M.Capriotti

Schizofrenia

Schizofrenia

Schizo: dividere

Phrenos: mente

Mente divisa:

Separazione della mente dalla realtà

SCHIZOPHRENIA

- Chronic and disabling brain disorder
- Incidence: 1% of the world population
- Diagnosis: late adolescence or early adulthood
- Male/Female: 1/1

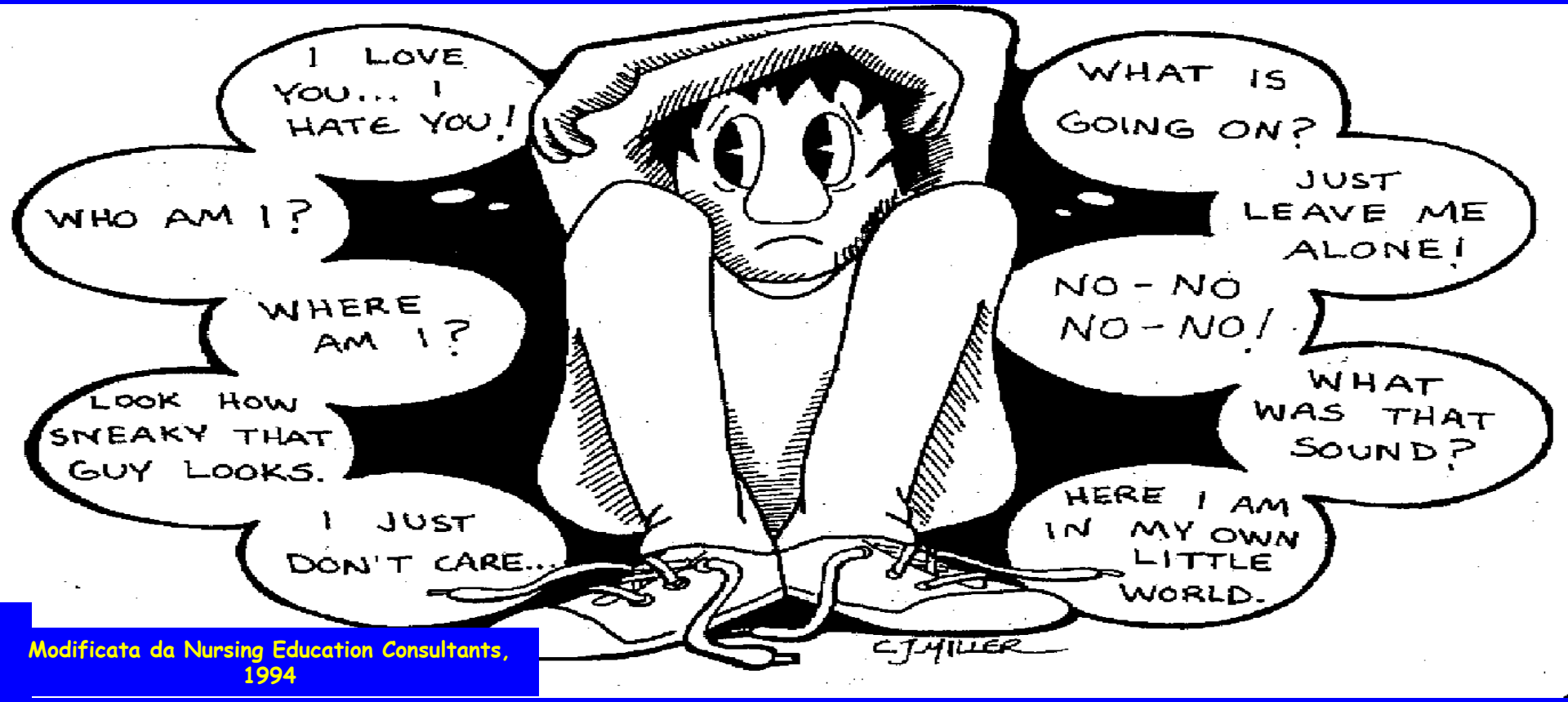
COS'E' LA SCHIZOFRENIA?

