NeuroImage 58 (2011) 579–587

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Impaired cerebral vasoreactivity to CO_2 in Alzheimer's disease using BOLD fMRI

S. Cantin [a,b,c], M. Villien [a,b], O. Moreaud [d,e], I. Tropres [c], S. Keignart [d], E. Chipon [a,b,f], J.-F. Le Bas [a,b,c], J. Warnking [a,b], A. Krainik [a,b,c,*]

[a] Inserm, U836, Grenoble, France
[b] Université Joseph Fourier, Grenoble Institute of Neurosciences UMR-S836, Grenoble, France
[c] Department of Neuroradiology and MRI, CHU Grenoble - IFR1, Grenoble, France
[d] Department of Neurology, CHU Grenoble, Grenoble, France
[e] Psychology and Neurocognition Laboratory, UMR 5105, CHU Grenoble, Grenoble, France
[f] Clinical Investigate Centre, Innovative Technology, INSERM 803, CHU Grenoble, Grenoble, France

ARTICLE INFO

Article history:
Received 31 January 2011
Revised 13 May 2011
Accepted 23 June 2011
Available online 1 July 2011

Keywords:
Alzheimer's disease
Mild cognitive impairment
Cerebral vasoreactivity
Carbon dioxide
BOLD fMRI

ABSTRACT

Objective: To evaluate the cerebral vasoreactivity using blood oxygenation level dependent functional MRI during carbogen inhalation with 7% CO_2 in Alzheimer's disease and amnestic mild cognitive impairment.
Participants and methods: Thirty nine subjects were included to be investigated using blood oxygenation level dependent (BOLD) functional MRI at 1.5 T during a block-design carbogen inhalation paradigm, with a high concentration face-mask under physiological monitoring. Basal cerebral perfusion was measured using pulsed arterial spin labeling. Image analyses were conducted using Matlab® and SPM5 with physiological regressors and corrected for partial volume effect.
Results: Among selected participants, 12 subjects were excluded because of incomplete protocol, leaving for analysis 27 subjects without significant microangiopathy diagnosed for Alzheimer's disease ($n=9$), amnestic mild cognitive impairment ($n=7$), and matched controls ($n=11$). No adverse reaction related to the CO_2 challenge was reported. Carbogen inhalation induced a whole-brain signal increase, predominant in the gray matter. In patients, signal changes corrected for gray matter partial volume were decreased (0.36 ± 0.13% BOLD/mmHg in Alzheimer's disease, 0.36 ± 0.12 in patients with mild cognitive impairment, 0.62 ± 0.20 in controls). Cerebral vasoreactivity impairments were diffuse but seemed predominant in posterior areas. The basal hypoperfusion in Alzheimer's disease was not significantly different from patients with mild cognitive impairment and controls. Among clinical and biological parameters, no effect of apoE4 genotype was detected. Cerebral vasoreactivity values were correlated with cognitive performances and hippocampal volumes. Among age and hippocampal atrophy, mean CVR was the best predictor of the mini-mental status examination.
Conclusion: This BOLD functional MRI study on CO_2 challenge shows impaired cerebral vasoreactivity in patients with Alzheimer's disease and amnestic mild cognitive impairment at the individual level. These preliminary findings using a new MRI approach may help to better characterize patients with cognitive disorders in clinical practice and further investigate vaso-protective therapeutics.

Introduction

Alzheimer's disease (AD) is the most common cause of dementia in the elderly and affects 25 million persons in the world. Recent epidemiological studies predict a doubling of the prevalence every 20 years (Ferri et al., 2005). Mild cognitive impairment (MCI) may correspond to a transition state before AD with an annual conversion rate of MCI to AD evaluated between 16% and 41% (Gauthier et al., 2006).

In pathology, AD is characterized by abnormal amyloid beta peptide deposition, neurofibrillary tangles, and neurodegeneration. Additionally, vascular disorders play a critical role in the occurrence of cognitive impairment and neurodegeneration (Bell and Zlokovic, 2009; Benarroch, 2007; Farkas et al., 2000; Iadecola, 2010; Zlokovic, 2005).

