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Biomarkers Workshop In Clinical Trials
Imaging for Schizophrenia Trials

- Research focused on the following areas
  - Brain pathology in schizophrenia and its modification
  - Effect of drug treatment on brain structure and function
- Studies were conducted on drug naïve , first-episode schizophrenics , remitters and non remitters , childhood onset, and chronic schizophrenics compared to controls ; subgroups positive, cognitive or negative symptoms
- Rarely compare different antipsychotics
- Volumetric studies of brain structures
- DTI: FA and Tractography
- FMRI
- FDG PET
- Receptor Ligand Studies SPECT and PET

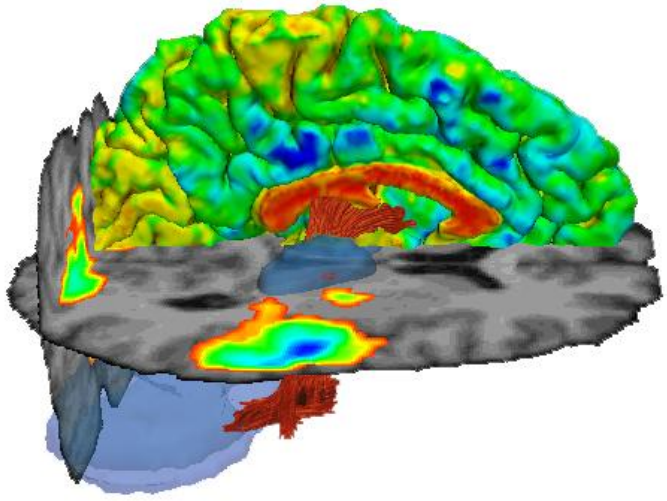

Table 1 Prototype "evidence map"—categorical description of different types of scientific evidence potentially relevant to biomarker qualification; subcategorical graded weight of evidence from least to most

Evidence type	Grade D	Grade D+/C–	Grade C	Grade C+/B–	Grade B	Grade B+/A–	Grade A
Theory on biological plausibility	Observed association only	Theory, indirect evidence of relevance of the biomarker from animals	As for lower grade but evidence is direct	Theory, indirect evidence of relevance in humans	Theory, direct evidence in humans, non-causal pathway possible	As for lower grade, but biomarker on causal path	Human evidence based mathematical model of biology showing biomarker is on causal pathway
Interaction with pharmacologic target	Biomarker identifies target in *in vitro* binding			Biomarker identifies target in *in vivo* binding in animals	Biomarker identifies target in *in vivo* studies or from human tissue, no truth standard		Biomarker identifies target in *in vivo* studies or from tissues in humans, with accepted truth standard
Pharmacologic mechanistic response	*In vitro* evidence that the drug affects the biomarker	*In vitro* evidence that multiple members of this drug class affects the biomarker	*In vivo* evidence that this drug affects biomarker in animals	As for lower grade but effect shown across drug class	Human evidence that this drug affects the biomarker OR animal evidence of specificity	Human evidence across this mechanistic drug class	Human evidence that multiple members of this drug class affect the biomarker and the effect is specific to this class/mechanism
Linkage to clinical outcome of a disease or toxicity		Biomarker epidemiologically associated with outcome without any intervention	Biomarker associated with change in outcome from intervention in another drug class	As for lower grade but in this drug class	As for lower grade but multiple drug classes albeit inconsistent or a minority of disease effect		As for lower grade but consistent linkage and explains majority of disease effect
Mathematics replication, confirmation		An algorithm is required to interpret the biomarker and was developed from this dataset		Algorithm was developed from a different dataset and applied here prospectively			Algorithm developed from different dataset, replicated prospectively in other sets and applied prospectively here
Accuracy and precision (analytic validation)				Sources of technical variation are unknown but steps are taken to ensure consistent test application	Major sources or variation known and controlled to be less than biological signal; standardization methods applied		All major sources of technical imprecision are known, and controlled test/assay accuracy is defined against standards
Relative performance		Does not meet performance of benchmark		Similar performance to benchmark			Exceeds performance of benchmark or best alternative biomarker

Not all types of evidence required all seven grades to be completed.

