygdala. Also compared to aMCI , the AD group had significant gray matter density reductions ($p<0.05$ FWER, peak T-value 6.28), located in the left parahippocampal area, and with smaller spatial extent. There were no differences between HC and aMCI in gray matter density. As shown below (region-level analysis), areas of reduced gray matter density in VBM do not correspond to regions that have a trend for differences in CVR velocity.

3.2. CVR analysis

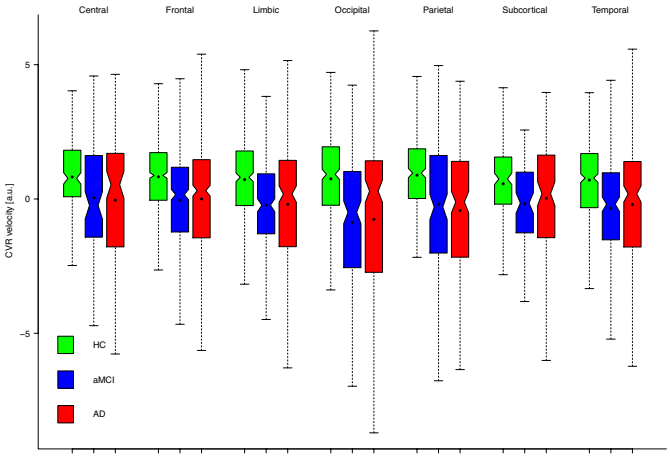
3.2.1. Overall analysis

Subjects reported no discomfort during MR imaging and CO2 administration. There was a significant main effect of group (χ^2=6.09, p=0.048) and lobe (χ^2=85.76, $p<10^{-15}$) on CVR velocity. There was no significant effect of group on CVR amplitude (χ^2=1.02, p=0.600), but a significant effect of lobe (χ^2=817.68, $p<10^{-15}$). CVR velocity was significantly larger in controls than in aMCI (z=1.03, p=0.034 FDR) and AD patients (z=0.99, p=0.034 FDR). Controls (HC) had a positive group mean CVR velocity (mean and standard error: 0.77 ± 0.03), while patients had a negative group mean CVR velocity (aMCI: -0.26 ± 0.06, AD:-0.22±0.06), indicating that CVR in controls was on average faster than the nominal response, while CVR in patients was slower than nominal. These values correspond to a mean time to reach 90% of peak response of 33 seconds for HC, and 59 seconds for aMCI and AD. There was no significant difference in CVR velocity between aMCI and AD.
There was no significant relationship between gray matter volume and CVR velocity (χ^2=1.42, p=0.234), nor between Fazekas score (representing microangiopathy severity) and CVR velocity (χ^2=0.23, p=0.633). There was also no significant relationship between CVR velocity and any of the 12 motion parameters (χ^2=0.07-1.51, p=0.786-0.219 uncorrected).

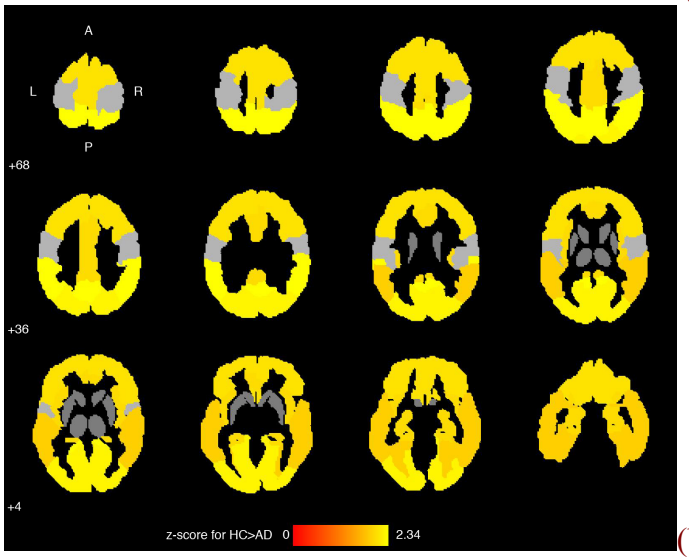
3.2.2. Lobe-level analysis

In the HC>aMCI contrast on CVR velocities, no lobe passed the FDR-corrected significance threshold, although values were low. The most different lobe was the occipital lobe (t=2.21, p=0.014 uncorrected), while the least different was the central lobe (t=1.36, p=0.087 uncorrected). For the HC>AD contrast, all lobes except central and the subcortical pseudo-lobe (putamen, caudate, thalamus) had significantly higher velocities in controls than in patients (p=0.028 FDR). No significant difference in velocity between aMCI and AD was found in the aMCI>AD contrast. No contrast showed a significant difference in CVR amplitude. Figure 2 (a) shows the distribution of CVR velocity values for all groups and lobes. Figure 2 (b) shows the brain

