Altered BOLD signal variation in Alzheimer’s disease and frontotemporal dementia

Timo Tuovinen*1,2, Janne Kananen1,2, Riikka Rytty3,3, Virpi Moilanen4, Ahmed Abou Elseoud2,5, Anne M Remes4,6,7,8, Vesa Kiviniemi1,2, ADNI^

1 Department of Diagnostic Radiology, Medical Research Center, Oulu University Hospital, Oulu, Finland
2 Oulu Functional NeuroImaging -group, Research unit of Medical Imaging, Physics and Technology, University of Oulu, Oulu, Finland
3 Department of Neurology, Hyvinkää Hospital, The Hospital District of Helsinki and Uusimaa, Hyvinkää, Finland
4 Department of Neurology, Medical Research Center Oulu, Oulu University Hospital, Oulu, Finland
5 Department of Radiology, Helsinki University Hospital, Helsinki, Finland
6 Research Unit of Clinical Neuroscience, Faculty of Medicine, University of Oulu
7 Institute of Clinical Medicine – Neurology, University of Eastern Finland, Kuopio, Finland;
8 Neurocenter, Neurology, Kuopio University Hospital, Kuopio, Finland

* Corresponding author
E-mail: timo.tuovinen@oulu.fi

^ Alzheimer’s disease neuroimaging initiative
Abstract

Recently discovered glymphatic brain clearance mechanisms utilizing physiological pulsations have been shown to fail at removing waste materials such as amyloid and tau plaques in neurodegenerative diseases. Since cardiovascular pulsations are a main driving force of the clearance, this research investigates if commonly available blood oxygen level-dependent (BOLD) signals at 1.5 and 3 T could detect abnormal physiological pulsations in neurodegenerative diseases. Coefficient of variation in BOLD signal (CV\textsubscript{BOLD}) was used to estimate contribution of physiological signals in Alzheimer’s disease (AD) and behavioural variant frontotemporal dementia (bvFTD). 17 AD patients and 18 bvFTD patients were compared to 24 control subjects imaged with a 1.5 T setup from a local institute. AD results were further verified with 3 T data from the Alzheimer’s disease neuroimaging initiative (ADNI) repository with 30 AD patients and 40 matched controls. Effect of motion and gray matter atrophy was evaluated and receiver operating characteristic (ROC) analyses was performed.

The CV\textsubscript{BOLD} was higher in both AD and bvFTD groups compared to controls (p < 0.0005). The difference was not explained by head motion or gray matter atrophy. In AD patients, the CV\textsubscript{BOLD} alterations were localized in overlapping structures in both 1.5 T and 3 T data. Localization of the CV\textsubscript{BOLD} alterations was different in AD than in bvFTD. Areas where CV\textsubscript{BOLD} is higher in patient groups than in control group involved periventricular white matter, basal ganglia and multiple cortical structures. Notably, a robust difference between AD and bvFTD groups was found in the CV\textsubscript{BOLD} of frontal poles. In the analysis of diagnostic accuracy, the CV\textsubscript{BOLD} metrics area under the ROC for detecting disease ranged 0.85 – 0.96.

Conclusions: The analysis of brain physiological pulsations measured using CV\textsubscript{BOLD} reveals diseasespecific alterations in both AD and bvFTD.
Introduction

The two most common forms of early-onset dementia are Alzheimer’s disease (AD) and behavioral variant frontotemporal dementia (bvFTD). Multiple resting-state functional MRI (rs-fMRI) studies concerning AD and bvFTD have been published. In AD the findings have been relatively consistent, with reduced default mode network (DMN) connectivity reported in numerous studies, and it seems to correlate with disease severity [Agosta et al., 2012; Binnewijzend et al., 2012; Greicius et al., 2004; Hafkemeijer et al., 2012; Li et al., 2002; Zhou et al., 2010]. In bvFTD, reduced salience network (SLN) connectivity has been most reported finding, although there has been some diverseness [Farb et al., 2013; Filippi et al., 2013; Lee et al., 2014; Rytty et al., 2013; Zhou et al., 2010]. Advanced artifact removal affects the reproducibility of the functional connectivity findings [Griffanti et al., 2015; Tuovinen et al., 2017].

The blood oxygen level-dependent (BOLD) signal used in fMRI is an indirect marker of neuronal activity and also reflects other vascular, respiratory and physiological factors [Birn et al., 2006; Shmueli et al., 2007; Liu et al., 2013; Mark et al., 2015; Kiviniemi et al., 2016]. Brain activity induces a complex combination of changes in cerebral blood volume, cerebral blood flow, and oxygen extraction fraction that all affect the de-phasing of the water protons and modulate the T2*-weighted MRI signal intensity in the brain measured as BOLD signal [Buxton, 2012]. BOLD signal has marked correlation with cardiorespiratory pulsations due to the high sensitivity to blood flow status [Hoge et al., 1999; Wise et al., 2004; Birn et al., 2006; Chang et al., 2009; Chang and Glover, 2010; Birn et al., 2014]. Physiological fluctuations in BOLD signal have traditionally been considered as a nuisance concealing neural activity [Keilholz et al., 2017]

Physiological pulsations has been shown to be of vital importance for the homeostasis of the brain [Aspelund et al., 2015; Buxton, 2012; Buxton et al., 2014; Dreha-Kulaczewski et al., 2015; Erdő et al., 2017; Fleisher et al., 2009; Garrett et al., 2017; Glomb et al., 2018; Grady and Garrett, 2018; Iliff et al., 2013; Iliff et al., 2015; Martin et al., 2012; Nedergaard, 2013; Plog and Nedergaard, 2018]. The brain clearance driven by physiological pulsations has recently been strongly linked to neurodegenerative diseases [Iliff et al., 2012; Iliff et al., 2013; Iliff et al., 2014; Iliff et al., 2015;
Kiviniemi et al., 2016; Kress et al., 2014; de Leon et al., 2017; Louveau et al., 2016; Peng et al., 2016; Plog et al., 2015; Snyder et al., 2015; Tarasoff-Conway et al., 2015. The disease process may also alter the physiological noise structure or variability of the BOLD signal in the way it alters the low-frequency connectivity. There may be yet unknown physiological factors that have been overlooked in prior rs-fMRI data.

The temporal signal-to-noise ratio (tSNR) has been used to measure BOLD signal stability [Triantafyllou et al., 2005]. The inverse of tSNR, i.e., the temporal coefficient of variation of the BOLD signal (CV_{BOLD}), is a similar quality assurance metric that also enables the detection of subtle artifacts from the fMRI data [Tuovinen et al., 2017]. Recently, CV_{BOLD} has been used to analyze changes in noise characteristics of BOLD data [Jahanian et al., 2014]. Using a similar approach, increased physiological fluctuations in white matter (WM) have been detected in AD [Makedonov et al., 2016] and small vessel disease [Makedonov et al., 2013]. CV_{BOLD} correlates with cerebral blood volume and cerebral blood flow measured using dynamic susceptibility contrast MRI in patients with acute ischemic stroke [Khalil et al., 2017].

Based on previous findings of abnormal noise characteristics of the BOLD data, it was hypothesized that the noise structure of the BOLD signal measured using CV_{BOLD} is altered in AD and bvFTD patients in specific ways. AD and bvFTD patients as well as healthy controls were imaged with a 1.5 T setup from a local institute. Results of AD patients were further verified with 3 T data from the Alzheimer’s disease neuroimaging initiative (ADNI) repository. Effect of motion and atrophy was evaluated.

Materials and Methods

Participants

The ethic committee of the Oulu University Hospital approved the study. Each participating site’s institutional review board approved the research protocols. Written informed consent was obtained from all participants or their legal guardians according to the Declaration of Helsinki.
The study sample consisted of 17 AD patients, 18 bvFTD patients and 24 control subjects. The patients were examined at Oulu University Hospital at the Memory Outpatient Clinic of the Department of Neurology. They all underwent a thorough neurological and neuropsychological examination, screening laboratory tests and brain MRI that are routine in the clinic. All patients in the AD group met the NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association) criteria for probable AD [McKhann et al., 1984]. Cerebrospinal fluid (CSF) AD biomarkers supported the diagnosis in all the cases with available results (n=12).

The bvFTD patients were clinically diagnosed according to the Neary criteria [Neary et al., 1998; Rascovsky et al., 2011]. Patients with progressive aphasia or semantic dementia phenotypes were excluded from the study. DNA samples were available for ten patients, and the C9ORF72 repeat expansion was found in seven of them [Renton et al., 2011]. Mutations in progranulin or microtubule-associated protein tau genes were not found in any of the genetically tested bvFTD patients.

The control subjects were interviewed, and Mini-Mental State Examination (MMSE) and Beck’s Depression Inventory (BDI) were performed. No psychiatric or neurological disorders or medications affecting the central nervous system were allowed in the control group. Structural MRIs were interpreted as normal by clinical neuroradiologist.

The fMRI scan was performed within six months of the examination. The patients were allowed to continue their ongoing medications. Functional connectivity findings have been previously reported [Tuovinen et al., 2017]. These participants passed strict quality control prerequisites using methods published in that article.

To verify the main results from local institute data a reference dataset was obtained for AD and control groups. Data used in the preparation of this article were obtained from the ADNI database (http://adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by
Principal Investigator, Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial MRI, positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early AD. For up-to-date information, see http://www.adni-info.org.