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Evidence Matrix – Question of Grade inflation

- Theory on Biological Plausibility
- Interaction with pharmacologic target
- Pharmacologic mechanistic response
- Linkage to clinical outcome of a disease or toxicity
- Mathematics replication, confirmation
- Accuracy and precision (analytic validation)
- Relative performance

Echoing mornings session we are looking for convergent validity & which parameters matter most.

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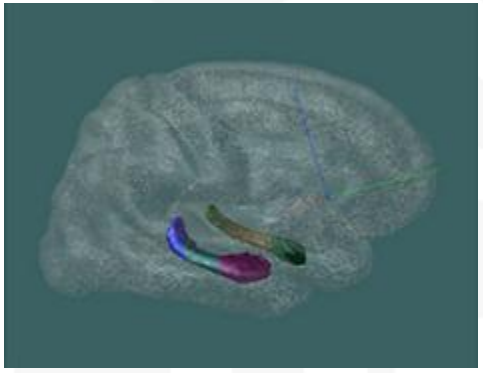
Volumetric Magnetic Resonance Imaging (vMRI)

- Measures volumes of brain structures
- Research focused on the following areas
  - Brain pathology in schizophrenia
  - Effect of drug treatment on brain structures

B

- Studies were conducted on drug naïve and drug treated first-episode schizophrenics (FES), remitters and non remiters FES, childhood onset schizophrenics, and chronic schizophrenics compared to controls (and various s.
- Studies reviewed compared different antipsychotics (typical vs atypical), treatment vs no treatment, schizophrenia vs control.
- **vMRI has mostly been used to measure drug effects (Grade A). Some studies evaluate disease vs no disease (Grade B or less)**
- **vMRI has been done in small samples using different measurement techniques**
  - Potential platform for larger "ADNI" type studies using consistent methods and imaging techniques



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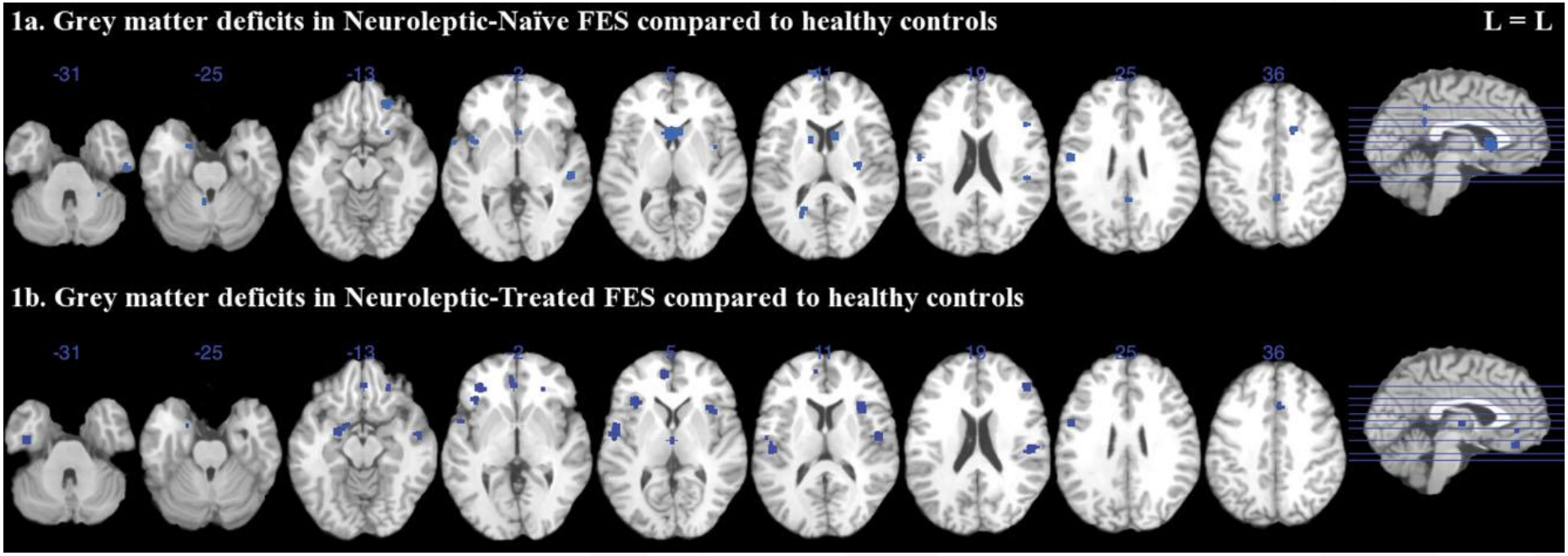
Gray Matter Deficits in FES



