NEUROIMAGING IN SCHIZOPHRENIA

OVERVIEW

- Introduction
- Historical landmarks
- Types of neuroimaging
- Structural neuroimaging
- Functional neuroimaging
- Molecular neuroimaging
- Summary and conclusion

INTRODUCTION

- Neuropathology of schizophrenia still remains elusive
- Brain abnormalities in schizophrenia have proven to be small and subtle
- Neuroimaging techniques responsible for renewed interest and research in neuropathology of schizophrenia

HISTORICAL LANDMARKS

- 1976- first CT study by Johnstone
- 1984- first MRI study by R.C. Smith
- 1998- first DTI study by Buchsbaum
- 1988-2000- burgeoning neuroimaging studies of schizophrenia
- 1983- first successful molecular imaging study with carbon labelled derivative of spiperone

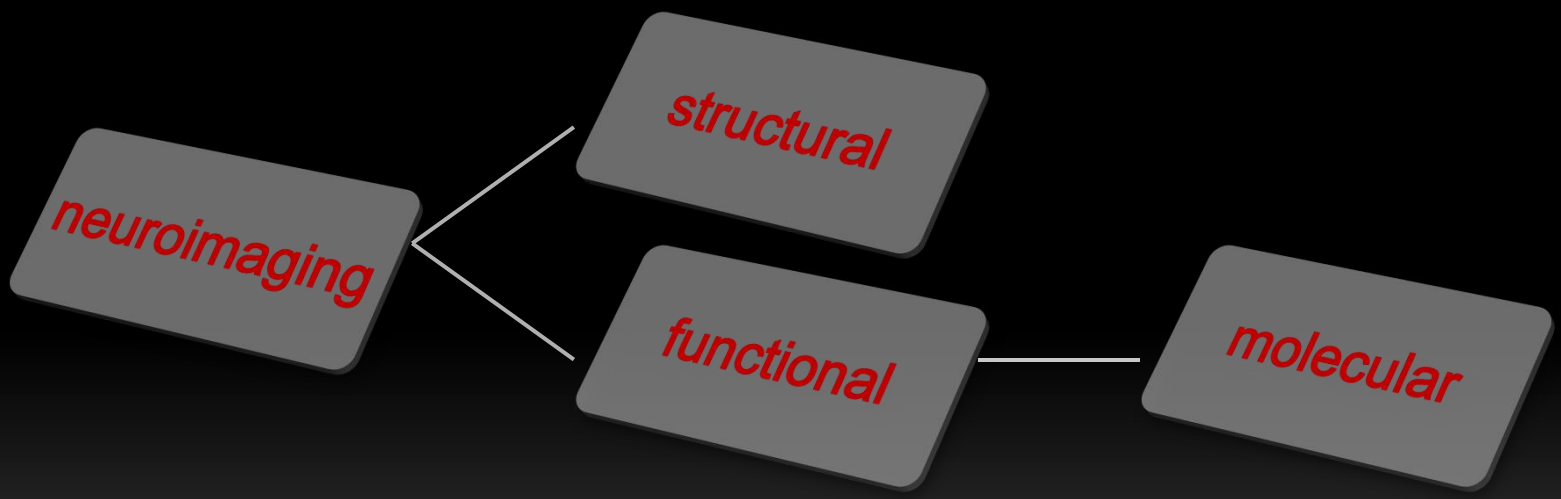
NEED FOR NEUROIMAGING

- Is schizophrenia a brain disease?
- Are some brain abnormalities more characteristic of schizophrenia than others?
- Are brain abnormalities present early in the course of illness, or even before the onset of illness?
- Do brain abnormalities change over time?

NEED FOR NEUROIMAGING

- Does this suggest neurodegenerative changes, or neurodevelopmental origin? Are two theories mutually exclusive?

TYPES OF NEUROIMAGING



TYPES OF NEUROIMAGING

- STRUCTURAL- Non-invasive visualization of brain morphology and precise demarcation of anatomical regions

1. Plain skull radiography
2. CT Scan (computed tomography)
3. MRI (magnetic resonance imaging)
4. DTI (diffusion tensor imaging)

TYPES OF NEUROIMAGING

- FUNCTIONAL- identify and characterize the dynamic chemical and biological changes of the brain under varying conditions.