- E' una **malattia mentale** che ha cause biologiche.

Le persone affette da schizofrenia:

- hanno difficoltà a distinguere sensazioni reali da quelle fittizie (allucinazioni).
- possono avere risposte emozionali inappropriate.
- possono avere comportamenti sociali inappropriati.
- possono avere difficoltà cognitive e di concentrazione.

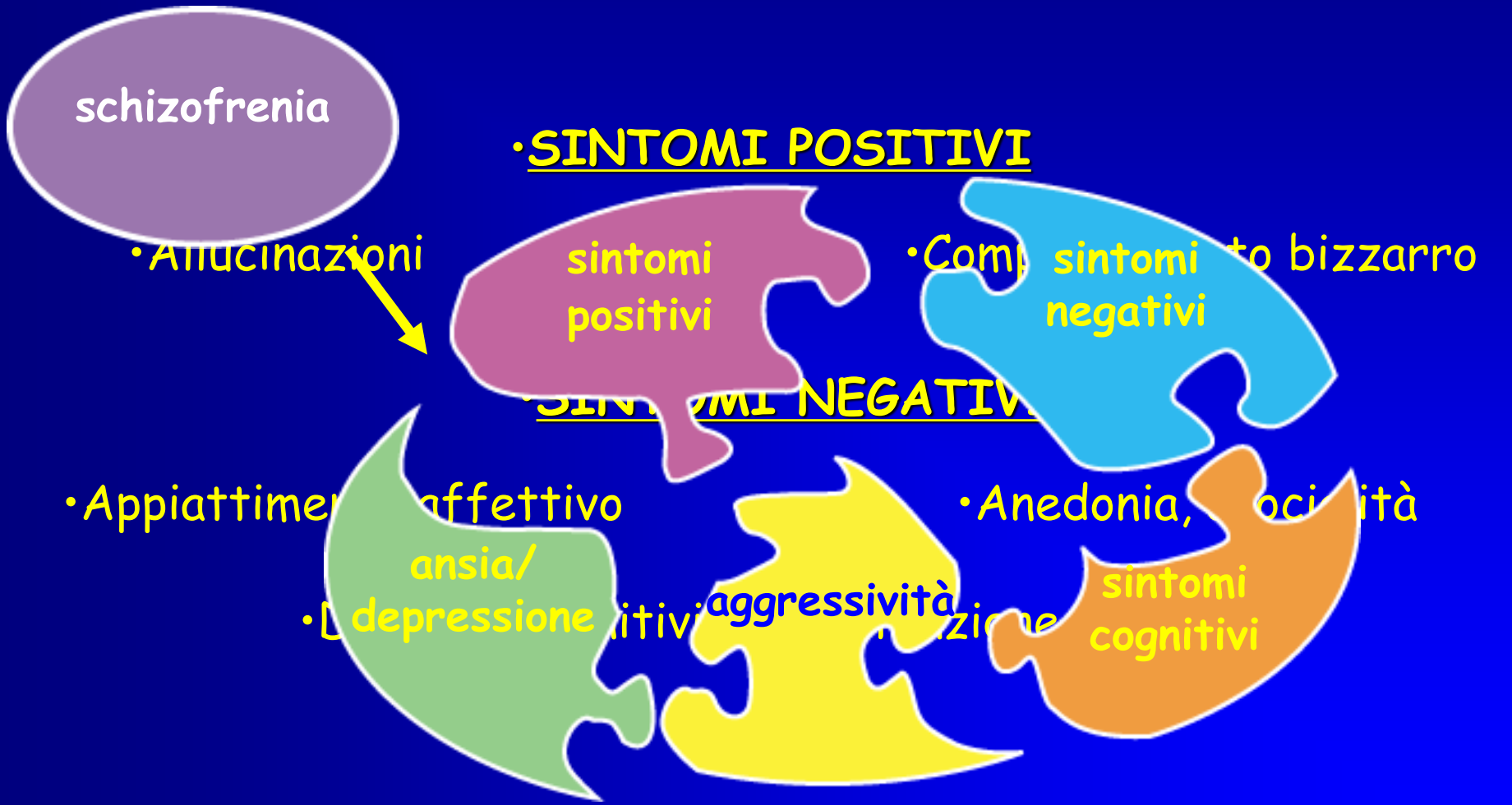
PHENOTYPE



Modificata da Nursing Education Consultants, 1994

DIAGNOSI

- E' complicata dalla presenza di diversi sintomi non specifici



(Stahl, Ess. Psychopharmacol. 2000)

POSITIVE SYMPTOMS

- *Allucinations*
- *Delusions*
- *Thought disorder*

NEGATIVE SYMPTOMS

- *Apathy*
- *Flat affect*
- *Lack of motivation*
- *Poverty of speech*
- *Social withdrawal*

COGNITIVE DEFICITS

- *Learning*
- *Memory*
- *Attention*
- *Concentration*

Sintomi della schizofrenia ed alterazioni funzionali

Sintomi positivi

Sintomi negativi

Disfunzione sociale/occupazionale

- Lavoro
- Relazioni interpersonali
- Self-care

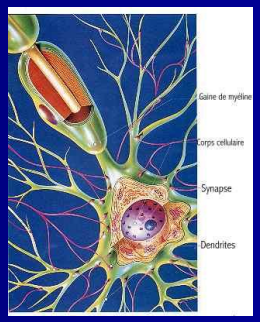
Disturbi cognitivi

Disturbi dell'umore

QUALI SONO LE CAUSE?

