SINAPSE

Annual Scientific Meeting and SPIRIT showcase

Monday 16th June 2014

Royal Society of Edinburgh

SINAPSE: Bridging the gap in medical imaging

Five RCR CPD credits anticipated

Thanks to Health Sciences Scotland for donation of prizes

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Welcome from the Director of SINAPSE

This will be my 4th Annual Scientific Meeting as Director of SINAPSE. By now it should be just another event in the calendar, a matter of routine; but it isn't. I am still thrilled by the quality of the imaging research that is taking place in Scotland. I had the pleasure of being one of the reviewers of the 61 abstracts that were selected for presentation at this meeting. The quality of research and the breadth of expertise are outstanding.

This year we have three themes to the meeting. Firstly we highlight the SPIRIT knowledge exchange programme led by Professor Joanna Wardlaw. Projects within this scheme require commercial partners. They might contribute financially, but the main benefit is the added experience that they bring and the focus on research that can be taken to the marketplace. Secondly we present projects that are designed to improve imaging - new devices, new analysis methods, new production methods or new tracers for PET. Finally there is a session on studies that use advanced forms of MRI, PET, CT, ultrasound or EEG as a central component of the research.

For a while we were concerned that the academic pooling groups set up by the Scottish Funding Council might struggle to survive beyond their initial round of funding. We are encouraged, however, that there are signs that the importance of collaboration is being recognised and we are now optimistic that there will be a 7th SINAPSE Annual Scientific Meeting.

The Executive would like to thank our advisory body, the Board for Academic Medicine, and in particular the chairman Sir David Carter, for their support, and also our International Advisory Board chaired by Professor John Pickard from Cambridge, for words of wisdom from afar.

There is a great deal of unrest just now around the Independence Referendum. We all have views on this. As a scientist who knows the importance of grant income I certainly do. This is not the forum for me to express my personal views, but perhaps I could be allowed to express disappointment in the quality of debate. As scientists we are trained to analyse data and we are well versed in predictive modeling. We are taught about the importance of errors, confidence limits and sensitivity analysis. Perhaps this is why the political debate grates so much. The certainty expressed by many debaters reduces the credibility of their arguments. There is far less statistical noise in a multi-centre MRI data set. Likelihood estimates don't win votes, but more awareness of the uncertainty would at least indicate honesty. Politics is important, but some of us are still more passionate about science. We need politics to give us infrastructure and to devise schemes for the fair distribution of our national wealth, but science will generate new knowledge and, in our case, improve health.

I hope that you enjoy listening to the talks and please take a much time as possible to visit posters and interrogate the presenters.

David Wyper

Programme			
Time	**Topic**	**Speaker**	
09:50 - 10:00	Welcome	**Joanna Wardlaw** , BRIC	
10:00 - 10:15	Report on SINAPSE activities	**Dave Wyper**, SINAPSE Director	
SESSION 1	**SPIRIT and SPRING Showcase:** Chair Prof D Wyper; SINAPSE		
10:15 - 10:30	Overview of SPIRIT Programme	**Joanna Wardlaw** , SPIRIT PI	
10:30 - 10:45	Dissociating voice from speech following fronto-temporal stoke.	**A.B. Jones**, A. Farrall, J. Wardlaw, P. Belin, C.R. Pernet	P1
10:45 - 11:00	Experimental Measurements of Preclinical fMRI (In)Stability	**G. D, Merrifield**, T. Anderson, M. A. Jansen, I. Marshall	P2
11:00 - 11:30	**Coffee and SPIRIT AND SPRING Posters**		
11:30 - 11:45	Extending the Synthetic Utility of the Fluorinase for Positron Emission Tomography	**S Thompson**, M Onega, S McMahon, I Fleming, J Naismith, J Passchier, D O'Hagan[1]	P3
11:45 - 12:00	Industry perspective of SPIRIT	**Ian Hallett**, Imanova Ltd	Invited
12:00-12:15	The expansion of e-Learning	**Jo-Anne Murray**, University of Edinburgh	Invited
12:15 12:30	Public engagement in Research	**Ourania Varsou**, University of Aberdeen	P4
12:30 - 13:30	**Posters, Lunch, exhibition & networking**		

SESSION 2	**Development of Imaging Technologies:** Chair Prof Richard Lerski, University of Dundee		
13:30 - 13:45	Elastography Software Library (ESL) for Rapid High-Resolution Magnetic Resonance Elastography (MRE) Image Processing	**E Barnhill**, C Brown, E van Beek, N Roberts	P5
13:45 - 14:00	Clinical Development of a Neutrophil and Bacterial Specific Optical Imaging Agents- Opening the Optical Door for Next Generation Molecular Sensing	**K Dhaliwal,** T Walton, A Akram, N McDonald, T Craven, N Avlonitis, M Vendrell, A Lilienkampf, D Collie, T Walsh, C Haslett, M Bradley.	P6
14:00 - 14:15	Development of novel tracers for molecular imaging of poly(ADP-ribose) polymerase-1	**F Zmuda,** A Blair, M Boyd, A Sutherland, A Chalmers, S Pimlott.	P7
SESSION 3	**Application of advanced imaging:** Chair Professor Alison Murray, University of Aberdeen		
14:15- 14:30	Dietary nitrate reduces skeletal muscle oxygenation response to physical exercise: a quantitative muscle functional MRI study	**R Bentley**; SR Gray; C Schwarzbauer; D Dawson; M Frenneaux; J He	P8
14:30-14:45	Ultrasound in a Needle for Neurosurgery and Other Applications	**Z Qiu,** R McPhillips, S Mahboob, Y Jiang, C Meggs, G Schiavone, T Button, M Desmulliez, S Eljamel, C Demore, S Cochran	P9
14:45-15:15	**Refreshments and Posters**		
15:15-15:30	In Vivo MR monitoring of Microrna-15 and 16 induction as potential targeted therapy in Chronic Lymphocytic Leukemia by ultrasmall superparamagnetic iron oxide nanoparticles (USPIO).	**G Baio**, G Cutrona**,** M Colombo, S Matis, C Massucco, D Reverberi, R Massara, S Fabris, S Boccardo, F Rosa, L Basso, S Salvi, F Morabito, CE Neumaier, M Negrini, P Tassone, M Truini, A Neri, M Ferrarini	P10
15:30 - 16:15	**Imaging in Dementia**	**Professor John O'Brien, University of Cambridge**	**KEYNOTE**
16:15- 16:30	**Prizes & Announcements** Prof Dave Wyper: SINAPSE Director Prizes will be awarded for the best proffered oral presentation, the best poster, the best lay summary on a poster and the project with most commercial potential. They have been donated by **Health Sciences Scotland.**		

PROFFERED ORAL ABSTRACTS

The Universities currently signed up to be SINAPSE partners are Edinburgh, Aberdeen, Dundee, Glasgow, St Andrews and Stirling.

P1	**A.B. Jones**	**A.B. Jones**
P2	**Experimental Measurements of Preclinical fMRI (In)Stability**	**G. D. Merrifield**
P3	**Extending the Synthetic Utility of the Fluorinase for Positron Emission Tomography**	**S. Thompson**
P4	**Public Engagement in Research: A Personal Perspective**	**O. Varsou**
P5	**Elastography Software Library (ESL) for Rapid High-Resolution Magnetic Resonance Elastography (MRE) Image Processing**	**E. Barnhill**
P6	**Clinical Development of a Neutrophil and Bacterial Specific Optical Imaging Agents- Opening the Optical Door for Next Generation Molecular Sensing**	**K. Dhaliwal**
P7	**Development of novel tracers for molecular imaging of poly(ADP-ribose) polymerase-1**	**F. Zmuda**
P8	**Dietary nitrate reduces skeletal muscle oxygenation response to physical exercise: a quantitative muscle functional MRI study**	**R Bentley**
P9	**Ultrasound in a Needle for Neurosurgery and Other Applications**	**Z Qiu**
P10	**In Vivo MR monitoring of Microrna-15 and 16 induction as potential targeted therapy in Chronic Lymphocytic Leukemia by ultrasmall superparamagnetic iron oxide nanoparticles (USPIO).**	**G. Baio**

P1

Dissociating voice from speech following fronto-temporal stoke.

A.B. Jones[1]**,** A. Farrall[1], J. Wardlaw[1], P. Belin[2] & C.R. Pernet[1]

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Following middle cerebral artery strokes, left hemisphere lesions can lead to aphasia. Similarly, right hemisphere lesions they can lead to phonagnosia (voice recognition disorder). In this study we investigated if the processing of phonemes could be dissociated from the processing of voice gender.

Twenty seven stroke patients were recruited: 10 left hemisphere patients with aphasia, 6 left hemisphere patients without aphasia, 10 right hemisphere patients without aphasia and a unique case of cross-aphasia. Participants had to rate sound stimuli as being male or female (gender task) and /pa/ or /ta/ (phoneme task). Because stimuli consisted in morphed sounds from 100% male /pa/ to 100% female /ta/ and 100% male /ta/ to 100% female /pa/, all normalized in f0 (i.e. same pitch height) and energy levels (root mean square normalization), the same sounds could be used in both tasks, thus controlling for acoustic differences between tasks.

Classification of response curves (impaired versus non impaired processing) revealed that gender categorization and phoneme categorization could not be dissociated in left MCA patients (McNemar =0.2 p=.8), i.e. either patients were impaired in both tasks or in none of them. In contrast, the 2 tasks were dissociated in right MCA patients showing no sign of aphasia (McNemar =8 p=.003). Finally, the case of cross-aphasia showed, like left aphasic patients, a deficit for both voice and phoneme categorization tasks. Lesion to symptom mapping (the association of lesion sites observed on CT scans with behavioural performances) additionally revealed that impairments in gender categorization were associated with lesions of the right inferior frontal gyrus, while no one-to-one mapping could be observed in the left hemisphere.

In conclusion we show that when processing speech, phonemic and voice related information are processed differently in the left and right hemispheres. The left hemisphere processes speech information along with voice information while the right hemisphere specializes in voice processing. Our result leaves the door open to new interventional therapies in aphasia where voice training could help recovering language function.

Acknowledgements: This work was funded under the SINAPSE SPIRIT scheme

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P2

Experimental Measurements of Preclinical fMRI (In)Stability

G. D. Merrifield (1), T. Anderson (3), M. A. Jansen (3, 3), I. Marshall (2,4)

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Functional Magnetic Resonance Imaging (fMRI) based studies are rapidly expanding in the field of preclinical research. Many of these studies use gradient-Echo Echo Planar Imaging (GE-EPI) to measure Blood Oxygenation Level Dependent (BOLD) signal contrasts in the brain. In such studies the magnitude and statistical significances of these contrasts are then related to brain function and cognition. It is assumed that observed signal contrast is due to differences in biological state and that scanner performance is stable and repeatable between subjects and studies. Due to confounding issues introduced by in vivo subjects, little work has been undertaken to test this assumption. As the BOLD signal contrasts generated in such experiments are often very low, even small changes in scanner performance may dominate the BOLD contrast, distorting any biological conclusions drawn.

A magnetic gradient based fMRI phantom was used to generate data sets emulating the BOLD signal contrast of in vivo imaging. Two studies examining scanner performance were conducted on high-field preclinical MRI scanners. Firstly, in a longitudinal study on a single scanner, measurements were taken over a number of scan sessions over a year long period. Secondly four preclinical scanners (three at 7T, one at 9.4T) were comparatively assessed. Measurements of several fMRI relevant parameters were obtained.

Parameter measurements showed significant differences for identical contrast settings generated by the phantom. Although signal contrast itself proved very comparable across the studies other parameters proved to be variable and not as would be expected solely from variations in experimental set up. Individual scan sessions often displayed further unexpected behaviours.

These results suggest a cautious approach should be taken with the conclusions of both preclinical fMRI and associated resting state connectivity studies that rely on GE-EPI. Clinical MRI scanners should also be assessed for similar aberrations in behaviour.

Acknowledgements: We thank Dr Jack Wells (UCL), Dr William M. Holmes (Glasgow) and Dr Po-Wah So (KCL) for help and scanner access. This work was performed as part of a SINAPSE-Spirit studentship sponsored by Agilent Technologies.

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P3

Extending the Synthetic Utility of the Fluorinase for Positron Emission Tomography

Stephen Thompson[1], Mayca Onega[2], Stephen McMahon[1], Ian Fleming[3], Jim Naismith[1], Jan Passchier[2], David O'Hagan[1]

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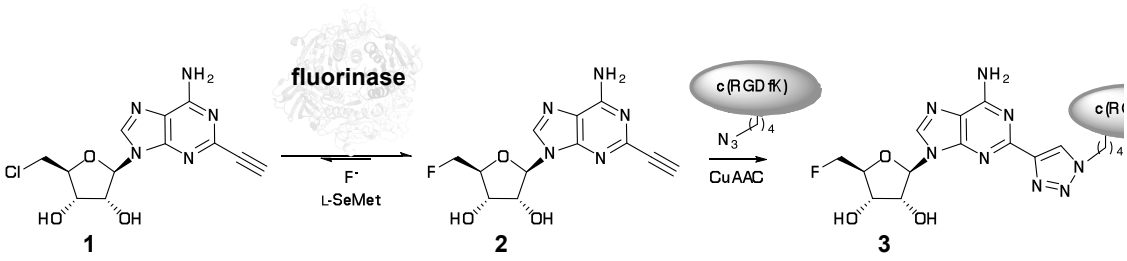
Positron emission tomography (PET) has emerged as an invaluable tool for molecular imaging in the clinic. The short lived nature of PET radioisotopes, e.g ^{18}F ($t_{1/2}$ 110 min), requires short, elegant syntheses of radiotracers, compatible with commonly available radionuclide production methods.[1]

The fluorinase (from soil bacterium *Streptomyces cattleya*) offers an enzymatic route to novel radiotracers. Using *S*-adenosylmethionine (SAM) as substrate, the fluorinase catalyses reaction with F^- giving 5′-fluoro-5′-deoxyadenosine.[2,3] Uniquely, the fluorinase catalyses formation of a C-F bond from aqueous F^-, which is also the most common form of ^{18}F produced by cyclotron radionuclide production facilities. Consequently, the fluorinase is ideally suited to using $^{18}F^-$ directly from the source for synthesis of new tracers.

To extend the utility of the fluorinase, acetylene-bearing substrates were desired for use in conjugations with peptides of interest. Synthesis of acetylene-bearing CLDEA (**1**) and the fluorinated product, FDEA (**2**), will be described. In the presence of aqueous fluoride ($^{19}F^-$) and L-selenomethionine, the fluorinase efficiently converted CLDEA (**1**) to FDEA (**2**).



Enzymatically synthesised FDEA (**2**) was also shown to undergo rapid coupling to an azide-bearing RGD peptide using a Cu-catalysed alkyne azide cycloaddition (CuAAC). This conjugate (**3**) was shown to have high affinity to immobilised $\alpha_V\beta_3$ integrin. The results of the radiolabelling experiments using $^{18}F^-$ and subsequent bioconjugation using the novel prosthetic group will also be presented.

References

1. L. Cai, S. Lu, and V. W. Pike, *Eur. J. Org Chem*., 2008, 2853-2873.
2. C. Dong, F. Huang, H. Deng, C. Schaffrath, J. B. Spencer, D. O'Hagan, and J. H. Naismith, *Nature*, 2004, **427**, 561–565.
3. L. Martarello, C. Schaffrath, H. Deng, A. D. Gee, A. Lockhart, and D. O'Hagan, *J. Labelled Compd. Radiopharm.*, 2003, **46**, 1181-1189.

