PredictAD – From Patient Data to Personalised Healthcare in Alzheimer's Disease

Jyrki Lötjönen[1], Lennart Thurfjell[2], Jarmo Laine[3], Marcello Massimini[4], Daniel Rueckert[5], Roman Zubarev[6], Matej Orešič[1], Mark van Gils[1], Jussi Mattila[1], Gunhild Waldemar[7], Hilkka Soininen[8]

[1]VTT Technical Research Centre of Finland, [2]GE Healthcare, [3]Nexstim Ltd, [4]University of Milan, [5]Imperial College London, [6]Karolinska Institutet, [7]Rigshospitalet, [8]University of Eastern Finland.

Correspondence: jyrki.lotjonen@vtt.fi, VTT Technical Research Centre of Finland, P.O. Box 1300, 33101 Tampere, Finland

Background:

Alzheimer's disease (AD), the most common cause of dementia, alone accounts for costs equivalent to about 1% of the gross domestic product of the whole world [1]. The number of persons affected currently is about 36 million but the number is expected to double in the next 20 years [1]. Many approaches are now under investigation targeting either treatments for pathology directly, such as anti-amyloid plaque agents, or prevention strategies, such as lifestyle changes. Especially when new drugs or prevention strategies become available, early diagnosis is essential to detect patients and to start medication and/or preventative treatments.

The main objective of the PredictAD (www.predictad.eu) EU-funded VPH research project (6/2008-11/2011) was to find efficient biomarkers from heterogeneous patient data and integrate them for making early diagnosis and progress monitoring of AD more efficient, reliable and objective. This work summarises the work done in biomarker discovery from different data sources and in developing a data-driven decision support tool combining all biomarker information.

Methods:

Quantification of molecular data. Various biomarkers extracted from CSF are known to be strongly related with the Alzheimer's disease. However, blood samples would be an excellent source for detecting AD at early phase as they are easily available and blood sampling is not considered an invasive technique. PredictAD made biomarker discovery focusing on metabolomic and protein compounds from blood samples [2-3]. Advanced mass-spectroscopy approaches combined with bioinformatics were used in the discovery.

Quantification of TMS/EEG data. Alzheimer's disease is known to affect the electromagnetic activity of the brain. Transcranial magnetic stimulation combined with electroencephalography (TMS/EEG) is a novel non-invasive tool for measuring the electrophysiological brain responses to direct cortical stimulation, unbiased by the cognitive impairment and subjective functional performance of patients with AD. A unified mathematical framework was developed to analyse TMS/EEG data, at the sensors as well as at the source level, including statistical analysis for identifying the spatio-temporal pattern of brain activity significantly evoked by TMS [4-5]. Data analysis methods were implemented in a software tool, working in the Matlab environment.

Quantification of image data. Methods for the segmentation and spatio-temporal feature extraction from MR and PET images were developed. More specifically, efficient tools for MR brain segmentation, especially for segmentation of the hippocampus, for atrophy rate measurement, for tensor-based morpohometry and for manifold-learning were developed [6-9]. In addition, tools for the

analysis of FDG PET and PET amyloid imaging were developed [10-11]. The clinical usefulness of the developed methods was evaluated in terms of robustness, accuracy and computation times in several patient cohorts.

Model & Software. A novel framework was developed combining heterogeneous multi-source data and providing an evidence-based index reflecting the probability of the disease in a patient [12]. The disease state index is computed by comparing patient measurements with a large number of measurements from healthy and diseased cases. In addition, the disease state fingerprint was developed for visualizing the state of the patient in a way that a clinician can easily see and understand the contributions of different measures to the index. The framework was realised in the PredictAD software tool (Fig. 1).

Results:

The methods developed were validated in many aspects and the summary is presented here.

Quantification of molecular data. The project produced promising results with novel molecular level signatures. Our findings primarily implicate the roles of hypoxia, oxidative stress, as well as membrane lipid remodeling in AD. Establishment of pathogenic relevance of predictive biomarkers such as ones produced in PredictAD may not only facilitate early diagnosis, but may also help identify new therapeutic avenues.

Quantification of TMS/EEG data. The results indicate that it is possible to extract from TMS/EEG data synthetic indices of cortical excitability and effective connectivity that significantly correlate with clinical measures of cognitive decline. PredictAD provided a proof-of-concept that TMS/EEG technology has clear potential in defining novel biomarkers for the diagnostics of Alzheimer's disease.

Quantification of image data. Comprehensive validation has been performed for MRI image analysis methods: data from six cohorts consisting of almost 2000 cases were used. In a specific comparison study, it was found that no single method appeared clearly superior to the others [13]. It was shown that the combination of the results from all developed method improves the diagnostic accuracy.

Model & Software. The validation of the software solution for decision support showed that its use improves clinicians' diagnostic accuracy and their confidence about their decisions compared with current diagnostic work-flows. The preliminary results show that using the tool diagnosis could be made with high accuracy for 50 % of mild-cognitive impairment cases about 12 months earlier than currently. As the ADNI data (adni.loni.ucla.edu) from about 400 cases was used in this study, these numbers do not contain improvements that are obtained by including the novel blood, amyloid-PET and TMS/EEG-based biomarkers.

Conclusions:

PredictAD took several steps towards more objective and efficient diagnostics in Alzheimer's disease on different fronts. The project provided several novel tools for biomarker discovery and a novel data-driven and evidence-based disease profiling approach for clinical decision support, demonstrating that the project reached its objective.

References:

1. Wimo A and Prince M. Alzheimer' Disease International: World Alzheimer Report 2010 – The Global Economic Impact of Dementia, 2010.
2. Orešič M, Hyötyläinen T, Herukka S-K, et al.. Metabolome in progression to Alzheimer's disease. Translational Psychiatry. 2011; 1: e57.

