

14th Kuopio Bio-NMR Workshop

MRI OF STROKE, EPILEPSY AND NEURODEGENERATIVE DISEASES

PredictAD Workshop

**FROM PATIENT DATA TO PERSONALISED HEALTHCARE IN
ALZHEIMER'S DISEASE**

Kuopio, Finland

June 13-15 2011

Foreword

MRI serves now as major imaging modality of brain disorders owing to high contrast between normal and abnormal brain tissue. Diffusion tensor imaging is increasingly used to assess microstructural changes in neurodegenerative diseases. With the advent of high field magnets and advanced pulse sequences and shimming techniques, MRS can now be done in the very highly reproducible manner and it has provided new surrogate markers to follow diseases progression. With hyperpolarization, sensitivity of NMR has increased dramatically and this approach has provided new means to study alterations in metabolism. fMRI has matured to become the technique that can now be exploited to answer clinically relevant questions that improve our functional understanding of the brain. New pulse sequences are being developed to obtain signal from fast relaxing spins and phase information of NMR signal and rotating frame relaxation are increasingly exploited, which may open up completely new application areas. We hope to provide opportunities for rewarding learning experiences to understand these advanced MR applications and for exciting scientific interaction. Thus both basic educational lectures and scientific presentations will be provided together with social program.

The MRI workshop is followed by Predict AD workshop, which makes possible for participants to deepen the understanding one of the very important application areas of MRI. Current diagnostic guidelines emphasize the role of biomarkers (from magnetic resonance images, cerebrospinal fluid, positron emission tomography images or genetic tests in addition to standard neuropsychological studies) and their combinations. PredictAD project is developing objective and efficient tools for early diagnostics of Alzheimer's disease. The project is searching new biomarkers (e.g., metabolomics, proteomics, TMS/EEG) and developing methods for extracting well known biomarkers in a reliable way (e.g., from magnetic resonance images and PET images). In addition, a decision support system integrating all these heterogeneous biomarkers is developed for improved diagnostic accuracy following the principles of evidence based medicine. The workshop presents and discusses recent findings in the diagnostics of Alzheimer's disease.

Finally, we wish to acknowledge the generosity of the funding sources for this meeting, which have made all our workshop events possible. We welcome you to Kuopio and hope you much enjoy this exciting joint course/workshop.

June 2011

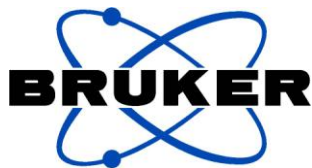
Olli Gröhn, Hilikka Soininen, Ritva Vanninen, Jyrki Lötjönen

Organizers: Biomedical Imaging Unit, A.I. Virtanen Institute for Molecular Sciences, University of Eastern Finland; Doctoral Program in Molecular Medicine; Institute of Clinical Medicine, Neurology, University of Eastern Finland, PredictAD project, the ESF project AlzPoint.

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MONDAY, JUNE 13 THEME: TECHNIQUES

08:30-09:00 Registration

SESSION: NMR BASICS

Chair Dr Olli Gröhn

09:00-09:15 Opening of the workshop

Dr Olli Gröhn, A.I.Virtanen Institute, University of Eastern Finland, Finland

09:15-09:45 Some NMR basics: what do we need to know about spins to be able exploit MRI and MRS in studies of neurodegenerative diseases

Dr Johanna Närväinen, A.I.Virtanen Institute, University of Eastern Finland, Finland

09:45-10:15 From NMR signal to MR image

Dr Timo Liimatainen, A.I.Virtanen Institute, University of Eastern Finland, Finland

10:15-10:45 Coffee

SESSION: ADVANCED TECHNIQUES

Chairs: Dr Timo Liimatainen and Dr Johanna Närväinen

10:45-11:30 Requirements for 7T human MRI – RF and shimming technology

Dr Hoby Hetherington, University of Yale, USA

11:30-12:15 Magnetic Resonance Spectroscopy in high magnetic field

Dr Gulin Oz, University of Minnesota, USA

12:15-13:15 Lunch

13:15-14:00 Basics and physiological origin of BOLD fMRI

Dr Risto Kauppinen, University of Bristol, UK

14:00-14:45 Molecular imaging by MRI and hyperpolarized ¹³C

Dr Mikko Kettunen, University of Cambridge, UK

14:45-15:15 Coffee

15:15-16:00 Diffusion tensor imaging - basics of data acquisition and analysis

Dr Derek Jones, Cardiff University, UK

16:00-16:45 MRI with ultrashort or zero echo time – potential applications in brain

Dr Ryan Chamberlain, University of Minnesota, USA

17:00-18:00 Social program: Tour at Biomedical Imaging Unit, A.I.Virtanen Insititute - snacks and wine served

TUESDAY, JUNE 14 THEME: APPLICATIONS

SESSION: EPILEPSY AND STROKE

Chair: Dr Alejandra Sierra-Lopez

09:00-09:45 Ultra-high field MR for human epilepsy

Dr Jullie Pan, University of Yale, USA

09:45-10:15 Multimodal MRI of traumatic brain injury and epileptogenesis in animal models Dr Riikka Immonen, A.I.Virtanen Institute, University of Eastern Finland, Finland

10:15-11:00 Assessment of stroke by multiparametric MRI including rotating frame relaxation contrasts, Dr Risto Kauppinen, University of Bristol, UK

11:00-12:00 Lunch

ORAL PRESENTATIONS SELECTED BASED ON SUBMITTED ABSTRACTS

12:00-12:15 Lauri Lehto: Calcification Detection *In Vivo* and *Ex Vivo* in Injured Rat Brain Using SWIFT

12:15-12:30 Otto Manninen: MRI and DTI utilizing Track based spatial statistics (TBSS) Reveal Progressive Volume-loss and White Matter Degeneration in *Cstb*-deficient Mouse model of Unverricht-Lundborg Disease EPM1

12:30-12:45 Eini Niskanen New insights into Alzheimer's disease progression: A combined TMS and structural MRI study

12:45-13:00 Teemu Paajanen: Neuropsychological total scores and cortical thinning in mild cognitive impairment and Alzheimer's disease

SESSION: NEURODEGENERATIVE DISEASES

Chair: Dr Riikka Immonen

13:00-13:45 DTI applications in neurodegenerative diseases

Dr Derek Jones, Cardiff University, UK

13:45-14:45 Coffee + Poster session

14:45-15:30 MRS in transgenic mice models of neurodegenerative diseases

Dr Gulin Oz, University of Minnesota, USA

15:30-16:15 Detection of amyloid plaques by MRI

Dr Ryan Chamberlain, University of Minnesota, USA

16:15-16:20 Closing remarks, Dr Olli Gröhn

19:00- Social Program: Boat Cruise and Dinner at Koivumäen kartano

WEDNESDAY, JUNE 15: PredictAD – FROM PATIENT DATA TO PERSONALIZED HEALTHCARE IN ALZHEIMER’S DISEASE

9:00-9:10 Opening of the workshop

Hilkka Soininen, University of Eastern Finland, Kuopio, Finland

9:10-9:30 PredictAD project – Concepts and progress

Jyrki Lötjönen, VTT, Tampere, Finland

9:30-10:30 Keynote lecture: Early diagnosis of Alzheimer’s disease

Wiesje M. van der Flier, the Vrije Universiteit Amsterdam, The Netherlands

10:30-10:45 Coffee break

10:45-11:15 Beyond current diagnostic protocols - Application requirements

Lennart Thurfjell, GEHC, Uppsala, Sweden

11:15-11:45 Molecular biomarkers

Matej Oresic, VTT, Helsinki, Finland

11:45-12:15 Transcranial magnetic stimulation and electrophysiological biomarkers in diagnosis of AD

Marcello Massimini, University of Milan, Milan, Italy

12:15-14:00 Lunch & Posters & Networking

14:00-14:30 Options for MRI analysis methods for diagnosis of AD

Daniel Rueckert, Imperial College London, London, UK

14:30-15:00 PredictAD software tool

Mark van Gils, VTT, Tampere, Finland

15:00-15:30 Clinical validation

Hilkka Soininen, University of Eastern Finland, Kuopio, Finland

15:30-16:15 Future of diagnostics

Panel: Wiesje M. van der Flier, Gunhild Waldemar, Lennart Thurfjell, Anne Koivisto and Pekka Laine

Monday 09:15-09:45

Some NMR basics: what do we need to know about spins to be able exploit MRI and MRS in studies of neurodegenerative diseases

Dr Johanna Närväinen, A.I.Virtanen Institute, University of Eastern Finland, Finland

A very short introduction to NMR signal generation and processes that affect the signal we obtain from living tissue. Spin dynamics and the effects of RF pulses are discussed. The basic concepts of relaxation (T_1 , T_2^* , $T_1\rho$) are introduced and other processes, such as molecular diffusion, are described. The pulse sequences for measuring these are briefly discussed.

The aim of the presentation is to demonstrate the unique sensitivity of NMR and MRI to a wide range of molecular-level processes that can be highlighted or suppressed by the choice of measurement technique and sequence details.

Literature:

- Basics and imaging: David Gadian: NMR and its applications to living system
- Spectroscopy, pulse sequences: James Keeler: Understanding NMR Spectroscopy
- More advanced spin gymnastics, a more mathematical approach: Malcolm Levitt: Spin Dynamics
- Hardcore: Anatole Abragam: The Principles of Nuclear Magnetism

WWW links:

- NMR wiki: A good collection of links and facts: <http://nmrwiki.org/wiki/>
- NMR lecture notes by J. Keeler <http://www-keeler.ch.cam.ac.uk/lectures/>
- MRI tutorial by Joseph Hornak <http://www.cis.rit.edu/htbooks/mri/>
- On clinical MRI
<http://www.magnet.fsu.edu/education/tutorials/magnetacademy/mri/fullarticle.html>

Monday 09:45-10:15

From NMR signal to MR image

Dr Timo Liimatainen, A.I.Virtanen Institute, University of Eastern Finland, Finland

On this lecture, description of MR signal detection and processing to image is given. Gradient and spin echo pulse sequences are introduced, as well as, more advanced techniques such like multi echo and echo planar techniques. Image contrast generated by these different image acquisition methods will be one of the primary topics of the lecture.

Suggested reading

1. David G. Gadian, NMR and its applications to living systems
2. Joseph P. Hornak, Basics of MRI <http://www.cis.rit.edu/htbooks/mri/inside.htm>
- 3 .Matt A. Bernstein, Kevin F. King and Xiaohong Joe Zhou, Handbook of MRI Pulse Sequences
4. Donald W. McRobbie, Elizabeth A. Moore, Martin J. Graves, Martin R. Prince, MRI from Picture to Proton

Monday 10:45-11:30

Requirements for 7T human MRI – RF and shimming technology

Dr Hoby Hetherington, University of Yale, USA

HP Hetherington, NI Avdievich and JW Pan

With the introduction of ultra-high field systems for human use, $>7T$, gains in SNR and spectral resolution have been anticipated for spectroscopic imaging studies. However, progress in this area has been slowed by technical issues associated with decreased RF coil homogeneity, increased power deposition for conventional sequences, increased chemical shift dispersion artifacts and decreased B_0 homogeneity. Unlike lower field studies where these issues can be easily separated, at $7T$, successful resolution of these issues requires an integrated approach to provide solutions. Specifically, developments in coil hardware, shim technology and pulse sequence design must “fit” together, otherwise technical innovation in one area, e.g. shim technology, may not be compatible with the needed RF technology.