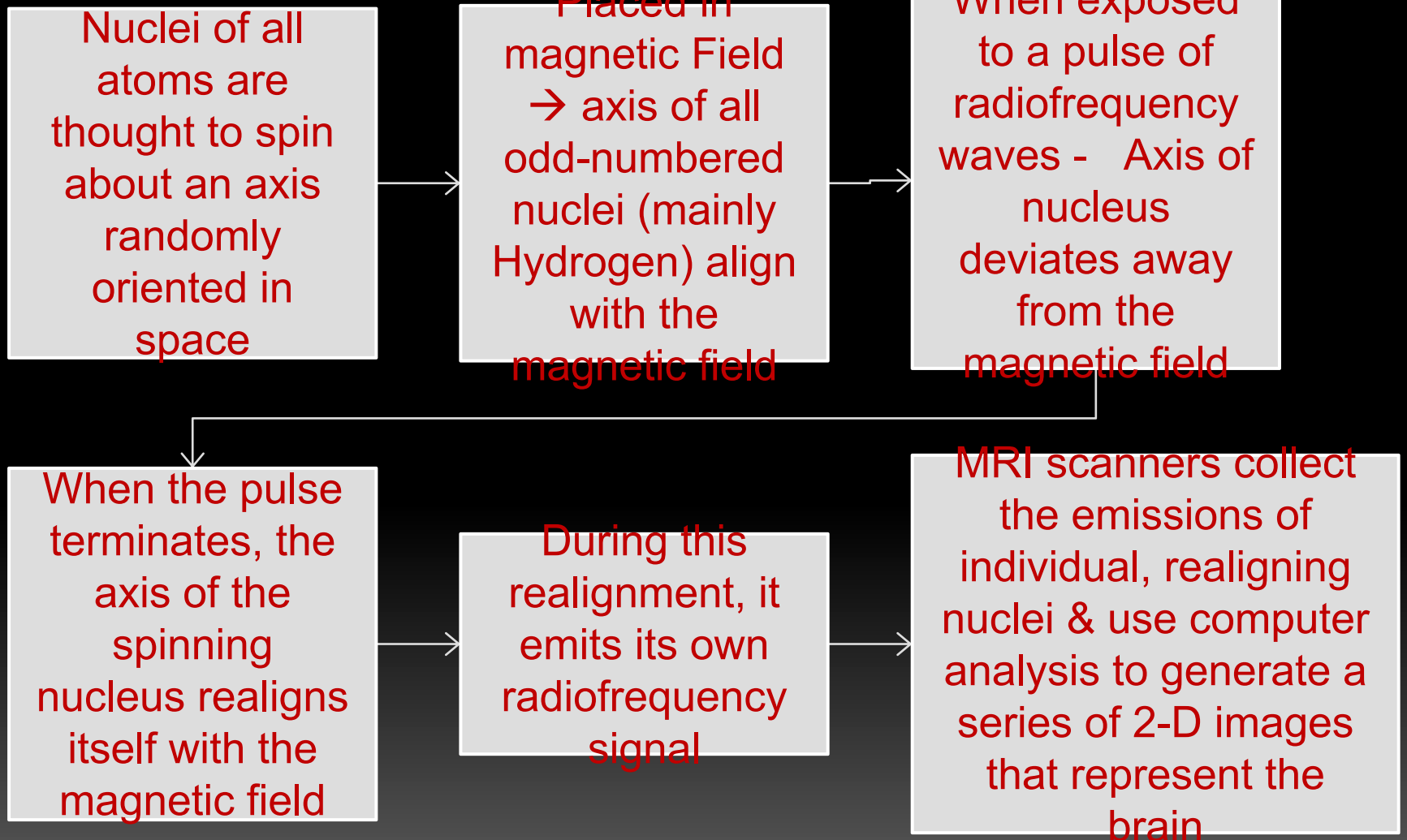
1. fMRI (functional MRI)
2. PET (positron emission tomography)
3. SPECT (single photon emission computed tomography)
4. MRS (magnetic resonance spectroscopy)
5. Multimodal neuroimaging

STRUCTURAL NEUROIMAGING

STRUCTURAL NEUROIMAGING

- CT scans - contrast between brain and CSF
- MRI provides important information about soft tissue (gray and white matter)
- Diffusion tensor imaging (DTI) is a relatively new imaging technology based on ability to detect water diffusion in living tissue- white tract visualization and abnormalities

MAGNETIC RESONANCE IMAGING



CT SCAN

- Enlarged lateral ventricles compared to healthy controls
- Most consistent and replicated finding till date

MRI
1988-2000

- 2001 review by Shenton and colleagues- 193 studies reviewed

1. 80%- Enlarged lateral ventricles

2. 74%- medial temporal volume reduction – amygdala, hippocampus, parahippocampus, STG

3. 73%- third ventricle enlargement

MRI
1988-2000

4. Others- parietal lobe, frontal lobe & occipital lobe volume reduction, thalamus and cerebellar volume reduction, basal ganglia and corpus callosum abnormalities

MRI
2000-2014
CHRONIC SCHIZOPHRENIA

- IMPORTANT STUDIES-

studies	result
Ho	White matter↓ medication
Tang	Volume deficit- ageing
Thompson	Postero-anterior ↓ cortical surface area
Nesvag	Lowered GI

MRI
2000-2014
CHRONIC SCHIZOPHRENIA

IMPORTANT FINDINGS-

- Abnormalities- prefrontal, frontal, temporal, and parietal cortical involvement, the amygdala and hippocampus.

Clinical deficit	Structural abnormalities
Facial recognition	fusiform gyrus and amygdala
hallucination	STG
Deficit syndrome	Pre-frontal cortex
Social cognition	Anterior cingulate
Language disturbances	medial temporal lobe
FTD	Posterior temporal lobe

MRI
2000-2014
FIRST EPISODE

IMPORTANT STUDIES

- Pantelis
- Hulshoff Pol
- Whitford
- Vita
- Nakamura
- Gur
- Leiberman

MRI
2000-2014
FIRST EPISODE

- FINDINGS
- Widespread gray matter reduction and progresssive changes
- Increased lateral ventricles
- Accelerated gray matter reduction in prefrontal cortex
- Frontal lobe volume reduction
- Reduced hippocampal volume
- Left superior temporal gyrus -progressive post-onset volume reduction

MRI
2000-2014
FIRST EPISODE

- Increased cortical sulcal CSF, increased frontal CSF, and reduced frontal gray matter and white matter in first-episode patients
- Cerebellum and occipital lobe- some studies show volume reduction, others don't
- Poorer outcome was associated with post-onset brain changes in patients diagnosed with a first-episode schizophrenia with more negative symptoms, and poor performance on neurocognitive measures

MRI
2000-2014
FIRST EPISODE

CONCLUSIONS

- Small abnormalities present at onset
- Progress in early post-onset period in some regions
- Incongruence between early improvement of clinical and cognitive symptoms and progressive structural abnormalities