ADNI-2 participants with both resting-state fMRI and preprocessed anatomical scans within the first year of participation in the study were selected to minimize potential retention bias from repeat scans. Participants were included if they were between 55 and 82 years old, spoke English or Spanish as their first language, and had completed at least six years of schooling. The diagnostic classification was made by ADNI investigators using established criteria [McKhann et al., 1984]. Participants in the AD cohort fulfilled the NINCDS-ADRDA criteria for probable AD. Control subjects had MMSE scores between 24 and 30 and no significant memory concerns.

Image Acquisition

Local Institute Data (1.5 T)

The subjects were imaged with a GE Signa HDx 1.5 T whole-body system with an eight-channel receiver coil. Subjects were given earplugs to reduce noise, and soft pads were fitted over the ears to protect hearing and to minimize motion. During MRI scanning all the subjects received identical instructions: to simply rest and focus on a cross on an fMRI-dedicated screen, which they saw through the mirror system of the head coil.

Structural high-resolution T1-weighted 3D FSPGR BRAVO images were taken under the following conditions: repetition time (TR) 12.1 ms, echo time (TE) 5.2 ms, flip angle (FA) of 20°, slice thickness 1.0 mm, field of view (FOV) 24.0 cm, matrix size 256 x 256 (i.e., 1 mm³ cubic voxels).

Resting-state BOLD data were acquired using a conventional gradient recalled echo-planar images (EPI) sequence under the following conditions: TR of 1800 ms, TE of 40 ms, 202 volumes (6 min 4 s), FA of 90°, 28 oblique axial slices, slice thickness 4 mm, inter-slice space 0.4 mm, covering the whole brain, FOV 25.6 cm x 25.6 cm, matrix size 64 x 64. The first three volumes were excluded from the time series due to T1 relaxation effects.
ADNI Data (3 T)

MRI images were collected on Philips 3 T MRI systems (Philips, Amsterdam, The Netherlands) from a total of 13 sites using a standardized protocol (http://adni.loni.usc.edu).

Structural T1 images were acquired with a TE of 3 ms, TR of 7 ms, FA of 9°, slice thickness of 1.2 mm, and a matrix size of 256 x 256 x 170. Preprocessing of the structural T1 images involved bias field correction using a histogram peak-sharpening algorithm (N3) [Sled et al., 1998] and was done already for the datasets downloaded.

Functional EPI images were acquired with a TR of 3,000 ms, TE of 30 ms, 140 volumes (7 min), FA of 80°, slice thickness of 3.3 mm, and a matrix size of 64 x 64 x 48. The first three volumes were excluded from the time series due to T1 relaxation effects.

Data Preprocessing

The BOLD rs-fMRI data were preprocessed with a typical FSL pipeline (http://www.fmrib.ox.ac.uk/fsl, FSL 5.0.8) including: head motion correction (FSL 5.0.8 MCFLIRT, motion estimates were also used in evaluating motion differences between groups), brain extraction (f = 0.5 and g = 0), spatial smoothing (Gaussian kernel 5-mm full width at half maximum), and high-pass temporal filtering by using a cutoff of 100 seconds. Multi-resolution affine co-registration within FSL FLIRT software was used to co-register mean, non-smoothed fMRI volumes to 3D FSGR volumes of corresponding subjects, and to co-register anatomical volumes to the Montreal Neurological Institute’s (MNI152) standard space template.

CV^BOLD maps

CV was used as a metric for the variation of fluctuations in the BOLD signal. The same method has been used in a study by [Jahanian et al., 2014] and is similar to the method used by [Makedonov et al., 2013; Makedonov et al., 2016].

For each preprocessed 4D fMRI dataset, a CV^BOLD map was calculated voxel-wise:
where $X$ is voxel time series, $\sigma$ is standard deviation and $\mu$ is mean.

Calculations were done using Matlab (version R2014b). Representative maps from one AD patient, one bvFTD patient and one control subject, as well as the group mean $CV_{BOLD}$ maps, are shown in Fig. 1 for both local institute and ADNI data.

**Regions-of-Interest analysis based on anatomical templates**

ICBM152 nonlinear asymmetric 2009c [Fonov et al., 2009; Fonov et al., 2011] atlases (probabilistic map, thresholded to 50–100 %) were used as gray matter (GM), WM and CSF templates for the regions-of-interest (ROI) analysis. This approach was used in a study by [Jahanian et al., 2014] where they also showed that results are somewhat independent of the precise GM, WM and CSF segmentation strategy employed. From these ROIs, mean $CV_{BOLD}$ was calculated subject-wise.

**Voxel-level statistical analysis of $CV_{BOLD}$ maps**

Differences between study groups in the $CV_{BOLD}$ maps were statistically tested using permutation-based nonparametric testing incorporating threshold-free cluster enhancement (TFCE) implemented in the FSL randomise tool with 10,000 random permutations [Smith and Nichols, 2009]. Resulting statistical maps were thresholded at $p<0.05$, 0.005 and 0.0005. The effect of GM atrophy on the $CV_{BOLD}$ maps was also evaluated repeating the randomize analysis using the GM volume as a regressor. The resulting statistic maps were spatially correlated to the ones without a GM regressor using the fslcc tool from FSL.

**Effect of motion**

Motion estimates computed by the MCFLIRT algorithm in the preprocessing step was used to assess the effect of motion on the $CV_{BOLD}$ values. Subject-wise absolute displacement vectors (in mm) were extracted, which describes the amount of movement in all directions over the whole scan as a marker of gross motion. Also, relative displacement vectors were extracted, as a marker of motion between each EPI volume. Both vectors were also averaged across volumes to get mean values. Additionally,
maximum motion value and the number of peaks in the subject-wise motion data were calculated using max and findpeak functions implemented in Matlab R2014b.

A univariate linear model analysis of covariance (ANCOVA) was conducted to determine a statistically significant difference between different study groups on the mean $\text{CV}_{\text{BOLD}}$ values in different ROIs (GM, WM and CSF) controlling for motion parameters. This was performed by using SPSS for Windows statistical software (version 24.0; SPSS, Chicago, Illinois).

Furthermore, the effect of removal of residual motion was assessed using the additional preprocessing step of spike removal from the time-series with the AFNI 3dDespike tool using default threshold settings. After 3dDespike, the $\text{CV}_{\text{BOLD}}$ maps were calculated and tissue-template-based mean $\text{CV}_{\text{BOLD}}$ values were compared to the ones calculated without despiking.

**Effect of gray matter atrophy**

Structural data were analyzed with FSL-VBM, a voxel-based morphometry-style analysis [Ashburner and Friston, 2000; Good et al., 2001]. Structural images were brain-extracted using BET [Smith, 2002]. This procedure was verified with visual inspection of the extraction results. Tissue-type segmentation into GM, WM and CSF was carried out using FAST4 (55). The resulting GM partial volume images were then aligned to the Montreal Neurological Institute’s (MNI152) standard structural space template using the affine registration tool FLIRT [Jenkinson et al., 2002; Jenkinson and Smith, 2001], followed optionally by nonlinear registration using FNIRT (www.fmrib.ox.ac.uk/analysis/techrep), which uses a b-spline representation of the registration warp field [Rueckert et al., 1999].

To analyze the between-group differences on GM atrophy patterns, these resulting images were averaged to create a study-specific template, to which the native GM images were then nonlinearly re-registered. The registered partial volume images were then modulated to correct for local expansion or contraction by dividing by the Jacobian of the warp field. The modulated segmented images were then smoothed with an isotropic Gaussian kernel with a sigma of 4 mm. Finally, GM differences between different study groups were statistically tested using permutation-based nonparametric testing.
incorporating TFCE implemented in the FSL randomise tool with 10,000 random permutations [Smith and Nichols, 2009]. Resulting statistical maps were thresholded at p<0.05 (TFCE-corrected for familywise errors).

To analyze the effect of GM atrophy on CV$_{\text{BOLD}}$ values GM volume in voxels was correlated subjectwise with mean CV$_{\text{BOLD}}$ values (within GM, WM and CSF) using Spearman’s rank correlation coefficient. Scatter plots were used to visualize the results. The effect of GM atrophy was also evaluated repeating the FSL randomise analysis but using this time the GM volume as a regressor. The resulting statistic maps were spatially correlated to the ones without GM regressor using fscc tool from FSL.

Receiver operating characteristic curves

We plotted receiver operating characteristic (ROC) curves to evaluate whether CV$_{\text{BOLD}}$ could be used to separate healthy controls from patients with either AD or bvFTD, or patient groups from each other. The mean CV$_{\text{BOLD}}$ was calculated using different ROIs: GM, WM, CSF (Fig. 2) and disease-specific templates (Fig. 3A). Area under the curve (AUC) was calculated as a measure of classification accuracy. The bootstrap approach was used to estimate the 95% confidence interval of AUC in SPSS v24.

Statistical Analysis

Statistical analyses were performed with the SPSS and Matlab software, and p values of less than 0.05 were considered to indicate a significant difference for all analyses. Between-group differences were assessed using Kruskal-Wallis, two-tailed t and X$^2$ tests, as appropriate. Subject-wise mean motion and GM volume values were correlated with the mean CV$_{\text{BOLD}}$ values using Spearman’s rank correlation coefficient.
Results

Characteristics of Participants

A total of 64 healthy controls, 47 AD and 18 bvFTD patients were eligible for analysis. Demographics and clinical data are summarized in Table 1 for the local institute and in Table 2 for the ADNI data.

CV_BOLD is elevated in both AD and bvFTD

Both AD and bvFTD patients showed higher CV_BOLD values than the controls based on visual inspection of the CV_BOLD maps. The group mean and examples of single-subject CV_BOLD maps are shown in Fig. 1.