space map of the effect size of CVR velocity in the HC>AD contrast in lobes. Supplementary table 1 shows the statistics for the three contrasts on CVR velocity.



(a)



(b)

Figure 2: Lobe-level differences in CVR velocity
(a) Distribution of CVR velocity parameter values for HC (green), aMCI (blue), and AD (red) groups in each lobe. The notch indicates the median, while the black dot indicates the mean of the distribution of values, and outliers are not shown. Patients have lower velocities than controls, but there is no difference between aMCI patients and AD patients. (b) Axial view of differences in CVR velocity at the lobe level, in neurological convention. Lobes are colorised by equivalent z-score for the p-value of the lobe-wise contrast HC>AD for the difference in CVR velocity. The brightest colour (yellow) corresponds to a z-score of 2.34, while the darkest colour (red) maps to 0. All lobes except the central and the subcortical pseudo-lobe (shown in gray) show significant difference between groups (p=0.028 FDR). The occipital and frontal lobes show the largest difference in CVR velocity.

3.2.3. Region-level analysis

There were no significant pairwise differences in either the HC > aMCI or HC > AD contrasts on CVR velocity in regions after FDR correction for multiple comparisons. Four regions had a trend for differences in the HC>aMCI contrast ($p<0.01$ uncorrected) in superior left occipital gyrus, left cuneus, and orbital part of the inferior frontal gyrus. Four regions had a trend for differences in the HC > AD contrast ($p<0.01$ uncorrected) in bilateral straight gyri, right posterior cingulate, and left precuneus. Supporting the hypothesis of regional differences between groups, uncorrected p-values were generally low (HC>aMCI: median 0.051, range 0.002-0.272, HC>AD: median 0.048, range 0.004-0.441. The full distribution is shown in Supplementary Table 2 and Supplementary Figure 1). The median AUC value of the controls versus patients (aMCI+AD) ROC analysis of CVR velocity in the 88 regions was 0.64 (range 0.55-0.72, confidence interval lower bound above 0.5 in 35 regions), indicating that the CVR velocity parameter has some limited diagnostic power, to a various degree depending on the region. Note these regions do not exhibit significant differences between groups in gray matter density, as shown by the VBM analysis. No significant difference was found in the aMCI>AD contrast, and uncorrected p-values were generally high (median 0.524, range 0.092-0.857). Regional time-courses for the HC>aMCI and HC>AD contrasts are illustrated in Figure 3.

