Biomarker Development for Risk Prediction of Postoperative Cognitive Impairment in the Elderly (BioCog)

Georg Winterer

BioCog Consortium Coordinator

What are Postoperative Cognitive Disorders?

Postoperative cognitive impairment: initially clouded consciousness, psychotic symptoms, apathy, disorientation (delirium) followed by deterioration of sensory and cognitive function after surgery with incidences of up to 30-80%

Postoperative Cognitive Delirium POD

DSM-IV: 293.0

Acute

Postoperative Cognitive Dysfunction POCD

DSM-IV: 294.0

Chronic

Postoperative Cognitive Disorders:
Multimorbid Condition

Multiple Factors associated with POD/POCD

- age *per se*

- (insidious) dementia

- low education status (low brain reserve capacity)
- multimorbidity
- chronic inflammation
- extent of surgical trauma (inflammatory response)
- medication: (e.g. anticholinergic, sedative medication, anesthesia)
- metabolic syndrome
- cardiovascular/hypovolemic shock
- neuropsychiatric disorders (depression, alcoholism etc.)

Important: Some of these factors also have been implicated in the development and acceleration of (Alzheimer) „dementia"

Why is research on POD/POCD important for our society?

In an aging society like the European Union, the socioeconomic implications of POD/POCD are profound:

- longer and more costly hospital treatment
- Diminished ability to cope with daily life
- dependency on social transfer payments
- Leaving the labour market prematurely
- increased mortality

Steinmetz et al *Anesthesiology* 2009 (ISPOCD Group)*

*ISPOCD was **funded by EU: Biomed-1 programme** (1994-2002)

Hip Replacement – A Real World Example

Most common reason for hip replacement is (painful) osteoarthritis in the hip joint

Possible Benefits (after surgery):

- no more pain
- no more pain killers
- better mobility

The Telegraph

Hip replacement surgery denied to thousands each year, despite NHS guidelines
Sarah Knapton, Science Editor, 27 April 2016

Possible Costs (for patients):

- perioperative complications incl. death
- persistent postoperative functional impairment (e.g. change in leg length)
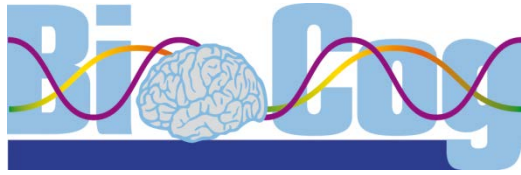- persistent postoperative cognitive impairment: POD/dementia

Possible Costs (for the society/family):

- surgical intervention is expensive
- daily care for the disabled (e.g. cognitively impaired patient) is expensive

Biomarker Development for Postoperative Cognitive Impairment in the Elderly (BioCog)

Goals:

- Primary Goal: Personalized Biomarker-based Clinical POD/POCD Outcome Prediction (Trait & State Markers)
- Establish a large Biobank: Postoperative Cognitive Disorders (Neuroimaging & Molecular Biomarkers)
- Understanding Pathological Mechanisms of POD/POCD (Acute Model of Dementia)
- Building a Preclinical Dementia Cohort
- Identify Potential Drug Targets

BioCog Consortium

Academic Institutions:

- Charité Universitätsmedizin Berlin (Germany)
  Anesthesiology, Psychiatry, Neurology, Neuropathology, Immunology, Neuroimaging (ECRC/BCAN)

- Universitair Medisch Centrum Utrecht (Netherlands)
  Anesthesiology, Neuroradiology, Neurology

- Cambridge University Hospital (United Kingdom)
  Anesthesiology, Neuroimaging (Center for Brain Science)

- Max-Delbrück Center for Molecular Medicine Berlin (Germany)
  Genetic Epidemiology (Biobanking), Neuroimaging (BUFF/PTB)

- Consiglio Nazionale delle Ricerche (Italy)
  Immunology

- University of Luxembourg (Luxembourg)
  Bioinformatics

70% of Funding

Private Partners:

30% of Funding

PharmaImage Biomarker Solutions GmbH (Biotech Park Berlin-Buch, Germany)

ATLAS Biolabs GmbH (Berlin, Germany), Immundiagnostik AG (Berlin, Germany),

Alta Ricerca e Sviluppo in Biotecnologie Srlu (Siena, Italy), Cellogic GmbH (Berlin, Germany)

Funding Period: 02/2014 – 01/2019: 6 Million € plus support from the Berlin Institute of Health (BIH) as „*Pathfinder Study*"
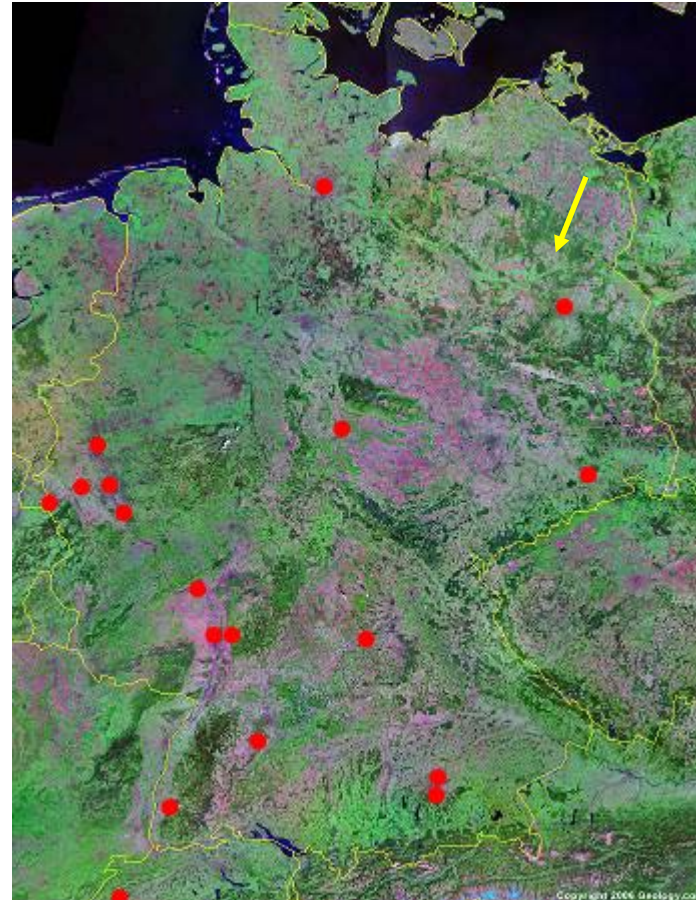
BioCog Blueprint: Nicotine: Molecular and Physiological Effects in CNS