To analyze this further, template-based ROI-analysis was conducted using ICBM152 tissue-template for WM, GM and CSF (Fig. 2). The CV_BOLD values on average were higher in both patient groups than in the control group (p-values ranging from 0.008 to 0.00001). This difference was confirmed using data from the ADNI study. The lowest CV_BOLD values were detected in the WM in all of the study groups. In the bvFTD group, mean CV_BOLD values were higher in WM and GM compared to both AD and the control group (Fig. 2). In the AD group, the mean CV_BOLD values were higher in the CSF compared to bvFTD and control group. However, the difference between bvFTD and AD groups in the large-scale ROI-analysis did not reach statistical significance (p=0.27).

The CV_BOLD demonstrates disease-specific changes

More-detailed voxel-level differences of CV_BOLD values between study groups were analyzed using permutation-based nonparametric testing incorporating TFCE with 10,000 random permutations. This revealed distinct differences between the patient and control groups. In the AD group, significantly higher CV_BOLD values compared to control group were located closer to the center in periventricular WM; in GM higher CV_BOLD values are located in the parietal, occipital and posterior part of frontal lobes as well as in frontal pole. In the bvFTD group differences extend more to external parts of the WM and towards the frontal and temporal lobes as well as the middle occipital gyri. There are also higher CV_BOLD values in the cerebellum near the 4th ventricle in both diseases. In AD higher CV_BOLD
values located more towards the horizontal fissure in posterior lobe. In order to pinpoint the most significant changes, the most statistically significant differences are illustrated with $p < 0.005$ and $p < 0.0005$ in Fig. 3 and in supplementary Fig. S1.

Statistically significant ($p < 0.005$) voxel-wise differences between AD patients and controls showed increased CV$_\text{BOLD}$ accumulated in a circular area around the CSF ventricles centered on WM. The increased CV$_\text{BOLD}$ values are found symmetrically in corpus callosum, thalamus, putamen, sagittal stratum, insula and also amygdala and anterior hippocampi areas as well as cerebellum. In the GM increased CV$_\text{BOLD}$ are found in Broca’s areas, somatosensory, supplementary and sensorimotor SM1 cortices, paracingulate gyri, and also in visual V1–V3 cortices. Notably, there was no statistically significant difference between AD and control group in the parts of the DMN (posterior cingulate, angular and medial prefrontal gyri). The spatial localizations of the statistically significant changes in CV$_\text{BOLD}$ values were markedly similar to the results of the ADNI data (Fig. 4).

The most prominent changes in bvFTD patients showed increased CV$_\text{BOLD}$ values more towards the frontal areas and lateral periventricular structures, and towards the temporal pole, premotor cortex and temporal fusiform cortex, and also in visual areas V3–V5 in lateral occipital cortex. Bilateral amygdala, putamen, insula, hippocampus, and areas in the cerebellum showed also higher CV$_\text{BOLD}$ values (Fig. 3).

The statistically significant differences between the AD and bvFTD (bvFTD$>$AD) patients on voxel-level CV$_\text{BOLD}$ were located bilaterally in anterior part of the frontal lobe (Fig. 3C).

The supplementary Tables S1–3 show the most significant group difference clusters and their anatomical labeling in the local institute data.

CV$_\text{BOLD}$ alterations are not explained by head motion or gray matter atrophy

There were no significant differences in the absolute or relative head motion parameters between any of the study groups in the local institute data (Fig. 5). In the ADNI dataset, the AD patients moved more before the motion correction (absolute: 0.20 mm for the control group and 0.30 mm for the AD
group, p=0.03; relative: control 0.15 mm and AD 0.21 mm, p=0.02). Head motion did not exceed half a voxel size.

Mean CV\textsubscript{BOLD} values did correlate to motion (Fig. 5A, correlation coefficient R ranging from 0.22 to 0.50). However, there is still a highly statistically significant effect of study group on the mean CV\textsubscript{BOLD} values after controlling for motion parameters, c.f. Table 3 (ANCOVA).

The number of peaks in the motion signal was also analyzed as markers of sudden head movement. No statistically significant differences were found between groups and there was no correlation to the CV\textsubscript{BOLD} values (data not shown, R ranging from -0.12 to 0.22, p>0.05 [0.17 to 0.45]).

We further verified the effects of motion by performing scrubbing of residual motion spikes (AFNI 3dDespike) and repeated the analysis of CV\textsubscript{BOLD} group differences. The results were not affected by despiking, and there was no significant difference between mean CV\textsubscript{BOLD} values calculated before and after 3dDespike (p>0.05 [0.68 – 0.98]).

The effect of GM atrophy on CV\textsubscript{BOLD} values was analyzed using the local institute dataset (Fig. 6). There was no correlation between the mean CV\textsubscript{BOLD} values and volume of GM (R=-0.01, p=0.91). The use of GM maps as a regressor in voxel-level analysis implementing FSL randomise resulted statistical maps that were 99 % the same as those without a regressor (spatial correlation coefficient R=0.99).

The accuracy of separating controls from patients with CV\textsubscript{BOLD}

The mean CV\textsubscript{BOLD} calculated from the disease-specific templates showed excellent diagnostic accuracy. Both AD and bvFTD can be differentiated from the controls in local data with 0.96 ROC AUC values. The method also enables differentiation between AD and bvFTD, AUC being 0.806 (Fig. 7, Table 4).

Discussion

The goal of this study was to investigate if physiological signal contributions of BOLD data measured using CV\textsubscript{BOLD} are altered in different types of dementia. We found that CV\textsubscript{BOLD} is markedly increased in both AD and bvFTD compared to age-matched controls (p<0.0005), and that the CV\textsubscript{BOLD} changes
are motion and GM atrophy independent and therefore presumably intrinsic physiological changes. Localizations of the CVBOLD alterations are somewhat disease-specific. However in both diseases, the most profound changes in the CVBOLD involve areas surrounding CSF, extending to WM, basal ganglia and multiple cortical structures. Suiting the disease pathology of the bvFTD, the most significant differences in CVBOLD comparison to AD were detected in frontolateral GM areas. Mean CVBOLD in the disease-specific templates was able to discern AD patients from controls with the receiver operating characteristic AUC values of 0.963 and bvFTD patients from controls with an AUC value of 0.958. The AD and bvFTD groups were separated from each other with an AUC value of 0.806.

Garrett et al. has suggested that it would be beneficial to broaden the analysis of BOLD signal to variability, as it seems to be more than just noise [Garrett et al., 2010]. BOLD signal variability has been measured with standard deviation of BOLD signal (SDBOLD) [McIntosh et al., 2010; Wang et al., 2008]. SDBOLD has been found to reflect brain status, and that is also related to aging, pathology, cognitive skills and AD [Garrett et al., 2010; Garrett et al., 2011; Garrett et al., 2013; Garrett et al., 2015; Grady and Garrett, 2014; Grady and Garrett, 2018; Guitart-Masip et al., 2016; Scarapicchia et al., 2018]. Recently, CVBOLD has been used to analyze physiological noise characteristics of BOLD data [Jahanian et al., 2014]. CVBOLD has been shown to correlate with cerebral blood volume and cerebral blood flow [Khalil et al., 2017]. The theoretical advantage of CVbold over SDbold is that any intensity level changes are normalized to the average BOLD signal level of the voxel minimizing the effects of local things like susceptibility alterations. While BOLD signal has conventionally been related to GM, recent studies have shown increasing evidence of WM contribution to BOLD signal, as well as that there are disease-related changes in it [Ding et al., 2018; Gawryluk et al., 2014; Özbay et al., 2018; Peer et al., 2017]. Using a similar approach as CVBOLD Makedonov et al. has shown increased physiological fluctuations in WM in AD [Makedonov et al., 2016] and in small vessel disease [Makedonov et al., 2013]. Makedonov et al. has suggested that the BOLD signal variation reflects end-arteriole intracranial pulsatility effects [Makedonov et al., 2013].

AD is usually been considered as a GM disease due to the distribution of hallmark pathological changes such as abnormal extracellular aggregates of amyloid-beta (Aβ) protein and intracellular
neurofibrillary tangles of hyperphosphorylated tau protein [Selkoe, 1991; Ryan et al., 2015]. However, the pathogenesis of AD is still controversial. AD is also linked to loss of synapsis and myelin, mitochondrial dysfunction, oxidative stress, metabolic disorders, neuroinflammation and loss of cholinergic and other neurons [Holtzman et al., 2011; Audano et al., 2018; Bartzokis, 2011; Mark et al., 2015; Olsson et al., 2016; Tracy and Gan, 2018; Wang et al., 2016]. Patients with clinically diagnosed AD have commonly mixed AD and cerebrovascular disease pathology, and there has been much interest in the interactions between these diseases [Toledo et al., 2013]. The cardiovascular and respiratory pulsations drive the glymphatic clearance of the brain. Glymphatic failure has been strongly linked to neurodegenerative diseases [Iliff et al., 2012; Iliff et al., 2013; Iliff et al., 2014; Iliff et al., 2015; Kiviniemi et al., 2016; Kress et al., 2014; de Leon et al., 2017; Louveau et al., 2016; Peng et al., 2016; Plog et al., 2015; Snyder et al., 2015; Tarasoff-Conway et al., 2015]. B-amyloid has been found to increase in the periventricular WM already after one night sleep deprivation, which suggests that absence of nighttime glymphatic brain clearance surge may predispose to amyloid deposition and neuronal degeneration [Shokri-Kojori et al., 2018; Xie et al., 2013].