Acknowledgements: Scottish Imaging Network (SINAPSE) and the John and Kathleen Watson Scholarship

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P4

Public Engagement in Research: A Personal Perspective

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Personal Profile

Public engagement is becoming an increasingly more important and integral part of scientific research. My journey in this exciting area began roughly at the same time as the start of my PhD at the Aberdeen Biomedical Imaging Centre in 2012. Since then, I have volunteered at and organised a variety of different public engagement activities. These span from science busking and participating with unique events in local festivals to school outreach visits throughout Aberdeenshire. What sparked my interest to get involved in such schemes was my work experience during the British Science Festival 2012 that was held at the University of Aberdeen. Shortly after this, I started volunteering with "Lab in a Lorry" at local schools, exploring science with hands-on experiments. Following these, I became more independent in my activities with the support of STEMNET, my colleagues and the University of Aberdeen Public Engagement with Research Unit. Specifically, I co-organised various events with the main theme being "Meet the Experts: Magnetising your Brain". This is an educational and exciting activity, which has always received excellent feedback from the public. Finally, I have participated in various other schemes with the most notable being FameLab, Bright Club, Car Boot Science, STEM-in-the-Body, and the Café Sci Family Day Specials organised either by Satrosphere Science Centre or the University of Aberdeen. The aim of all these events is to combine tailor-made demos along with talks to raise awareness about various scientific concepts and at the same time inspire young pupils from different backgrounds to pursue a career as a scientist. This presentation will give an insight into the exciting world of public engagement and some of the ways in which it can be successfully implemented within a neuroscience context.

Websites

- STEMNET: http://www.stemnet.org.uk
- Bright Club: http://www.brightclub.org
- FameLab: http://famelab.org
- Lab in a Lorry: http://www.labinalorry.org.uk/index.html

Acknowledgements: Dr Ourania Varsou would like to acknowledge: i) Mr Michael Stringer and Miss Catarina Dinis Fernandes for their invaluable help with most of the above public engagement activities; ii) Professor Christian Schwarzbauer, Dr Mary Joan MacLeod, Professor Alison Murray, Professor David Lurie, and Dr Gordon Waiter for their support; iii) the staff of the Aberdeen Biomedical Imaging Centre for their on-going help with most of the above public engagement activities; iv) SINAPSE for funding the PhD project; v) the staff of the University of Aberdeen Public Engagement with Research Unit for their on-going support and advice; and vi) STEMNET for providing training in science communication.

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P5

Elastography Software Library (ESL) for Rapid High-Resolution Magnetic Resonance Elastography (MRE) Image Processing

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MR Elastography (MRE) [1] measures tissue viscoelastic parameters, which identify alterations to microstructural tissue lattice across a range of applied frequencies. MRE has moved from a low-resolution Region of Interest (ROI) based technique to a technique approaching parity with anatomy scans; however, image processing for high resolution MRE requires analysis of multiple 4D scans using a complex pipeline of phase unwrapping [2], noise filtering, image decomposition, wave inversion [3] and image fusion. To reach feasibility as a Radiological technique, MRE must deliver 3D viscoelastic parameter maps within clinically relevant time frames.

In the present work the procedures described above have been coded in a newly developed software which we have named Elastography Software Library (ESL). ESL comprises three main modules -- PhaseTools, TFilter, and MRE-3D -- that together enable rapid high-resolution MRE processing via corresponding menus with appropriate choice of relevant input parameters. A fully automatic version of ESL has been implemented on the proprietary IDEA operating system for the 3 T Verio MRI system (Siemens Medical Systems, Erlangen, Germany) [4], and a cross-platform version of ESL, which enables off-line analysis of images from any MRI scanner or operating system, is also available in Java for the ImageJ platform [5].

This presentation will provide an overview of the various steps in the rapid high-resolution MRE Image Processing pipeline and via the use of relevant examples, illustrate the key mathematical principles and their practical application. An instructional video has also been produced to demonstrate the operation and application of the pipeline.

[1] Muthupillai et al. *Science,* 5232:1854-7 (1995).
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[3] Barnhill et al. *Physio. Meas.,* 34:1675 (2013).
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[5] Barnhill et al. *Proc. ImageJ Dev. Conf. (2012).*

Acknowledgements: This work was supported by SINAPSE and Mentholatum

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P6

Clinical Development of a Neutrophil and Bacterial Specific Optical Imaging Agents- Opening the Optical Door for Next Generation Molecular Sensing

Kev Dhaliwal, Tashfeen Walton, Ahsan Akram, Neil McDonald, Tom Craven, Nicos Avlonitis, Marc Vendrell, Annamaria Lilienkampf, David Collie, Tim Walsh, Chris Haslett, Mark Bradley.

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Acute Lung Injury (ALI) has a mortality of 40% and afflicts over 40 % of all ventilated patients in intensive care. Neutrophil-mediated lung injury (NMLI) and bacterial infection are central to the pathogenesis of ALI. No molecular stratification tools exist in clinical practice to aid in the accurate diagnosis of NMLI and bacterial infection. We have developed a family of clinically applicable bespoke optical molecular imaging agents to detect neutrophils and bacteria. The lead molecule is called NAP (neutrophil activation peptide). NAP is a dendrimeric self quenched peptide-based optical molecular imaging agent that has been synthesised to clinical grade and progressed through regulatory toxicology and GMP stability assays. NAP is detected with bedside optical molecular imaging sensing through fibre-based confocal microendoscopy. This bedside-based approach offers a new molecular imaging platform to detect pathological processes at microscopic resolution in humans in vivo. To improve detection, an advanced clinical development programme has been established to develop novel fibre-based imaging tools to improve inflammation and bacterial sensing in patients in intensive care.

Acknowledgements: MRC, Wellcome Trust, EPSRC

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P7

Development of novel tracers for molecular imaging of poly(ADP-ribose) polymerase-1

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Poly(ADP-ribose) polymerase-1, PARP-1, is involved in repair of DNA breaks and in the presence of DNA damaging agents its inhibition leads to cell death. Thus, PARP-1 inhibitors, such as olaparib, are being investigated in clinical studies as a means of sensitising tumorous tissue to conventional chemotherapy. Despite PARP-1 inhibitors being relatively non-toxic on their own, concomitant chemotherapy has been associated with enhanced myelosupression. Clinically, this is limiting the advancement of PARP-1 inhibitors as chemosensitising agents. This body of work aims to address the above issue by developing Positron Emission Tomography (PET) and Single Photon Emission Tomography (SPECT) tracers based on the structure of olaparib, which could then be used in imaging studies to assess PARP-1 activity and treatment with PARP-1 inhibitors.

A total of 18 (4 methoxy, 6 fluorinated and 8 iodinated) cold analogues of olaparib were synthesised. Four were selected as potential candidates (**1**–**4**) based on their cell-free PARP-1 inhibitory and physiochemical properties (cell-free IC_{50} ≤5.6 nM, log P_{oct} ≤3.00 and %PPB ≤96.2). These compounds retained their PARP-1 inhibitory properties in G7 and T98G human glioblastoma cell lines (cellular IC_{50} ≤7.4 nM). In all cases, olaparib was used as a gold standard (cell-free IC_{50} 11.9 nM, cellular IC_{50} 1.6 nM, log P_{oct} 1.95 and %PPB 75.9). Compounds **1** and **4** were chosen as lead PET and SPECT tracer candidates respectively. Initial radioiodination efforts to generate [^{125}I]-**4** via interhalogen exchange have produced very promising results with >99% ^{125}I incorporation (*n*=2). Radiofluorination to form the PET tracer [^{18}F]-**1** proved more challenging; to date only 19% ^{18}F incorporation was achieved via nucleophilic substitution of a nitro precursor and alternative avenues are being pursued.

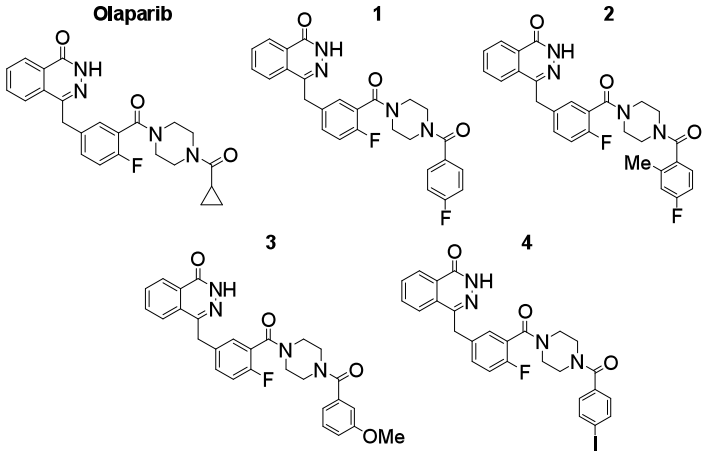

Figure 1. Lead analogues of olaparib.

This presentation will focus on the challenges associated with developing novel tracers for the molecular imaging of PARP-1 as well as the broader application of such an imaging platform.

Acknowledgements: EPSRC, the University of Glasgow College of Medical, Veterinary and Life Sciences, and the WeCan: CRUK West of Scotland Cancer Centre.

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P8

Dietary nitrate reduces skeletal muscle oxygenation response to physical exercise: a quantitative muscle functional MRI study

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Dietary inorganic nitrate supplementation (probably via conversion to nitrite) increases skeletal muscle metabolic efficiency. In addition, it may also cause hypoxia dependent vasodilation and this has the potential to augment oxygen delivery to exercising skeletal muscle. However direct evidence for the latter with spatial localisation to exercising muscle groups does not exist. We employed quantitative functional MRI (fMRI) to characterise skeletal muscle oxygen utilisation and replenishment by assessment of tissue oxygenation maximal change and recovery change respectively.

11 healthy subjects were enrolled, of whom 9 (age 33.3 ± 4.4 years, 5 males) completed the study. Each subject took part in 3 MRI visits, with dietary nitrate (7cl concentrated beetroot juice) consumed before the third visit. During each visit fMRIs were conducted concurrently with plantar flexion exercise at workloads of 15% and 25% maximum voluntary contraction (MVC).
No significant changes were found between visits 1 and 2 of the fMRI measures. A decrease in maximal change was found at 15% MVC in soleus between visits 2 and 3 (5.12±2.36 to 2.55±1.42 ,p=0.004) and between visits 1 and 3 (4.43±2.12 to 2.55±1.42, p=0.043), but not at 25% MVC. There was no difference in recovery change between visits. These changes do not correlate with the changes in BP oxygen saturation.

Our results indicate that enhancement of muscle metabolic function from nitrate occurs mainly on type 1 fibres at lower exercise intensity. At higher exercise intensities, an hypoxia dependent vasodilation would increase T2 as a result of vascular dilation effects, and reduce R2*.

Dietary nitrate does not induce a hypoxia dependent augmentation in oxygen delivery to exercising skeletal muscle in healthy young subjects, and its improvement in muscle efficiency is likely to originate from enhanced mitochondrial function. Our results may have potential benefits in peripheral arterial diseases, angina, heart failure and ischemic brain disorders.

Acknowledgements: The authors would like to thank Gordon Buchan for technical support, Baljit Jagpal, Nichola Crouch, Katrina Klaasen and Beverley MacLennan for radiographic support.
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P9

Ultrasound in a Needle for Neurosurgery and Other Applications

Zhen Qiu[1], Rachael McPhillips[1], Syed Mahboob[1], Yun Jiang[2], Carl Meggs[2], Giussepe Schiavone[3], Tim Button[2], Marc Desmulliez[3], Sam Eljamel[1], Christine Demore[1], Sandy Cochran[1]

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Ultrasound (US) is gaining increasing attention in image-guided neurosurgical resection for its true real-time feedback, the reduced side effects of brain shift, the ability to be used in an unaltered operating room environment, and a high total resection rate. With improved imaging resolution, ultrasound enables fine-scale tissue visualisation and localization, which will provide accurate guidance to biopsy or resection processes.

In order to overcome the trade-off between imaging resolution and imaging depth, a miniaturized ultrasound device with high operating frequency can be integrated within interventional tools, such as biopsy needles. Such a device fuses microultrasound (mUS) with high imaging resolution and sufficient imaging depth for clinical need. Combining two orientations of ultrasound device within one biopsy needle, forward facing and side facing, the device can aid many possible clinical applications. Forward facing mUS can be used to guide a biopsy needle safely into tissue, avoiding critical structures such as blood vessels in the brain. Once the needle is positioned accurately at the tissue region of interest, side viewing mUS can offer accurate tissue diagnostics and targeting.

The work presented here has taken the form of a feasibility study of mUS devices in biopsy needles for neurosurgery. The design and fabrication challenges are explored including pseudorandomly structured piezoelectric - polymer composite development, multiple element mUS array packaging and integration. Microfabrication and micromachining techniques are investigated on the wafer scale. Three single-element prototyped devices have been fabricated within standard biopsy needles, 2 mm in diameter, two with front facing mUS and one with side facing mUS. A 32-element array transducer in a breast biopsy needle was also prototyped. All devices work at 15 MHz. Basic characterization tests were carried out on the devices, and preliminary images from sheep brains have been obtained to demonstrate the feasibility of concept.

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P10

In Vivo MR monitoring of Microrna-15 and 16 induction as potential targeted therapy in Chronic Lymphocytic Leukemia by ultrasmall superparamagnetic iron oxide nanoparticles (USPIO).

Gabriella Baio[1], Giovanna Cutrona[2], Monica Colombo[2], Serena Matis[2], Carlotta Massucco[2], Daniele Reverberi[2], Rosanna Massara[2], Sonia Fabris[2], Simona Boccardo[2], Francesca Rosa[2], Luca Basso[2], Sandra Salvi[2], Fortunato Morabito[2], Carlo Emanuele Neumaier[2], Massimo Negrini[2], Pierfrancesco Tassone[2], Mauro Truini[2], Antonino Neri[2] and Manlio Ferrarini[2]

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Chronic Lymphocytic Leukemia (CLL) is a type of slow growing leukaemia, characterized by a gradual increase in the number of B lymphocytes, first in the blood and bone marrow and, as the disease progresses, in the lymph nodes, liver, and spleen. Despite its indolent nature, it remains an incurable disease. Computed tomography (CT), is clinically used as the first-line modality for imaging of lymphoid malignancies but, specifically for CLL, the role of CT has not yet been clearly defined. In our study, we aimed to establish a specific MR technique by using USPIO-nanoparticles, to better visualize the presence of the CLL within the spleen and to follow up a possible treatment in a sperimental mouse model (NOD/Shi-scid,γcnull (NSG) mouse, xenograft model of CLL). Since more than 50% of CLL have deletions in chromosome 13 [del(13q14)] with the loss of expression of miR-15 and miR-16, we investigated the potential therapeutic effect of miR15. To follow the progression of the disease, peripheral blood cells were analyzed by flow cytometry (CD19/CD5+ CLL cells) and MRI was used to evaluate size, morphology and changes in signal intensity (SI) of the spleen due to the different uptake of USPIO-nanoparticles. Scanning was performed on a clinical 3T MR scanner and the mice were positioned in a prototype coil (linear birdcage transmit/receive coil, Flick Engineering Solutions BV-General Eletric-Baio G.), before and 24 hours after 100μL/25g mouse of USPIO administration. USPIO-MRI, well detected and characterized the focal lesions of CLL within spleen. Mice treated with miR15 showed regression of the focal aggregates, with a parallel decrease in SI at the MRI, due to the increased uptake of USPIO from the treated spleen. Fibrous areas previously occupied by the neoplastic clone, was also observed. CD20-positive B cells displaying low BCL-2 and ki67 proliferation marker expression, were detected at immunohistochemistry. Our results suggest, the feasibility and utility of USPIO-MRI in order to detect the presence and development of a non-solid tumor, such as CLL and, to follow up is possible treatment. The induction of miR15 in biallelic del13q14 CLL allow the modulation of proteins involved in the apoptosis pathways and could represent a possible target therapy for this subgroup of CLL patients.

