てんかんと認知症

認知症とてんかんの関係

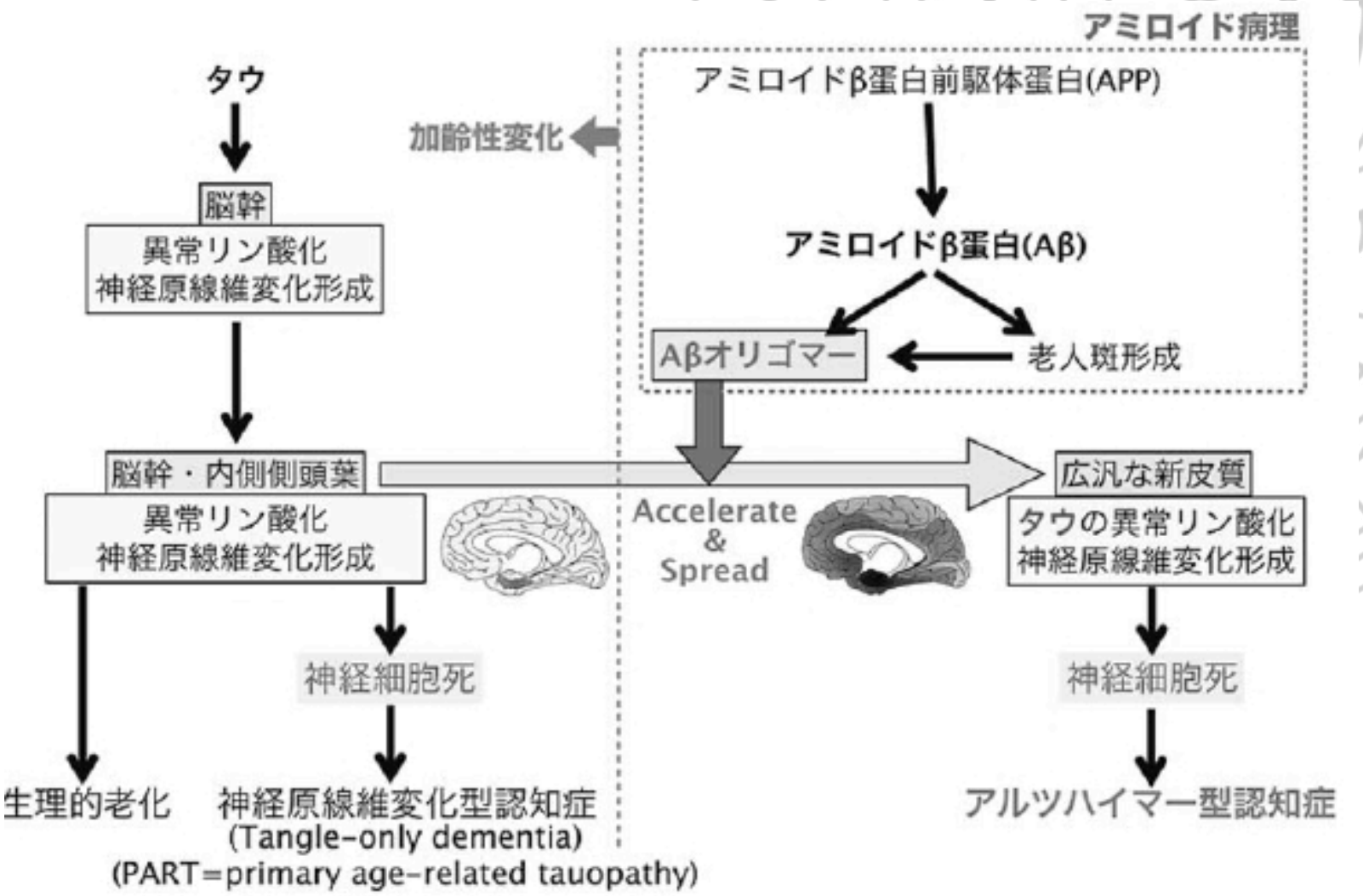
認知症はてんかんの合併率が高い！！！

1. アルツハイマー病　(AD)；
   経過中にてんかんを呈する危険率は6-10倍(10-20%)
   発症時期はAD発症早期

2. レビー小体認知症；
   てんかんの発病率10%程度
   発作の発現率がADと異なり認知症の進行に伴い上昇する

