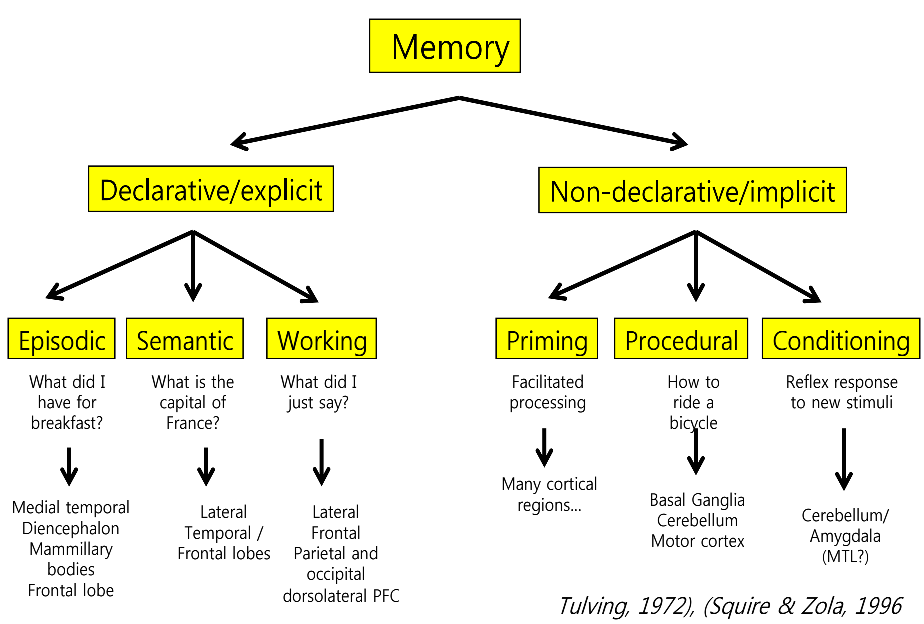
Modulating Memory Through Brain Stimulation

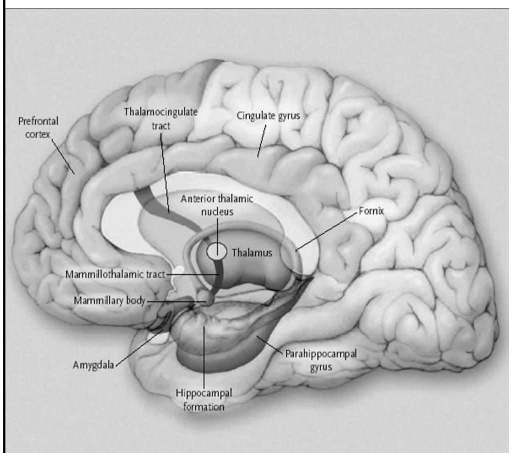
박 용 숙

중앙대학교 의과대학 신경외과학교실

Taxonomy of (long-term)Memory

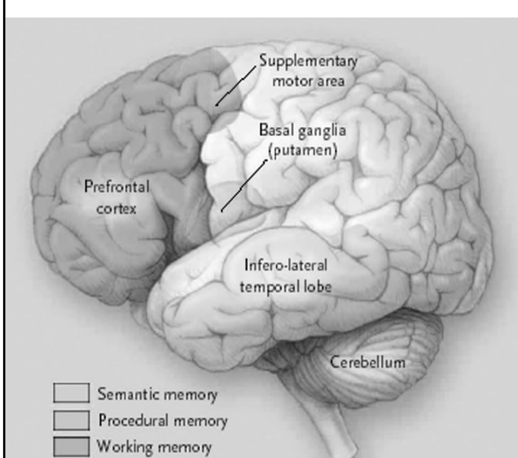


Episodic memory



- Core of the episodic memory system: medial temporal lobes (hippocampus, parahippocampus)
- Other related structures: basal forebrain with the medial septum and diagonal band of Broca, the retrosplenial cortex, the presubiculum, the fornix, mammillary bodies, the mammillothalamic tract, and the anterior nucleus of the thalamus
- 이 부분이 손상된 환자들은 일화기억을 인출해내는데 문제를 보이는데, 그에 비해 의미기억에 대해서는 큰 문제를 나타내지 않는다.