Cerebral small vessel disease is increasingly linked to cognitive decline and dementia [Bos et al., 2018]. On T2-weighted MRI, white matter disease (WMD) is represented as white matter hyperintensities (WMH), which are thought to reflect demyelination and axonal loss. WMH is a good predictor of AD incidence and early AD patients with micro- and macro-structural abnormalities in the white matter have higher risk of disease progression [Brickman et al., 2012; Brickman, 2013; Brickman et al., 2015; Sjöbeck et al., 2006; Tosto et al., 2014]. Magnetic susceptibility differences has been associated with tau pathology and increased staining for reactive microglia and astrocytes [Acosta-Cabronero et al., 2013; O’Callaghan et al., 2017].

In the present study, analysis of $CV_{BOLD}$ was not limited to WM as in previous study by [Makedonov et al., 2016]. However, $CV_{BOLD}$ was altered in AD most dominantly in the periventricular WM structures like corpus callosum. A decrease of vessel density in the periventricular region has been observed in AD [Brown et al., 2009]. Demyelinated lesions tend to distribute within the areas with relatively low cerebral blood flow, which are usually found in profound, periventricular WM. Our
results add further proof into the vascular abnormalities by showing changes in CV$_{BOLD}$ within the WM.

We also analyzed CV$_{BOLD}$ in different type of dementia (bvFTD). The neuropathology associated with bvFTD is heterogeneous, and at the moment there is no clear relationship between the clinical phenotype and the underlying pathogenesis. One of the most consistent pathological finding of bvFTD is the relatively selective atrophy of the frontal and temporal lobes. In most cases post-mortem immunohistopathology shows abnormal protein inclusions in neural and glial cells. Based on immunohistochemical staining there are multiple subtypes of bvFTD (major subtypes being tau and TDP) [Mackenzie et al., 2010]. bvFTD has been found to be associated with progressive degeneration of the SLN resting-state network [Lee et al., 2014; Seeley et al., 2009; Seeley et al., 2012]. SLN is a resting-state network that includes the anterior cingulate and frontoinsular cortex, amygdala, striatum, and medial thalamus. These region bridges the frontal lobes and limbic system, and it has been proposed to represent the emotional significance of internal and external stimuli and coordinate contextualized viscero-autonomic, cognitive, and behavioural responses [Lee et al., 2014; Seeley et al., 2007; Whitwell and Josephs, 2012]. The other resting-state networks have received much less interest, and there have been more controversies between results [Farb et al., 2013; Filippi et al., 2013; Hafkemeijer et al., 2012; Rytty et al., 2013; Tuovinen et al., 2017].

In areas that are part of the SLN, CV$_{BOLD}$ is higher in bvFTD, compared to control group. Interestingly, the regions of the DMN were not found to have higher CV$_{BOLD}$ values in the AD group. Recent study showed that bvFTD patients displayed more fixations to the eyes of the emotional faces, compared to controls [Hutchings et al., 2018]. Regions associated with fixations to the eyes included the left inferior frontal gyrus, right cerebellum and middle temporal gyrus; in this study these areas were found to have higher CV$_{BOLD}$ values. Both of the diseases seem to affect the CV$_{BOLD}$ measured from the cerebellum. Cerebellar atrophy have been found in both AD and bvFTD [Gellersen et al., 2017].

In the present study the significant difference between the AD and bvFTD was shown to be in bilateral frontal poles. The known neuropsychological differences between AD and bvFTD can be in part explained by the CV$_{BOLD}$ differences between the conditions in the frontopolar areas. These areas are
known have a role in resolving indeterminate relations in un-certain situations and intensity of emotions [Goel et al., 2009]. Left ventral prefrontal cortex is involved in active and strategic operation of the mnemonic representation and retrieval success for words [Iidaka et al., 2000]. Study by Wong et al. contrasted prefrontal cortex atrophy with episodic memory dysfunction in AD and bvFTD [Wong et al., 2014]. Episodic memory deficits are underpinned by divergent prefrontal mechanisms: left side frontal pole for AD and right side for bvFTD, similar to our results. Our results indicate that the most marked alterations in bvFTD occur in the right lateral areas of frontal poles with increased CV BOLD. A study comparing AD and bvFTD revealed non-atrophy related perfusion deficits in frontal areas in accordance with our results [Du et al., 2006].

When compared to bvFTD, CV BOLD changes in AD occur more on the basal, periventricular areas where cardiovascular pulsations dominate in physiological studies [Kiviniemi et al., 2016]. The bvFTD changes are occurring more towards the frontal cortical edges of the brain, which was recently shown to be connected to respiratory brain pulsations of the glymphatic system [Kiviniemi et al., 2016]. Interestingly, arterial hypertension and other vascular risk factors are known risk factors for AD, but not for bvFTD [Baborie et al., 2011; Baborie et al., 2012; De Reuck, 2012; De Reuck et al., 2012a; De Reuck et al., 2012b; Snyder et al., 2015].

The changes in CV BOLD in present study are not explained by difference in age, gender, motion or GM atrophy. There were no statistically significant differences in age, gender or motion parameters between different study groups in the local institute data. As expected, there was a positive correlation with CV BOLD values and motion parameters in all groups alike. However, the patient groups had increased CV BOLD values with the same amount of motion. The effect of motion was also evaluated using an ANCOVA, where differences between groups prevailed as statistically significant after motion parameters were used as covariates. Also, the effect of sudden motion “peaks” was evaluated and this did not explain the group differences in the CV BOLD values. Furthermore, removal of residual motion spikes by despiking had no significant effect on the CV BOLD results. GM atrophy patterns were in line with previous literature [Du et al., 2006; Hartikainen et al., 2012; Tartaglia et al., 2011;
Whitwell and Josephs, 2012]. CV$_{BOLD}$ values and GM volume had no correlation. The use of GM maps, as a regressor in voxel-level analysis did not affect the results.

The previous literature and our results suggest that the changes in CV$_{BOLD}$ are not only due to motion, but rather the changes may be due to yet unknown intrinsic properties of the degenerated brain tissue. ADNI data may be more sensitive to hemodynamically coupled BOLD signal changes due to the higher magnetic field strength (3 T) than in local institute data (1.5 T) [van der Zwaag et al., 2009]. However, the increased motion in ADNI data may partly mask the CV$_{BOLD}$ differences between groups. Furthermore, the local institute data is also nearly two times faster in sampling rate (TR 1.8 vs. 3 seconds). This may partially increase the sensitivity to physiological pulsation noise due to somewhat reduced aliasing with faster TR [Kiviniemi et al., 2005; Smith et al., 2007]. Furthermore, as the differences predominate in CSF and WM structures, the source of T2*-weighted GRE EPI signal's CV$_{BOLD}$ alterations in AD and bvFTD are most likely due to physiological brain pulsations rather than secondary hemodynamic changes to neuronal activity. Both local institute and ADNI data still suffer from cardiorespiratory signal aliasing and cannot pinpoint the physiological origin of the changes in CV$_{BOLD}$. In future studies, one could investigate the source of altered CV$_{BOLD}$ in neurodegenerative diseases with ultra-fast, critically sampled multimodal neuroimaging data. Such data can differentiate cardiorespiratory pulsations and bring forth a mechanistic explanation to the detected alteration in CV$_{BOLD}$.

These results should be verified with larger sample sizes and the relationship between CV$_{BOLD}$ and clinical parameters, including precise co-analysis of structural images, should be evaluated. Previous studies have employed a number of different variations of ‘BOLD variability’ measures, with different methodologies used by different groups. There have not been comparative studies of different methodologies in this field. However, these results are inline with previous literature and together with previous studies, our findings suggest that analysis of physiological pulsations using BOLD signal variability may provide useful information in the context of neurodegenerative diseases.
Conclusions

There are disease specific alterations in CV_{BOLD}. In AD these alterations was confirmed in two different datasets and in different imaging setups (1.5 T and 3 T). CV_{BOLD} changes are motion and GM atrophy independent and therefore presumably intrinsic physiological changes. Together with previous studies, our findings suggest that analysis of physiological pulsations may provide useful information in the context of neurodegenerative diseases.

Acknowledgements

Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer’s Association; Alzheimer’s Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer’s Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California.
Funding

This work was supported by grants from Academy of Finland grants 117111 and 123772 (VK), Finnish Medical Foundation (VK, AMR, TT), Finnish Neurological Foundation, JAES-Foundation (VK), KEVO grants from Oulu University hospital (VK, AMR), National Graduate School of Clinical Investigation (RR), Finnish Brain Foundation (RR), Epilepsy Research Foundation (JK), Finnish Cultural Foundation, North Ostrobothnia Regional Fund (JK), Orion Research Foundation (TT, JK), Tauno Tönnning Foundation (JK)
Acosta-Cabronero J, Williams GB, Cardenas-Blanco A, Arnold RJ, Lupson V, Nestor PJ (2013): In Vivo Quantitative Susceptibility Mapping (QSM) in Alzheimer’s Disease. Ed. James R. Connor. PLoS ONE 8:e81093.

Agosta F, Pievani M, Geroldi C, Copetti M, Frisoni GB, Filippi M (2012): Resting state fMRI in Alzheimer’s disease: beyond the default mode network. Neurobiology of Aging 33:1564–1578.

Ashburner J, Friston KJ (2000): Voxel-Based Morphometry—The Methods. NeuroImage 11:805–821.

Aspelund A, Antila S, Proulx ST, Karlsen TV, Karaman S, Detmar M, Wiig H, Alitalo K (2015): A dural lymphatic vascular system that drains brain interstitial fluid and macromolecules. The Journal of Experimental Medicine 212:991–999.

