Epilepsy Benchmark IA2

Benchmark Area I: Understanding basic mechanisms of epileptogenesis
Section A: Discover the range of anatomical, physiological, and molecular substrates associated with the epilepsies; define unambiguous markers of epileptogenicity.
Specific Benchmark 2a: Create a large-scale imaging database comprised of high-resolution MRI studies of patients with epilepsy (analyzing both cross-sectional and longitudinal populations) including demographic, historical and phenotypic data, and analyze this information in light of the normative database developed by the International Consortium for Brain Mapping (ICBM).
Specific Benchmark 2b: Use a portion of the imaging database and co-register the anatomical information with functional studies (e.g., fMRI, MEG, MRS, SPECT, PET, EEG, and cutting edge modalities) to identify potential structure-function relationships.

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Background of the benchmark goal:

Current status of field:
PET as a surrogate marker
- Likely to be more useful to study long-term epileptogenesis than varying epileptogenicity, due to ‘physiologic time frame’ (hours) of studies, and limits on replicability due to radiation exposure.
- 5HT1A decreases confirmed by several studies (1-3). Decreases are not due to cell loss (4), raises issue of relation of increased precursor (AMT) and decreased receptors, potential role in onset of MTS—seizure-related HF neurogenesis.
- BZP receptor studies—studies of clinical role continue
- Other receptors—some groups working on several potential EAA-related tracers; Radioactivity uptake of intravenously administered reduced (S)-[N-methyl-11C]ketamine activity in TLE may reflect reduced NMDA-receptor density, focal atrophy, or other factors (5).

MEG
Most studies directed toward comparing clinical value of MEG and EEG, and role of the former in epilepsy surgery (6-11). Analysis of MEG dipoles may reveal participation of additional structures in epileptogenicity, and varying modes of spread of cortical excitation. In some cases it may be possible to obtain ictal MEG (12). It is uncertain how much MEG adds to multichannel EEG electrical activity modeling.

MR Spectroscopy:
Recent studies suggest that proton MRS measurements reflect neuro/glial dysfunction rather than neuronal cell loss. MRS is more sensitive than MRI to detect early changes in the epileptogenic area and thus, it may be a suitable tool to study progression in epilepsy.

MRS studies in humans have shifted to 1) High resolution combined Phosphorus/Proton studies of the temporal lobes and adjacent structures 2) editing techniques to quantify absolute neurotransmitters (Glutamate, GABA) in cortical structures. Studies demonstrate absolute reductions in Glutamate in the epileptogenic temporal lobe.

**MRI Techniques**
Several studies under way to evaluate sensitivity of higher field Magnets (3T Vs 1.5T) in epilepsy. DTI studies have not yielded significant findings to-date.

**MRI in animal models**
There has been increasing use of MRI in rodent models of epilepsy, including excitatory amino acids, febrile seizures, and other approaches (13-19). So far, most studies have used structural imaging, although both BOLD signal and arterial spin tagging CBF measurements, and diffusion weighted imaging have been performed as well. The short ‘time window’ of MRI allows study of fluctuating physiologic states. EEG and MRI have been combined in animal models by some investigators, although not all the technical details have been worked out (20-1).

**Imaging cognitive / psychological / structural consequences of epilepsy**
Both MEG and fMRI are being used for both preoperative cognitive mapping, and studies of functional reorganization due to epilepsy, generally confirming older data showing early onset of seizures is strongly associated with atypical language lateralization, and that Lesions in the dominant hemisphere tend to result in an intrahemispheric reorganization of linguistic function (21-27). Studies using structural MRI or PET to follow long-term structural consequences of ‘new-onset’ epilepsy have found much less evidence of initial injury, or progression, than reported previously in populations of patients with established intractable epilepsy, due possibly to subject heterogeneity, relatively short follow-up, or the higher chance of a benign course in some patient samples (28-30).

**Activities update:**
The conclusions / recommendations were:
- A need for preclinical imaging studies to develop and evaluate methods in animal models
- need to use animal models to develop imaging markers that could be linked to electrophysiological abnormalities
- new ictal mapping methods to detect structures participating in seizure spread
- Prospective collaborative clinical investigations with event-related (such as first febrile or afebrile seizure or traumatic brain injury) entry
need for technical and infrastructure development

**Top priorities for next 5-10 years:**
- Establish validity of imaging markers of both epileptogenicity and epileptogenesis, followed by intervention trials in animal models.
- Refinement of fMRI-EEG techniques for both animal and human studies.
- Additional human collaborative imaging studies such as current consequences of prolonged febrile seizures.
- Develop additional PET ligands, and refine techniques to allow more studies in children with new onset epilepsy.
- Validation of new MRS editing techniques to quantify neurotransmitters in humans.
- Encourage / support more widespread use of ICBM database (http://www.loni.ucla.edu/ICBM/).

**Roadblocks to progress:**
- Lack of knowledge of complementary techniques
- Insufficient interaction of ‘imagers’ and ‘epileptologists’.

**References:**


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