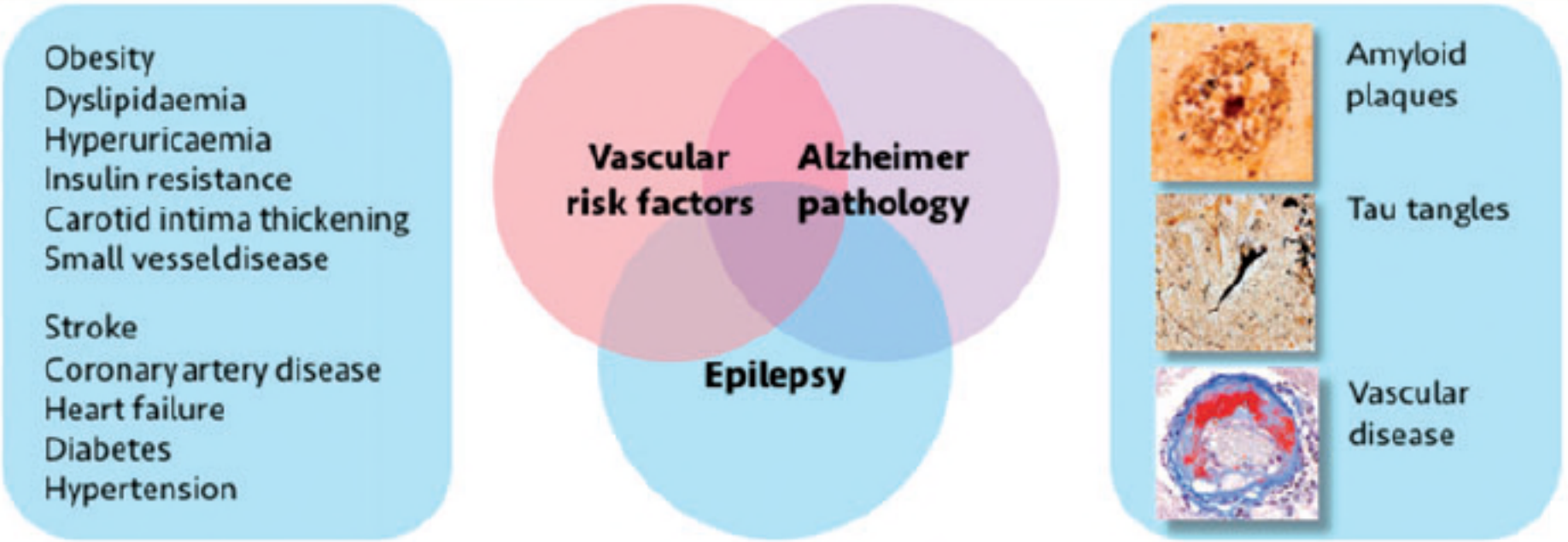
渡辺裕貴　ほか、2018

アルツハイマー病



徳田隆彦、2016

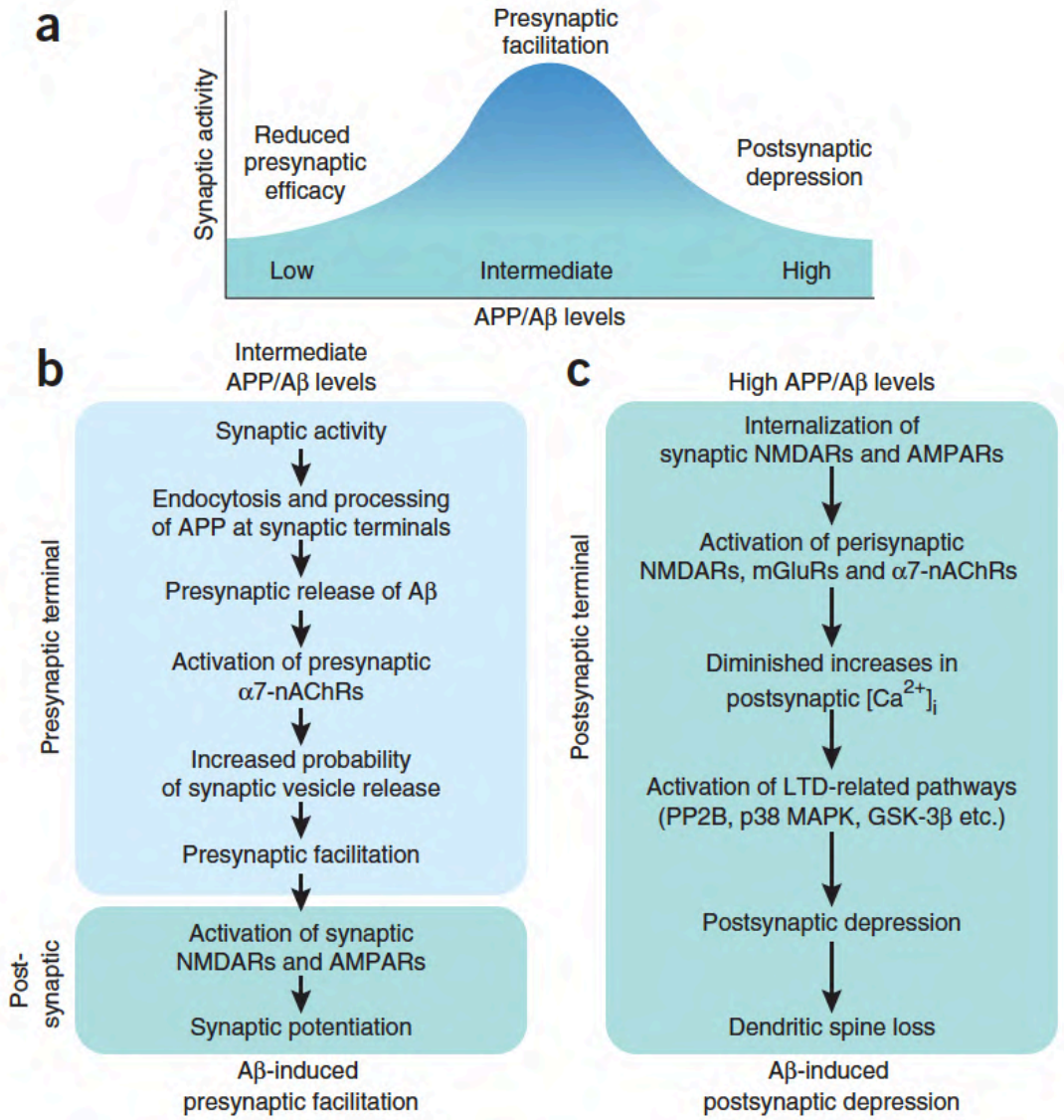
アルツハイマー病とてんかん



様々なリスクファクターが混在している

Sen et al. Brain 2018

アルツハイマー病のシナプス変化



アミロイドβによる神経細胞への影響

Presynaptic facilitation

