Modifying Therapies in Alzheimer’s disease

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From the first preclinical evidence of effectiveness of vaccination against Aβ in mice...

**Immunization with amyloid-β attenuates Alzheimer-disease-like pathology in the PDAPP mouse**


*Elan Pharmaceuticals, 800 Gateway Boulevard, South San Francisco, California 94080, USA*

**Nature, 1999**

to the development of many disease-modifying drugs....
<table>
<thead>
<tr>
<th></th>
<th>Avagacestat</th>
<th>ACC-001</th>
<th>NewGam, IVIG</th>
<th>Gantenerumab</th>
<th>BAN2401</th>
<th>BIIB 037</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sponsor</strong></td>
<td>Bristol-Myers Squibb</td>
<td>Janssen Alzheimer Immunotherapy</td>
<td>Octapharma, Sutter Health</td>
<td>Roche</td>
<td>Eisai</td>
<td>Biogen Idec</td>
</tr>
<tr>
<td><strong>Clinicaltrials.gov EudraCT number</strong></td>
<td>NCT00890890</td>
<td>NCT01227564</td>
<td>NCT01300728</td>
<td>NCT01224106 ECT2010-19895-66</td>
<td>NCT01767311</td>
<td>NCT01677572</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td>Prodromal AD</td>
<td>Early AD</td>
<td>MCI</td>
<td>Prodromal AD</td>
<td>MCI due to AD or early AD</td>
<td>Prodromal or mild AD</td>
</tr>
<tr>
<td><strong>Sample size; number of sites</strong></td>
<td>270; 72</td>
<td>63; 35</td>
<td>50; 1</td>
<td>770; 159</td>
<td>800; 67</td>
<td>160; 12</td>
</tr>
<tr>
<td><strong>Clinical criteria</strong></td>
<td>Memory complaint, MMSE 24–30, CDR 0.5, impairment on WMS Logical Memory II or FCSRT</td>
<td>Concern about cognition, MMSE ≥25, CDR 0.5, not dementia</td>
<td>Amnestic MCI, MMSE 24–30 CDR 0.5</td>
<td>Age 50–85 years, worsening memory, MMSE ≥24, impairment on Logical Memory II or FCSRT</td>
<td>Age 50–90 years, MMSE 23–30, CDR 0.5, impairment on Logical Memory II</td>
<td>MMSE 20–30, including cut-off on FCSRT &lt;27 CDR 0.5 or 1</td>
</tr>
<tr>
<td><strong>Biomarker criteria</strong></td>
<td>CSF Aβ_{42} &lt;200 pg mL^{-1} or t-tau/Aβ_{42} ≥0.39</td>
<td>Positive Aβ PET scan</td>
<td>Moderate or severe cortical or hippocampal atrophy</td>
<td>Positive Aβ PET scan</td>
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</tr>
<tr>
<td><strong>Duration</strong></td>
<td>2 years</td>
<td>2 years</td>
<td>2 years</td>
<td>2 years</td>
<td>1.5 years</td>
<td>2.5 years</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Primary: safety, CSF markers</td>
<td>Primary: brain Aβ, safety, tolerability; secondary: biomarkers, immunogenicity, clinical outcomes</td>
<td>MRI ventricular volume, AD, clinical ratings</td>
<td>Primary: CDR-SB and brain Aβ; secondary: ADAS-cog, FAQ, safety, pharmacokinetics</td>
<td>Primary: composite clinical score at 1 year; secondary: hippocampal volume, brain amyloid</td>
<td>Primary: safety, tolerability; secondary: Aβ PET, PK, immunogenicity</td>
</tr>
</tbody>
</table>

MCI, Mild Cognitive Impairment; MMSE, Mini Mental State Examination; CDR, Clinical Dementia rating scale; CDR-SB, Clinical Dementia rating scale, sum of boxes; CSF, cerebrospinal fluid; Aβ_{42}, amyloid-beta 1-42; t-tau, total tau; PET, positron emission tomography; MRI, magnetic resonance imaging; ADAS-cog, Alzheimer Disease Assessment Scale-Cognitive; IVIG, intravenous immunoglobulin; WMS, Wechsler Memory Scale; FCSRT, Free and Cued Selective Reminding Test; FAQ, Functional Activities Questionnaire.

Other drugs in prodromal Alzheimer's disease trials include the BACE-1 inhibitor MK-8931.

