Mentis Cura

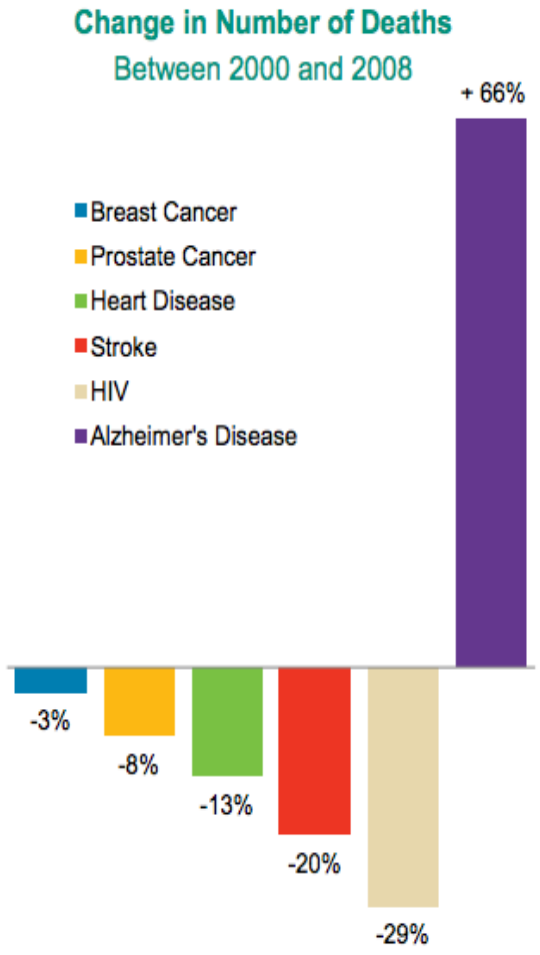
November 29 2012

www.mentiscura.com

New Facts on Alzheimer´s

- Death rank – nr. 2-5 in western countries
- Fastest growing disease in:
  - Cost
  - Incedence
  - Death rate

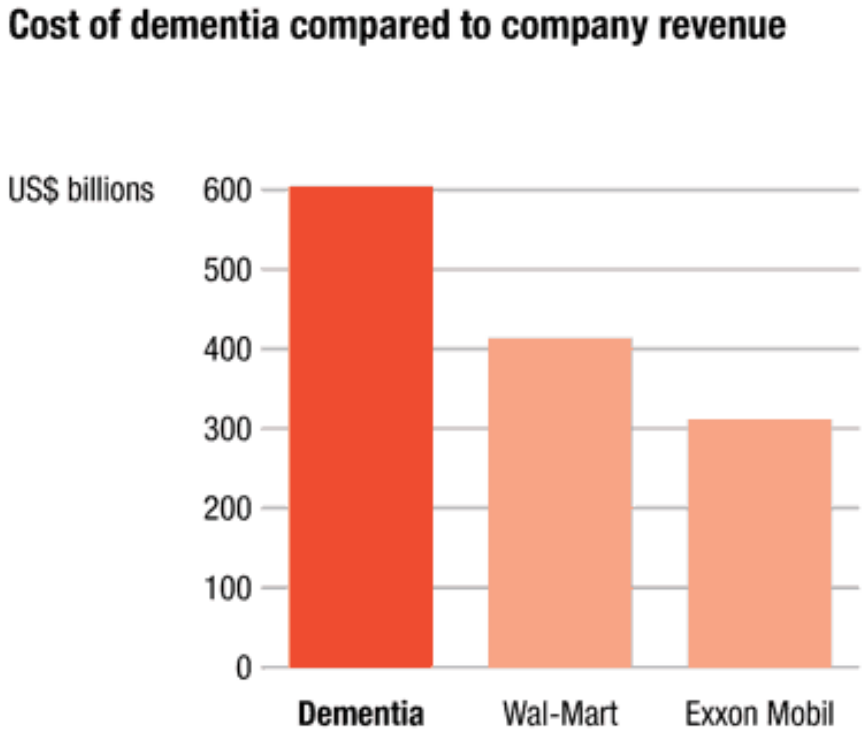
- People with Alzheimer´s
- 2012 – 36 million
- 2050 – 115 millon



Soaring Costs

- 18th largest economy in the world
- Costs to rise by 80% by 2030
- Will cripple healthcare
- 70% of cost occurs in Western Europe and North America

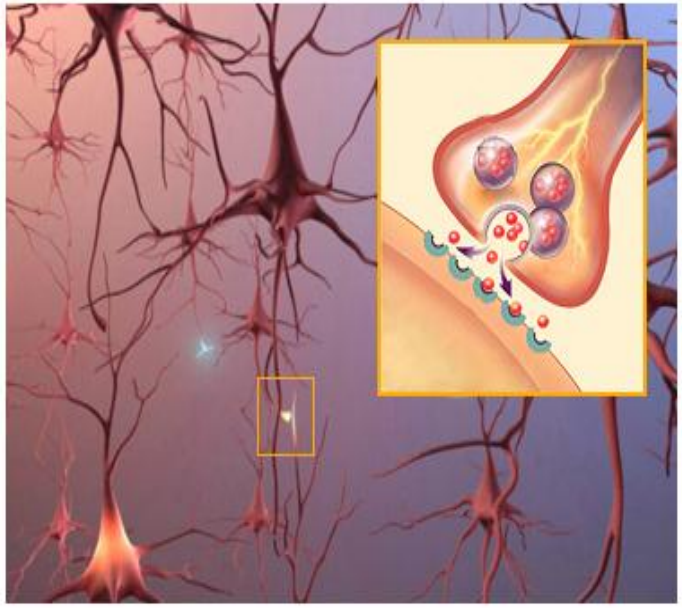
- Call for early detection and biomarkers
- Alz. Association 10 year call for biomarker development
- UK Chief Medical Officer calling for early detection
- Economical diagnosis needed



EEG as the biomarker, 1st line of defense://www.alz.org/braintour/3_main_parts.asp

6. Cell signaling

← NEXT →



Signals that form memories and thoughts move through an individual nerve cell as a **tiny electrical charge**.

Nerve cells connect to one another at **synapses**. When a charge reaches a synapse, it may trigger release of tiny bursts of chemicals called **neurotransmitters**. The neurotransmitters travel across the synapse, carrying signals to other cells. Scientists have identified dozens of neurotransmitters.

Alzheimer's disease disrupts both the way electrical charges travel within cells and the activity of neurotransmitters.

- EEG measures electrical charges which are disrupted from onset of disease.
- More data showing disease developing earlier, 10-15 years before clinical symptoms
- New data on relationship with sleep apnea & lifestyle factors

mentis cura

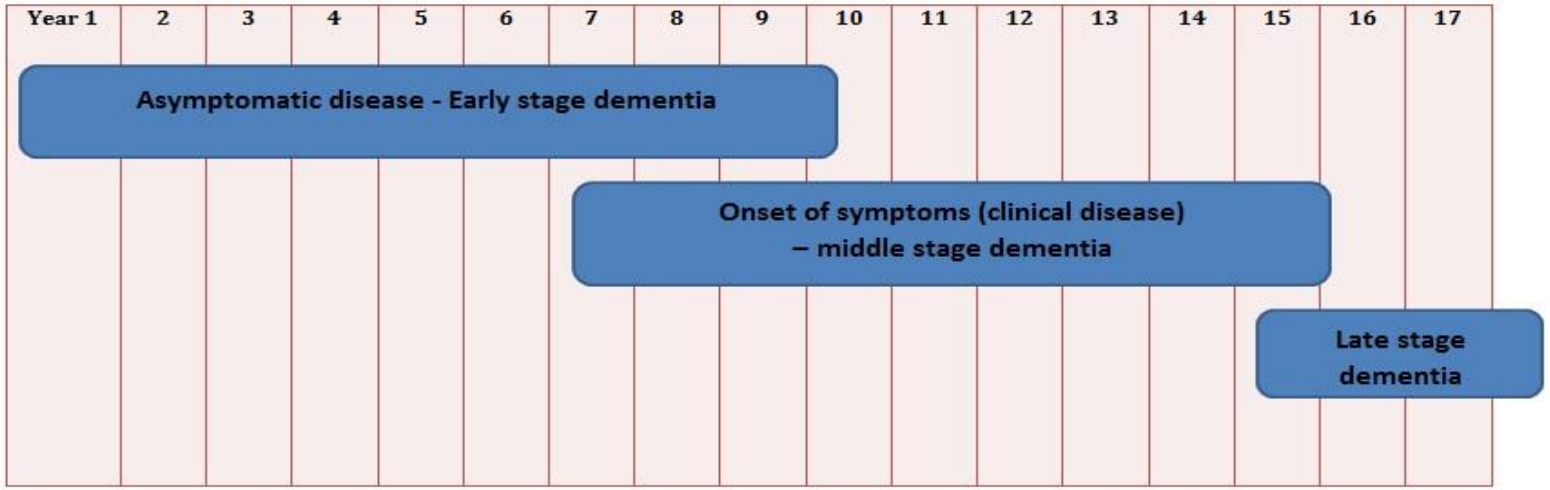
Other biomarkers & diagnostics

- Mainly used to rule out other disease and are not able do diagnose dementia until in **later stages**
- CT and MRI
  - Volumetric loss: secondary changes to decrease in synaptic density, neuronal loss, and cell shrinkage
- fMRI
  - Functional MRI: detects abnormal (secondary) changes in cerebral blood flow with contrast

