So you want to write a grant?

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Grants

- Provide ongoing source of funding
- “Peer review” – gives validation to your ideas
- Forces critical review of literature and how your ideas fit into it
- Forces research plan to be well articulated and examined by colleagues and peers

Getting Started

- Think of an idea
- Run it by scientific and clinical colleagues
- Search literature
- Has it been done?
  - If not
    - is it feasible
    - is it affordable
    - can you do it
  - If so
    - can you improve on it?
    - are improvements likely to be significant

Finding the "Killer App"

- Wow the reviewer
  - "gee I wish I had thought of that!"
- Exploit novel technology
  - Improve existing methods
- Exciting, risky but plausible given proposed research team
- Disruptive technology
  - Enable a new approach
- Avoid "solution looking for a problem" syndrome
  - "Fishing expedition" = Kiss of Death!

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Literature survey

- Use on-line resources
  - Pubmed, Ovid, Engineering Index
- Recent review articles lead to relevant papers
- Abstracts
  - Not always necessary to read every paper in the field. Abstract often tells you what you need.
- Ref Database
  - Build up ref database (Refman, Endnote, BibTeX) during literature search
  - Reference management can be huge time sink – get it right early
  - Include all your relevant work – but balance with work from others.

Collaborators

- Researchers with experience and track record
  - Good idea to be co-applicant on your first grant.
- Clinical collaborator – very important
  - Establishes that you have a feasible clinical focus
  - That there is real interest in the technique from medical community
- Individuals with complementary skills
- More than mere window dressing
  - Should contribute to research and publications

Structure 1

(Based on CHR grant format)

- Summary of research proposal (1 page)
- Summary of Progress (1 page)
- Research Proposal
  - Background (half allotted pages i.e. 5-6)
    - Literature survey that cites your own work in context of the field
    - Preliminary results *(very important)*
    - Rationale for your proposal
      - What are the limitations
      - What needs to be done

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Structure 2

- Research Proposal (cont)
  - Research Plan (Another 5-6 pages)
    - General objectives and Specific Aims (3-4)
    - Specific Aim 1
      - Proposed Research Plan
      - Anticipated Results
      - Expected difficulties *(very important)*
      - Validation methodology incl statistical testing
      - Timeline (if appropriate)
    - Specific Aim 2 ...etc

Research Plan

- Begin – short para summarizing points in background
  - Where have current knowledge / prelim results led you?
- Rationale
  - Indicate why you are particularly well equipped to undertake this research
  - Why topic is compelling
  - Why your approach is best

Research Plan

- Write around Specific Aims
- For each state
  - Expected outcome
  - Potential Problems
  - Alternative strategies
  - Approaches/Techniques
  - Timelines
- What will experiment tell you? Why is this outcome important?
- Stick to a small number of strategies
  - If we are not successful with approach A, we will employ the methodology proposed by Smith *et al.* (2009)

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Writing Order

- Summary of Proposal
- Summary of Progress
- Research Proposal
  - Research plan
    - Aim1
    - Aim2
    - Aim3
  - Background and preliminary results

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Summary

- Set stage (1/3 page)
  - Prostate cancer kills 5,000 people in Canada per year because the screening methods lack the ability to detect potential tumours before they become aggressive. However, a new approach using the analysis of raw ultrasound signals promises a high sensitivity and specificity the the disease.....
- Present General Objectives and Specific Aims
  - Hypothesis if appropriate
    - Helps formulate how you will validate results
  - 3-4 specific aims (view each as a potential paper)

Summary

- Proposed research
  - Why you want to undertake proposed research
    - There is a rich source of information in the raw rf signals generated by a US transducer that contains tumour information, that is lost when these signals are converted into images.
  - Why you are proposing to use a specific strategy
    - Through an interaction with company X we have gained access to the rf signal processing chain – we will therefore capture these signals for on-line processing in a PC....
  - What you expect to find
- Significance
  - This work will lead to a new diagnostic imaging device that can detect potential prostate cancer and guide the physician directly to a biopsy location...It will result in the confirmation of disease xx years earlier than previously...