In AD, the underlying mechanisms of this vascular dysfunction rely on the association of acetylcholine depletion and amyloïd beta peptide deposition that induce functional vascular disorders (Claassen and Jansen, 2006; de la Torre and Stefano, 2000; Iadecola, 2010). The structural alterations of the neurovascular unit could be provoked by the functional alterations themselves (Farkas and Luiten, 2001).

Indeed, perfusion imaging studies showed a cerebral blood flow (CBF) decrease of 10–25% in temporal, parietal and frontal regions

* Corresponding author at: Unité IRM, BP 217-CHU Grenoble, F-38043 Grenoble cedex, France. Fax: +33 4 76 76 52 86.
E-mail address: akrainik@chu-grenoble.fr (A. Krainik).

1053-8119/$ – see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.neuroimage.2011.06.070

(Chao et al., 2010; Dai et al., 2009; Du et al., 2006; Johnson et al., 2005; Kogure et al., 2000). Nevertheless, these studies on basal perfusion have not investigated vasomotor properties. None of them affords individual diagnosis.

Besides regional hypoperfusion of the brain, vasomotor impairments have been detected in animal and humans (Iadecola, 2004; Mueggler et al., 2002; Princz-Kranz et al., 2010; Shin et al., 2007). In patients, functional alterations of the vessel contractility were assessed using a vascular property, the cerebral vasoreactivity (CVR) to circulating gases and particularly to CO_2. The capnic modulation is commonly induced by apnea or acetazolamide injection. Despite methodological and practical limitations, transcranial Doppler (TCD) and computed tomography during stable Xenon inhalation (CT-Xenon) have shown impaired CVR (Oishi et al., 1999; Silvestrini et al., 2006).

TCD may provide a breath holding index by measuring blood velocity in the proximal portion of the middle cerebral arteries. This parameter was related to the mini-mental status examination (MMSE) (Silvestrini et al., 2006). However, TCD during apnea is heavily dependent on the operator expertise and the patient cooperation. Moreover, TCD estimates a global parameter, and is not a brain imaging technique able to depict potential regional changes that may better characterize AD.

CT-Xenon after acetazolamide injection has shown a reduction of the consecutive hyperperfusion of 6–8% in frontal, parietal and temporal cortices (Oishi et al., 1999). However, CT-Xenon is not commonly performed in clinical settings and results were not demonstrative at the individual level.

In AD, recent advances in MRI confirmed impaired hemodynamics, especially using blood oxygenation level dependent (BOLD) contrast, a widely available and non-invasive technique to investigate brain function. Indeed, BOLD functional MRI (fMRI) allows mapping brain regions involved in cognitive tasks, by measuring signal changes induced by the neurovascular coupling. Besides potential neuronal dysfunction that may explain differences of activation across populations, a delayed hemodynamic response has been identified (Rombouts et al., 2005). Yet, signal modifications related to neuronal activity can hardly be distinguished from those related to hemodynamic changes (Brown et al., 2003; Buxton et al., 2004; Cohen et al., 2002). Thus, recent BOLD fMRI studies during hypercapnic challenge with CO_2 inhalation have been conducted to estimate CVR in steno-occlusive pathology (Haller et al., 2008; Mandell et al., 2008; van der Zande et al., 2005; Ziyeh et al., 2005) and neurooncology (Jiang et al., 2010). In this way, a recent work has shown a forebrain deficit of CVR in prefrontal, anterior cingulated and insular cortices in AD (Yezhuvath et al., in press). In AD, vascular dysregulation would advocate for further developments of vasoprotective treatments (de la Torre, 2010; Luzzi et al., 2010).

Therefore, we looked at whether basal perfusion and hemodynamic responses to controlled inhalation of carbogen (a gas mixture of 93% O_2 and 7% CO_2) could be altered in AD and patients at risk with amnestic MCI. These patients were compared to controls using basal perfusion imaging with arterial spin labeling and dynamic BOLD response to carbogen. We paid attention to select individuals without moderate or severe microangiopathy. We hypothesized regional CVR impairment in patients. We also estimated the potential interest of this method to help for diagnosis at the individual level.