Data sources: www.clinicaltrials.gov; www.clinicaltrialsregister.eu; and http://www.medicine.ox.ac.uk/alois.

*Schneider et al, 2014*
2015: state of the art

- 2003: **AN 1792** → failed due to adverse events
- 2014: **Bapineuzumab** → failed to reach primary endpoints *(Salloway et al., 2014)*
- 2014: **Gantenerumab** → withdrawn in Dec 2014
- 2014: **i.v. Ig** → failed *(Dodel et al., 2014)*
- 2014: **Solanezumab** in moderate AD: failed *(Doody et al., 2014)*

- **semagacestat**
- **avagacestat** \(\gamma\)-secretase inhibitors → failed *

*Doody et al., 2014*

- **Solanezumab** → phase III: positive results only in mild AD
- **MK-8931** → BACE inhibitor, phase II-III
- **CAD 106** → phase II complete
Active immunotherapy: CAD106 first study in AD patients

Safety, tolerability, and antibody response of active Aβ immunotherapy with CAD106 in patients with Alzheimer’s disease: randomised, double-blind, placebo-controlled, first-in-human study

Bengt Winblad, Niels Andreasen, Lennart Minthon, Annette Floesser, Georges Imbert, Thomas Dumortier, R Paul Maguire, Kaj Blennow, Joens Lundmark, Matthias Staufenbiel, Jean-Marc Orgogozo, Ana Graf


- phase I, 52-ws study in 58 mild to moderate AD pts (2 cohorts), aged 50-80 yrs, randomly allocated to receive either CAD 106 or placebo
- primary objectives: safety and tolerability and to identify Aβ-antibody response (responders: patients with Ab-IgG serum titers>16 units at least once during the study)
- 56/58 reported minor adverse events. No cases of meningoencephalitis
- 67% of treated patients in cohort I and 82% in cohort 2 developed Aβ antibody response.
Alternative approaches: targeting inflammation

- Indomethacin
- Ibuprofen
- Rofecoxib
- Naproxen
- Diclofenac
- COX-2
- Aspirin
- Hydroxychloroquine
- Prednisone

Failed

Latta et al., 2014
Why did so many trials fail?

1) **Preclinical models:** the gap between mice and humans

2) Population: patient may not have AD but **other dementias** instead + too late treatment

3) Amyloid cascade: removal of plaques is **not sufficient** to halt the disease progression

*Sperling et al., 2014*
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*Sperling et al., 2014*
Mice: chosen because of the high degree of homology between coding sequences

But: low homology in terms non-coding/intronic DNA

Similar proteins, but completely different regulation (miRNA, methylation, etc ➔ epigenetics!)
Animal models for AD: limits of mice

- mice reflect the $\text{A}\beta$, **but not** $\tau$, pathology

- **do not have** a homologous $\text{A}\beta$ → they express a **human** $\text{A}\beta$ → antibodies do **not** cross-react with murine epitopes

- in **humans**: $\text{A}\beta$ multiple localizations (i.e. brain vessels)
Monkeys as models for AD

- Express Aβ

- With aging: develop senile plaques, although to a lesser extent as compared with humans, but no NFTs

- High amount of senile plaques and NFTs in an obese monkey

Now:
- drugs tested on monkeys (i.e. CAD 106)
Immunization of Rhesus Monkeys

Histology with antibodies from CAD 106 immunized Rhesus monkeys

**CAD106**-induced Aβ antibodies:

- **selectively bind** to amyloid plaques in mouse and human brain
- do not crossreact with cellular APP or brain cells
- no reactivity with peripheral tissues: **specific**!

*Staufenbiel, M. et al., 2006*
Independent replication of data

Bexarotene (Retinoid X Receptors antagonist)

ApoE-Directed Therapeutics Rapidly Clear β-Amyloid and Reverse Deficits in AD Mouse Models

Paige E. Cramer¹, John R. Cirrito², Daniel W. Wesson¹,³, C. Y. Daniel Lee¹, J. Colleen Karlo¹, Adriana E. Zinn¹, Brad T. Casali¹, Jessica L. Restivo², Whitney D. Goebel², Michael J. James⁴, Kurt R. Brunden⁴, Donald A. Wilson⁵, and Gary E. Landreth¹,*
Why did so many trials fail?

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*Sperling et al., 2014*
Pre-dementia phase

Use of biomarkers to **enrich** the cohort studied with subjects with an ongoing **AD pathology**

“MCI” with a positive biomarker

“Prodromal AD” *(Dubois et al., 2010)*
Which biomarker?