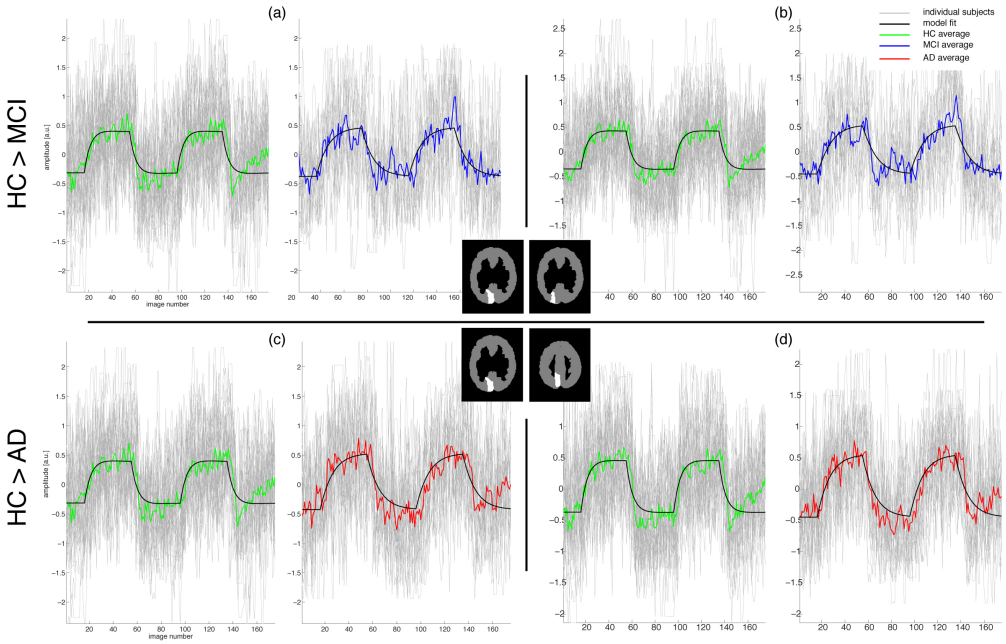


Figure 3: Illustrative regional time courses in controls and patients
Regional time courses for all subjects (gray lines) and their average (green for HC, blue for aMCI, red for AD), and model predicted response (black). Illustrative regions with the most difference in CVR velocity parameter and significant average model fit across subjects in both groups. Top row: HC > aMCI, bottom row: HC > AD. (a) left cuneus (p=0.007 uncorrected), (b) left superior occipital gyrus (p=0.002 uncorrected), (c) left cuneus (p=0.01 uncorrected), (d) left precuneus (p=0.007 uncorrected). The insets show an axial view through the mean z-coordinate of the corresponding region, highlighted in white. Patients' response is noticeably slower than controls' in reaching steady-state.

3.2.4. Relationship between CVR and cognitive scores

35 regions had a significant model fit (p=0.019 FDR, minimum adjusted R^2 0.12, maximum 0.25, mean and std 0.17±0.03, corresponding on average to a large effect size), and showed a significant positive relationship between MMSE and CVR (p=0.037 FDR), as well as a significant negative age x MMSE interaction (p=0.038 FDR). Several regions of the DMN show a significant fit: the left anterior and posterior cingulates, bilateral precuneus, bilateral middle frontal gyri, left parietal inferior gyrus, bilateral angular gyri, and left middle temporal gyrus (the mapping between default-mode network and the corresponding 26 AAL labels is found in (Fransson and Marrelec, 2008, Richiardi et al., 2012)). Significant regions were uniformily distributed between lobes, expect for the temporal lobe, where only 1 out of 14 temporal lobe regions was significant, instead of the expected 6 out of 14 regions if all lobes had an equal proportion of significant regions. The baseline model with only age and gender had no significant fits, suggesting that MMSE and age x MMSE interaction are indeed related to CVR velocity. Supplementary Table 2 shows coefficients of determination and corresponding F-test p-value for all regional models. Figure 4 shows the brain space map of the equivalent z value for the p-values of the region-level F-test for model fit of CVR velocity on MMSE, age, and their interaction, corrected by gender.