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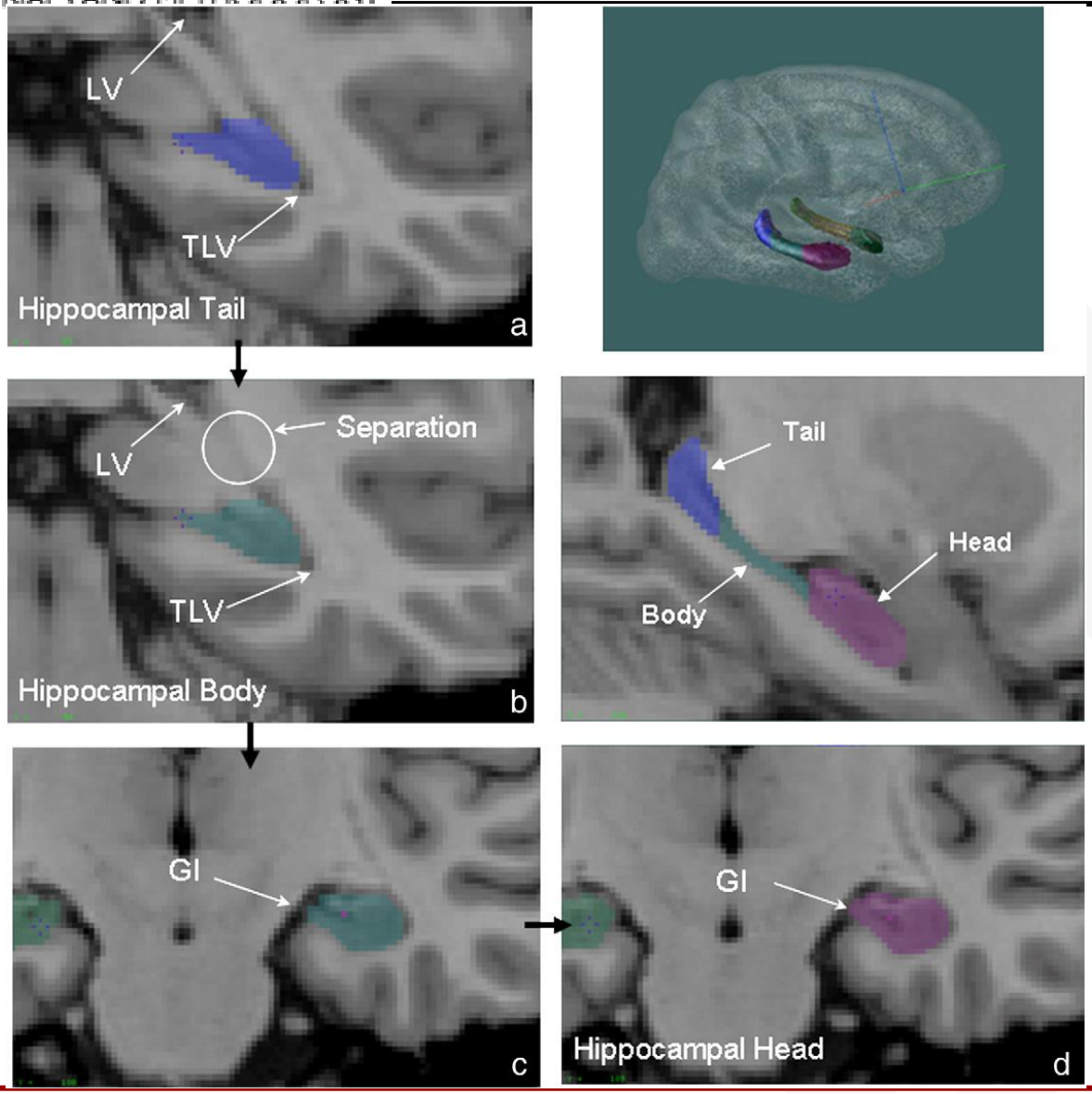
Hippocampal Formation in FES