Subjects and methods

Participants

Thirty nine subjects were recruited to participate to the study that was approved by the institutional review board (DGS2007-0239). All subjects gave their informed consent according to the Declaration of Helsinki. Patients were prospectively recruited, in the Memory Center of the Grenoble University Hospital. Patients were referred for memory complains. They were not previously identified as patients with AD or MCI. Controls were selected among the general population after a recruitment announcement.

All subjects had a clinical and a neuropsychological examination including the Mini-Mental State Examination (MMSE) (Folstein et al., 1975) and the Clinical Dementia Rating (CDR) scale score (Hughes et al., 1982), a blood chemistry analysis (glycemia, triglycerids and total cholesterol level), and an ApoE genotyping. Subjects were classified into 3 groups according to the NINCDS-ADRDA criteria (McKhann et al., 1984) and the Petersen criteria (Petersen, 2004): AD group (MMSE = [14–24], CDR = 1); amnestic MCI group (MMSE = [24–30], CDR = 0.5); and control group (MMSE = [29–30], CDR = 0). Educational level was recorded. Inclusion criteria were: 1°) no contraindication to MRI scanning; 2°) right-handedness according to the Edinburgh Handedness Inventory (Oldfield, 1971); 3°) age range: 50–80 years; 4°) no active smoking; 5°) no alcohol or other drug addiction; 6°) no psychoactive medication; 7°) no untreated dyslipidemia or arterial hypertension; 8°) no stroke history; 9°) no general, neurological or psychiatric evolutive disease; and 10°) no guardianship procedure.

Exclusion criteria were: 1°) a severe stenosis (>70%) of the supra-aortic arteries on the MR angiography; 2°) stroke sequellae or moderate to severe micro-angiopathy on T2-FLAIR weighted images (simplified Fazekas scale>1) (Inzitari et al., 2009); 3°) inappropriate imaging protocol; and 4°) anxiety induced by the hypercapnic challenge rated on a visual anxiety scale with a post-MRI increase>20 mm (Hornblow and Kidson, 1976).

MR protocol

Imaging protocol was carried out on a 1.5 T Achieva MR scanner (Philips Healthcare®) at the Grenoble University Hospital, using a whole-body RF transmit and 8-channel head receive coils.

Anatomical studies

Anatomical studies consisted in a 3D gradient recalled echo (GRE) T1-weighted image (WI) (TR: 8.1 ms, TE: 3.8 ms, 1 × 1 × 1.3 mm voxel matrix, 256 mm field of view, 100 contiguous slices), axial transverse T2 FLAIR-WI (TR: 10,000 ms, TE: 110 ms, 1 × 1 × 4 mm voxel Matrix, 256 mm field of view, 29 contiguous slices). These sequences were acquired parallel to the anterior commissure–posterior commissure (AC–PC) plane. Orthogonal reformations were computed orthogonally to the hippocampal plane. An MR angiography was performed using a time of flight (TOF) sequence on the supra-aortic arteries.

Basal perfusion study

Basal perfusion was estimated using Pulsed ASL (PASL) with a Q2TIPS scheme, implemented by modifications of the Philips-distributed STAR sequence. A 200-mm label region was positioned axially to include the circle of Willis. Q2TIPS saturation was performed at a TI_1 adjusted on a per-subject basis. Twelve axial slices (4 × 4 × 5 mm voxel size) were acquired with a 15 mm label gap at TI_1 + 600 ms.

BOLD study

BOLD imaging consisted in a T_2*-WI GRE Echo Planar Imaging (EPI) acquisition (TR: 3000 ms, TE: 45 ms, alpha: 90°, 4 × 4 × 4 mm voxel size, 32 axial planes) with a whole brain coverage.

The capnic modulation was obtained using medical air and carbogen, a gas mixture of O_2 (93%) and CO_2 (7%), administered on simple blind mode, throughout the MRI, by a high concentration mask according to the following paradigm: [air (1 min) − carbogen (2 min) − air (1 min)] × 3, for a total duration of 12 min (Jiang et al., 2010). Physiological parameters including end-tidal CO_2 ($EtCO_2$), arterial oxygen saturation (SaO_2), heart rate and respiratory