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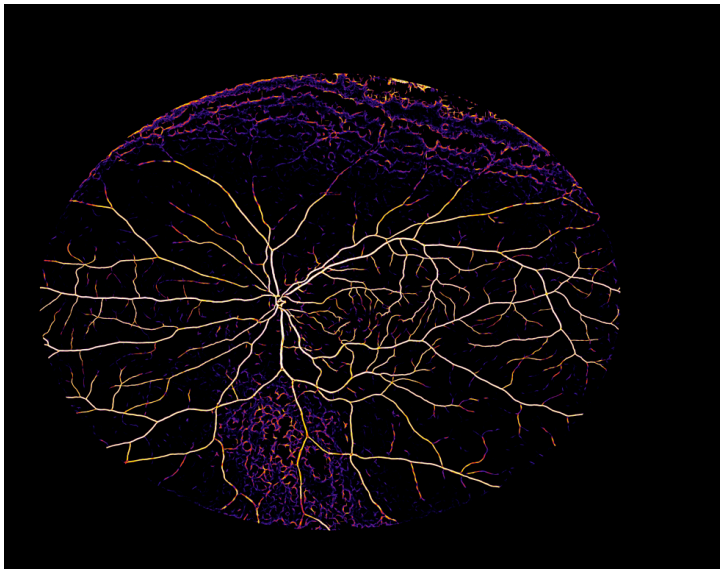
PROFFERED POSTER ABSTRACTS

SPIRIT PROGRAMME



A neural network classifier was used to create this probability map of the human retinal vasculature imaged with a scanning laser ophthalmoscope (Optos P200C).

The bright pixels represent a high probability of vascular structure.

Such images are used to investigate biomarkers of neurological and systemic disease via the eye.

Credit: Gavin Robertson – VAMPIRE Project; Clinical Research Imaging Centre and Centre for Clinical Brain Sciences University of Edinburgh.

The following companies are engaged in KE work with SINAPSE, either through the SPIRIT programme or subsequent projects:

Toshiba Medical Visualisation Systems Europe; Optos; Mentholatum; Vascular Flow Technologies; Propeller; Molecular Neuroimaging; Bruker; Agilent Technologies; ReNeuron; GE; Siemens; Pfizer; AstraZenca; GSK

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PS1

A Novel ^{18}F-Labelled High Affinity TSPO Agent for PET Imaging of Neuroinflammation

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University of Glasgow and Molecular Neuroimaging LLC

The translocator protein (TSPO) is an important target for imaging focal neuroinflammation in diseases such as brain cancer, stroke and neurodegeneration, but current tracers for non-invasive imaging of TSPO have important limitations. We present the synthesis and evaluation of a novel 3-fluoromethylquinoline-2-carboxamide, AB5186, which has superior characteristics as a potential PET tracer for TSPO. AB5186 was prepared in eight steps using a one-pot two component indium(III)-catalyzed reaction for the rapid and efficient assembly of the 4-phenylquinoline core. Biological assessment and the implementation of a physicochemical study showed AB5186 to have low nanomolar affinity for TSPO, as well as lower binding to plasma protein and better permeability than the standard TSPO PET imaging agent, PK11195. Incorporation of radioactive fluorine (^{18}F) into AB5186 and in vitro autoradiography revealed the ability of this compound to image tumour tissue in a mouse model of glioblastoma.

Acknowledgements: Financial support from the Scottish Funding Council, University of Glasgow, MNI and SINAPSE is gratefully acknowledged.

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PS2

Development of Novel PET-Isotope Labelling Methods

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University of Edinburgh (Department of Chemistry and Clinical Research Imaging Centre)

Fulfilment of the considerable potential of PET relies upon increasing the range of radiotracers available to encompass more biological targets. However, the development of efficient, widely applicable methods for radiolabelling tracers remains challenging due to the requirements of rapid reactions, efficient purification strategies and amenability to automation.

The objective of this project was two-fold:
(i). To develop a generic method for radiolabelling tracers with ^{11}C or ^{18}F in which an unlabelled pre-tracer is attached to a solid support, and addition of the radioisotope cleaves the desired radiolabelled tracer from the support into solution. This way, all unlabelled material remains bound to the support, thereby simplifying purification.
(ii). Optimise this approach to allow the routine synthesis of ^{11}C labelled peptides in which phenylalanine is simply replaced by 4-[^{11}C]-methylphenylalanine.

This was achieved by firstly functionalising a polystyrene resin to allow attachment of boronic acids via a boronate ester linkage. A Suzuki reaction utilising methyl iodide was developed and employed to methylate and simultaneously cleave model compounds from the resin within 5 minutes. This reaction was adapted to ^{11}C using the GE TRACERlab FX C Pro automated synthesiser, and has been successfully employed to cleave and radiolabel a model compound, thus providing us with proof of concept for this novel method. Simultaneous cleavage and labelling was also explored with potassium bifluoride to liberate trifluoroborates. These reactions were shown to reach completion within 2 minutes at ambient temperature, suggesting their feasibility for development with ^{18}F.

Work is in progress to extend the scope of the ^{11}C chemistry to a known radiotracer, M-MTEB, and to peptides.

Acknowledgements: Prof. Mark Bradley (Principal Investigator); Dr Christophe Lucatelli (radiochemistry supervisor); Dr Sue Champion, Prof. John Clark (radiochemistry support); Dr Jeff Walton (organic synthesis advice) and NHS-Lothian R&D

Contact: Elizabeth Jameson

PS3

Development of new PET tracers to study liver transporters

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Transporter polypeptides are expressed in the cell membranes of hepatocytes, mediating the transport of endogenous compounds and xenobiotics across the membrane. Several clinically used drugs are substrates or inhibitors of these transporters (OATP1B1 and OATP1B3), which can lead to pharmacokinetic drug-drug interactions when they are co-administered.

Inhibition of the transporter may affect both drug disposition and elimination of the substrate drug, and it would be useful to visualize and quantitate the changes occurring in this process. The aim of our research project is the development of a fluorinated positron emission tomography (PET) tracer to study the involvement of liver transporters in drug pharmacokinetics. Three potential fluorinated PET tracers were designed and synthesized starting from three different bile acids. The compounds were labelled with tritium through a palladium-mediated dehalogenation with tritium gas. Cell-based assays were performed using HEK293-OATP1B1 and HEK293-MOCK cell lines in order to assess the transporter-mediated accumulation of the tritiated tracers into the cells (time-dependent accumulation and inhibition experiments). Kinetic transport parameters (Km, intrinsic clearance and passive diffusion) were also determined. Among the proposed fluorinated bile acid derivatives, a promising potential PET tracer was identified, and its fully automated 18Fsynthesis, from the mesylate precursor, was optimized (35% radiochemical yield, > 99% radiochemical purity). Imaging experiments and metabolism studies on preclinical models (wild-type rodents) will be performed shortly, in order to assess the biodistribution of the tracer and its blockage by different OATP1B1 substrates or inhibitors.

Acknowledgements: SINAPSE, ASTRAZENECA, UNIVERSITY OF ABERDEEN

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PS4

Preterm infant brain pathology revealed in individuals by voxel ranking against a normal term atlas

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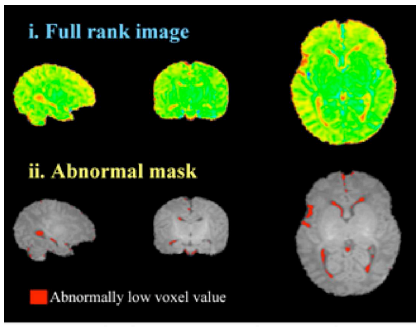
Introduction: Preterm birth is associated with alterations in brain structure detected by group wise comparisons with term controls using voxel-based null hypothesis significance testing, e.g. *t*-tests. However, this approach does not describe how 'normal' an individual subject is. Percentile rank atlases have been developed to measure the 'normality' of individual subjects. Hypothesis: voxel-based ranking against an atlas created from term controls will detect alterations in individual preterm infants.

Methods: 43 preterm VLBW infants (postmenstrual age [PMA] at birth < 32 weeks' gestation; birth weight <1500g) were recruited with approval from the NHS Research Ethics Service. A Siemens Verio 3T system was used to acquire T1 weighted MP-RAGE images in the sagittal plane with 1x1x1mm resolution; 13 subjects were excluded due to severe motion artefact. Semi-automatic brain extraction and spatial and intensity normalisation to the Montreal Neurological Institute 36-44 weeks' PMA normal infant atlas. Deviation from normal was calculated by % difference in each voxel: (Ui-Xij/Ui)x100, where Ui is voxel i in the atlas and Xij is voxel i in subject j.

Results: The output for each subject is a fully ranked image (i) and an abnormal mask visualised in atlas space at a specified threshold (ii). In the example: (i) green regions show where the preterm infant voxel value=atlas, and yellow-red is where preterm voxel value < atlas; (ii) regions where the individual voxel is < 12.5th percentile with respect to atlas. Lower voxel values indicate CSF where tissue is present in controls.

Voxel-based ranking detected lateral ventricle enlargement in 30/30 preterms, with 37% showing localisation of enlargement to the temporal horns of the lateral ventricles.
Conclusions: Voxel-based ranking against a term control neonatal atlas detects regional structural variation associated with preterm birth at the level of the individual. Our method and data will be made available online:



http://www.sinapse.ac.uk/research-resources/brains-project.

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PS5

Imaging functional improvement following neural stem cell therapy for stroke: A Longitudinal Study Design

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[b] School of Psychology, University of Glasgow
[c] ReNeuron Ltd. Guildford, UK.

Introduction

The human neural stem cell line CTX0E03 has evidence of improved functional recovery in rodent stroke models. MRI provides a non-invasive means of investigating structural and functional changes following stroke and may offer insight into the effects of intra-parenchymal stem cell transplantation. A longitudinal study will determine if serial diffusion tensor and resting-state BOLD imaging indices are correlates of functional change after transient middle cerebral artery occlusion (tMCAO) and CTX0E03 treatment up to 12 weeks post transplantation.

Groups

Male Sprague-Dawley rats will be grouped according to baseline functional forelimb performance via the staircase test. Animals will be randomised to one of three groups: tMCAO+CTX cells; tMCAO+Vehicle and Sham+Vehicle (n=12 per group). Assessors will be blinded to group allocation by recoding via a third party independent of the experiment.

Surgeries

4 weeks following 70min tMCAO or sham surgery, 450,000 cells in 4.5µl vehicle, or vehicle alone, will be stereotaxically injected into two sites in the peri-infarct striatum at coordinates defined by structural MRI.

Imaging

MRI experiments will be performed on anesthetised animals on a Bruker Biospec 7T/30cm system at GEMRIC using the following sequences: 3D T1, RARE T2 (determination of infarct), DTI (diffusion properties of parenchyma) and BOLD EPI (resting-state BOLD for baseline connectivity). Imaging will be conducted at weeks -2, +6 and +12 post CTX-cell transplantation with corresponding functional assessment.

Analysis

Novel p:q segmentation software (T.Barrick, SGUL) will be used to analyse the DTI data. Whole-brain voxels are clustered into 9 groups by k-means segmentation. Global distributions of these clusters will be assessed as well as changes in voxels per cluster within pre-selected ROIs. Seed regions will be chosen at the implantation site and sensorimotor regions S1f1 and M1 for analysis of resting-state data.

Conclusion

This project will elucidate MRI correlates of functional recovery relevant to future clinical translation.

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Contact: Tristan Hollyer

PS6

Cortical Parcellation of Healthy Middle-Aged Subjects Across Four Software Packages

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Introduction: Numerous techniques have been developed to characterize structural changes in the brain using magnetic resonance imaging (MRI) data. These tools, mostly semi- or fully-automated have been implemented in numerous packages and applied to a broad spectrum of clinical studies, promoting a better understanding of the brain and its variations in different populations, age groups and brain disorders. Outputs are depicted in the form of labelled cortical parcellations and/or subcortical segmentations, along with corresponding maps and morphometrics.

Materials & Methods: We have evaluated cortical parcellations of 5 gyri in 4 software packages, using 3 healthy middle-aged subjects and default settings. The 5 gyri were chosen to meet the following criteria: (1) be situated in the various cortical lobes, (2) be of significance for ageing and dementia studies, and (3) vary with gender. They are the cingulate gyrus, inferior temporal gyrus (ITG), superior frontal gyrus (SFG), precentral gyrus, and supramarginal gyrus. The four software packages are FreeSurfer, BrainGyrusMapping, BrainSuite, and BrainVisa. All possible morphometrics were extracted and compared.

Results: Total brain grey matter volume averaged at 625266.292mm^3, with a standard deviation of 62388.006 mm^3. The four packages yielded similar results. Minimum gyral volume was seen at the supramarginal gyrus (mean= 6707.31mm^3, std dev= 77.643mm^3), while maximum volume was at the SFG (mean= 21922.517mm^3, std dev= 5273.309); the precentral gyrus had the smallest **grey matter** thickness (mean= 2.854mm, std dev=0.024), while the ITG had the largest (mean= 3.513mm, std dev=0.075; gyral surface area on the white matter-cortical surface was smallest for the ITG (mean= 2393.563mm^2, std dev=499.240) and largest for the SFG (mean=6041.322mm^2, std dev 543.460).

Conclusion: We shall process more subjects with the 4 packages for a better understanding of each package's performance, and for evaluating significance of our findings. Ground truth shall also be drawn on all brains for a thorough validation of the packages.

Acknowledgements: This work has been funded by SINAPSE, TMVSE, and the Row Fogo Charitable Trust.

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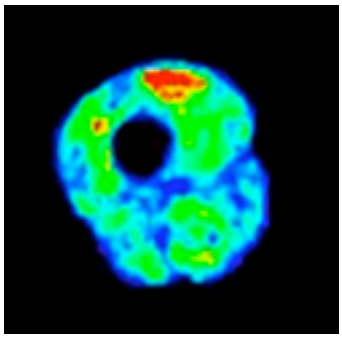
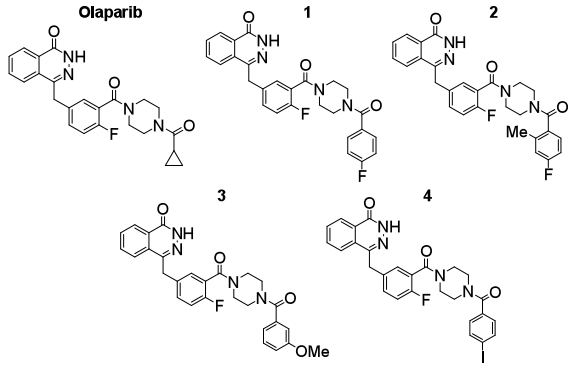
PROFFERED POSTER ABSTRACTS

DEVELOPMENT OF IMAGING TECHNOLOGIES



MR elastography is a novel development of MRI. One of the pioneering groups is that of Professor Roberts in Edinburgh. This illustration is taken from Paul Kennedy's poster PD7.



Novel tracers for PET and SPECT are needed to measure the effects of therapies on specific molecular systems. This will be a key component of stratified medicine. This illustration is taken from Filip Zamuda's talk P7

Helped by SINAPSE funding, internationally competitive programmes to develop novel imaging technologies are underway.

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PD2	**Micro-ultrasound: detection and characterisation of early colorectal dysplasia.**	**S Sharma**
PD3	**Automatic generation of synthetic retinal fundus images**	**S. Fiorini**
PD4	**Modelling Brain Temperature and Cooling Methods using CFD**	**S. Blowers**
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PD18	**Compensation of the parasitic magnetic fields in Ultra-Low Field Cycling NMR relaxometry**	**V Zampetoulas**
PD19	**Laser-plasma wakefield accelerator driven production of copper-62, a positron emitter used in medical imaging**	**P. Lepipas**
PD20	**Next Generation Fibre-Based Molecular Optical Molecular Imaging- Introducing the PROTEUS Project**	**H. Szoor-McElhinney**

PD1

Visualization of Nerve Trauma Caused by Anaesthetic Needles During Regional Anaesthesia.

Anu Chandra[1], Paul Felts[2], Qiuhua Hu[1], George Corner[1], Roos Eisma[2], Shilpa Munirama[3,4], Christine Demore[1], Graeme McLeod[3]

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The real time monitoring of anaesthetic agents and improved spatial resolution makes Ultrasound Guided Regional Anaesthesia (UGRA) popular for performing nerve blocks. However about 7.7% of transient neuropathy has been reported from our recent meta-analysis of UGRA studies. Decrease in acoustic impedance, poor visibility of the needle and limited resolution of the conventional ultrasound can account for nerve trauma caused.