**Reflecting Aβ deposition:**
- CSF low Aβ
- PET Aβ tracers (PiB, Fluorbetapir, Fluorbetaben, etc.)
- presence of a known causal mutation (\textit{APP, PSEN 1 and 2})

**Reflecting tau deposition:**
- CSF high tau
- PET tau tracers (\textsuperscript{18}F]AV-1451)

Attempts to select cohort have been done so far targeting Aβ, on the basis of the «\textit{amyloid hypothesis}»

\textbf{BUT}
Amyloid hypothesis

Does Aβ accumulation correlate well with the extent of neuronal loss or cognitive dysfunction?

NO, because:
Cerebrospinal Fluid Levels of $\beta$-Amyloid 1-42, but Not of Tau, Are Fully Changed Already 5 to 10 Years Before the Onset of Alzheimer Dementia

Peder Buchhave, MD, PhD; Lennart Minthon, MD, PhD; Henrik Zetterberg, MD, PhD; Åsa K. Wallin, MD, PhD; Kaj Blennow, MD, PhD; Oskar Hansson, MD, PhD

Arch Gen Psychiatry. 2012;69(1):98-106

Amyloid CSF levels: changed 10 years before symptoms appearance

Tau CSF levels: changed 5 years before symptoms appearance
Use of BMs in clinical trials

**Ideally**: treat subjects with **low CSF Aβ** but **normal tau** (no cell death yet) → **prevent** all pathogenic mechanisms related to Aβ deposition, responsible for neurodegeneration

**But**: **tau** is a **symptom proximity marker**, therefore should be used (together with amyloid)

*Sperling et al., 2014*
The pattern of increased $[^{18}\text{F}]$AV-1451 retention highly overlapped with regions that showed decreased $[^{18}\text{F}]$FDG uptake → hypometabolism and symptomatology are more closely linked to tau than to $\text{A}\beta$. 

**PET TAU tracers: $[^{18}\text{F}]$AV–1451**
• Stage 0: **no biomarker abnormalities**: people not thought to be on the AD trajectory
• Stage 1: cerebral **amyloidosis**
• Stage 2: **amyloidosis** plus markers of **neurodegeneration**
• Stage 3: **amyloidosis + neurodegeneration + evidence of subtle cognitive and behavioral decline** that is not yet sufficient to meet criteria for MCI
• SNAP (Suspected Non-Alzheimer Pathology): evidence of **neurodegeneration without amyloidosis**

*Sterling et al., 2014; Jack et al., 2011, modified*
Stage 0: primary prevention

- In this stage: about 40-50% of elderly people (>65)
- What to do? ➔ primary prevention

- Cardiovascular risk factors
- Mediterranean diet
- Physical activity........

(MCI ➔ Dementia due to AD)

Stage 1: Asymptomatic amyloidosis
- High PET amyloid retention
- Low CSF Aβ1-42

Stage 2: Amyloidosis + Neurodegeneration
- Neuronal dysfunction on FDG-PET/fMRI
- High CSF tau/τ
cortical thinning/hippocampal atrophy on sMRI

Stage 3: Amyloidosis + Neurodegeneration + Subtle Cognitive Decline
- Evidence of subtle change from baseline level of cognition
- Poor performance on more challenging cognitive tests
- Does not yet meet criteria for MCI

SNAP: Suspected non-Alzheimer pathology
- Neurodegeneration markers without evident amyloidosis

Sterling et al., 2014; Jack et al., 2011, mod.
Nature and nurture: the case of Romania

Cornutiu et al, 2011
Stage 1: secondary prevention

Stage 1 (10-15%): secondary prevention with a treatment interfering with Aβ deposition

- What to do? ➔ secondary prevention

Immunization: from treatment for symptomatics to prevention in asymptomatics

Sterling et al., 2014
Cognitive trajectory in normal aging and AD

Sterling et al., 2014
# Stopping Alzheimer’s Before It Starts

Three new clinical trials expected to begin next year will attempt to prevent dementia by treating people at risk for the disease before they develop symptoms.