- Fattori genetici

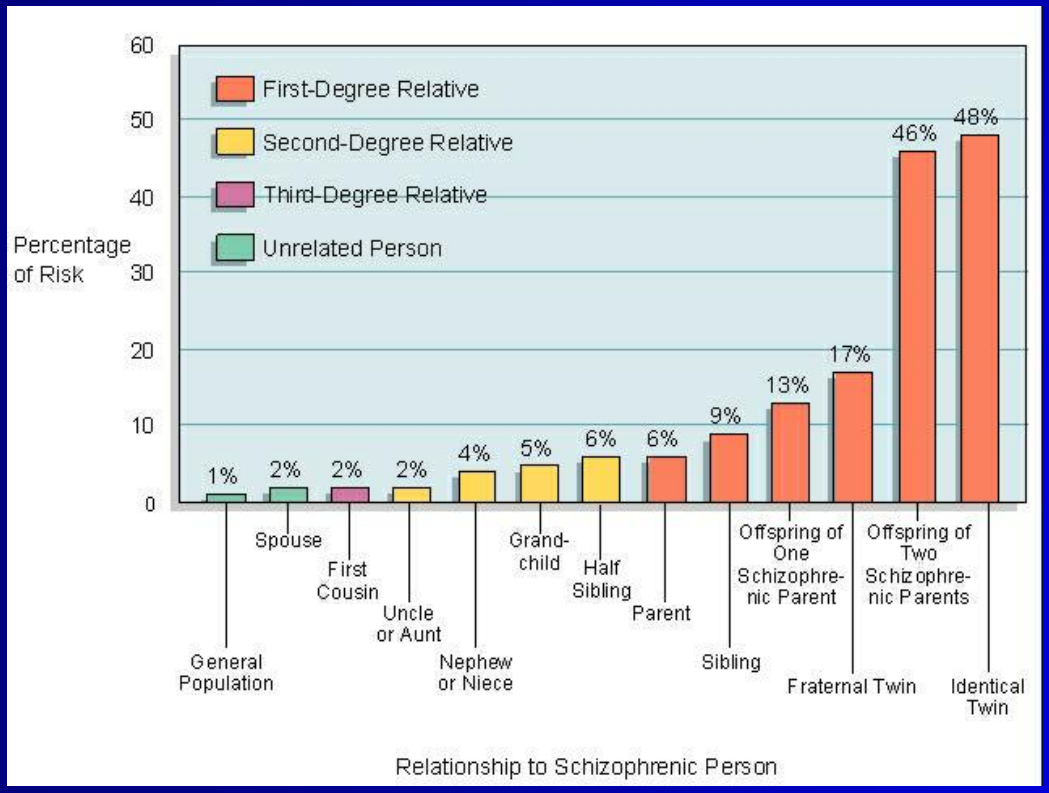
- Fattori biologici



- Fattori ambientali

❖ FATTORI GENETICI

Esiste una **vulnerabilità genetica**.
La probabilità di sviluppare questi disturbi è maggiore in soggetti i cui parenti sono affetti.



Il rischio di malattia é tanto più elevato quanto più é stretta la parentela.

1. GENETIC COMPONENT

- FAMILY STUDIES
- TWIN STUDIES
- ADOPTION STUDIES.

Only 30–50% concordance rate for schizophrenia among monozygotic twins

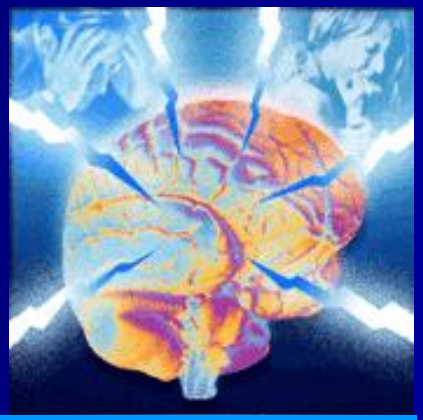
ENVIRONMENTAL OR EPIGENETIC FACTORS THAT INFLUENCE THE EXPRESSION OF THE ILLNESS.

Candidate genes

- Catecol o – metiltransferasi
- Monoamino ossidasi
- Recettori dopaminergici
- Trasportatori per la dopamina
- Recettori per la serotonina
- Recettori per il glutammato
- Neuregulin
- BDNF
- ….

- Studi di associazione

❖ FATTORI AMBIENTALI



❖ Eventi stressanti nella prima fase di vita prenatale o postnatale (es.infezioni virali, inedia, etc nella madre).

❖ Eventi avversi nei primi anni di vita (traumi,abbandono, abusi, etc).

2. NEURODEVELOPMENTAL HYPOTHESIS

- Early brain developmental disorder
- Present as early as at time of birth
- Psychotic picture later (in the second or third decades of life)

RELATIONSHIP BETWEEN SCHIZOPHRENIA INCIDENCE AND FACTORS THAT LEAVE THEIR MARK IN THE EMBRYONIC OR FETAL PERIODS

- Obstetrical complications
- Prenatal exposure to infectious agents or toxins
- Maternal nutritional deficiency
- Birth trauma

Patogenesi dei disturbi psichiatrici

EVENTI AMBIENTALI

Sistemi

Interazioni
nei circuiti neuronali

Espressione genica
e proteica

Geni di suscettibilita'

