Aberrant cognitive processing in schizophrenia: Insights from fMRI research

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Life time prevalence of 0.5 to 1.5 % in all known populations
- The relative numbers affected are the same in all races and all continents

Origins of schizophrenia related to the speciation event and origins of language
- (Crow, 1993, Lancet)

- "The biochemical features of schizophrenia are what made us human"
  - Horrobin, 1998

- "We are human... because some members of the human race are schizophrenic"
  - Horrobin, 1998

- But, at what costs to the sufferers??

What is schizophrenia?

Schizophrenia—History

- Egyptian Book of Hearts, part of the Ebers papyrus (2000 BC)
  - Psychological symptoms thought to emanate from heart and uterus; blood vessels, purulent or fecal matter, poisons or demons

- Hindu descriptions—in Atharva Veda (1400 BC)
  - Imbalance between the 5 bhutas (elements) and 3 doshas (humors)

- Chinese text—Yellow Emperor’s Classic of Internal Medicine (1000 BC)
  - Demonic or supernatural possession was implicated to cause psychotic behaviours
Schizophrenia: Biblical description

Lycanthropy: King Nebuchadnezzar, King of Babylon, 6th century B.C.

Pioneers of the modern concept

Emil Kraepelin (1846-1926)

Eugen Bleuler (1857-1939)

Schizophrenia

(1911)

Dementia praecox

(1893)

Major advances in the 20th century

- Dopamine: a neurotransmitter in the brain
- Antipsychotics: exert their action by blocking dopamine receptors
- First-generation antipsychotics
  - Effective against positive symptoms
  - Ineffective for / possibly worsen negative symptoms
- Second generation antipsychotics
  - Serotonin-Dopamine antagonists

DA model of schizophrenia pathophysiology

Pitfalls of the DA model

- No demonstrable intrinsic DA deficits
- "Subcortical hyperdopaminergia co-existing with cortical hypodopaminergia"—paradoxical mechanism
- DA dysfunction, in general, accounts poorly for symptom classes in schizophrenia other than positive symptoms
  - Thus, alternative conceptual models of schizophrenia are required.
Glutamate hypothesis of schizophrenia

Tested the glutamate hypothesis of schizophrenia

Gordon, 2010, Nature Neuroscience

- The most abundant endogenous amino acid excitatory neurotransmitter
- Plays an important role in functions of learning and memory
- Under abnormal conditions, may behave as neurotoxin

L-Glutamate

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NMDA Receptor—Structure

NMDA receptor modulators

- Magnesium
- Phenylcyclidine
- Zinc
- Glycine
- Polyamines

NMDA hypofunction theory of schizophrenia

- Initial studies conducted with PCP in the early 1960s showed psychiatric symptoms and cognitive deficits that are highly reminiscent of schizophrenia
- Impaired working memory, response inhibition and executive processing
- These findings support the etiological involvement of NMDA dysfunction in the pathophysiology of schizophrenia

Javitt, 2010

NMDA hypofunction theory of schizophrenia

Confirmation using a knock-out mouse model

Postnatal NMDA receptor ablation in corticolimbic interneurons confers schizophrenia-like phenotypes

Belforte et al., 2010, Nature Neuroscience
Functional Magnetic Resonance Imaging (fMRI)

Magnetic Resonance Imaging

- Very strong magnetic field \((B_0) = 3\) Tesla
- Earth’s magnetic field: 0.5 Gauss
- 1 Tesla = 10,000 Gauss
- 3 Tesla = 3 x 10,000 Gauss
- 0.5 = 60,000 x Earth’s magnetic field

Nuclear Magnetic Resonance (NMR)

- Atoms with odd number of protons/neutrons spin in a magnetic field
- NMR:
  - Nuclear: properties of nuclei of atoms
  - Magnetic: magnetic field required
  - Resonance: interaction between magnetic field and radio frequency

1946: Block and Purcell
Atomic nuclei absorb and re-emit radio frequency energy

\(1^H\) aligns with \(B_0\)
Protons are abundant, high concentration in human body have high sensitivity yields large signals

Source: Robert Cox’s web slides

Longitudinal magnetization

Protons are abundant, high concentration in human body have high sensitivity yields large signals

Source: Robert Cox’s web slides

NMR

Excitation
- Increased angle of precession axis (tilts towards XY plane), becomes more synchronized
- Reduces longitudinal magnetization (along Z axis)
- Increases transverse magnetization (along XY plane)

Relaxation
- Dephasing of spins – rapid
- Transverse relaxation – T2 relaxation
- Overall magnetization vector in the XY plane

- Return of spin axis to vertical
- Longitudinal relaxation – T1 relaxation
- Overall magnetization vector in the Z direction
**Contrast in MRI**

- RF excitation and reading sequences are referred to as "MRI protocols".
- MRI protocols can be tweaked to bias towards T1 relaxation predominance or T2 relaxation predominance (T1 weighted images or T2 weighted images).