Semantic Memory

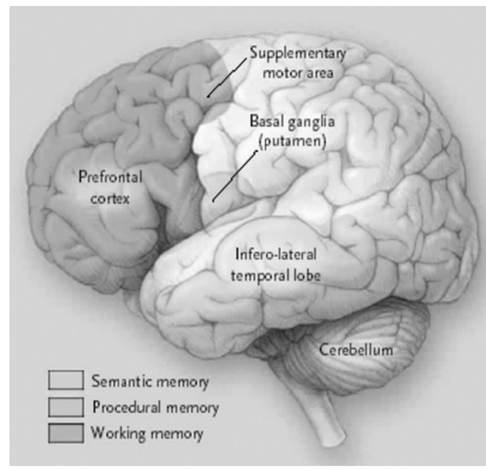


- Semantic memory may reside in **multiple and diverse cortical areas**
- **The anterior and inferolateral temporal lobes** are important in the naming, categorization tasks by which semantic memory is typically assessed.

- Refers to store of **knowledge** (color of broccoli, what a fork is used for)
- Separate memory systems with episodic memory
- Previously acquired semantic memory is spared in patients with severe impairment of the episodic memory system

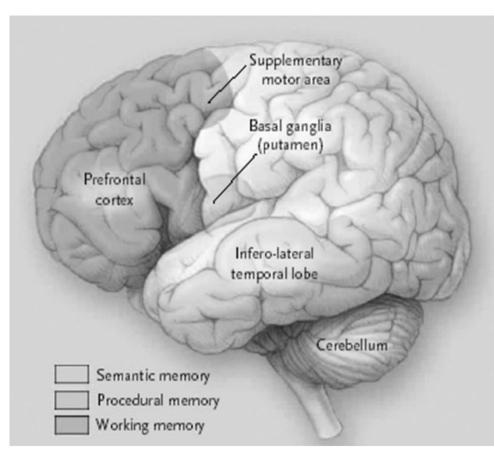
Working Memory

- Attention, concentration, short-term memory
- **Prefrontal cortex**
- Spatial working memory: more involved right side
- Phonologic working memory: more involved left side

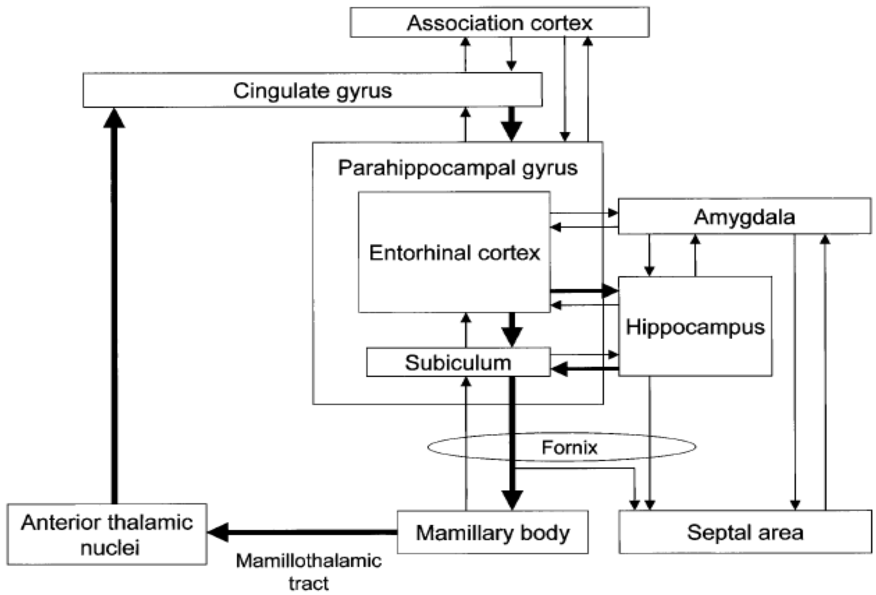


Procedural Memory

- ability to learn cognitive and behavioral skills, automatic, unconscious level (to ride a bike, play the piano)
- Separate and distinct from the episodic memory system
- Functional image: **supplementary motor area, basal ganglia, and cerebellum**