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Summary of progress

- Always include this
  - Even on a new grant
- Summarise previous work and progress
- Present related research results that lead to topic in grant
- Establish to committee that you have track record to do the research

How do I get preliminary results?

- Most new faculty positions will include some start-up funds
  - (if they don't you didn't negotiate hard enough!)
- Universities often have internal competitions for additional funding for pilot projects
- Side-projects through collaborations with experienced faculty.

Bottom line

- Need to convince reviewers that project is essential – better than competition in panel
  - Save more lives
  - Improve diagnosis
  - Save money
  - Achieve better accuracy/speed
  - Enable new technique
    - Less invasive surgery
    - New implant

Establish Local Review Team

- Not your collaborators
- Read your grant
- Comment on it
- Discuss it as group
- Set up review at least two weeks before deadline
- Some institutions demand internal reviews before signing off

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Layout of proposal

- CIHR (11–13 pages) + figures and refs
- NSERC (6 pages incl refs and figs)
- CHRP (10 pages incl refs and figs)
- NIH (10 pages incl figs)
- Carefully observe font, spacing and margin requirements, and page limits
  - Agencies
    - will remove excess pages
    - will disqualify grants not observing rules

The Good

surgery while the patient is awake, which either produces a response, (e.g. movement), or disrupts function, (e.g. speech arrest). ESM is believed to directly identify cortex essential for a specific task, and can be performed preoperatively in patients with implanted electrodes, or intra-operatively with the brain exposed at surgery. Currently, fMRI is being applied to reduce the need for these invasive and hazardous procedures, and Diffusion Tensor Imaging is beginning to be employed to generate images of nerve pathways that must be avoided to during surgery.

There is a clear need to develop image-based alternatives to these invasive mapping procedures. Our team has expertise in both the clinical and engineering aspects of image-guided neurosurgery, has developed new rapid MR relaxation mapping techniques for the brain, and has access to a dedicated research 3T MRI. LHSC is a National Epilepsy Referral Centre, placing us in an excellent position to pursue our research goal by integrating new imaging modalities into our mature image-guided surgery environment.

2.3 Imaging Modalities

2.3.1 MR Imaging and Relaxation Mapping

Traditional MR imaging presents images to the observer in the form of T1- or T2-weighted images, and although the images are usually dominated by one of these relaxation parameters, they are actually influenced by both T1 and T2, as well as the regional proton density (PD). As illustrated by Figure 9, in some cases, the influences of T1, T2 and PD work in opposite directions to reduce the contrast in the final image[25] and it is often preferable to analyze the data on the basis of T1 and T2 values separately. Many studies report strong correlations between abnormal T2 values and epilepsy[41,51-53,54] with some conditions being associated with abnormal T1 values as well[55,56]. Techniques recently developed in our own lab permit both T1 and T2 maps to be acquired rapidly at high isotropic resolution (~$1mm^3$)[20]. Our work on the analysis and classification of brain structure based on these maps[19,20]. Figures 4 and 5 clearly demonstrate the value of working with the raw relaxation data.

2.3.2 Diffusion-weighted (DWI) and Diffusion Tensor Imaging (DTI)

DWI computes the mean diffusivity (MD) and fractional anisotropy (FA), key parameters that describe the nature of regional diffusion characteristics within the brain. MD (the average diffusion within each image voxel regardless of direction), varies less than the FA throughout the brain, reflecting the relatively uniform density of neurons and glial cells within all regions of the brain[57]. If the diffusion-weighted sequences are executed with multiple diffusion encoding directions in a DTI sequence, tensors can be computed at each voxel. The principle components of these tensors can be interpreted as flow along white matter fibres. Tractography[44,57-62] reconstructs from DTI, the three-dimensional connectivity of the white matter fibre tracts from the apparent directions of maximum diffusivity at the voxel level. This technique offers the potential[63,159,160] for non-invasive *in vivo* visualization of tracts that relate the seizure focus to other brain areas, potentially leading to methods for isolating the seizure focus from remote cortex. Tractography can also delineate nerve fibre tracts connecting eloquent cortical areas, allowing the surgeon to avoid damaging them during the resection of the focal region. DWI and DTI have been identified as important components as an important component in the identification of epileptogenic regions in MR images[57].