To overcome the problems with RF coil homogeneity we have developed 8 and 16 channel transceiver arrays which provide highly efficient B_1 generation while retaining good homogeneity (8-12% standard deviation in B_1). To overcome limitations in B_0 homogeneity, we have demonstrated that very high order shims (>4 th order) based on well established spherical harmonic designs provide significant improvements and can be deployed as a circumscribing shim insert outside of the transceiver array’s shield. Utilizing the transceiver array’s capability to generate different spatially varying RF distributions we have developed pulse sequences that eliminate CSDE errors associated with in-plane selection and reduce power deposition. Together this combination has allowed us to acquire high resolution spectroscopic images from single planes and 3D volumes, in a variety of patient groups including, brain tumors, traumatic brain injury and epilepsy.

Monday 11:30-12:15

Magnetic Resonance Spectroscopy in High Magnetic Fields

Dr Gülin Öz, Center for Magnetic Resonance Research, University of Minnesota, USA

Neurochemical profiling by in vivo MRS has experienced rapid improvements over the recent years [1]. This was primarily due to increased sensitivity provided by higher magnetic fields and development of sophisticated spectral deconvolution methods [2]. Together these improvements facilitate the non-invasive quantification of numerous metabolites in the rodent and human brain [1, 3]. This presentation will cover the information content of MR spectra acquired at high magnetic fields [4-6] and the requirements for obtaining high quality MR spectra in the human [7, 8] and rodent brain [9].

Suggested Reading:

1. Pfeuffer, J., I. Tkáč, S.W. Provencher, and R. Gruetter, Toward an in vivo neurochemical profile: quantification of 18 metabolites in short-echo-time ¹H NMR spectra of the rat brain. *J Magn Reson*, 1999. 141(1): 104-120.
2. Provencher, S.W., Estimation of metabolite concentrations from localized in vivo proton NMR spectra. *Magn Reson Med*, 1993. 30(6): 672-9.
3. Tkáč, I., G. Öz, G. Adriany, K. Ugurbil, and R. Gruetter, In vivo ¹H NMR spectroscopy of the human brain at high magnetic fields: Metabolite quantification at 4T vs. 7T. *Magn Reson Med*, 2009. 62(4): 868-879
4. Choi, I.Y., S.P. Lee, D.N. Guilfoyle, and J.A. Helpem, In vivo NMR studies of neurodegenerative diseases in transgenic and rodent models. *Neurochem Res*, 2003. 28(7): 987-1001.
5. Choi, J.K., A. Dedeoglu, and B.G. Jenkins, Application of MRS to mouse models of neurodegenerative illness. *NMR Biomed*, 2007. 20(3): 216-37.
6. Michaelis, T., S. Boretius, and J. Frahm, Localized proton MRS of animal brain in vivo: Models of human disorders. *Prog NMR Spect*, 2009. 55: 1-34.
7. Tkáč, I. and R. Gruetter, Methodology of ¹H NMR Spectroscopy of the Human Brain at Very High Magnetic Fields. *Appl Magn Reson*, 2005. 29: 139-157.
8. Emir, U.E., E.J. Auerbach, P.F. Van De Moortele, M. Marjańska, K. Ugurbil, M. Terpstra, I. Tkáč, and G. Öz, Regional neurochemical profiles in the human brain measured by ¹H MRS at 7 tesla using local B1 shimming. *NMR Biomed*, 2011: in press.
9. Tkáč, I., P.G. Henry, P. Andersen, C.D. Keene, W.C. Low, and R. Gruetter, Highly resolved in vivo ¹H NMR spectroscopy of the mouse brain at 9.4 T. *Magn Reson Med*, 2004. 52(3): 478-84.

Monday 13:15-14:00

Basics and physiological origin of BOLD fMRI

Dr Risto Kauppinen, CRIC-Bristol and School of Experimental Psychology, University of Bristol, UK

Blood is an excellent contrast agent for both optical and NMR spectroscopies, because oxygen saturation state of haemoglobin (Hb) strongly influences the light absorption spectrum and the transverse relaxation rate of water, respectively. Mismatch in cerebral haemodynamic response to brain oxygen demand imposed by neuronal activity, often referred to as the neurovascular coupling, works in favour for indirect imaging of 'brain functions' with both optics and NMR. Local hyperaemia with an increase in oxyHb in response to synaptic activity involving glutamate release provide substrates for blood oxygenation level dependent (BOLD) signal to be detected by (N)MR imaging (MRI). The BOLD MRI signal comprises of time-dependent negative and positive deflections, all of these apparently have specific physiological underpinnings. The presentation will focus on physiological mechanisms underpinning the BOLD signal components and overall, on mechanisms behind the neurovascular coupling.

Suggested reading:

1. Ogawa, S., et al., Functional brain mapping by blood oxygenation level-dependent contrast magnetic resonance imaging: a comparison of signal characteristics with a biophysical model. *Biophys. J.*, 1993. 64: p. 803-812.
2. Attwell, D. and S.B. Laughlin, An energy budget for signaling in the grey matter of the brain. *J Cereb Blood Flow Metab*, 2001. 21: p. 1133-1145.
3. Silvennoinen, M.J., et al., Comparison of the dependence of blood R2 and R2* on oxygen saturation at 1.5 and 4.7 tesla. *Magn Reson Med*, 2003. 49: p. 47-60.
4. Shmuel, A., et al., Negative functional MRI response correlates with decreases in neuronal activity in monkey visual area V1. *Nat Neurosci*, 2006. 9: p. 569-577.
5. Attwell, D., et al., Glial and neuronal control of brain blood flow. *Nature*, 2010. 468: p. 232-43.

Monday 14:00-14:45

Molecular imaging by MRI and hyperpolarized ^{13}C

Dr Mikko I. Kettunen, Cancer Research UK Cambridge Research Institute & Department of Biochemistry, University of Cambridge, UK

^{13}C -MRS spectroscopy in systems incubated with ^{13}C -labeled substrates gives a dynamic measurement of metabolism but has traditionally suffered from low sensitivity. Recent advances in hyperpolarisation of ^{13}C nuclei allow >10,000-fold increase in liquid-state sensitivity and therefore make real-time ^{13}C molecular imaging *in vivo* possible. The talk summarises the most commonly used hyperpolarized ^{13}C molecules and their applications so far, and discusses the potential applications and challenges for brain imaging.

References

- Kurhanewicz J et al. *Analysis of cancer metabolism by imaging hyperpolarized nuclei: prospects for translation to clinical research*. *Neoplasia*, 13(2):81-97, 2011.
- Tyler DJ. *Cardiovascular Applications of Hyperpolarized MRI*. *Curr Cardiovasc Imaging Rep*, 4(2):108-115, 2011.
- Ross BD et al. *Hyperpolarized MR imaging: neurologic applications of hyperpolarized metabolism*. *AJNR Am J Neuroradiol*, 31(1):24-33, 2010.
- Ardenkjaer-Larsen JH et al. *Hyperpolarized ^{13}C magnetic resonance imaging - Principles and applications*. In: Weissleder R, Gambhir SS, Ross BD, Rehemtulla A, editors. *Molecular Imaging: Principles and Practice*: McGraw-Hill Medical; 2010.
- Gallagher FA et al. *Biomedical Applications of Hyperpolarized ^{13}C Magnetic Resonance Imaging*. *Prog Nucl Mag Res Sp*, 55(4):285-295, 2009.

Monday 15:15-16:00

Diffusion Tensor Imaging - Basics of Data Acquisition and Analysis

Dr Derek K Jones, CUBRIC, School of Psychology, Cardiff University, UK

In this introduction to diffusion tensor imaging, we will begin by reviewing what diffusion is – and introducing the basic mechanism of diffusion weighting in MRI (Le Bihan, 1985, 1986). We will then review the initial observations of diffusion anisotropy *in vivo* (Moseley *et al.* 1990), which will motivate the introduction of the diffusion tensor – and the invention of diffusion tensor MRI (Basser *et al.* 1994a, 1994b). The basic experiment for encoding the diffusion tensor will then be described, before introducing the quantitative indices that can be derived from diffusion tensor MRI (DT-MRI), (Pierpaoli *et al.* 1996) including the trace of the diffusion tensor and the fractional anisotropy. (Pierpaoli and Basser, 1996). Next, we will consider the orientational information encoded in the diffusion signal – and how this can be exploited to reconstruct fibre pathways in tractography. Finally, if time permits – we will take a closer look at the impact of data acquisition strategies on the data we extract from DT-MRI – and touch briefly on the limitations of the tensor model.

References

1. Le Bihan D, Breton E. Imagerie de diffusion *in vivo* par résonance magnétique nucléaire. *C. R. Acad. Sc. Paris* . 1985 ; **T.301, Série II**, 1109-1112.
2. Le Bihan D, Breton E, Lallemand D, Grenier P, Cabanis E, Laval Jeantet M. MR Imaging of intravoxel incoherent motions : application to diffusion and perfusion in neurologic disorders. *Radiology* 1986; **161** : 401-407.
3. Moseley; Cohen, Y; Kucharczyk, J; Mintorovitch, J; Asgari, HS; Wendland, MF; Tsuruda, J; Norman, D (1990). "Diffusion-weighted MR imaging of anisotropic water diffusion in cat central nervous system". *Radiology* **176** (2): 439–45
4. Basser PJ, Mattiello J, Le Bihan D. MR diffusion tensor spectroscopy and imaging. *Biophys. J.* 1994a; **66**:259-67.
5. Basser PJ, Mattiello J, Le Bihan D. Estimation of the effective self-diffusion tensor from the NMR spin echo. *Journal of Magnetic Resonance* 1994b; **103**: 247-254.
6. Pierpaoli C, Jezzard P, Basser PJ, Barnett AS. Diffusion tensor MR imaging of the human brain. *Radiology* 1996; **201**: 637–648.
7. Pierpaoli C, Basser PJ. Towards a quantitative assessment of diffusion anisotropy. *Magn. Reson. Med.*, 1996; **36**: 893-906.

Suggested further reading:

Review Articles

- Jones DK, Leemans A. Diffusion tensor imaging. *Methods Mol Biol.* 2011;**71**: 127-44.
- Jones DK, Cercignani M. 2010. 25 pitfalls in the analysis of diffusion tensor MRI data. *NMR in Biomedicine* **23**:803-820.
- Jones DK. 2010. Challenges and limitations of quantifying connectivity in the human brain *in vivo* with diffusion MRI. *Imaging in Medicine* **2**: 341-355

- Jones DK. 2008. Studying connections in the living human brain with diffusion MRI *Cortex* **44**:936-52

Books / Book Chapters

- Jones DK (Ed). *Diffusion MRI: Theory, Methods and Applications* Ed. Jones DK, Oxford University Press, (2010)
- Jones DK. "Gaussian Modeling of the Diffusion Signal" in *Diffusion MRI: from Quantitative Measurement to In-Vivo Neuroanatomy*. Eds. Behrens TEJ, Johansen-Berg H. Elsevier (2009)
- Jones DK. "Fundamentals of Diffusion MR Imaging", in *Clinical MR Neuroimaging – Second Edition* Eds. Gilliard J, Waldman A, Barker P. Cambridge University Press, (2009).