Other biomarkers & diagnostics

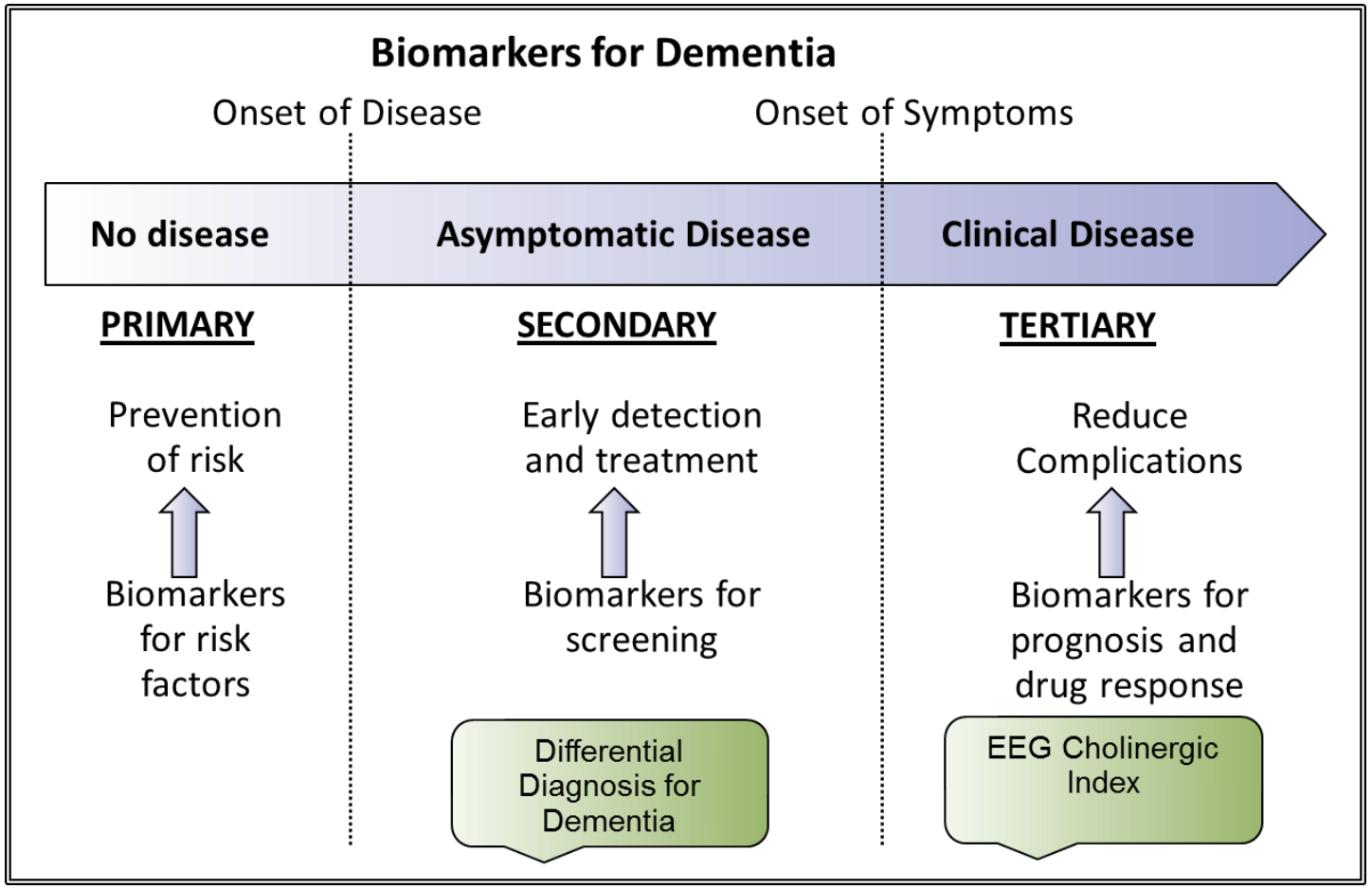
- PET (Positron Emission Tomography)
  - Relevant in the study of dementia, no clinical use
  - Measures cerebral glucose metabolic rate
- SPECT (Single-Photon Emission Computed Tomography
  - Measures blood flow in certain regions of the brain
- Spinal Fluid
  - Invasive and risky. No standards acknowledged
  - Not specific to dementia

Stages of Dementia



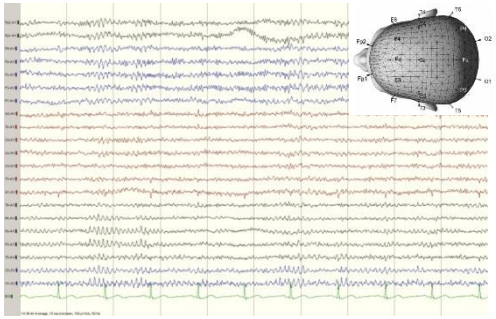
Early symptoms	Pre-dementia symptoms	Moderate symptoms	Advanced symptoms
• Impairment of learning • Memory deficit – recent memories • Shringking vocabulary and decreased word fluency	• Recent memory loss • Subtle executive functions of attentiveness, planning, flexibility • Semantic memory impairment	• Increased dependency • Speech difficulties • Reading and writing progressively lost • Poorer motor sequences coordination • Not recognising relatives • Neropsychiatric change • Sundowning • Delusional symptoms • Loss of insight in own limitations	• Completely dependent on others • Language reduced severely • Extreme apathy • Bedridden • Lose the ability to feed themselves

Mentis Cura Biomarker



Building the Dementiagram

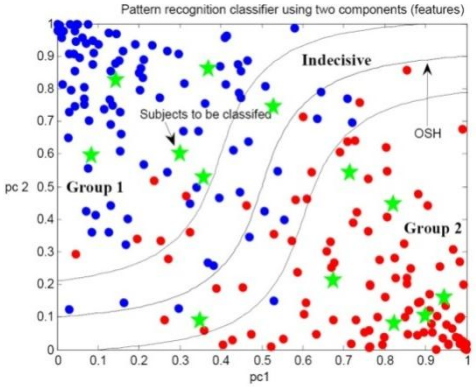
EEG Recording



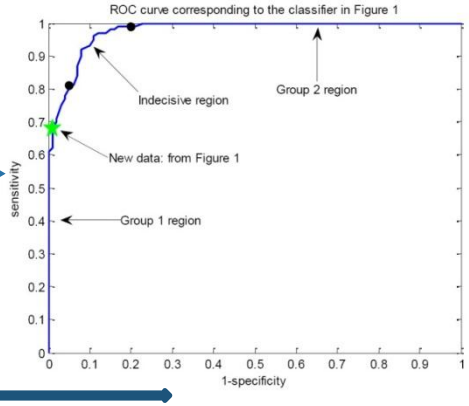
Extract features

-Classical Spectral features; $\delta,\theta,\alpha,\beta$, and γ bands. Coherences in same frequency range
-A total of 1000+ features are extracted from each EEG recording

Generate Multidementional Classifier



Generate Index



This process is repeated ten times for the Dementiagram

- Classifiers are generated for each possible pair of groups in the EEG database to make a differential analysis possible.
- There are a total of 10 classifers pairs included in the Mentis Cura Dementiagram
- As a result of this, the system generates 2 indices for each classifier in the dementiagram, i.e. for the Dementiagram which includes NRM, MCI, DPR, AD, & L-P 20 indeces are generated.