National DFG Priority Program SPP1226

Coordinator: Georg Winterer

Clinical Multicenter Study

- Aachen
- Berlin
- Bonn
- Cologne
- Dresden
- Düsseldorf
- Erlangen
- Freiburg
- Geneva
- Göttingen
- Hamburg
- Heidelberg
- Jülich
- Mainz
- Mannheim
- Munich
- Neuherberg

http://www.nicotine-research.de

2007 - 2010 (1. Funding Period)
2011 - 2017 (2. Funding Period)

10-yrs. Follow-up Study (Transregio) in Preparation

SPP1226 - Translational Approach

24 Clinical and Preclinical Projects

SPP: > 200 papers (incl. 2x Nat. Genetics)

Multicenter Study: 20 papers (incl. PNAS)
(genomewide papers in preparation)

Total Funding: 10 Million EUR

Neuroimaging Biomarkers:

Window into the brain:

-    allows studying abnormal brain structure (trait) and function
     (state) with <u>high sensitivity</u>
-    In part independent of specific molecular pathology

Molecular Biomarkers:

-    Detecting/Tracking <u>specific</u> molecular processes
-    Limited sensitvity (plasma/blood) because of blood-brain barrier
     (except CSF)

Biomarker Establishment

Industry-standard biomarker development requires taking the technical, biometrical and organisational steps to ensure that valid biomarkers are selected

- Standardized data collection/analysis - with advice from European Medicines Agency (EMA)

- Training set (N = 400), test set (N = 800) after optimization of data analysis/reduction of multivariate solution space

- Deliverables: reference ranges, sensitivity and specificity with receiver operating characteristic (ROC), positive and negative predictive values (PPV, NPV), false discovery rate (FDR), reliability

Molecular Biomarker

Dual Approach:

- **Hypothesis-free** using Omics Platforms etc.

   We will creat a biobank which will become an integral part of the European Biobanking and Biomolecular Resources Research Infrastructure (BBMRI)

- **Hypothesis-based**

   Based on the cholinergic anti-inflammatory pathway hypothesis of POD/POCD, specific molecular biomarkers will be investigated *

*Mostly based on experimental animal studies (incl. work from Dept. of Anesthesilology, Charite.
In part, these investigations also follow-up previous work from the DFG-funded Schwerpunktprogramm
SPP1226: Nicotine: Molecular and Physiological Effects in CNS (Coordinator: G Winterer)

Consortium Structure
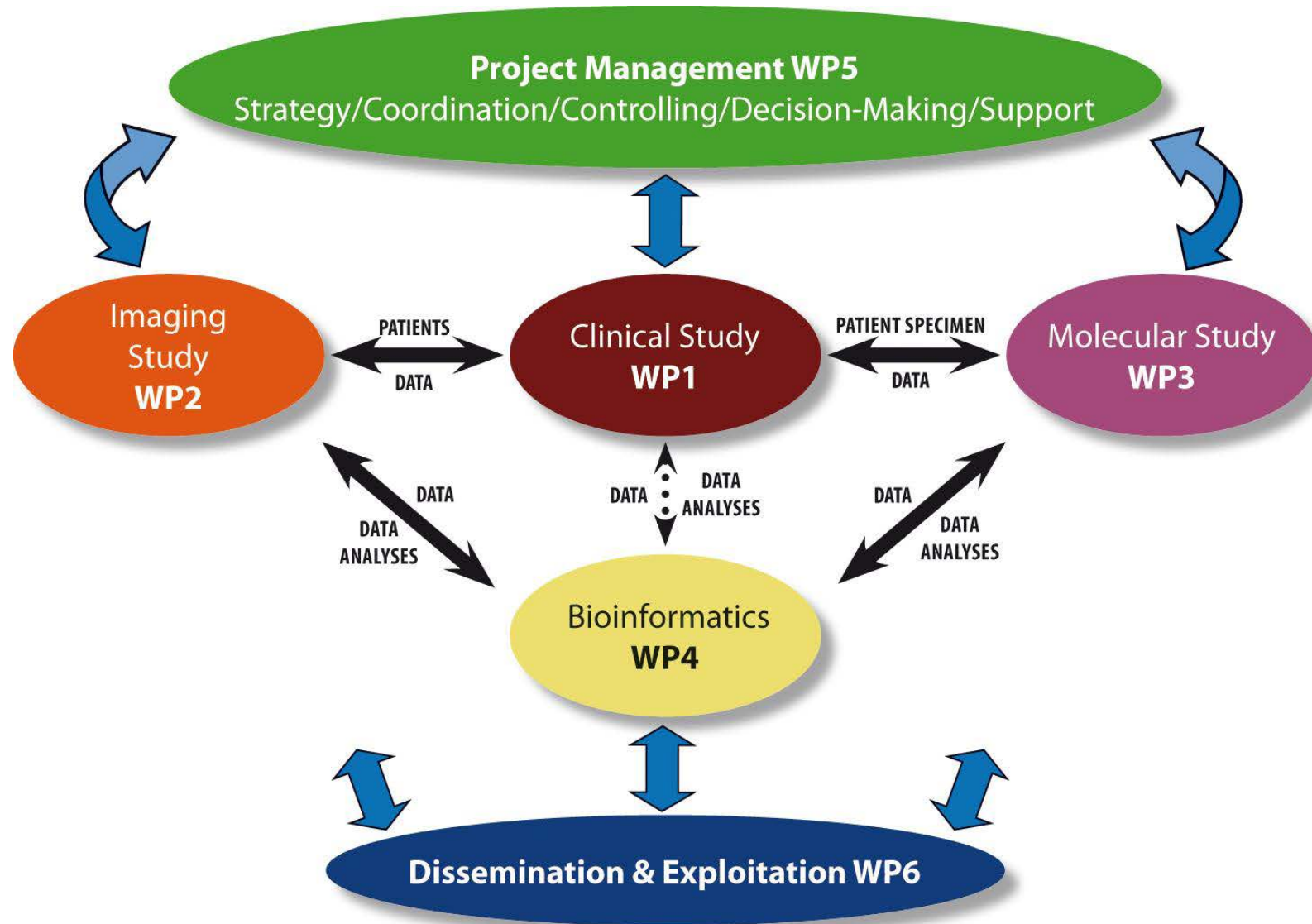
Screening Phase and Inclusion Criteria:

- Age > 65 years

- Elective surgical intervention

- Operating time > 60 min.

- Hospital length of stay > 7 days

Target: enrolling 1200 surgical patients incl. 100 control patients (without surgery)

Prof. Arjen Slooter

Prof. Claudia Spies

BioCog: Largest study of its kind worldwide

Cooperation with SAGES study Harvard (USA)

Exclusion Criteria

- Mini-Mental-State Examination (MMSE) ≤ 23

- Contraindications MRI

- Current neuropsych medication (tranquilizers/antidepressants etc.)

- Neurological or psychiatric disorders

- Severe visual/auditory disorders
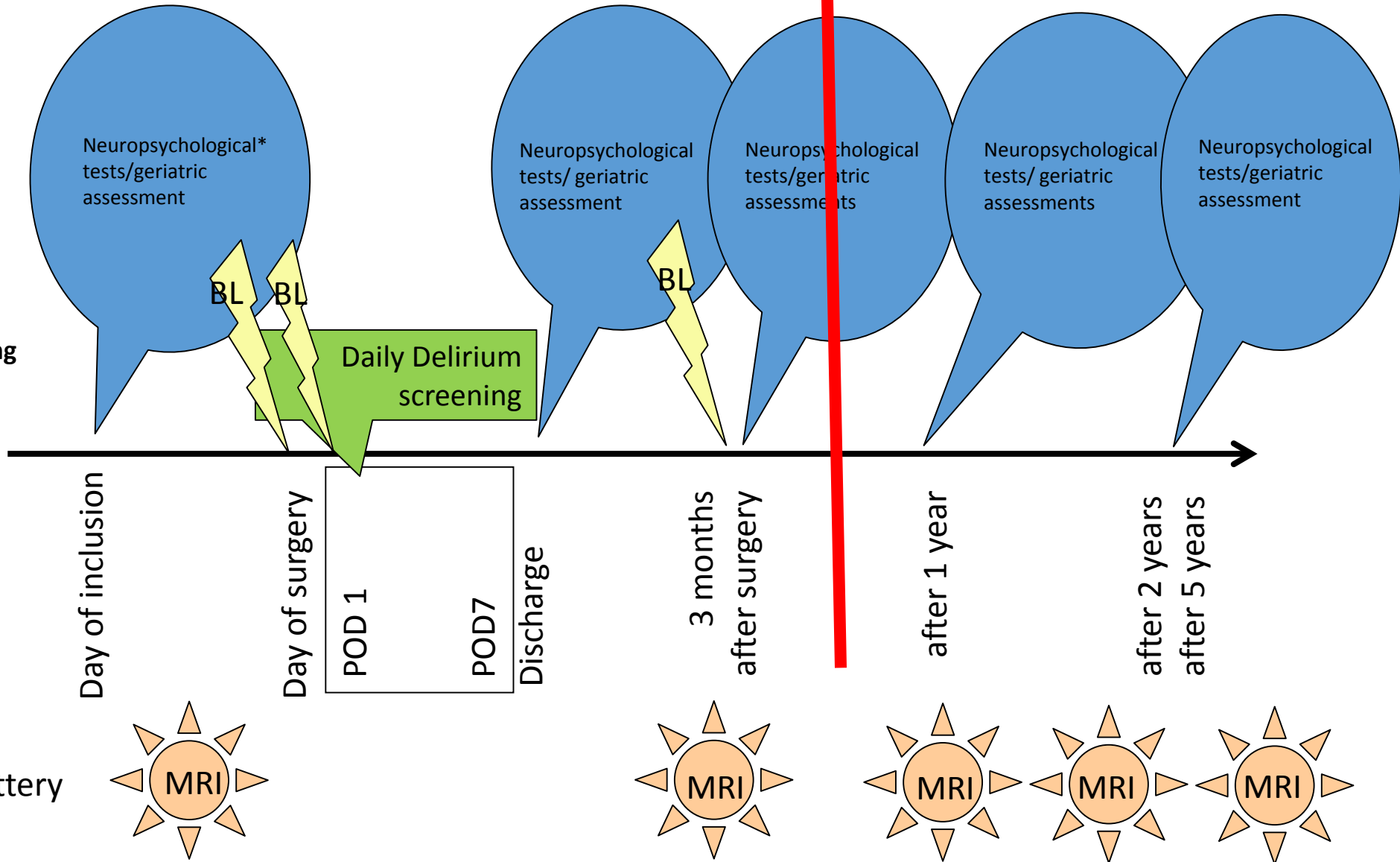