MRI
2000-2014
HIGH RISK STUDIES

1. Edinburgh High Risk study –
- Based on Structural Interview for Schizotypy
- Schizotypal features and increased right PFC folding are predictive

2. Personal Assessment and Crisis Evaluation Study (PACE)-
- Focuses on individuals at risk for developing psychosis
- Based on number of trait and risk factors
- Increase in medial temporal and prefrontal abnormalities

MRI
2000-2014
HIGH RISK STUDIES

3. North American Prodrome Longitudinal Study

- Multisite cohort study
- Significantly faster rate of gray matter loss in right superior frontal, right middle frontal, and right medial frontal gyri

MRI
2000-2014
FAMILY STUDIES

- 2007 – Boos reviewed 25 studies
- First degree relatives have reduction of left hippocampal volume and increased third ventricle volume
- Associated with verbal and declarative memory deficits

MRI
2000-2014
FAMILY STUDIES

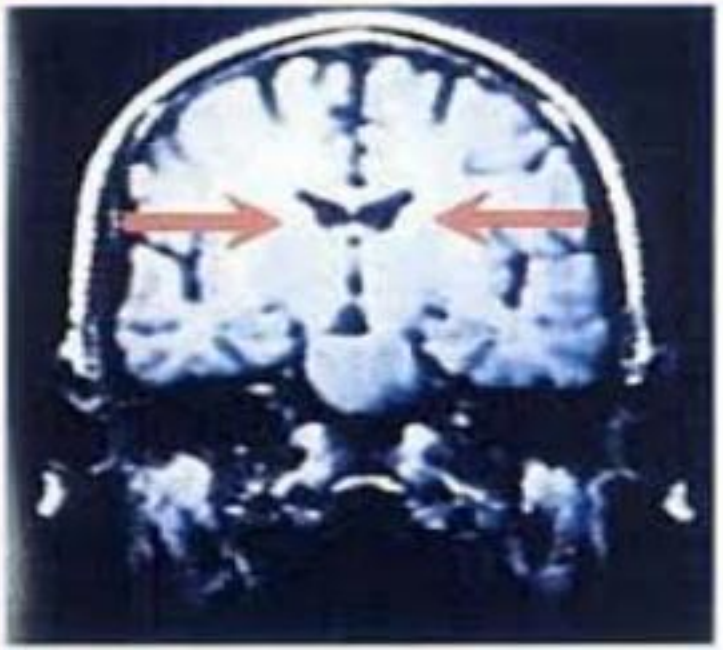
- 2015- Bois review
- Diffuse gray matter decrease in first degree relatives
- No early insult in non-converters supported by equivocal gyrification findings
- Different developmental trajectory in converters

Ventricular Enlargement

- Ventricular enlargement consistent and replicated finding but not generalized
- Associations between ventricular enlargement and illness chronicity
- Third ventricular enlargement
- Additionally, lateral ventricular enlargement shows some regional specificity.

Ventricular Enlargement

- Left temporal horn is selectively enlarged in schizophrenia.
- Degreef and colleagues (1992) found that ventricular enlargement was most pronounced in the frontal and temporal horns (bilaterally)
- They found enlargement of temporal horns to be associated with the presence of positive symptoms.



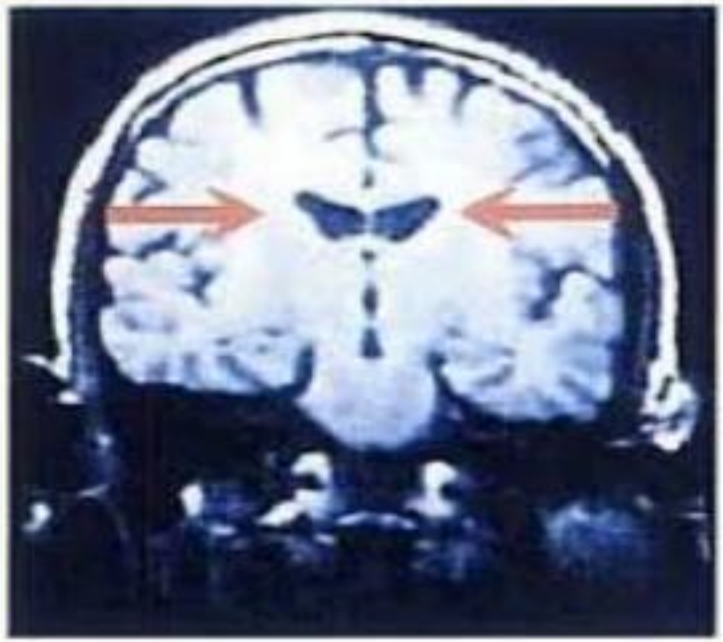
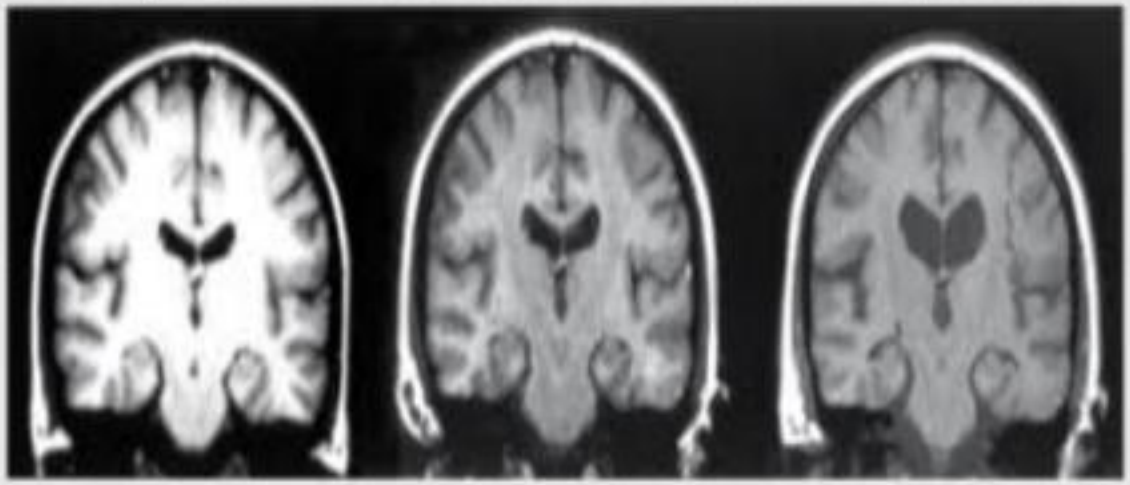