The Mentis Cura Dementiagram

	NRM	MCI	DPR	AD	L-P
NRM		53,82	72,43	56,72	99,28
MCI	46,18		45,07	47,13	99,83
DPR	27,57	54,93		49,63	99,8
AD	43,28	52,87	50,37		98,64
L-P	0,72	0,17	0,2	1,36	
DGW	0	0	0	0	100

Progress Score: 6,11

Mentis Cura Report

Differential Diagnosis

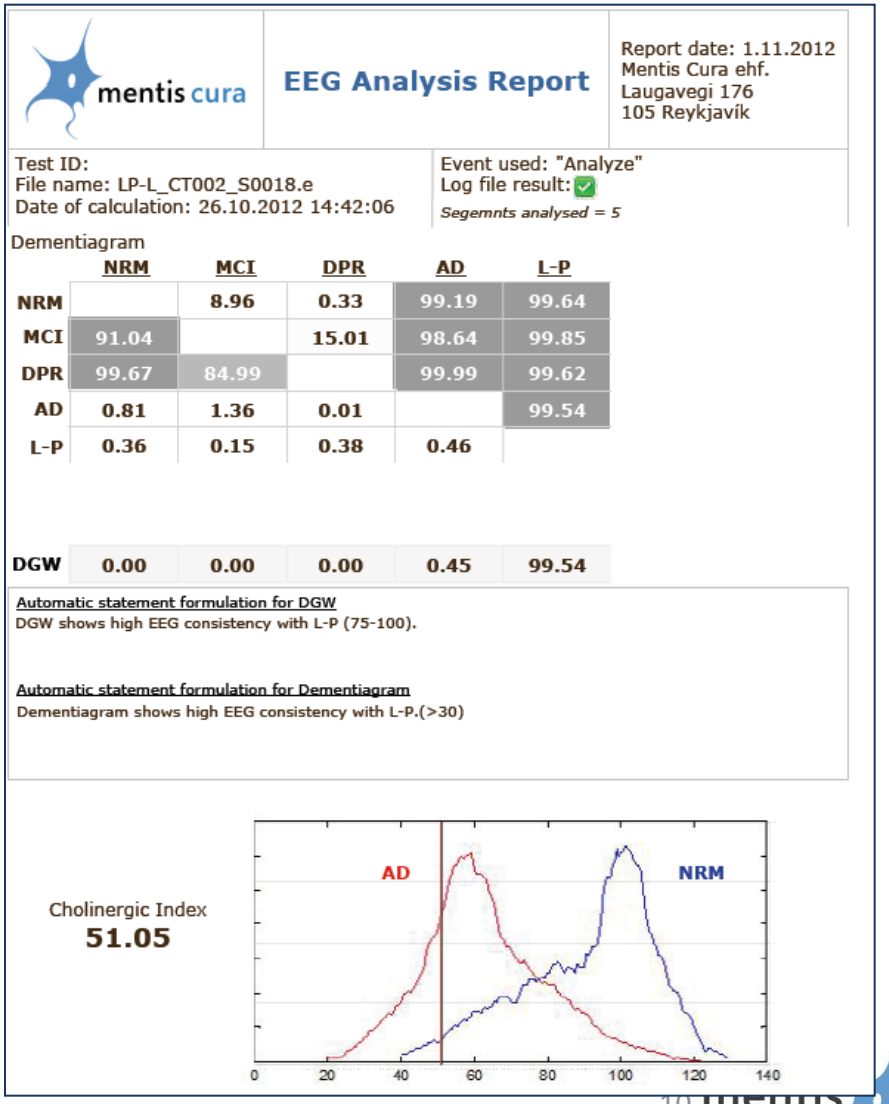
- *Mild Cognitive Impairment*
- *Depression*
- *Alzheimer´s Disease*
- *Lewy Body Parkinson Dementia*

Automatic Statements

- *Easy interpretation of DementiaGram*

Cholinergic Index

- *Baseline*
- *Monitor progression*
- *Treatment effect*
- *Dose response*



mentis cura

EEG Analysis Report

Report date: 1.11.2012
Mentis Cura ehf.
Laugavegi 176
105 Reykjavík

Test ID:
File name: LP-L_CT002_S0018.e
Date of calculation: 26.10.2012 14:42:06

Event used: "Analyze"
Log file result:
Segemnts analysed = 5

Dementiagram

	NRM	MCI	DPR	AD	L-P
NRM		8.96	0.33	99.19	99.64
MCI	91.04		15.01	98.64	99.85
DPR	99.67	84.99		99.99	99.62
AD	0.81	1.36	0.01		99.54
L-P	0.36	0.15	0.38	0.46	
DGW	0.00	0.00	0.00	0.45	99.54

Automatic statement formulation for DGW
DGW shows high EEG consistency with L-P (75-100).

Automatic statement formulation for Dementiagram
Dementiagram shows high EEG consistency with L-P.(>30)

Cholinergic Index
51.05

Dementiagram

	NRM	MCI	DPR	AD	L-P
NRM		8.96	0.33	99.19	99.64
MCI	91.04		15.01	98.64	99.85
DPR	99.67	84.99		99.99	99.62
AD	0.81	1.36	0.01		99.54
L-P	0.36	0.15	0.38	0.46	

DGW	0.00	0.00	0.00	0.45	99.54

Automatic statement formulation for DGW

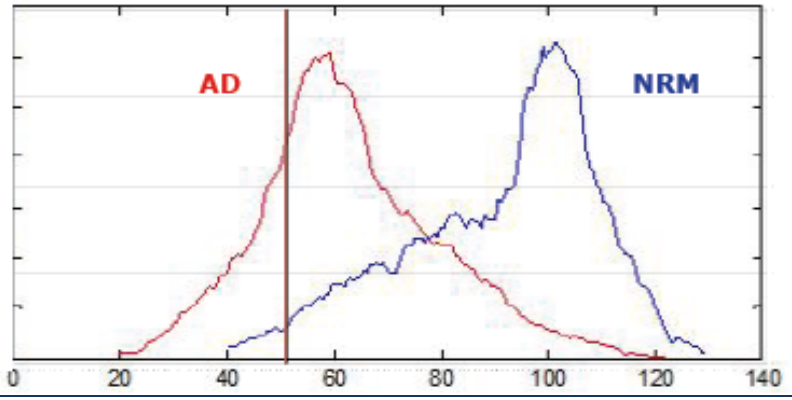
DGW shows high EEG consistency with L-P (75-100).

Automatic statement formulation for Dementiagram

Dementiagram shows high EEG consistency with L-P.(>30)

Cholinergic Index

51.05



EEG Cholinergic Index®

A biomarker measuring activity of the Cholinergic system

Monitor disease progression of dementia

Monitor treatment efficacy of cholinesterase inhibitors

Monitor during titration / dose response

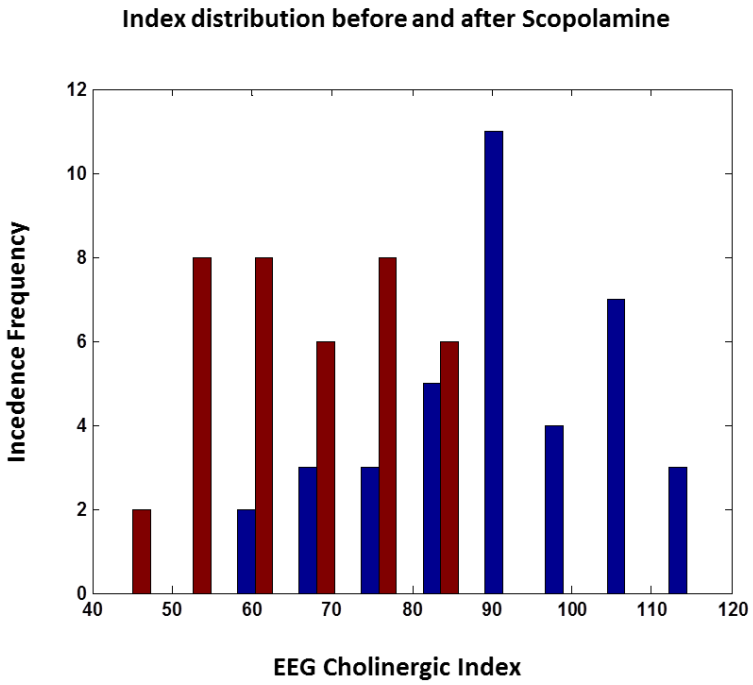
mentis cura

Background

- Leading medications indicated for treatment of mild AD are cholinesterase inhibitors. The effects of the medicines are measured by cognitive tests and by caregiver reports without the support of biomarkers.
- Physicians face the challenge of choosing from a wide range of dozes. With the recent FDA Approval of high dose formulations of Rivastigmine and Donepezil, the difference between low and high doze is more than fourfould!
  - Rivastigmine is available in 4.6 – 9.5 and 13.3mg
  - Donepezil is available in 5 – 10 and 23mg
- A theoretically possible method is to measure the cholinergic response to these drugs in the brain. It has been proposed that the EEG changes seen in AD are primarily a reflection of cholinergic dysfunction.
- We suggest that by establishing a "cholinergic index" in EEG registration, the treatment effects of cholinergic drugs could be measured and thereby the treatment response.