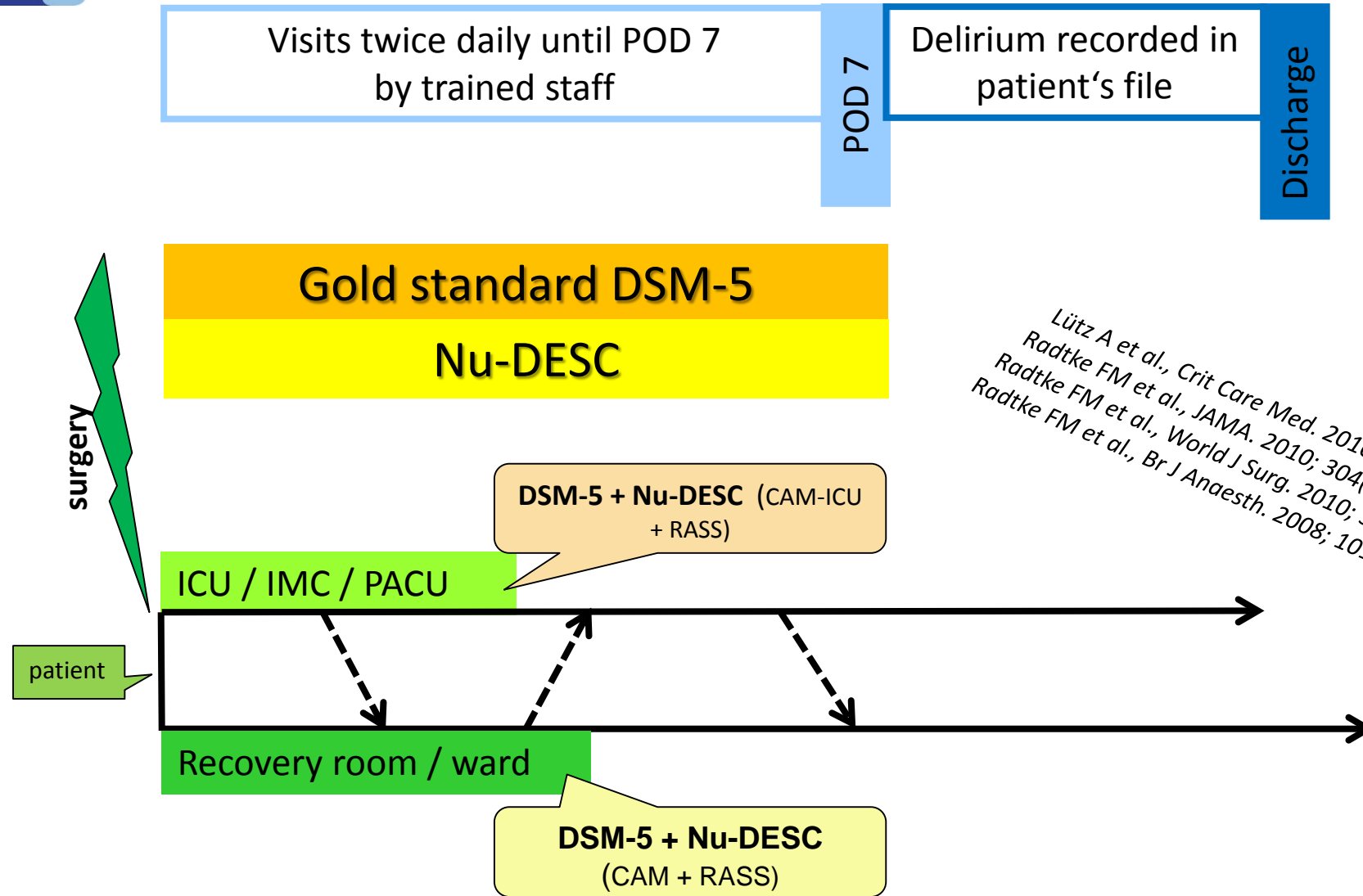- Drug and alcohol dependence within the last 5 years

Co-Primary Endpoints: POD & POCD

Visits twice daily until POD 7 by trained staff

POD 7

Delirium recorded in patient's file

Discharge

Gold standard DSM-5

Nu-DESC

surgery

DSM-5 + Nu-DESC (CAM-ICU + RASS)

ICU / IMC / PACU

patient

Recovery room / ward

DSM-5 + Nu-DESC (CAM + RASS)

Lütz A et al., Crit Care Med. 2010; 38(2): 409-418.
Radtke FM et al., JAMA. 2010; 304(19): 2124-2127.
Radtke FM et al., World J Surg. 2010; 34(3): 487-494.
Radtke FM et al., Br J Anaesth. 2008; 101(3): 338-343.