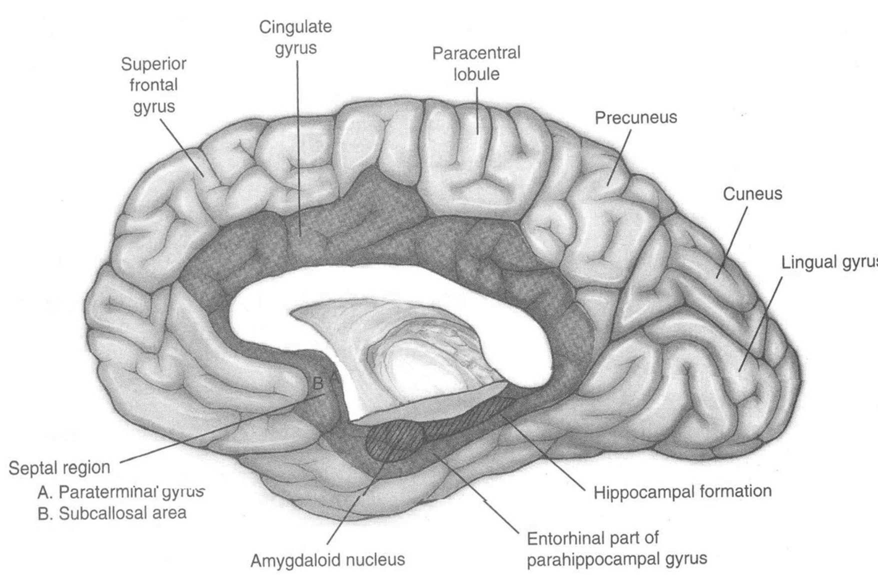
Limbic system with circuit of Papez



H.Oikawa, et al. Neuroradiology 43, 2001

Limbic lobe: **Cingulate gyrus, Septal area, Parahippocampal gyrus**

Limbic System: **Limbic lobe, Hippocampal formation, Amygdala, Hypothalamus**



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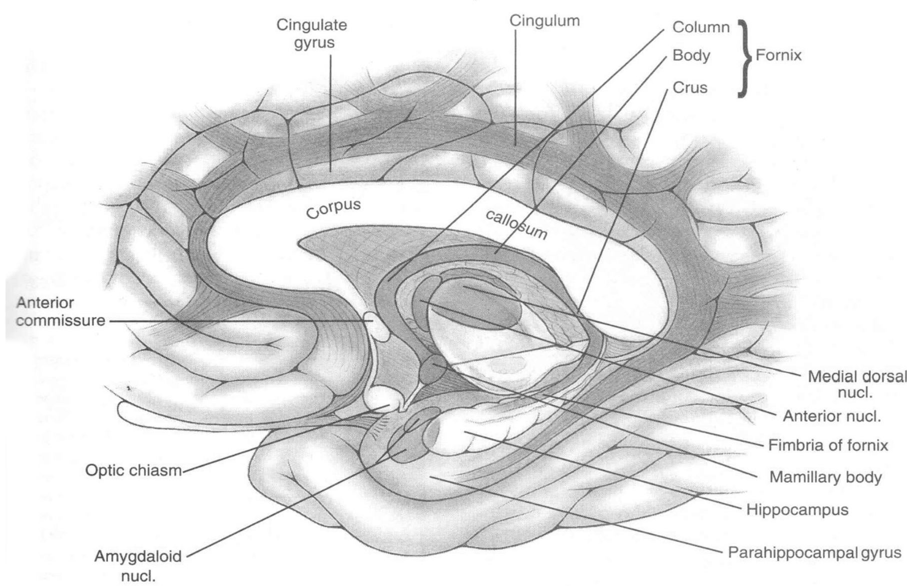
Limbic system and Papez circuit



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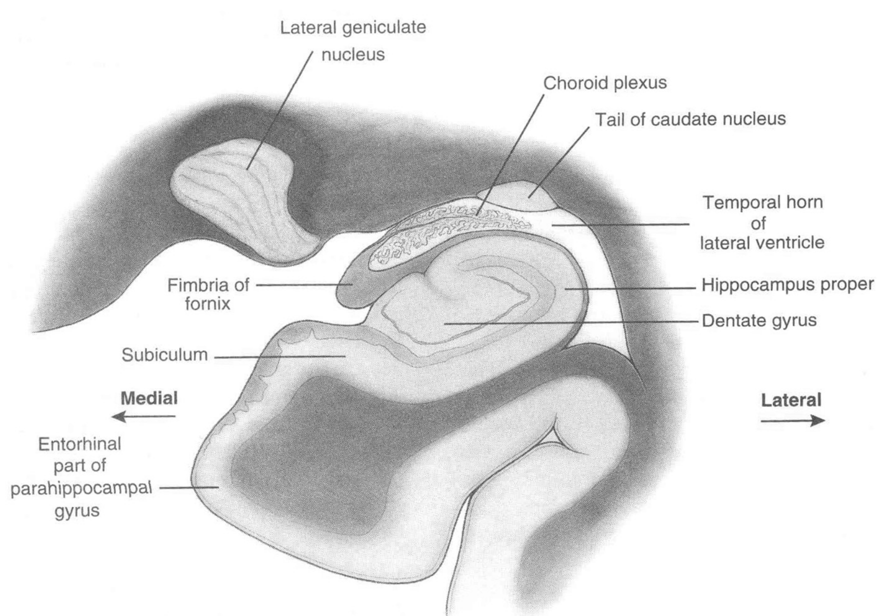
Hippocampal formation