Monday 16:00-16:45

MRI with ultrashort or zero echo time – potential applications in brain

Dr Ryan Chamberlain, University of Minnesota, USA

Conventional MRI receives signal many milliseconds after the magnetization has been excited, which results in images that are dominated by protons with long relaxation time constants. In ultrashort echo time techniques signal reception takes place less than 100 microseconds after excitation. This allows MRI to visualize quickly relaxing proton populations typically ignored in MRI. An overview of ultrashort echo time pulse sequences will be given along with a few possible applications in neuroimaging.

Tuesday, June 14 Theme: Applications; 09:00-09:45

Ultra-high field MR for human epilepsy

Dr Jullie Pan, University of Yale, USA

JW Pan, DD Spencer, NI Avdievich, HP Hetherington

It is clear that the scientific understanding and management of human epilepsy and brain metabolism has benefited substantially from the technologic developments and implementations of magnetic resonance imaging. However it is also clear that the close relationship between scientific or clinical goal and methodology in MR, a “one-size-fit-all” approach does not commonly work well. This statement is even more relevant at ultra-high field, where the RF wavelength approaches the size of the human head, and the advantageous increase in susceptibility also means difficulties for B₀ homogeneity.

For imaging purposes, issues in epilepsy can be categorized into (at least) three large major groups, 1) medial temporal lobe epilepsy MTLE, 2) neocortical epilepsy, 3) drug pharmacology or generalized epilepsies. The first two are “localized” (i.e., where is the seizure onset zone?); the latter is relatively “non-localized”. We will discuss how research grade imaging in human epilepsy has evolved and benefited from ultra-high field, e.g., in MTLE as a common type of epilepsy where shimming is a critical issue, in neocortical epilepsy where abnormalities are not a priori localized and for the detection of metabolites such as glutamine and GABA that are of high relevance for metabolism and pathophysiology. In these studies, consistent performance of B₀ shimming, RF homogeneity and amplitude are needed to achieve individual subject accuracy and to define pathophysiological mechanisms.

Tuesday 09:45-10:15

Multimodal MRI of traumatic brain injury and epileptogenesis in animal models

Dr Riikka Immonen, A.I.Virtanen Institute, University of Eastern Finland, Finland

Traumatic brain injury (TBI) is a devastating disease with variety of cognitive and motor function deficits manifesting both immediately after the impact and even several years later. Epilepsy can develop as a consequence of TBI. Non-invasive imaging and animal models are needed for understanding the complex and progressive brain alterations after TBI and during epileptogenesis. Magnetic resonance imaging (MRI) methods offer a variety of approaches to study the different features of the brain pathologies. In addition to characterizing the anatomy, extent and type of cortical contusion, hematomas and atrophy, the multimodal MRI techniques can probe spatio-temporal developments of the gray matter degradation, white matter damage and repair, and hemodynamical disturbances thereby providing more insight into the disease mechanisms.

Slow progressive neurodegeneration after trauma may not show in anatomical images in their early phase but they cause alterations in magnetic relaxation properties of tissue locally and can thereby be detected and followed by quantitative T2, T1 ρ , and mean diffusivity mapping. Particularly the gray matter areas surrounding the primary contusion site, and the hippocampus, appear normal in conventional anatomical images but the quantitative mapping picks out the regions that are exposed to destructive cellular cascades.

White matter shear injury and diffuse axonal injury are caused by impact forces. Susceptibility weighted imaging (SWI) and phase contrast images detect diffuse axonal injury associated microbleeds after TBI, myelin loss and calcifications. Susceptibility weighted imaging, diffusion tensor imaging (DTI), and manganese enhanced MRI (MEMRI) are techniques to probe axonal and myelin degeneration as well as regeneration (plasticity). Axonal sprouting in the hippocampus is one well characterized plastic process during epileptogenesis that has been linked with seizure susceptibility.

Autoregulation is impaired after head injury. Region specific and temporally developing hypo- and hyperperfusion can be followed by mapping cerebral blood flow (CBF) using arterial spin labeling (ASL), while intravascular iron oxide contrast agents can assess regional cerebral blood volume (CBV) alterations, BBB leakage, thromboses and angiogenesis.

Tuesday 10:15-11:00

Assessment of stroke by multiparametric MRI including rotating frame relaxation contrasts

Dr Risto Kauppinen, CRIC-Bristol and School of Experimental Psychology, University of Bristol, UK

Imaging research has provided a large arsenal of techniques that detect the presence of acute stroke in humans with high sensitivity and specificity. Perhaps the most well know of these is diffusion MRI. Indeed, there is an overwhelming clinical consensus that diffusion MRI is the best imaging tool to detect acute (ischaemic) stroke. Diffusion MRI, however, plays a much lesser role in predicting long-term tissue outcome. It is a clinical expectation that any modern neuroimaging technique should, beside diagnostics, guide clinical management of stroke victims. In this scenario, with very limited pharmacological repertoires in hand, imaging should also be able to inform clinicians for treatability of stroke patients. Furthermore, these data must be obtained in a short single imaging session for timely treatment decision.

We, working with preclinical stroke models, have examined potentials of multi-parametric MRI, incorporating T_1 , T_2 , $T_{1\rho}$, $T_{2\rho}$, ASL, and APTR, to inform about tissue status and duration of ischaemia from a single scan session. These two factors are considered central in decision making of stroke patients.

Relevant publications:

1. Gröhn, O.H.J., et al., Early detection of irreversible cerebral ischemia in the rat using dispersion of the MRI relaxation time, T_{1r} . *J Cereb Blood Flow Metab*, 2000. 20: p. 1457-1466.
2. Jokivarsi, K.T., et al., Proton transfer ratio, lactate, and intracellular pH in acute cerebral ischemia. *Magn Reson Med*, 2007. 57: p. 647-653.
3. Jokivarsi, K., et al., Correlating tissue outcome with quantitative multiparametric MRI of acute cerebral ischemia in rats. *J Cereb Blood Flow Metab*, 2010. 30: p. 415-427.
4. Jokivarsi, K.T., et al., Estimation of the onset time of cerebral ischemia using T_{1r} and T_2 MRI in rats. *Stroke*, 2010. 41 p.2335-2340.
5. Jokivarsi, K.T., et al., Quantitative assessment of water pools by T_{1r} and T_{2r} MRI in acute cerebral ischemia of the rat. *J Cereb Blood Flow Metab*, 2009. 29: p. 206-16.
6. Yoo, A.J. and R.G. Gonzalez, Clinical Applications of Diffusion MR Imaging for Acute Ischemic Stroke. *Neuroimaging Clin N Am*, 2011. 21: p. 51-69.

Tuesday 13:00-13:45

**Diffusion Tensor Imaging
in Neurodegenerative Diseases**

Dr Derek K Jones, CUBRIC, School of Psychology, Cardiff University, UK

In this talk, I will first review a selection of examples from the literature where diffusion tensor MRI has been used to address questions concerning microstructural changes in neurodegenerative diseases, including motor neurone disease, Alzheimer's disease, vascular dementia and Huntington's disease. It will be seen that a variety of methods have been used to extract / compare quantitative parameters between the 'disease' and 'control' group, or to correlate white matter microstructural measurements against a metric of performance on a particular task or on a clinical scale.

The second part of the talk will therefore address the heterogeneity of methods in the literature – and how different approaches are susceptible to different confounds. In this, we will consider things like partial volume artefacts, signal to noise ratio, and spatial extent of the disease process.

Finally, we will also consider the sensitivity and specificity of diffusion tensor MR to pathological changes – and discuss how this might be supplemented by data from other sources.

Suggested reading:

- Jones DK. 2010. Challenges and limitations of quantifying connectivity in the human brain in vivo with diffusion MRI. *Imaging in Medicine* **2**: 341-355
- Jones DK, Cercignani M. 2010. 25 pitfalls in the analysis of diffusion tensor MRI data. *NMR in Biomedicine* **23**:803-820.

Tuesday 14:45-15:30

MRS in Transgenic Mouse Models of Neurodegenerative Diseases

Dr Gülin Öz, Center for Magnetic Resonance Research, University of Minnesota, USA

Neurochemical profiles obtained by high field MRS can provide multiple biomarkers to monitor disease progression and reversal in transgenic models of neurodegenerative diseases. For example, concentrations of neurotransmitters (glutamate, γ -aminobutyric acid), antioxidants (glutathione, vitamin C) and energy metabolites (glucose, lactate, creatine/phosphocreatine) can provide measures of biochemical processes relevant to many neurodegenerative diseases, such as excitotoxicity, oxidative stress and energy failure. However, such potential MRS biomarkers need to be validated prior to successful translation to human applications.

First, alterations in neurochemical profiles with disease need to be similar in the model mice and humans. Transgenic models of hereditary conditions are advantageous since they usually faithfully reproduce the pathology of the human disease. Next, the MRS biomarkers need to be sensitive to early biochemical alterations due to pathology, as well as reliably gauge the progression of pathology. This can be investigated by comparing MRS data to histology obtained in the same animals. Finally, the MRS biomarkers need to be sensitive to disease reversal such that they can be used in preclinical and clinical trials to monitor treatment effects. Conditional transgenic mouse models where the expression of the mutant protein can be turned on and off at will provide an opportunity to investigate the sensitivity of MRS biomarkers to disease reversal. Examples for these points will be given with data obtained from transgenic models of spinocerebellar ataxia type 1, a hereditary movement disorder caused by a polyglutamine repeat expansion in the affected protein.

Tuesday 15:30-16:15

Detection of amyloid plaques by MRI

Dr Ryan Chamberlain, University of Minnesota, USA

One of the hallmark pathologies of Alzheimer's disease is amyloid plaque deposition. Transgenic mouse models of AD allow controlled study of this phenomenon and enable testing of anti-amyloid interventions that might be useful in humans. Magnetic resonance imaging of these mouse models is an attractive modality to monitor plaque deposition because it is non-invasive and has the spatial resolution necessary to visualize individual plaques. However, due to the very high resolution needed in vivo plaque imaging has proven difficult. In this work we measured the relaxation parameters of plaques and normal brain tissue to determine the imaging techniques best suited for plaque imaging. Then, we quantitatively compared the ability of various imaging methods to visualize cortical plaques ex vivo with the multi-asymmetric spin echo pulse sequence determined to be the optimal imaging sequence. We then demonstrated the ability of that pulse sequence to measure plaque density over time.

