

- 1 La Joie, R., Landeau, B., Perrotin, A., Bejanin, A., Egret, S., Pelerin, A. et al. (2014). Intrinsic connectivity identifies the hippocampus as a main crossroad between Alzheimer's and semantic dementia-targeted networks. *Neuron*, 81, 1417-1428.
Notes: Alzheimer's disease (AD) and semantic dementia (SD) are both characterized by severe atrophy in the hippocampus, a brain region underlying episodic memory; paradoxically, episodic memory is relatively preserved in SD. Here, we used intrinsic connectivity analyses and showed that the brain networks differentially vulnerable to each disease converge to the hippocampus in the healthy brain. As neurodegeneration is thought to spread within preexisting networks, the common hippocampal atrophy in both diseases is likely due to its location at the crossroad between both vulnerable networks. Yet, we showed that in the normal brain, these networks harbor different functions, with episodic memory relying on the AD-vulnerable network only. Overall, disease-associated cognitive deficits seem to reflect the disruption of targeted networks more than atrophy in specific brain regions: in AD, over hippocampal atrophy, episodic memory deficits are likely due to disconnection within a memory-related network
- 2 de Flores, R., La Joie, R., Landeau, B., Perrotin, A., Mezenge, F., et al. (2014). Effects of age and Alzheimer's disease on hippocampal subfields: Comparison between manual and freesurfer volumetry. *Human Brain Mapping*.
Notes: Growing interest has developed in hippocampal subfield volumetry over the past few years and an increasing number of studies use the automatic segmentation algorithm implemented in FreeSurfer. However, this approach has not been validated on standard resolution T1-weighted magnetic resonance (MR) as used in most studies. We aimed at comparing hippocampal subfield segmentation using FreeSurfer on standard T1-weighted images versus manual delineation on dedicated high-resolution hippocampal scans. Hippocampal subfields were segmented in 133 individuals including 98 cognitively normal controls aged 19-84 years, 17 mild cognitive impairment and 18 Alzheimer's disease (AD) patients using both methods. Intraclass correlation coefficients (ICC) and Bland-Altman plots were computed to assess the consistency between both methods, and the effects of age and diagnosis were assessed from both measures. Low to moderate ICC (0.31-0.74) were found for the subiculum and other subfields as well as for the whole hippocampus, and the correlations were very low for cornu ammonis (CA)1 (<0.1). FreeSurfer CA1 volume estimates were found to be much lower than those obtained from manual segmentation, and this bias was proportional to the volume of this structure so that no effect of age or AD could be detected on FreeSurfer CA1 volumes. This study points to the differences in the anatomic definition of the subfields between FreeSurfer and manual delineation, especially for CA1, and provides clue for improvement of this automatic technique for potential clinical application on standard T1-weighted MR.
- 3 La Joie, R., Perrotin, A., de la Sayette, V., Egret, S., Doeuvre, L., Belliard, S. et al. (2013). Hippocampal subfield volumetry in mild cognitive impairment, Alzheimer's disease and semantic dementia. *NeuroImage: Clinical*, 3, 155-162.
Notes: BACKGROUND: Hippocampal atrophy is a well-known feature of Alzheimer's disease (AD), but sensitivity and specificity of hippocampal volumetry are limited. Neuropathological studies have shown that hippocampal subfields are differentially vulnerable to AD; hippocampal subfield volumetry may thus prove to be more accurate than global hippocampal volumetry to detect AD. METHODS: CA1, subiculum and other subfields were manually delineated from 40 healthy controls, 18 AD, 17 amnesic Mild Cognitive Impairment (aMCI), and 8 semantic dementia (SD) patients using a previously developed high resolution MRI procedure. Non-parametric group comparisons and receiver operating characteristic (ROC) analyses were conducted. Complementary analyses were conducted to evaluate differences of hemispheric asymmetry and anterior-predominance between AD and SD patients and to distinguish aMCI patients with or without beta-amyloid deposition as assessed by Florbetapir-TEP. RESULTS: Global hippocampi were atrophied in all three patient groups and volume decreases were maximal in the CA1 subfield (22% loss in aMCI, 27% in both AD and SD; all $p < 0.001$). In