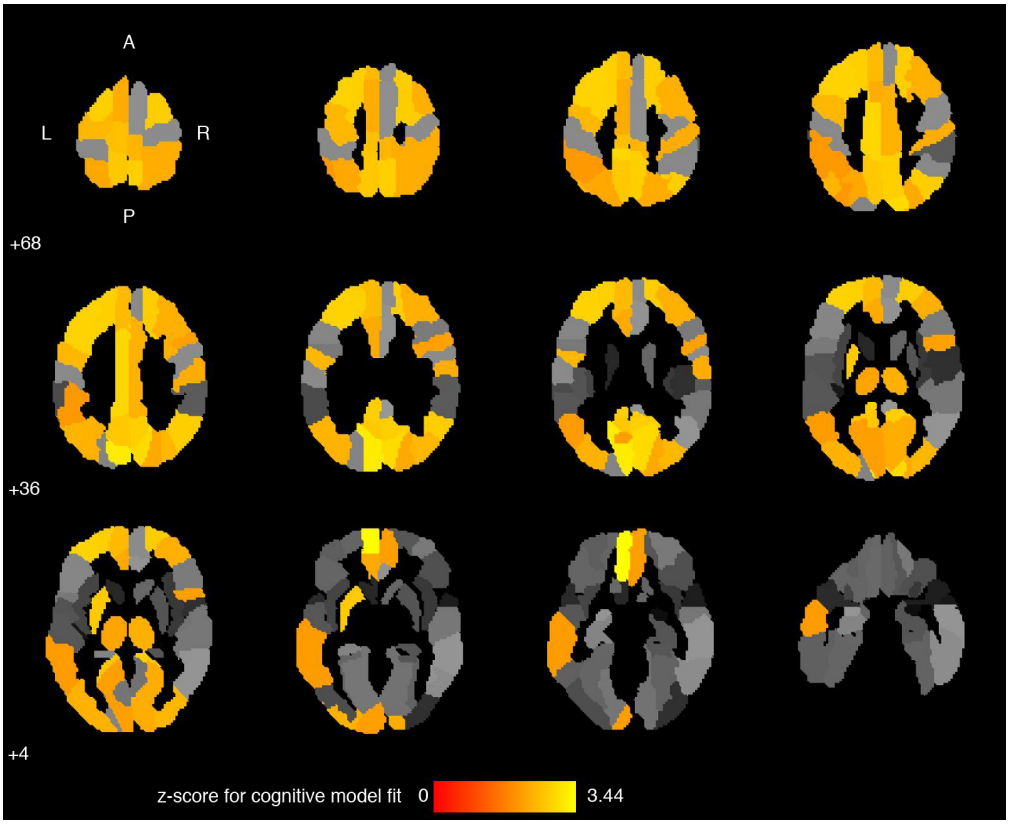


Figure 4: Relationship between CVR velocity and MMSE score
Axial view of the relationship between CVR velocity parameter and MMSE score at the regional level, in neurological convention. Regions are colorised by equivalent z-score for the p-value of the full cognitive model fit (comprising age, gender, MMSE, age x MMSE). The brightest colour (yellow) corresponds to a z-score of 3.44, while the darkest colour (red) maps to 0. Regions with insignificant relationship between MMSE and CVR velocity are shown in gray, while regions with an orange-yellow hue show a significant association (p=0.019 FDR). Note that this relationship is particularly strong in frontal and occipital areas, while temporal areas show less effect.

In the regions with a significant fit, MMSE had a positive relationship with CVR velocity, and this relationship was modulated by age. The interaction between age and MMSE was antagonistic, that is, the relationship between MMSE and CVR velocity is smaller when age is higher. Figure 5 shows the moderating effect of age on the relationship between MMSE interaction plot for subjects who are at the mean age in our sample (73), as well as one standard deviation above (81) and below (65). Microangiopathy severity was not a significant predictor (over 88 regions, t-statistic range -0.835-2.284, median 0.461, uncorrected p-value range 0.026-0.988, median 0.629).

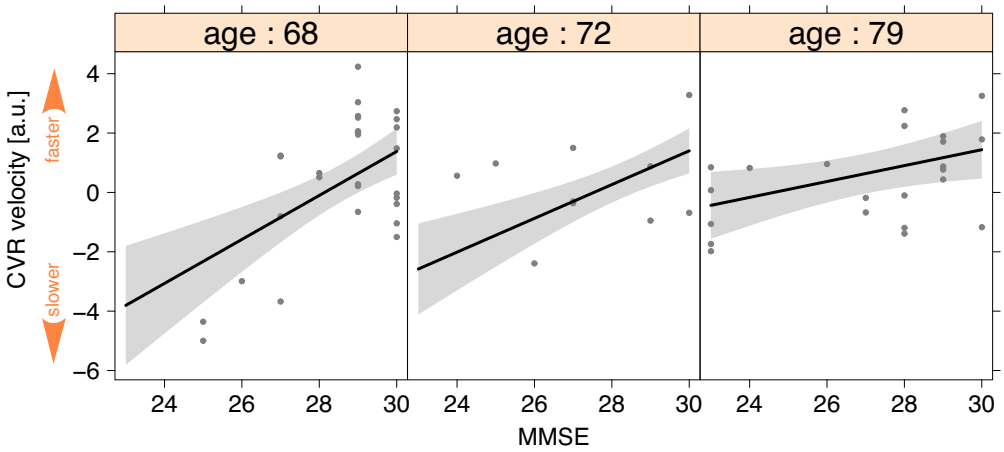


Figure 5: Age modulates the relationship between CVR velocity and cognitive performance

The relationship between cognitive performance and CVR velocity is modulated by age. This plot, for the left cuneus, shows that a higher CVR velocity (higher value) corresponds to a higher MMSE score for relatively younger subjects. Subjects in the lowest and highest 5% of MMSE scores were trimmed for display (leaving 60 cases). The left panel shows the relationship if a subject is 68 years old (1st quartile of the trimmed sample), while the middle and right panel show the relationship if a subject is 72 years old (median) and 79 years old respectively (3rd quartile). The grey band shows the 95% confidence interval for the regression line. The dots indicate partial residuals (conditional on the age in that panel).