POCD: based on Cantab Neuropsych Battery
Incl. verbal memory, attention, working memory tests

MRI Imaging

- Resting State fMRI/EEG (simultaneous acquisition)

  (seed-based network, graph analyses, EEG power, coherence, EEG-informed fMRI)

- Structural MRI

  (volumetric: whole brain, BPV/ICV, regional surface, thickness)

- Dedicated T2 High-Resolution Hippocampus Sequence

  hippocampal subfields

- Diffusion Tensor Imaging (DTI)

  Fiber tracking with ROI analyses (FA, AD, MD, RD)

- Perfusion MRI (ASL)

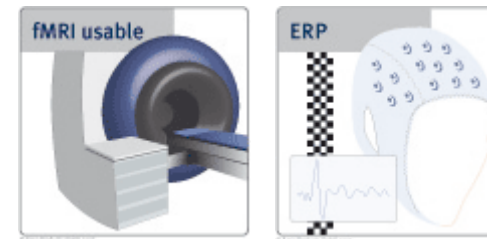 Vascular brain perfusion

- T2-weighted (FLAIR)

  Small Vessel Disease Burden

EEG/ERP

fMRI usable

ERP

32-Channel
BrainCap MR

Continuous EEG-Recording

during MR-Scan. Sampling: 5000Hz

π PharmaImage

Biomarker Solutions

www.pi-pharmaimage.com

EPI Sequence:
33 Slices (3mm)
TR = 2000ms

3Tesla

BCAN Berlin (Siemens)
Utrecht Neuroradiology (Philipps)

Siemens Magnetom Trio

BRAINAMP MR PLUS

BRAIN PRODUCTS
Solutions for neurophysiological research
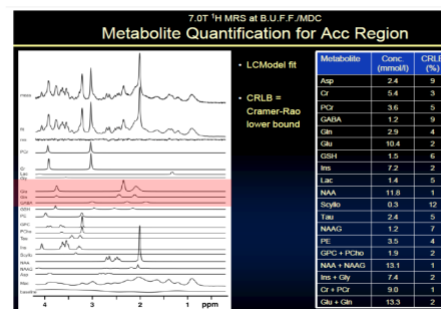
Partnership in Product Development

N = 80 surgical patients: pre-operatively

Charité/ECRC, MDC (BUFF) & Physikalisch-Technische Bundesanstalt

<u>7Tesla because: superior sensitivity</u>

- Glutamate/GABA MR Spectroscopy (hippocampus, ACC):
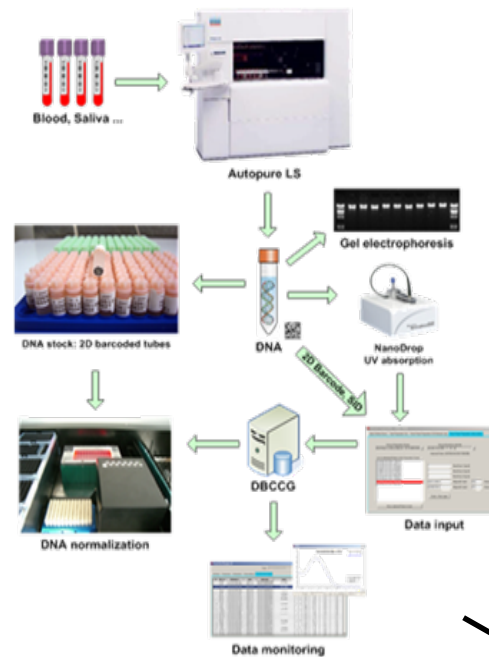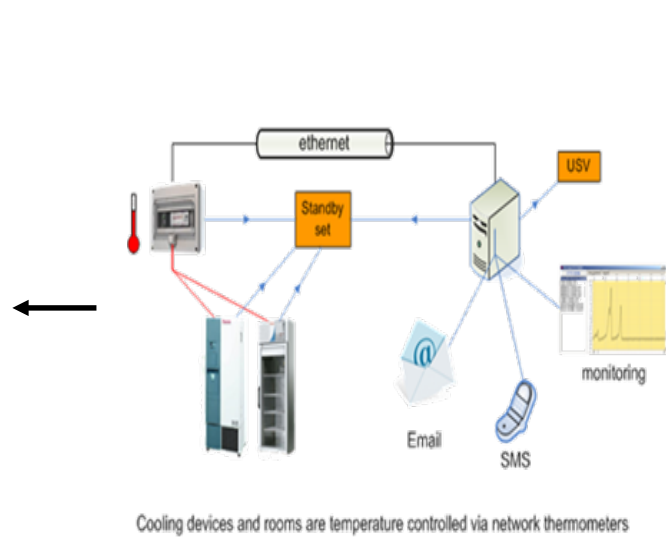 SPECIAL (spin-echo full-intensity acquired localized)

Biobanking

Biorepository

Sample tracking, processing, biobanking & sample distribution is conducted at the *Max-Delbrück Center (MDC) Berlin (Prof. Tobias Pischon)* taking advantage of existing infrastructure (*German National Cohort Study, CentraXX Databank*)

