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Cognitive functioning in patients with disorders along the heart-brain axis: the role of cerebral blood flow

Leeuwis, Anna E.; Hooghiemstra, Astrid M.; Bron, Esther E.; Kuipers, Sanne; Oudeman, Eline A.; Kalay, Tugba; Brunner-La-Rocco, Hans-Peter H.P.; Kappelle, L. Jaap; Niessen, Wiro; More Authors

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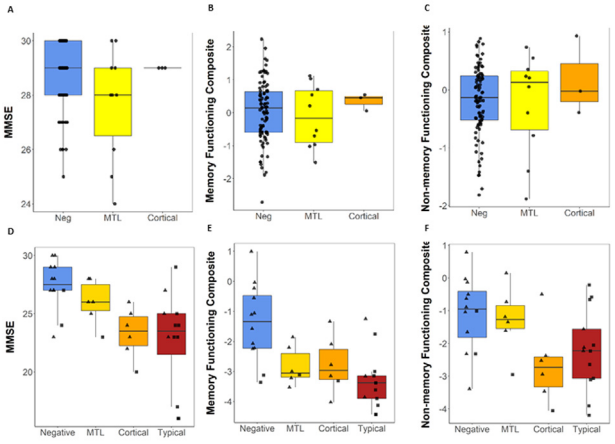
Table 1. Participant Characteristics

Variable	Cognitively Normal (n=106)	MCI or AD diagnosis (n=37)	P-value
Age, yrs, range, mean (SD)	55.1-96.6, 75.2 (5.4)	51.5-93, 71.6 (8.7)	0.003
Female, %	53.8	51.4	0.799
Yrs of Education, range, mean (SD)	8-20, 13.7 (2.9)	8-19, 12/86 (3.2)	0.146
APOE4 positive, %	31.9	61.9	0.010
CDR global, 0, 0.5, ≥1, % (n)	88.7,11.3,0.0 (94,12,0)	8.1, 73.0, 18.9 (3, 27, 7)	<.001
CDR SOB, range, mean (SD)	0-2.0, 0.1 (0.3)	0-12, 2.9 (2.9)	<.001
MMSE, range, mean (SD)	24-30, 28.6 (1.3)	16-30, 27.7 (2.7)	<.001
Memory functioning composite, range, mean (SD)	-2.7-2.2, 0.0 (0.9)	-4.4-1.0, -2.5 (1.3)	<.001
Non-memory functioning composite, range, mean (SD)	-1.9-0.9, -0.2 (0.6)	-4.2-0.8, -1.8 (1.3)	<.001
Beta-amyloid positive, % (n)	18.4 (18/98)	70.6 (24/34)	<.001
Visual Rating, Neg, MTL, Cortical, Typical, % (n)	87.7, 9.4, 0.0, 2.8 (93,10,0,3)	32.4, 16.2, 16.2, 35.1 (12,6,6,13)	<.001

P-values from t-tests or χ^2 tests, as appropriate, to evaluate group differences between cognitively normal and MCI/AD groups.

MCI= Mild Cognitive Impairment; AD= Alzheimer's disease; Yrs= years; CDR= Clinical dementia Rating; SOB= Sum of Boxes; MMSE= Mini Mental State Exam; Neg= Negative; MTL=Medial Temporal Lobe

Figure 2. Association between NFT Subtype Classification and Memory and Cognitive Functioning



Plots depicting the relationship between NFT subtype classification and MMSE (A and D), Memory Functioning (B and E), and Non-Memory Functioning (C and F) for the CN group and MCI/AD group, respectively. Cognitively normal=circle; MCI=triangle; AD=square.

(^{18}F-MK-6240) and whether NFT pattern is associated with decrements on distinct cognitive and memory domains. **Methods:** 106 cognitively-normal (CN) and 37 Mild Cognitive Impairment (MCI)/AD Australian Imaging, Biomarkers and Lifestyle (AIBL) Study participants completed ^{18}F-MK-6240 tau-PET imaging and cognitive evaluation. Tau-PET scans were visually rated on a 4-point scale. Figure 1 depicts the rating categories with representative images. Memory functioning and Non-memory functioning composite z-scores were calculated from neuropsychological tests. Regression analyses were used to test the association between NFT subtypes and memory and cognitive performance, adjusting for age, sex, and years of education. **Results:** Distinct NFT patterns were clearly identified in our cohort. Twelve percent of CN group showed tau tracer binding, mostly limited to MTL (Table 1). This was associated with a one-point decrement on MMSE, but no difference on memory or non-memory functioning, compared to tau Negative CN (Figure 2a-c). In the clinical MCI/AD patients MTL-predominant performed worse on MMSE and Memory functioning, but had preserved Non-memory functioning, compared to the tau Negative group. The Cortical-predominant Group had decrements on MMSE, Memory, and Non-memory functioning, compared to Negative group (Figure 2d-f). **Conclusions:** NFT pattern subtypes, identified by visual inspection, were identified using ^{18}F-MK-6240 PET in our cohort of CN and MCI/AD individuals. These subtypes were associated with distinct memory and cognitive functioning. Identification of NFT subtypes may be beneficial for future clinical trials and clinical diagnosis. Longitudinal studies are needed to determine if MTL predominant pattern in clinically impaired patients persists as a distinct subtype of AD or is an earlier stage of disease preceding progressive cortical tau accumulation.