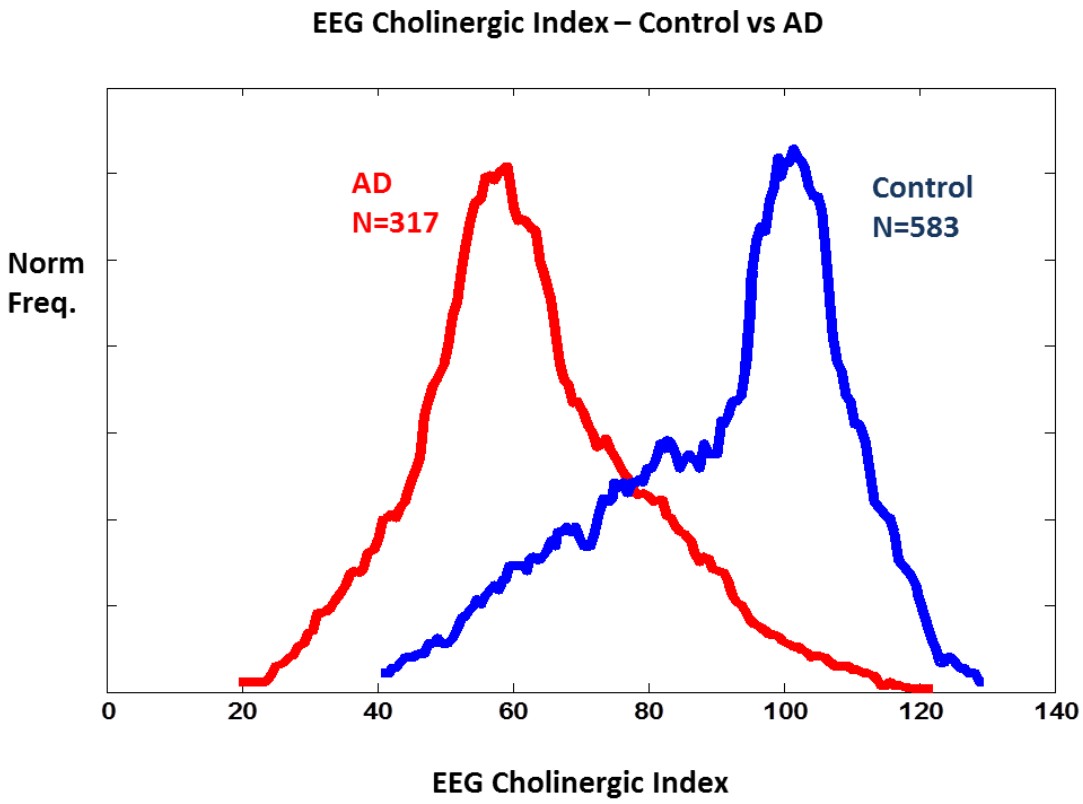
Developing the Index

- In a clinical trial, 38 healthy elderly participants participated an EEG registration
- Recordings were obtained from each participant before and after a 5 mg sc administration of scopolamine.
- Since scopolamine affects the cholinergic neurotransmitter system, a cholinergic EEG index was created by applying Statistical Pattern Recognition (SPR) to a large set of EEG features, by considering the group before and after scopolamine administration as two distinct groups.
- The resulting classifier results in an index that correlates with the cholinergic activity in the subject.



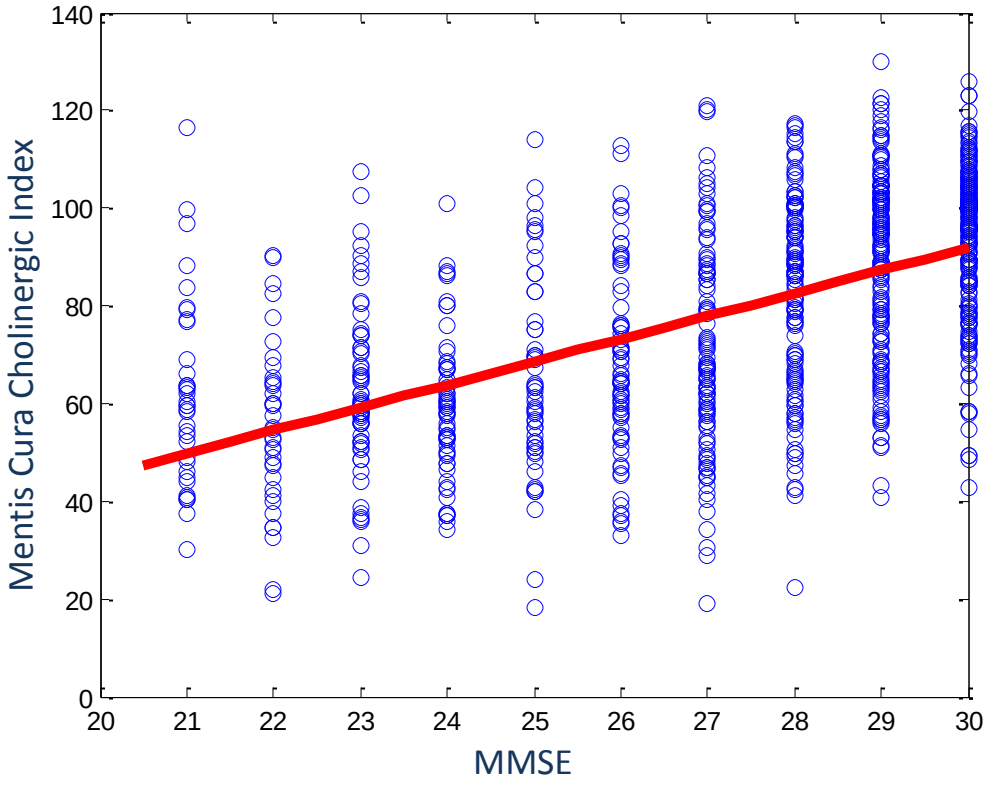
The EEG cholinergic index calculated for 38 individuals before (blue) and after (red) 5 mg scopolamine sc injection. The second EEG recording took place 2.5 hours after injection.

Control vs AD



- The EEG Cholinergic Index ® calculated for 317 healthy elderly individuals and 583 AD individuals.
- Groups are distinctively different

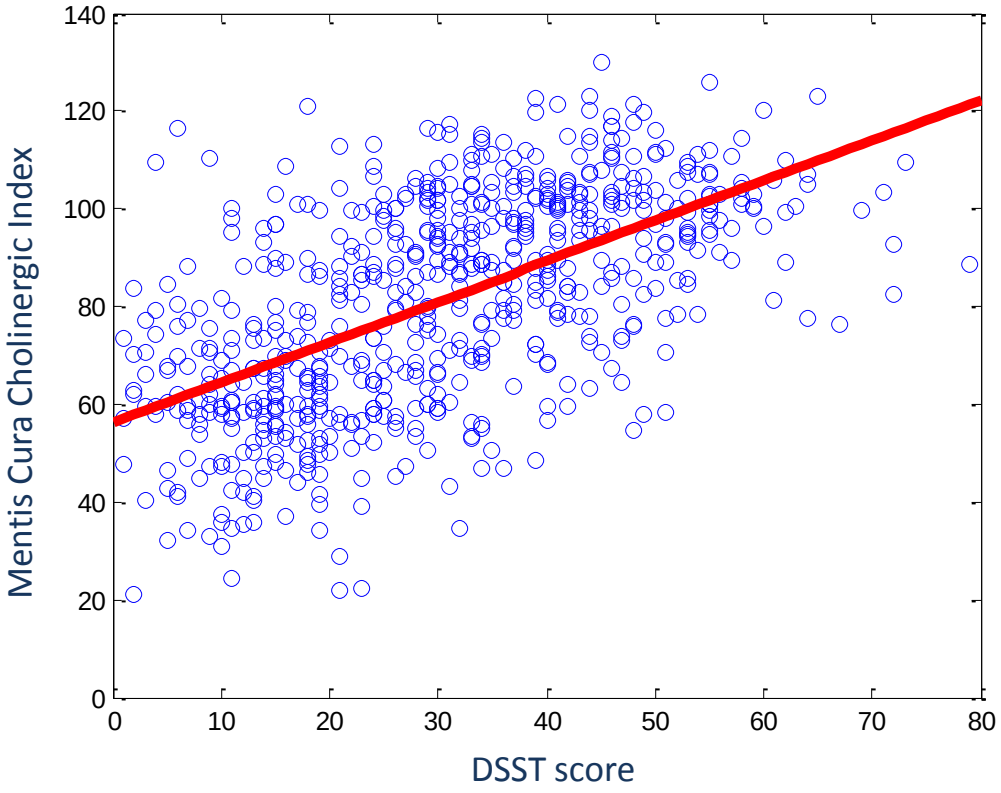
Correlation to cognitive measure: MMSE



- The EEG Cholinergic Index ® calculated for 317 healthy elderly individuals and 620 individuals with dementia.
- Correlates to Mini Mental State Examination (MMSE)
- Alzheimer's
- Dementia with Lewy bodies
- Parkinson's Disease Dementia
- Vascular Dementia
- Mild Cognitive Impairment
- Depression leading to dementia symptoms