L hippocampal tail is smaller in FES non remitters compared to FES remitters and CNT

R hippocampal tail and R Amygdala are smaller in FES non remitters compared to CNT

Bodnar, et al., Schizophrenia Research, 2010

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Diffusion Tensor Imaging (DTI)

D-

- Key Findings:
  - No study prospectively examined between group treatment effects
  - FA in pts generally lower than healthy controls; lower still in pts with "poor outcomes"
  - Anisotrophy reductions in pts take place earlier in the course of illness, closer to the time of first psychotic episode and stabilize in its chronic phase.
    - Results confounded by age, duration of illness
    - At least 3 studies found no relationship between medication or daily dose and FA
    - ROI analysis differed from voxel-based approach
  - Neuropsyc correlates examined in 2 studies
    - **Lower FA in uncinate fasicuclus correlated with greater negative symptoms, higher FA in inferior fronto-occipital fasiculus correlated with greater positive symptoms, which remained significant after controlling for antipsychotic tx duration.**
    - FA significantly correlated with neuroleptic dose; no significant correlation of FA with PANSS scores.
- Gaps: need prospective studies with between group analysis

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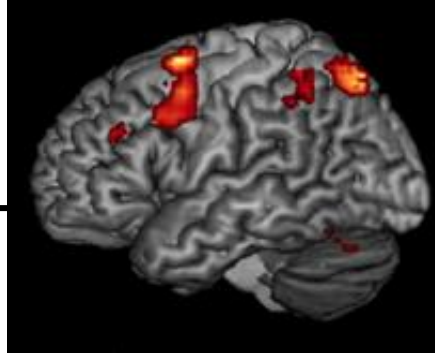
Functional Magnetic Resonance Imaging (fMRI)



- Measures blood oxygenation level dependent (BOLD) signal associated with neuronal activity.
- Two reviews exist (Davis et al. 2005; Röder et al. 2010)
- Pubmed database searches were performed from 1972 – August 16, 2011.
- Key words: *antipsychotic* AND *fMRI* AND *longitudinal*, as well as the search terms used by Davis et al. (2005)
- ~1881 papers identified; abstracts reviewed
  - 15 abstracts selected and reviewed. Reference list reviewed for additional papers. 15 total "on target"
    - Typical-Atypical (n=4)
    - Pre-Post (n=5)
    - Switch (n=2)
    - Conjunctive (n=2)
    - Other (n=2)

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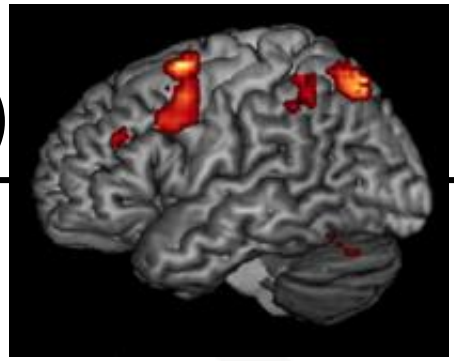
Functional Magnetic Resonance Imaging (fMRI)



- **Key Findings:**
  - **Evidence for psychopharmacological effects on cerebral physiology (e.g., percent signal change in frontal lobe regions).**
  - **Evidence for psychopharmacological effects on functional connectivity**
- Evidence Map: B – fMRI has great potential, but more systematic research is warranted
- Gaps
  - replication of findings with larger samples
  - evidence of task reliability/consistency
  - systematic prospective investigations of multiple different drug types
  - longer-term investigations (e.g. >8 weeks)
  - combined PET-fMRI studies
  - taking into account patients' genetic background
  - patient control groups