Wednesday 9:10-9:30

PredictAD project – Concepts and progress

Jyrki Lötjönen, VTT, Tampere, Finland

Jyrki Lötjönen¹, Lennart Thurffjell², Jarmo Laine³, Hilikka Soininen⁴, Daniel Rueckert⁵, Marcello Massimini⁶, Gunhild Waldemar⁷, Roman Zubarev⁸

PredictAD is an EU-funded FP7 project (6/2008-11/2011) under the theme Virtual Physiological Human (VPH) with a budget of about 4 Me. The project has two major scientific objectives: 1) to find efficient biomarkers from heterogeneous patient data and integrate them for making early diagnosis and progress monitoring of Alzheimer's disease more efficient, reliable and objective, and 2) to improve the cost-effectiveness of AD diagnostics by optimizing diagnostic protocol.

The project has had two focus areas in reaching the objectives: biomarker discovery and data integration. In biomarker discovery, we have developed efficient state-of-the-art methods for extracting biomarkers from imaging and electrophysiological data. We have also searched novel biomarkers from blood samples using metabolomics and proteomics. In data integration, we have studied the performance of different biomarkers in diagnostics and developed a novel evidence-based decision support concept for diagnostics. The decision support software solution has been developed in a close collaboration with clinicians and it provides an index and graphical representation about the status of the patient studied compared with other database cases.

PredictAD has progressed as planned and is now finalizing the project. This workshop provides an opportunity to represent our achievements under this important topic – diagnostics of Alzheimer's disease.

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Wednesday 9:30-10:30

Keynote lecture: Early diagnosis of Alzheimer's disease

Wiesje M. van der Flier, the Vrije Universiteit Amsterdam, The Netherlands

Wiesje M. van der Flier, PhD, Philip Scheltens, MD, PhD.

Alzheimer's disease (AD) is the most prevalent type of dementia, characterized by gradual cognitive decline and loss of independence. The pathological hallmarks are senile plaques and neurofibrillary tangles. The diagnosis of AD has always been hampered by the fact that the pathological hallmarks could not be demonstrated during life. Therefore, a diagnosis has always been based on clinical criteria that work largely *per exclusionem*. The development of new techniques, including MRI, but also biomarkers in cerebrospinal fluid and amyloid imaging using positron emission tomography, has fueled the field, as it is now possible to demonstrate the presence of Alzheimer pathology during life in a relatively non-invasive way. This has led to the description of new research criteria which have a more inclusionary approach. According to these criteria, a diagnosis of AD can be made when in addition to episodic memory impairment, at least one type of ancillary investigations provides positive evidence of the presence of Alzheimer pathology. The first experience with this set of criteria is that they result in high specificity, at the cost of a lower sensitivity. In addition, the availability of new methods that reliably demonstrate Alzheimer pathology poses new questions and challenges. Potentially, one out of three elderly may be amyloid-positive on imaging. Currently, it is not sure if all these individuals will go on to develop clinical AD, or if some of them have characteristics that protect them from doing so. A paradigm shift is called for, which now takes into account the different entities of the clinical syndrome of AD on the one hand and the pathological characteristics of Alzheimer's disease on the other.

Alzheimer Center, VU University Medical Center, Amsterdam, the Netherlands.

Wednesday 10:45-11:15

Beyond current diagnostic protocols - Application requirements

Lennart Thurfjell, GEHC, Uppsala, Sweden

Lennart Thurfjell¹, Jyrki Lötjönen², Marketta Niemelä², Hilikka Soininen³,
Anja Hviid Simonsen⁴, Gunhild Waldemar⁴

The original NINCDS–ADRDA criteria for the clinical diagnosis of Alzheimer’s disease (AD) were established in 1984. These criteria rested on an expectation that there was a close correspondence between clinical symptoms and underlying pathology. However, in the intervening time it has become clear that this is not the case and new diagnostic criteria emphasize the use of biomarkers in early and prodromal diagnosis.

The EU funded PredictAD research project fits well into this picture with its goal to develop robust methods for extraction of AD related biomarkers and to develop an application, the PredictAD tool, that would enable earlier diagnosis of AD and improved methods for monitoring of disease progression and response to therapy. The PredictAD tool combines biomarkers with clinical information and makes this comprehensive information available to the physician. As development of this tool is central to PredictAD, it was important to define application requirements early in the project. These initial application requirements were based on guidelines combined with information from focus group meetings and interviews. Based on the initial requirements, a mock-up of a tentative tool was implemented. This was presented to focus groups and feedback was used to refine application requirements. Later in the project, this process was repeated with a fully functional version of the tool. We also conducted a survey involving 30 centres across Europe.

In this presentation we will discuss requirements, results from interviews, learning so far as well as hurdles for implementing the PredictAD tool or similar diagnostic support systems in clinical routine.

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⁴Rigshospitalet, Denmark

Wednesday 11:15-11:45

Molecular biomarkers of Alzheimer's disease

Matej Orešič, VTT, Helsinki, Finland

Wednesday 11:45-12:15

Transcranial magnetic stimulation and electrophysiological biomarkers in diagnosis of AD

Marcello Massimini, University of Milan, Milan, Italy

Silvia Casarotto¹, Sara Määttä², Adenauer G. Casali¹, Sanna-Kaisa Herukka^{3,4}, Andrea Pigorini¹, Mario Rosanova¹, Kaisu Lankinen⁵, Marcello Massimini¹, Hilikka Soininen^{3,4}

Transcranial magnetic stimulation (TMS) combined with electroencephalography (EEG) is a novel tool to measure the immediate cortical response (excitability) and its spread (connectivity) after a direct cortical stimulation. These functional measures of brain activity may be applied to investigate Alzheimer's disease (AD) at an early stage and to monitor disease progression. To the same, we developed and implemented a unified mathematical framework specifically designed for the analysis of TMS-evoked potentials. This software allows to optimally control stimulation parameters, to estimate statistically significant cortical sources from scalp potentials, and to compute quantitative indices of cortical excitability and effective connectivity. These tools were applied to AD patients and to patients with Mild Cognitive Impairment (MCI) and the results were compared with the ones obtained in age-matched controls (CTR). Both excitability and connectivity indices were found to progressively decrease from CTR subjects to MCI and AD patients. The combination of TMS/EEG provides quantitative measures of brain functionality without requiring the patient to collaborate or participate in a task. This study shows that AD produces a disruption of both excitability and connectivity patterns in cortical circuits. These findings suggest that TMS/EEG might be employed in the diagnosis and monitoring of Alzheimer's disease.

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⁵Nexstim Ltd., Helsinki, Finland

Wednesday 14:00-14:30

Options for MRI analysis methods for diagnosis of AD

Daniel Rueckert, Imperial College London, London, UK

Daniel Rueckert, Imperial College London, London, UK; Robin Wolz, Imperial College London, London, UK; Dong Ping Zhang, Imperial College London, London, UK; Jyrki Lötjönen, VTT Technical Research Centre of Finland, Tampere, Finland; Juha Koikkalainen, VTT Technical Research Centre of Finland, Tampere, Finland, Lennart Thurfjell, GE Healthcare, Uppsala, Sweden, Roger Lundqvist, GE Healthcare, Uppsala, Sweden; Gunhild Waldemar, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark; Valtteri Julkunen, University of Eastern Finland, Kuopio, Finland; Hilka Soininen, University of Eastern Finland, Kuopio, Finland

Three-dimensional (3D) and four-dimensional (4D) imaging plays an increasingly important role in computer-assisted diagnosis, intervention and therapy. However, in many cases the interpretation of these images is heavily dependent on the subjective assessment of the imaging data by clinicians. Over the last decades image registration has transformed the clinical workflow in many areas of medical imaging. At the same time, advances in machine learning have transformed many of the classical problems in computer vision into machine learning problems.

This talk will focus on the convergence of image registration and machine learning techniques for the discovery and quantification of clinically useful information in form of biomarkers from medical images. To illustrate this we will show several examples from the PredictAD project such as the segmentation of neuro-anatomical structures, the discovery of biomarkers for neurodegenerative diseases such as Alzheimer's.

Wednesday 14:30-15:00

The PredictAD software tool

Mark van Gils, VTT, Tampere, Finland

Mark van Gils¹, Jussi Mattila¹, Juha Koikkalainen¹, Lennart Thurfjell², Marketta Niemelä¹, Jyrki Lötjönen¹, Hilikka Soininen³ and Gunhild Waldemar⁴

One objective of PredictAD is to develop a usable, clinically relevant software solution for AD diagnostics that supports a physician in diagnosing and monitoring the progress of AD in real clinical conditions using heterogeneous patient data.

A software application was developed in close collaboration with clinical experts from different countries to fulfil clinical needs. It computes an evidence-based estimate of a patient's AD-related state by comparing her many-modal biomarker data to those of previously diagnosed cases. This AD-state captures a patient's degree of similarity to cases in a previously diagnosed disease population (containing, e.g., AD cases and cases with mild cognitive impairment (MCI)). The result is a graded index, Disease State Index (DSI), describing how likely it is that an individual belongs to a certain population and thus indicates the 'severity' of the disease. Additionally, the solution implements a novel concept for integrating, visualising and exploring complex heterogeneous data using a Disease State Fingerprint (DSF) visualisation. Finally, the software solution provides state-of-the-art tools to extract biomarkers from data acquired from a patient, such as tools for segmenting the hippocampus and atrophy measures from magnetic resonance images.

Besides clinical applicability, diagnostic performance measures play a key role in acceptance of the tool. Using data from the Alzheimer's Disease Neuroimaging Initiative (ADNI), DSI's ability to capture disease progression and to predict conversion from MCI to AD were assessed. DSI provides AD-state estimates that correspond well with actual diagnoses. For predicting conversion from MCI to AD, it attains performance similar to state-of-the-art classifiers.

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Wednesday 15:00-15:30

**Clinical validation of Software tool for predicting Alzheimer's disease
- PredictAD project**

Hilkka Soininen, University of Eastern Finland, Kuopio, Finland

H. Soininen¹, J. Mattila², J. Koikkalainen², M. van Gils², A.H. Simonsen³, G. Waldemar³, D. Rueckert⁴, M. Oresic², Massimini⁵ L., Laine J⁶, R. Zubarev⁷, Thurfjell⁸, J. Lötjönen²

New diagnostic criteria of Alzheimer's disease (AD) emphasize use of biomarkers in early and prodromal diagnosis. In the clinical practice diagnostic procedures vary across different countries and clinics. Use of an objective clinical decision support system could reduce diagnostic errors and reveal early predictors of AD. The PredictAD tool organizes patient data, and biomarkers, analyzes them statistically against previously diagnosed cases. The tool provides Disease State Index (DSI) (value 0-1) and Disease State Fingerprint (DSF) visualising the data. In addition, methods for image analyses such as automatic hippocampal volumetry, TMS-EEG were developed and validated in this project. DSI was evaluated using ADNI baseline data on controls and progressive and stable mild cognitive impairment (MCI) subjects and patients with AD. The results showed that there is well-behaving correlation between DSI and ADNI diagnoses and DSI performs as well as state-of-the-art classifiers. We also investigated whether the PredictAD tool could assist physicians in the early diagnosis of AD. Our hypothesis was that physicians using the software could predict conversion from MCI to AD better than without using the tool. For this purpose we used data from the ADNI study. Diagnostic performance of clinicians using the tool was compared to evaluations of the same patient data with paper charts and a computer-based state-of-the-art classifier. Use of PredictAD software was related to better correct classification rate and higher confidence to predict AD among MCI subjects compared to traditional paper version. Validation of DSI, DSF and imaging tools are ongoing in other large cohorts.