2.3.3 Functional MRI (fMRI)

FMRI is widely employed to map cerebral functions non-invasively in normal subjects, and to measure the brain activation resulting from performance on different tasks. Signals elicited via the BOLD effect, allow the comparison of the regional hemodynamics under the different task conditions, which permits inferences to be drawn about the brain areas performing the task in question. Advances in safety[64] and on-line MRI artifact removal[65] now permit continuous EEG recording inside the scanner during continuous

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data acquisition[66]. It is now possible to map the brain region that shows a hemodynamic response correlating with EEG spiking[67,68].

2.3.4 Magnetic Resonance Spectroscopic Imaging (MRSI)

MRSI enables the simultaneous detection and quantitation of a number of brain metabolites using conventional MRI equipment. In patients with Hippocampal Sclerosis (HS), N-acetyl aspartate is typically reduced, while choline, creatine and phosphocreatine are elevated relative to normal controls[69]. The contralateral hippocampus may be normal or show a lesser degree of abnormality[70,71]. MRSI can detect which hippocampus is more likely to be epileptogenic in individual patients. However, long MR examination times and resolution limitations have restricted the use of MRSI to guide surgery.

2.3.5 Positron Emission Tomography (PET)

In the past, ^{18}F-fluorodeoxyglucose (FDG) PET was used to map the epileptogenic zone in MRI-normal cases. Temporal lobe epilepsy is characterized by an extensive area of reduced metabolism, typically encompassing a region much larger than the epileptogenic zone[72], and possibly including irritative and functional deficit zones. Today, MRI usually reveals a lesion in such patients[73-76]. Much of the early literature compared FDG PET to older MRI techniques with low field strength, and included few quantitative methods. Patients regarded as 'MRI-normal' in these studies may well not have proven so with contemporary MR imaging techniques.

2.3.6 Single Photon Emission Computed Tomography (SPECT)

SPECT, using blood flow markers such as HMPAO also has a long history in the field of epilepsy[77]. The typical findings in patients with localization-related epilepsy are regions of relative hypo-perfusion interictally and an ictal focal increase in perfusion. Although the interictal findings alone are too insensitive and non-specific to be useful, ictal findings are much more helpful[73,76,78].

2.4 Image Analysis for Epilepsy Diagnosis and Surgery Planning

Recently, high resolution anatomical imaging[79,80] combined with voxel-based morphometry (VBM)[56,81-83] has been employed by various investigators to identify anomalous regions in white matter (WM) and grey matter (GM). This process generally involves acquiring T1-weighted images, rigidly registering them to a standard stereotaxic coordinate space[38], normalizing their intensities to remove artifacts introduced by RF inhomogeneity,[84,85] and classifying the volumes with respect to WM, GM and CSF[86]. The volumes are then analyzed using VBM, which identifies regional differences in the volume of WM and GM.[87] However, as pointed out by Colliot et al.[56], the VBM process is subject to errors in segmentation and normalization. Therefore, rather than performing our analysis based on segmented volumes, we propose to analyze the raw relaxation maps explicitly, using the T1 and T2 data directly to compare epileptogenic brains with those of normals. This approach has two significant advantages over the traditional VBM approach: i) relaxation maps are devoid of the intrinsically troublesome shading artifacts caused by rf inhomogeneities, even when a surface coil is employed[88]. Although these artifacts can be corrected using algorithms such as "N3" [89], day-to-day variations in the absolute signal values in images from the same individual can still be apparent[88]. As illustrated by Figure 7, in the case of a surface coil there is of course a reduction of SNR as one moves away from the surface coil elements. Nevertheless, with the coil illustrated in Figure 6, the SNR at brain centre is equivalent to that obtained with a standard GE 8 channel coil; ii) if these T1 and T2 maps are used to generate synthetic T1 and T2–weighted images, subject-to-subject, day-to-day and scanner-to-scanner differences may be eliminated[26] (Figure 8).