MDC Berlin
Metabolic profiling

Atlas Biolabs GmbH (Berlin)
Omics: genomewide genotyping,
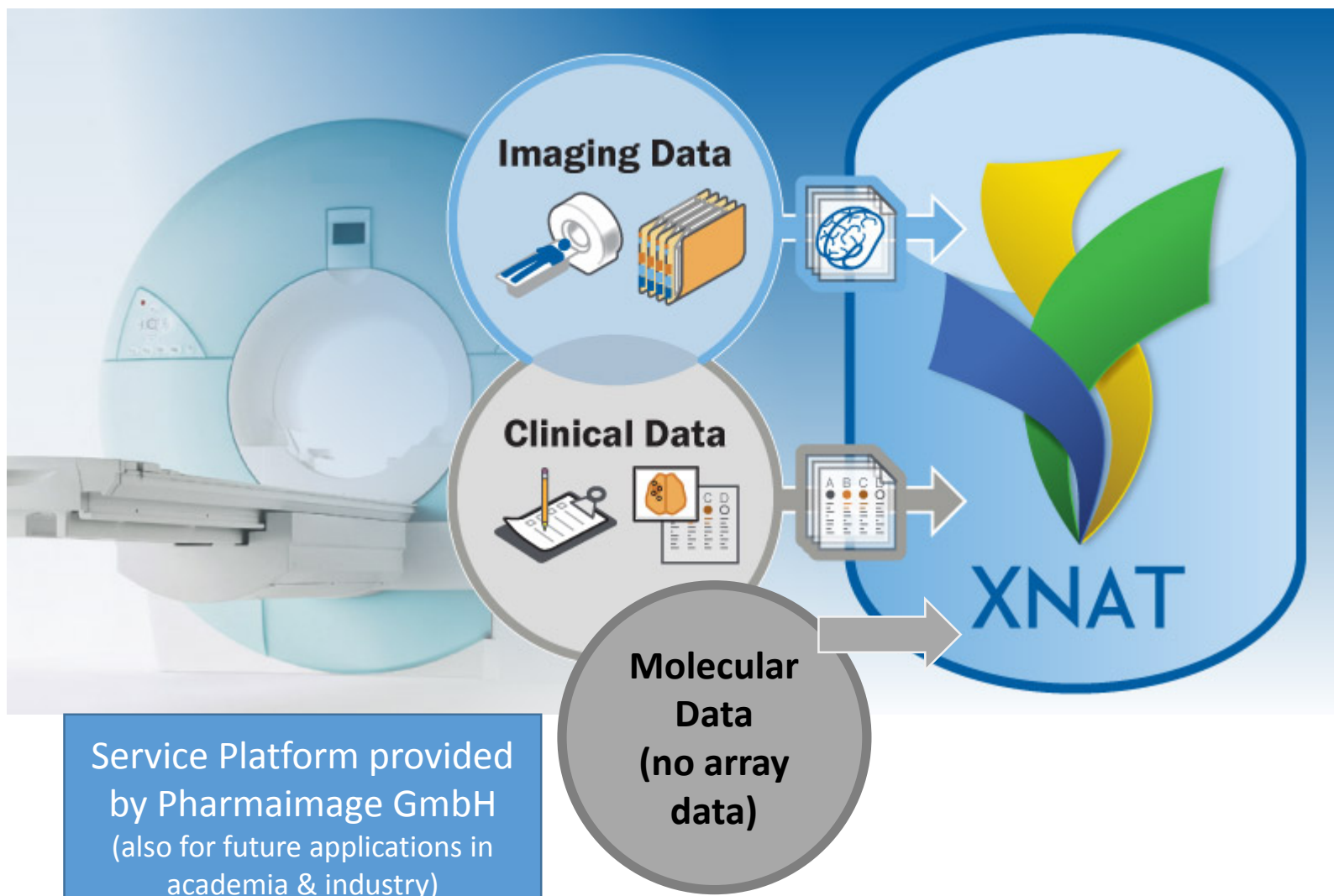miRNA/RNA profiling, Targeted sequencing

Immundiagnostik AG (Berlin)
immunological profiling

Consiglio Nazionale
delle Richerche (Italy)
immunological profiling

Bioinformatics Core Luxembourg

POD/POCD: Establish a European Biobank!!!

XNAT - Imaging Neuroinformatics Platform

Service Platform provided by Pharmaimage GmbH (also for future applications in academia & industry)

Molecular Data (no array data)

Imaging Data Management System

Software Core functions:

- Importing
- Archiving
- QC (quality control)
- Processing Plugins
  (SPM, Freesurfer, Matlab etc.)
- Distributing

of Imaging Data and related Data

Integration of multimodal data sets: Neuroimaging, Clinical, Neuropsych, Molecular