This paper inspects the nerve trauma caused by anaesthetic needles during regional anaesthesia. The objective of this study is to observe the anatomical changes caused by interfascicular and intrafascicular injections and validate the results using histology.

Soft embalmed Thiel human nerves and Fresh Cadaveric human nerves were used as specimens. Conventional clinical ultrasound systems use frequencies about the range 5-15 MHz which does not provide enough resolution to image the internal structure of the nerve. Thus microultrasound scanning was used for visualizing the nerve trauma caused by 22G needles. The frequency used is greater than 30 MHz which provides a resolution of around 100 µ. The specimens are fixed in formaldehyde and 1% Osmium Tetroxide once the scanning is completed. The anatomical changes caused by inserting the anaesthetic needles into the nerve were determined by conducting a comparative study between the microultrasound scan results and histology results.

The microultrasound images and histology images showed a strong correlation in size of nerve, individual size of fascicles etc. The histology images showed a greater number of fascicles than the microultrasound images which were of size less than 0.5 mm; this can be improved with optimization of the microultrasound scanner. The fascicles in the nerve were found to move away or bent when the needle insertion experiments were conducted. The pre-clinical data obtained shows that microultrasound had a great potential for showing nerve trauma caused by anaesthetic needles and requires further study.

Acknowledgements: Sandy Cochran, Holly Lay, RAUK

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PD2

Micro-ultrasound: detection and characterisation of early colorectal dysplasia.

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2. Division of Cell and Developmental Biology, University of Dundee

Neoplasms of the colon are a leading cause of morbidity and mortality in the UK. Current methods of early detection may be complemented by the addition of micro-ultrasound (μUS) devices. μUS operates at >30MHz, allowing higher resolution imaging of tissue than standard clinical frequencies, permitting transmural imaging with micro-scale resolution. With higher frequencies comes greater sensitivity to architectural and distributive transformations of the colon epithelium, with the potential to detect early dysplastic changes qualitatively and quantitatively.

Quantitative imaging analysis, utilizing acoustic impedance (Z) and backscatter co-efficient (BSC), has shown *in vitro* evidence of an ability to differentiate between normal and pathologic tissue of murine models. Z and BSC measurements are relevant as they relate directly to the 2D and 3D ultrasound images produced, which are of prime importance in clinical diagnostics. The comparison of ultrasound images with high resolution optical images reveals similar tissue organization and features, and this correlation between imaging modes is an important step towards μUS tissue classification and stratification.

The clinical implications of this mode of ultrasound imaging are predicated on the ability of μUS to provide high resolution imaging of the gut wall. By employing qualitative and quantitative ultrasound modes, there is potential for early identification and characterisation of epithelial dysplastic changes *in situ*.
This aspect of μUS in turn has the potential to be incorporated into pre-existing medical devices such as US mini-probes used with colonoscopy or paired with video capsule endoscopy (VCE).

Incorporation of μUS into clinically deployable devices also brings possibilities for expansion of medical applications. μUS probes may allow for improved local tumour staging and assisting treatment decisions with image guided assistance.
Furthermore, the incorporation of μUS into capsule form would assist in upper gastrointestinal and small bowel examination with full thickness μUS imaging and complementary video imaging for improved gastrointestinal diagnosis of cancerous and non-cancerous pathology.

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PD3

Automatic generation of synthetic retinal fundus images

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2. Department of Information Engineering, University of Padova, Italy.

Retinal fundus imaging has been shown to provide easily accessible biomarkers for high-incidence systemic conditions like diabetic retinopathy, stroke and cardiovascular disease. Biomarker discovery requires computer-based image analysis with validate algorithms, and, in turns, validation requires ground truth in the form of significant voumes of images annotated by experts. Obtaining such annotations sets is expensive, laborious, and not always feasible.

This study aims to generate realistic retinal fundus colour images (phantoms), similar in appearance to a given dataset, and associated with full ground-truth values. In the synthesised retinal phantoms, textural and anatomical features can be controlled to simulate a wide range of situations, hence different populations and their characteristics.

Image are built by superimposing a synthetic vascular network and optic disc onto a synthetic background. For backgrounds (including the fovea) we developed a patch-based tiling algorithm inspired by image quilting whereby novel images are synthesized by stitching together small tiles from existing images under suitable continuity constraints. For the generation of synthetic optic discs, we propose a novel model-based approach, which learns the distributions of key morphometric quantities from real images and reproduces them in the phantom. A model-based synthesis technique has also been implemented for the generation of the retinal vessel tree, using distributions of values for shape parameters like vessel calibre, tortuosity and length. Texture is added on the synthetic vessels using a patch-based learning technique.

The validity of our synthetic retinal images has been demonstrated by visual inspection and quantitative experiments. Learning in the current protoype has used the publicly available High-Resolution Fundus (HRF) database and results from the VAMPIRE software suite.

Acknowledgements: Research partially supported by Leverhume trust grant RPG-419 and ERASMUS studentships. We thank R. Annunziata[1] and E. Pellegrini[1] for valuable comments and inspiring ideas.

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PD4

Modelling Brain Temperature and Cooling Methods using CFD

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Neuroimaging Sciences, Centre for Clinical Brain Sciences, University of Edinburgh

It is now widely accepted in medicine that elevation of core brain temperature can lead to irreversible damage to cells. Although the body contains an effective thermoregulatory system to keep a constant temperature, extreme circumstances from disease or head trauma can cause the temperature in the brain to rise to dangerous levels. Currently there are no proven methods that significantly and selectively reduce brain temperature rapidly. Experimental trials are few and expensive due to the difficulties in measuring core brain temperature. Current mathematical models rely on an outdated bioheat transfer model developed by Pennes in 1948 - which is based on unrealistic and severe assumptions that ignore any impact of head geometry and the associated convective heat transfer and thermal transport due to blood flow.

Our current work looks into developing CFD models based on full governing equations of flow and heat transfer that require fewer assumptions and will provide more realistic results. This requires knowledge of the arteries and veins inside the head to determine the flow distribution of blood in the brain. In order to achieve this, they must be extracted from MRI scans and processed to minimise errors associated with surface interference. The process for this is from Cerefy Clinical Brain Atlas which involves: 1) isolating the required arteries or veins from a cerebral MRI scan, 2) extracting a skeleton of 3D centrelines of the vessels from the image slices, 3) lofting a circular surface of relevant across the skeleton. This prevents surface roughness appearing if the 3D model is extracted directly from the images themselves.

Using these realistic 3D models with a CFD solver, a more accurate representation of brain temperature profiles can be created. With this, various treatment methods such as nasal or scalp cooling can be modelled theoretically without expensive and lengthy clinical trials.

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PD5

How accurately can we assess longitudinal white matter changes?

MC. Valdés Hernández, D. Ghandour, X. Wang, E. Sakka, S. Makin, F. Doubal, K. Schuler, M. Dennis, J. M. Wardlaw

University of Edinburgh

BACKGROUND: Volumetric assessment of white matter hyperintensities (WMH) from structural Magnetic Resonance Imaging (MRI) is challenging. We investigated the influence that subtle hyperintensities can have in longitudinal measurements of WMH volumes in brain MRI of patients with minor stroke.

METHODS: We obtained WMH volumes from brain structural MRI from 46 mild stroke patients at baseline and 3 years later with a validated method (MCMxxxVI), independently and blind to previous data. In addition, we assessed longitudinal WMH changes by subtracting contrast adjusted (namely gamma correction) FLAIR images at both time points. Recent and old stroke lesions were masked from the signal analyses. We quantitatively and visually analysed the effect of each method on the measured WMH change. We then, independently, on baseline and 1 year follow-up assessed WMH change on images of 190 patients with mild stroke using MCMxxxVI and, in addition, subdivided the extracted WMH into intense and less-intense regions by a validated criterion to evaluate the influence that the less-intense regions have on the assessment of WMH change.

RESULTS: In the set of 46 patients, the WMH change over 3 years(median= 2.9ml,IQR=8) with MCMxxxVI was significantly different ($p<0.001$) than when subtracting post-processed FLAIR images (median=7.6ml,IQR=8.5). Visually, this last method was less influenced by subtle WMH. In the set of 190 patients, the WMH change over 1 year with MCMxxxVI was median=1.4ml(IQR=7, min=-32ml, max=29.1ml), with a decrease in 66/190 patients. In 28/66, the intense WMH increased but the subtle WMH change (median=0.9ml, IQR=7.1) considerably influenced the total WMH change (robust correlation $\rho=0.93$;95%CI[0.89;0.96]).

CONCLUSION: Measurement of WMH volume progression remains challenging. Subtracting the FLAIR images at both time points following gamma correction seems promising but is adversely affected by subtle WMH, which significantly influences the measurement of WMH change.

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PD6

DICOM Confidential - Data Anonymisation Software

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The DICOM Confidential project develops an open source DICOM (Digital Imaging and Communications in Medicine) de-identification toolkit that provides the necessary flexibility to account for different de-identification requirements.

DICOM is a standard for handling, storing, printing, and transmitting information in medical imaging. It includes a file format definition and a network communications protocol, and is used world wide.

The DICOM Confidential project was developed by David Rodriguez Gonzalez at Edinburgh University, in conjunction with SINAPSE. This project is open source, written in Java, and was registered on SourceForge.net on Apr 20, 2010. DICOM Confidential is licensed under the Apache License V2.0.

What DICOM Confidential does:

1) It anonymises DICOM data, in practically every and any way you could need, apart from e.g. removing face/ears/mouth within 3D MR images of the human head. This can be achieved through integration with other existing tools.

2) It can act as a 'DICOM receiver/sender', e.g. to receive images from a scanner.

3) Internal (University of Edinburgh) add-ons also include a 'catalogue' function, that catalogues the data to a database (mysql). NB: It does not provide search/interrogation of the database, but this can simply be achieved through the database interface (SQL).

4) It can interface with other tools e.g. to convert DICOM to Nifti or Analyze format.

5) There are many configurable options, they include:

1. File and folder naming options.
2. The ability to keep/delete or modify standard tags, in addition to private tags.
3. The ability to rename sequences with the sequence type.
4. Automated quarantine of unsafe data, e.g. images with burned in information.
5. A modular construction to allow integration with other tools.

To get the software please go to SourceForge.net

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PD7

BRAINS: Brain Images for Normal Subjects

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Brain Images of Normal Subjects bank is being developed with more than 1000 normal subjects from across the lifespan. It is collating images, and associated information (metadata) about health (e.g. blood pressure) already collected from people participating in research projects throughout Scotland. Many of these studies include detailed information from across the whole lifecourse, including socioeconomic status, current and previous health, medication use and cognitive ability tests. We are initially focussing on collecting data from studies at the extremes of life (old age and pre- and neo-natal) where there is most variability in brain structure, but we aim to expand the bank to include subjects of all ages.

The bank may be expanded in future to include subjects from other geographical locations, and patients with a range of neurological disorders, e.g. Alzheimer's disease, stroke, and schizophrenia.

The images have been collected in imaging centres across Scotland and are in a range of magnetic resonance (MR) sequences, including T1, T2, T2*, and fluid attenuated inversion recovery (FLAIR). When BraINS is released (2014) these will be searchable by a wide range of metadata, e.g. blood pressure, age, MMSE.

BRAINS atlases are based on calculated distributions of brain structure rather than parametric estimates. These will be used to support image analysis research and clinical reporting of brain images.

Website - http://www.sinapse.ac.uk/research-resources/brains-project

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PD8

Multishot spiral Magnetic Resonance Elastography: Application in skeletal muscle

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Magnetic resonance elastography (MRE) is an emerging technique which allows the quantification of tissue mechanical properties in-vivo. MRE has been applied to multiple organ systems in the body with significant success. Skeletal muscle poses an imaging problem due to the inherently short T2 decay exhibited during MRI acquisitions. This limitation necessitates the use of short echo times (TE) to capture sufficient signal. This problem is further compounded by the requirement for motion encoding gradients to be applied before the readout gradients in order to encode the propagation of shear waves in the muscle. As a result, SNR is a significant problem in muscle studies.

Here we present data acquired using a multishot spiral Echo Planar Imaging (EPI) MRE sequence. The sequence captures all three wave field displacements at an isotropic resolution of 2mm. A 32 channel receiver coil (Invivo, Gainesville, USA) is used to further boost image quality.

SNR is significantly increased over that of Cartesian EPI MRE (110% increase). This increased signal means signal dropout is no longer a contributing factor when producing elastograms of the leg. Muscle structure is visible in elastograms produced by the multishot MRE technique as shown in Figure 1. Thigh stiffness values are in range with published data (1.5-2kPa) and exhibit strong inter-subject reproducibility.

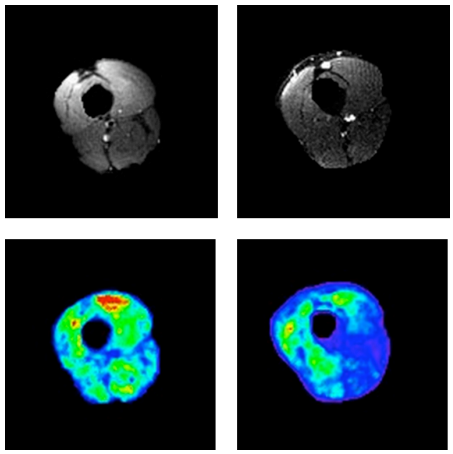

Figure 1: Clockwise from top left. Magnitude images from multishot spiral and Cartesian EPI. Elastograms of the resulting phase data from the Cartesian EPI and multishot spiral EPI.

Muscle belly delineation is present in the multishot spiral elastogram. The Cartesian EPI data exhibits significant signal dropout, producing incorrect stiffness values in the areas affected.

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PD9

VAMPIRE: Vasculature Assessment and Measurement Platform for Images of the REtina

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The black void behind the pupil was optically impenetrable before the invention of the ophthalmoscope by von Helmholtz over 150 years ago. Advances in retinal imaging and image processing, especially over the past decade have opened a route to another unexplored landscape, the retinal neurovascular architecture and the retinal ganglion pathways linking to the central nervous system beyond. Exploiting these research opportunities requires multidisciplinary teams to explore the interface sitting at the border between ophthalmology, neurology and computing science. It is from the detail and depth of retinal phenotyping from which novel metrics and candidate disease biomarkers are likely to emerge. Unlocking this hidden potential requires integration of structural and functional datasets, i.e. multimodal mapping and longitudinal studies spanning the natural history of the disease process. And with further advances in imaging, it is likely that this area of retinal research will remain active and clinically relevant for many years to come.

It is against this backdrop that the VAMPIRE project was conceived. It is led by imaging scientists and clinicians from the Universities of Edinburgh and Dundee and features collaborative input from 10 other research centres in Italy, Singapore, Australia, Japan and the US. With funding from EPSRC, MRC, Leverhulme Trust, Optos plc and the EU, we are translating cutting-edge image processing and analysis to the clinical research environment to deliver software that users without specialist knowledge can apply easily to their images to generate valuable data that they normally would not have been able to obtain. To date, our software has been used to analyse more than 10,000 images in studies investigating retinal biomarkers for cardiovascular disease, diabetes, stroke, MS, cerebral malaria, and age-related cognitive change. VAMPIRE has been the first software tool ever to analyse retinal images from UK Biobank.

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PD10

Suitability of UK Biobank retinal fundus images for automatic analysis of morphometric properties of the vasculature: a VAMPIRE study

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Purpose: To assess the suitability of retinal fundus images held in the UK Biobank (the largest retinal data repository in a prospective population-based cohort) for computer assisted vascular morphometry, generating measures that are commonly investigated as candidate biomarkers of systemic disease.