Manji e Lenox 2000

Susceptibility genes

Early cerebral hazard

CNS development

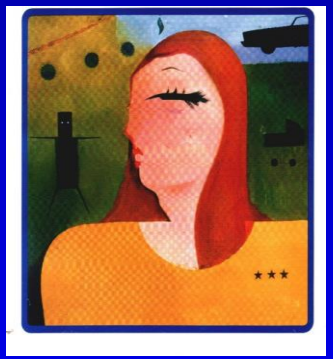
Reduced plasticity

Increased vulnerability

Social adversity

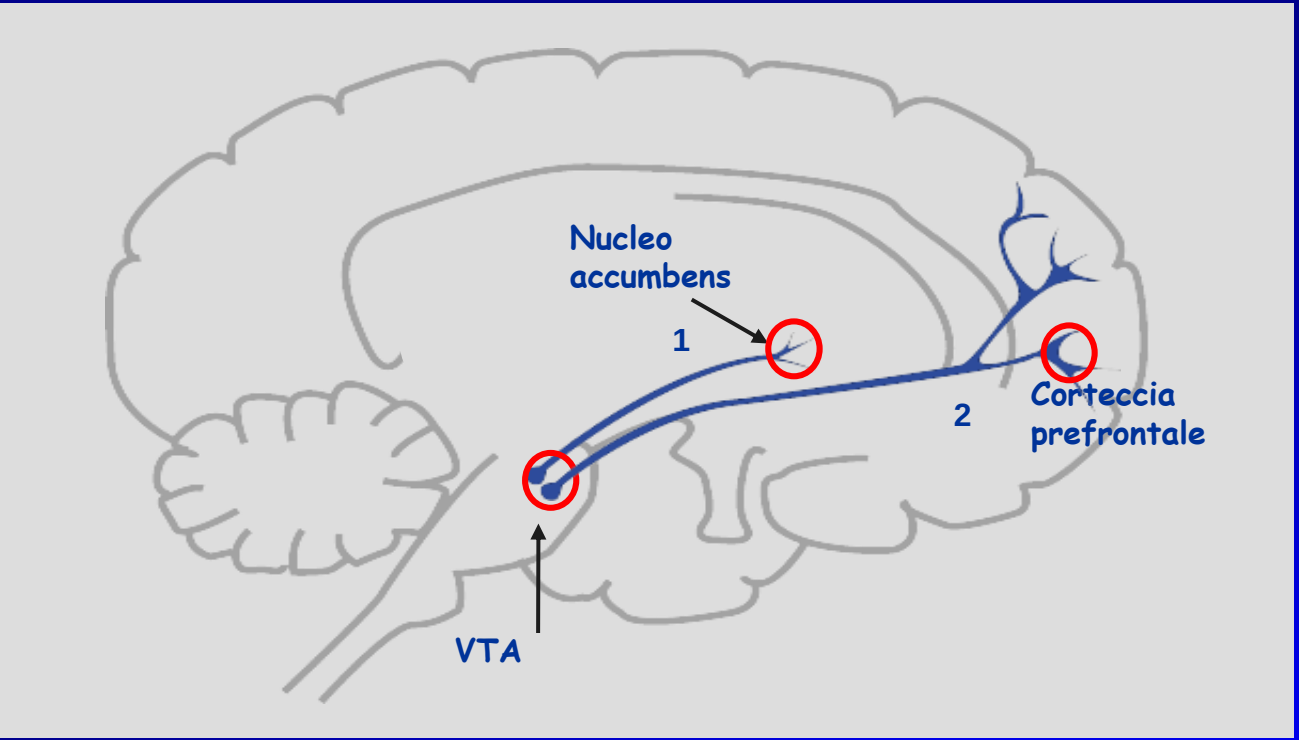
Drug abuse

Psychiatric disorders



DOPAMINE HYPOTESIS

DOPAMINERGIC PROJECTIONS TO BRAIN REGIONS IMPLICATED IN SCHIZOPHRENIA



- **Overactivity** in neurotransmission from **DA** cell bodies, located in the ventral tegmental area **VTA** of the midbrain, results in the development of psychotic symptoms.

- The **hypodopaminergic** state in the frontal cortical terminal fields of the mesocortical DA neurons has been hypothesized to be the basis of the **'negative symptoms'** and cognitive deficits of schizophrenia.

DOPAMINE HYPOTESIS

- Amphetamine abuse (wich increase the synaptic DA availability) can produce symptoms that mimic positive symptoms of schizophrenia.

- The D2 receptor is the common target of antipsychotic drugs

- Correlation between the therapeutic doses of typical antipsychotic drugs and their binding affinity for the D2 dopamine receptor.