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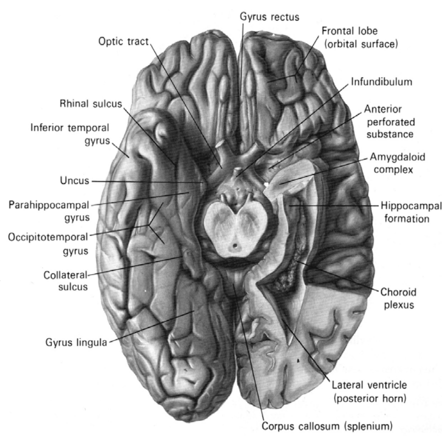
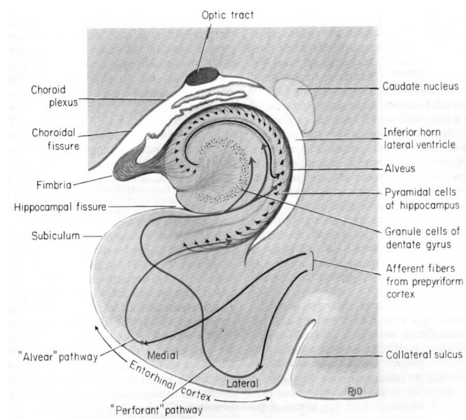
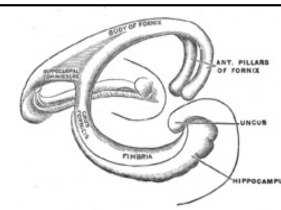
Hippocampal formation and aff. pathways

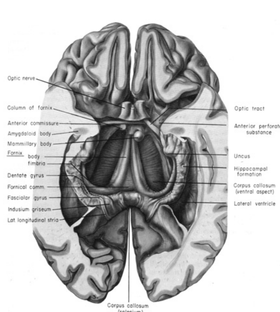


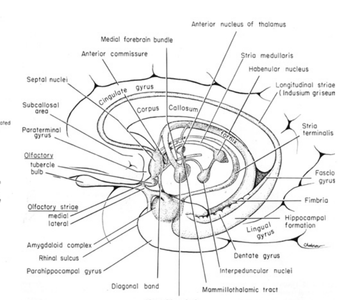


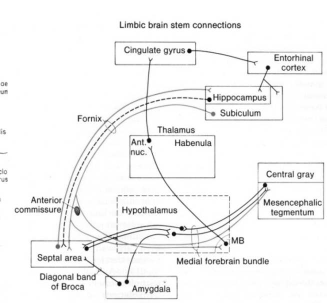
Fornix



- large axonal bundle, 1.2 million axons
- major inflow and output pathway from the hippocampus and medial temporal lobe