P2-392 COGNITIVE FUNCTIONING IN PATIENTS WITH DISORDERS ALONG THE HEART-BRAIN AXIS: THE ROLE OF CEREBRAL BLOOD FLOW

Anna E. Leeuwis[1], Astrid M. Hooghiemstra[1], Esther E. Bron[2], Sanne Kuipers[3], Eline A. Oudeman[3], Tugba Kalay[4], Hans-Peter H. P. Brunner-La Rocca[5], Jaap Kappelle[3], Robert J. van Oostenbrugge[4], Jacoba P. Greving[6], Wiro J. Niessen[7,8], Mark A. van Buchem[9], Matthijs J. P. van Osch[10], Albert van Rossum[11], Niels D. Prins[1], Geert Jan Biessels[3], Frederik Barkhof[12,13], Wiesje M. van der Flier[1,14],
[1]Alzheimer Center Amsterdam, Department of Neurology, Amsterdam Neuroscience, VU University Medical Center, Amsterdam UMC, Amsterdam, Netherlands; [2]Biomedical Imaging Group Rotterdam, Departments of Medical Informatics and Radiology and Nuclear Medicine, Erasmus MC, Rotterdam, Netherlands; [3]Department of Neurology, Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht, Netherlands; [4]Department of Neurology, Maastricht University Medical Center, Maastricht, Netherlands; [5]Department of Cardiology, Maastricht University Medical Center, Maastricht, Netherlands; [6]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, Netherlands; [7]Imaging Physics, Applied Sciences, Delft University of Technology, Delft, Netherlands; [8]Biomedical Imaging Group Rotterdam, Departments of Medical Informatics and Radiology and Nuclear Medicine, Rotterdam, Netherlands; [9]Department of Radiology, Leiden University Medical Center, Leiden, Netherlands; [10]C.J. Gorter Center for High Field MRI, Department of Radiology, Leiden University Medical Center, Leiden, Netherlands; [11]Department of Cardiology, Amsterdam UMC, VU University Medical Center, Amsterdam, Netherlands; [12]Institutes of Neurology and Healthcare Engineering, University College London, London, United Kingdom; [13]Department of Radiology and Nuclear Medicine, Amsterdam Neuroscience, Vrije Universiteit Amsterdam, Amsterdam UMC, Amsterdam, Netherlands; [14]Department of Epidemiology and Biostatistics, Vrije Universiteit Amsterdam, Amsterdam UMC, Amsterdam, Netherlands.
Contact e-mail: a.leeuwis@vumc.nl

Background: Lower cerebral blood flow (CBF) is associated with cardiovascular disease and is increasingly recognized as an important contributor to cognitive decline. We examined the cross-sectional association between CBF, measured with arterial spin labeling (ASL), and cognitive functioning in patients with disorders along the heart-brain axis, including vascular cognitive impairment (VCI), carotid occlusive disease (COD) and heart failure (HF). **Methods:** We included 442 participants (129 VCI; 75 COD; 124 HF; and 114 controls) from the Heart-Brain Study (67±9yrs; 38%F; MMSE 28±2). We used 3T pseudo-continuous ASL to

estimate whole-brain and regional partial volume-corrected CBF. Using a standardized neuropsychological assessment, we measured global cognitive functioning and four cognitive domains. Compound *z*-scores were constructed for each cognitive domain. Associations were investigated using linear regression analyses, adjusted for age, sex, education, center and additionally for diagnosis (using dummy variables). To investigate whether associations with CBF differed according to diagnosis, interaction terms were included in our analysis. **Results:** Whole-brain and regional CBF values were lowest in patients with COD, then VCI and HF, compared to controls. Global cognitive functioning was lowest in patients with VCI. Overall, we found hardly any association between whole-brain and regional CBF values and cognitive functioning (standardized beta [stβ]=0.00-0.10, $p>0.05$). Lower CBF values in the parietal region were associated with worse performance on language (stβ=0.10, $p<0.05$). We found some significant interaction terms without a specific pattern of particular regions and cognitive domains. Stratification for diagnosis showed that lower whole-brain CBF values were associated with worse performance on the domain of executive functioning, but only in the control group (stβ=0.19, $p<0.05$). We found no association between CBF and cognitive functioning in patients with HF, COD or VCI. **Conclusions:** Our results suggest that the association between CBF and cognitive functioning in patients with disorders along the heart-brain axis appears to be scarce. The predisposition of cognitive impairment in those patients is likely to be driven by other (haemodynamic) mechanisms than CBF.