Methods: Non-mydriatic fundus images from both eyes of 2,690 participants were analysed using VAMPIRE software. These images were drawn from those of 67,716 UK Biobank participants who underwent retinal imaging at recruitment. Four operators were trained in the use of the VAMPIRE software to measure retinal vessel parameters - tortuosity and bifurcation geometry, both arteriolar and venular.

Results: Total operator time for analysing the 5,380 images was approximately 360 hours (4 minutes per image). 76% of the images were of sufficient quality for the software to process, i.e. retinal vessels could be detected with sufficient accuracy to estimate the target parameters. The remainder were of insufficient quality for the VAMPIRE software, i.e. the vessels were partially or fully obscured, preventing automatic detection by the software. The number of participants with a fundus image of at least one eye that was adequately analysed by the software was 1,604 - 60% of the total assessed.

Conclusions: This is the first ever access to UK Biobank retinal fundus images. A proportion of images in the databank were of insufficient quality for automated analysis. However, the UK Biobank has the advantage that the subgroup with fundus imaging is substantially larger than similar prospective, population-based studies and that the retinal measures derived can be studied in association with a very wide range of other data of unparalleled depth and breadth from the baseline assessment, subsequent enhancements and follow-up

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Acknowledgements: Fin This research has been conducted using the UK Biobank Resource. The collection of eye & vision data in UK Biobank was supported in part by a grant from the NIHR Biomedical Research Centre at Moorfields Eye Hospital and UCL Institute of Ophthalmology. The UK Biobank Eye and Vision Consortium is supported by a grant from The Special Trustees of Moorfields Eye Hospital.

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PD11

Retinal imaging for biomarker discovery in coronary heart disease

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Evidence shows that features of the retinal vasculature are early biomarkers of hypertension, stroke and cardiovascular disease. Our aim is to identify retinal image biomarkers of coronary heart disease (CHD).

At the Clinical Research Imaging Centre in Edinburgh and the Clinical Research Centre at Ninewells Hospital in Dundee we have captured ultra-widefield scanning laser ophthalmoscope (SLO) images of the retina from 985 participants as part of the CARMEN project. These state-of-the-art images detail the majority of the retinal vasculature (up to and exceeding 80% compared with ~15% for a fundus camera) offering unique peripheral locations for studying microvascular health and for biomarker discovery.

Automated segmentation and width estimation are the first steps needed for computation of retinal vascular features. These challenges are addressed for the first time in ultra-widefield SLO images. We have developed a novel segmentation algorithm specifically for SLO images, with a segmentation accuracy (ACC) of 96.4 (±1.4)%, a true positive rate (TPR) of 72.6 (±17.2)% and a false positive rate (FPR) of 1.1 (±0.8)%. The state-of-the-art from fundus camera is ACC 95.8 (±5.6)%, TPR 75.9 (±10.9)% and FPR 2.1 (±5.8)%. A ground-truth set consisting of 70 windows (~350 x 250 pixels) taken from 10 SLO images (3900 x 3072 pixels) was used to measure performance. We also achieved state-of-the-art width estimation (Pellegrini), with a mean (standard deviation) width bias of -0.11 (±1.36) pixels; compared to the next best performing algorithm which had bias -0.34 (±1.62) pixels.

Our tools will be used to analyse images captured from patients of the SCOT-HEART trial (NCT01149590) and participants of the TASCFORCE study. SCOT-HEART is evaluating the added benefit of CT coronary angiography in the diagnosis of suspected CHD and TASCFORCE aims to assess risk of cardiovascular events using standard SIGN guidelines plus MRI; participants with low risk score and clean MRI will be used as a control group.

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PD12

Evaluation of the "GroBa" method for arterial lumen calibre estimation in Whole-Body MRA Examinations

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In Europe, over 4 million deaths are caused annually by cardiovascular disease (CVD) and it's complications. There is therefore strong interest in the early staging of CVD (identifying its severity & distribution) to improve patient outcomes.

Contrast-enhanced Whole-Body Magnetic Resonance Angiography (WBMRA) is performed by injecting a contrast agent into the vein and acquiring MR images as the agent passes through the arteries of interest, generating high contrast in the channel within the artery where the blood is flowing (the lumen). This allows local narrowings (stenoses) to be detected and measured, providing a non-invasive, comprehensive imaging method for assessing CVD throughout the entire body. However, analysing these large datasets is both time-consuming and clostly, necessitating the development of robust, automated, quantitative analysis tools to aid clinicians with their diagnoses.

"GroBa" is a lumen calibre measurement technique developed at Dundee University, based on growing "balloons" inside the segmented vessel. GroBa has been integrated into a fully automatic system that segments the vasculature, obtains the corresponding vessel centrelines and measures the lumen calibre throughout each vessel, presenting the calibre as a colour overlay on the maximum intensity projection (MIP); all without any human intervention.

Here we present the results of a study examining a MATLAB implementation of the "GroBa" system developed at Dundee University. It was found that the current implementation works well with simple synthetic models, but has a number of issues when applied to more complex real WBMRA datasets, obtaining inaccurate measurements in many situations. Despite this, it was found that when compared to a small number of graded stenoses in large vessels the measurements fell within the expected ground truth range. We conclude with a short discussion of possible future improvements which should yield a more robust system for real WBMRA examinations.

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PD13

Gradient scaling on preclinical magnetic resonance imaging scanners assessed with a dedicated phantom

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Gradient accuracy in magnetic resonance imaging (MRI) scanners is critical for applications where geometric measurements are important biomarkers, such as infarct volume in stroke imaging. In preclinical centres standardised quality assurance (QA) protocols for monitoring this are uncommon. Only recently phantom designs have been proposed [1, 2], which however, lack temporal stability and their size limits their use with different coil configurations. We aimed to develop a simple and accurate phantom for monitoring geometric accuracy to facilitate multicentre rodent stroke studies.

A phantom was constructed from LEGO® parts (manufacturing tolerance 0.02mm) and imaged with a 7 Tesla preclinical scanner using T_2-weighted fast spin echo (FSE) sequences. A surface radiofrequency coil (72mm diameter) coupled with a 120mm bore gradient coil was used, a set-up optimised for rat brain imaging. Measurements of phantom's internal dimensions were compared with the true values and allowed the quantification of the scaling induced to images due to gradient miscalibration.

A highly significant stretching of images along all orthogonal directions was observed. The scaling factors were 0.958, 0.955, and 0.950 for the x-gradient, y-gradient, and z-gradient respectively, when each gradient was used for frequency encoding (mean scaling error 4.7±0.4%, $p<0.001$ one-sample t-test). Distortion was significant but less evident when the gradients encoded phase (4.1±0.2%, $p<0.001$). Additional data suggest that variation also exists between types of sequences. The very low cost, precise dimensions and worldwide availability of LEGO® make this phantom a wise choice for routine preclinical MRI QA for monitoring geometric accuracy. We used it to quantify gradient scaling reliably. This study will further examine the impact of imaging parameters on geometric measurements, assess the accuracy of other gradient coils, and determine the within- and between-scanner variability.

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PD14

A 4D Patient-specific Metamorphosis-based Method to Model Ischemic Stroke Lesion Evolution from Acute Diffusion-weighted to Final T2-defined Outcome

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There is considerable interest in how well acute DWI can predict the infarct on final T2-w imaging at >1month after stroke. We estimated the 4D dynamic change, from the acute DWI to the final T2-w lesion, to assess DWI predictive ability. Our model dynamically simulates the evolution of uni- or multi-component lesions.

We applied a 4D metamorphosis, modeling the morphogenesis of the acute (<6hr) DWI lesion boundary into that of the final (90 day) T2-w in 10 representative patients, dividing the 90 days into 10 equal intervals. We estimated the mean contraction and expansion deformation velocities that drive change in the acute DWI to the final T2-w boundary, focusing on areas where the DWI volume differed from the final T2-w volume (DWI\T2).

In DWI\T2, over the 10 patients, time-evolving contraction velocity values show a rapid decrease from 0.206+/-0.0091 (mean over time, mm/9days +/- sd) to 0.00097+/-0.001 with time, indicating that contracting DWI\T2 areas were very dynamic acutely and rapidly slowed. Expansion areas displayed a rapid and quasi-monotonic fall from 0.025+/-0.01 to 0.00075+/-0.00028 showing that some parts of DWI tissue had an early high expansion velocity which slowed with time, leading to appearance of newly infarcted areas not present in the acute DWI. A high correlation index ($r=0.72$, $p<0.001$) between contraction (also expansion) velocity curves of all patients shows that the 4D evolution patterns of DWI\T2 were similar between patients.

Our imaging derived 4D model of acute DWI-final T2-W lesion evolution shows a consistent pattern, with both ‘recovery’ and ‘new’ infarct happening rapidly at early time points. This confirms that a) acute DWI lesion includes salvageable tissue and is not all statically dead, b) acute DWI lesion does not include all final T2-w dead tissue and c) the method can accurately assess and quantify early treatment response, eg in clinical trials.

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PD15

Cerebrovascular Reactivity by MRI: repeatability and tolerability

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Introduction: Measurement of cerebrovascular reactivity (CVR) using BOLD MRI in response to hypercapnia is a potential surrogate of endothelial health in studies of cerebral small vessel disease. The aim of our study was to assess the repeatability and tolerability of this technique in healthy volunteers.

Methods: 1.5T BOLD MRI (GE-EPI;TR/TE = 3000/45 ms) was acquired in 13 healthy volunteers (22-50 years) during two different breathing paradigms (A: 2 x 3 min and B: 3 x 1 min spells of 6% CO_2). Physiological measurements including end-tidal CO_2 and subjective feedback were recorded, and volunteers were asked to attend a second scanning appointment in order to measure repeatability. CVR was calculated in GM and WM regions of interest [2].

Results: Mean CVR in GM/WM was higher for paradigm B (0.27/0.054 %/mmHg) than for Paradigm A (0.22/0.033 %/mmHg; $P<0.0001$); the BOLD response in WM was delayed relative to GM by 19.7 and 6.1 s respectively. Differences (mean±sd) between repeated measurements in GM/WM were -0.017±0.046/-0.003±0.011 %/mmHg for Paradigm A and -0.012±0.031/-0.001±0.009 %/mmHg for Paradigm B. Paradigm A was rated as more tolerable at 5/23 visits, while Paradigm B was preferred at 2/23 visits; neither paradigm was preferred in the remaining 16/23 visits.

Conclusion: Use of a longer breathing paradigm improves the repeatability of CVR measurements. However, this should be balanced against the need to maximise tolerability.

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PD16

Advanced statistical analysis for EEG.

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In recent years, the analysis of EEG data has moved from the selection of a few components, peaks or single tine*frequency map to a mass-univariate approach in which the whole data space is analysed. The LIMO EEG is a Matlab toolbox that gives a suite of tools based around linear modelling and robust statistics for EEG data. It allows analysis of all EEG electrodes simultaneously in the time, frequency and time-frequency domains.

Here, we report the recently developed applications, in particular the analysis of Event-Related Spectral Perturbations (ERSP) in conjunction with cluster-mass and Threshold Free Cluster Enhancement statistical methods to correct for multiple comparisons.

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PD17

A varactor-tuned RF coil for nuclear quadrupole double resonance with Fast Field-Cycling MRI

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Fast Field-Cycling magnetic resonance imaging (FFC MRI), being developed at the University of Aberdeen, allows for an additional image contrast originating from the relationship between a spin's relaxation rate and the external field strength [1]. Features in the acquired dispersion plots, known as quadrupole peaks, have been shown to reveal information regarding the chemical composition of the sample being imaged [2]. This has applications for the in vivo detection and quantification of medical conditions such as thrombosis and osteoarthritis for which data has already been obtained by Broche et al [3-4].

Previous research has focused solely on quadrupole peaks caused by Nitrogen-14 which is a prevalent constituent of many organic molecules, especially proteins; however, there are a number of other quadrupolar nuclei which could be studied. Further to this, double resonance techniques established in solid-state nuclear magnetic resonance (NMR) could allow for much more sensitive detection [5] of relaxation caused by quadrupole interactions which would enable biologically scarcer nuclei to be utilised.

The irradiation frequencies required for double resonance experiments can span over a few MHz and, as such, it is necessary to design and construct an RF coil capable of covering this range of frequencies. Through integrating a varactor diode within a series-resonance circuit it was possible to change the RF coil's resonant frequency by applying a DC voltage across the diode. In order to vary the voltage given to the varactor a 16-bit DAC715 Digital-to-Analogue Converter was used in association with two 8-bit 74HC595 shift registers, controllable through three Transistor-Transistor Logic (TTL) lines from a commercial console (MR Solutions Ltd., U.K.). An anti-series/anti-parallel varactor set up, as described in [6], was used in order to minimise second and third-order distortion of the varactor's capacitance caused by the applied voltage. In order to use the coil and the control circuit simultaneously it was important to separate the DC control voltage and the AC used to drive the RF coil. This was achieved by placing large value capacitors (1000 pF) either side of the varactor and RF chokes on the control voltage lines. This design has allowed selection of a specific resonance frequency of an RF coil to be performed during a pulse sequence such that it can be made to match the frequency of the RF field to be irradiated.

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PD18

Compensation of the parasitic magnetic fields in Ultra-Low Field Cycling NMR relaxometry

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Introduction: In Fast-Field Cycling (FFC) MRI the field switches to different levels, allowing for the measurement of T_1 or T_2 over a range of fields. Ultra-low FFC aims to extend the minimum values of the applied field in the area close to zero for the investigation of the slowest motional processes that occur in polymers and complex structures in tissues.

Aim: To estimate and compensate for the parasitic magnetic fields that come from external sources and interfere with the field applied by a benchtop FFC relaxometer (SMARtracer, Stelar s.r.l.).

Method: Approximate values of the magnitude and orientation of the longitudinal and transverse component of the parasitic fields (B_{ex_long} and B_{ex_tran} respectively) are obtained with the use of a Gaussmeter (GM05, Hirst Magnetic Instruments Ltd). The precise determination is based on the way magnetization evolves (plotted with the use of Matlab) with the application of FC experiments in the ultra-low range. For the estimation of B_{ex_long} the applied field B_o varies over a range of few hundreds of Hz around the value measured by the Gaussmeter. Compensation (B_o=B_{ex_long}) is achieved when magnetization is precessing around B_{ex_tran} as opposed to decaying exponentially in the case of $B_o \neq B_{ex\_long}$. B_{ex_tran} is then determined with the application of a field B_{tr} that rotates along the transverse plane. Compensation (B_{tr}=B_{ex_tran}) in this case is achieved at the minimum frequency of the precessions observed.

Results: Measurements with the Gaussmeter indicated B_{ex_long}=550 Hz and B_{ex_trans}=250 Hz with daily variations in the order of ±50 Hz. However with the application of these values in the method described above the behavior of the magnetization does not allow for an accurate compensation of the parasitic fields yet.

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PD19

Laser-plasma wakefield accelerator driven production of copper-62, a positron emitter used in medical imaging

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The laser-plasma wakefield accelerator (LWFA), a compact source of quasi-monoenergetic, high energy electron beams has the potential to be utilised for the production of medical radioisotopes. In this study we demonstrate the ability of LWFA technology to drive a photonuclear reaction that is stimulated by high energy bremsstrahlung photons created when the LWFA electron beam (energy 130 MeV, charge 5 pC) is directed through a tungsten or tantalum convertor. Copper-62 (^{62}Cu) was produced from Zinc-64 (^{64}Zn) via (g,*np*) reaction using a natural zinc target. With a pulse repetition rate of 1 Hz, 18 kBq of ^{62}Cu were produced after 900 shots. A comparable amount of ^{63}Zn (half-life 38 mins) was produced via (g,*n*) reaction, in this proof-of-principle experiment. The experimental results are compared with simulations performed with FLUKA Monte Carlo code.

Acknowledgements: We acknowledge support of the U.K. EPSRC (grant no. EP/J018171/1), the EC's LASERLAB-EUROPE/LAPTECH (grant no. 228334), EuCARD-2 (grant no. 312453) and the Extreme Light Infrastructure (ELI) European Project. PL is in receipt of a studentship jointly funded by the EPSRC and the SINAPSE Collaboration (www.sinapse.ac.uk), a Pooling Initiative funded by the Scottish Funding Council and the Chief Scientist Office of the Scottish Executive. We thank D. Clark and T. McCanny for technical support.