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Wednesday 15:30-16:15

Future of diagnostics

Panel: Wiesje M. van der Flier, Gunhild Waldemar, Lennart Thurffjell,
Anne Koivisto and Pekka Laine

Oral Presentation # 1 Lauri Lehto

Calcification Detection *In Vivo* and *Ex Vivo* in Injured Rat Brain Using SWIFT

Lauri Lehto¹, Alejandra Sierra¹, Curtis Corum², Djaudat Idiyatullin², Asla Pitkänen^{1,3}, Michael Garwood², Olli Gröhn¹

Introduction

Phase imaging is usually conducted with gradient echo (GE) sequences. SWIFT is a virtually zero acquisition delay pulse sequence. Even though there is no time for phase accumulation at the top of the FID, SWIFT phase is still sensitive to susceptibility differences. SWIFT phase imaging was applied to calcification detection in brain.

Materials and Methods

Rats with a systemic pilocarpine injection induced status epilepticus (n=5) and with lateral fluid percussion traumatic brain injury (TBI, n=5) were imaged in chronic state *in vivo* and *ex vivo* at 9.4 T. A histological comparison was made.

Results

All animals showed calcifications. Total of 44 calcifications in the pilocarpine brains were detected with SWIFT. In TBI animals, *ex vivo* and *in vivo* imaging revealed one calcification per animal in four animals. The smallest detected *ex vivo* calcification was 0.0037 mm³ in histology and 0.0151 mm³ in MRI. A good correlation between size of calcification measured with MRI and histology was achieved.

Discussion and Conclusion

We were able to show that SWIFT can detect and differentiate calcifications based on their dipole like fields without post-processing of the phase images. Compared to GE methods, SWIFT is likely to excel near high susceptibility differences due to its extremely short acquisition delay and broad excitation bandwidth.

¹ University of Eastern Finland, ² University of Minnesota, ³ Kuopio University Hospital

Oral Presentation # 2 Otto Manninen

MRI and DTI utilizing Track based spatial statistics (TBSS) Reveal Progressive Volume-loss and White Matter Degeneration in *Cstb*-deficient Mouse model of Unverricht-Lundborg Disease EPM1

O Manninen 1, T Laitinen 2, K Lehtimäki 2, S Tegelberg 1, O Kopra 1,
O Gröhn 2, A Lehesjoki 1.

Rationale - Unverricht-Lundborg disease (EPM1) is an neurodegenerative disorder belonging to the Finnish disease heritage. It has an onset at age of 6 to 18 years, myoclonus, tonic-clonic epileptic seizures and ataxia. Mutations in the *Cystatin B* gene (*CSTB*) underlie EPM1, and we utilize a *Cstb*-deficient (-/-) mouse to study the disease. Pathology and MRI show EPM1 patients undergoing atrophic changes, and tract based spatial statistics analysis of DTI data revealed white matter (WM) degeneration in EPM1 patients, with similar alterations detected in adult (6 mo) *Cstb*^{-/-} mice.

Methods. We conducted a longitudinal MRI and DTI follow-up study in comparing *Cstb*^{-/-} mice to controls from pre-symptomatic to fully symptomatic stage of disease (1-6 mo) in order to gain a comprehensive picture of the disease progression in the brain. We performed *in vivo* MRI for volumetry from 1 to 6 months of age. *Ex vivo* DTI was performed at 2, 4 and 6 months age, and DTI data was analyzed using TBSS.

Results *In vivo* volumetry showed significant volume loss in *Cstb*^{-/-} mice over time and DTI detected progressing WM changes with most severe changes in the cerebellum and the thalamus.

Conclusion

Results illustrate progressing degeneration, rate of which is neither spatially nor temporally uniform over the brain. Importantly, the findings point towards developmental alterations in EPM1, a novel area of study in EPM1, acting as a starting point for future studies.

Folkhälsan Institute of Genetics, Department of Medical Genetics and Neuroscience Center, University of Helsinki, Helsinki, Finland; Department of Biotechnology and Molecular Medicine, A.I. Virtanen Institute for Molecular Sciences, University of Eastern Finland, Kuopio, Finland.

Oral Presentation # 3 Eini Niskanen

New insights into Alzheimer's disease progression:

A combined TMS and structural MRI study

Eini Niskanen^{a,b,*}, Mervi Könönen^{b,c}, Sara Määttä^c, Merja Hallikainen^d, Miia Kivipelto^{d,e},
Silvia Casarotto^f, Marcello Massimini^f, Ritva Vanninen^{b,g}, Esa Mervaala^{c,h},
Jari Karhu^{i,j} and Hilikka Soininen^{d,k}

Combining structural and functional data of the human brain can provide detailed information of neurodegenerative diseases on various cortical brain areas. In this study, structural information was assessed by cortical thickness analysis based on anatomical magnetic resonance images whereas the functional information is provided by navigated transcranial magnetic stimulation study of motor cortex excitability. To examine the relationship between structure and function we correlated cortical thickness and motor cortex excitability in patients with Alzheimer's disease (AD) or mild cognitive impairment (MCI) and age-matched healthy controls. Motor cortex excitability correlated negatively with cortical thickness on the sensorimotor cortex, the precuneus and the cuneus. The negative correlation means that the thinner the cortex, the stronger the stimulation intensity needed to produce MEPs. On the sensorimotor cortex the correlation was strongest in MCIs, whereas ADs and controls showed no correlation. In AD, the motor cortex hyperexcitability seems to protect the motor functions by counteracting the prominent loss of cortical volume, whereas in MCI this protective mechanism has not yet emerged. On the precuneus and cuneus the correlation was strongest in ADs implicating that there is no similar protective mechanisms on the precuneus or cuneus as on the sensorimotor cortex. To conclude, our results indicate that the progression of the disease proceeds with different dynamics in the structure and function of neuronal circuits from normal conditions via MCI to AD.

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Oral Presentation # 4 Teemu Paajanen

Neuropsychological total scores and cortical thinning in mild cognitive impairment and Alzheimer's disease

Teemu Paajanen¹, Andrew Aitken², Tuomo Hänninen¹, Merja Hallikainen¹, Eric Westman³, Lars-Olof Wahlund³, Tomasz Sobow⁴, Patrizia Mecocci⁵, Magda Tsolaki⁶, Bruno Vellas⁷, Sebastian Muehlboeck⁸, Christian Spenger³, Simon Lovestone^{2,9}, Andrew Simmons^{2,9}, Hilikka Soininen¹ for the AddNeuroMed Consortium

Background: A lot of interest has been focused on development of screening methods for mild cognitive impairment (MCI) and Alzheimer's Disease (AD). Episodic memory impairment and medial temporal lobe atrophy have been studied intensively, however, research into sensitive neuropsychological global scores and their relationship with cortical thickness has been largely ignored.

Objective: To evaluate relationship between two cognitive global scores, CERAD total score (CERAD-TS) and Mini-Mental State Examination (MMSE), and cortical thinning patterns in MCI and AD.

Methods: Baseline data of 301 subjects (103 AD, 100 amnesic MCI and 98 controls) from the prospective European multi-center AddNeuroMed study was analyzed. All subjects went through neuropsychological assessments and uniform magnetic resonance imaging pipeline analysis. CTH was measured by using an automatic computer-based method, including vertex-based thickness measures of the entire cortical mantle. Relationships between CTH and cognitive scores were analyzed in the pooled data of MCI and control subjects. Cognition related CTH maps were contrasted to cortical areas that showed thinning in MCI and AD.

Results: CERAD-TS correlated with cortical thickness on significantly broader cortical areas than MMSE. Of all vertex clusters that presented thinning in MCI, 72.3% were related to CERAD-TS and 3.2% to MMSE. Corresponding test overlap figures for AD signature were 27.0% and 0.5%, respectively.

Conclusions: Cortical areas that are associated with CERAD-TS correspond highly with areas that present thinning in MCI. CERAD total score is a valid global cognitive measure which is significantly more sensitive than MMSE to cortical thinning especially in mild cognitive impairment.

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Poster # 1

**New insights into susceptibility microstructure using
spin-locking magnetic resonance imaging**

Joonas Autio, Lauri Lehto, Olli Gröhn

A.I. Virtanen Institute, Department of Neurobiology, University of Eastern Finland

Magnetic resonance imaging (MRI) can provide noninvasive measurements of magnetic susceptibility differences in biological tissues and has been used for clinical and research applications. Currently available MRI techniques are sensitive to field inhomogeneities in different spatial scales ranging from long background gradients to intermediate gradients around blood vessels and further to micro scale gradients around ferritine, that water molecules experience over measurement time. In this study we have explored the possibility to use on-resonance spin-locking (SL) MRI to selectively suppress the influence of large- and intermediate-scale magnetic field inhomogeneities and specifically obtain MRI contrast from field inhomogeneities in shorter spatial scales, much shorter than the field inhomogeneities induced by vascular compartments. Para- and diamagnetic phantoms were measured using SL MRI. The results show that in paramagnetic ferritin molecule rotating frame spin-lattice relaxation rate ($R_{1\rho}$) is independent of SL power which is in contrast to diamagnetic protein samples that show strong reduction in $R_{1\rho}$ with increasing pulse power. These results suggest that the SL contrast is more specific and may significantly increase sensitivity to microscopic paramagnetic substances when compared with conventional spin- or gradient-echo MRI methods. The presented method may be useful for searching surrogate markers in iron loading diseases.

Poster # 2

Characterization of somatosensory BOLD response deficit and recovery after traumatic brain injury in rat

J-P. Niskanen^{1,2}, A. M. Airaksinen¹, A. Sierra¹, J. K. Huttunen¹, P. A. Karjalainen², J. Nissinen¹, A. Pitkänen^{1,3}, and O. Gröhn¹

Traumatic brain injury (TBI) is a major cause of death and disability worldwide with an estimated 10 million people affected annually. In a previous fMRI study, we detected functional deficit and subsequent recovery in the BOLD response of rat primary somatosensory cortex (SI) following fluid percussion induced TBI, although SI is far from the injury site and appeared normal in structural T₂-w MRI. The aim of this study was to further investigate the previously observed functional deficit and recovery in the rat SI after TBI using simultaneous local field potential (LFP)/fMRI measurements and histology.

Simultaneous LFP/fMRI and histology were performed 2 and 35 days after moderate lateral fluid percussion TBI in rats. The ipsilateral BOLD and LFP responses were lost at 2d, but only partially at 35d. Furthermore, histology revealed gliosis in the ipsilateral ventral posterolateral (VPL) thalamic nucleus and a loss of myelinated fiber in layer 6 of the ipsilateral SI.