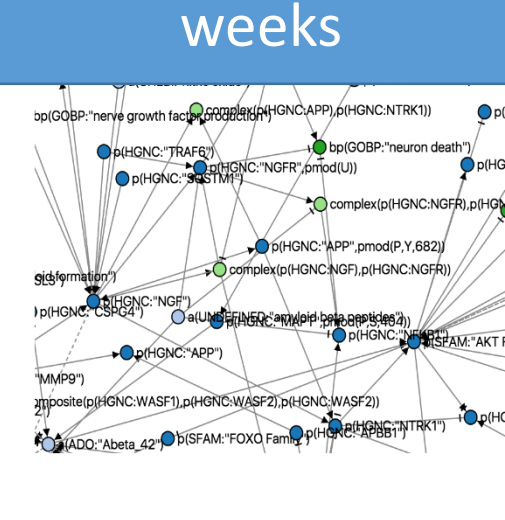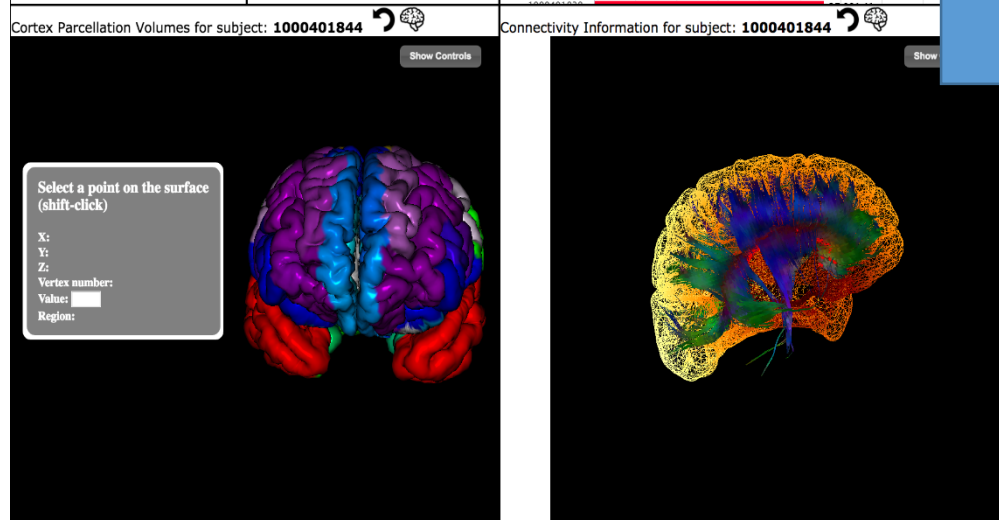**Integration with Bioinformatics** (tranSMART-Brain Mesh platforms)

Integration of Neuroinformatics (XNAT) with Bioinformatics via tranSmart – Brain Mesh Platforms
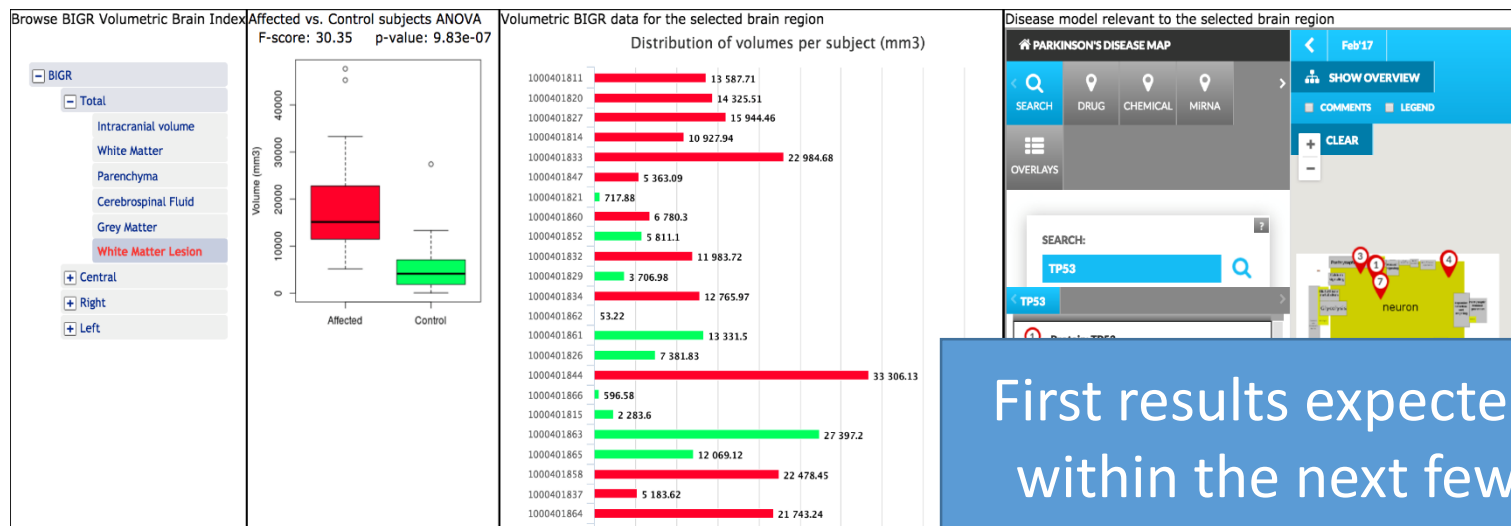
First results expected within the next few weeks
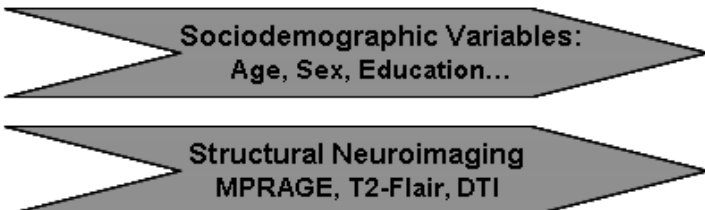
Public-Private Partnership

Link based on Allen Brain Atlas

Bioinformatics/Neuroinformatics
Expert System

Prediction of POD/POCD Risk & Tracking State-Related Changes:
Building a Multivariate Expert System for Research and Clinical Applications

Variable Sets

Sociodemographic Variables:
Age, Sex, Education...

Structural Neuroimaging
MPRAGE, T2-Flair, DTI

Training Set
N = 400

Test Set
N = 800

Selection of Variables

Prediction of Disease Risk

Additional Markers:

- DNA (blood) custom-designed GSA Global screening array (Illumina): GWAS-based Dementia Risk Markers
- Blood transcriptome (Affymetrix Clariom S)
- Affymetrix miRNA Array Plate*

*BIH-CRU support

CHRNA7, AChE, ChAT...