Postsynaptic depression

Palop et al. Nature Neuroscience 2010

アルツハイマー病でてんかんが生じる？

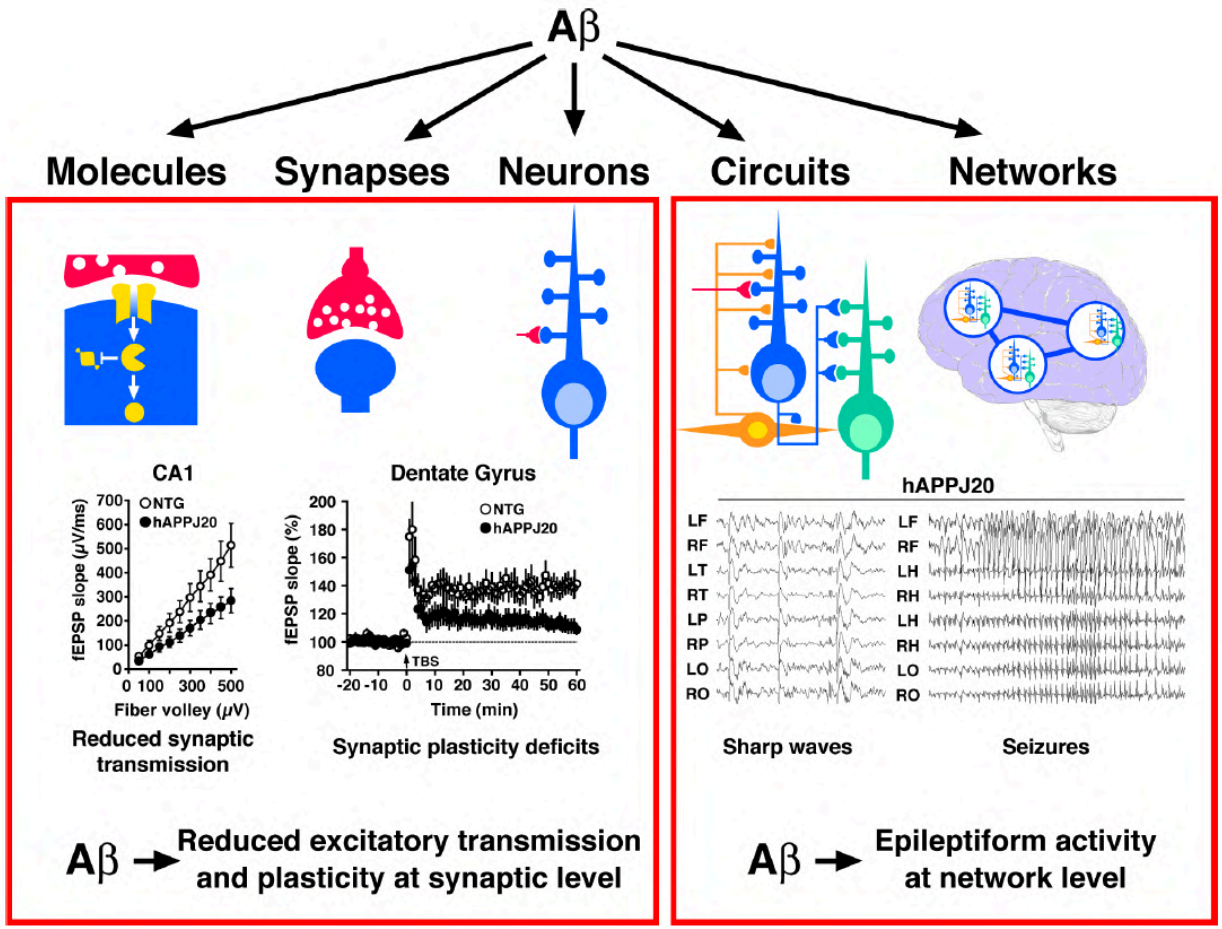


Figure 1. βAmyloid (Aβ) can affect neuronal activity at multiple levels of complexity