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PD20

Next Generation Fibre-Based Molecular Optical Molecular Imaging- Introducing the PROTEUS Project

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Universities of Edinburgh, Heriot Watt University and The University of Bath

The PROTEUS project is the UK's largest optical imaging project geared towards clinical application. Funded by the EPSRC and launched in October 2013, it brings together a multidisciplinary team of chemists, clinicians, biologists, engineers, optical physicists, image analysts, machine learners, signal processors, NHS partners, Industry and commercialisation support to deliver a transformative point-of-care immediate sensing device for pulmonary critical care. The team comprises 16 Post Doctoral Scientists, 24 PhDs and 10 Investigators with 200 man years of effort focussed on developing a next generation platform. PROTEUS will develop a Fibre-based Optical Sensing and Imaging Platform (FOSIP) that will provide ground-breaking dynamic sensing of key physiological and pathological events in the distal lung and blood of critically-ill ventilated patients that will lead to significant healthcare improvement.

FOSIP aims to allow clinicians to simultaneously and dynamically sense and image multiple pivotal physiological and pathological targets in the distal lung and in the blood of critically ill ICU patients. This will be achieved through the integration of fibre-based multiplexed optical sensing capability with unique Surface-Enhanced Raman Spectroscopy (SERS) to measure physiological parameters and fluorescent molecular SmartProbes to allow simultaneous multiplexed real-time monitoring of biological targets via a single optical fibre inserted directly into an arterial/standard blood sampling-line and via pulmonary micro-endoscopy and the local instillation of 'microdoses' of exquisitely sensitive and disease target specific SmartProbes.

Acknowledgements: EPSRC

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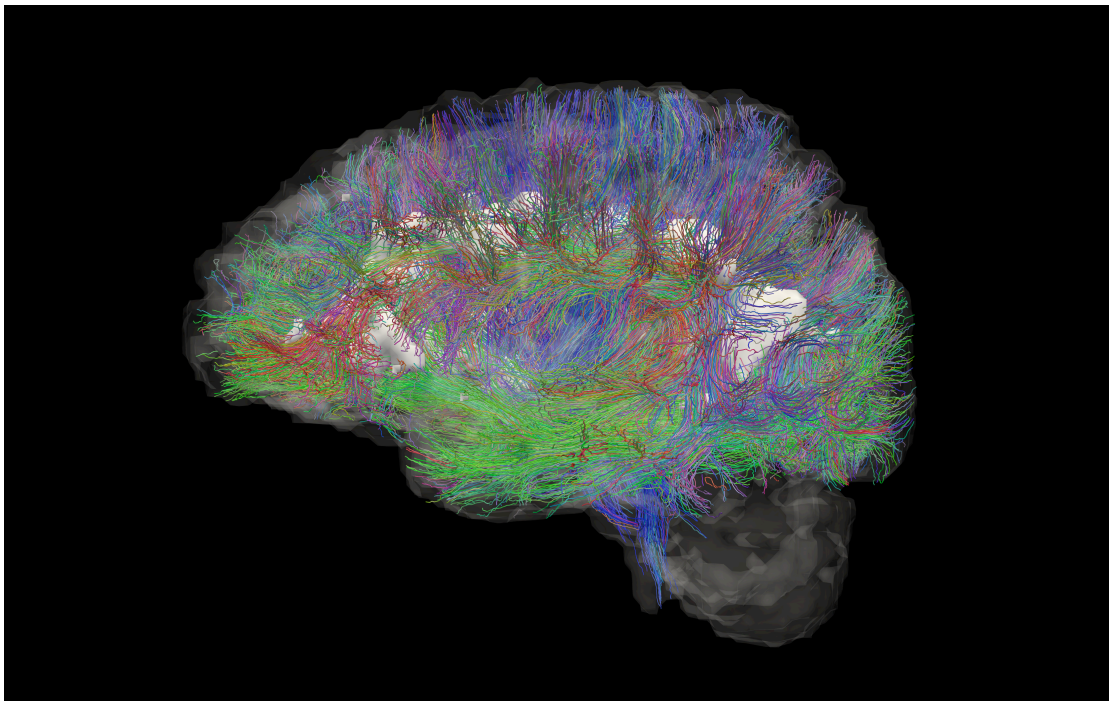
PROFFERED POSTER ABSTRACTS

APPLICATION OF ADVANCED IMAGING:



'Image of whole brain white matter and white matter hyperintensities obtained using diffusion and structural MRI in a Lothian Birth Cohort 1936 subject. Tracts running left/right are coloured red, anterior/posterior green and inferior/superior blue; the white matter hyperintensities are coloured white.'

Courtesy Mark Bastin

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PA1

Brain Morphological biomarkers of fatigue in rheumatic disorders: an sMRI study

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Background: There is growing evidence that inflammatory rheumatic disorders, such as Vasculitis, can have adverse effects on the brain. Fatigue is an unexplained, persistent, or relapsing fatigue that cannot be explained by other medical conditions. 75% of patients who have granulomatosis with polyangiitis (GPA), a subsection of Vasculitis, complain of fatigue. **Aim**: To determine whether there are structural alterations in white matter associated with GPA compared with a control fatigue population. We hypothesise that fatigue is associated with volumetric changes in the white matter.

Methods: Fourteen patients with GPA and 14 controls all with fatigue, and 14 GPA non-fatigued patients were examined with high resolution 3D T1-weighted magnetic resonance imaging (MRI). Fatigue was defined as self-reported fatigue >3 months and a score >3 on the Chalder fatigue scale (CFS), an 11-item tool designed to quantify core aspects of fatigue (range 0-11, with high scores indicating high levels of fatigue). Mean age was 58.6±15.1 and 53.6±11.4 years for fatigued GPA and controls respectively, and 51.6±13.7 for non-fatigued GPA. High resolution structural scans were processed using "freesurfer". Volumes were corrected for age, gender, and total brain volume and an ANCOVA test with correction for multiple comparisons was used.

Results: GPA-Fatigue showed significantly greater ($p<0.05$) right hemisphere cortical white matter volume compared with **Control-Fatigue**. **Non-Fatigue GPA** showed significantly reduced ventricle volumes compared to **GPA-Fatigue,** particularly in right lateral ventricle, 3rd ventricle, left Inferior lateral ventricle and right choroid plexus. Furthermore, significant lower volumes were also found in left hemisphere cortical white matter volume, right hemisphere cortical white matter volume, and total cortical white matter volume compared with **GPA-Fatigue** ($p<0.05$). No other significant differences were found at this stage.

Conclusion: This study indicates that there are differences in cortical white matter volumes between fatigue and non-fatigued GPA patients. Furthermore, it shows a significant difference in right hemisphere cortical white matter volume in fatigue GPA compared with fatigue control.

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PA2

Relationships between white matter integrity and information processing speed in the ageing brain

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Cognitive ageing and loss of mental abilities are one of the most feared aspects of ageing. A degree of mental decline is associated with normal ageing in absence of any neurological diseases like dementia or Alzheimer's disease. It has been hypothesized, and supported by a number of studies, that cognitive deterioration might be due to cortico-cortical disconnection in the brain, i.e. white matter deterioration, neuronal cell death and white matter hyperintensity formation and growth. In this paper we present the results from a study performed on Wave 2 diffusion MRI data (age 73 years) from the Lothian Birth Cohort 1936 which investigates links between brain white matter deterioration and decline in information processing speed. We found that all five measures of information processing speed included in the analysis were significantly associated with white matter FA across the whole brain using voxel-based analyses (TBSS). Age 11 IQ was added as a covariate to the regression model as a measure of intelligence prior to age and lifestyle related cognitive decline; we have shown that in some (but not other) models it was significantly associated with age 73 white matter FA. Several age-related gender differences were identified in the course of the analysis: females had higher white matter integrity in the genu and splenium of corpus callosum, while males had higher FA in mid-brain subcortical areas. Overall these data show that white matter integrity, as measured by FA, is a significant predictor of information processing speed in old age.

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PA3

Empathy correlates with insula and cingulate cortex activity during encoding but not enactment of manual imitation

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Imitation is thought to be closely related to empathy, as both processes involve simulation and interpretation of another's intentions, yet it is not known what neural mechanisms might mediate this relationship. Adaptation of a touchscreen to the Magnetic Resonance Imaging (MRI) environment enabled us to investigate how empathic ability relates to neural activation during kinematic imitation.

18 participants were asked to draw shapes based on videos of a model drawing, without seeing the actual shape. During functional MRI, videos were shown with either the model drawing (Imitate) or a dot tracing out the same shape (Ghost), and participants drew on an MRI-compatible touchscreen with their finger to copy the shape and speed being demonstrated. They also completed the Empathy Quotient (EQ; Baron-Cohen, 2004).

Overall, EQ correlated positively with brain activity during Imitate > Ghost in right frontal gyrus, insula, medial temporal gyrus and putamen. After separating instances where participants were watching from those where they were drawing, it was further found that EQ correlated positively with Imitate-Drawing > Ghost-Drawing in the right hippocampus only, but much more extensively with Imitate-Watching > Ghost-Watching in the bilateral insula, anterior cingulate, left medial frontal lobe, calcarine sulcus, midcingulate, superior temporal lobe and right caudate. EQ was not correlated to imitative performance, eliminating the possibility of this being a mediating factor.

When encoding a model's manual action with the goal to imitate it, people with greater empathic abilities make greater use of areas traditionally associated with empathic emotional responses. This is in contrast with the enactment component of imitation whereby only memory is implicated in the relationship. These findings suggest that the link between manual imitation and empathy is best explained by action perception activating viscero-motor mechanisms in more empathic individuals rather than a simulation mechanism.

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PA4

Modifiable life-course determinants of reserve in cognitive aging: a systematic review

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Background: Cognitive reserve (CR) is defined as a moderator which allows an individual to preserve cognitive functions despite underlying brain pathology. To study CR properly, three measures have to be performed: neuropathology, cognitive performance and moderating factors which might explain this discrepancy. There is no consensus of what determinants are of greater importance and whether specific CRs are malleable throughout a life-course. The aim of this review was to identify modifiable life-course factors which protect older individual from expressing cognitive decline despite the presence of brain pathology. **Methods:** A systematic review search was performed in MEDLINE, EMBASE and PsycheInfo (no date restriction). The search strategy reflected the synonyms of CR. Only studies which included in a single model the measurements of biomarkers underlying dementia-related neuropathology, cognitive function test, and factors providing CR were included. **Results:** 39 studies out of 9,229 screened records met our inclusion criteria. Education was examined the most and in 23 out of 28 studies was classified as a reserve against different neuropathologies and across the spectrum of cognitive functions. Both occupation and pre-morbid cognition provided reserve in 5 out of 6 studies. Childhood intelligence, bilingualism, early linguistic ability, personality and life-time SES were assessed only once and the first four were determined as reserve factors. **Conclusion:** This review demonstrates that education provides reserve against brain pathology. Future research should examine what specific features of education might provide greater reserve, look at the interactions between education/occupation/pre-morbid IQ in providing reserve and explore what other aspects of early-life environment contribute to CR in late-life.

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PA5

Quantification of subtle blood-brain barrier permeability in white matter using DCE-MRI

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Recently, there is growing interest in the application of dynamic contrast-enhanced MRI (DCE-MRI) to pathologies associated with subtle blood-brain barrier (BBB) permeability, such as white matter disease. The purpose of this study was to quantify BBB permeability in normal-appearing white matter (NAWM) and white matter lesions (WML) using model-based and model-free estimations of permeability.

183 mild stroke patients underwent DCE-MRI (1.5T, spoiled gradient echo, TR/TE/FA=8.2ms/3.1ms/12°) with 20 post-contrast (0.1 mmol/kg Gd-DOTA) acquisitions over 23 minutes; an additional acquisition (FA=2°) was acquired for T1 estimation. Following alignment of the dynamic series and tissue segmentation, signal enhancement curves over time were generated and converted into contrast agent concentrations. We fitted the Patlak model to the curves in order to estimate the pharmacokinetic parameters K^{Trans} (volume transfer constant) and v_p (fractional plasma volume). Moreover, we calculated the area under the curve (*AUC*) and the late slope of the curve ($m_{5\text{-}23}$), representing non-model based approaches.

All four calculated parameters were significantly higher in WML compared to NAWM (Wilcoxon's signed-rank test P<0.0001). We found a strong positive correlation between $m_{5\text{-}23}$ and Patlak's K^{Trans} (Pearson's ρ=0.73, P<0.0001), while showing a moderate negative correlation with v_p (ρ=-0.57, P<0.0001). The *AUC* values were shown to be positively correlated with K^{Trans} (ρ=0.50, P<0.0001) and v_p (ρ=0.56, P<0.0001). There was no correlation between the two model-free estimates *AUC* and $m_{5\text{-}23}$ (ρ<0.1, P=0.27).

This study illustrates that model-free measurements show a correlation with pharmacokinetic parameters. Hence, in situations with unclear underlying physiology or low temporal resolution, model-free estimates are a robust alternative to pharmacokinetic modelling. All parameters suggest that permeability is higher in WML than in NAWM. This gives further insight into subtle brain tissue changes with white matter disease and could be used to investigate whether an underlying pathology of the BBB is present in mild stroke.

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PA6

MRI of Pregnant Mice and its Application to the Foetal Brain *In Utero*

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MRI has been used *in vivo* to measure murine placental perfusion [1] and foetal development [2], however currently there are no reported methods in the use of MRI to study the mouse foetal brain *in utero* during pregnancy. We have developed novel protocols for both Proton Magnetic Resonance Spectroscopy (^{1}H-MRS) and T2* mapping techniques which are being applied successfully to the study of foetal brains of mice *in vivo* at late gestational (E16) ages.

^{1}H-MRS - Premature babies are particularly vulnerable to brain injury [3]. In a mouse model of preterm birth, we used ^{1}H-MRS to study the biochemical and metabolic profile in foetal brains *in utero* (Figure 1).

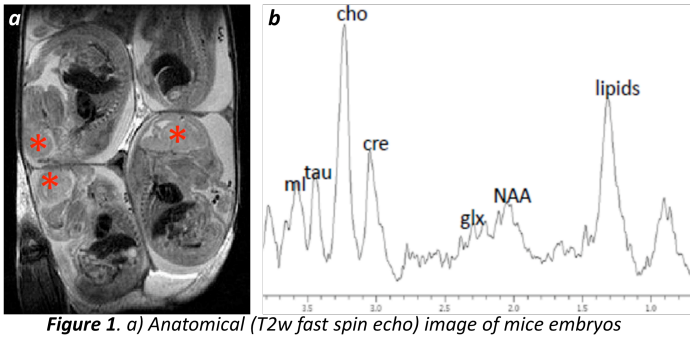

Figure 1*. a) Anatomical (T2w fast spin echo) image of mice embryos and b) ^{1}H-MRS spectrum of a control mouse foetal brain at E16 (*)*

T2* Mapping - The complement system is involved in the pathogenesis of numerous inflammatory diseases [4]. We have developed an MRI based method that could be applied to the noninvasive detection of complement deposition in the foetal brains of preterm mice.

To our knowledge, these are some of the first MRI studies involving foetal brains during pregnancy in mice *in utero*. Increased levels of glutamate in foetal brains in a mouse model of preterm birth have been detected. This ability to non-invasively measure metabolic abnormalities in a preclinical pregnancy model has the potential to be translated to the clinic as a biomarker for bad pregnancy outcomes in humans and explain the neurodevelopmental disorders that can be experienced in life by babies born prematurely. There is also the potential to be able to measure increased brain complement deposition in preterm mouse foetuses by MRI using SPIO-conjugated anti-complement antibodies which could provide a direct indicator of foetal brain tissue inflammation *in vivo*.

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PA7

Independent effects of emotional valence and arousal on source memory.