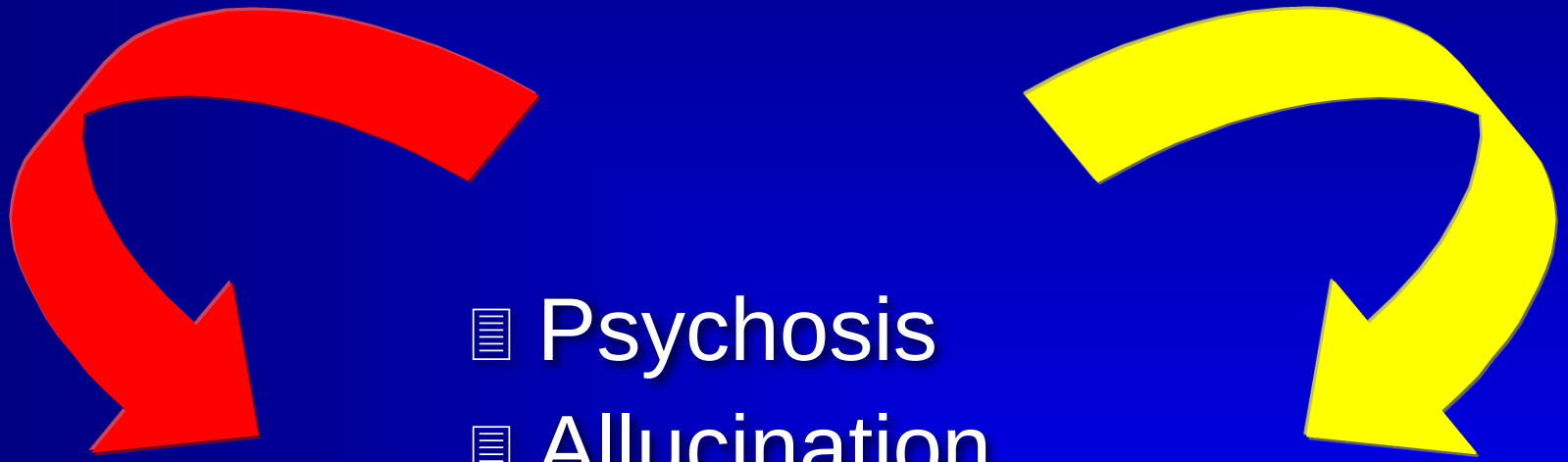
GLUTAMATE HYPOTESIS

- Phencyclidine PCP, 'angel dust', which can induce a psychotic condition mimicking schizophrenia, is a powerful antagonist of NMDA receptor.
- Hypofunction of NMDA receptor is implicated in the onset of negative symptoms and cognitive deficits.
- Hypofunction of NMDA receptor seems to be implicated in alterations of synaptic plasticity mechanisms.
- Links between DA and NMDA receptors activity

The glutamate hypothesis of schizophrenia

Schizophrenia

PCP abusers



- Psychosis
- Allucination
- Thought disorders
- Cognitive dysfunction
- Social withdrawal
- Ipofrontality

GLUTAMATE HYPOTESIS

Molecular Psychiatry (2007), 1–10

www.nature.com/mp

ORIGINAL ARTICLE

Mice lacking the AMPA GluR1 receptor exhibit striatal hyperdopaminergia and 'schizophrenia-related' behaviors

LM Wiedholz[1], WA Owens[2], RE Horton[2], M Feyder[1], R-M Karlsson[1], K Hefner[1], R Sprengel[3], T Celikel[3], LC Daws[2,4] and A Holmes[1]