—Greg Miller  17 August 2012  Vol 337  Science

## Alzheimer’s Prevention Trials at a Glance

<table>
<thead>
<tr>
<th>Trial</th>
<th>Participants</th>
<th>Treatment</th>
<th>Outcome Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>API: Alzheimer’s Prevention Initiative</td>
<td>300 members of Colombian families, including 100 carriers of a mutated <em>PSEN1</em> gene</td>
<td>Crenezumab (Genentech)</td>
<td>Primary: Cognitive. Secondary: Biomarkers, including brain scans to measure amyloid accumulation and brain atrophy</td>
</tr>
<tr>
<td>DIAN: Dominantly Inherited Alzheimer Network</td>
<td>240 members of families with early-onset Alzheimer’s; 60 have a mutation in one of three genes</td>
<td>Three anti-amyloid therapies to be determined</td>
<td>An initial phase will use biomarkers to identify the most promising drug candidate for a follow-up phase to examine cognitive effects</td>
</tr>
<tr>
<td>A4: Anti-Amyloid Treatment of Asymptomatic Alzheimer’s</td>
<td>1500 healthy seniors, including 500 with amyloid-positive brain scans</td>
<td>One anti-amyloid therapy to be determined</td>
<td>Primary: Cognitive. Secondary: Biomarkers</td>
</tr>
</tbody>
</table>
Alzheimer Prevention Initiative (API)
Phase II: Crenezumab tested in a large Colombian PSEN1 cohort

Dominantly Inherited Alzheimer Network (DIAN)
Phase II: Solanezumab vs gantenerumab in carriers of mutations in APP, PSEN1 and PSEN2

Anti-Amyloid Treatment in Asymptomatic Alzheimer’s disease (A4)
Phase III: Solanezumab vs placebo in cognitively normal people (65-85 years) with evidence of Aβ accumulation
Additional vaccines waiting for clinical trials

- **ACI-24** (AC Immune): Ab1-15 peptide to which on both ends two lysines were attached. Antigen embedded in a liposome membrane. Currently evaluated in a phase I/II clinical trial in Denmark, Finland and Sweden.

- **Affitope AD-02** (Affiris, Vienna AT and licensee GSK Biol.): is 6-aminoacid peptide vaccine targeting the N-terminus of Aβ. European phase II clinical trial in 420 patients ongoing.

- **Affitope-AD-03** (Affiris and licensee GSK Biol.): phase I completed in 2011, results not yet published.

- **ACC-001** (vanutide cridificar; Pfizer). Two Phase II studies in patients with mild to moderate AD: one in Japan (completed) and one ongoing in USA.

- **UB-311** (United Biomedical): intramuscularly administered vaccine targeting N-terminal amino acids 1-14 of Aβ in phase I clinical trials in Taiwan in patients with mild to moderate AD.

- **V-950** (Merck): Phase II, double-blind, randomized, placebo-controlled, dose escalating study completed, but results not yet published.

*Galimberti D., Scarpini E., J. Neurol Sci, 2013*
Additional monoclonal antibodies waiting for clinical trials

• **PF-04360365** (Pfizer, phase II completed)

• **GSK933776A** (GlaxoSmithKline, phase I completed)

• **NI-101** (Biogen Idec, phase I clinical trial in patients with mild to moderate AD ongoing)

• **PF-05236812** (Janssen Alzheimer Immunotherapy and Pfizer, phase I trial ongoing)

• **RN6G** (Rinat Neuroscience Corp., New York, now Pfizer, phase I completed)

• **SAR-228810** (Sanofi, phase I ongoing)

• **BAN-2401** (Eisai, phase I trial in 80 patients with mild to moderate AD ongoing).
PRIME: Phase 1b randomized, double-blind, placebo-controlled, multiple-dose study evaluating safety, tolerability, pharmacokinetics, pharmacodynamics of aducanumab in 166 patients with prodromal-mild AD placebo (n=40), 1 mg/kg (n=31), 3 mg/kg (n=33) and 10 mg/kg (n=32) dose arms [and up to week 30 data for the 6 mg/kg (n=30) dose arm]

Safe, well tolerated.
Most frequently AE: ARIA (amyloid-related imaging abnormalities)

For dosage ≥ 3:
-dose- and time-dependent reduction of amyloid plaque on PET with Fluorobetapir
-significant improvement on neuropsychological testing (MMSE, CDR-SB)
The future: vaccination as primary prevention
Stages 2-3: acting on tau

Strategies (preclinical):

- **Inhibition of GSK3β** (kinase phosphorylating tau)
- **Activation of phosphatases** (PP2A)
- **Vaccination°** (more difficult as tau is intracellular)

- Methylene blue (Rember), Phase II - ongoing
- *Tideglusib, Phase II – failed
- ° AADvac1, Phase I, ongoing but not recruiting