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Examining how emotional experience affects human memory has interested cognitive neuroscientists in recent years. When stimuli such as photographs containing some emotional content are used in memory experiments, previous research suggests that the arousal elicited by the stimuli has a bigger effect on memory than the valence (i.e., negative/positive). In the typical experiment, however, emotionally arousing stimuli are compared to neutral stimuli such that both arousal and valence differ between experimental and control conditions. While there has been a general pattern of memory enhancement by emotion reported, the independent effects of arousal and valence have rarely been investigated. MacKenzie, Powell & Donaldson (*in press*) equated arousal between conditions and found a general pattern of source memory impairment for emotional scenes. On this basis it might be inferred that differences in arousal between emotional and neutral conditions explains why memory enhancement by emotion has been so widely observed. Here, we will describe experiments investigating the effects of arousal and valence on source memory. Both experiments involve analysis of Event-Related Potentials and use of geometric patterns superimposed on scenes during encoding which need to be retrieved when scenes are presented alone later at test. In Experiment 1, arousal was carefully manipulated while valence was held constant, and it was predicted that high arousal scenes would be recollected better than low arousal scenes, and that this recollection benefit would be manifest both in source memory performance and the magnitude of the left-parietal ERP old/new effect. Contrary to our predictions, however, arousal did not affect recollection. In Experiment 2, which is currently underway, we are manipulating the valence of scenes that are matched for arousal, and based on the memory impairment observed by MacKenzie *et al*. we predict that recollection will be enhanced for positive scenes with respect to negative scenes.

Acknowledgements: Tim F. Powell, Emma Neilson, Erminia Fiorentino, SINAPSE, University of Edinburgh

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PA 8

Do poor adult glycaemic control and hypertension link childhood poverty to increased late-life brain pathology?

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Poor childhood socio-economic circumstances (cSEC) increase the risk of brain hyperintensities and smaller hippocampi during late life (1,2). Hypertension and poor glycaemic control (GC) are risk factors for these markers of brain deterioration and are programmed by early life stress (3). We examined the hypothesis that childhood poverty indirectly influences late-life brain pathology through impaired adult GC and hypertension. Members of the Aberdeen Birth Cohort of 1936 were asked their father's occupation in 1947 and this was graded by status (4). At age 68, brain MRI was performed. T2 and FLAIR images were used to assess WMH burden and T1 images were used to quantify hippocampal volumes. Plasma glucose and insulin levels were measured at age 64y. Hypertension status was assessed by medical history or testing. Relationships between imaging biomarkers, cSEC and adult diseases were examined using correlation coefficients, general linear and structural equation models.

Poor cSEC did not correlate with late life measures of GC or hypertension ($p>0.05$) but was associated with WMH burden and smaller hippocampi ($r=0.15$, $p<0.05$; $r=-0.18$, $p<0.01$). Hypertension and elevated glucose correlated with WMH burden and smaller hippocampi. Linear models suggested that hypertension and cSEC, but not GC, independently affected WMH burden and hippocampal volume. Structural equation modelling supported the finding that hypertension and cSEC are independent risks for WMH, but found only cSEC significantly influenced hippocampal size.

We find no evidence that the correlation between cSEC and brain pathology is mediated through adult metabolic disease. Poor cSEC is a robust, independent risk factor for late life brain pathology and probably programmes resilience to late life brain deterioration during the perinatal or childhood period.

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PA9

Effects of physical exercise on mediating affect and behaviour: a systematic literature review of neuroimaging studies

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Introduction: It is commonly believed that physical exercise improves affective states, however, self-report clinical trials are inconsistent. Electrophysiological studies have used electroencephalogram (EEG) to provide a more quantitative measurement of the affective benefits of exercise. While these studies demonstrate effects of exercise on the brain, they have focussed on gross hemispheric disparity, and as such lack the power to localise effects. Other neuroimaging methods though, can identify more specifically which brain areas are most affected by exercise and how they relate to behaviour.

Aim: To provide a systematic review of the literature covering the effects of exercise on mood and behaviour, identifying key brain regions affected by exercise.

Method: A literature search was conducted on five electronic databases: Embase; MEDLINE; Web of Knowledge; Cochrane Library; and PsycINFO.
Results: 2639 articles were retrieved from the initial search. After exclusion criteria were applied, seven relevant studies remained. Four studies used functional MRI, one used PET imaging, one MRS, and one structural MRI. Most consistent effects were located in the left insula, anterior cingulate cortex, and middle cingulate cortex.

Discussion: The insula is mostly implicated in reward processing studies, and seems to be related to sensitivity to rewards. As sensitivity increases, BOLD activity decreases. It is possible this improves structural stability, but more studies are needed to replicate this finding. In mood related studies the cingulate cortex has reduced BOLD signal after exercise, while another has correlated ACC opioid levels with euphoria. This suggests the cingulate cortex is involved in mood processing. Studies have mostly used affective scales as a secondary measure, so more are needed to investigate this effect directly.

Conclusion: Findings are tentative, but the insula is implicated in reward sensitivity and the cingulate cortex in emotional processing. More studies are required in this field to confirm these relationships.

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PA10

Cross-domain control in semantic and episodic memory: Evidence from simultaneous EEG-fMRI

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Recent functional neuroimaging research has highlighted the importance of cognitive control in the domain of memory evaluation, yet neural substrates which differentially support control- and memory-specific processes have not been dissociated. A related question with relevance to theories of cognitive control is whether control is signalled in analogous fashion across different processing domains. We hence employed a simultaneous EEG-fMRI paradigm involving two decision-making tasks that were equated for underlying controlled processing, but which differed in the processing domain being evaluated: the semantic (pleasant/unpleasant?) and episodic (old/new?) memory tasks. In both tasks, participants had to decide if the status of to-be-judged words matched the status of preceding cue screens. 'Mismatch' trials heightened cognitive control relative to 'match' trials, as confirmed by behavioural slowing of reaction times and reduction of response confidence for mismatch trials. Standard task-evoked fMRI BOLD analyses revealed a network of 'episodic control' regions in which activation increased for mismatch compared to match trials. EEG analyses of the event-related potential (ERP) yielded two central-parietal positivities, emerging at 'early' and 'late' trial stages respectively, which differentiated mismatch from match trials across both task domains. The imaging modalities were subsequently integrated by using the averaged ERP amplitudes to predict the BOLD response on a trial-by-trial basis. This final set of analyses revealed positive ERP relationships for two episodic control regions: left thalamus (with both 'early' and 'late' ERPs) and left inferior frontal gyrus (with the 'late' ERP only). These findings reveal the neural substrates of cross-domain cognitive processing, and raise important implications for theories of memory and cognitive control.

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PA11

Incidental Findings on Brain MR Imaging in Older Community-dwelling Subjects are Common but Serious Medical Consequences are Rare. A Cohort Study

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Background

Incidental findings occur in approximately 3% of neuroimaging research volunteers, but data on prevalence is largely derived from younger subjects (1). Incidental findings cause anxiety and may have lifestyle or financial consequences. Improved estimates of the frequency of incidental findings on brain imaging are required to clarify the risks and benefits to inform older research participants. We examined the MRI results of The Lothian Birth Cohort 1936 (LBC1936), community-dwelling older subjects, to determine the prevalence of incidental findings at about age 72.

Methods

LBC1936 participants, aged 71-74 years, underwent brain MRI including structural T1-, T2-, T2*- and FLAIR-weighted sequences. These scans were reported by a consultant neuroradiologist (JMW) after being transferred to the national PACS. The imaging reports were reviewed (EMS) and incidental findings (vascular, neoplastic, developmental, other, intra- and extra-cranial) were extracted. Leukoaraiosis and atrophy were not included in the present analysis as they were frequent and were measured separately using qualitative scales.

Results

Amongst 700 subjects with any form of structural imaging, there were 281 findings including 5 aneurisms (0.7%), 5 meningiomas (0.7%), 3 pituitary tumours (0.43%), 1 intracranial tumour (0.14%), 4 extracranial tumours (1.14%), 85 old infarctions including lacunes (12.1%), 7 old haemorrhages (1%), 39 microhaemorrhages (5.57%) and 16 developmental abnormalities (2.28%). Several subjects had more than one abnormality. These findings resulted in 1 urgent (giant MCA aneurism) and 9 routine referrals (1 meningioma, 2 pituitary tumours, 1 cerebellar tumour, 2 salivary adenomas, 2 aneurisms and 1 mastoid problem), while 271 subjects did not require any follow up.

Conclusions

Brain incidental findings are very common in older people, but most do not require intervention. Ethical considerations should balance the risks (e.g. increased anxiety, etc.) against early intervention which may prevent further illness such as aneurism bleeding. Volunteers need to be informed of the potential for incidental findings in the consent procedure and researchers should have procedures in place to deal with any serious (albeit infrequent) conditions.

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PA12

A longitudinal study of human brain complexity and cognitive decline in ageing

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Brain morphological changes occur during ageing together with cognitive decline while successful cognitive ageing is associated with higher cortical volumes. The purpose of the current study is to examine if the individual differences in white matter complexity are also associated with differences in cognitive ability in a well-characterized group of healthy people - the Aberdeen 1936 Birth Cohort.
White matter complexity and brain volumes were extracted from brain magnetic resonance images at both 68 and 73 years. Five cognitive domains were examined at both ages through a battery of cognitive tests: reasoning - Raven's Standard progressive Matrices, information processing speed - Digit Symbol Score, memory - Auditory Verbal Learning Test, visuospatial function - Block Design, executive functions - use of objects. Childhood ability was measured at age 11 using the Moray House Test.

Using a multilevel linear modelling approach, we conclude that individual decreases in late life white matter complexity are not associated with differences in executive function but are linked to information processing speed, auditory-verbal learning, and reasoning in specific models-with adjustment for childhood mental ability. We have also observed that greater white matter complexity is associated with retention of cognitive ability across the lifespan and individual differences in ability in late life.

The results indicate that brain complexity may be a measure of resilience to cognitive decline and allow us to hypothesise that those with less structural complexity may be more vulnerable to cognitive decline, mild cognitive impairment and dementia.

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PA13

Identifying novel structural imaging biomarkers in patients presenting with minor stroke symptoms

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Introduction: The diagnosis of minor stroke poses significant challenges, often lesions are small and difficult to detect during diagnostic investigations. Magnetic resonance imaging is frequently used in such cases, however, in up to 40% of cases this remains insufficient to give a clear-cut diagnosis. Voxel-based morphometry (VBM) has previously been applied in studies of stroke patients detecting significant differences in grey matter (GM) volume at a group level. This study aims to investigate whether such analysis methods applied to a group of DWI positive minor stroke patients provide any additional information.

Methods: High-resolution T_1 structural images were collected for 10 minor stroke patients and 10 healthy controls. The images were brain extracted and segmented prior to non-linear registration of the GM images to the MNI-152 space using FSL. A study specific GM template was created, with the images being averaged and flipped across the x-axis to ensure symmetry. The GM images from each subject were non-linearly registered to the template followed by smoothing. Lastly, permutation tests were used to perform threshold-free cluster enhancement to correct for multiple comparisons.

Results: The VBM analysis showed significant differences in GM volume (FWE-corrected; $p<0.05$). Specifically two clusters showed decreased GM volume in minor stroke patients relative to controls.

Conclusion: The changes detected accord well with existing studies, which have shown decreased GM in stroke patients previously. That such changes are also present in patients who have suffered minor strokes implies that this may be a potential approach in furthering our understanding of this condition, particularly in relation to conditions such as transient ischaemic attacks and migraines that can closely mimic the symptomatology. Further work is required to substantiate whether the changes are a consequence of minor stroke, with particular focus on what bearing the position of the lesions have.

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PA14

White matter hyperintensities variation with age and grey matter changes in migraine with aura

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Introduction: White matter hyperintensities (WMH) are frequently identified in magnetic resonance imaging (MRI) amongst individuals presenting with migraine symptoms. Differences in grey matter (GM) volume have also been identified previously in migraine patients. However, such differences are not routinely assessed in patients imaged as part of a diagnostic clinical pathway. This study assessed whether there are significant differences in grey matter volume in migraine with aura patients, who also display visible WMH lesions on structural scans and whether such changes may be clinically relevant.

Methods: T_1-weighted images were collected for 25 patients diagnosed with migraine with aura after scanning and 13 controls with no known neurological problems. Voxel-based morphometry (VBM) was performed using FSL, permutation tests were used to correct for multiple comparisons. WMH were assessed for the patients on T_2-weighted and fluid-attenuated inversion recovery (FLAIR) images by two blinded clinically trained assessors. The Scheltens semiquantitative scoring scale was used, which provides detailed information regarding the anatomical location of WMH.

Results: The Scheltens score positively correlates with age (Pearson; $r=0.722$; $p<0.01$). The VBM analysis found significant differences in GM (FWE corrected; $p<0.05$). A cluster of 19 voxels showed increased GM volume in the left thalamus of migraine with aura patients relative to controls.

Conclusions: The difference in the thalamus, associated with sensory processing, accords with previous studies that detected increased GM in pain processing areas of migraine patients. This study demonstrates the potential relevance of structural changes in migraine patients with aura. In particularGM differences could be relevant to the condition, with a sufficiently well defined group it may be possible to localise the differences to a thalamic nucleus to determine whether they directly relate to symptomatology. Further work is required to investigate these changes, in particular whether their presence predisposes to or is a side-effect of migraine with aura.

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PA15

Basal ganglia perivascular spaces are associated with reduced von Willebrand Factor in patients with mild stroke – evidence of cerebral endothelial dysfunction.

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Background

Perivascular spaces (PVS) are associated with cerebral small vessel disease (SVD). Recent studies suggest that associations of PVS with inflammation and blood brain barrier permeability. We assessed risk factors for PVS and associations with peripheral blood markers of endothelial function, inflammation, and haemostasis in patients with mild stroke.

Methods

In prospectively recruited patients with recent mild ischemic stroke, we investigated the influence of age, sex, hypertension, diabetes and smoking on the severity of PVS in the basal ganglia (BG PVS) seen on T2-weighted magnetic resonance imaging. We assessed whether plasma markers of endothelial function (von-Willebrand factor, vWF; intracellular adhesion molecule 1), inflammation (interleukin-6, tumor necrosis factor alpha, C-reactive protein) and thrombosis (fibrinogen, prothrombin fragments 1+2, thrombin-antithrombin complex, tPA and D dimer) were associated with BG PVS count or volume. We used a validated semi-automated method to measure BG PVS count and volume. We tested uni- and multivariate associations.

Results

In 100 patients (median age 67 years, range 37 to 92), age and hypertension were strongly associated with BG PVS count (r=0.117, p=0.003; r=2.225, p=0.013). On univariable linear regression, the blood thrombosis markers thrombin-antithrombin complex and prothrombin fragments 1 and 2 were significantly associated with BG PVS count. After adjusting for age, sex, hypertension, smoking and diabetes, reduced vWF was associated with increased BG PVS count (r=-0.025, p=0.032).

Conclusion

The association of increased BG PVS count with reduced vWF is novel and consistent with dysfunctional cerebral endothelium. As vWF has recently been shown to promote cerebral endothelial flexibility, lack of vWF could explain why an increase in BG PVS occurs in cerebral small vessel disease. Quantitative PVS measurement may increase sensitivity to detect cerebral endothelial dysfunction.

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PA16

Systematic review of MR imaging characteristics of cerebrovascular disease in systemic lupus erythematosus.

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Background

Patients with systemic lupus erythematosus (SLE) are at higher risk of cerebrovascular events compared to the general population but most studies report events as 'stroke' rather than by ischemic stroke subtype. Little is known about possible associations between SLE and 'silent' small vessel disease (SVD) on imaging, which is characterised by perivascular inflammation seen pathologically. We conducted a review of published data for evidence of SVD on imaging in patients with SLE, an inflammatory arthropathy.

Methods

We used MeSH search terms in Ovid to search MEDLINE from 1980, found 448 titles and reviewed 40 papers. We extracted data on clinical characteristics of the study populations and the results of imaging.