異常な神経ネットワークにより
てんかん性放電を生じる

Palop et al. Arch Neurol.2009

アルツハイマー病でのepileptogenesis

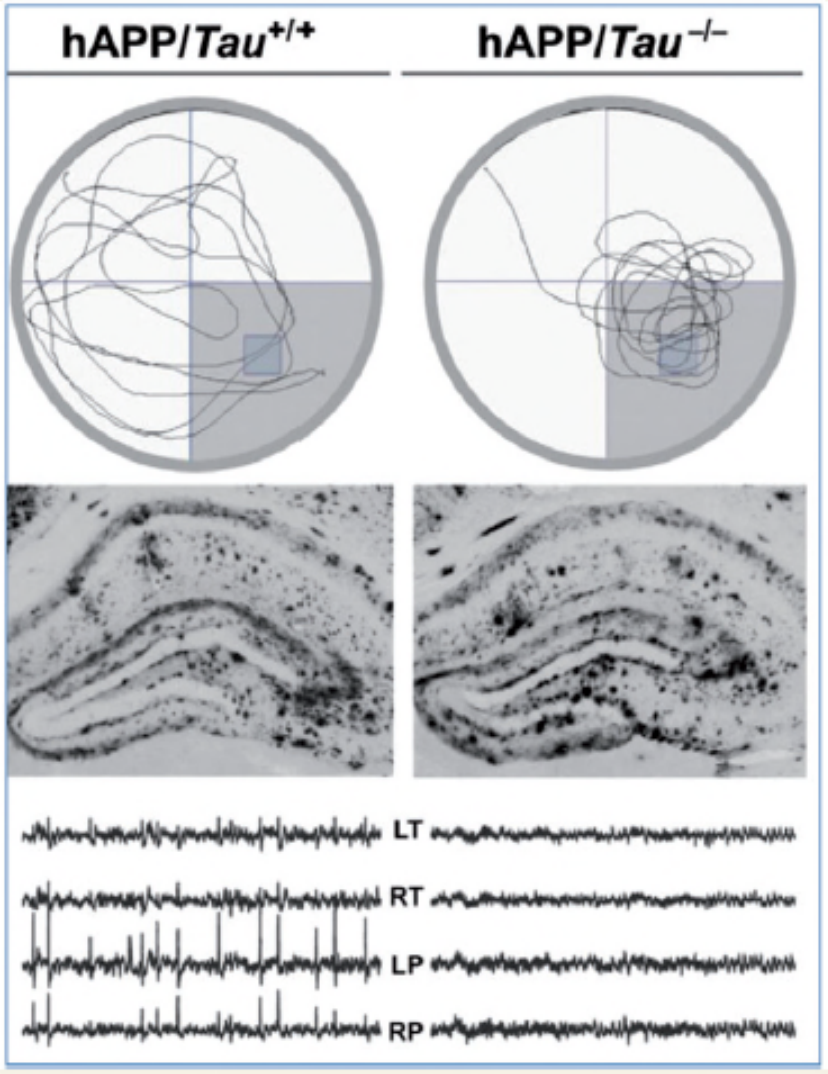
Panel: **Proposed mechanisms of epileptogenesis in Alzheimer's disease**

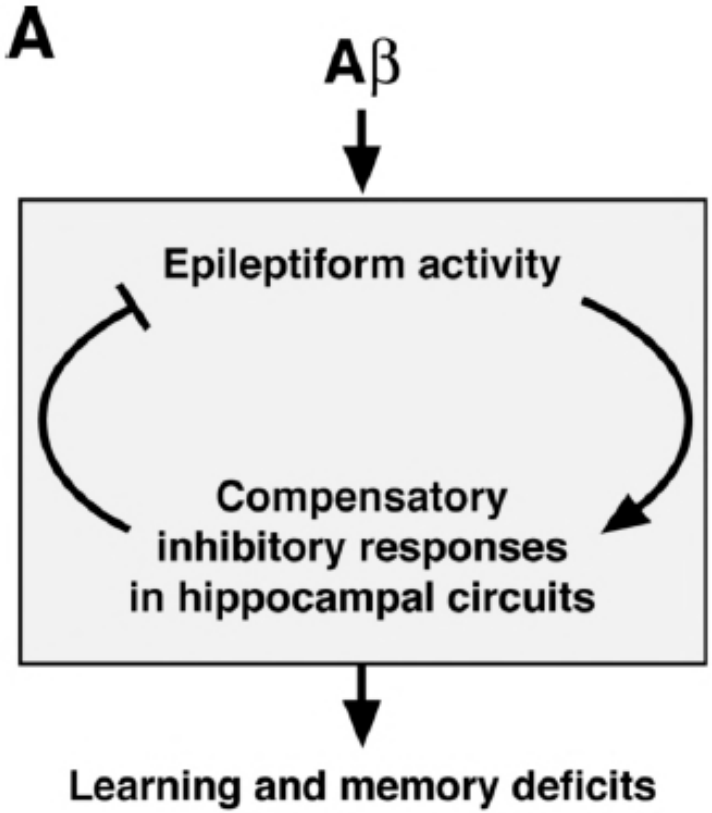
1. Extrasynaptic glutamate spillover due to impaired glial or neuronal glutamate transporters[30,31]
2. Tau-induced enhancement of presynaptic glutamate release[32]
3. Reduced axonal and dendritic transport of cargoes (eg, mitochondria) that regulate neuronal excitability[33-35]
4. Altered trafficking and surface expression of postsynaptic AMPA and NMDA receptors[29,36]
5. Altered amounts of voltage-gated ion channels in the brain[37-39]
6. Fyn-mediated alterations in NMDA activity[29,40-42]
7. Selective impairment of GABAergic interneurons in the hippocampus and parietal cortex[31,37,43-46]
8. Shortened dendrites, lowering threshold for action potential generation[47]
9. Impaired cortical input to the reticular thalamic nucleus and subsequent disinhibition of thalamic relay nuclei and their cortical and limbic targets[48]
10. Increases in cholinergic tone before the degeneration of cholinergic pathways[49]