Pearson's Linear Correlation : 0.56±0.02 (Evaluated by Bootstrap)

Correlation to cognitive measure: DSST



- The EEG Cholinergic Index ® calculated for 317 healthy elderly individuals and 374 individuals with dementia.
- Correlates to Digital Symbol Substitution Test (DSST)
- Alzheimer's
- Dementia with Lewy bodies
- Parkinson's Disease Dementia
- Vascular Dementia
- Mild Cognitive Impairment
- Depression leading to dementia symptoms

Pearson's Linear Correlation : 0.59±0.02 (Evaluated by Bootstrap)

Post operative cognitive function following coronary artery bypass grafting (CABG)

CABG/ Overview

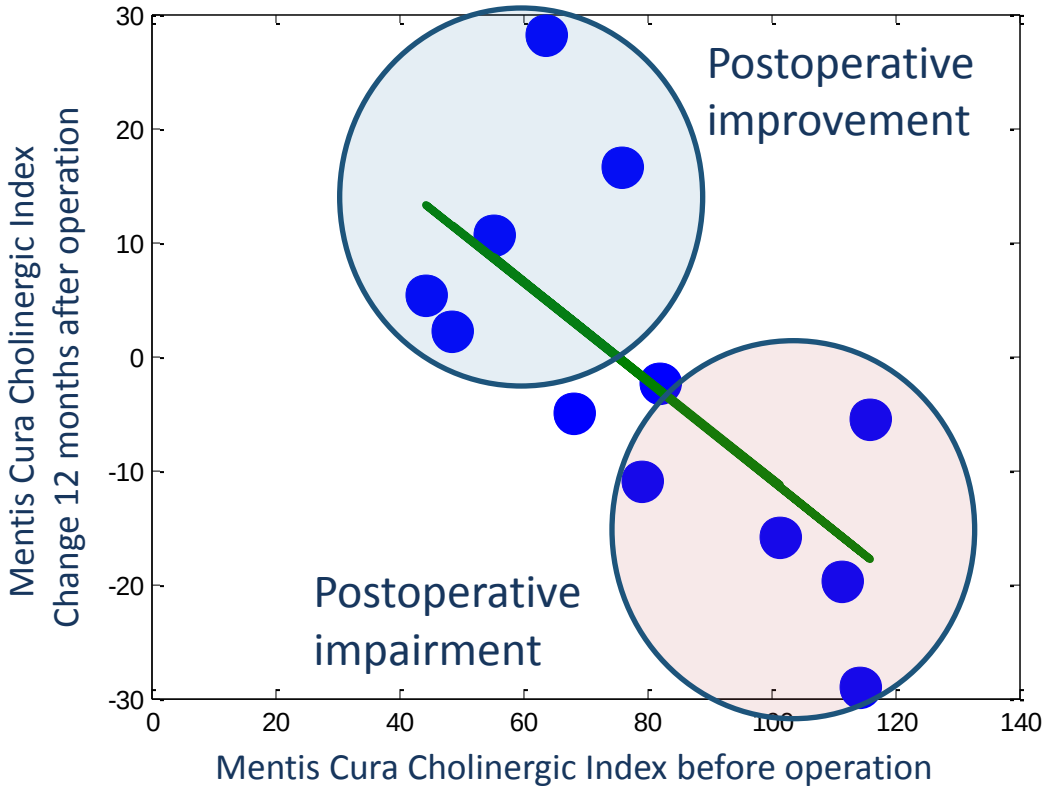
- Around 1 million CABG surgeries are conducted annually worldwide
- Due to advance in surgical medicine CABG surgeries are now being conducted on older individuals than before and on individuals with comorbid diseases such as hypertension and diabetes.
- This has lead to increased awareness of the many serious and life threatening neurological difficulties associated with CABG surgeries.
- Stroke and postoperative delirium are well known and studied difficulties following CABG with incidence rates around 3% and up to 9 % in those older than 75 years of age.
- Post Operative Cognitive Deficits (POCD) and depression following CABG have gained increased interest in recent years.
- Studies have shown incidence rates of POCD from 33-83% and around 25% for depression.
- Findings on POCD are conflicting and there is great need for further studies

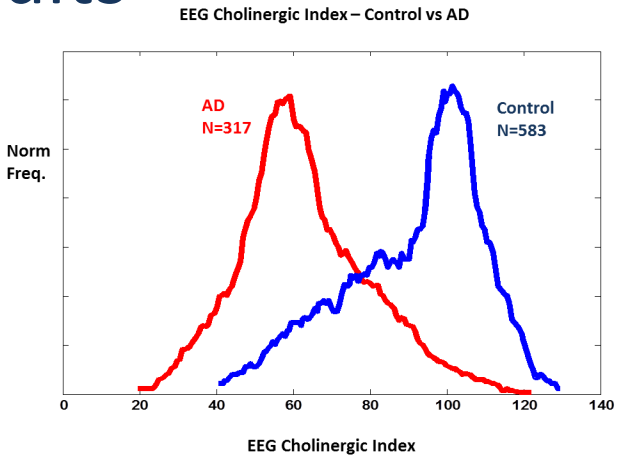
Study Design

- Trial period: Started in 2010 – on-going.
- Estimated population size: 30 individuals who have undergone CABG surgery at the Landspitali University Hospital in Iceland.
- Purpose: An informative study using EEG as neurophysiologic parameters to reflect the effect of CABG on depression, anxiety and cognition of patients
- Procedure: Following measures will be conducted at baseline (at least one week before surgery) and post-operative at 3-5 months and at one year follow up:
  - **Questioners** assessing depression (BDI) and anxiety (BAI)
  - **Neuropsychological assessment** measuring memory, motor speed, executive function and visuo-spatial abilities
  - **EEG** with a protocol of 5 min. resting eyes closed, 5 min eyes open/closed.
- Additional data: Clinical data such as physical parameters will be gathered from the Department of Surgery and Cardiothoracic Surgery clinical database.

CABG

Ach EEG Index results





- Subjects with low cholinergic activity benefit from operation
- Subjects with cholinergic activity within normal range show postoperative impairment
- Change evident 12 months postoperatively

