Topography and significance of the dopaminergic dysfunction in schizophrenia

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Disclosures (last 36 months)

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OUTLINE

1- Schizophrenia as a global brain disease
2- The role of dopamine within this global pathology
3- Imaging dopamine
4- Findings in striatum
5- Findings in extrastriatal brain areas
6- Modeling dopamine dysfunction in mice
7- Synthesis and future directions
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Natural course of schizophrenia

Healthy

Worsening severity of signs and symptoms

Premorbid | Prodromal | Onset/deterioration | Residual/stable

Gestation/birth | 10 | 20 | 30 | 40 | 50 | Years

After Lieberman et al
Symptom clusters involve all functional domains

**Perception:** Psychosis
- Hallucinations
- Paranoia
- Thought disturbance

**Cognition:** Cognitive deficits
- Working memory
- Executive function
- Social cognition

**Movement abnormalities:**
- Stereotypies
- Catatonia

**Reward deficits**
- Anhedonia

**Mood disturbances**

Schizophrenia is a GLOBAL brain disease
Structural (anatomical) MRI

Relevant findings: morphometry in schizophrenia

Ellison-Wright et al. AJP 2008
Prefrontal Cortex in Schizophrenia: abnormal microcircuitry

Lewis DA, Lieberman JA. Neuron 2000
Functional MRI

Auditory cortex is abnormal: hyperactive during silence

Horga G, Schatz KC, Abi-Dargham A, Peterson BS, J Neurosci 2014
Diffusion Tensor Imaging (DTI) MRI

Structural connectivity in schizophrenia: abnormal fronto-temporal and genu of corpus callosum connectivity

Lener et al. Schizophr Bull 2015
Gadolinium-enhanced T1

CBV in schizophrenia is enhances in CA1 of hippocampus in schizophrenia and prodrome, predicts conversion

Schobel et al. AGP 2009
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Dopaminergic Pathways

mPFC OFC

DLPFC

MOTOR

VTA

SN

Courtesy of Suzanne Haber
Howes et al, Archives of Gen Psychiatry 2009
Dopamine encodes reward prediction-error (rPE)

Schultz et al., O’Doherty et al., Daw et al., Glimcher et al.
Dopamine modulates the balance of Excitation/inhibition in the prefrontal cortex

Adapted from D. Lewis
Dopamine is historically related to symptomatology and treatment

- Antipsychotic properties of chlorpromazine (Delay & Denicker, 1952)
- Dopamine turnover increased by antipsychotics (Carlsson & Lindqvist, 1963)
- Overstimulation of DA receptors in SCZ (Van Rossum, 1966)
- DA agonists produce psychosis (Angrist and Van kammen 1984, Lieberman 1987)
- All antipsychotics are D2 drugs, D2 potency dictates clinical dose (Seaman, Snyder…).

**This lead to numerous hypotheses:**
- First hypothesis: mesolimbic DA excess
- Second hypothesis: subcortical excess and cortical deficit (Weinberger 1987, Davis, 1990)
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Imaging the striatal dopaminergic synapse

[18F]f-DOPA: synthesis and presynaptic storage (activity of Aromatic L-amino acid decarboxylase, AADC)
(but also uptake in DA neurons, VMAT activity and uptake in vesicles, pH in vesicles, metabolism in cytoplasm...)

VMAT2 radiotracers: [11C]DTBZ


(but also affected by dopamine occupancy, internalization, affinity state...)

Presynaptic

Postsynaptic STR medium Spiny neuron
Imaging synaptic Dopamine

Baseline

Amphetamine Challenge

Alpha-methyl-para-tyrosine

D2 radiotracer

Dopamine
D2/3 PET radiotracers

[11C]raclopride

[11C]Fallypride

[11C]FLB457
FUNCTIONAL SUBDIVISIONS OF STRIATUM

LIMBIC ASSOCIATIVE SENSORIMOTOR

PRECOMMISSURAL (ANTERIOR)

POSTCOMMISSURAL (POSTERIOR)
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STRIATAL dopamine alterations in schizophrenia

Dopamine “synthesis”
- Reith et al., 1994
- Hietala et al., 1995, 1999
- Lindstorm et al., 1999
- Meyer-Lindenberg et al., 2002
- McGowan et al., 2004
- Nozaki S et al., 2009
- Howes et al., 2009

Dopamine “release”
- Amphetamine challenge
  - Laruelle et al., 1996
  - Breier et al., 1997
  - Abi-Dargham et al., 1998
- AMPT
  - Abi-Dargham et al., 2000
  - Kegeles et al., 2010

$D_2$ receptors
- Meta analyses
  - Weinberger & Laruelle, 2001
  - Howes et al., 2012