Recent work using DTI[90,91] to compare language lateralization, indicates that the white-matter tracts computed from the DT images may be disrupted from their normal pathways by epileptogenic malformations. Gross et al.[61,92] established the validity of DTI in identifying abnormalities in focal cortical dysplasia and the limbic system, while Tessa et al.[93] have employed FA and MD maps to examine structural anomalies in TLE. Rugg-Gunn[57] at the Institute of Neurology, London, UK, recently outlined the following key issues with respect to the use of DW/DTI in epilepsy imaging:

The Bad

normal pathways by epileptogenic malformations. Gross et al[1,2] established the validity of DTI in identifying abnormalities in focal cortical displasia and the limbic system. Using a methodology similar to that described in Specific Objective 1, we will use the DTI information from patients to compute the Mean Diffusivity (MD) and Fractional Anisotropy (FA) maps that will be compared with similar information compiled from normal subjects, to identify possible focal regions. We will also reconstruct nerve fibre pathways near eloquent cortical tissue close to the projected resection region.

Methods:1. DTI volumetric images will be acquired on the same normal subjects at the same time as the relaxation mapping studies. Their DTI maps will be mapped to Standard Brain space, using the deformation fields resulting from the mapping described in Specific Objective 1. To preserve the correct tensor dimensions after warping, the correction approach described by Xu et al[3] will be implemented within the non-linear warping procedure. The result of this average atlas will be a volume whose elements contain the population means of the MD and FA of the DT images along with their standard deviations at each voxel. This dataset will be a reference volume against which patient DTI volumes can be compared.

2. From the DTI image volumes, we also will reconstruct the fibre tracts associated with the eloquent cortex in the vicinity of the epileptogenic zone. This will be accomplished by "seeding" the DTI maps with fMRI-derived language areas (Figure 10a), and reconstructing the fibres associated with these regions, following the approach recently outlined by Guye et al[4]. Important Fibres to avoid include those connecting language areas in the inferior frontal operculum and the superior temporal gyrus. We will examine whether these fibres correspond to the superior temporal gyral areas activated during language mapping. Visual fibres connecting the lateral geniculate body of the thalamus and the occipital cortex define the optic radiations. This group of fibres (Meyer's loop - Figure 10b) travels anteriorly in the temporal lobe in the roof of the temporal horn of the lateral ventricle. These fibres must be avoided during the course of temporal lobe surgery to preserve visual fields. Fibre-tract volumes will be reconstructed following Campbell et al[5], using FACT and be integrated into the surgical planning environment (See Specific Objective 5). Note that since the resolution of the raw DTI data is lower than the T1/T2 maps and any synthetic images derived from them, there is an uncertainty approximately equal to the voxel dimensions in the positioning of any fibres reconstructed by Tractography. We will indicate the SD of this uncertainty in the image presented to the surgeon by displaying a semi-transparent envelope surrounding the fibre data.

Analysis: The form of the DTI datasets will be similar to those created using RM. In this case the mean and standard deviations of the MD and FA parameters are stored for each voxel location. Again, these data will also be analyzed as described in 6.2 above to develop a second set of Z-score maps, and will also contribute to the multi-spectral mapping outlined in Specific Objective 3 below.

6.3 Specific Objective 3We expect each of the four distinct mapping techniques (T1, T2, MD, FA) to show multiple regions that demonstrate abnormalities. This multi-spectral data set is similar to that employed by our colleagues Clarke et al.[6] for analyzing carotid plaque load, and Mitchell and Rutt[7,8], the analysis of Multiple Sclerosis lesions, from multiple imaging modalities, and Ruan et al[9] for classification of cancer ous regions in the brain from multispectral MRI. We will develop a robust multi-spectral image analysis approach to enhance the sensitivity of the multi-modality imaging approach for the identification of epileptogenic tissue. In addition, we will use the Z-score maps computed in Specific Objectives 1 and 2 to provide an indication of the confidence that each of these parameters falls within the normal range.