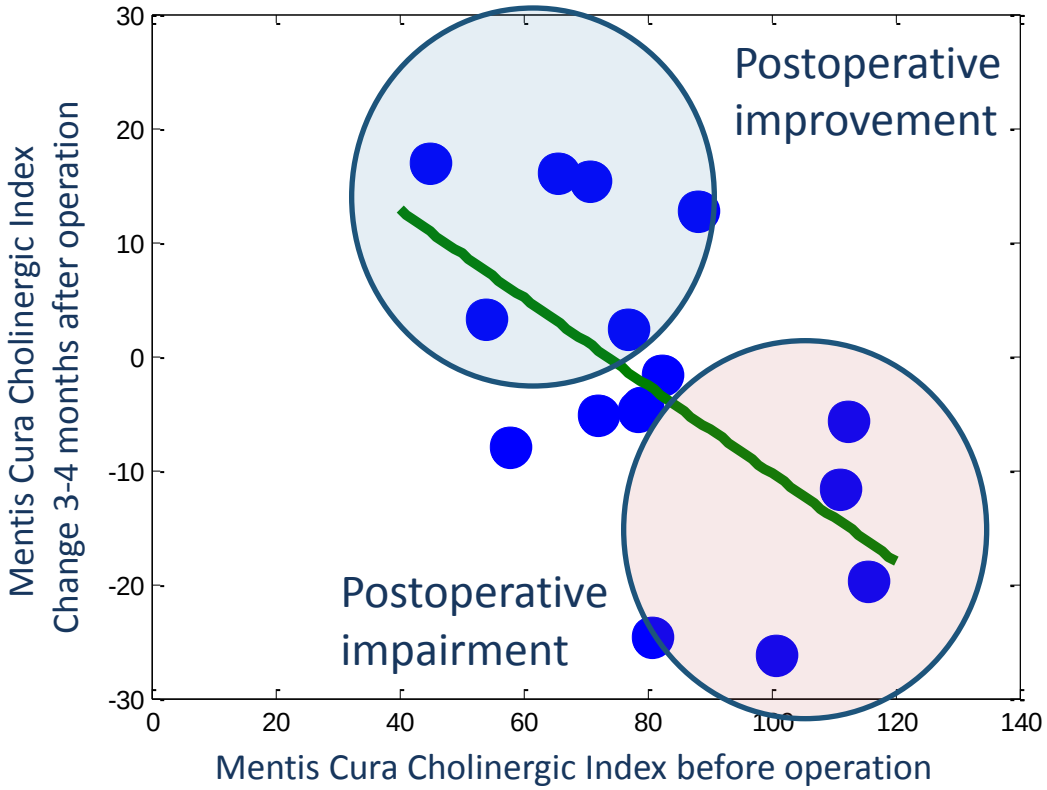
Correlation : -0.70

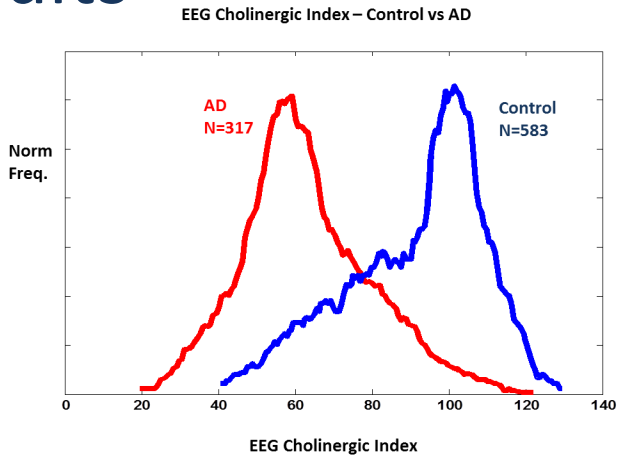
12 Subjects

mentis cura

CABG

Ach EEG Index results





Correlation : -0.58

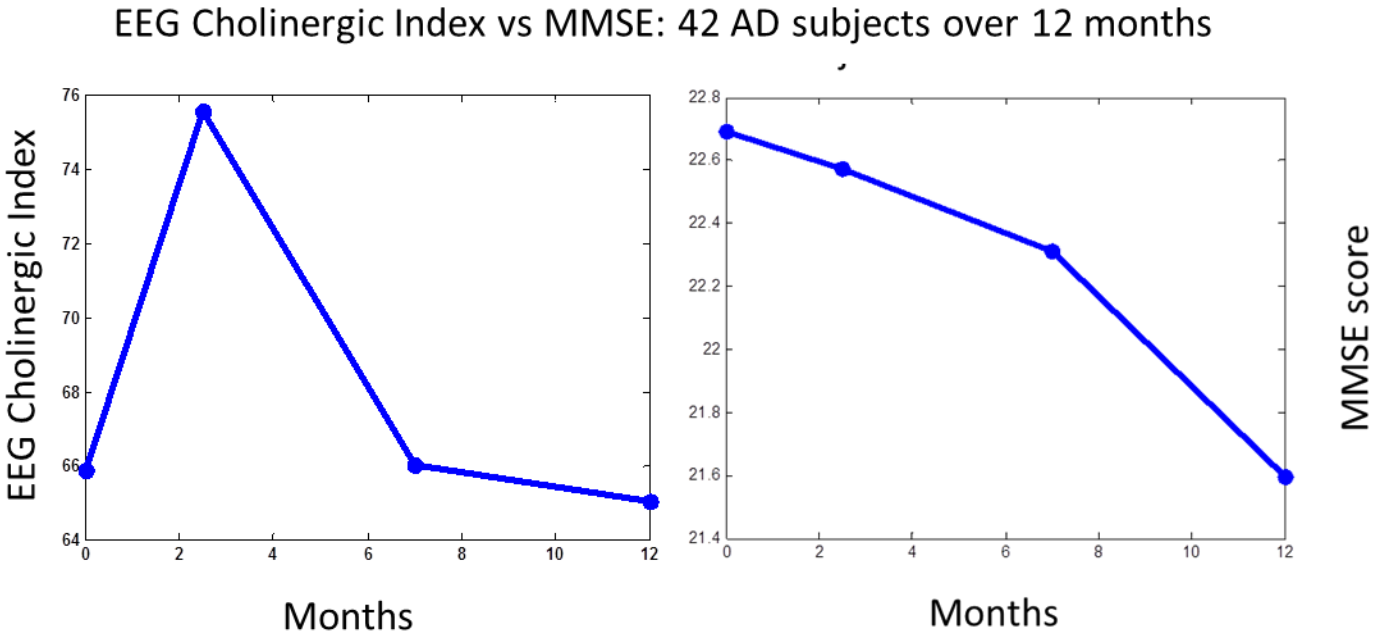
16 Subjects

- Subjects with low cholinergic activity benefit from operation
- Subjects with cholinergic activity within normal range show postoperative impairment
- Change evident 3-4 months postoperatively. Not as clear as after 12 months.

mentis cura

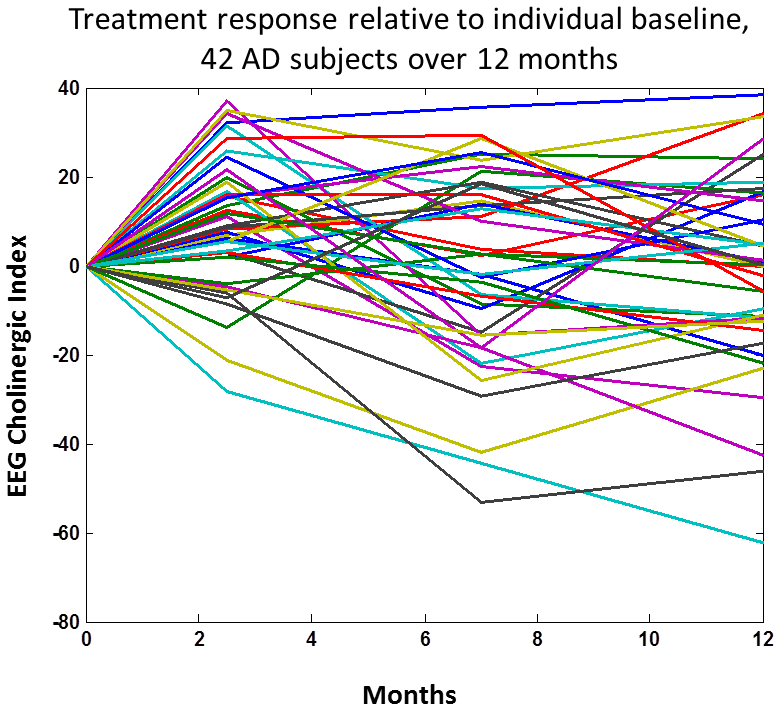
Monitoring Cholinesterase Inhibitor treatment in Alzheimer's patients

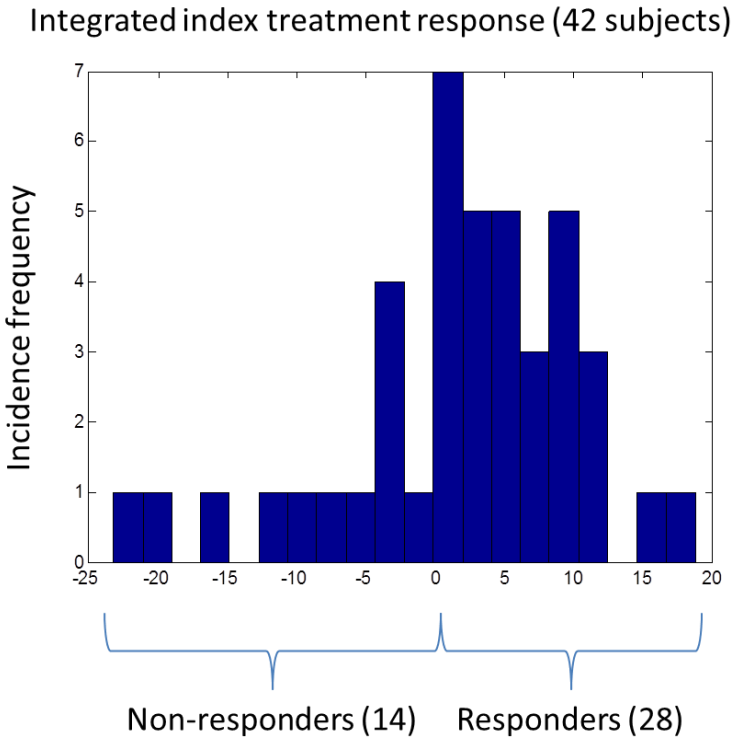
Monitor Treatment Efficacy



- A longitudinal study with 42 AD patients over 12 months (4 visits) was performed. The Cholinergic Index® was calculated for each participant at each visit. The initial EEG recording takes place before treatment for AD is initiated. A week later treatment for AD starts.
- Results from a longitudinal trial. The average EEG Cholinergic Index® is calculated for 42 AD individuals over a 12 month period. The average MMSE score for the same individuals is shown for comparison. The first point is calculated before treatment for AD is initiated.
- Two months after treatment with acetylcholinesterase inhibitors began the Cholinergic Index® rose by almost 19 points.