The functional deficit was detected in both LFP and fMRI, indicating that coupling between the hemodynamic and neuronal response is preserved. The combined effect of neurodegeneration in the thalamic VPL and loss of myelinated fibers in the ipsilateral SI could offer an explanation for the observed functional deficit in the ipsilateral SI. However, the changes in thalamic and somatosensory areas fail to explain the detected recovery of the ipsilateral BOLD and LFP responses. The recovery of the somatosensory function could be caused by damage induced plasticity reorganizing the SI signaling pathways in response to the thalamic damage.

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Poster # 3

Implementation of migraine aura model for fMRI studies

Artem Shatillo, Rashid Giniatullin, Olli Gröhn

The main underlying event in aura phase of migraine is cortical spreading depression (CSD) which is a slow wave of neuronal and glial depolarization that spreads across the cortex with a speed of 2-7 mm/min. The aim of this work was to implement a robust protocol for induction of CSD in the 9.4T magnet for continuous BOLD fMRI data acquisition with simultaneous local field potentials (LFP) recording in rats.

Animal preparations, consisting of femoral artery and vein cannulation, cranial window opening and insertion of LFP electrode to ipsilateral frontal cortex was conducted under isoflurane anesthesia. Urethane anesthesia 1.25 g/kg and muscle relaxation with ventilation (pancuronium bromide, 0.5 mg/kg/h i.v.) was used for data collection.

We induced CSD after 100 baseline BOLD images by applying 1M KCl solution (10 μ l) to intact meninges for 13 Wistar rats. The following imaging time was 1h (900 images). During that period, 1-5 CSD waves were observed on LFP and BOLD recordings. Based on BOLD data we calculated CSD properties: mean propagation speed of 5.3 ± 1.4 mm/min and duration of 129 ± 25 s. Developed protocol allowed us to elicit CSD with very characteristic properties in all KCl treated animals, which makes this model usable for further migraine fMRI studies.

Department of Neurobiology, A.I. Virtanen Institute for Molecular Sciences,
University of Eastern Finland

Poster # 4

Diffusion tensor imaging of intact and injured rat hippocampus-Histopathological correlates for alterations caused by status epilepticus and traumatic brain injury

A. Sierra¹, T. Laitinen¹, A. Pitkänen^{1,2} and O. Gröhn¹

Purpose: Microstructural characteristics of water diffusion within the tissue can be detected by diffusion tensor imaging (DTI). The aim of this study was to investigate detailed changes in DTI parameters of injury-induced plasticity in the hippocampus after status epilepticus (SE) or traumatic brain injury (TBI).

Methods: SE was induced with an injection of pilocarpine and TBI with lateral fluid-percussion brain injury in adult rats. *Ex vivo* DTI was performed at 6-12 months after SE, or at 7 months after TBI. Maps of fractional anisotropy (FA), axial (D_{\parallel}) and radial (D_{\perp}) diffusivities were obtained. After imaging, brain sections were stained with Timm, Nissl, or gold chloride protocols.

Results: After both injuries, DTI parameters were remarkably changed in selected hippocampal subfields. Changes in FA, D_{\parallel} and D_{\perp} were mainly found in the CA3 and dentate gyrus. Changes in orientation of the principal eigenvector were more pronounced in the CA3 and stratum lacunosum-moleculare of CA1. As expected based on histology, DTI changes after SE were more robust and widespread than after TBI. Moreover, in TBI the changes were the most clearly in the distal CA3 where the most severe principal cell degeneration occurs.

Conclusion: DTI parameters of each hippocampal subfield can provide additional information about the dynamics of ongoing plasticity in injured hippocampus. The detection of differences in hippocampal plasticity between SE and TBI creates a scenario for the use of DTI to understand the etiology-specific circuitry reorganization during epileptogenesis.

Acknowledgements: Academy of Finland

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Poster # 5

Rotating Frame Relaxation Mapping in Infarcted Mouse Myocardium In Vivo

Haja Sherief Nazimutheen Musthafa¹, L Petrov², G Dragneva¹, L Lottonen¹,
S Ylä-Herttua¹, O Gröhn¹, Timo Liimatainen¹

Introduction Despite the availability of improved therapies and diagnosis of heart failure, cardiovascular diseases are the leading cause of death in the Western world. The rotating frame relaxation ($T_{1\rho}$) techniques have provided promising results in imaging of acute cerebral ischemia and in imaging of glioma gene therapy response in experimental models. In this study, $T_{1\rho}$ was applied to map mouse myocardium after occlusion of left anterior descending coronary artery (LAD).

Materials and methods In Seven female c57bl mice, LAD was ligated. $T_{1\rho}$ imaging at 9.4T was performed with continuous wave (CW) on resonance spin-lock RF pulse (spin-lock durations 0 - 54 ms, $\gamma B_1/(2\pi)=1.25$ kHz (LAD experiment) and $\gamma B_1/(2\pi)=1.25 - 5$ kHz) using spin echo readout (LAD) or Turbo-FLASH ($T_{1\rho}$ Dispersion). $T_{1\rho}$ was estimated by linear fitting into logarithm of signal intensities.

Results The averaged $T_{1\rho}$ shows significant increase (from 0.037 ± 0.007 day 1 to 0.050 ± 0.006 ms day 7) after LAD occlusion, while $T_{1\rho}$ in remote myocardium remained stable. Dispersion in myocardium and skeletal muscle are reasonably similar while stronger effect is measured in the blood of left ventricle.

Conclusions The $T_{1\rho}$ increase in infarcted myocardium verifies the biochemical process leading to myocardium remodeling, scar formation and cell death. The CW $T_{1\rho}$ is suitable method to map $T_{1\rho}$ in infarcted myocardium in-vivo.

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Poster # 6

Amyloidogenic app processing as a mechanism for development of post-traumatic epilepsy

Diana Miszczuk [1,2], Heikki Tanila [1,3], Katarzyna Lukasiuk [2], Asla Pitkänen [1,3]

Growing evidence suggests a strong association between Alzheimer disease (AD) and epilepsy in animal models and humans. To elaborate the role of increased amyloid load in epileptogenesis we investigated whether traumatic brain injury (TBI) triggering amyloidogenic APP processing and facilitates epileptogenesis in AD mouse model.

TBI was triggered using control cortical impact (CCI) in 13-15wk old male APP/PS1 mice (n=11) and their wild type (Wt) littermates (n=8). Mice were assessed with Neuroscore for at 2, 7, 14d post-TBI. Morris water-maze (MWM) and fear-conditioning (FC) were performed at 14d post-TBI. Mice were followed-up for 2-wk (24h/7d) with continuous video-EEG monitoring starting at 6wk and 14wk post-TBI to assess occurrence of spontaneous seizures and epileptiform discharges (EDs).

APP/PS1 injured mice showed motor deficits at 2d ($p<0.01$) and 7d ($p<0.05$) post-injury as compared to sham-operated APP/PS1 mice. There was no difference in MWM and FC results between the groups ($p>0.05$). Video-EEG performed at 6wk post-TBI revealed spontaneous seizures in 43% of injured and sham-operated APP/PS1 mice ($p>0.05$). None of the injured or sham Wt mice had seizures ($p<0.01$ as compared to APP/PS1 injured or sham-operated). EDs were observed in 29% of APP/PS1 sham mice but in none of the injured APP/PS1 mice ($p>0.05$), whereas Wt group, neither injured nor sham-operated mice displayed no EDs.

APP/PS1 injured and sham-operated mice showed epileptiform activity whereas Wt injured mice did not exhibit spontaneous seizures at 6wk post-TBI. Results suggest that longer follow-up is needed to reveal whether TBI facilitates epileptogenesis in mice with amyloidogenic APP processing.

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Poster # 7

Evaluation of pharmacological responses by quantitative T2 fMRI

Joanna Huttunen¹, Antti Airaksinen¹, Kimmo Lehtimäki², Juha-Pekka Niskanen^{1,3}, Juha Yrjänheikki², and Olli Gröhn¹

Pharmacological magnetic resonance imaging (phMRI) is a novel application of functional MRI where the activation in the brain is induced by a pharmacological agent and measured e.g. with blood oxygenation level dependent (BOLD) contrast. The possible fluctuations (e.g. room temperature, hardware drifts) in the BOLD time series that are in the time scale of the pharmacological activation may not be filtered easily but could be eliminated with the T2 maps, since the drifts are presumed to be roughly similar in two sequential datasets with different echo times (32 ms and 50 ms). 11 male Sprague-Dawley rats were anesthetized with urethane (1.25 g/kg, i.p.), ventilated and paralyzed with pancuronium bromide (0.5 mg/kg/h, i.v.). A bolus of nicotine (n=5, 0.25 mg/kg, s.c.) or apomorfine (n=6, 0.25 mg/kg, s.c.) was administered after 500 baseline images (250 T2 maps) and the functional scan was continued for 1000 images (500 T2 maps) using 7.0 T magnet. Nicotine caused large positive cortical activation while smaller positive apomorfine responses were mainly detected bilaterally in the lateral entorhinal cortices. The T2 map method in pharmacological studies could be beneficial in studying new pharmacological agents with small or unknown responses in the brain.

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Poster # 8

DTI detects FA changes in the thalamus and several white matter areas in rat after traumatic brain injury

Teemu Laitinen¹, Alejandra Sierra¹, Tamuna Bolkvadze¹, Asla Pitkänen¹, Olli Gröhn¹

After traumatic brain injury (TBI), a complex combination of molecular and cellular alterations occurs in the central nervous system leading to functional disabilities such as somatomotor impairment or epilepsy. This study demonstrates the capability of diffusion tensor imaging to detect changes in the thalamus and in the white matter of rats with TBI.

TBI was induced in adult male Sprague Dawley rats (n=14) by lateral fluid percussion (LFP) injury. Age- and weight matched adn sham operated animals (n=10) served as controls. Six months after TBI, the brains of 9 trauma animals and 7 controls were scanned using ex vivo DTI. Five trauma rats and three controls underwent in vivo DTI.

Region of interest analysis of the ex vivo DTI data revealed FA changes in the trauma animals ipsilaterally in the laterodorsal (THLD) and the ventral posterolateral and –medial (THVP) thalamic nuclei, in the corpus callosum, anterior commissure, internal capsule and the angular bundle. Similar changes were seen by in vivo DTI in THVP, internal capsule, angular bundle, and in the corpus callosum.

As DTI provides a non-invasive method to be used also in clinical settings, our observations may have implications for the detection of neurobiological changes in patients at risk of functional disabilities after closed head brain trauma.

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Poster # 9

**MRI And Optical Imaging Of GFP-labelled Prostate Cancer In
Chicken Egg Tumor Model**

Anne Pink, Ott Rovgeiša, Pille Pata, Maarja Laos, Illar Pata, Johanna Närväinen, Priit Kogerman, Jaak Nairismägi

Bird embryo, i.e. the egg models, are widely used in preclinical science as they are cheap, not labor-intensive and they are considered as non-animal experiments which do not require a special permission for experimental animal work in most of the countries. The chicken egg tumor model allows tumor follow-up during 10-12 days. The aim of this work was to combine advanced oncobiological methods with MRI to create a protocol for drug development studies. We transduced human prostate cancer tumor cells with GFP containing lentiviral vector and implanted these to the chorioallantoic membrane of chicken eggs and followed tumor growth up to day 10 with MRI. The movement artifacts of chicken embryo *in vivo (in ovo)* imaging were avoided by cooling down the egg temperature. T2-weighted MRI detects the tumors starting from size of few millimeters. GFP luminescence under the UV light can point out also very small metastases not detectable in MRI. We suggest chicken embryo tumor model as a practical and cost effective method for MRI studies. Further, combining the GFP-labelled tumor cell lines with egg models reduces the efforts in selecting the targets for more expensive studies like MRI, PET etc.