Sub-hypothesis: Spectral-phase maps that compare multi-spectral vectors of suspected pathological WM and GM with that of normal WM/GM, will enhance regions of abnormal tissue related to epileptogenisis.

Methods: 1. The first phase in the construction of a spectral map image is the creation of multi-dimensional "feature-space" vectors for each voxel in the image volumes. In our case the four features are T1, T2, MD, FA. The image features obtained from different imaging techniques (T1, T2, MD, FA) will be incorporated into our multi-spectral analysis technique to predict the epileptogenic status of each voxel in the 3D tissue dataset. The independent features will be used in the prediction models described

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below to determine to optimal approach. Statistical prediction models to be explored include Mitchell's spectral phase approach,[10] Fisher's linear discriminant analysis (LDA)[11], quadratic discriminant analysis (QDA)[12,13], logistic regression[14], and support vector machine analysis[9]. Both prediction accuracy and the area under the ROC curve will be used to select the best model. Permutation tests will be employed to evaluate the differences between the statistics for prediction methods to determine their relative significance. The best prediction model will then be applied to predict epileptogenic abnormalities in the images. Examples of one of these classification techniques, (Spectral Phase mapping) created from T1, T2, MD and FA data with respect to normal GM and WM respectively are shown in Figure 11.

6.4 Specific Objective To acquire and fuse multi-modality imaging datasets obtained from patients prior to TL removal, with high quality ex-vivo imaging, and histological analysis of the extirpated tissue along with volumetric pathology datasets.

Sub-hypothesis: The creation of 3D "digital histology" volumes that can be registered to high quality ex-vivo images of surgically removed tissue, will enable direct interpretation of the multi-spectral image maps in terms of post operative histology.

Methods:The following protocol will build on infrastructure (funded by another project – see letter from Dr Aaron Fenster) currently being put in place at the Robarts Research Institute, for histological correlation of prostate samples with pre-operative imaging. Patients who have been selected for TL surgery will enrolled in a UWO Research Ethics Board approved clinical protocol. Preoperatively, the multi spectral data will be acquired and analyzed as described above. At the time of the surgery, the extirpated TL sample will be prepared for step sectioning and digitization. Different coloured ink markings will identify the different specimen surfaces (right vs. left, anterior vs. posterior) to assist in subsequent alignment and registration. The specimen will be orientated into the proper anatomic position, facilitated by an appropriately shaped cradle to approximately maintain the shape of the specimen during scanning. While still fresh, the sample will undergo high-resolution T1, T2, and DT imaging using the 3T scanner with small-animal-sized gradient and rf inserts. High SNR images will be acquired using multiple image averages. After scanning, the sample will be embedded in histomer solution and then step sectioned at 100μm intervals in coronal planes that will be submitted for laser capture dissection. After digitization, images will be transferred and stored on our RRI-based. image analysis platform, where they will be corrected and smoothed to remove artifacts such as tiling effects and adjusted to establish correct layer-to-layer registration of the sequential digital images. On the digitized pathology sections, regions of normal tissue, anatomic landmarks and suspected epileptic foci will be independently outlined by 3 observers (2 pathologists + a pathology resident or fellow); and a "consensus" 3D map will be constructed from the areas of agreement (2/3 observers; sub-analyses will include looking at concordance between observers in segmenting the different components). A grid corresponding to the resolution of the 3 dimensional maps will be superimposed onto the digitized sections, and each tissue "voxel" will be scored as 0 = normal brain tissue; 1 = suspected epileptogenic tissue.