アミロイドβがトリガーとなり、様々なメカニズムが想定さてている。

Vossel et al. Lancet Neurol 2017

アルツハイマー病での負の連鎖





Palop et al. Arch Neurol.2009
Sen et al. Brain 2018

アルツハイマー病と海馬硬化症

doi:10.1093/brain/awr053 Brain 2011: 134; 1506–1518 | 1506

BRAIN
A JOURNAL OF NEUROLOGY

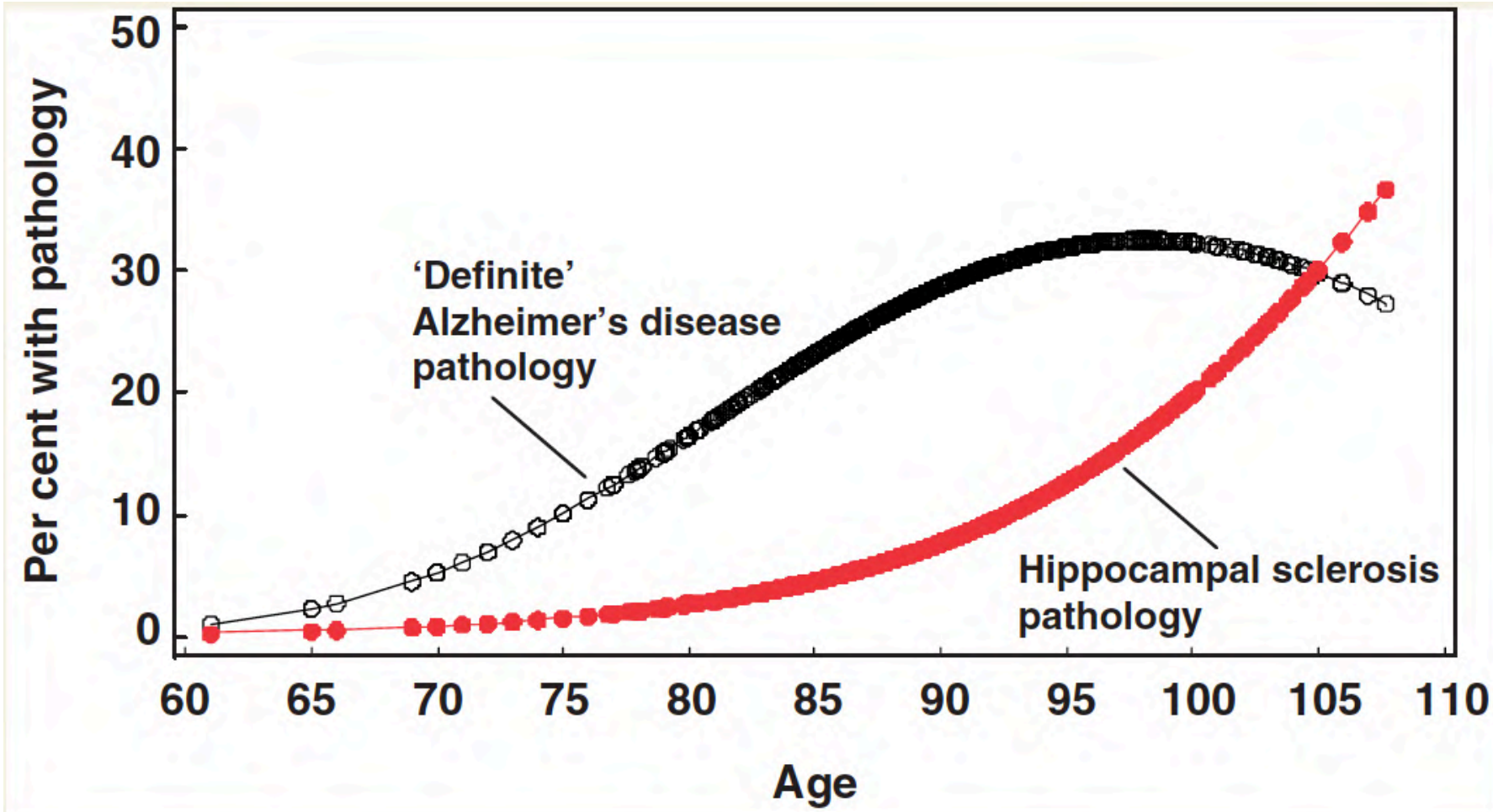
Hippocampal sclerosis in advanced age: clinical and pathological features

Table 1 Cases with hippocampal sclerosis ($n = 106$) and controls ($n = 1004$) by Alzheimer's disease (Braak V/VI) status; mean age and final MMSE scores (±SD)

	Hippocampal sclerosis positive				Hippocampal sclerosis negative			
	Alzheimer's disease positive	*n*	Alzheimer's disease negative	*n*	Alzheimer's disease positive	*n*	Alzheimer's disease negative	*n*
UK-Alzheimer's Disease Centre								
Age at death	87.2 ± 6.1	24	88.2 ± 8.2	20	81.1 ± 8.4	262	83.0 ± 9.9	259
Final MMSE	9.4 ± 8.1	23	19.6 ± 8.6	16	11.7 ± 9.0	225	24.6 ± 7.5	245
Nun Study								
Age at death	93.1 ± 4.6	22	93.7 ± 5.8	31	91.5 ± 4.3	90	89.5 ± 5.4	351
Final MMSE	6.1 ± 6.8	22	11.9 ± 9.2	31	10.1 ± 10.3	90	21.0 ± 8.9	351
Georgia Centenarians								
Age at death	102.7 ± 2.7	4	101.4 ± 2.7	5	102.0 ± 2.7	13	102.3 ± 2.4	29
Final MMSE	0.0 ± 0.0	4	14.2 ± 7.8	5	8.2 ± 7.6	12	18.3 ± 7.7	29
All groups								
Age at death	91.1 ± 6.9	50	92.4 ± 7.5	56	84.4 ± 9.3	365	87.4 ± 8.8	639
Final MMSE	7.2 ± 7.6	49	14.5 ± 9.4	52	11.1 ± 9.4	325	22.3 ± 8.6	625
Total (*n*)	106				1004			