B

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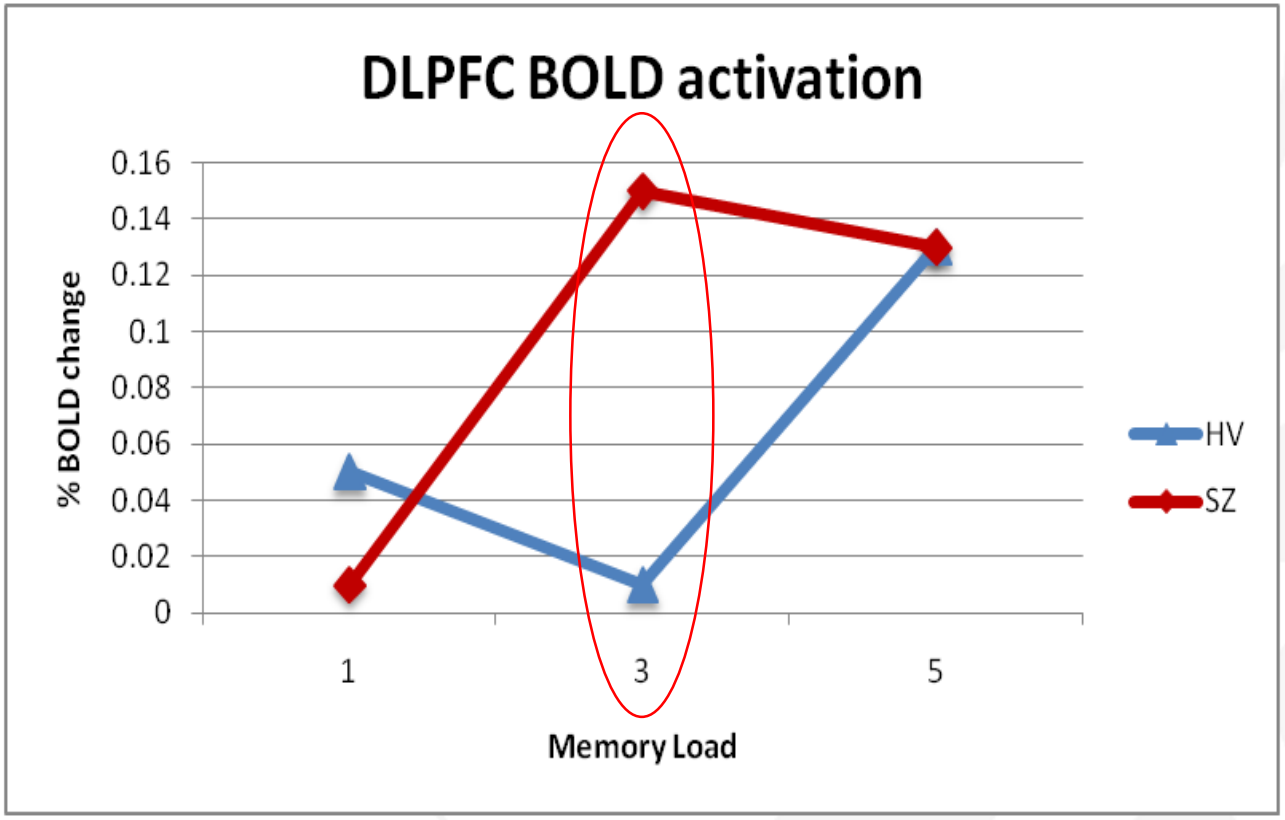
Multi-center study of working memory in Sz and Controls



Potkin, S.G., et al., 2009. Working memory and DLPFC inefficiency in schizophrenia: the FBIRN study. Schizophrenia Bulletin 35, 19-31.

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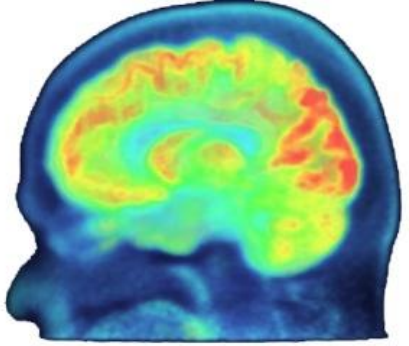
Cerebral Perfusion & Metabolism



- **Measures cerebral blood flow or perfusion in ROI to evaluate antipsychotic effect in schizophrenia**
- Key words: FDG-PET, Cerebral Perfusion, cerebral Metabolism, Schizophrenia, Clinical Response
- 7 articles reviewed
- FDG-PET, Magnetic Resonance Imaging, Perfusion Weighted Imaging (PWI)
- Patient population
  - Both clinic setting and hospitalized patients
  - Treated with 1st or 2nd generation of antipsychotics
- Efficacy responses measured by PANSS, BPRS