4. Discussion

Using a simple and well-tolerated MR imaging paradigm, we found that the neurocognitive decline in aMCI and AD, as represented by MMSE score, is paralleled by reduced CVR velocity, and that this change in velocity is not related to general or focal gray matter atrophy, microangiopathy, or motion.

4.1. CVR velocity in Alzheimer disease

Decreased CVR velocity is consistent with literature. In a visual task fMRI experiment, AD patients were shown to have widespread decreases of early response, corresponding to delayed response to a stimulus (Rombouts et al., 2005). Velocity decreases have also been observed in mouse models of AD, with slower return to the normal diameter of blood vessels after a vaso-constrictive drug was applied (Rancillac et al., 2012). While many neurovascular factors may contribute to the difference between controls and patients in CVR velocity, changes in vessel stiffness would be consistent with our observations. Sabayan et al. (Sabayan et al., 2012) reported in a meta-analysis that AD patients have higher pulsatility index (Gosling and King, 1974) in the middle cerebral artery, indicating higher downstream resistance. Results on pulse wave velocity also suggest stiffer vessels in AD, which may contribute to our observed velocity differences. In resting-state studies of Alzheimer without CO_2 challenge, activity is often desynchronized between specific regions (Greicius et al., 2004, Barkhof et al., 2014), including preferentially the DMN, of which 10 regions have significant association between MMSE and CVR velocity in our results. Such a decrease in functional connectivity can be explained by a number of factors, one of which may be regional differences in CVR velocity (itself potentially modulated by spontaneous respiration rate changes during resting-state (Murphy et al., 2013)).

4.2. CVR velocity and cognitive performance

The frontal and occipital lobes are notable because they have significantly lower CVR velocity in patients and several regions where lower CVR velocity is associated with lower MMSE scores, a widely used and accepted yet coarse measure of the overall cognitive status. This agrees with previous studies reporting abnormal CVR in the frontal lobe of patients (Cantin et al., 2011, Yezhuvath et al., 2012). Because the amplitude of cerebral blood flow in the frontal lobe is not significantly different between controls and patients under CO_2 challenge (Cantin et al., 2011, Oishi et al., 1999), this velocity difference could be functionally relevant in cognitive performance. This is consistent with reports of a positive correlation between CVR amplitude and MMSE score in several lobes (Cantin et al., 2011), and between CVR amplitude and Boston Naming Test scores in the frontal lobe (Yezhuvath et al., 2012) (although that study found no correlation with MMSE). Alternatively, a difference of baseline function could also explain the CVR velocity difference between groups. For example, MCI can lead to higher neuronal activation when performing simple cognitive tasks (Kochan et al., 2010). Thus, while the aMCI subjects in our study can maintain relatively intact cognitive

function (MMSE slightly but not significantly lower than controls), their vascular reserve is already showing signs of depletion, as reflected in our results. Conversely, it has been reported that AD and MCI patients have a widespread decrease in baseline T2* signal (Rombouts et al., 2007), although it was ascribed to grey matter atrophy differences which are mostly insignificant in our data. The dynamics difference observed in our results, where cognitive demands are minimal, could stem from a possible non-linearity of vessel dilation speeds: vessel dilation in patients could start from a different baseline (either higher or lower) than controls. Finally, the modulatory effect of age on the relationship between MMSE and CVR velocity can be attributed to several factors, for example increasing medication or hypertension with age could disrupt the relationship. Additionally, age-related cholinergic system impairment could impact both CVR function and cognitive performance (Glodzik et al., 2013).

In the absence of established reference methods for in-vivo assessment of cognitive reserve in the workup of cognitive decline, this study offers an additional vascular parameter, CVR velocity, which is linked to cognition, and could be used in future studies as a factor to model when examining the cognitive reserve hypothesis, in addition to more established measures such as blood flow or structural/volumetric features.