Audano M, Schneider A, Mitro N (2018): Mitochondria, lysosomes and dysfunction: their meaning in neurodegeneration. Journal of Neurochemistry. http://doi.wiley.com/10.1111/jnc.14471.

Baborie A, Griffiths TD, Jaros E, Momeni P, McKeith IG, Burn DJ, Keir G, Larner AJ, Mann DM, Perry R (2012): Frontotemporal dementia in elderly individuals. Arch Neurol 69:1052–1060.

Baborie A, Griffiths TD, Jaros E, McKeith IG, Burn DJ, Richardson A, Ferrari R, Moreno J, Momeni P, Duplessis D, Pal P, Rollinson S, Pickering-Brown S, Thompson JC, Neary D, Snowden JS, Perry R, Mann DMA (2011): Pathological correlates of frontotemporal lobar degeneration in the elderly. Acta Neuropathologica 121:365–371.

Bartzokis G (2011): Alzheimer’s disease as homeostatic responses to age-related myelin
breakdown. Neurobiology of Aging 32:1341–1371.

Binnewijzend MAA, Schoonheim MM, Sanz-Arigita E, Wink AM, van der Flier WM, Tolboom N, Adriaanse SM, Damoiseaux JS, Scheltens P, van Berckel BNM, Barkhof F (2012): Resting-state fMRI changes in Alzheimer’s disease and mild cognitive impairment. Neurobiology of Aging 33:2018–2028.

Birn RM, Cornejo MD, Molloy EK, Patriat R, Meier TB, Kirk GR, Nair VA, Meyerand ME, Prabhakaran V (2014): The influence of physiological noise correction on test-retest reliability of resting-state functional connectivity. Brain Connect 4:511–522.

Birn RM, Diamond JB, Smith MA, Bandettini PA (2006): Separating respiratory-variation-related fluctuations from neuronal-activity-related fluctuations in fMRI. Neuroimage 31:1536–1548.

Bos D, Wolters FJ, Darweesh SKL, Vernooij MW, de Wolf F, Ikram MA, Hofman A (2018): Cerebral small vessel disease and the risk of dementia: A systematic review and meta-analysis of population-based evidence. Alzheimer’s & Dementia. https://linkinghub.elsevier.com/retrieve/pii/S1552526018301298.

Brickman AM (2013): Contemplating Alzheimer’s disease and the contribution of white matter hyperintensities. Curr Neurol Neurosci Rep 13:415.

Brickman AM, Provenzano FA, Muraskin J, Manly JJ, Blum S, Apa Z, Stern Y, Brown TR, Luchsinger JA, Mayeux R (2012): Regional white matter hyperintensity volume, not hippocampal atrophy, predicts incident Alzheimer disease in the community. Arch Neurol 69:1621–1627.

Brickman AM, Zahodne LB, Guzman VA, Narkhede A, Meier IB, Griffith EY, Provenzano FA, Schupf N, Manly JJ, Stern Y, Luchsinger JA, Mayeux R (2015): Reconsidering
Tuovinen et al.

harbingers of dementia: progression of parietal lobe white matter hyperintensities predicts Alzheimer’s disease incidence. Neurobiol Aging 36:27–32.

Brown WR, Moody DM, Thore CR, Anstrom JA, Challa VR (2009): Microvascular changes in the white mater in dementia. Journal of the Neurological Sciences 283:28–31.

Brun A, Englund E (1986): A white matter disorder in dementia of the Alzheimer type: a pathoanatomical study. Ann Neurol 19:253–262.

Buxton RB (2012): Dynamic models of BOLD contrast. Neuroimage 62:953–961.

Buxton RB, Griffeth VEM, Simon AB, Moradi F (2014): Variability of the coupling of blood flow and oxygen metabolism responses in the brain: a problem for interpreting BOLD studies but potentially a new window on the underlying neural activity. Frontiers in Neuroscience 8. http://journal.frontiersin.org/article/10.3389/fnins.2014.00139/abstract.

Chang C, Cunningham JP, Glover GH (2009): Influence of heart rate on the BOLD signal: the cardiac response function. Neuroimage 44:857–869.

Chang C, Glover GH (2010): Time–frequency dynamics of resting-state brain connectivity measured with fMRI. NeuroImage 50:81–98.

De Reuck J, Deramecourt V, Cordonnier C, Auger F, Durieux N, Bordet R, Maurage CA, Leys D, Pasquier F (2012a): Detection of microbleeds in post-mortem brains of patients with frontotemporal lobar degeneration: a 7.0-Tesla magnetic resonance imaging study with neuropathological correlates. European Journal of Neurology 19:1355–1360.

De Reuck JL (2012): The significance of small cerebral bleeds in neurodegenerative dementia syndromes. Aging Dis 3:307–312.

De Reuck JL, Deramecourt V, Cordonnier C, Leys D, Pasquier F, Maurage CA (2012b):
Cerebrovascular Lesions in Patients with Frontotemporal Lobar Degeneration: A Neuropathological Study. Neurodegenerative Diseases 9:170–175.

Ding Z, Huang Y, Bailey SK, Gao Y, Cutting LE, Rogers BP, Newton AT, Gore JC (2018): Detection of synchronous brain activity in white matter tracts at rest and under functional loading. Proc Natl Acad Sci USA 115:595–600.

Dreha-Kulaczewski S, Joseph AA, Merboldt K-D, Ludwig H-C, Gartner J, Frahm J (2015): Inspiration Is the Major Regulator of Human CSF Flow. Journal of Neuroscience 35:2485–2491.

Du AT, Jahng GH, Hayasaka S, Kramer JH, Rosen HJ, Gorno-Tempini ML, Rankin KP, Miller BL, Weiner MW, Schuff N (2006): Hypoperfusion in frontotemporal dementia and Alzheimer disease by arterial spin labeling MRI. Neurology 67:1215–1220.

Erdő F, Denes L, de Lange E (2017): Age-associated physiological and pathological changes at the blood–brain barrier: A review. Journal of Cerebral Blood Flow & Metabolism 37:4–24.

Farb NAS, Grady CL, Strother S, Tang-Wai DF, Masellis M, Black S, Freedman M, Pollock BG, Campbell KL, Hasher L, Chow TW (2013): Abnormal network connectivity in frontotemporal dementia: Evidence for prefrontal isolation. Cortex 49:1856–1873.

Filippi M, Agosta F, Scola E, Canu E, Magnani G, Marcone A, Valsasina P, Caso F, Copetti M, Comi G, Cappa SF, Falini A (2013): Functional network connectivity in the behavioral variant of frontotemporal dementia. Cortex 49:2389–2401.

Fleisher AS, Podraza KM, Bangen KJ, Taylor C, Sherzai A, Sidhar K, Liu TT, Dale AM, Buxton RB (2009): Cerebral perfusion and oxygenation differences in Alzheimer’s disease risk. Neurobiology of Aging 30:1737–1748.

Fonov V, Evans AC, Botteron K, Almli CR, McKinstry RC, Collins DL (2011): Unbiased
average age-appropriate atlases for pediatric studies. NeuroImage 54:313–327.

Fonov V, Evans A, McKinstry R, Almli C, Collins D (2009): Unbiased nonlinear average age-appropriate brain templates from birth to adulthood. NeuroImage 47:S102.

Garrett DD, Kovacevic N, McIntosh AR, Grady CL (2010): Blood Oxygen Level-Dependent Signal Variability Is More than Just Noise. Journal of Neuroscience 30:4914–4921.

Garrett DD, Kovacevic N, McIntosh AR, Grady CL (2011): The Importance of Being Variable. Journal of Neuroscience 31:4496–4503.

Garrett DD, Lindenberger U, Hoge RD, Gauthier CJ (2017): Age differences in brain signal variability are robust to multiple vascular controls. Scientific Reports 7. http://www.nature.com/articles/s41598-017-09752-7.

Garrett DD, Nagel IE, Preuschhof C, Burzynska AZ, Marchner J, Wiegert S, Jungehülsing GJ, Nyberg L, Villringer A, Li S-C, Heekeren HR, Bäckman L, Lindenberger U (2015): Amphetamine modulates brain signal variability and working memory in younger and older adults. Proceedings of the National Academy of Sciences 112:7593–7598.

Garrett DD, Samanez-Larkin GR, MacDonald SWS, Lindenberger U, McIntosh AR, Grady CL (2013): Moment-to-moment brain signal variability: A next frontier in human brain mapping? Neuroscience & Biobehavioral Reviews 37:610–624.

Gawryluk JR, Mazerolle EL, D’Arcy RCN (2014): Does functional MRI detect activation in white matter? A review of emerging evidence, issues, and future directions. Front Neurosci 8:239.

Gellersen HM, Guo CC, O’Callaghan C, Tan RH, Sami S, Hornberger M (2017): Cerebellar atrophy in neurodegeneration—a meta-analysis. Journal of Neurology, Neurosurgery & Psychiatry 88:780–788.
Glomb K, Ponce-Alvarez A, Gilson M, Ritter P, Deco G (2018): Stereotypical modulations in dynamic functional connectivity explained by changes in BOLD variance. NeuroImage 171:40–54.

Goel V, Stollstorff M, Nakic M, Knutson K, Grafman J (2009): A role for right ventrolateral prefrontal cortex in reasoning about indeterminate relations. Neuropsychologia 47:2790–2797.