Poster # 10

**MRI Of A Novel, Inexpensive Tumor Model Using The
Chorioallantoic Membrane Of A Duck Egg**

Ott Rovgeiša, Anne Pink, Olga Bragina, Johanna Närväinen,
Priit Kogerman, Jaak Nairismägi

This work is a part of a larger study on suitability of different bird species for oncobiological applications and non-invasive imaging modalities, including MRI. The main advantage compared to chicken egg as the most common *in ovo* model, is one week longer time window for experiments – ducks reach hatching in 28-30 days, and thus the duck egg has more potential as a tumor model. Mice melanoma tumor cells were implanted at day 9 and MRI was performed at days 18 and 26. T2*-weighted MRI showed inhomogeneities within the tumors and the necrotic cores appeared when the tumor size exceeded in 4-5 millimeters. Melanoma B16F0 cell line produced also metastases along the blood vessels. More than 3 million of implanted melanoma cells caused multiple metastases inside the embryo and in some cases killed the embryo before the hatching age. We suggest to prefer the duck embryo model as one of the first options in many oncobiological experiments, especially in preliminary studies, as it offers a wider time window for monitoring the tumor growth than the commonly used chicken egg model.

Poster # 11

**Decrease in cortical thickness predicts forthcoming Alzheimer's disease
– a two cohort study**

Valtteri Julkunen, Juha Koikkalainen, Eini Niskanen, Robin Wolz, Miia Kivipelto,
Ritva Vanninen, Jyrki Lötjönen, Hilikka Soininen, and
The Alzheimer's Disease Neuroimaging Initiative

We assessed how accurately an automated cortical thickness (CTH) analysis forecasts the conversion from mild cognitive impairment (MCI) to Alzheimer's disease (AD) at a single-subject level, compared its predictive power to that of clinical variables and combined both to obtain improved prediction accuracy. We assessed 195 healthy controls, 384 MCI subjects ($2.6 \pm SD 1.3$, maximum of 7.4 years follow-up time) and 141 AD patients from two separate cohorts (ADNI and Kuopio). CTH measures were calculated using an automatic pipelining method. Regions of interest based on statistical analysis were used to classify the subjects into groups according to baseline clinical characteristics. Classification was done with four methods: logistic regression, linear discriminant analysis, Support Vector Machines and voting based on the other three classifiers. Total accuracies in predicting AD converters in MCI using CTH features were 0.61 (ADNI, classifiers trained in Kuopio) and 0.64 (Kuopio, classifiers trained in ADNI). Clinical variables provided similar correct classification rates (CCR). Combining all features improved the results by 9-10 % units to 0.71-0.74. CTH features classified the controls and AD subjects correctly with an accuracy of 0.73 (ADNI, classifiers trained in Kuopio) and 0.72 (Kuopio, classifiers trained in ADNI). Adding age and gender information to the classification improved the results in Kuopio but not in ADNI. In conclusion, CTH features provide similar accuracy than clinical variables in predicting forthcoming AD. Combining both provides substantial improvement in the classification. None of the classification methods performed constantly better than the others.

Poster # 12

Alzheimer's disease and mild cognitive impairment are associated with elevated levels of isoaspartyl residues in blood plasma proteins

Hongqian Yang, Yaroslav Lyutvinskiy and Roman A. Zubarev

Increased levels of isoaspartyl residues (isoAsp) have previously been found in proteins of Alzheimer's disease (AD) brains and in blood proteins of patients suffering from uremia, the disease sharing common pathological features with AD. One can hypothesize that higher levels of isoAsp should be present in blood proteins of AD patients. Also, because of stronger AD prevalence in females, they can be expected to have higher level of isoAsp than males. Here we modified our recently developed proteome-wide isoAsp analysis approach for testing these hypotheses. Eight blood plasma samples pooled from 218 individuals suffering from either mild cognitive impairment (MCI), AD or healthy controls were analyzed by tandem mass spectrometry using electron transfer dissociation. Based on specific fragmentation pattern of isoAsp, the healthy controls were found to contain lower level of isoAsp compared with age-matched MCI and AD patients ($p=0.03$). This result was further validated ($p=0.05$) by 96 individual sample analyses, giving the combined value of $p\approx 0.01$. Female pooled samples were found to contain higher level of isoAsp than male in both pooled and individual samples, with overall $p\approx 0.01$. These findings verify the above hypotheses, and provide protein candidates for further investigation of the link between isoAsp and AD.

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Poster # 13

Genetic analysis of genes involved in amyloid- β degradation and clearance in Alzheimer's disease

Teemu Natunen, Seppo Helisalmi, Saira Vepsäläinen, Timo Sarajärvi, Leila Antikainen, Petra Mäkinen, Sanna-Kaisa Herukka, Anne Maria Koivisto, Annakaisa Haapasalo, Hilikka Soininen, and Mikko Hiltunen

Accumulation of amyloid β -peptide ($A\beta$) in the brain of Alzheimer's disease (AD) patients has been postulated to reflect defects in $A\beta$ degradation or clearance. Here, we have selected 12 genes involved in $A\beta$ degradation or clearance and elucidated their genetic role in AD among Finnish case-control cohort consisting of ~1300 AD patients and controls in total. Cerebrospinal fluid (CSF) levels of $A\beta_{42}$, total-tau and phospho-tau (p-tau) were correlated with the genetic data. Association analysis of the liver X receptor α (*NR1H3*) gene SNPs showed a protective effect for C allele carriers of rs7120118 ($p=0.014$; OR=0.70, 95% CI 0.53-0.93). Consistent with this, the phospho-tau levels were significantly decreased in the cerebrospinal fluid (CSF) of AD patients carrying the C allele. Moreover, a significant decrease in the age of onset was observed in AD patients carrying the A allele of rs723744 and the C allele of rs3794884 in transthyretin (*TTR*) gene. The phospho-tau levels in CSF were again increased among AD patients carrying the G allele of rs1080093 in *TTR* gene. These results suggest that genetic alterations in *NR1H3* and *TTR* may play a role in AD pathogenesis.

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Poster # 14

Multi-template tensor-based morphometry: Application to analysis of Alzheimer's disease

Juha Koikkalainen¹, Jyrki Lötjönen¹, Lennart Thurfjell², Daniel Rueckert³, Gunhild Waldemar⁴, Hilikka Soininen⁵, for the Alzheimer's Disease Neuroimaging Initiative

Morphometric techniques are widely utilized in computational neuroanatomy to study differences in the anatomy of the brain across populations and in decision support to characterize and diagnose single patients. Whereas voxel-based morphometry measures gray-matter density, differences in brain shape are characterized in tensor-based morphometry (TBM). In TBM, images are non-rigidly registered to a common reference space, and the analysis is done by comparing the parameters of resulting deformation fields or measures derived from them.

In PredictAD, a multi-template TBM approach has been developed. When using multiple templates and, therefore, multiple registrations, it can be assumed that the registration errors are averaged and eventually compensated. Four different methods are proposed for multi-template TBM and compared to the conventional single-template approach. The methods are evaluated using magnetic resonance images from the ADNI database (N=772).

Classification results show that the multi-template methods are statistically significantly better than the single-template method in discriminating patient groups. The classification accuracy was 86.0% for the classification of control and AD subjects, and 72.1% for the classification of stable and progressive MCI subjects. The statistical group-level difference maps produced using multi-template TBM were smoother, formed larger continuous regions, and had larger t-values than the maps obtained with single-template TBM.

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Poster # 15

Alzheimer's Disease and Seizures: Interleukin-18, Kynurenine pathway and Quinolinic Acid Production

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Emergent seizures are common in Alzheimer's disease (AD). The mechanisms mediating this are unknown. We propose that N-methyl-D-aspartate receptor (NMDAR) agonist quinolinic acid (QA), a neurotoxic tryptophan metabolite of the kynurenine pathway, increases seizures and concurrently contributes to neuronal loss via excitotoxicity, including via QA impact on glutamate transport. We previously found that expression of interferon- γ inducing factor interleukin-18 (IL-18) is increased in AD-brain, being detectable in microglia, neurons, astrocytes and amyloid- β -plaques. Interferon- γ is an inducer of indoleamine-2,3-dioxygenase, a key enzyme in induction of the kynurenine pathway. Now we clarified the role of stress inducible IL-18 in regulation of kynurenine pathway.

We exposed neuron-like differentiated SH-SY5Y neuroblastomas and normal human astrocytes (NHA) to IL-18, interferon- γ other inflammatory cytokines or QA. The expression changes of kynurenine pathway members were detected with immunoblotting. Interferon- γ was the strongest inducer of indoleamine-2,3-dioxygenase in both cell types. IL-18, IL-1 β and TNF- α increased its expression modestly, whereas impact of IL-6 was minor. In SH-SY5Y, IL-18 and IL-1 β dose-dependently increased the expression of kynureninase. QA increased expression of kynurenine aminotransferase-II (KAT-II), producer of the alpha7-nicotinic receptor and NMDAR antagonist kynurenic acid (KynA), in both cell types.

Conclusions: Inflammatory cytokines have a direct impact on kynurenine pathway and therefore on tryptophan metabolism in neuronal cells. QA increased KAT-II which converts kynurenine to KynA and may therefore contribute to suboptimal arousal induced deficits in cognition. As to whether the production of KynA reaches a high enough concentration to inhibit the NMDAR, and therefore negatively feedback on seizure susceptibility requires further investigation.

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Poster # 16

ApoE ϵ 4 Effect on Cortical Thicknesses and Volumes – The Addneuromed Study

Yawu Liu, Teemu Paajanen, Yi Zhang, Eric Westman, Lars-Olof Wahlund, Andrew Simmons, Catherine Tunnard, Tomasz Sobow, Patrizia Mecocci, Magda Tsolaki, Bruno Vellas, Sebastian Muehlboeck, Alan Evans, Christian Spenger, Simon Lovestone, Hilikka Soininen for the AddNeuroMed Consortium

Background: Apolipoprotein E (ApoE) ϵ 4 allele is known as a risk factor for Alzheimer's disease (AD). However, the ϵ 4 effect on brain volumes is controversial. Moreover, only a few structures were manually or semi-manually measured in the most of the morphological studies. Our aim was to explore the effect of ϵ 4 allele on brain regional cortical thickness and volume measured by using automated whole brain measurements.

Materials and Methods: Regional cortical thicknesses on 33 cortical regions and volumes on 31 brain structures were measured with a fully automated pipeline in 111 (36 ϵ 4/-, 5 ϵ 4/ ϵ 4) subjects with mild cognitive impairment (MCI), 115 AD patients (29 ϵ 4/-, 4 ϵ 4/ ϵ 4), and 107 age-matched healthy controls (46 ϵ 4/-, 18 ϵ 4/ ϵ 4).