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**BOLD: basis**

- Inhomogeneities in magnetic field can result from changes in blood O2 level.
- DeoxyHb: paramagnetic (weakly magnetic).
- OxyHb: diamagnetic (not magnetic or weakly anti-magnetic).

\[ \text{Hb} + \text{O}_2 \leftrightarrow \text{HbO}_2 \] (deoxyHb) (oxyHb)

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**BOLD signal**

- Neural activity \(\rightarrow\) blood flow \(\rightarrow\) oxyhemoglobin \(\rightarrow\) T2* \(\rightarrow\) MR signal.

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**BOLD: basis**

- Neuro-vascular coupling:
  - Vascular density proportional to synaptic density.

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**fMRI: BOLD time series**

- Most energy is spent on glutamate re-uptake.

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**Ogawa**

**Source:** Brief Introduction to fMRI by Irene Tracey

**Source:** Jorge Jovicich

**Ogawa**

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**Source:** Ogawa 1992: Ogawa and colleagues - first functional images using BOLD signal.
fMRI: hemodynamic response

Semantic word generation

- The best candidate cognitive endophenotype of schizophrenia
  - Szoke et al., 2008
- Semantic verbal fluency has higher discriminatory power than phonological verbal fluency
  - to differentiate schizophrenia v. healthy subjects

Word generation vs. word repetition

- Experimental condition
  - Overt, paced, visually-cued, semantic category word generation task with clustered volume acquisition
  - Categories: animals, vegetables, birds, fruits, flowers, trees
- Baseline condition
  - Overt, paced, visually-cued, word repetition task with clustered volume acquisition
  - Repeat the word ‘pass’

Verbal fluency fMRI task design

Overview of SPM analysis

fMRI analysis: GLM
The General Linear Model

\[ y = X\beta + \varepsilon \]

- **Observed data** = Predictors * Parameters + Error

\[ y = X\beta + \varepsilon \]

**Design matrices for second-level analysis**

- Uncorrected threshold of \( p < .001 \)
- Familywise Error (FWE)
- Bonferroni correction
  - E.g.: \( .05/100,000 = .0000005 \)
- False Discovery Rate (FDR)
  - Adjusts the criterion used based on the amount of signal present in the data
  - Reduce the number of comparisons
    - E.g.: Instead of examining the entire brain, examine just a small region
    - IMPORTANCE of taking into account the multiple comparisons across voxels but also the multiple comparisons across contrasts (i.e., the number of contrasts tested)

**Choosing a statistical threshold**

**Aberrant activations and deactivations during semantic word generation**

- BOLD activations in Healthy Controls \( N=24 \)
- BOLD activations in Schizophrenia subjects \( N=24 \)
- BOLD deactivations in Healthy Subjects \( N=24 \)

**Healthy vs. Schizophrenia subjects**

- John et al., British J Psychiatry, 2011
Implications for schizophrenia pathophysiology

- Inefficient activations and deficient deactivations
  - ? the core neurophysiological disturbance in schizophrenia

- Deficient deactivations - ? neurophysiological signature of the "defective cognitive filter" in schizophrenia

- ? Aberrant Glu-signalling underlying the above aberrant neurophysiology

Clinical implications

- Provides a more comprehensive and accurate model of schizophrenia pathophysiology

- Potential to guide future drug development
Take home points!!

- Schizophrenia—a heterogeneous disorder
- Aberrant cognitive processing
- Probably mediated by aberrant glutamatergic signaling with involvement of other neurotransmitters
- NMDA hypofunction results in excessive activations and deficient deactivations

Take home points!!

- fMRI research provides in vivo evidence for excessive activations and deficient deactivations in schizophrenia
- The above findings constitute supportive evidence for the glutamate-centric hypothesis of schizophrenia
- Implications for schizophrenia pathophysiology and therapeutics

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fMRI methods: Sources

- Wellcome Department of Imaging Neuroscience, UK
- Ashburner, Friston et al.
- Sebastian & Fontaine
- Schwingenschuh
- Hutton
- Denison & Quailo
- SPM: Methods for Dummies 2007