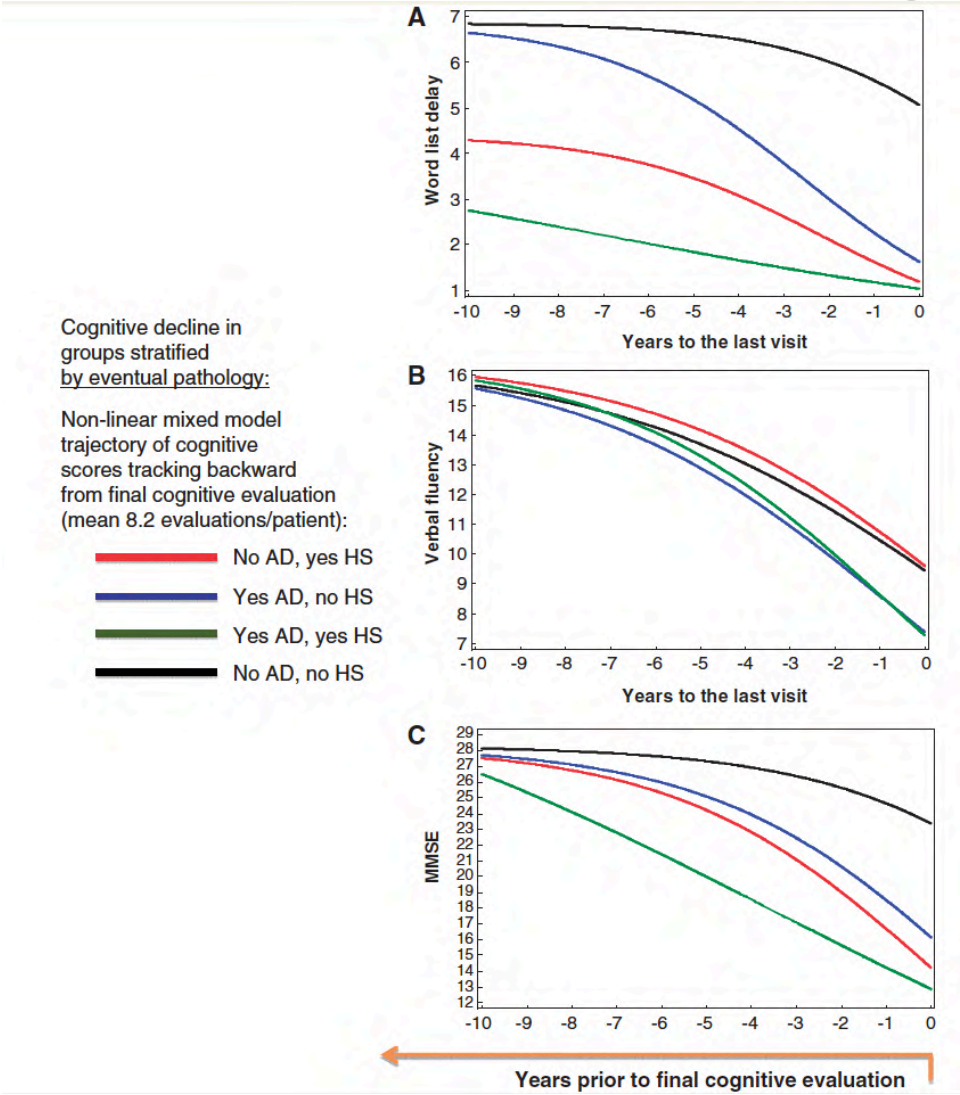
Nelson et al. Brain 2011

アルツハイマー病と海馬硬化症



Nelson et al. Brain 2011

アルツハイマー病と海馬硬化症



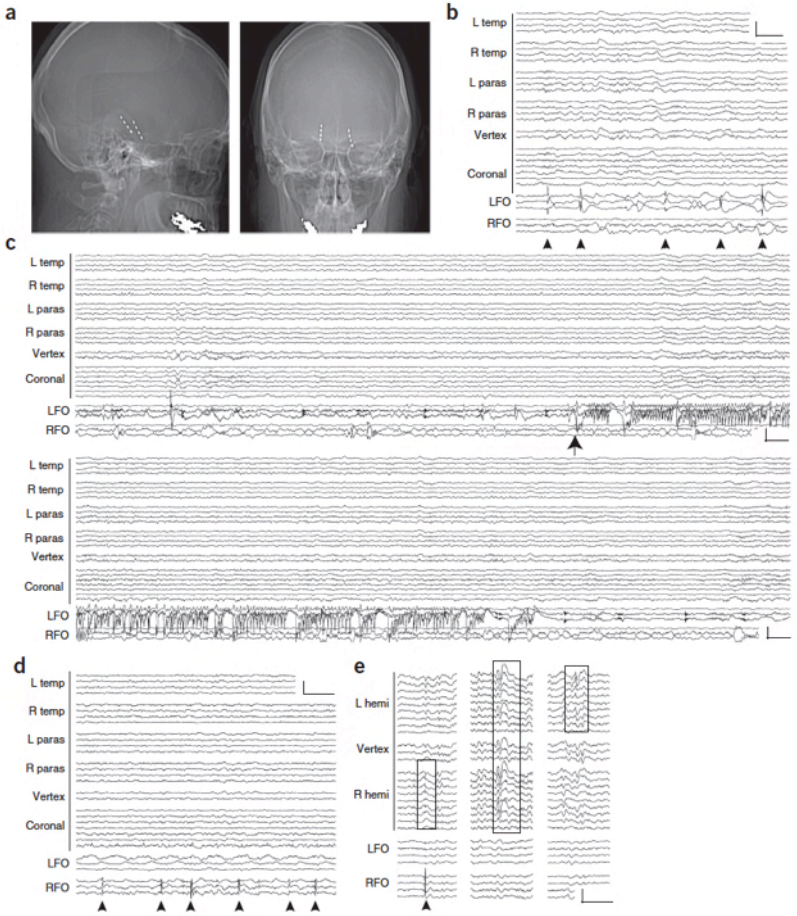
アルツハイマー病
+ 海馬硬化症

→高次機能低下が著明

Nelson et al. Brain 2011