P2-394 TAU PET IMAGING IN LGI1 ENCEPHALITIS: DECIPHERING THE CONTRIBUTORS TO COGNITIVE IMPAIRMENT IN AUTOIMMUNE ENCEPHALITIS

Gregory S. Day[1,2], Brian A. Gordon[3,4], Austin A. McCullough[1], Richard J. Perrin[1,2], Jinbin Xu[1], Beau M. Ances[1,2], *[1]Washington University School of Medicine, Saint Louis, MO, USA; [2]Knight Alzheimer Disease Research Center, St. Louis, MO, USA; [3]Washington University School of Medicine, St. Louis, MO, USA; [4]Knight Alzheimer's Disease Research Center, St. Louis, MO, USA. Contact e-mail: gday@wustl.edu*

Background: Autoimmune encephalitis associated with leucine-rich glioma-inactivated 1 (LGI1) antibodies is most common in older cohorts, may be mistaken for a neurodegenerative dementing illness at presentation, frequently results in persistent cognitive impairment in patients who recover, and is associated with changes on structural and functional neuroimaging in the bilateral hippocampi. The neuropathological underpinnings that contribute to long-term sequelae remain unknown. We investigated whether neurofibrillary tangle (tau) pathology contributed to persistent cognitive impairment in patients with LGI1 encephalitis. **Methods:** Flortaucipir (18F-AV-1451) "tau PET" neuroimaging was completed in four cognitively impaired LGI1 encephalitis patients (3 males, 1 female; median 67 years, range 37-88; median CDR 0.5, range 0.5-2), a median of 27.4 months (range, 4.2-54.6) following symptom onset. Regional SUVRs were derived using standard techniques with the cerebellar gray matter serving as a reference. Flortaucipir retention patterns were compared between LGI1 encephalitis patients and age-similar cognitively normal (CDR 0) amyloid negative participants (n=127) and amyloid positive individuals with symptomatic Alzheimer disease (AD, CDR>0; n=18) enrolled in longitudinal studies of memory and aging (Knight Alzheimer Disease Research Center; Saint Louis, Missouri). **Results:** Flortaucipir retention was not increased in any brain region in 3/4 LGI1 encephalitis patients relative to cognitively normal individuals. In the remaining patient—an 88 year-old female with moderate dementia (CDR 2) persisting despite treatment with prednisone and rituximab—Flortaucipir retention was increased relative to cognitively normal controls in the lateral occipital, caudal middle frontal, temporal, fusiform, pericalcarine cortices, in a pattern indistinguishable from individuals with symptomatic AD. This patient died 2.4 months following tau-PET imaging. Neuropathological assessment confirmed "intermediate" AD neuropathologic change (NIA-AA criteria), with frequent neurofibrillary tangles in areas of greatest Flortaucipir uptake. **Conclusions:** The absence of substantial Flortaucipir retention in the majority of LGI1 encephalitis patients suggests that neurofibrillary tangles are unlikely to contribute to cognitive impairment in recovering patients. However, the possibility that autoimmune encephalitis may accelerate the accrual of tau pathology in individuals with preclinical AD, or other age-related pathologies associated with neurofibrillary tangles, warrants consideration in larger cohorts of patients followed longitudinally. Acknowledgements: Flortaucipir precursor and technology was supported by Avid Radiopharmaceuticals.

P2-395 PERIORBITAL CSF CLEARANCE IN ALZHEIMER'S DISEASE

Yi Li[1], Emily Tanzi[2], Hande Can[3], Jingyun Chen[2], John Babich[4], P. David Mozley[4], Henry Rusinek[1], Mony J. de Leon[1], *[1]NYU School of Medicine, New York, NY, USA; [2]NYU School of Medicine, New York, NY, USA; [3]New York University School of Medicine, New York, NY, USA; [4]Weill Cornell Medicine, New York, NY, USA. Contact e-mail: liyi73@gmail.com*

Background: Impairments in CSF turnover have been suspected for many years in the etiology of Alzheimer disease (AD). We previously reported CSF clearance abnormalities in AD and found that the human nasal turbinate is part of the CSF clearance system. Based on animal work, the CSF clearance pathway includes the perineural spaces of the cranial nerves. In this study, we extended our previous study to the eye, and report for the first time the turnover of CSF egress in human eye by using dynamic PET and its reduction in AD. **Methods:** 8 normal controls and 15 AD subjects (61-90y), participated in this IRB approved study. Each study participant received a 60min dynamic 18F-THK5351 PET exam and a high resolution T1 weighted MRI for anatomical regions of interest (ROI) sampling. ROIs were created for the grey matter using FreeSurfer (v. 6.0) and were manual traced for the globe of the eye, orbital fat and the posterior globe (pG). Sampling was made 10min post injection to avoid tracer contamination from blood. **Results:** Tracer binding in pG did not differentiate AD from NL. However, only the pG site showed increased tracer uptake (Figure 1). The 14% signal increase in pG in NL was 70% greater than the increase in AD ($p<0.05$). **Conclusions:** The subarachnoid space surrounding the optic nerve (ON) is part of the brain CSF clearance system. Known also as glymphatic, this is an increasingly known pathway for CSF irrigation with drainage into lymphatics and the venous circulation. The ON is covered by the meninges and surrounded by CSF throughout its length. It is intriguing that recent work shows that the blood vessels of sclera contain lymphatic-like