Analyses currently running
Parameter Selection 09/2017

Luxembourg Centre for Systems Biomedicine (LCSB)/PharmaImage Biomarker Solutions GmbH (PI)

Prediction Algorithms: Stepwise Linear Regression, Support Vector Machine, Neural Networks
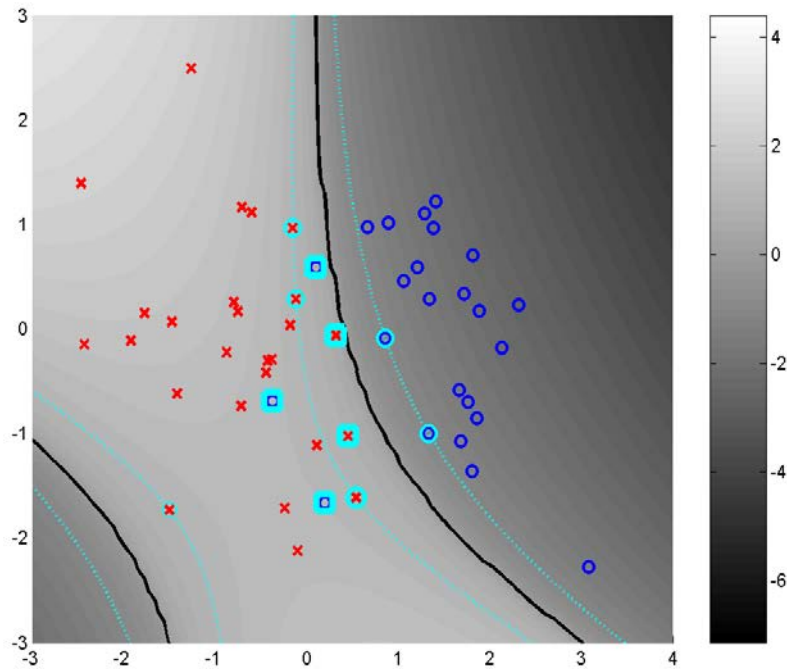
Dimensions in Vector Space
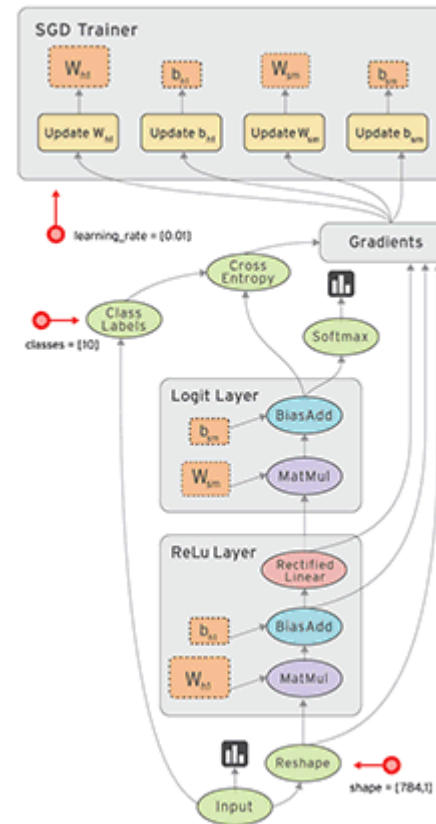
TensorFlow
Google Brain

Other machine learning/ deep learning algorithms are also tested

π PharmaImage

XNAT & Pattern Recognition:
Google Brain - Machine Learning Algorithms

BioTech Park Berlin-Buch (Germany)

Boston – Kendall Square (MA, USA)

π PharmaImage
Biomarker Solutions GmbH

π PharmaImage
Biomarker Solutions Inc.

Chief Executive Officer
Georg Winterer

www.pi-pharmaimage.com

President
Georg Winterer

Cooperation with Univ. St Louis/Harvard/Radiologics Inc. & TU Berlin
Supported by NIH

Exploitation

- **Usefulness and Practicability of Multivariate Expert system in Clinical Care: Health Economic Risk vs Benefit Evaluation of Surgical Interventions**

- **Patent Application in Preparation (through Charite Technology Transfer Office)**

- **Biomarker used for R&D (Drug Development): e.g. miRNA Biomarker**

Where do we stand now?

- N = 1150 patients enrolled (62% with MRI, 60% with 3-month follow up): Study goal achieved !
First patient in 11/2014, last patient in 04/2017

- Data processing (clinical, neuropsych, neuroimaging, molecular incl. -omics) almost completed (finished by 08/2017)

- Data bases/databanks (clinical, neu_____most
curated (clean) and currently integr_____tranSmart
– Brain Mesh Platforms (finished by_____

> We have already very promising results!
> But sorry: too early to call.
> We are going public end of this year

- Exploratory statistical analyses (trai_____
POD/POCD odds ratios, predictive values, test-retest stability (incl. MRI-scanner Utrecht/Berlin)

- Annual Meeting Sept. 03-06 2017 (Palma, Mallorca):
Parameter selection for multivariate predictor based on exploratory stat. analyses (training set)

Thank you for your attention!

Prof. Georg Winterer
Coordinator – BioCog Consortium

www.biocog.eu

Clinical Neurocognitive & Neuroimaging Research Group (CNNR)
Experimental & Clinical Research Center (ECRC)

www.pi-pharmaimage.com

Biotech Park Berlin-Buch (Germany)
Kendall Square Boston/Cambridge (USA)