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

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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 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

**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*

Private Partners:

- Pharmalimage 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

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

http://www.nicotine-research.de
POD/POCD Risk Prediction
Neuroimaging & Molecular Biomarkers

Neuroimaging Biomarkers:

Window into the brain:
- allows studying abnormal brain structure (trait) and function (state) with high sensitivity
- In part independent of specific molecular pathology

Molecular Biomarkers:
- Detecting/Tracking specific molecular processes
- Limited sensitivity (plasma/blood) because of blood-brain barrier (except CSF)
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 create 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 Anesthesiology, 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

Project Management WP5
Strategy/Coordination/Controlling/Decision-Making/Support

Imaging Study WP2

Clinical Study WP1

Molecular Study WP3

Bioinformatics WP4

Dissemination & Exploitation WP6
Screening Phase and Inclusion Criteria:

- Age > 65 years
- Elective surgical intervention
- Operating time > 60 min.
- Hospital length of stay > 7 days

BioCog: Largest study of its kind worldwide

Cooperation with SAGES study Harvard (USA)
Exclusion Criteria

- Mini-Mental-State Examination (MMSE) \( \leq 23 \)
- 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
**Schedule**

- **Day of inclusion**
  - Neuropsychological tests/geriatric assessment

- **Day of surgery**
  - Daily Delirium screening
  - BL (blood sampling)
  - MRI

- **POD1**
  - Neuropsychological tests/geriatric assessment

- **POD7**
  - Neuropsychological tests/geriatric assessment
  - MRI

- **Discharge**
  - BL

- **3 months after surgery**
  - Neuropsychological tests/geriatric assessments

- **1 year after surgery**
  - Neuropsychological tests/geriatric assessments

- **2 years after surgery**
  - Neuropsychological tests/geriatric assessments

- **5 years after surgery**
  - Neuropsychological tests/geriatric assessments

**EU Funding**

- Not yet funded

**Notes**

- BL= blood sampling
- *Cantab Test Battery
- *MRI

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*BioCog*
Co-Primary Endpoints: POD & POCD

Visits twice daily until POD 7 by trained staff

Delirium recorded in patient’s file

Gold standard DSM-5

Nu-DESC

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

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

Continuous EEG-Recording during MR-Scan. Sampling: 5000Hz

Siemens Magnetom Trio
BCAN Berlin (Siemens)
Utrecht Neuroradiology (Philipps)
N = 80 surgical patients: pre-operatively

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

7Tesla because: superior sensitivity

- 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)

POD/POCD: Establish a European Biobank!!!
XNAT - Imaging Neuroinformatics Platform

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, Neuropsy, Molecular

Integration with Bioinformatics (tranSMART-Brain Mesh platforms)

Service Platform provided by Pharmimage GmbH (also for future applications in academia & industry)
Integration of Neuroinformatics (XNAT) with Bioinformatics via tranSmart – Brain Mesh Platforms

Public-Private Partnership

First results expected within the next few weeks

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

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

Variable Sets
- Sociodemographic Variables: Age, Sex, Education...
- Structural Neuroimaging: MPRAGE, T2-Flair, DTI

Training Set
N = 400

Test Set
N = 800

Selection of Variables

Analyses currently running
Parameter Selection 09/2017

Luxembourg Centre for Systems Biomedicine (LCSB)/Pharmalimage 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
XNAT & Pattern Recognition:
Google Brain - Machine Learning Algorithms

BioTech Park Berlin-Buch (Germany)

Boston – Kendall Square (MA, USA)

PharmaImage
Biomarker Solutions GmbH

Chief Executive Officer
Georg Winterer

www.pi-pharmaimage.com

PharmaImage
Biomarker Solutions Inc.

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, neuropsych, neuroimaging, molecular incl. -omics) almost curated (clean) and currently integrated into XNAT and linked with bioinformatics via tranSmart – Brain Mesh Platforms (finished by 08/2017)

- Exploratory statistical analyses (training data set: N = 400) currently running
  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)

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

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