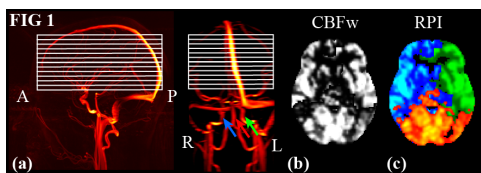# Planning-free Regional Arterial Spin Labeling Provides Evidence for Flow Asymmetry as a Possible Risk Factor for Alzheimer's Disease

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Introduction. The overall aim of this work is to apply a novel, planning-free regional perfusion imaging (RPI) approach in patients with varying cognitive impairment to better understand the relationship between flow territory asymmetry, cognitive performance, and dementia risk. Alzheimer's disease (AD) is a neurodegenerative condition, representing the most common form of dementia in older adults. There is presently no cure for AD, and etiogenesis and progression are incompletely understood. Accumulation of amyloid beta (αβ) plaque is believed to be a hallmark of AD onset and progression. However, additional evidence has been provided for vascular contributors to AD with one hypothesis that chronic, even mild, perfusion aberration can induce oxidative stress and ultimately mitochondrial failure over the lifespan [1]. However, there is considerable debate regarding the role and causative implications that complex hemodynamic adjustments impose on AD risk. This is largely attributable to a lack of sensitive methodology capable of noninvasively measuring such effects and corresponding longitudinal studies of hemodynamic and cognitive modulations. Psuedocontinuous arterial spin labeling (pCASL) allows for noninvasive quantification of cerebral blood flow (CBF) through magnetic labeling of arterial blood water via a pulse train applied to inflowing blood water. Gradients can be inserted between labeling pulses, in conjunction with phase-cycling, to create a spatially varying labeling efficiency which can then be used to uniquely label blood water in feeding vessels [2]. This RPI technique has been applied successfully in patients with cerebrovascular disease to quantify collateral flow, however has not been applied to measure flow territory asymmetry in dementia patients. The purpose of this study was therefore to implement a novel RPI approach with user-independent planning and probabilistic flow-territory quantification to noninvasively assess collateral flow in patients at risk for AD. The hypothesis to be investigated was that perfusion asymmetry would be highest in volunteers with increased dementia risk (quantified from genetic risk factors, neuropsychological scores, and/or familial history) owing to higher prevalence of vascular disease.
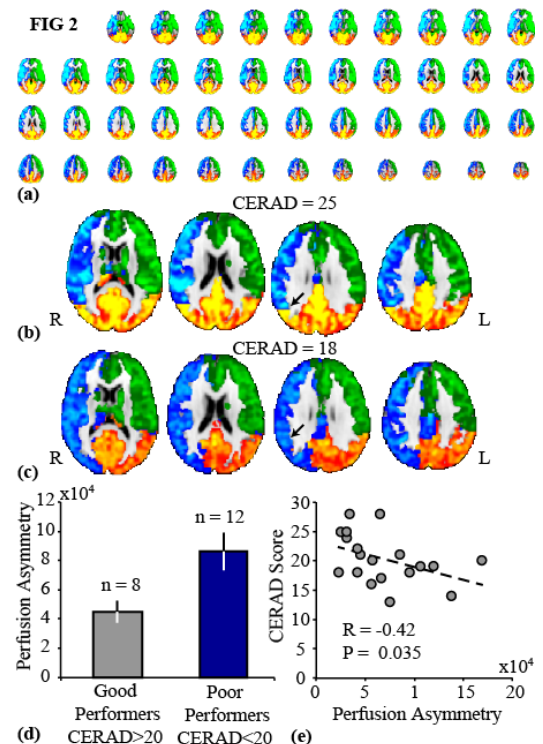

FIG 1. (a) Labeling locations and example (b) CBFw and corresponding (c) flow-territory map.