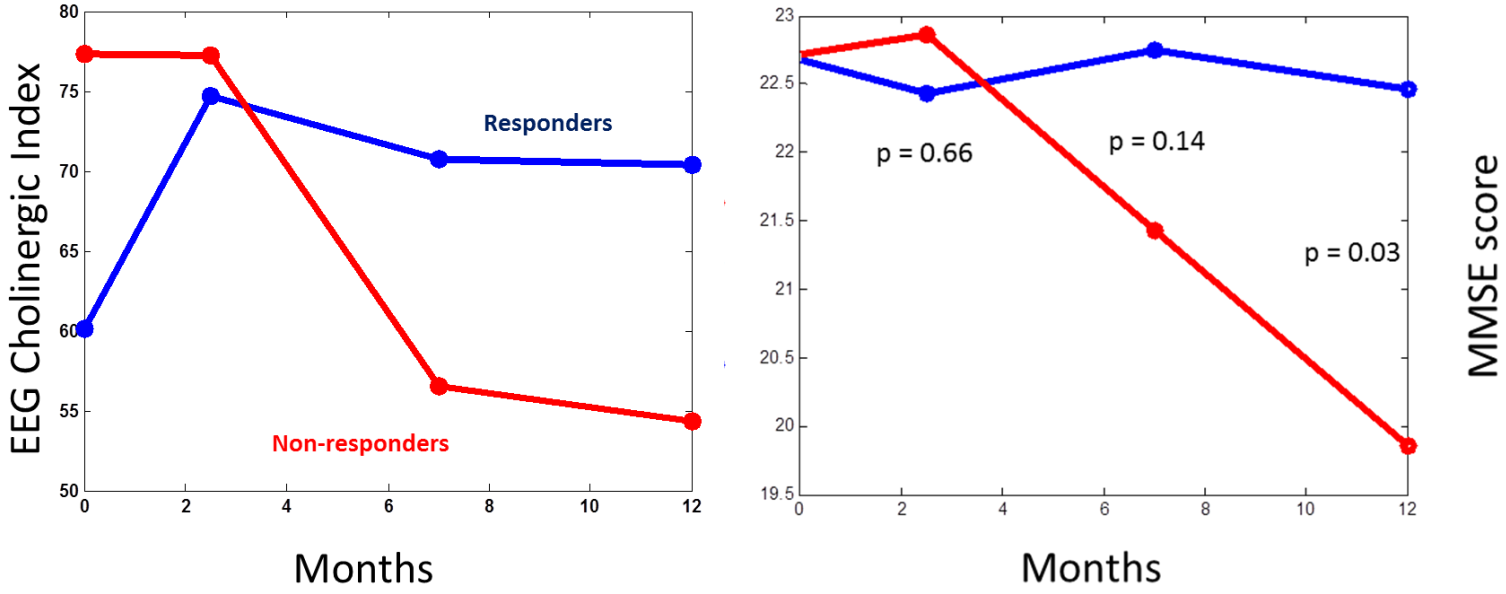
Responders and non-responders





Integrated treatment response for 42 AD patients over the course of one year as evaluated by the EEG Cholinergic Index®. The individuals are classified as responders (positive overall response) or non-responders (negative overall response).

Responders Maintain a higher score on MMSE



- The EEG Cholinergic Index® correlates significantly with MMSE, with a coefficiant of 0,42
- This suggests that the EEG Cholinergic Index can be used to:

a) Monitor cholinergic activity at the patient level – establish a baseline or a reference point
b) Monitor treatment response
c) Monitor dose response
d) Monitor disease progression

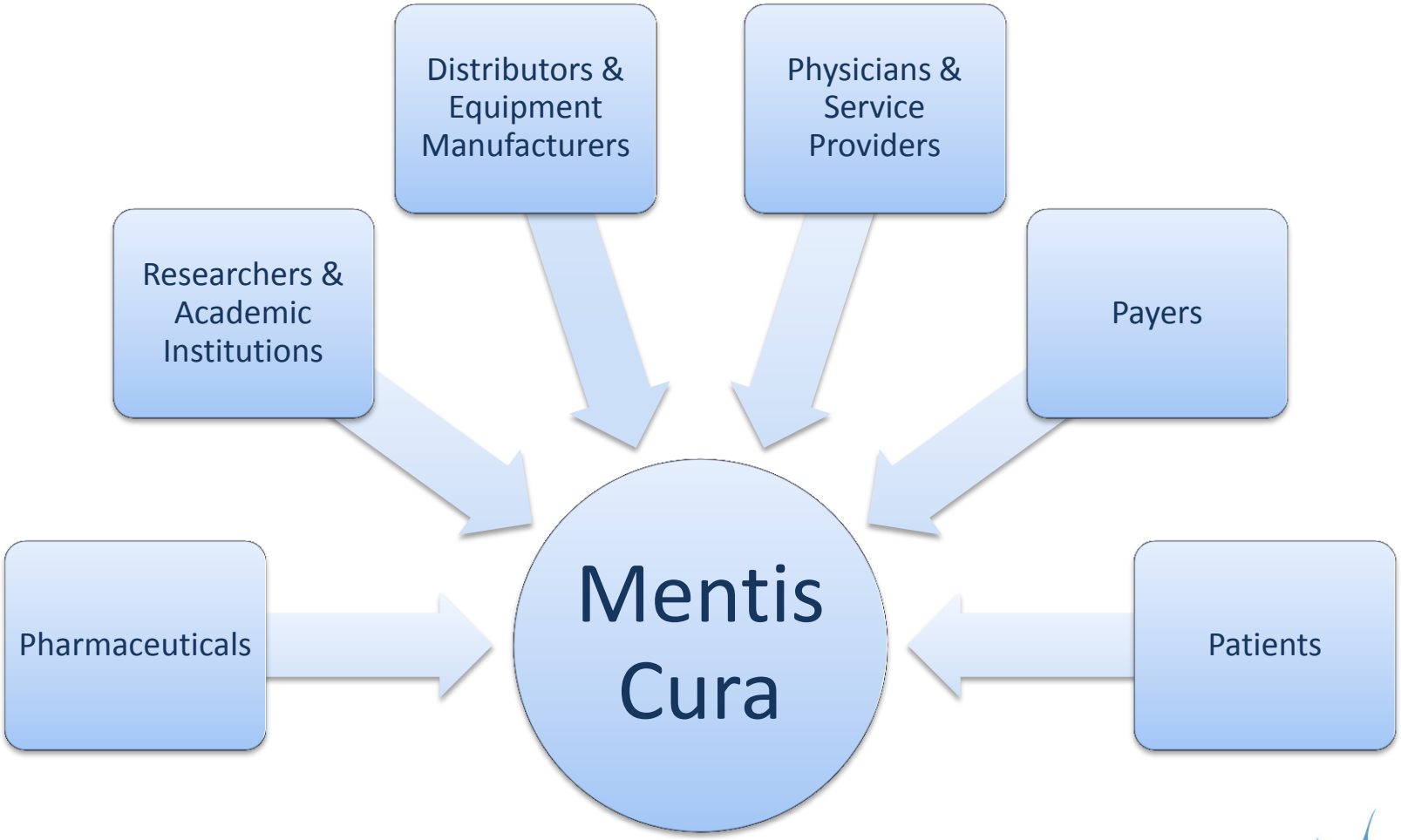
The EEG Cholinergic Index®

- A biomarker for Cholingergic activity and dementia
  - Non-invasive
  - Affordable
  - Readily available
  - Provides relevant information
  - Suitable for research
  - Monitor patients in the clinical environment

- The EEG Cholinergic Index® is a part of the Mentis Cura Dementia Analysis software. The index is based on a standardized EEG recordings. The user can upload any EEG file in an EDF file format and receive the dementia report within minutes