Figure 2:
"Enlarged lateral ventricles in schizophrenia: These MRI scans are from the brains of identical twins. The sibling on the left (top) was normal; the one on the right was diagnosed with schizophrenia. Notice the enlarged lateral ventricles in the schizophrenic sibling, indicating a loss of brain tissue." (Barondes 1993, p. 153 in Bear, Connors & Paradiso 2007, p. 684)

10-year MRI follow-up
34-year-old female with chronic schizophrenia



Feb. 1990
1st episode

Feb. 1995
5 years later

Jan. 2000
10 years later

MRI FINDINGS

- Medial temporal volume reduction of structures that includes the amygdala, hippocampus, parahippocampal, and neocortical temporal regions such as superior temporal gyrus (STG)

- Volume reduction in frontal lobe, occipital lobe, thalamus and cerebellum

MRI FINDINGS

- Parietal lobe studies showed volume reduction, particularly in areas involving the inferior parietal lobule, which includes supramarginal and angular gyrus

- Basal ganglia abnormalities (some increased volume, some decreased volume)

MRI FINDINGS

- Corpus callosum abnormalities (some area, some shape measures)

- Studies of cavum septum pellucidum showed enlarged cavum, indicative of a neurodevelopmental disorder, although such findings are not specific to schizophrenia

Gender-specific findings

- Structural brain abnormalities occur more frequently and are more pronounced in male patients with schizophrenia
- This is in accordance with epidemiologic observations
- It is also in accordance with the belief that male patients with schizophrenia are more likely to express neurodevelopmental processes.

Conclusions from MRI studies

- MRI findings confirm structural brain abnormalities in schizophrenia
- Pattern and number of abnormalities – Neurodevelopmental origin of connectivity disruption
- Diffuse gray matter loss
- Left STG – FTD
- Problems in abstraction and verbal memory- parahippocampal volume reduction

Minor physical anomalies(MPA) and neuroimaging

- Minor physical anomalies (MPAs) are commonly found in elevated frequency -neurodevelopmental hypothesis.

- Dean and colleagues found that patients with high MPAs showed larger gray matter volume of basal ganglia (bilateral), thalamus (bilateral), inferior temporal gyrus (right), lingual gyrus (bilaterally), and cuneus (right).

Minor physical anomalies(MPA) and neuroimaging

- They also showed smaller gray matter volume at the level of the lobulus paracentralis (bilaterally), with extension anteriorly into the dorsal frontal gyrus, posteriorly into the precuneus, and inferiorly into the cingulate gyrus (left).

- The authors concluded that high MPA frequency was associated with gray matter volume changes on MRI even in first-episode psychosis.

Treatment response and brain abnormalities

- Relation between treatment response and neuroimaging
- Kolakowska and colleagues- cortical atrophy with poor outcome
- Lieberman and colleagues -ventricular enlargement predicted treatment response
- Friedman and colleagues -prefrontal sulcal prominence inversely related to clozapine response.

Treatment response and brain abnormalities

- Typical neuroleptics may increase volume, metabolism, and relative blood flow in the basal ganglia, can be reverted or not apparent with atypical antipsychotics.

- Lieberman -comparative study of olanzapine and haloperidol in first-episode schizophrenia- loss of gray and white matter with enlarged ventricles in haloperidol

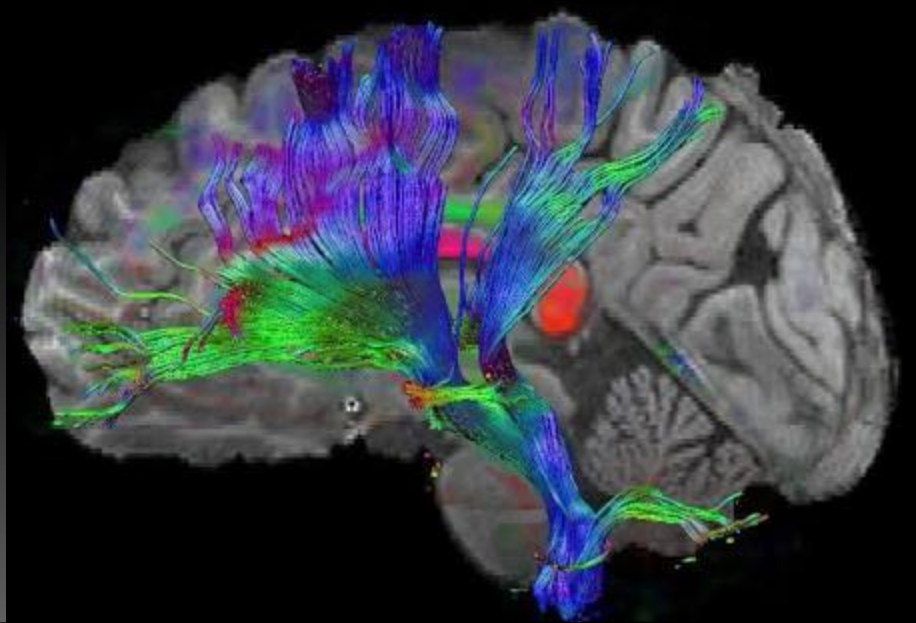
Treatment response and brain abnormalities