Methods. *Experiment.* Volunteers (n=21; age=69±7 yrs) with varying degrees of cognitive ability and dementia risk provided informed consent and were scanned at 3T (Philips). Each volunteer underwent a neurocognitive battery including MMSE [3] and CERAD [4]. MMSE was used for excluding AD diagnosis; The CERAD word list requires subjects to encode a list of 10 words into memory over 3 trials. Higher performance indicates better memory, with a maximum score of 30; encoding relies on an intact cortical interaction between prefrontal regions and hippocampus. *Scan parameters.* RPI: pCASL labeling (1650 ms Hanning pulse train), post-labeling delay = 1650 ms, labeling offset = 90 mm, slices=15, spatial resolution = 3.5x3.5x7 mm, SENSE-factor=2.5, TE/TR=17/4000 ms. Labeling was performed separately for left ICA (LICA), right ICA (RICA) and vertebrobasilar arteries (VBA), yielding three separate flow territories (**FIG 1**). This was achieved in an automated fashion by performing five separate labeling scenarios: (i) no labeling (control), (ii) complete labeling (inter-pulse gradients off), (iii) varying inversion efficiency by 25 mm in R/L direction (LICA vs. RICA labeling), as well as (iv) 9 mm in A/P direction and (v) 9 mm in A/P direction shifted by 4.5 mm (VBA labeling). T$_1$-weighted (MPRAGE: 1x1x1 mm^3; TR/TE=8.9/4.6 ms) and T$_2$-weighted FLAIR (0.9x0.9x1 mm^3; TR/TE=11000/120 ms) images were acquired for volumetric and white matter lesion quantification, respectively. *Analysis.* Data were corrected for motion, baseline drift and a k-means clustering algorithm, accounting for SNR variations, was used to group the different labeling geometries into three perfusion territories: flow from LICA, RICA, and VBA [5] (**FIG 1**). The mean territory map of all volunteers was computed to understand the spatial extent of the average flow territories. Next, an asymmetry index was calculated for each volunteer, denoting how many flow territory voxels fell outside the mean map, separately for each territory. Periventricular disease, white matter lesion count, and cortical CBF were also recorded.

Results and Discussion. One volunteer was excluded from analysis due to motion. Remaining volunteers fell into two groups: mild cognitive impairment (MCI; n=5; MMSE=27.2+/-1.1), and controls with no symptoms of MCI or AD but variable familial risk (n=15; MMSE=29.5+/-0.7). **FIG 2a.** Average (n=20) flow-territory maps demonstrate high symmetry between VBA (red), RICA (blue) and LICA (green) territories. **FIG 2b.** Representative maps from a volunteer with a high (good performer) CERAD score and corresponding normal symmetry in the flow territories. **FIG 2c.** Representative slices from a volunteer with a lower (CERAD=18) score, who shows higher asymmetry specifically in RICA and VBA territories (black arrow). Mean CERAD score was 20.0+/4.6; when volunteers were grouped into good responders (CERAD>20) vs. poor responders (CERAD<20), perfusion asymmetry was significantly (P=0.018) increased for poor performers (**FIG 2d**), a trend that was observed over all subjects (**FIG 2e**). No correlation was found between perfusion asymmetry and white matter lesion count (P=0.14) yet a strong trend for significance (P=0.05) was found inversely between perfusion asymmetry and cortical CBF. To our knowledge, *these results demonstrate the first application of RPI in patients with cognitive impairment, and furthermore support an association between cognitive performance and asymmetric collateral flow patterns.* Experimentally, this work shows that a planning-free RPI approach, in conjunction with a probabilistic clustering routine, can be applied successfully in dementia patients. Clinically, this work provides additional support for hemodynamic mechanisms preceding clinical symptoms and structural changes in dementia patients. It is likely that small intracranial stenosis and intravascular atherosclerotic and/or intravascular αβ plaque underlie the observed flow asymmetry. It has recently been demonstrated that both functional connectivity as well as hemodynamic hyperactivation are present in healthy volunteers predisposed for AD through genetic risk factors or familial risk [6-8]. These findings complement this work, as well as the growing hypothesis attributing vascular phenomena to AD risk. Ongoing work is focused on using the proposed, and related hemodynamic MRI approaches, to longitudinally track cognitive decline in patients to better understand the mechanistic origins of AD.

FIG 2. (a) Mean (n=20) flow territory maps and (b) representative slices from a high cognitive performer and (c) lower performer. (d,e) Elevated perfusion asymmetry is apparent in lower cognitive performers.

References. **[1]** de la Torre JC et al. Lancet Neurol. 2004. **[2]** Gevers S et al. AJNR. 2011. **[3]** Wong E et al. ISMRM. 2008. **[4]** Hodkinson H et al. Age and Ageing. 1972. **[5]** Morris J et al. Neurology. 1989. **[6]** Quiroz Y et al. Ann Neurol. 2010. **[7]** Filippini N et al. PNAS. 2009. **[8]** Fleisher A et al. Neurobiol Aging. 2009.