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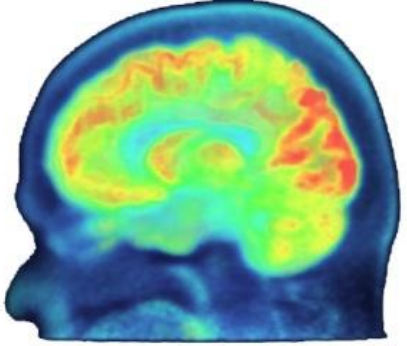
Cerebral Perfusion & Metabolism

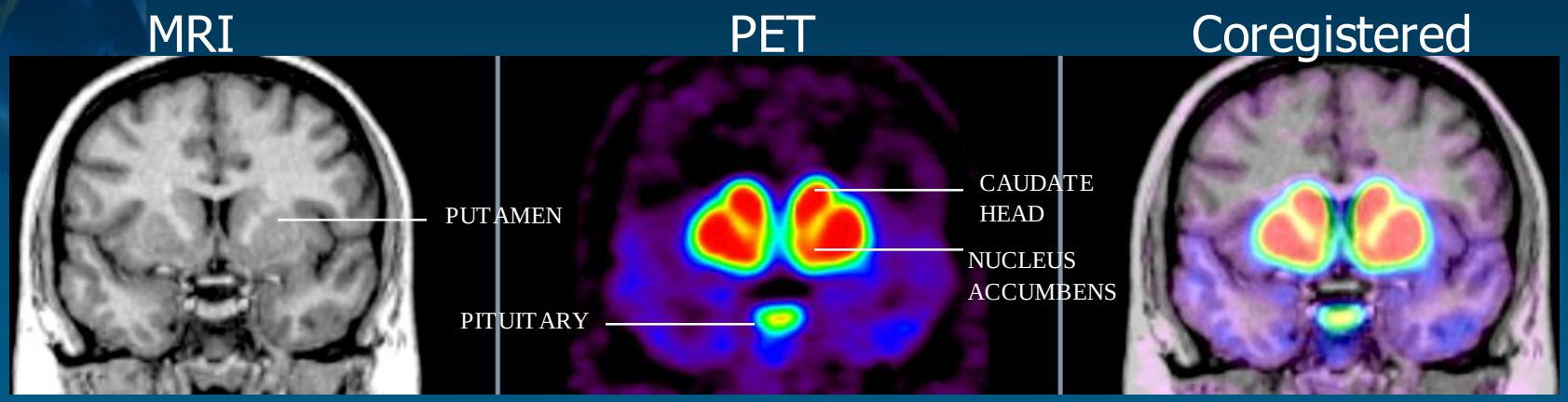


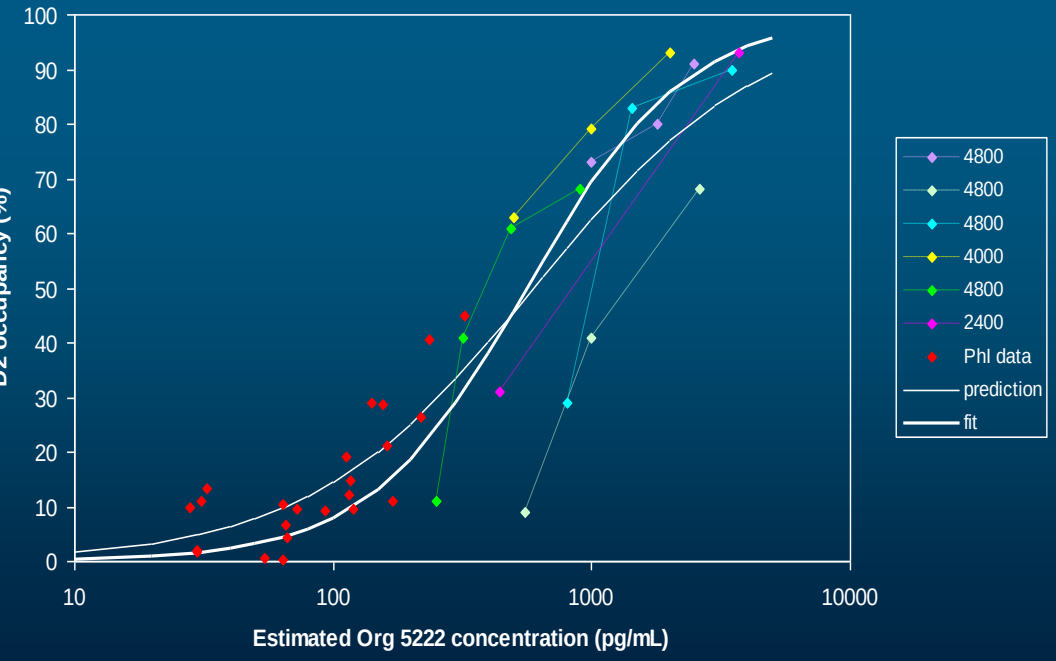
- Key Findings:
  - **Resting rCBF was significantly lower** in schizophrenia compared to normal controls
    - Rostral Prefrontal cortex, Left temporal lobe, Posterior Cingulate and Mediodorsal Thalamus.
  - Schizophrenics has significantly higher right and left contrast enhancement compared to normal controls
  - Right middle frontal gyrus (BA46) uptake significantly increase in subjects with high verbal hallucination score
    - Resting metabolism of the area positively correlated with intensity of hallucination
  - **Antipsychotic administration was associated with greater change toward normal values** and away from the values found in the unmedicated comparison group for dorsolateral prefrontal cortex gray matter and white matter underlying medial prefrontal and cingulate cortex.