Good CD, Johnsrude IS, Ashburner J, Henson RNA, Friston KJ, Frackowiak RSJ (2001): A Voxel-Based Morphometric Study of Ageing in 465 Normal Adult Human Brains. NeuroImage 14:21–36.

Grady CL, Garrett DD (2014): Understanding variability in the BOLD signal and why it matters for aging. Brain Imaging and Behavior 8:274–283.

Grady CL, Garrett DD (2018): Brain signal variability is modulated as a function of internal and external demand in younger and older adults. NeuroImage 169:510–523.

Greicius MD, Srivastava G, Reiss AL, Menon V (2004): Default-mode network activity distinguishes Alzheimer’s disease from healthy aging: Evidence from functional MRI. Proceedings of the National Academy of Sciences 101:4637–4642.

Griffanti L, Dipasquale O, Laganà MM, Nemni R, Clerici M, Smith SM, Baselli G, Baglio F (2015): Effective artifact removal in resting state fMRI data improves detection of DMN functional connectivity alteration in Alzheimer’s disease. Frontiers in Human Neuroscience 9. http://journal.frontiersin.org/Article/10.3389/fnhum.2015.00449/abstract.

Guitart-Masip M, Salami A, Garrett D, Rieckmann A, Lindenberger U, Bäckman L (2016): BOLD Variability is Related to Dopaminergic Neurotransmission and Cognitive Aging. Cerebral Cortex 26:2074–2083.
Hafkemeijer A, van der Grond J, Rombouts SARB (2012): Imaging the default mode network in aging and dementia. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease 1822:431–441.

Hartikainen P, Räsänen J, Julkunen V, Niskanen E, Hallikainen M, Kivipelto M, Vanninen R, Remes AM, Soininen H (2012): Cortical thickness in frontotemporal dementia, mild cognitive impairment, and Alzheimer’s disease. J Alzheimers Dis 30:857–874.

Hoge RD, Atkinson J, Gill B, Crelier GR, Marrett S, Pike GB (1999): Investigation of BOLD signal dependence on cerebral blood flow and oxygen consumption: the deoxyhemoglobin dilution model. Magn Reson Med 42:849–863.

Holtzman DM, Goate A, Kelly J, Sperling R (2011): Mapping the road forward in Alzheimer’s disease. Sci Transl Med 3:114ps48.

Hutchings R, Palermo R, Bruggemann J, Hodges JR, Piguet O, Kumfor F (2018): Looking but not seeing: Increased eye fixations in behavioural-variant frontotemporal dementia. Cortex 103:71–81.

Iidaka T, Sadato N, Yamada H, Yonekura Y (2000): Functional asymmetry of human prefrontal cortex in verbal and non-verbal episodic memory as revealed by fMRI. Brain Res Cogn Brain Res 9:73–83.

Iliff JJ, Chen MJ, Plog BA, Zeppenfeld DM, Soltero M, Yang L, Singh I, Deane R, Nedergaard M (2014): Impairment of Glymphatic Pathway Function Promotes Tau Pathology after Traumatic Brain Injury. The Journal of Neuroscience 34:16180–16193.

Iliff JJ, Goldman SA, Nedergaard M (2015): Implications of the discovery of brain lymphatic pathways. The Lancet Neurology 14:977–979.

Iliff JJ, Wang M, Liao Y, Plogg BA, Peng W, Gundersen GA, Benveniste H, Vates GE,
Deane R, Goldman SA, Nagelhus EA, Nedergaard M (2012): A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β. Sci Transl Med 4:147ra111.

Iliff JJ, Wang M, Zeppenfeld DM, Venkataraman A, Plog BA, Liao Y, Deane R, Nedergaard M (2013): Cerebral arterial pulsation drives paravascular CSF-interstitial fluid exchange in the murine brain. J Neurosci 33:18190–18199.

Jahanian H, Ni WW, Christen T, Moseley ME, Tamura MK, Zaharchuk G (2014): Spontaneous BOLD Signal Fluctuations in Young Healthy Subjects and Elderly Patients with Chronic Kidney Disease. Ed. Yoko Hoshi. PLoS ONE 9:e92539.

Jenkinson M, Bannister P, Brady M, Smith S (2002): Improved Optimization for the Robust and Accurate Linear Registration and Motion Correction of Brain Images. NeuroImage 17:825–841.

Keilholz SD, Pan W-J, Billings J, Nezafati M, Shakil S (2017): Noise and non-neuronal contributions to the BOLD signal: applications to and insights from animal studies. NeuroImage 154:267–281.

Khalil AA, Ostwaldt A-C, Nierhaus T, Ganeshan R, Audebert HJ, Villringer K, Villringer A, Fiebach JB (2017): Relationship Between Changes in the Temporal Dynamics of the Blood-Oxygen-Level-Dependent Signal and Hypoperfusion in Acute Ischemic Stroke. Stroke 48:925–931.

Kiviniemi V, Ruohonen J, Tervonen O (2005): Separation of physiological very low frequency fluctuation from aliasing by switched sampling interval fMRI scans. Magn Reson
Kiviniemi V, Wang X, Korhonen V, Keinänen T, Tuovinen T, Autio J, LeVan P, Keilholz S, Zang Y-F, Hennig J, Nedergaard M (2016): Ultra-fast magnetic resonance encephalography of physiological brain activity - Glymphatic pulsation mechanisms? J Cereb Blood Flow Metab 36:1033–1045.

Kress BT, Iliff JJ, Xia M, Wang M, Wei HS, Zeppenfeld D, Xie L, Kang H, Xu Q, Liew JA, Plog BA, Ding F, Deane R, Nedergaard M (2014): Impairment of paravascular clearance pathways in the aging brain. Ann Neurol 76:845–861.

Lee SE, Khazenzon AM, Trujillo AJ, Guo CC, Yokoyama JS, Sha SJ, Takada LT, Karydas AM, Block NR, Coppola G, Pribadi M, Geschwind DH, Rademakers R, Fong JC, Weiner MW, Boxer AL, Kramer JH, Rosen HJ, Miller BL, Seeley WW (2014): Altered network connectivity in frontotemporal dementia with C9orf72 hexanucleotide repeat expansion. Brain 137:3047–3060.

de Leon MJ, Li Y, Okamura N, Tsui WH, Saint Louis LA, Glodzik L, Osorio RS, Fortea J, Butler T, Pirraglia E, Fossati S, Kim H-J, Carare RO, Nedergaard M, Benveniste H, Rusinek H (2017): CSF clearance in Alzheimer Disease measured with dynamic PET. J Nucl Med.

Li S-J, Li Z, Wu G, Zhang M-J, Franczak M, Antuono PG (2002): Alzheimer Disease: evaluation of a functional MR imaging index as a marker. Radiology 225:253–259.

Liu X, Chang C, Duyn JH (2013): Decomposition of spontaneous brain activity into distinct fMRI co-activation patterns. Frontiers in Systems Neuroscience 7. http://journal.frontiersin.org/Journal/10.3389/fnsys.2013.00101/full.

Louveau A, Da Mesquita S, Kipnis J (2016): Lymphatics in Neurological Disorders: A Neuro-Lympho-Vascular Component of Multiple Sclerosis and Alzheimer’s Disease? Neuron
Mackenzie IRA, Neumann M, Bigio EH, Cairns NJ, Alafuzoff I, Kril J, Kovacs GG, Ghetti B,
Halliday G, Holm IE, Ince PG, Kamphorst W, Revesz T, Rozemuller AJM, Kumar-Singh S,
Akiyama H, Baborie A, Spina S, Dickson DW, Trojanowski JQ, Mann DMA (2010):
Nomenclature and nosology for neuropathologic subtypes of frontotemporal lobar
degeneration: an update. Acta Neuropathol 119:1–4.

Makedonov I, Black SE, MacIntosh BJ (2013): BOLD fMRI in the White Matter as a Marker
of Aging and Small Vessel Disease. Ed. Linda Chao. PLoS ONE 8:e67652.

Makedonov I, Chen JJ, Masellis M, MacIntosh BJ (2016): Physiological fluctuations in white
matter are increased in Alzheimer’s disease and correlate with neuroimaging and cognitive
biomarkers. Neurobiology of Aging 37:12–18.

Mark CI, Mazerolle EL, Chen JJ (2015): Metabolic and vascular origins of the BOLD effect:
Implications for imaging pathology and resting-state brain function. J Magn Reson Imaging
42:231–246.

Martin BA, Reymond P, Novy J, Balédent O, Stergiopulos N (2012): A coupled
hydrodynamic model of the cardiovascular and cerebrospinal fluid system. American Journal
of Physiology-Heart and Circulatory Physiology 302:H1492–H1509.

McIntosh AR, Kovacevic N, Lippe S, Garrett D, Grady C, Jirsa V (2010): The development
of a noisy brain. Arch Ital Biol 148:323–337.

McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM (1984): Clinical
diagnosis of Alzheimer’s disease: Report of the NINCDS-ADRDA Work Group* under the
auspices of Department of Health and Human Services Task Force on Alzheimer’s Disease.
Neurology 34:939–939.
Nedergaard M (2013): Garbage Truck of the Brain. Science 340:1529–1530.

O’Callaghan J, Holmes H, Powell N, Wells JA, Ismail O, Harrison IF, Siow B, Johnson R, Ahmed Z, Fisher A, Meftah S, O’Neill MJ, Murray TK, Collins EC, Shmueli K, Lythgoe MF (2017): Tissue magnetic susceptibility mapping as a marker of tau pathology in Alzheimer’s disease. NeuroImage 159:334–345.