aMCI, CA1 volumetry was more accurate than global hippocampal measurement to distinguish patients from controls (areas under the ROC curve = 0.88 and 0.76, respectively; $p = 0.05$) and preliminary analyses suggest that it was independent from the presence of beta-amyloid deposition. In patients with SD, whereas the degree of CA1 and subiculum atrophy was similar to that found in AD patients, hemispheric and anterior-posterior asymmetry were significantly more marked than in AD with greater involvement of the left and anterior hippocampal subfields. CONCLUSIONS: The findings suggest that CA1 measurement is more sensitive than global hippocampal volumetry to detect structural changes at the pre-dementia stage, although the predominance of CA1 atrophy does not appear to be specific to AD pathophysiological processes

- 4 Chetelat, G., La Joie R., Villain, N., Perrotin, A., de la Sayette, V, Eustache, F. et al. (2013). Amyloid imaging in cognitively normal individuals, at-risk populations and preclinical Alzheimer's disease. *NeuroImage: Clinical*, 2, 356-365.
Notes: Recent developments of PET amyloid ligands have made it possible to visualize the presence of Abeta deposition in the brain of living participants and to assess the consequences especially in individuals with no objective sign of cognitive deficits. The present review will focus on amyloid imaging in cognitively normal elderly, asymptomatic at-risk populations, and individuals with subjective cognitive decline. It will cover the prevalence of amyloid-positive cases amongst cognitively normal elderly, the influence of risk factors for AD, the relationships to cognition, atrophy and prognosis, longitudinal amyloid imaging and ethical aspects related to amyloid imaging in cognitively normal individuals. Almost ten years of research have led to a few consensual and relatively consistent findings: some cognitively normal elderly have Abeta deposition in their brain, the prevalence of amyloid-positive cases increases in at-risk populations, the prognosis for these individuals is worse than for those with no Abeta deposition, and significant increase in Abeta deposition over time is detectable in cognitively normal elderly. More inconsistent findings are still under debate; these include the relationship between Abeta deposition and cognition and brain volume, the sequence and cause-to-effect relations between the different AD biomarkers, and the individual outcome associated with an amyloid positive versus negative scan. Preclinical amyloid imaging also raises important ethical issues. While amyloid imaging is definitely useful to understand the role of Abeta in early stages, to define at-risk populations for research or for clinical trial, and to assess the effects of anti-amyloid treatments, we are not ready yet to translate research results into clinical practice and policy. More researches are needed to determine which information to disclose from an individual amyloid imaging scan, the way of disclosing such information and the impact on individuals and on society
- 5 Arenaza-Urquijo, E. M., Landeau, B., La Joie, R., Mevel, K., Mezenge, F., Perrotin, A. et al. (2013). Relationships between years of education and gray matter volume, metabolism and functional connectivity in healthy elders. *NeuroImage*, 83, 450-457.
Notes: More educated elders are less susceptible to age-related or pathological cognitive changes. We aimed at providing a comprehensive contribution to the neural mechanism underlying this effect thanks to a multimodal approach. Thirty-six healthy elders were selected based on neuropsychological assessments and cerebral amyloid imaging, i.e. as presenting normal cognition and a negative florbetapir-PET scan. All subjects underwent structural MRI, FDG-PET and resting-state functional MRI scans. We assessed the relationships between years of education and i) gray matter volume, ii) gray matter metabolism and iii) functional connectivity in the brain areas showing associations with both volume and metabolism. Higher years of education were related to greater volume in the superior temporal gyrus, insula and anterior cingulate cortex and to greater metabolism in the anterior cingulate cortex. The latter thus showed both volume and metabolism increases with education. Seed connectivity analyses based on this region showed that education was positively related to the functional connectivity between the anterior cingulate cortex and the hippocampus as well as the inferior frontal lobe, posterior cingulate cortex and angular gyrus. Increased connectivity was in turn related with improved cognitive performances. Reinforcement of the connectivity of the anterior cingulate cortex with distant cortical areas of the frontal, temporal and parietal lobes appears as