4.3. CVR dynamics assessment in clinical practice

The clinical protocol employed is easy to administer and well-tolerated by patients with aMCI and mild AD. The simple on-off "square wave" CO_2 stimulus is straightforward to apply and a robust probe for CVR dynamics (Mutch et al., 2012). Our results show that a simple nasal canula is sufficient to induce significant whole-brain BOLD response under CO_2 challenge with acceptable acquisition time, and the setup necessary for the CO_2 clinical protocol doesn't interfere with the structural MRI typically performed in routine workup on cognitive decline. The alternative setup including a tight facemask segregating inflow and outflow allows not only more accurate application of CO2 but also assessing expiratory CO2 concentrations, and is clearly more accurate in a research setting. However, there are constraints for the clinical applications, which should be considered. The experimental setup should be simple, inexpensive and easy to use, attributes of the nasal cannula setup of the current investigation yet not of setups with tight facemasks requiring additionally devices to apply and measure CO2 as well as compensation of the airflow resistance induced by the facemask. Moreover, a tight facemask setup substantially reduces patient comfort and in our experience further increased already present head motion artifacts (Haller et al., 2014). Standard MR imaging is routinely performed for the workup of neurocognitive decline in many centers. In our opinion, one of the fundamental requirements for the CVR assessment in this setting is the minimal interference with this standard MR imaging. Using a tight facemask there are two options. The first option is installing the facemask during the entire MR imaging, yet this unnecessary reduces the patient comfort even during anatomic imaging, and probably increased motion artifacts. The other option is installing the facemask after structural imaging only before the CVR

imaging. This however requires additional installation during MR imaging, potentially the need to repeat scout scans, thereby prolonging the total measurement time. In contrast, the nasal cannula is easily and rapidly installed, does not interfere with anatomic imaging, and was well tolerated by all participants. Our setup is very simple and cheap, takes less than a minute to put in place, was well tolerated by all participants, did not interfere with standard MRI imaging and can with only minimal demands be applied in any MRI center and clinical routine. The only requirement is the gas bottle with a ready to use mix of CO_2, while silicone tubes and nasal canals are standard equipment in most centers.

4.4. Limitations of the study

There were several limitations to this study. First, the relatively low number of aMCI patients and lack of follow-up could explain not finding a difference with AD patients. While our results show that CVR dynamics are also impaired in aMCI patients, it is possible that changes in aMCI converters are gradual and could not be observed here. Second, our model cannot distinguish between dilation (wash-in) and contraction (wash-out) velocities because a single parameter controls both, but it is possible that they are differentially affected by disease status and progression. Third, our results do not show a difference in the CVR velocity of the hippocampus or parahippocampal formation. This may be due to field inhomogeneity in that region, but literature on hippocampal blood flow differences in dementia is inconclusive; observed differences may depend on image processing choices (Binnewijzend et al., 2013). Fourth, the absence of differences in the amplitude of CVR between study groups might be related to the relatively weaker hypercapnic stimuli using a nasal cannula as compared to a tight facemask. As discussed above, simple experimental setup and non-interference with routine structural MR imaging were fundamental prerequisites for our study setup. Consequently we deliberately took into account the less potent application of CO_2. Fifth, proximal vascular stenosis could potentially confound the dynamics of the CVR assessment (Haller et al., 2008b). This potential confound could in principle be assessed by adding MR angiography of the cerebral vessels. Finally, our measure of cognitive performance, MMSE, encompasses several functional domains: many functional aspects of cognition are affected by cognitive decline, and it would be interesting to pinpoint more specifically which cognitive domain links with CVR parameters.

4.5. Conclusion

In sum, aMCI and AD patients showed slower CVR response than controls to CO_2 BOLD challenge, and CVR response velocity was related to cognitive performance, modulated by age. The dynamics of cerebrovascular reactivity could be a useful tool in the study of the relationship between neurovascular reserve, cognitive performance, and cognitive reserve. CVR dynamics can be assessed by a simple and well-tolerated clinical protocol, enabling use of the technique in a routine clinical setting.

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Disclosure Statement

The authors have no actual or potential conflicts of interest.

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