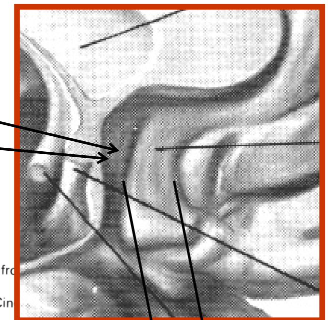


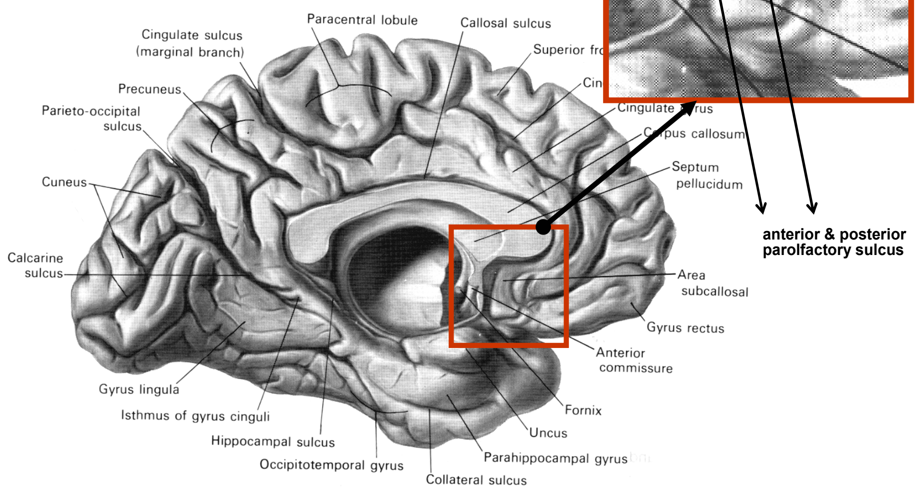




Septal Area

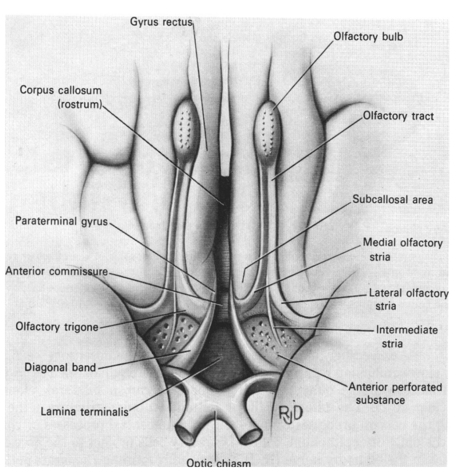
1. Subcallosal (parolfactory) area
2. Paraterminal (subcallosal) gyrus

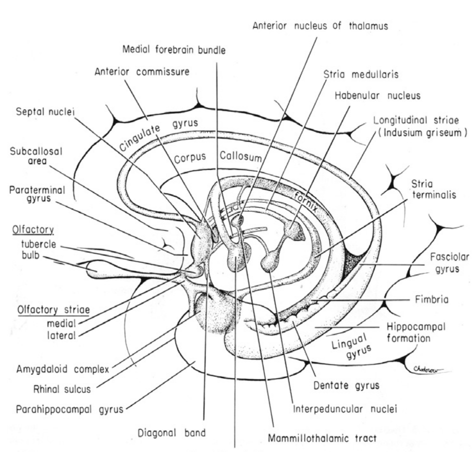




Septal nuclei

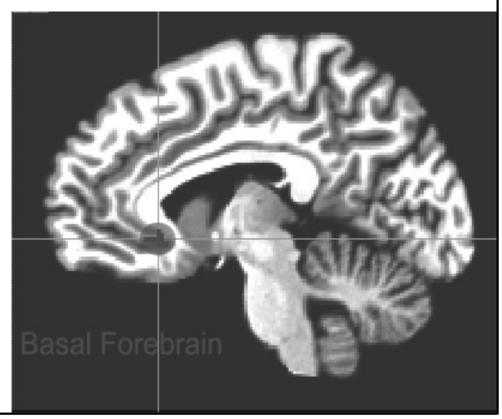
- Medial septal nuclei → diagonal band → amygdala complex: cholinergic
- Lateral septal nuclei



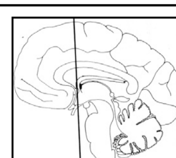


Basal forebrain

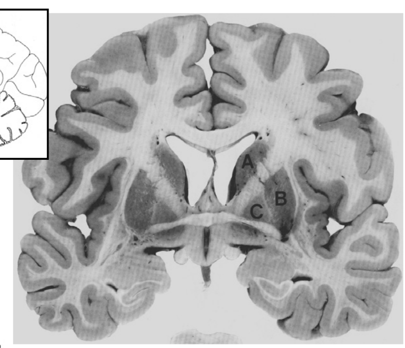
- A collection of structures: nucleus basalis Meynert, diagonal band of Broca, medial septal nuclei, substantia innominata
- Located rostrally and ventrally to the striatum.
- Major cholinergic output of CNS
- Critical for declarative memory