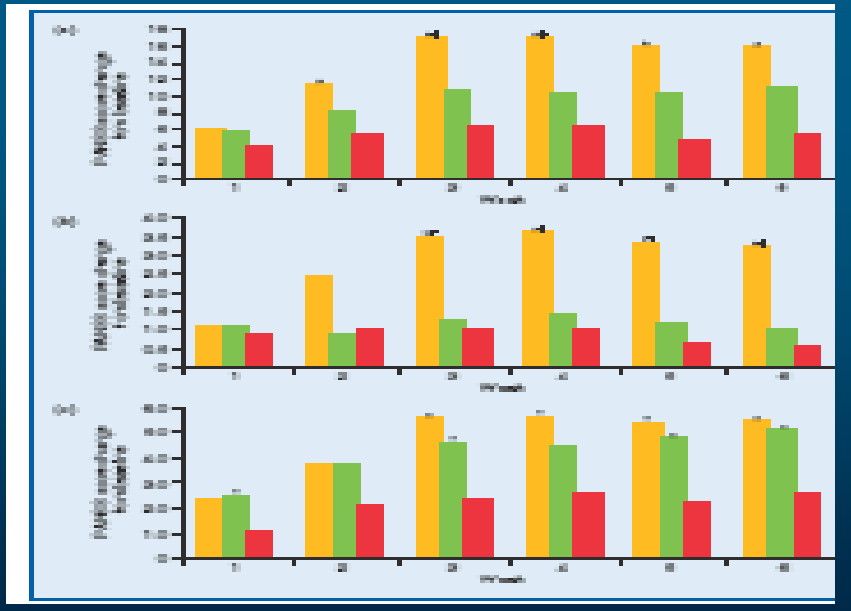
A- to C

- Gaps: correlation with treatment response and long-term prospective study

^{18}F-Fallypride Binding to Dopamine D2/D3 Receptors To Speed Drug Development







Potkin et al , JCP, 2007

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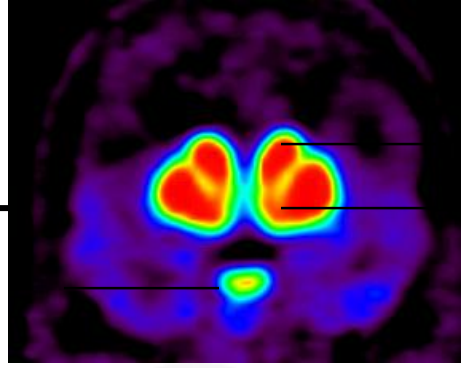
Receptor Occupancy (PET & SPECT)



- Very good plasma concentration-D2 receptor occupancy relationship
- Striatal D2 Occupancy correlated to change of PANSS positive score after antipsychotic treatment
- 60-70% D2 occupancy ensures treatment response
- Drug development
  - Brain penetration & target binding
  - Aid dose selection and dose regimen
  - Confirm mode of action
  - Explore clinical response and AE

A-

Can small studies be valuable?