- The therapeutic implications of such studies for the selection of second-generation antipsychotic medications over first generation antipsychotics are important and compelling.

- Additionally, there is some, evidence that second-generation antipsychotic medications may help “recovery” of brain cells (ie, stimulate neurogenesis)

DTI

- Anisotropic diffusion principle
- Visualize and quantify white matter
- Disconnectivity in schizophrenia a core prinicple



DTI

- progressive white matter changes – predict schizophrenic conversion
- Other studies suggest that white matter pathology is likely present before schizophrenia onset.
- Neuroinflammation in first episode- change in fractional anisotropy while cellular pathology in chronic changes
- Longitudinal changes- medication

DTI findings

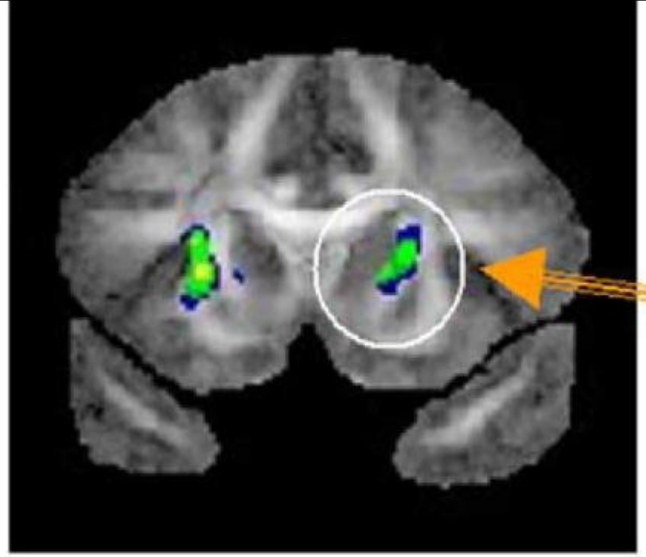
- Reductions in anisotropy were reported within the majority of white matter connections
- Decrease in left to right fractional anisotropy in uncinate fasciculus (UF),
- Studies of cingulum bundle (CB) showed reduced anisotropy in patients

DTI findings

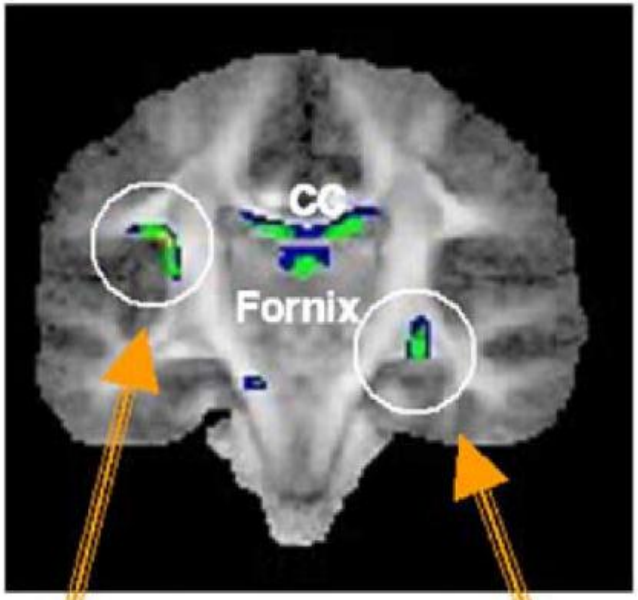
- Left-lateralized reductions in anisotropy in arcuate fasciculus
- Fractional anisotropy was increased in the AF and corpus callosum –hallucinations
- Reduced anisotropy within the entorhinal cortex, amygdala, and hippocampus
- Wang -reduction of left–right asymmetry in schizophrenia
- Asymmetries are key to understanding the pathology of schizophrenia, which relates to altered development in the region of the brain subserving language.