Olsson B, Lautner R, Andreasson U, Öhrfelt A, Portelius E, Bjerke M, Hölttä M, Rosén C, Olsson C, Strobel G, Wu E, Dakin K, Petzold M, Blennow K, Zetterberg H (2016): CSF and blood biomarkers for the diagnosis of Alzheimer’s disease: a systematic review and meta-analysis. The Lancet Neurology 15:673–684.

Özbay PS, Chang C, Picchioni D, Mandelkow H, Moehlman TM, Chappel-Farley MG, van Gelderen P, de Zwart JA, Duyn JH (2018): Contribution of systemic vascular effects to fMRI activity in white matter. Neuroimage 176:541–549.

Peer M, Nitzan M, Bick AS, Levin N, Arzy S (2017): Evidence for Functional Networks within the Human Brain’s White Matter. The Journal of Neuroscience 37:6394–6407.

Peng W, Achariyar TM, Li B, Liao Y, Mestre H, Hitomi E, Regan S, Kasper T, Peng S, Ding F, Benveniste H, Nedergaard M, Deane R (2016): Suppression of glymphatic fluid transport in a mouse model of Alzheimer’s disease. Neurobiol Dis 93:215–225.

Plog BA, Dashnaw ML, Hitomi E, Peng W, Liao Y, Lou N, Deane R, Nedergaard M (2015): Biomarkers of traumatic injury are transported from brain to blood via the glymphatic system. J Neurosci 35:518–526.
Plog BA, Nedergaard M (2018): The Glymphatic System in Central Nervous System Health and Disease: Past, Present, and Future. Annual Review of Pathology: Mechanisms of Disease 13:379–394.

Rascovsky K, Hodges JR, Knopman D, Mendez MF, Kramer JH, Neuhaus J, van Swieten JC, Seelaar H, Dopper EGP, Onyike CU, Hillis AE, Josephs KA, Boeve BF, Kertesz A, Seeley WW, Rankin KP, Johnson JK, Gorno-Tempini M-L, Rosen H, Prioleau-Latham CE, Lee A, Kipps CM, Lillo P, Piguet O, Rohrer JD, Rossor MN, Warren JD, Fox NC, Galasko D, Salmon DP, Black SE, Mesulam M, Weintraub S, Dickerson BC, Diehl-Schmid J, Pasquier F, Deramecourt V, Lebert F, Pijnenburg Y, Chow TW, Manes F, Grafman J, Cappa SF, Freedman M, Grossman M, Miller BL (2011): Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain 134:2456–2477.

Renton AE, Majounie E, Waite A, Simón-Sánchez J, Rollinson S, Gibbs JR, Schymick JC, Laaksovirta H, van Swieten JC, Myllykangas L, Kalimo H, Paetau A, Abramzon Y, Remes AM, Kaganovich A, Scholz SW, Duckworth J, Ding J, Harmer DW, Hernandez DG, Johnson JO, Mok K, Ryten M, Trabzuni D, Guerreiro RJ, Orrell RW, Neal J, Murray A, Pearson J, Jansen IE, Sondervan D, Seelaar H, Blake D, Young K, Halliwell N, Callister JB, Toulson G, Richardson A, Gerhard A, Snowden J, Mann D, Neary D, Nalls MA, Peuralinna T, Jansson L, Isoviita V-M, Kaivorinne A-L, Hölttä-Vuori M, Ikonen E, Sulkava R, Benatar M, Wuu J, Chiò A, Restagno G, Borghero G, Sabatelli M, Heckerman D, Rogaeva E, Zinman L, Rothstein JD, Sendtner M, Drepper C, Eichler EE, Alkan C, Abdullaev Z, Pack SD, Dutra A, Pak E, Hardy J, Singleton A, Williams NM, Heutink P, Pickering-Brown S, Morris HR, Tienari PJ, Traynor BJ (2011): A Hexanucleotide Repeat Expansion in C9ORF72 Is the Cause of Chromosome 9p21-Linked ALS-FTD. Neuron 72:257–268.

Rueckert D, Sonoda LI, Hayes C, Hill DLG, Leach MO, Hawkes DJ (1999): Nonrigid registration using free-form deformations: application to breast MR images. IEEE
Transactions on Medical Imaging 18:712–721.

Ryan NS, Rossor MN, Fox NC (2015): Alzheimer’s disease in the 100 years since Alzheimer’s death. Brain 138:3816–3821.

Rytty R, Nikkinen J, Paavola L, Abou Elseoud A, Moilanen V, Visuri A, Tervonen O, Renton AE, Traynor BJ, Kiviniemi V, Remes AM (2013): GroupICA dual regression analysis of resting state networks in a behavioral variant of frontotemporal dementia. Frontiers in Human Neuroscience 7. http://journal.frontiersin.org/article/10.3389/fnhum.2013.00461/abstract.

Scarapicchia V, Mazerolle EL, Fisk JD, Ritchie LJ, Gawryluk JR (2018): Resting State BOLD Variability in Alzheimer’s Disease: A Marker of Cognitive Decline or Cerebrovascular Status? Frontiers in Aging Neuroscience 10. http://journal.frontiersin.org/article/10.3389/fnagi.2018.00039/full.

Seeley WW, Crawford RK, Zhou J, Miller BL, Greicius MD (2009): Neurodegenerative diseases target large-scale human brain networks. Neuron 62:42–52.

Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, Reiss AL, Greicius MD (2007): Dissociable intrinsic connectivity networks for salience processing and executive control. J Neurosci 27:2349–2356.

Seeley WW, Zhou J, Kim E-J (2012): Frontotemporal dementia: what can the behavioral variant teach us about human brain organization? Neuroscientist 18:373–385.

Selkoe DJ (1991): The molecular pathology of Alzheimer’s disease. Neuron 6:487–498.

Shmueli K, van Gelderen P, de Zwart JA, Horovitz SG, Fukunaga M, Jansma JM, Duyn JH (2007): Low-frequency fluctuations in the cardiac rate as a source of variance in the resting-state fMRI BOLD signal. Neuroimage 38:306–320.
Shokri-Kojori E, Wang G-J, Wiers CE, Demiral SB, Guo M, Kim SW, Lindgren E, Ramirez V, Zehra A, Freeman C, Miller G, Manza P, Srivastava T, De Santi S, Tomasi D, Benveniste H, Volkow ND (2018): β-Amyloid accumulation in the human brain after one night of sleep deprivation. Proc Natl Acad Sci USA 115:4483–4488.

Sjöbeck M, Haglund M, Englund E (2006): White matter mapping in Alzheimer’s disease: A neuropathological study. Neurobiology of Aging 27:673–680.

Sled JG, Zijdenbos AP, Evans AC (1998): A nonparametric method for automatic correction of intensity nonuniformity in MRI data. IEEE Trans Med Imaging 17:87–97.

Smith S, Jenkinson M, Beckmann C, Miller K, Woolrich M (2007): Meaningful design and contrast estimability in FMRI. Neuroimage 34:127–136.

Smith SM (2002): Fast robust automated brain extraction. Human Brain Mapping 17:143–155.

Smith SM, Nichols TE (2009): Threshold-free cluster enhancement: addressing problems of smoothing, threshold dependence and localisation in cluster inference. Neuroimage 44:83–98.

Snyder HM, Corriveau RA, Craft S, Faber JE, Greenberg SM, Knopman D, Lamb BT, Montine TJ, Nedergaard M, Schaffer CB, Schneider JA, Wellington C, Wilcock DM, Zipfel GJ, Zlokovic B, Bain LJ, Bosetti F, Galis ZS, Koroshetz W, Carrillo MC (2015): Vascular contributions to cognitive impairment and dementia including Alzheimer’s disease. Alzheimers Dement 11:710–717.

Tarasoff-Conway JM, Carare RO, Osorio RS, Glodzik L, Butler T, Fieremans E, Axel L, Rusinek H, Nicholson C, Zlokovic BV, Frangione B, Blennow K, Ménard J, Zetterberg H, Wisniewski T, de Leon MJ (2015): Clearance systems in the brain—implications for Alzheimer disease. Nature Reviews Neurology 11:457–470.
Tartaglia MC, Rosen HJ, Miller BL (2011): Neuroimaging in Dementia. Neurotherapeutics 8:82–92.

Toledo JB, Arnold SE, Raible K, Brettschneider J, Xie SX, Grossman M, Monsell SE, Kukull WA, Trojanowski JQ (2013): Contribution of cerebrovascular disease in autopsy confirmed neurodegenerative disease cases in the National Alzheimer’s Coordinating Centre. Brain 136:2697–2706.

Tosto G, Zimmerman ME, Carmichael OT, Brickman AM, Alzheimer’s Disease Neuroimaging Initiative (2014): Predicting aggressive decline in mild cognitive impairment: the importance of white matter hyperintensities. JAMA Neurol 71:872–877.

Tracy TE, Gan L (2018): Tau-mediated synaptic and neuronal dysfunction in neurodegenerative disease. Current Opinion in Neurobiology 51:134–138.

Triantafyllou C, Hoge RD, Krueger G, Wiggins CJ, Potthast A, Wiggins GC, Wald LL (2005): Comparison of physiological noise at 1.5 T, 3 T and 7 T and optimization of fMRI acquisition parameters. NeuroImage 26:243–250.

Tuovinen T, Rytty R, Moilanen V, Abou Elseoud A, Veijola J, Remes AM, Kiviniemi VJ (2017): The Effect of Gray Matter ICA and Coefficient of Variation Mapping of BOLD Data on the Detection of Functional Connectivity Changes in Alzheimer’s Disease and bvFTD. Frontiers in Human Neuroscience 10.