アルツハイマー病とてんかん性放電

Silent hippocampal seizures and spikes identified by foramen ovale electrodes in Alzheimer's disease



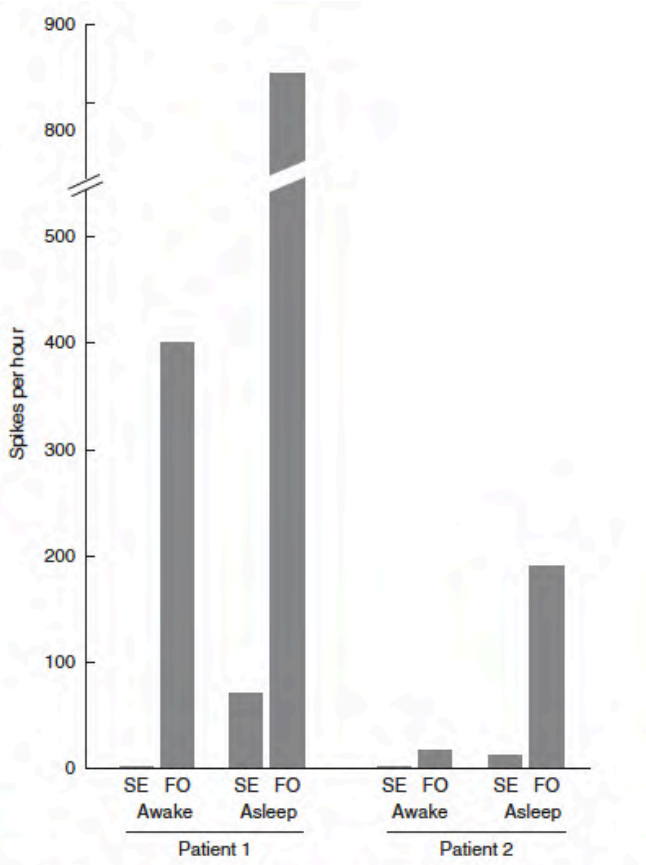
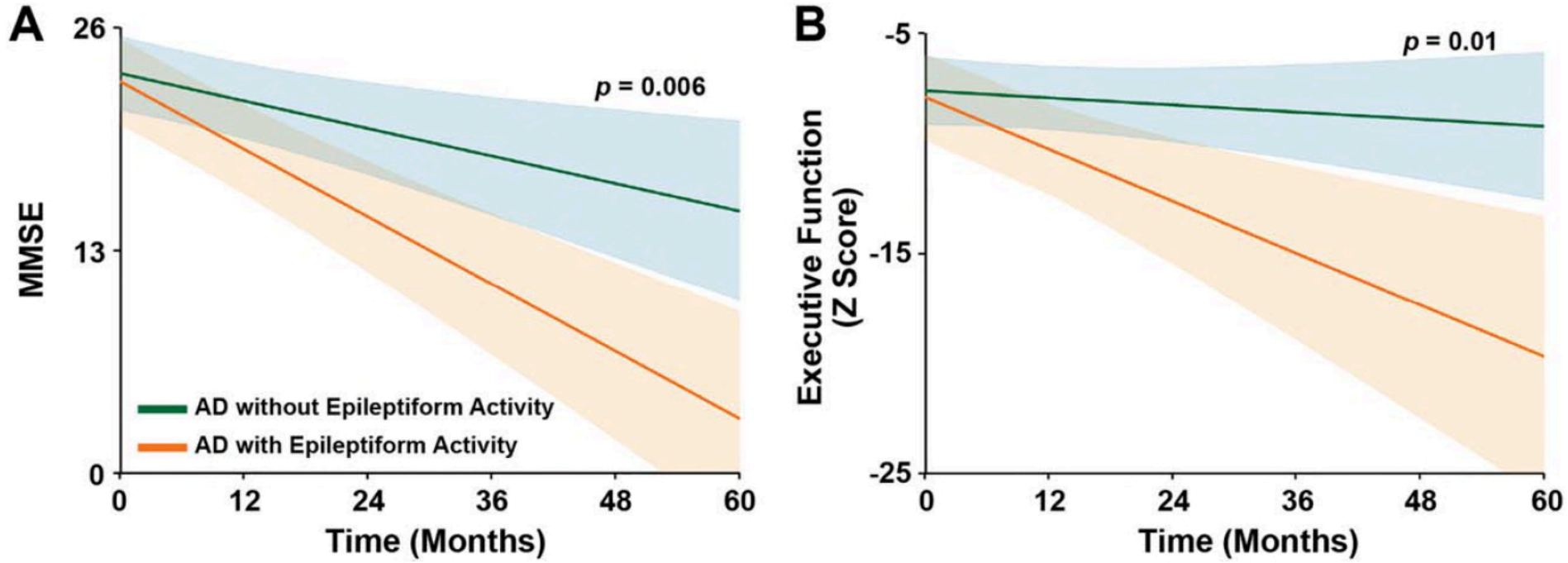