Review

Identifying gene regulatory networks in schizophrenia

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ABSTRACT

The imaging genetics approach to studying the genetic basis of disease leverages the individual strengths of both neuroimaging and genetic studies by visualizing and quantifying the brain activation patterns in the context of genetic background. Brain imaging as an intermediate phenotype can help clarify the functional link among genes, the molecular networks in which they participate, and brain circuitry and function. Integrating genetic data from a genome-wide association study (GWAS) with brain imaging as a quantitative trait (QT) phenotype can increase the statistical power to identify risk genes. A QT analysis using brain imaging (DLPFC activation during a working memory task) as a quantitative trait has identified unanticipated risk genes for schizophrenia. Several of these genes (RSRC1, ARHGAP18, ROBO1-ROBO2, GPC1, TNIK, and CTXN3-SLC12A2) have functions related to progenitor cell proliferation, migration, and differentiation, cytoskeleton reorganization, axonal connectivity, and development of forebrain structures. These genes, however, do not function in isolation but rather through gene regulatory networks. To obtain a deeper understanding how the GWAS-identified genes participate in larger gene regulatory networks, we measured correlations among transcript levels in the mouse and human postmortem tissue and performed a gene set enrichment analysis (GSEA) that identified several microRNA associated with schizophrenia (448, 218, 137). The results of such computational approaches can be further validated in animal experiments in which the networks are experimentally studied and perturbed with specific compounds. Glypican 1 and FGF17 mouse models for example, can be used to study such gene regulatory networks. The model demonstrates epistatic interactions between FGF and glypican on brain development and may be a useful model of negative symptom schizophrenia.

nature genetics

Feb 2011 on-line

Genome-wide association study identifies five new schizophrenia loci

The Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium[1]

We examined the role of common genetic variation in schizophrenia in a genome-wide association study of substantial size: a stage 1 discovery sample of 21,856 individuals of European ancestry and a stage 2 replication sample of 29,839 independent subjects. The combined stage 1 and 2 analysis yielded genome-wide significant associations with schizophrenia for seven loci, five of which are new (1p21.3, 2q32.3, 8p23.2, 8q21.3 and 10q24.32-q24.33) and two of which have been previously implicated (6p21.32-p22.1 and 18q21.2). The strongest new finding ($P = 1.6 \times 10^{-11}$) was with rs1625579 within an intron of a putative primary transcript for *MIR137* (microRNA 137), a known regulator of neuronal development. Four other schizophrenia loci achieving genome-wide significance contain predicted targets of *MIR137*, suggesting *MIR137*-mediated dysregulation as a previously unknown etiologic mechanism in schizophrenia. In a joint analysis with a bipolar disorder sample (16,374 affected individuals and 14,044 controls), three loci reached genome-wide significance: *CACNA1C* (rs4765905, $P = 7.0 \times 10^{-9}$), *ANK3* (rs10994359, $P = 2.5 \times 10^{-8}$) and the *ITIH3-ITIH4* region (rs2239547, $P = 7.8 \times 10^{-9}$).

MIR137 has been implicated in regulating adult neurogenesis[15,16] and neuronal maturation[17], mechanisms through which variation at this locus could contribute to brain development abnormalities in schizophrenia. Of relevance, two independent schizophrenia imaging studies found *MIR137* to be one of three microRNAs with targets significantly enriched for association[18]. In stage 1, SNPs in or near 301

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Conclusions

- Match the imaging modality to research question
- Match the imaging details to research question & logistics
  - Lowest common denominator vs specialized centers
  - Task v no task, number of trials (group v individual)
  - Normals v patients and conditions
  - Standardization and complete data collection
  - Convergent validity , cross-design synthesis, consistency
  - Behavior associated with fMRI change, normalization may not be good – need empirical agnostic data

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Future

- Match the imaging modality to research question
- Many issues in modality , application, task, populations
- Surrogate, sample enrichment, POC
- There are standardization methods for imaging current available using phantoms, CIGAL, automatic QC, automated analytics and data sharing.

- Perhaps need agnostic approach such as ADNI to address the diagnostic , course, treatment response and side-effect biomarkers