one of the mechanisms underlying education-related reserve in healthy elders

- 6 Perrotin, A., Mormino, E. C., Madison, C. M., Hayenga, A. O., & Jagust, W. J. (2012). Subjective cognition and amyloid deposition imaging: a Pittsburgh Compound B positron emission tomography study in normal elderly individuals. *Archives of Neurology*, 69, 223-229.
Notes: OBJECTIVE: To study the relationship between subjective cognition and the neuropathological hallmark of Alzheimer disease (AD), amyloid-beta (Abeta) deposition, using carbon 11-labeled Pittsburgh Compound B (PiB) positron emission tomography in normal elderly individuals. DESIGN: Cross-sectional analysis. SUBJECTS: Forty-eight cognitively normal elderly subjects (11 with high PiB uptake and 28 with low PiB uptake) were included. All underwent clinical and neuropsychological evaluations, magnetic resonance imaging, and positron emission tomography. SETTING: Berkeley Aging Cohort Study. MAIN OUTCOME MEASURE: Relationship between PiB uptake and subjective cognition measures. RESULTS: Subjects with high PiB uptake showed significantly lower performance than those with low PiB uptake on an episodic memory measure and were less confident about their general memory abilities when required to evaluate themselves relative to other people of the same age. High and low PiB uptake groups did not differ on the accuracy of their cognitive self-reports compared with objective cognitive performance. General memory self-reports from the whole group were significantly correlated with regional PiB uptake in the right medial prefrontal cortex and anterior cingulate cortex and in the right precuneus and posterior cingulate cortex. Reduced confidence about memory abilities was associated with greater PiB uptake in these brain regions. All results were independent of demographic variables and depressive affects. CONCLUSIONS: A decrease of self-confidence about memory abilities in cognitively normal elderly subjects may be related to the neuropathological hallmark of AD measured with PiB-positron emission tomography. Subjective cognitive impairment may represent a very early clinical manifestation of AD
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- 7 Perrotin, A., Tournelle, L., & Isingrini, M. (2008). Executive functioning and memory as potential mediators of the episodic feeling-of-knowing accuracy. *Brain and Cognition*, 67, 76-87.
Notes: The study focused on the cognitive determinants of the accuracy of feeling-of-knowing (FOK) judgments made on episodic memory information. An individual differences approach was used on a sample of healthy older adults assessed on an episodic FOK task and on several neuropsychological measures. At a global level of analysis of FOK accuracy, the contributions of four general cognitive processes--episodic memory, executive functioning, fluid intelligence and processing speed--were examined concurrently. Stepwise regression analyses showed that executive functioning accounted for the major part of variance on FOK accuracy, followed by a significant contribution of episodic memory. After controlling for executive and memory involvement, fluid intelligence and processing speed no longer accounted for significant variance. At a more detailed level of analysis of FOK accuracy, the contributions of three specific executive processes--shifting, updating and inhibition--were assessed. The results revealed shifting function as the primary executive process engaged in the production of accurate FOK judgments in episodic memory. Some hypotheses are put forward to better understand the central role of executive functioning in the production of accurate FOK judgments
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- 8 Perrotin, A., Belleville, S., & Isingrini, M. (2007). Metamemory monitoring in mild cognitive impairment: Evidence of a less accurate episodic feeling-of-knowing. *Neuropsychologia*, 45, 2811-2826.
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This study aimed at exploring metamemory and specifically the accuracy of memory monitoring

in mild cognitive impairment (MCI) using an episodic memory feeling-of-knowing (FOK) procedure. To this end, 20 people with MCI and 20 matched control participants were compared on the episodic FOK task. Results showed that the MCI group made less accurate FOK predictions than the control group by overestimating their memory performance on a recognition task. The MCI overestimation behavior was found to be critically related to the severity of their cognitive decline. In the light of recent neuroanatomical models showing the involvement of a temporal-frontal network underlying accurate FOK predictions, the role of memory and executive processes was evaluated. Thus, participants were also administered memory and executive neuropsychological tests. Correlation analysis revealed a between-group differential pattern indicating that FOK accuracy was primarily related to memory abilities in people with MCI, whereas it was specifically related to executive functioning in control participants. The lesser ability of people with MCI to assess their memory status accurately on an episodic FOK task is discussed in relation to both their subjective memory complaints and to their actual memory deficits which might be mediated by the brain vulnerability of their hippocampus and medial temporal system. It is suggested that their memory weakness may lead people with MCI to use other less reliable forms of memory monitoring