Figure 2 mTL spikes detected on FO electrodes are absent from scalp EEG recordings. Quantification and comparison of spike frequencies simultaneously observed on scalp EEG (SE) and FO electrodes during wakefulness and sleep for patients 1 and 2.

Lam et al. Nature Medicine 2017

アルツハイマー病とてんかん性放電

アルツハイマー病患者において42.4%で
subclinical epileptiform activity



Vossel et al. Neurology 2017

アルツハイマー病とてんかん性放電

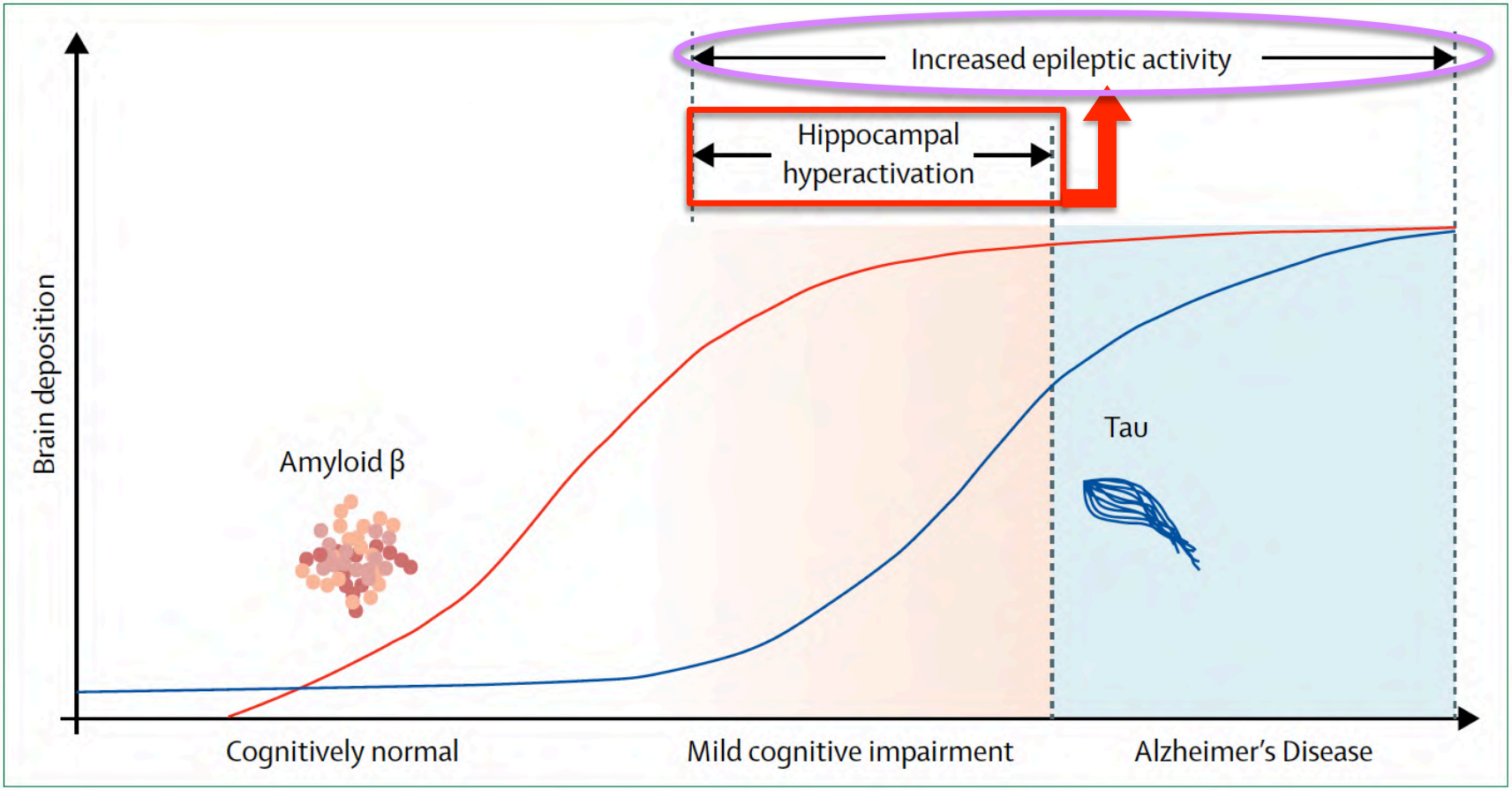


Figure: **Hypothetical model of the correlation between amyloid β and tau deposition and network alterations in Alzheimer's disease**

Vossel et al. Lancet Neurol 2017