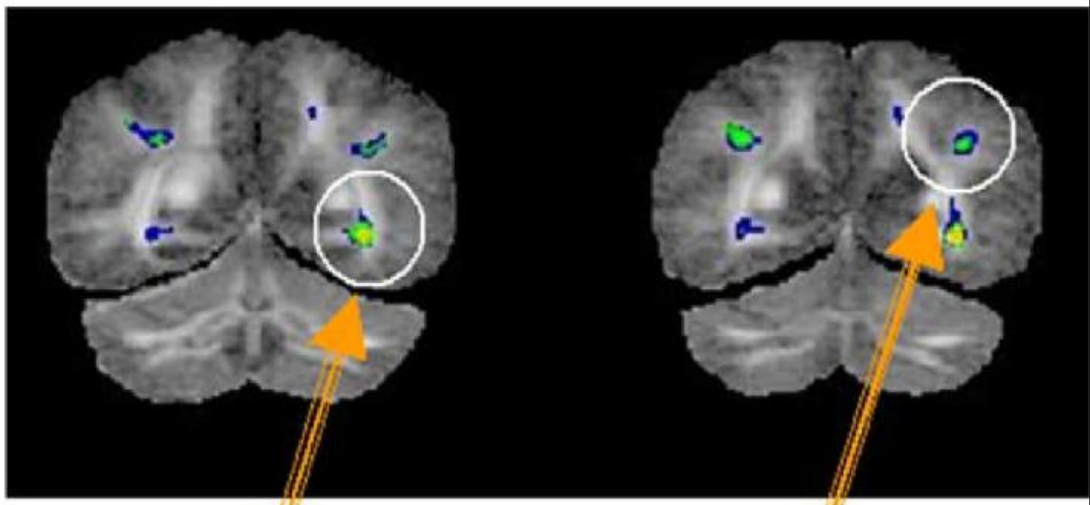
DTI findings

White matter pathology	Cognitive deficit
cingulam	Attention deficits
Uncinate fasciculus	Episodic memory loss
Arcuate fasciculus	Auditory hallucinations



Anterior limb of the internal capsule





Parietal portion of the cingulum bundle

Superior occipito-frontal fasciculus

Arcuate fasciculus

Inferior occipito-frontal fasciculus

Diffusion Tractography

- Fiber tractography is a new method to visualize white matter fiber bundles to understand brain connecticity using

- Studies suggest that the most prominent white matter abnormalities in schizophrenia appear to be in the inferior and superior longitudinal fasciculi, uncinate fasciculus, and corpus callosum

FUNCTIONAL NEUROIMAGING

- A procedure that measures brain activity by detecting associated changes in blood flow
- PET studies – receptor function
- fMRI- Brain-behaviour research

fMRI

- Sub-type of MRI
- Maps brain function
- Blood oxygenation level–dependent (BOLD)

1. Block
2. Event

- arterial spin–labeled (ASL)

FINDINGS IN SCHIZOPHRENIA

- COGNITION
- Diffuse deficits in fronto-temporal systems- impairment in learning, memory and executive function
- Long-term memory- Decreased activation of inferior pre-frontal area with hippocampal dysfunction- disrupted fronto-temporal connectivity
- Verbal task- positive correlation between STG and prefrontal cortex
- Verbal encoding- reduced temporal–dorsolateral prefrontal cortex connectivity

FINDINGS IN SCHIZOPHRENIA

- Reduced activation in parietal lobes, right thalamus, and prefrontal cortex, implicated in the dorsal visual processing pathway in patients

- Reduced activation in regions involved in target and novelty processing in patients

FINDINGS IN SCHIZOPHRENIA

- EMOTION

- Reduced limbic activation
- Abnormally increased limbic activation time locked to the appearance of threat-related facial emotions
- increased amygdala activation for fear was associated in patients both with failure to identify the emotion and with more severe flat affect

FINDINGS IN SCHIZOPHRENIA

PHARMACOLOGY

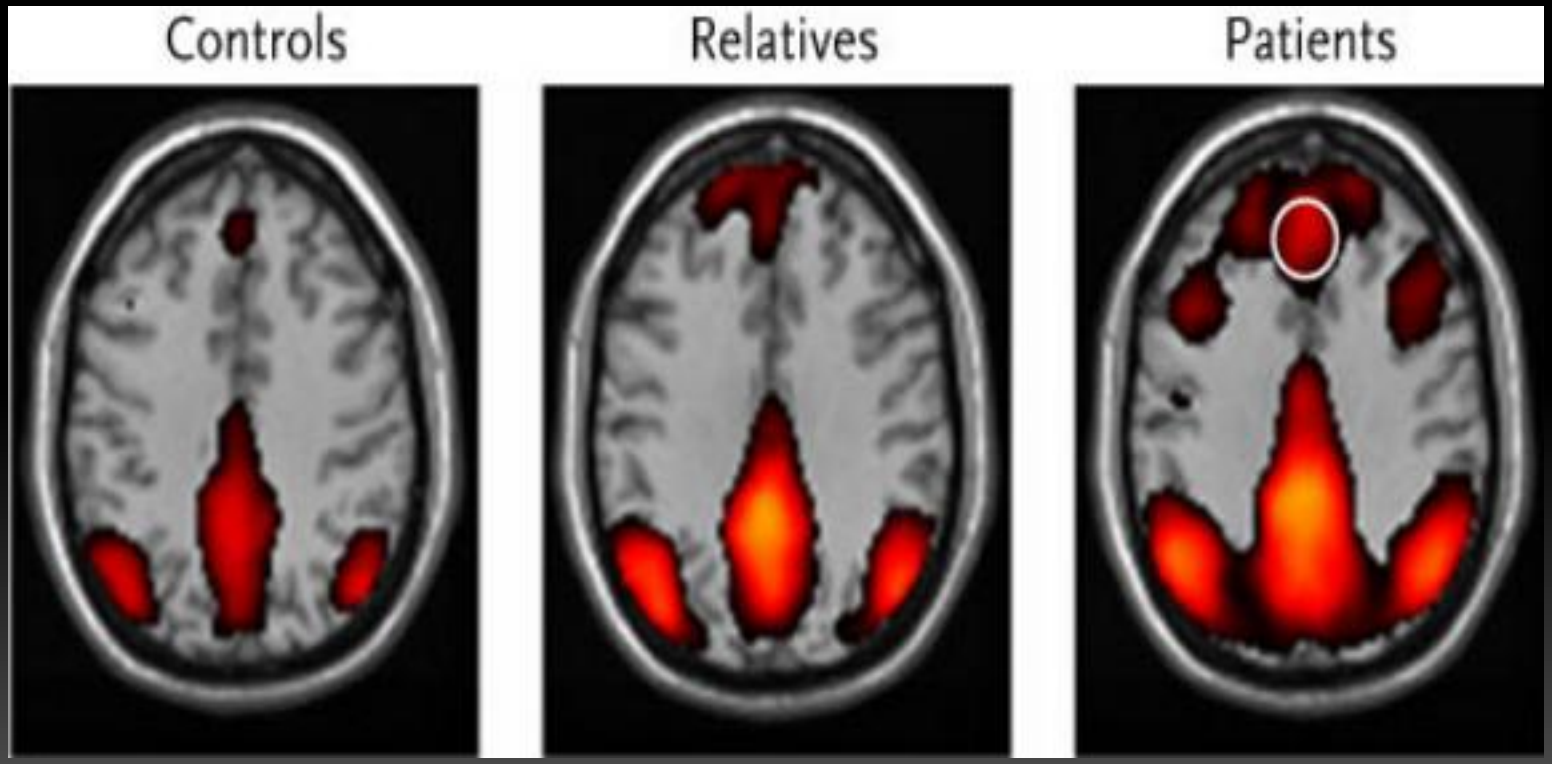
- In 2nd generation antipsychotics as compared to 1st generation

