Functional Neuroimaging in Schizophrenia

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Epidemiology and Impact

- 1% of the population
- Young people (15 – 35 years)
- Most devastating psychiatric disease
- 30% of psychiatric admissions
- Limited response to antipsychotics in many patients
- Functional imaging has a major role in research
- Not formally indicated in clinical practice
Hipofrontality in Schizophrenia

- Present before treatment
- Not specific for schizophrenia
- Enhanced by neuroleptics
- Related with:
  - cognitive function
  - negative symptoms
  - chronicity
Hipofrontality in Schizophrenia

Berman KF, et al. Arch Gen Psychiatry 1992;49(12)
Cognitive dependent hipofrontality

Weinberger DR et al. Arch Gen Psychiatry 1986;43:113-124
Cognitive dependent hipofrontality

Lower activations in chronic vs. recent onset schizophrenia

Working memory dysfunction in schizophrenia

Neural correlates of symptoms in schizophrenia

- **REALITY DISTORTION**
  - (+) hippocampus, ventral striatum
  - (-) left lateral temporal

- **DESORGANIZATION**
  - (+) anterior cingulate, dorsomedial thalamus
  - (-) lateral orbitofrontal

- **PSHYCOMOTOR POVERTY**
  - (+) striatum
  - (-) dorsolateral prefrontal

*Liddle PF, Friston KJ, et al. 1992*
X y/o male. Negative symptoms, desorganization, violent behavior.

Decreased rCBF (arrowheads) - Increased rCBF (white arrows)
X y/o male. Desorganization, antisocial behavior, not aggressive or violent.
Decresed rCBF (arrowheads) - Increased rCBF (white arrows)
X y/o female. Desorganization, psychomotor poverty, cognitive impairment.
Decresed rCBF (arrowheads) - Increased rCBF (white arrows)
Functional neuroanatomy of hallucinations in schizophrenia

5 treated schizophrenia patients with auditory verbal hallucinations

1 patient with auditory verbal and visual hallucinations

Dopamine hyperactivity in schizophrenia

Increased amphetamine induced dopamine release

Laruelle M et al. PNAS USA 1996
D2 receptor occupancy by antipsychotics

- Clozapine (x10 mg)
- Risperidone (x0.2 mg)
- Haloperidol

Graph showing the relationship between dose (mg/kg BW) and D2 receptor occupancy, with regression lines and their respective coefficients.
D2R occupancy, clinical response, extrapyramidal signs and hyperprolactinemia

22 schizophrenia patients treated with haloperidol

A) Clinical response
B) Prolactinemia

D2 and 5HT2 receptor occupancy by haloperidol, olanzapine and risperidone and clinical response

Kapur S et al.
Am J Psychiatry 2001;158:360
Fast dissociation of atypical antipsychotics: a possible explanation of the mechanism of action

Serotonin modulation of DA response

Decreased D2R availability (increased occupancy by DA) in 11 normal subjects 3 hs after fenfluramina administration (serotonin release stimulant and reuptake inhibitor)

Prefrontal D1R and WM: cortical DA hypofunction

Compensatory D1R increase correlated with WM dysfunction

Prefrontal control of subcortical DA activity

Meyer-Lindberg A et al.

*Nature Neuroscience*

2002;5(3):267-271

a) rCBF WCST > basal
b) WCST

c) rCBF WCST > basal

normal controls vs. patients

18F-DOPA

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PF rCBF vs F-DOPA

NC

patients
Deficit in prefrontal-subcortical connectivity

Prefrontal control of subcortical DA function

A deficit in glutamate (1) and/or GABA (2) and/or DA (3) neurotransmission can result in a failure of prefrontal cortex inhibition of subcortical DA activity under conditions of excessive stimulation (stress, amphetamine, etc.)
Dopamine hypothesis of schizophrenia
Glutamate and schizophrenia

NMDA (n-metil-D-aspartate) receptors

- Pre and post-synaptic post-mortem alterations

- Pharmacological blockade (ketamine, MK801):
  - psychotic symptoms including negative
  - increase of mesolimbic DA release
Ketamine increases AMP induced DA release

GLUTAMATERGIC MODULATION OF MESOLIMBIC DOPAMINE

8 normal subjects. NMDA receptor blockade induced an excessive DA release similar to that described in schizophrenic patients.

Kegeles LS et al. Biol Psychiatry 2000; 48:627-40
First in vivo evidence of an NMDA receptor deficit in medication-free schizophrenic patients

Glu-DA hypothesis of schizophrenia

(-) SYMPTOMS
- Synaptic plasticity
- Dysconnectivity

(+ ) SYMPTOMS
- mGluR
- 5-HT
- Ach
- NA

GLU

Mesolimbic DA

GLU

Cortex

D2

D1

NMDA

GABA

Striatum
Functional imaging in patients at risk for schizophrenia

**Increased AMP induced DA release in 13 patients with schizotypal personality disorder**

Pharmacogenomics in schizophrenia: the quest for individualized therapy

Imaging Genomics and Response to Treatment with Antipsychotics in Schizophrenia

COMT genotype

FIG. 3. Hypothetical effect of COMT val$^{158}$met genotype in contributing to determine individual variability in response to treatment with second-generation antipsychotics in schizophrenia. Second-generation antipsychotics increase dopamine levels in prefrontal cortex and they might also increase dopamine receptor D1/D2 ratio, thus improving prefrontal cortex function. Given the slower inactivation of prefrontal dopamine of the COMT metmet enzyme, these subjects may benefit from greater prefrontal dopaminergic signaling in terms of prefrontal cortex efficiency compared with valval subjects.

Summary

- Hypofrontality correlated with negative symptoms
- Cognitive dependent hypofrontality
- Impaired prefronto-lymbic functional connectivity
- (+) symptoms
  - Excessive DA release
  - Prefrontal hypoactivity
- (-) symptoms
  - NMDA hypofunction
  - Cortical DA hipoactivity
- Drug development, individualized therapy
- Biological marker of risk for schizophrenia