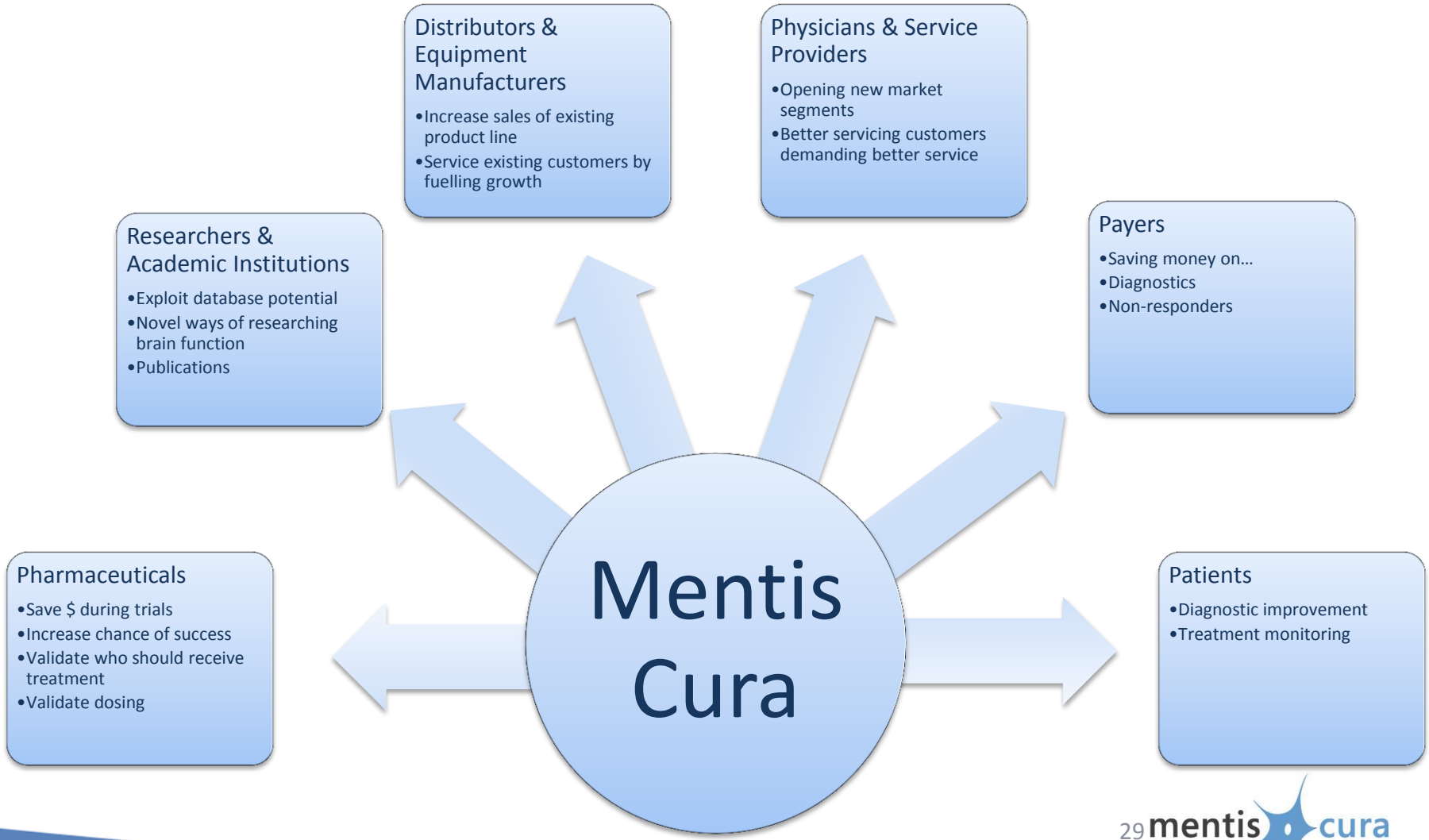
Mentis Cura Environment

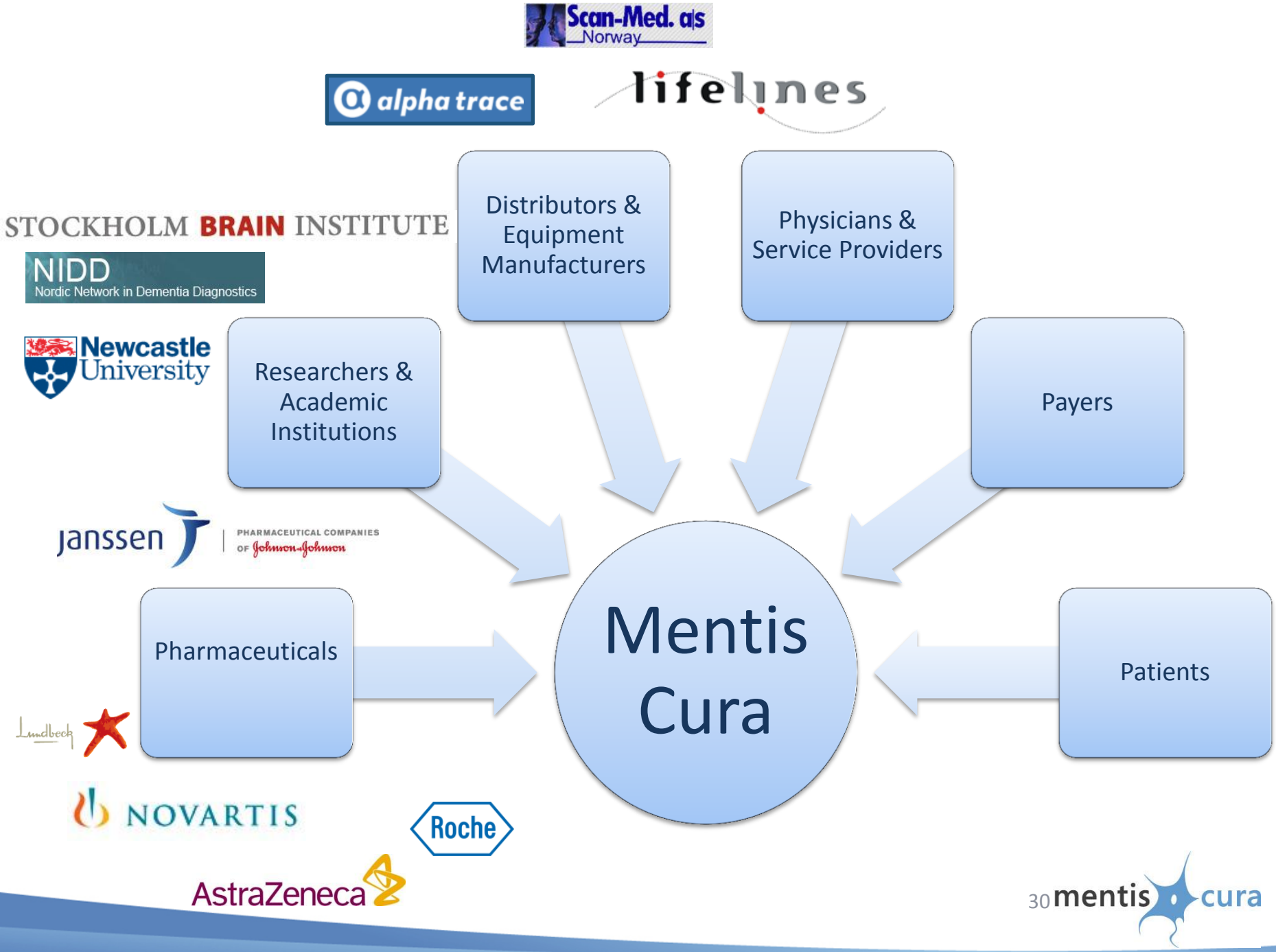
Stakeholders



Mentis Cura Contribution

Aligned with key stakeholders




Scan-Med. as
Norway
alpha trace
lifelines
STOCKHOLM BRAIN INSTITUTE
NIDD
Nordic Network in Dementia Diagnostics
Newcastle University
Distributors & Equipment Manufacturers
Physicians & Service Providers
Researchers & Academic Institutions
Payers
janssen
PHARMACEUTICAL COMPANIES OF Johnson&Johnson
Pharmaceuticals
Mentis Cura
Patients
Lundbeck
NOVARTIS
Roche
AstraZeneca

Stockholm Brain Institute

- One of World´s leading brain research centers
- External Partnership Agreement by January
- Major recognition of Mentis Cura work
- Partnership to focus on monitoring the following:
  - Dementia Diagnostics
  - Clinical Trials and Research
  - Analysing Existing Data
  - Monitoring of cognitive decline in trauma, post surgery etc
  - ADHD