Results

We identified 7 studies (totaling 39,630 patients with SLE) in which an increased risk of stroke was reported in SLE as compared with controls. The hazard ratios were between 1.5 and 2.0. Little information was given on ischemic subtype.

We identified 23 studies using MR imaging which indicated that patients with SLE were more likely to have brain atrophy or white matter hyperintensities than controls. However, most studies were small and most focused only on patients with neurological symptoms. Few studies collected data on traditional risk factors such as hypertension, hyperlipidemia or diabetes and none corrected for these. In two studies pathology was available and showed evidence of microinfarcts, small vessel vasculopathy, cortical atrophy, and demyelination.

Conclusion

There is an association between SLE and stroke. However, small, uncontrolled, non-risk factor corrected studies and lack of ischemic stroke subtyping limit the determination of how well imaging abnormalities relate to clinical features. The role of inflammation versus traditional risk factors has not been extensively studied but imaging features in SLE appear similar to sporadic cerebral SVD, justifying further well-controlled and adequately powered studies.

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PA17

A Magnetic Resonance Imaging Case Report on Acute Isolated Bilateral Ischaemic Pontine Infarction

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Introduction: Although pontine infarction accounts for a small percentage of all ischaemic events, it is still a serious condition that can lead to severe disability or even death. The aetiopathogenesis of isolated pontine infarcts, not attributable to a large compromise (occlusion or dissection) in the vertebrobasilar circulation territory, still remains to be fully characterised. Pontine infarcts present with different symptoms, depending on the portion of the pons that has been affected. In addition, neurological deterioration is relatively common and it has been associated with the enlargement of lesions.

Case presentation: A 49-year-old man presented with left-sided weakness, incoordination, unsteadiness, cerebellar ataxic dysarthria, and dysphonia. An admission magnetic resonance imaging scan showed an acute isolated bilateral pontine infarct, which reduced by 57.5% on the follow-up T_1-weighted scan that took place 42 days later. This reduction was also visibly noticeable when comparing the anatomical scans from the two visits and it mirrored the improvement noted in clinical assessments along with the symptoms reported by the patient. It is very interesting that in such a short time interval, under standard stroke rehabilitation care, there was more than 50% decrease in the pontine infarct. It is also of note that the patient has managed to resume his usual activities and he returned to work within six months from the onset of symptoms.

Conclusion: This case report discusses the significant clinical improvement and lesion reduction noted for a patient who presented with worsening neurological symptoms and he was diagnosed with acute isolated bilateral ischemic pontine infarction. Further studies, utilising rapidly expanding imaging technologies, are needed to provide a greater insight into the underlying aetiopathological and recovery mechanisms of pontine stroke. An improved understanding of these areas will allow for better diagnosis and also inform the development of relevant rehabilitation programs for this group of patients.

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PA18

Patient Satisfaction and Understanding of Scan Results in an MRI Neuroimaging department

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Introduction/Background

Patient satisfaction surveys can help to identify ways of improving practice, which can ultimately translate into better care and happier patients. Studies have shown, that using confidential questionnaires to collect patient feedback is necessary to identify any problems that need to be resolved in order to improve the service which we provide.

Our aims were to review the quality of our service for all patients and subjects visiting our department and evaluate how our research subjects would like their MRI scans and scan reports handled, as well as their understanding of this procedure.

Methods

All patients and research subjects attending for an MRI examination over a 3 month period were surveyed. This included private, NHS and patients referred from stroke clinic. The questionnaire comprised of two parts, the first with 15 questions measuring the patients MRI experience. The second part only to be completed by research subjects had six Y/N questions relating to their scan results. 115 subjects took part in the questionnaire.

Results

Overall patients and subjects were very satisfied with their scan experience. Areas which could be improved upon were shown to be: instructions on finding our department, explaining the scan and allowing for questions and informing patients how they would receive their results. Only 94 out of 115 participants answered question 15 (how satisfied were you with your MRI visit today) therefore accurate evaluation cannot be made.

Out of the 52 Research subjects who were asked, 40% were not told by the consenting researchers the probability of an abnormality being observed on MRI scans. Also, 50% of those asked were not told that some abnormalities present on scans may have an effect on their insurance policies.

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PA19

Intracranial lesion classification: Semi-automated MR Spectroscopy software package (INTERPRET) versus histology/clinical follow up

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Introduction

Over the last decade, the use of MR Spectroscopy has increased significantly. However it is not routinely used in clinical practice. Semi-automated software packages containing validated data have been created to try and make MR Spectroscopy more relevant to clinicians. This project aims to retrospectively analyse Magnetic Resonance (MR) Spectra, acquired in clinical practice, comparing the semi-automated software package (INTERPRET) with histology/clinical follow up. The project incorporates MR spectra collected over a 5 year period and formal histopathology acquired from biopsy. In those cases where biopsy was not undertaken clinical/radiological follow up was used as a comparator.

Results

55 patients with adequate MR spectra were identified. Cases were split into tumour and non-tumour groups. Within both groups, the INTERPRET package was unable to replicate accuracy rates published in the literature. An accuracy of 51.0% was found for the tumour group. Within the smaller non-tumour group, INTERPRET could not identify whether the lesion was tumour or pseudo-tumour in approximately half the cases.

Conclusion

Within this retrospective study, incorporating data acquired in clinical practice, I was unable to replicate accuracy rates published in the literature for the semi-automated INTERPRET MR Spectroscopy software package.

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PA20

1H MRS AS A BIOMARKER FOR PLACENTAL INSUFFICIENCY IN THE GROWTH RESTRICTED FETUS

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Placental insufficiency commonly leads to Fetal Growth Restriction (FGR) and stillbirth[1]. The current recommendation is to deliver the baby prematurely which is not without risk. As such there is a need for an acute biomarker to inform optimal timing of delivery. Placental glutamine and glutamate (Glx), detected in utero using 1H Magnetic Resonance Spectroscopy (1H MRS), could provide this. In particular we hypothesise that the ratio of Glx to choline (Cho) could be a marker of placental function.

In-utero placenta spectra were acquired from 7 FGR and 7 normal pregnancies on a 3T Siemens Verio MR system (Siemens Healthcare, Germany). The PRESS technique was employed with TR/TE/NSA = 1500ms/30ms/96, bandwidth = 2000Hz and water suppression bandwidth = 50Hz. A 20×20×40mm voxel was positioned within the placenta. Placenta spectral peak amplitudes were estimated using the Quest algorithm available in JMRUI (http://www.mrui.uab.es/mrui). Amplitude ratios of Glx and choline (Glx/Cho) were calculated. A paired t-test (Minitab® Statistical Software, www.minitab.com) with level of significance $p<0.05$ was performed to determine whether differences exist between Glx/Cho ratios of FGR and control placentas.

In each case the Glx/Cho ratio of the placenta from the FGR pregnancy was reduced ($p=0.003$) compared to that of their gestation matched control. Detection of Glx is simpler in placenta than in brain as there are no overlapping contributions from NAA in placenta. Although other metabolites (e.g. alanine, leucine) may also be detected at the same frequency range as the Glx peaks, there is evidence that Glx is present in much higher concentrations in the placenta compared to other amino acids[2].

Placenta Glx/Cho may provide an in vivo marker of placental function in these difficult to manage cases. However further testing on a larger cohort of FGR and control subjects is still required.

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PA21

3D Visualisation of 'Hotspots' of Inflammation in Abdominal Aortic Aneurysms (AAA)

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Abdominal Aortic Aneurysms (AAA) are responsible for 1-3% of deaths in men between 65 and 85 years in the western world. Repair of AAA is considered when the diameter exceeds 5.5cm. However, the size of the diameter is an imperfect criterion since 60% of AAA bigger than 5.5 cm never rupture, while 10-20% of AAA smaller than 5.5 cm do rupture. Ruptured AAA cause 80%-90% mortality, thus better criteria of AAA expansion and rupture are required. A pilot study by our group demonstrated a strong correlation between inflammation and AAA expansion with the use of Magnetic Resonance Imaging (MRI): the uptake of Ultrasmall Superparamagnetic Particles of Iron Oxide (USPIO), expressed by the R2* changes in AAA, identifies cellular inflammation and appears to distinguish those patients with more rapidly progressive AAA expansion.

We are currently expanding on the pilot data, with 350 patients involved, providing important additional information to the current simplistic gold-standard of ultrasound measurement of aneurysm diameter. More automated and robust techniques and algorithms are implemented in order to improve our image analysis. Our goal is to achieve a clinically useful tool by automating all processes possible and facilitating labour-intensive manual tasks that the clinicians still have to make. The USPIO uptake that reflects the regions of inflammation is quantified and visualised in 2D in an automated way, following manual selection of regions of interest by a trained observer. The novel realisation of the method in 3D has recently proved successful and we have achieved automatic detection of hotspots of inflammation in individual trials. Our methods are in the process of being further developed with the goal of accomplishing fully automated classification of the AAA.

These visualisation, quantification and classification techniques hold major promise as clinically useful tools that can effectively assist in the decision making process during the assessment of future AAA patients. These tools will provide clinicians with fast, reliable and unbiased data processing applicable not only to AAA, but also areas such as identification of carotid artery plaques and assessment of myocardial infarction.

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PA22

Feasibility of T1 mapping for assessing idiopathic pulmonary fibrosis at 3T.

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Introduction: Idiopathic pulmonary fibrosis (IPF) is a chronic progressive condition. Monitoring disease progression is challenging. Calculating T1 values has been used successfully to evaluate tissue fibrosis, eg. in myocardium. This pilot study examines whether this technique may be useful in the assessment of pulmonary fibrosis.

Methods: T1 mapping was performed at 3T using the Modified Look-Locker Inversion sequence in 9 patients with IPF and 13 healthy controls. All cases were imaged before and after intravenous gadolinium administration. The mean signal intensity within regions of interest drawn in areas of high resolution CT defined fibrotic and morphologically normal lung were obtained. T1 values were estimated by modelling these data with an inversion-recovery curve.

Results: The average T1 value of fibrotic lung tissue without gadolinium contrast was significantly greater than that of morphologically normal lung tissue of IPF patients (1308.9±123.4ms vs 1069.2±71.4ms; $p<0.05$) and controls (1011.4±171.9ms; $p<0.05$). Ten minutes after intravenous gadolinium administration, T1 values of lung tissue of controls were significantly lower than those of normal lung tissue of patients with IPF (484.6±40.7ms vs 618.5±40.6ms; $p<0.01$) and fibrotic lung tissue (669.7±62.5ms; $p<0.01$). Fibrotic lung tissue had a significantly lower T1 value than morphologically normal lung tissue 20 minutes after gadolinium administration (476.9±42.0ms vs 537.0±34.0ms; $p<0.05$) Normal lung tissue of IPF patients has significantly greater signal intensity than lung tissue of controls at inversion times 100ms, 180ms and 260ms before and after intravenous gadolinium administration which may represent early fibrotic changes that is not yet visible on HRCT.

Conclusions: T1 mapping at 3T demonstrates established fibrosis, and may be feasible to distinguish pulmonary tissue with early fibrotic changes, compared to normal lungs but larger samples are needed to confirm this.

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PA23

A supervised approach for classifying corneal nerves images in 4 tortuosity levels

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In vivo confocal microscopy is currently used to image corneal layers with satisfactory resolution and good contrast. Recently, a significant correlation between nerve tortuosity and the severity of diabetic neuropathy has been found. The main issue in this field is that there is no definition of tortuosity, which affects intra- and inter-observer agreement. All tortuosity indices reported in the literature propose a single mathematical formula of tortuosity combining various shape features.

We propose a novel supervised approach for the automatic classification of the tortuosity of corneal nerve images. Unlike previous methods, we apply a supervised approach to learn the combination of 3 shape features at different spatial scales extracted from individual fibres which best associates with the ophthalmologist's perception of tortuosity (annotations).

Accurate and reliable digital curvature estimation, a critical step, is achieved by an original multiple-window approach which selects the optimal window for digital curvature estimation automatically and robustly, in a range of curvature values, discretisation levels and noise. We use ordinal logistic regression to assign tortuosity values to ranked classes. A wrapper procedure is used to choose automatically the most discriminative set of features and scales.

A balanced data set of 100 images showing the corneal sub-basal nerve plexus with 4 different grades of tortuosity was made available by our clinical collaborators (Harvard authors) who also annotated the images independently.

Tests suggest that our method is capable of automatically classifying corneal nerves images in 4 levels of tortuosity with the same performance as the annotators. We find, importantly, that scale information seems to be relevant in tortuosity assessment.

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PA24

PET/CT imaging activity at Dundee's Clinical Imaging Research Facility (CRIF)

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The CRIF is located on the ground floor of the Clinical Research Centre at Ninewells Hospital and lends itself to the possibility of multi-modality imaging and image-guided procedures. It houses a Siemens Biograph mCT-128 PET/CT scanner and a Siemens 3T MRI scanner. The PET/CT is jointly funded by the University of Dundee for research and the Chief Scientist's Office as part of Scotland's National PET/CT Service. This unit comprises a 3-ring PET scanner combined with a 128-slice CT scanner.

Equipped with the latest software, the PET/CT system has the ability to acquire both static and dynamic images, as well as respiratory and ECG gated scans. Full radiotherapy positioning facilities are also available.

Since its installation in 2010, the CRIF PET/CT has been used for protocols that include:

- clinical and research PET and CT

In excess of 600 NHS PET and 200 CT scans are carried out annually, with a catchment area including Tayside, Perthshire and Fife.

- dynamic PET

Wide field-of-view PET scanning allowing the dynamic imaging of glucose uptake in primary tumours and axillary nodes for patients with cancer. Assessment of brain activity pre and post implantation of deep brain stimulator electrodes.

- diagnostic CT

The 128-slice CT scanner and dual-headed contrast injector have enabled high-resolution CT coronary angiography to detect and quantify arterial stenosis with calcium scoring, using either retrospective or prospective ECG gating. Dynamic perfusion CT, permits assessment of prognostic value of tumour perfusion in cancer

- non-clinical CT

In conjunction with the CAHiD, Art Galleries and Museums in Dundee and elsewhere, we have imaged a number of historical artefacts for providing further insight into their hidden features and internal structure.

The intent is to produce a poster representing the broad range of procedures available through the use of the CRIF PET/CT.

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PA25

3-Tesla MR imaging activity at Dundee's Clinical Research Imaging Facility (CRIF)

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The aim of this poster is to showcase the diverse and advanced capabilities of the CRIF 3T MRI scanner for clinical and clinical research applications.

We will highlight a wide range of work from head to foot, which will give an overview to researchers, participants, staff and patients of the present and future capabilities for research within the CRIF.

The CRIF MR scanner is a 3 Tesla Siemens Magnetom TIM Trio, which has been in operation since June 2008. The magnetic field strength is twice as strong as 1.5 Tesla MRI scanners that are more commonly used in clinical environments. The higher magnetic field generally allows for the faster production of high-quality, high-resolution imaging, as well as the use of advanced applications.

The MRI scanner at CRIF has facilitated the imaging cohort of multiple studies, with the main focus so far being on cardiovascular disease, cancer, diabetes and neuroscience. We will demonstrate:

- Whole Body Angiography
- Advanced coil combinations of the Siemens Trio allow for fast high-resolution imaging, used to detect atheroma and sclerosis within the blood vessels.
- Cardiac Imaging
- Images are obtained using the dedicated 32 channel cardiac coil or body matrix coils. Left ventricular analysis, aortic pulse wave velocity and segmentation of epicardial and endocardial fat have been performed.
- fMRI
- The increased SNR at 3T has been exploited in a variety of fMRI studies, including simultaneous EEG-fMRI work using a SINAPSE funded EEG system.
- DTI acquisitions also benefit from the stronger signal and sequences with 64 directions have been shown to produce good white matter tract mapping within the brain.
- We will also demonstrate high quality images of abdominal adiposity, breast perfusion, lymphangiography, brain, cardiac and prostate spectra.

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