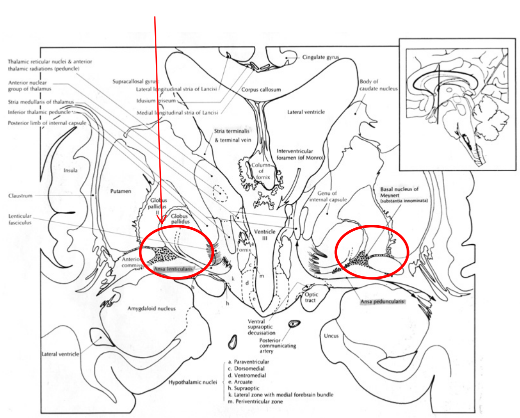


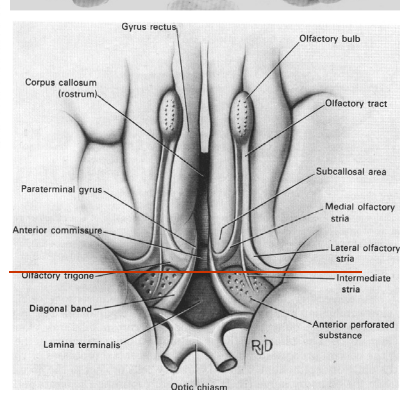
Substantia innominata
(basal nucleus of Meynert)



- anterior commissure의 복측
- nucleus of diagonal band of Broca 등과 함께 APS에 포함됨.
- Major source of cholinergic innervation of the entire cerebral cortex







Modulating memory through brain stimulation

- stimulate structures of the memory circuit
- fornix, entorhinal cortex, basal nucleus of Meynert (NBM), hippocampus, anterior thalamus

Hescham S. Neurosci Biobehav Rev. 2013 Dec;37:2666-75.

Preclinical study in animals

Structure	Subject	Type of stimulation	Memory task	Effect	Reference
Anterior thalamic nucleus	Rats $N=4$	Bilateral, 2.5 V, 130 Hz and 90 µs pulse width, duration 1 h		High-frequency stimulation of the ANT restores corticosterone-suppressed hippocampal neurogenesis	Toda et al. (2008)
	Rats $N=12$	Bilateral, 500 µA, 130 Hz and 90 µs pulse width, acute stimulation	Contextual fear conditioning, spatial alternating test	High frequency stimulation of 500 µA disrupted the acquisition of contextual fear conditioning and impaired spatial memory	Hamani et al. (2010)
	Rats $N=17$	Bilateral, 2.5 V, 130 Hz and 90 µs pulse width, duration 1 h	Non-matching-to-Sample and delayed non-matching-to-sample	ANT stimulation administered to corticosterone-treated rats one month prior to testing improved performance on a delayed non-matching to sample task and increased hippocampal neurogenesis	Hamani et al. (2011)
Fornix	Rats (model of experimental dementia) $N=10$	Bilateral, 100 and 200 µA, 10 and 100 Hz, 100 µs pulse width, acute stimulation	OLT	Memory enhancement in high current densities (frequency-independent)	Hescham et al. (2013)
Entorhinal cortex	Mice $N=25$	Bilateral, 50 µA, 130 Hz and 90 µs pulse width, for 1 h during surgery	Morris water maze	Water-maze memory was facilitated 6 weeks after stimulation due to hippocampus-dependent neurogenesis	Stone et al. (2011)
Ncl. Basalis Meynert (NBM)	Rats $N=10$	Unilateral, 200 µA, 50 Hz and 0.5 ms pulse width, duration of 100 min		In adult, but not aged rats, NGF levels were significantly increased	Hotta et al. (2009)