6.5 Specific Objective Through the use of multi-modality imaging and multi-channel statistical analysis we will develop a hybrid imaging map/predictive model (HIMM) that is registered to pathological tissue volumes.

Methods: The three-dimensional digitized tissue "voxel" data and the imaging voxel data sets will be co-registered using techniques available to us in the laboratory. In the case of pathology to image co-registration, increased reliance on anatomic landmarks and correction for any tissue processing artifacts (i.e. overall volume shrinkage) is anticipated and will be incorporated into the fusion which will be facilitated by the acquisition of the specimen MR dataset. As HIMMs are derived from the multi-feature analysis techniques above, they will be correlated with the actual histopathology in an iterative fashion to select the most robust model.

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Keep it simple

- Keep to the point
- Avoid complex math, convoluted discussions
- Avoid temptation to include everything about the project
- Tell a compelling story
- Tie specific aims together
- The review is a busy guy. Convince him/her in the first couple of pages.

- "If I had more time I would have written a shorter letter" – T S Elliot

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Common Pitfalls

- No WOW factor
- Too ambitious
- Low perceived impact
- Team and resources not convincing
- Bad writing
- Poor layout

Final Edits

- Spelling?
- Grammar?
- Repetition?
- References consistent?
- Figure captions consistent with text?
- Logical numbering system for sections?
- Language consistent throughout?
  - Summary consistent point-by point with text in grant
- Margin, font size, line-spacing limits respected?
- Have colleague (outside field) read it.

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Budget

- Typical
  - 2 students, postdoc, part of programmer/lab manager/research asst; give names and background; their current position, if possible.
  - Modest supplies
  - Animal costs
  - Scanner time
  - Computer infrastructure maintenance costs
  - Minor equipment (yearly expendables)
- Apply for appropriate term
- Don't go overboard

Junk

- The boring stuff
  - Letters of support
  - Quotes
  - CV Module(s) for all applicants
  - Budget module
  - Funding History module
    - Includes summary pages of all grants held
    - Overlap if any
    - How your current staff are paid.
- University required e-paperwork
  - Rola forms
- Get it done early – don't leave till last moment!

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Review Criteria

(specifics vary from agency to agency)

- Overall impact of research project
- Significance
- Investigators track record
  - Research
  - Training
- Innovation
- Approach
- Research and Training Environment
- Progress

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I didn't get funded. Now what?

- Funding rate ~20% for CIHR, ~70% NSERC
  - ~50% CIHR applicants funded by 3rd submission
  - 1995 CIHR rate 45%
- Seek advice of senior colleagues
- Consider reviewers comments carefully
- Write courteous response in the two page "response to reviewers" section
- Address most important criticisms in professional manner
- Develop good rapport with panel
- Become a panellist!
  - Inside track worth weigh in gold!

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When should I apply

- Only apply if track record supports it
- First grant needs evidence of good productivity from PhD/Postdoc
- Subsequent grants require good evidence of productivity from previous funding.
- Avoid multiple grants to same panel if possible
  - May be OK if your have two “Killer” applications
  - Sometimes hard to avoid if one grant is a renewal

Agency Reviewers

- Internal panel primary reviewers (two)
- Remainder of panel 10–12 (read and score, no reports)
- External reviewers (2–4)
- Scientific officer summary
- Score (CIHR) 1–5
  - (4.1 – 4.2 current funding threshold)
- Can suggest external reviewers in grant application
  - Respected investigators in area
  - Avoid “buddies”, conflicts of interest
  - Agency may of may not go with your suggestions

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Grantsmanship

- Objective is to get funded!
- Many programs concerned with productivity rather than replicating research program explicitly
- Even if you are convinced your idea will work, maybe reviewers will not
- Tone your application down and deliver a believable story

Final Thoughts

- It's a great deal of hard work!
- The process can be a rewarding experience
  - You are forced to review the field carefully
  - Syntheses of literature generates new ideas
  - Forced to engage collaborators
- Great sense of accomplishment when finally submitted
- Even greater when awarded
- Then the hard work begins!