$D_1$ receptors Normal
DAT and VMAT2: Normal

Presynaptic

Postsynaptic STR medium Spiny neuron

Tyrosine $\xrightarrow{DOPA}$ Tyrosine hydroxylase
\[ \xrightarrow{DOPA} \]
\[ \xrightarrow{AADC} \]

Dopamine $\xrightarrow{VMAT}$$D_2$ receptor

MAO $\xrightarrow{COMT}$$D_2$ receptor

DAT

STRIATAL dopamine alterations in schizophrenia
Intrasynaptic dopamine in STR subdivisions in SCZ

Healthy controls (n = 18)  Patients with schizophrenia (n = 18)

* p < 0.05

Kegeles et al, Archives of Gen Psychiatry, 2010
Striatal Dopamine Release predicts Psychotic Symptoms

Schizophrenia, n= 34

$r_p = 0.55$

STRIATUM

Change in Psychosis scores (PANSS)
Intrasynaptic baseline DA predicts psychosis treatment response

\[ r^2 = 0.58, p < 0.001 \]

Abi-Dargham et al, PNAS, 2002
DA synthesis predicts psychosis treatment response

Demjaha et al, AJP, 2012

a The treatment-resistant group showed significantly lower dopamine synthesis capacity than the treatment responders (p=0.02, corrected for multiple comparisons). There were no significant differences between treatment-resistant patients and healthy volunteers. Error bars indicate standard deviation.
Striatal Dopamine Release predicts Psychotic Symptoms

Schizophrenia, n= 34

\[ r_p = 0.55 \]

STRIATUM

SCZ DD, n=10

\[ r_s = 0.69 \]
\[ (r_p = 0.62) \]

ROSTRAL caudate

Change in Psychosis scores (PANSS)
Negative Symptoms inversely related to Dopamine Levels in Ventral Striatum

Kegeles LS et al. Arch Gen Psychiatry 2010;67(3):231-239
Striatal D2 stimulation predicts Psychotic Symptoms

Schizophrenia, n= 34
\[ r_p = 0.55 \]  
STRIATUM

SCZ DD, n=10
\[ r_s = 0.69 \]
\[ (r_p = 0.62) \]
ROSTRAL caudate

[\[^{123}\text{I}]\text{IBZM} \text{displacement (% baseline)}\]

Change in Psychosis scores (PANSS)
Figure 1. Baseline $D_{2/3}$ agonist positron emission tomography radiotracer $[^1C]N$-propyl-norapomorphine binding potential ($[^1C]NPA \text{BP}_{ND}$) in healthy control subjects (white bars) and subjects with schizophrenia (blue bars) in the striatal subdivisions. A trend-level difference was observed between healthy control subjects and subjects with schizophrenia (repeated-measures analysis of variance, $F_{1,26} = 3.34, p = .08$). Subjects with schizophrenia showed trend-level higher $[^1C]NPA \text{BP}_{ND}$ in the ventral striatum (VST; $p = .08$), precommissural dorsal caudate (pre-DCA; $p = .07$), and postcommissural putamen (post-PU; $p = .08$). Post-CA, postcommissural caudate; pre-DPU, precommissural dorsal putamen; STR, striatum.

Figure 2. Amphetamine-induced percentage change in $D_{2/3}$ agonist positron emission tomography radiotracer $[^1C]N$-propyl-norapomorphine binding potential ($[^1C]NPA \text{ BP}_{ND}$) in healthy control subjects (white bars) and subjects with schizophrenia (blue bars) in the striatal subdivisions. Amphetamine administration significantly decreased $\text{BP}_{ND}$ in all striatal regions in both groups. No differences were observed between healthy control subjects and subjects with schizophrenia on the omnibus repeated-measures analysis of variance test. A region-by-region comparison revealed a trend-level lower displacement in the precommissural dorsal caudate (pre-DCA) for subjects with schizophrenia compared with healthy control subjects ($-11.2 \pm 7.2$ vs. $19.1 \pm 13.0$, respectively, $p = .06$). Post-CA, postcommissural caudate; post-PU, postcommissural putamen; pre-DPU, precommissural dorsal putamen; STR, striatum; VST, ventral striatum.

Frankle et al
Pre or Post synaptic: the striatal DA dysregulation in schizophrenia

Slifstein and Abi-Dargham, 2018, Biol Psychiatry
Pre or Post synaptic: the striatal DA dysregulation in schizophrenia

Slifstein and Abi-Dargham, 2018, Biol Psychiatry
Dopamine synthesis in the prodrome: $[18F]f$-DOPA increased in striatum

Howes et al, Arch Gen Psych 2009
Howes et al, Molecular Psych 2011
Howes et al, Am J Psychiatry 2011