3. Yang H, Lyutvinskiy Y, Soininen H, et al. Alzheimer's disease and mild cognitive impairment are associated with elevated levels of isoaspartyl residues in blood plasma proteins. Journal of Alzheimer's Disease. 2011.
4. Casarotto S, Määttä S, Herukka S-K, et al. TMS-evoked potentials in physiological and pathological aging. Neuroreport. 2011; 22: 592-597.
5. Niskanen E, Könönen M, Määttä S, et al**.** New insights into Alzheimer's disease progression: a combined TMS and structural MRI study. PloS One. 2011; 6(10):e26113.
6. Lötjönen J, Wolz R, Koikkalainen J, et al. Fast and robust extraction of hippocampus from MR images for diagnostics of Alzheimer's disease. NeuroImage. 2011; 56: 185-196.
7. Wolz R, Heckemann R, Aljabar P, et al.Measurement of hippocampal atrophy using 4D graph-cut segmentation: Application to ADNI. NeuroImage. 2010; 52:109-118.
8. Koikkalainen J, Lötjönen J, Thurfjell L, et al. Multi-Template Tensor-Based Morphometry: Application to Analysis of Alzheimer's Disease, NeuroImage. 2011; 56: 1134-1144.
9. Wolz R, P. Aljabar, J. V. Hajnal, et al. Nonlinear Dimensionality Reduction Combining MR Imaging with Non-Imaging Information. Medical Image Analysis. 2012; 16:819-830.
10. Gray K, Wolz R, Heckemann R, et al. Multi-region analysis of longitudinal FDG-PET for the classification of Alzheimer's disease. NeuroImage, 2012, in press.
11. Thurfjell L, Lötjönen J, Lundqvist, et al. Combination of biomarkers from PET [18F]flutemetamol amyloid imaging and structural MRI in dementia. Neurodegenerative Diseases, in press, 2012.
12. Mattila J, Koikkalainen J, Virkki A, et al. Disease State Fingerprint for Evaluating the State of Alzheimer's Disease in Patients. Journal of Alzheimer's Disease. 2011, 27: 163-17.
13. Wolz R, Julkunen J, Koikkalainen J, et al.. Multi-Method Analysis of MRI Images in Early Diagnostics of Alzheimer's Disease. PLoS One. 2011; 6(10):e25446.

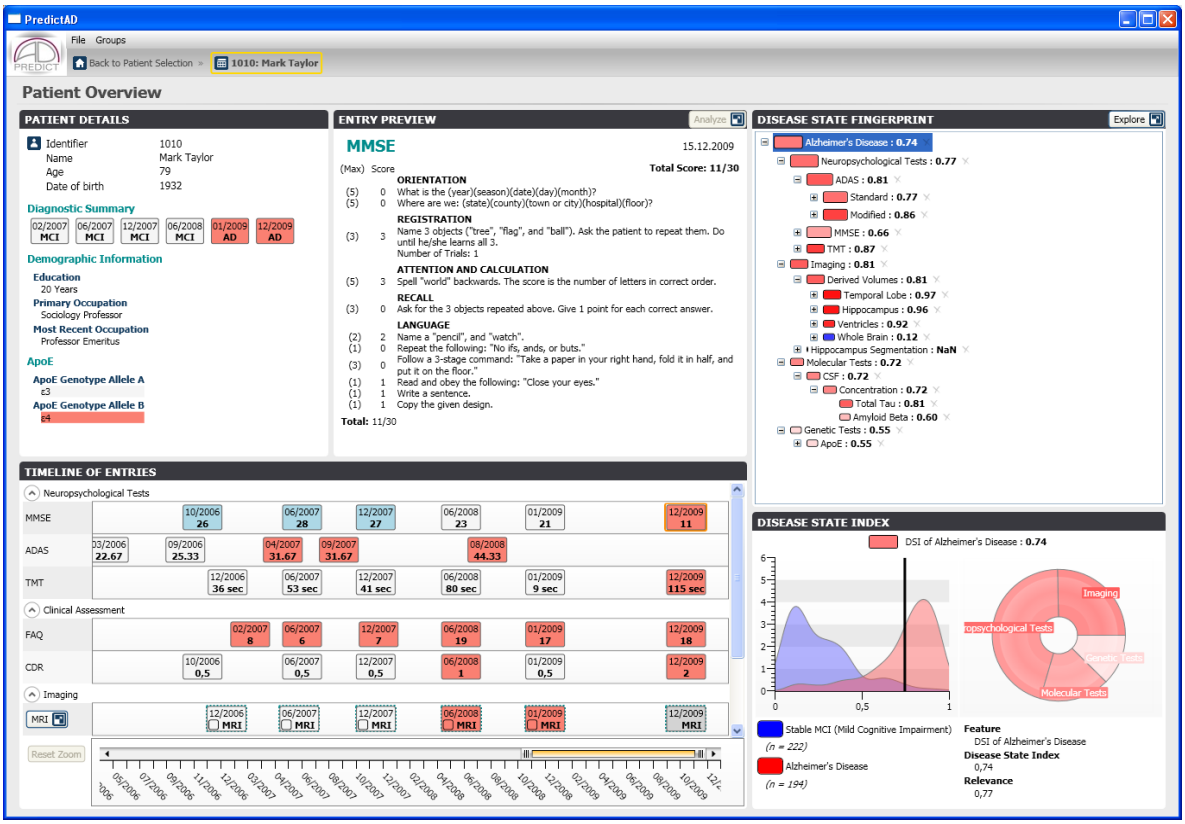

Fig. 1. A screenshot from the PredictAD software tool.