Aβ: normal

Tau: increased

Other pathogenic proteins (TDP-43, FUS, Synuclein)?
Neuronal uptake of tau/pS422 antibody and reduced progression of tau pathology in a mouse model of Alzheimer’s disease

Ludovic Collin,1 Bernd Bohrmann,1 Ulrich Göpfert,2 Krisztina Oroszlan-Szovik,1 Laurence Ozmen1 and Fiona Grüninger1

1 Roche Pharmaceutical Research and Early Development, Neuroscience Ophthalmology and Rare Diseases Discovery & Translational Area, Roche Innovation Center Basel, Grenzacherstrasse 124, CH-4070 Basel, Switzerland
2 Roche Pharmaceutical Research and Early Development, Large Molecule Research, Roche Innovation Center Penzberg, Nonnenwald 2, D-82377 Penzberg, Germany

- Triple transgenic mouse model of AD
- Anti-tau/pS422 anti-body **binds** to membrane-associated tau/pS422 and antigen-antibody complexes are cleared intracellularly
- Chronic, peripheral administration of anti-tau/pS422 antibody **reduces** the accumulation of tau pathology
Karran and Hardy: Amyloid Hypothesis for AD

Nonclinical testing

- Compound testing
  - Target
    - In vitro assays
    - Cell assays
    - In vivo models

Drugs Candidate

Clinical testing

- Phase 1
- Phase 2
- Phase 3
- Approved drug

Purpose

- Mechanism of action, potency/selectivity vs. isolated target.
- Drug mechanism of action vs. target in cellular context, potency/selectivity, cell permeability.
- Drug action vs target in efficacy, pharmacodynamic, or biomarker response assays. Safety studies.
- Safety, pharmacokinetic/dynamic/biomarker data.
- Safety, pharmacokinetic/dynamic/biomarker efficacy data.
- Safety, biomarker/efficacy data suitable for regulatory approval.

Translation

- Drug should be active in cell assays at a concentration that is commensurate with in vitro data.
- Free drug levels should be similar in vivo at the site of action to efficacious concentrations in cell assays.
- Dose escalation studies based on safe doses from in vivo toxicology studies and related to efficacious doses in in vivo models.
- Doses based on safe doses from phase 1 and related to efficacious doses in in vivo models.
- Select doses for phase 3 trials.

Karran & Hardy, 2014
Conclusions: open questions for early intervention

• Are subjects in early intervention trials **early enough in disease process to respond** to interventions? Which **clinical outcomes** are available? **None** so far

• **How early is early enough?**
  – In the presence of:
    • Cognitive impairment?
    • Neurodegeneration (evidence of tau deposition)?
    • Evidence of Aβ deposition?

• **Are earlier trials feasible?**
  – Prodromal AD trials are hard to enroll
  – Earlier stages of illness: TBD (use of BMs? Feasibility?)

• **What is optimal design of early intervention trials**
  - duration (more than 2-3 years)?
  - costs
  - ethical issues
Caveat

Are there concerns on inappropriately labeling individuals with «preclinical Alzheimer’s disease» people who might never progress to manifest dementia in spite of biomarker evidence of amyloid deposition?

BUT: in other fields, terms as «precancerous lesions» or «prediabetes» did not raise any ire....

Apprehension over preclinical AD terminology reflects the stigma of the clinical syndrome of AD

Sperling et al., 2014
Review

Deep brain stimulation in dementia-related disorders

Sarah Hescham a,e, Lee Wei Lim d, Ali Jahanshahi a,e, Arjan Blokland c,e, Yasin Temel a,b,e,*

a Department of Neuroscience, Maastricht University Medical Center, Maastricht, The Netherlands
b Department of Neurosurgery, Maastricht University Medical Center, Maastricht, The Netherlands
c Department of Neuropsychology and Psychopharmacology, Faculty of Psychology and Neuroscience, Maastricht University, Maastricht, The Netherlands
d School of Biological Sciences, Nanyang Technological University, Singapore
e European Graduate School of Neuroscience (Euron), Maastricht, The Netherlands

ABSTRACT

Memory loss is the key symptom of dementia-related disorders, including the prevalent Alzheimer's disease (AD). To date, pharmacological treatments for AD have limited and short-lasting effects. Therefore, researchers are investigating novel therapies such as deep brain stimulation (DBS) to treat memory impairment and to reduce or stop the progression of it. Clinical and preclinical studies have been performed and stimulations of the fornix, entorhinal cortex and nucleus basalis of Meynert have been carried out. The results of these studies suggest that DBS has the potential to enhance memory functions in patients and animal models. The mechanisms underlying memory enhancement may include the release of specific neurotransmitters and neuroplasticity. Some authors suggest that DBS might even be disease-modifying. Nevertheless, it is still premature to conclude that DBS can be used in the treatment of AD, and the field will wait for the results of ongoing clinical trials.