Experimental findings in human

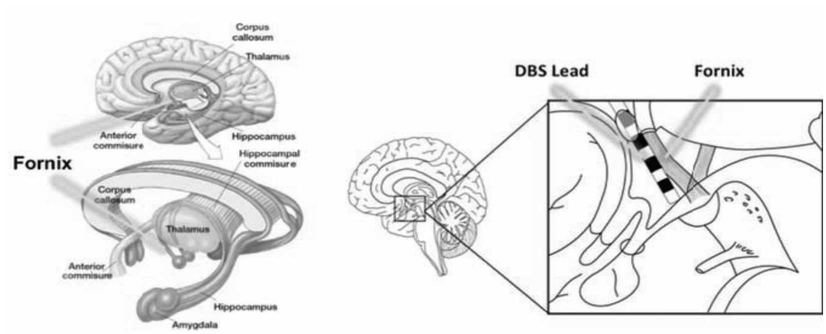
Structure	Subject	Type of stimulation	Memory task	Effect	Reference
Fornix	Human (morbid obesity patient) $N = 1$	Bilateral, 3–5 V, 130 Hz and 60 µs pulse width, continuous for 3 weeks	Neuropsychological tests, e.g. verbal learning test, WAIS attention index, spatial associative learning, etc.	Significant improvements on the California Verbal Learning Test and Spatial Associative Learning Test	Hamani et al. (2008)
	Human (AD patients) $N = 6$	Bilateral, 3.0–3.5 V, 130 Hz, and 90 µs pulse width, continuous for 12 months	ADAS-cog, MMSE	Possible improvements and/or slowing in the rate of cognitive decline at 6 and 12 months in some patients	Laxton et al. (2010)
	Human (AD patient) $N = 1$	Bilateral, 2.5 V, 130 Hz and 210 ms pulse width, continuous for 12 month	ADAS-cog, MMSE, Free and Cued Selective Reminding Test	Cognitive scores worsened after 6 months but returned to baseline after 12 months of chronic DBS	Fontaine et al. (2013)
Entorhinal cortex	Human (epilepsy patients) $N = 7$	Bilateral, 0.5 to 1.5 mA, 50–130 Hz and 300–450 µs pulse width, cycle of 5 s on and 5 s off	Virtual memory task	Memory enhancement and theta-phase resetting	Suthana et al. (2012)
Ncl. Basalis Meynert (NBM)	Human (senile dementia of Alzheimer's type patient) $N = 1$	Unilateral, 3 V, 50 Hz and 210 µs pulse width, cycling between 15 s on and 12 min off throughout the day and night, repetitive for 9 months		No clinical effect, but increased cerebral glucose metabolism	Turnbull et al. (1985)
	Human (Parkinson patient) $N = 1$	NBM: Bilateral, 1 V, 20 Hz, and120 µs pulse width STN: bilateral, 3.5–4.2 V, 130 Hz and 60 µs pulse width	Neuropsychological tests, e.g. clock drawing, letter-number-span, auditory verbal learning, etc.	Combined bilateral stimulation lead to improvement in attention, concentration, alertness, drive, and spontaneity	Freund et al. (2009)
Hippocampus	Human (epileptic patients) $N = 12$	Bilateral, 4–6 mA, single pulse, 1 ms pulse width	Computerized recognition test	Bilateral stimulation was associated with a pronounced decrease in memory scores	Lacruz et al. (2010a,b)

Experimental findings in human

- These experimental findings suggested that the fornix and the entorhinal cortex may be considered as interesting targets for dementia.
- Hippocampus appeared to be a less appealing structure for DBS to enhance memory.

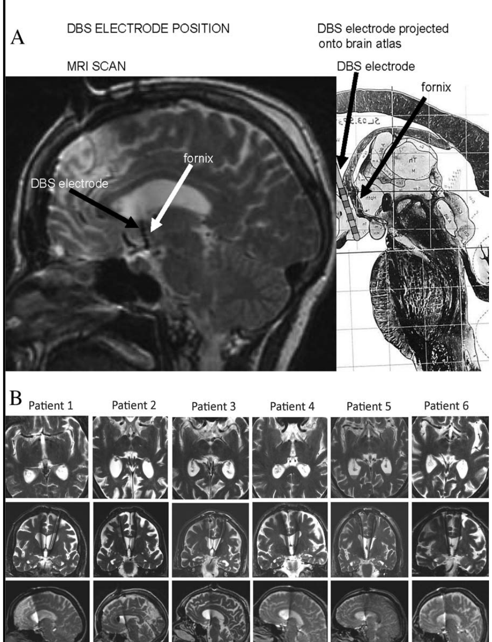
Clinical studies - Fornix/hypothalamus DBS for AD

- Aim: stimulation to alter activity in medial temporal memory circuits
- 6 patients. aged 40 to 80 years old, probable AD, diagnosis within the past 2 years, CDR score of 0.5 or 1.0, MMSE 18-28, cholinesterase inhibitors for a minimum of 6 months
- chronic stimulation 3.0-3.5V, 130Hz, 90µsec
- neuropsychological assessments at baseline, 1, 6, and 12 months



Laxton et al: ANN NEUROL 2010;68:521–534

Electrode target



- 2 mm anterior and parallel to the vertical portion of the fornix within the hypothalamus.
- The ventralmost contact was 2 mm above the dorsal surface of the optic tract,
- 5 mm from the midline
- implanted bilaterally

Laxton et al: ANN NEUROL 2010;68:521–534

Results of Fornix/hypothalamus DBS

- FDG PET: increases in cortical glucose metabolism
- Clinical evaluation suggested possible slowing in the rate of progressive cognitive decline.
- The authors hypothesized that stimulation of the fornix leads to an enhanced neurogenesis and the release of neurotrophic factors in the hippocampus.