Results: The ϵ 4 carriers had significantly smaller volume than non-carriers in caudate ($p=0.028$) in control group; in amygdala and caudate in MCI group ($p\leq 0.049$); and in hippocampus and amygdala in AD group ($p\leq 0.001$). In the female control subjects, the regional cortical thickness of medial orbitofrontal gyrus and volume of caudate were significantly smaller ($p\leq 0.014$) for ϵ 4 carriers ($n=17$) than for non-carriers ($n=41$). In the female MCI group, the volume of amygdala was significantly smaller ($p=0.047$); in the female AD group, the volumes of hippocampus and amygdala were significantly smaller ($p\leq 0.024$) in carriers ($n=23$) than in non-carriers ($n=32$). However, in the male MCI subjects the regional cortical thicknesses of inferior temporal gyrus, lingual gyrus, pericalcarine cortex, rostral anterior cingulate cortex, and superior frontal gyrus, and the volumes of hippocampus, amygdala, caudate, pallidum, cerebral gray and white matter were significantly smaller ($p\leq 0.043$) in ϵ 4 carriers ($n=18$) than in non-carriers ($n=38$). Comparing to the non-carriers, the homozygous ϵ 4 carriers showed significant volume loss in hippocampus, deep nuclei (amygdala, caudate nucleus, nucleus accumbens, putamen, and pallidum), and caudal anterior cingulate cortex in MCI. In AD group, the homozygous ϵ 4 carriers had significant volume loss in hippocampus and amygdala, but significantly thicker regional cortex in the middle frontal gyrus, precentral gyrus, and post central gyrus.

Conclusion: The ϵ 4 modulates the regional cortical thickness and volume in relation to diagnostic group and gender. The ϵ 4 has dose-dependent and regional specific effect on brain structures, indicative of increasing volume loss in hippocampus and amygdala and relative volume persevered in frontoparietal region in homozygous ϵ 4 carriers with AD.

Poster # 17

**Robust and accurate segmentation of hippocampus for diagnostics
of Alzheimer's disease**

Jyrki Lötjönen¹, Robin Wolz², Juha Koikkalainen¹, Lennart Thurfjell³, Valtteri Julkunen⁴,
Gunhild Waldemar⁵, Hilikka Soininen⁴, Daniel Rueckert²,
the Alzheimer's Disease Neuroimaging Initiative

Current diagnostic guidelines support the use of magnetic resonance imaging in diagnostics of Alzheimer's disease. As the delineation of hippocampus from images manually is difficult and time consuming, automated tools are needed in clinical settings. In PredictAD, our approach is based on multi-atlas segmentation where several atlases are registered non-rigidly to patient data and propagated segmentations are fused. Our extension includes: atlas selection and expectation maximization classification.

The ADNI (www.loni.ucla.edu/ADNI) was used to evaluate the performance of the segmentation algorithm. Automatic segmentations were compared with semi-automatic segmentation for 340 cases. The Dice similarity index (0=no overlap, 1=perfect overlap) between automatic and semi-automatic was 0.869 ± 0.035 which compares well with the similarity between segmentations made manually by clinicians. The intra-class correlation coefficient for the hippocampus volumes generated automatically and semi-automatically was 0.94. We studied also the consistency of segmentations by comparing the volumes obtained from 3T and 1.5T images. The test-retest variability was 3.17 ± 2.47 % when two outliers were excluded. The computation time of the algorithm in a standard laptop computer was less than two minutes.

We have developed a segmentation method for hippocampus that has clinical potential. The accuracy of segmentations is comparable to manual segmentations.

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Poster # 18

Brain biopsy in the prediction of Alzheimer's disease

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Introduction

Amyloid- β ($A\beta$) plaques, along with intracellular neurofibrillary tangles largely comprising hyperphosphorylated tau ($HP\tau$), are considered the hallmarks of Alzheimer's disease (AD) but brain biopsies are seldom used in the diagnosis of AD. The aim of this study was to evaluate the predictive value of brain biopsy for the clinical diagnosis of AD in patients with primarily suspected normal pressure hydrocephalus (NPH).

Methods

From 1991 until 2006 468 patients with suspected NPH were evaluated with intraventricular pressure monitoring and a right frontal cortical biopsy immunostained for $A\beta$ (6F3D) and $HP\tau$ (AT8). Adequate clinical follow-up data, available in 433 cases, were reviewed for the clinical signs of dementia, especially AD.

Results

Of the 433 biopsies, 42 (10%) displayed both $A\beta$ and $HP\tau$, 144 (33%) $A\beta$ only, and 247 (57%) neither $A\beta$ nor $HP\tau$. In a median follow-up time of 4.4 years, 94 patients (22%) developed clinical AD. $A\beta$ together with $HP\tau$ was strongly (OR 68.2, 95% CI, 22.1-210) and $A\beta$ alone significantly (OR, 10.8; 95% CI, 4.9-23.8) associated with AD. The presence of both $A\beta$ and $HP\tau$ indicated later diagnosis of AD with a high specificity (98%) but with a rather low sensitivity (36%). $A\beta$ alone was sensitive (87%) for AD but less specific (69%). The absence of both $A\beta$ and $HP\tau$ nearly excluded the later appearance of AD.

Conclusions

Brain biopsies - when available - are a useful diagnostic tool of AD, can validate advanced imaging techniques for AD, and may help to identify novel markers for AD.

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The authors have no conflicts of interest.

Poster # 19

**Measurement of hippocampal atrophy using 4D graph-cut segmentation:
Application to ADNI**

R. Wolz, R.A. Heckemann, P. Aljabar, J.V. Hajnal, A. Hammers,
J. Lotjonen and D. Rueckert

The longitudinal change of brain structures is a well-established biomarker for Alzheimer's disease. The accurate measurement of atrophy rates can be an important factor in clinical trials when quantifying the influence of disease modifying treatment. This work describes a method for the accurate measurement of hippocampal atrophy in large clinical studies using magnetic resonance imaging. LEAP, a previously described multi-atlas segmentation method is used to automatically segment the hippocampus in all baseline images using multiple manually segmented atlas images. After affinely aligning the available follow-up image (s) to the baseline, the multiple segmentations give a spatial estimate of the hippocampus in the image sequence. In addition, a model of the hippocampus' intensity distribution is estimated from all target images. Both, the spatial and the intensity model are used to consistently segment the hippocampus on all longitudinal images. Aligning the whole image sequence before estimating all segmentations in one time-step, allows to define constraints that enforce the same segmentation on all time points in areas where no consistent gray value exists. Intensity-differences caused by atrophy are detected by the defined intensity model and result in segmentation differences allowing to accurately measure atrophy. Measured atrophy rates in ADNI over 1 year allow a classification accuracy of 82% between healthy controls and AD subjects. The method requires 103 subjects per arm in a hypothetical two-arm study of MCI subjects to detect a 25% change in atrophy rate with 80% power and 5% significance.

Poster # 20

Sensorimotor, visual and auditory cortical atrophy in Unverricht-Lundborg disease (EPM1) mapped with cortical thickness analysis

Päivi Koskenkorva¹, Eini Niskanen^{1,3}, Jelena Hyppönen⁴, Mervi Könönen^{1,4}, Esa Mervaala⁴, Hilikka Soininen⁵, Reetta Kälviäinen⁵, Ritva Vanninen¹

Rationale:

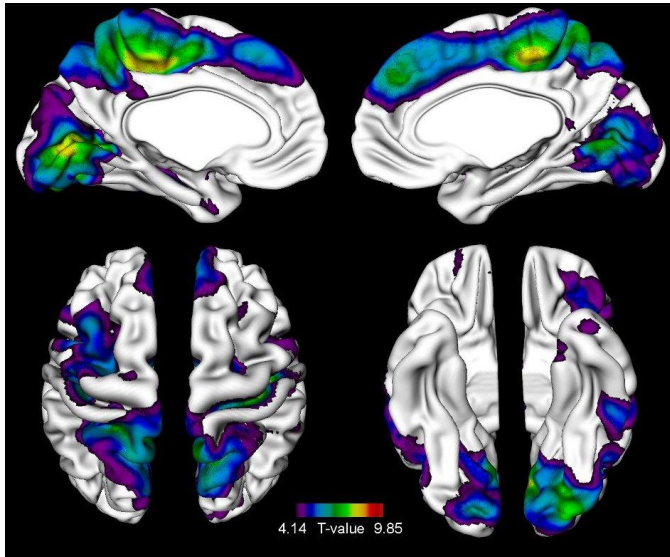
Unverricht-Lundborg disease (EPM1), caused by mutations in the cystatin B gene, is the most common form of progressive myoclonus epilepsies. The most incapacitating symptom of EPM1 is action-activated and stimulus-sensitive myoclonus. The severity of EPM1 varies considerably between patients, but no correlations between quantitative structural changes in the brain and clinical parameters such as duration of the disease, age at onset or myoclonus severity have been observed so far. The aim of the study was to evaluate possible changes in cortical thickness (CTH) of patients with EPM1 compared with healthy controls, and to correlate those changes with clinical parameters.

Methods:

Fifty-five genetically verified patients and 70 healthy volunteers matched for age and gender underwent MRI. MR images were analyzed with cortical thickness analysis to detect alterations in CTH. The patients were clinically evaluated for myoclonus severity using the Unified Myoclonus Rating Scale. Higher UMRS scores indicate more severe myoclonus.

Results:

Cortical thickness analysis revealed significant thinning of the sensorimotor, visual and auditory cortices of patients with EPM1 compared with healthy controls (Fig.). CTH was reduced with increasing age in both groups, but in patients the changes were confined specifically to the aforementioned areas, while in controls the changes were more diffuse. Duration of the disease and the severity of myoclonus correlated negatively with CTH.



Conclusion:

The alterations in cortical thickness of patients with EPM1 correlated significantly to the degree of the complex clinical motor symptoms and seem to be congruent with the stimulus-sensitive nature of the symptoms.

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Poster # 21

Manifold Learning Combining Imaging with Non-Imaging Information

R. Wolz, P. Aljabar, J. V. Hajnal, J. Lotjonen, D. Rueckert

This work describes a novel method based on machine learning for extracting biomarkers for Alzheimer's disease. It is based on manifold learning, a technique to represent a population of high-dimensional magnetic resonance images in a significantly lower dimension. Such a low-dimensional representation is learned by estimating the pairwise similarities between all images in the population. Assuming a subset of the images is clinically labeled, inferences can be made about the unlabeled images in the manifold space. The presented method describes a way to incorporate non-imaging information in such a learned manifold space to better describe the population of interest. Using the proposed method based on MR imaging allows a classification accuracy of 86% between healthy controls and AD patients in the ADNI database. In addition, 62% of the subjects that convert from MCI to AD can be identified based on baseline MRI only. Incorporating the level of CSF A β -42 as well as the subject's ApoE genotype as non-imaging information into manifold learning, improves these classification rates to 88% and 69% respectively.