1. Increased dorsolateral prefrontal cortex and parietal cortex activity
2. normalization of brain activity in performing n-back task
3. Normalization of prepulse inhibition

Genes and brain abnormalities

- The risk allele for GRM3 in the promoter region - decreased activation of prefrontal and temporal lobe cortex- impaired working memory
- Study of activation in probands, siblings and healthy subjects
- The incorporation of functional neuroimaging into genomic studies has potential for constructing mechanistic models for the pathophysiology of schizophrenia

Inappropriate activity of default network during mental tasks and atypical synchrony such as in medial prefrontal cortex



MOLECULAR IMAGING

Molecular Imaging

- To visualize the metabolism and other physiological processes in the living brain- PET , SPECT, MRS
- MRS has the ability to image amino acids
- PET and SPECT molecular image methods provide information of neurotransmitter metabolism, transporters and receptors

SPECT

Molecular Imaging

- A radioactive isotope is injected & decays, emitting a β^+ particle.
- Within a short distance, the β^+ particle bumps into an electron & the two annihilate, producing a pair of g - rays.
- By detecting & reconstructing where the g - rays come from, we can measure the location & concentration of radio-isotope.

PET

Definition of NMR Spectroscopy

Nuclear magnetic resonance spectroscopy: commonly referred to as NMR, is a technique which exploits the magnetic properties of certain nuclei to study physical, chemical, and biological properties of matter

Compared to mass spectrometry, larger amounts of sample are needed, but non-destructive

Molecular Imaging..

- [^{18}F]-FDG PET is a technique used to estimate the density and distribution of [^{18}F]-FDG, a radioligand incorporating a metabolite of glucose in the brain to indirectly measure glucose concentration

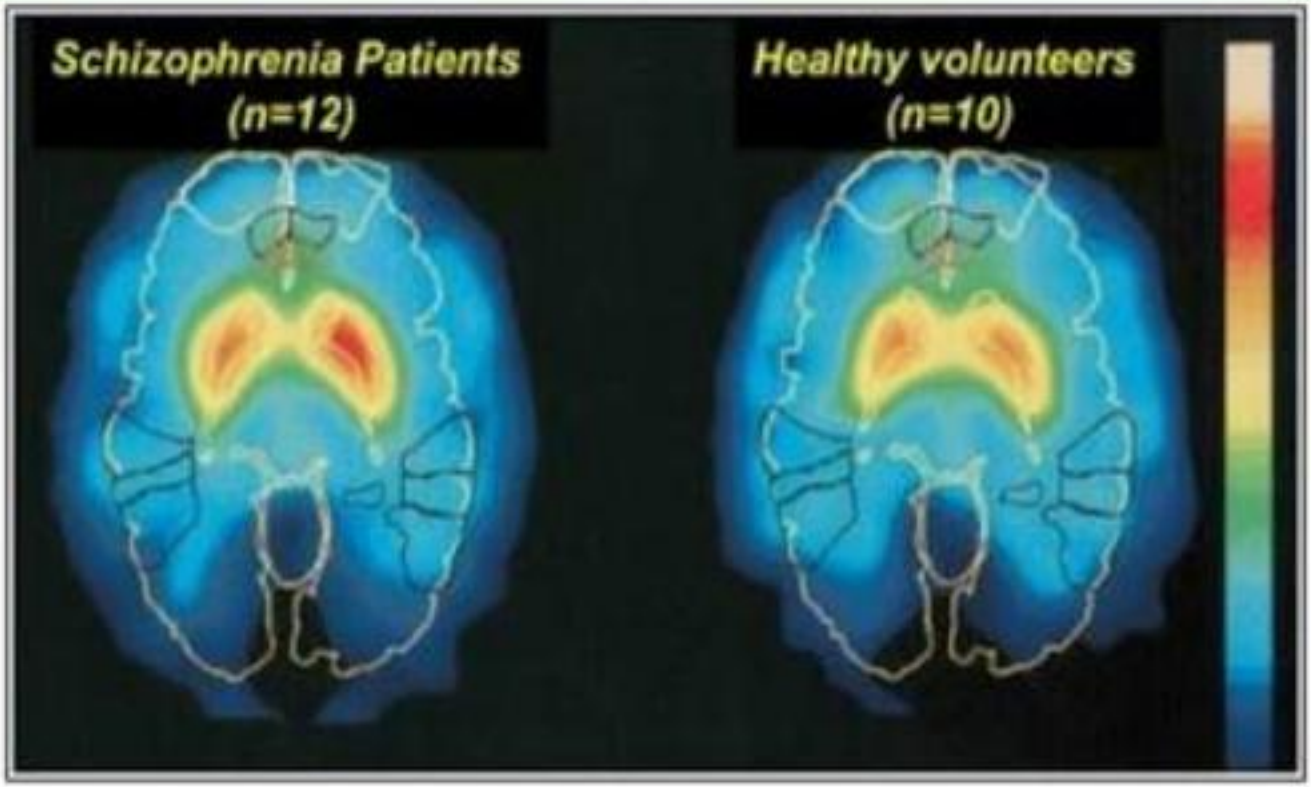
- Concentrations of dopamine and serotonin cannot be directly measured in the brain
- Radiotracers exist to estimate the density and distribution of the presynaptic and post-synaptic dopamine transporter (DAT) and serotonin transporter (SERT)