Wang HH, Menezes NM, Zhu MW, Ay H, Koroshetz WJ, Aronen HJ, Karonen JO, Liu Y, Nuutinen J, Wald LL, Sorensen AG (2008): Physiological noise in MR images: An indicator of the tissue response to ischemia? Journal of Magnetic Resonance Imaging 27:866–871.

Wang M, Norman JE, Srinivasan VJ, Rutledge JC (2016): Metabolic, inflammatory, and
microvascular determinants of white matter disease and cognitive decline. Am J Neurodegener Dis 5:171–177.

Whitwell JL, Josephs KA (2012): Recent Advances in the Imaging of Frontotemporal Dementia. Current Neurology and Neuroscience Reports 12:715–723.

Wise RG, Ide K, Poulin MJ, Tracey I (2004): Resting fluctuations in arterial carbon dioxide induce significant low frequency variations in BOLD signal. Neuroimage 21:1652–1664.

Wong S, Flanagan E, Savage G, Hodges JR, Hornberger M (2014): Contrasting Prefrontal Cortex Contributions to Episodic Memory Dysfunction in Behavioural Variant Frontotemporal Dementia and Alzheimer’s Disease. Ed. Linda Chao. PLoS ONE 9:e87778.

Xie L, Kang H, Xu Q, Chen MJ, Liao Y, Thiyagarajan M, O’Donnell J, Christensen DJ, Nicholson C, Iliff JJ, Takano T, Deane R, Nedergaard M (2013): Sleep Drives Metabolite Clearance from the Adult Brain. Science 342:373–377.

Zhou J, Greicius MD, Gennatas ED, Growdon ME, Jang JY, Rabinovici GD, Kramer JH, Weiner M, Miller BL, Seeley WW (2010): Divergent network connectivity changes in behavioural variant frontotemporal dementia and Alzheimer’s disease. Brain 133:1352–1367.

van der Zwaag W, Francis S, Head K, Peters A, Gowland P, Morris P, Bowtell R (2009): fMRI at 1.5, 3 and 7 T: characterising BOLD signal changes. Neuroimage 47:1425–1434.
Table 1. Descriptive characteristics of the study groups in local institute data.

| Local institute data | Controls | AD       | bvFTD    |
|----------------------|----------|----------|----------|
| Participants         | 24       | 17       | 18       |
| Age (yrs)            | 60.0 ± 5.1 | 60.0 ± 5.4 | 60.2 ± 7.3 |
| Female               | 12 (50 %) | 11 (65 %) | 9 (50 %)  |
| Disease duration (yrs)| -       | 2.6 ± 1.3 | 2.9 ± 1.9 |
| MMSE                 | 29.0 ± 1.1 * | 23.0 ± 2.6 | 24.2 ± 4.1 |
| FBI                  | NC       | NC       | 23.5 ± 4.7 |
| BDI                  | 3.2 ± 3.3 | NC       | NC       |

Medication

|             | Controls | AD       | bvFTD    |
|-------------|----------|----------|----------|
| Memantine   | 0        | 2        | 3        |
| Acetylcholin-esterase inhibitors | 0   | 14       | 5        |
| Neuroleptic | 0        | 4        | 8        |
| Valproate   | 0        | 0        | 4        |

Values represent mean±SD or N (%). AD = Alzheimer’s disease. bvFTD = behavioral variant frontotemporal dementia. MMSE = Mini Mental State Examination (maximum total score is 30). FBI = Frontal Behavioral Inventory Score (maximum total score is 72). BDI = Beck’s Depression Inventory (maximum total score is 63). NC = not collected. * p <0.05.
Table 2. Descriptive characteristics of the study groups in ADNI data.

| ADNI data                  | Controls | AD |
|----------------------------|----------|----|
| Participants               | 40       | 30 |
| Total rs-FMRI datasets     | 87       | 63 |
| Average visits per participant | 2.2     | 2.1 |
| Age (yrs)                  | 72.7 ± 4.3 | 71.8 ± 6.5 |
| Female                     | 25 (62 %) | 15 (50 %) |
| MMSE                       | 29.0 ± 1.3 * | 21.9 ± 3.6 |

Values represent mean±SD or N (%). AD = Alzheimer’s disease. MMSE = Mini Mental State Examination (maximum total score is 30). *p <0.05.
Table 3. Effect of motion.

| Template (ROI) | Absolute head motion | Relative head motion |
|---------------|-----------------------|----------------------|
|               | F(2,54)               | Sig. (p-value)       |
| WM            | 10.089                | 0.000189             |
| GM            | 15.006                | 0.000007             |
| CSF           | 7.191                 | 0.002                |

Results of the ANCOVA analysis (local data). There is a statistically significant difference between different study groups on the mean $CV_{\text{BOLD}}$ values in different ROIs (GM = gray matter, WM = white matter, CSF = cerebrospinal fluid) even when controlling for absolute or relative head motion parameters.
Table 4. Results of the ROC analysis.

| Template | Local institute data | ADNI data |
|----------|----------------------|-----------|
|          | AUC | CI 95%       | AUC | CI 95% |
| **AD vs control** | | | | |
| AD disease-specific ROI (local) | 0.963 | [0.914–1.000] | 0.681 | [0.596–0.766] |
| AD disease-specific ROI (common, local and ADNI) | 0.914 | [0.826–1.000] | 0.717 | [0.636–0.798] |
| WM template | 0.801 | [0.668–0.935] | 0.641 | [0.553–0.729] |
| GM template | 0.804 | [0.669–0.939] | 0.631 | [0.542–0.719] |
| CSF template | 0.811 | [0.681–0.942] | 0.626 | [0.538–0.715] |
| **bvFTD vs control** | | | | |
| bvFTD disease-specific ROI | 0.958 | [0.906–1.000] | | |
| WM template | 0.846 | [0.725–0.966] | | |
| GM template | 0.897 | [0.801–0.993] | | |
| CSF template | 0.75 | [0.601–0.899] | | |
| **AD vs bvFTD** | | | | |
| AD disease-specific ROI (local) | 0.806 | [0.659–0.954] | | |
| bvFTD disease-specific ROI | 0.197 | [0.044–0.350] | | |

AD = Alzheimer’s disease. bvFTD = behavioral variant frontotemporal dementia. AUC = area under the curve. CI = confidence interval.
Fig. 1. Coefficient of variation mapping of BOLD signal. Examples of randomly selected single subject and group mean CV$_{\text{BOLD}}$ maps for both local institute and ADNI data in MNI152 space.
Fig. 2. Mean CV\textsubscript{BOLD} values in GM, WM and CSF. On top is the ICBM152 template used as ROI for calculating mean CV\textsubscript{BOLD} values that are represented here as a boxplot with respective color encoding. Additional motion correction using despiking did not affect these results.
Fig. 3. Statistically significant voxel-wise CV_{BOLD} differences between study groups and their TFCE-corrected p-values. A and B shows the AD and bvFTD results with different p-value thresholds indicated in the image. In C, the cluster of voxels is presented where CV_{BOLD} values are higher in the bvFTD group vs. AD group.
Fig. 4. Comparison of the voxel-wise CV_{BOLD} differences between local institute and ADNI data (AD>control). B shows the common areas and mean p-value between local institute and ADNI data in two different p-values (p<0.05 and p<0.005, TFCE-corrected for familywise errors). 56% of the statistically significant voxels (p<0.05) are shared in both data sets.
Fig. 5. Effect of motion on CV_BOLD values (local institute data). Scatter plot (A) for the mean CV_BOLD value within template vs. head displacement (relative and absolute). Correlation between mean CV_BOLD and head displacement is also shown. The mean CV_BOLD values are higher in the patient groups (red and yellow circles) than in the control group (blue circles) with the same amount of motion both in the absolute and relative head displacement. Subject-wise absolute displacement values (in mm) were extracted, describing the amount of movement in all directions over the whole scan as a marker of gross motion. Also, relative displacement values were extracted, as a marker of motion between each EPI volume. Boxplot of the mean absolute and relative head displacement is shown in B. Differences in subject-wise mean absolute and relative motion values with CV_BOLD values were tested using Spearman’s rank correlation coefficient. Additionally, a number of peaks (C) and the maximum value (D) in the subject-wise motion data were evaluated.
Fig. 6. Gray matter atrophy patterns when compared to controls (local institute data). In AD, the most prominent atrophy was detected in precuneus and posterior cingulate gyrus. Significant atrophy was also detected in other temporoparietal areas. In bvFTD, atrophy was detected in posterior cingulate gyrus and also in widespread frontotemporal areas and insula.
Fig. 7. Receiver operating characteristic (ROC) curves and area under the curve values (AUC, p<0.003) for differential diagnosis based on mean CV$_{BOLD}$ values within region-of-interest. A, ROC curve for distinguishing patients with AD from control subjects on the basis of CV$_{BOLD}$ values within AD template as ROI. Red lines represent the template created using the most significant differences (p<0.0005) between groups in local data (Fig. 3B) and in blue the significant differences (p<0.005) common in both ADNI and local data (Fig. 4B). B, Same as in A for the ADNI data. C, ROC curve for distinguishing patients with bvFTD from control subjects on the basis of CV$_{BOLD}$ values within the bvFTD template as ROI. The template for ROI was created using the most significant differences (p<0.0005) between groups in local data (Fig. 3B). D, ROC curve for distinguishing patients with bvFTD from those with AD on the basis of AD or bvFTD template. Confidence intervals are shown in Table 4.