Laxton et al: ANN NEUROL 2010;68:521–534

A prospective pilot study: feasibility of DBS of the fornix in AD patients (France)

- **Inclusion criteria**
  under 70 years of age,
  MMSE between 20 and 24
  predominant impairment of episodic memory
  fulfil the AD DSM IV criteria
  less than 2 years of symptoms
  9/110 patients were suitable
  only one patient underwent surgery
- **Results**: Cognitive scores worsened after 6 months but returned to baseline after 12 months of chronic DBS.

Fontaine D, et al. J Alzheimers Dis. 2013 Jan 1;34(1):315-23.

New clinical trials - ADvance study

- a double-blind randomized controlled feasibility study to evaluate acute and long-term safety
- being conducted in the U.S. and in Canada
- will involve 20 mild AD patients
- DBS electrodes implantation in the fornix
- immediately on for half of the patients
- after 12 months on for the other half
- Efficacy outcomes will be measured at 12 months - ADAS-cog, clinical dementia rating, glucose metabolism by FDG-PET

Stimulation of the Basal Nucleus of Meynert in Senile Dementia of Alzheimer's Type

- Chronic, cyclical, unilateral, monopolar stimulation of the left NBM in a patient with mild to moderate AD
- Stimulation parameters: 3 V, 50 Hz, 210 μs, cycling between 15 s on and 12 min off through-out the day and night
- For enhancing residual NBM cholinergic output

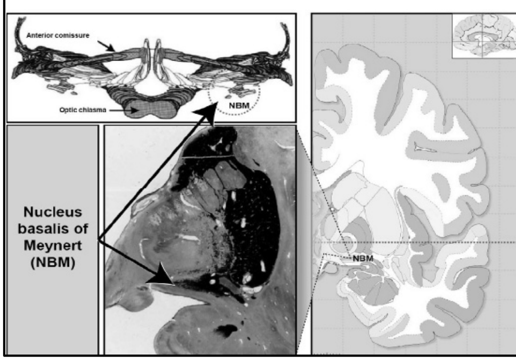
Results

- No clinical response to the stimulation 8 months after the procedure
- FDG-PET scans
  - Rt hemisphere: decreased glucose metabolism in the frontal (21%), temporal (24%), parietal (10%), occipital lobes (7.5%)
  - Stimulated Lt hemisphere
    decreased glucose metabolism in the frontal (12%), occipital lobes (4.1%) no change in the parietal lobe increased metabolism in the temporal lobe (1.5%)

Turnbull I.M. Appl Neurophysiol 1985;48:216–221

Nucleus basalis Meynert DBS in a patient with Parkinson apraxia

- A parkinson patient with prominent symptoms regarding working memory, concentration, attention deficits, apraxia
- DBS of nucleus basalis Meynert and STN
- **Result: slight but sustained improvement of cognitive functioning (attention, concentration, alertness, spontaneity, apraxia, ataxia)**



Barnikol TT, et al. Mov Disord. 2010

A clinical study in Germany

- is currently being performed with six mild AD (http://clinicaltrials.gov/ct2/show/NCT01094145).
- two weeks after DBS electrodes in the NBM
- conventional stimulation will take place as a double blind, randomized change between on and off stimulation periods.
- assessment: after one year, cognitive abilities, psychopathological well being, quality of life, praxia, nutritional condition

Summary 1

- DBS of the fornix is expected to provide symptomatic relief for verbal recollection, recall and recognition as well as episodic memory
- NBM stimulation might modulate apraxia and alertness.
- Promising results have also been observed with entorhinal cortex stimulation.

Summary 2

- **The fornix**
  - Not dependent on the frequency of stimulation
  - On current densities
  - High current produced beneficial effects on memory irrespective of the frequency
- **The NBM**
  - Rather dependent on frequency
  - Low to medium frequency stimulation (50 Hz): increased NGF(nerve growth factor) release from the NBM in anaesthetized rats

Summary 3

- **The entorhinal cortex**
  - Demonstrates effects on neurogenesis
  - Theta-phase resetting within the hippocampus
  - when stimulated with low current densities
  - Perforant pathway might be activated upon stimulation inducing neurogenesis in the dentate gyrus
- **Anterior nucleus of the thalamus**
  - Contradictory stimulation effects on memory
  - High frequency stimulation of 130 Hz: effects on neurogenesis
  - Application of high currents (500 μA) within this structure produced memory disruption