Molecular Imaging findings

- Studies of regional cerebral glucose metabolism- hypofrontality

- PET with radioactive water -reduced blood flow in the frontal cortex, anterior cingulate, cerebellum, and thalamus in the left hemisphere with possibly compensatory increased blood flow in the right hemisphere

SCHIZOPHRENIA



FDG PET comparing patients with schizophrenia (left) with normal subjects (right) shows increased metabolism in the stratum and medial prefrontal cortex in schizophrenia patients.

Molecular Imaging of Dopamine

- Significant elevation of striatal D_2 receptors, association between increased D_2 receptor density and positive symptoms
- DOPA uptake was higher in people with schizophrenia and other psychoses in contrast to healthy matched controls
- Elevated fluorodopamine turnover shown to coexist with decreased steady-state storage of FDOPA and its decarboxylated metabolites in the caudate nucleus and amygdala of untreated people with schizophrenia- correlate inversely with positive symptoms

Molecular Imaging of Dopamine

- Reduced striatal D_1 receptors in the affected twins who were on medications compared to the unaffected co-twins

- Associations between D_1 receptor density in the dorsolateral prefrontal cortex and impairments in working memory performance and negative symptoms

Molecular Imaging of Dopamine

- Researchers showed significantly greater decreases in benzamide binding potentials- an increase in occupancy of the D_2-like sites such that the radiolabeled benzamides cannot bind to them

- dopamine release is greater in patients who have more positive symptoms at the time of scanning

Molecular Imaging of Dopamine

- Patients with greater elevations in D_2 receptor binding demonstrated greater improvement in positive symptoms with antipsychotic treatment
- Small but definite elevation of D_2 receptors in schizophrenia
- Decreased D_2-like receptor binding in the thalamus.
- Also decreases have been shown in the temporal cortex, amygdala, and cingulate cortex

Molecular Imaging of Dopamine

- A lower tonic and Higher phasic dopamine
- Up-regulation of the presynaptic enzymes of DOPA decarboxylase
- Elevated amphetamine-induced dopamine release
- Elevated D_2-like receptor postsynaptic in response to the lower tonic dopamine

Molecular Imaging of Serotonin

- Significant decreases in 5-HT_{2A} receptor binding in prefrontal cortex in drug-naive schizophrenic patients
- Decrease in cortical binding in drug-free patients
- Increase in 5-HT_{1A} receptor binding in multiple brain regions, including medial temporal cortex using PET
- Decreased binding in the amygdala
- Decrease in SERT in frontal cortex and in cingulate cortex

Molecular Imaging..

Molecular Imaging of Cholinergic Receptors:

- marked decrease of muscarinic acetylcholine receptor (mAChR) in schizophrenia

Molecular Imaging of Histamine H_1 Receptors:

- reductions of BP values for H_1 receptors in the frontal and prefrontal cortices and the cingulate gyrus among medicated patients with schizophrenia

Molecular Imaging

D_2 Receptor Occupancy and Effects of Antipsychotics:

- Clinically effective doses of typical neuroleptics occupy D_2-like dopamine receptors in the range between 65 and 90%
- A "therapeutic window" between 60 and 80% striatal D_2 receptor occupancy for sufficient treatment response
- A "ceiling" of around 80 percent occupancy for EPS – protective efffect of 5-HT_2 antagonism of 2nd generation antipsychotics lost above D2 receptor occupancy above 80%

Molecular Imaging and Genetics

- Increased cortical D_1 and caudate D_2 densities observed in monozygotic compared to dizygotic siblings of patients

- Decrease in the prefrontal and cortical binding of 5-HT_{2A} receptors in subjects at enhanced risk of schizophrenia

- Subjects at risk who developed a first-episode psychosis showed decrease of 5-HT_{2A} receptor binding potential in the caudate compared to “nonconverters” -

SUMMARY

- MRI- Diffuse grey matter loss with ventricle enlargement
- DTI- Reduced anisotropy in majority white matter connections, reduced left-right asymmetry
- fMRI- Diffuse deficits in fronto-temporal systems
- Clinical deficits linked to specific area abnormalities
- Molecular imaging- dopamine and seretonin abnormalities
- Neurodevelopmental origin

CONCLUSION

- BRAIN DISEASE
- Global deficits, lateral ventricular enlargement, and fronto-temporal deficits pronounced
- Clinical and diagnostic relevance yet to be established
- Future direction- multimodal studies, genetic association, larger homogenous populations

THANK YOU