# PROJECT SUMMARY

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**Justification :** While typical Alzheimer's disease (AD) is the main cause of progressive amnesia in aging, neuropathological studies demonstrated that other diagnoses, mimicking early AD, are not rare. They were grouped under the term of Suspected non-Alzheimer disease pathophysiology (SNAP). SNAP is a biomarker-based concept used to define individuals with normal amyloid-β (Aβ) biomarkers, but in whom biomarkers of neurodegeneration are abnormal. The main causes of SNAP are tauopathy not due to AD, synucleinopathy, cerebrovascular disease, TDP-43 inclusions associated with hippocampal sclerosis (HS), and argyrophilic grain disease. HS is not rare, its prevalence being from 10 to 30% during aging. HS is characterized by selective neuronal cell loss and astrocytosis affecting the subiculum and cornu ammonis subfield 1 of the hippocampal formation, unrelated to AD. Positron Emission Tomography (PET) imaging using new tracers of brain tau deposition coupled with amyloid PET imaging allows to explore the pathophysiological process of progressive amnesia. 7T MRI provides information about hippocampal subfield damage, micro- infarcts, cortical neural density and Papez circuit atrophy. Understanding the biological pathophysiological pathways of progressive amnesia is a main objective of neuroscience research in order to develop new drugs against specific molecular targets.

**Objectives and means**: We aim to study brain tau ([$^{18}$F]-AV-1451) and amyloid ([$^{11}$C]-PiB) deposition by PET, coupled with ultra-high field MRI (7Tesla) in patients with progressive amnesia due or not due to AD (prodromal AD patients or patients with SNAP) defined by clinical-biological criteria.

We will use [$^{18}$F]-AV1451 tracer, which showed a good affinity for neurofibrillary tangles (NFT), to assess tau deposition by PET. In AD, the topographic binding profile is associated with the severity of the disease, following the NFT progression pattern described in neuropathological studies. We will use PET imaging with [$^{11}$C]-PiB tracer to quantify regional fibrillary amyloid deposition and amyloid plaques. According to the amyloid cascade hypothesis, the positivity of PiB-PET is considered as a marker of preclinical AD, and its negativity in amnesic patients permits to exclude AD diagnosis. In addition, we will use NODDI sequences on 3T MRI to study neurite density and 7T MRI to analyze specific hippocampal subfields atrophy and detect microinfarcts. A two-year clinical and 3T MRI follow-up will provide information about prognostic factors. At the last visit, a second longitudinal tau PET scan will provide information about the progression of tau deposition.

**Expected results**: By combining PET imaging for assessing both proteinopathies with 3T MRI including new diffusion model (NODDI) for assessing neurite density and ultra-high-field 7 Tesla MRI for assessing brain microvasculature and hippocampal subfields, we aim to identify, *in vivo*, specific molecular and vascular signatures of patients with SNAP by comparison with AD patients, FTD patients, PSP/DCB patients and control subjects. According to neuropathological studies, we hypothesize that different patterns of molecular signatures will be observed among patients with progressive amnesia: TAU+ and Aß+ for AD patients, Tau+ and Aß- for patients with non-AD tauopathies, Tau- and Aß- for HS-TDP43 patients. In addition, 7T MRI could identify micro-vascular lesions in each subgroup of patients. The 2-year tau PET imaging, MRI and clinical follow-up will permit to study cognitive progression according to the specific physiopathological process and to identify new prognostic markers in AD. Identifying pathophysiological process of amnesia due and not due to AD pathology will permit to optimize the design of future therapeutic trials.

**Phases of production:** A total of 130 subjects will be included (40 SNAP, 40 AD, 20 controls, 20 FTD, 10 PSP/DCB). All regulatory agreement have been obtained. The study has already begun and inclusions are ongoing. We request complementary funding to complete the neuroimaging part of the study (PET coupled with 3T MRI), for which the funding for slightly over half (54%) of the subjects is lacking. The first analyses of PET imaging are in progress. We plan to publish first results in 2019-2020.

**Three publications on the subject**

Jack et al. Suspected non-Alzheimer disease pathophysiology. Concept and controversy. Nature Review, 2016; 12: 117-124.

Mormino et al. Heterogeneity in Suspected Non-Alzheimer Disease Pathophysiology Among Clinically Normal Older Individuals. JAMA neurology, 2016, 73: 1185-1191

Sarazin et al. Distinct tau PET imaging patterns in typical and atypical Alzheimer's disease. Brain 2016, 139:1321