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Fig. 2. Schematic representation of the potential mechanisms involved in enhancing memory functions by deep brain stimulation. Stimulation of a target area within the memory circuit (e.g. fornix) can provoke NGF release in the NBM, hippocampal-dependent neurogenesis, neural hijacking by resetting theta activity and increased acetylcholine release within the hippocampal region.
<table>
<thead>
<tr>
<th>Structure</th>
<th>Subject</th>
<th>Type of stimulation</th>
<th>Memory task</th>
<th>Effect</th>
<th>Reference</th>
</tr>
</thead>
</table>
| 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 | Neuropsychological tests, e.g. clock drawing, letter-number-span, auditory verbal learning, etc. | No clinical effect, but increased cerebral glucose metabolism                            | Turnbull et al. (1985)  |
| Human (Parkinson patient)       | N = 1                                         | NBM: Bilateral, 1 V, 20 Hz, and 120 μs pulse width  
STN: bilateral, 3.5–4.2 V, 130 Hz and 60 μs pulse width | Combined bilateral stimulation lead to improvement in attention, concentration, alertness, drive, and spontaneity | Combined bilateral stimulation lead to improvement in attention, concentration, alertness, drive, and spontaneity | Freud et al. (2009)   |
<p>| 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          | In adult, but not aged rats, NGF levels were significantly increased                      | Hotta et al. (2009)   |
| Anterior thalamic nucleus        | Rats                                         | 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 | 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)  |
| Hippocampus                     | Human (epileptic patients)                   | 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) |</p>
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<tbody>
<tr>
<td><strong>Fornix</strong></td>
<td>Human (morbid obesity patient) N=1</td>
<td>Bilateral, 3–5 V, 130 Hz and 60 μs pulse width, continuous for 3 weeks</td>
<td>Neuropsychological tests, e.g. verbal learning test, WAIS attention index, spatial associative learning, etc.</td>
<td>Significant improvements on the California Verbal Learning Test and Spatial Associative Learning Test</td>
<td>Hamani et al. (2008)</td>
</tr>
<tr>
<td></td>
<td>Human (AD patients) N=6</td>
<td>Bilateral, 3.0–3.5 V, 130 Hz, and 90 μs pulse width, continuous for 12 months</td>
<td>ADAS-cog, MMSE</td>
<td>Possible improvements and/or slowing in the rate of cognitive decline at 6 and 12 months in some patients</td>
<td>Laxton et al. (2010)</td>
</tr>
<tr>
<td></td>
<td>Human (AD patient) N=1</td>
<td>Bilateral, 2.5 V, 130 Hz and 210 ms pulse width, continuous for 12 month</td>
<td>ADAS-cog, MMSE, Free and Cued Selective Reminding Test</td>
<td>Cognitive scores worsened after 6 months but returned to baseline after 12 months of chronic DBS</td>
<td>Fontaine et al. (2013)</td>
</tr>
<tr>
<td></td>
<td>Rats (model of experimental dementia) N=10</td>
<td>Bilateral, 100 and 200 μA, 10 and 100 Hz, 100 μs pulse width, acute stimulation</td>
<td>OLT</td>
<td>Memory enhancement in high current densities (frequency-independent)</td>
<td>Hescharm et al. (2013)</td>
</tr>
<tr>
<td><strong>Entorhinal cortex</strong></td>
<td>Mice N=25</td>
<td>Bilateral, 50 μA, 130 Hz and 90 μs pulse width, for 1 h during surgery</td>
<td>Morris water maze</td>
<td>Water-maze memory was facilitated 6 weeks after stimulation due to hippocampus-dependent neurogenesis</td>
<td>Stone et al. (2011)</td>
</tr>
<tr>
<td></td>
<td>Human (epilepsy patients) N=7</td>
<td>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</td>
<td>Virtual memory task</td>
<td>Memory enhancement and theta-phase resetting</td>
<td>Suthana et al. (2012)</td>
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</table>
Acknowledgements

Thank you for your attention