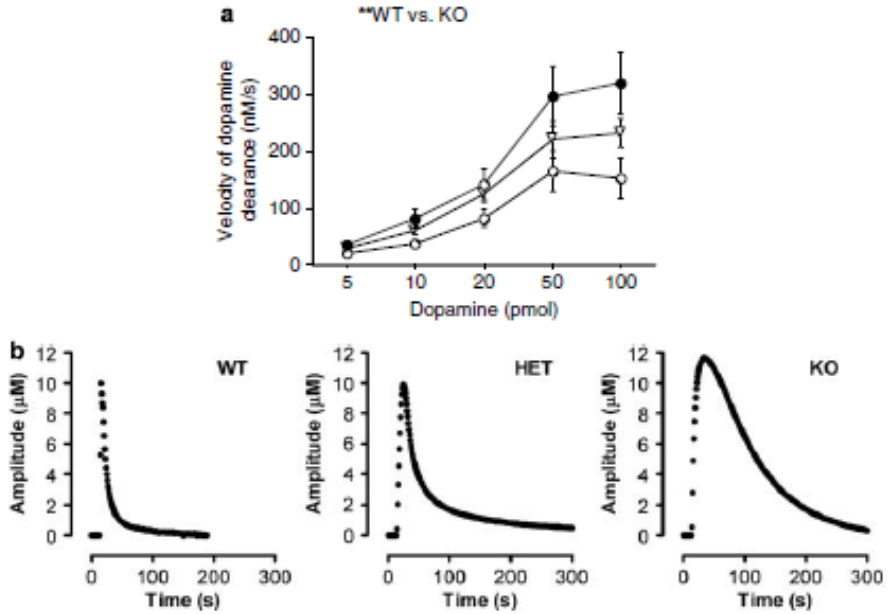
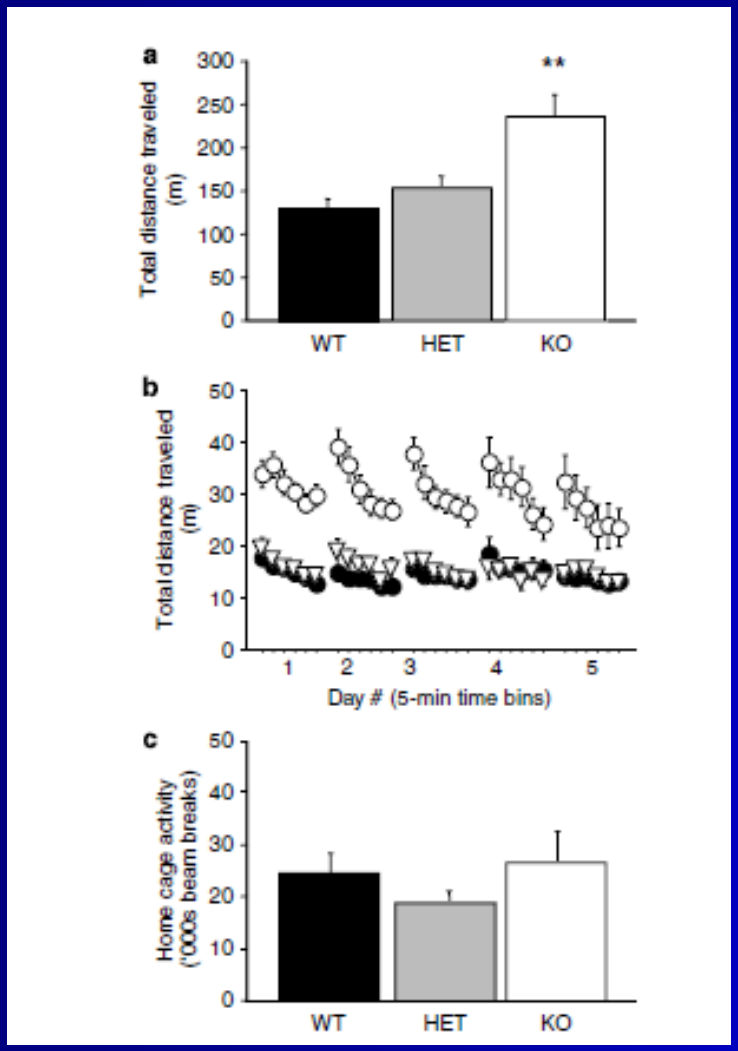
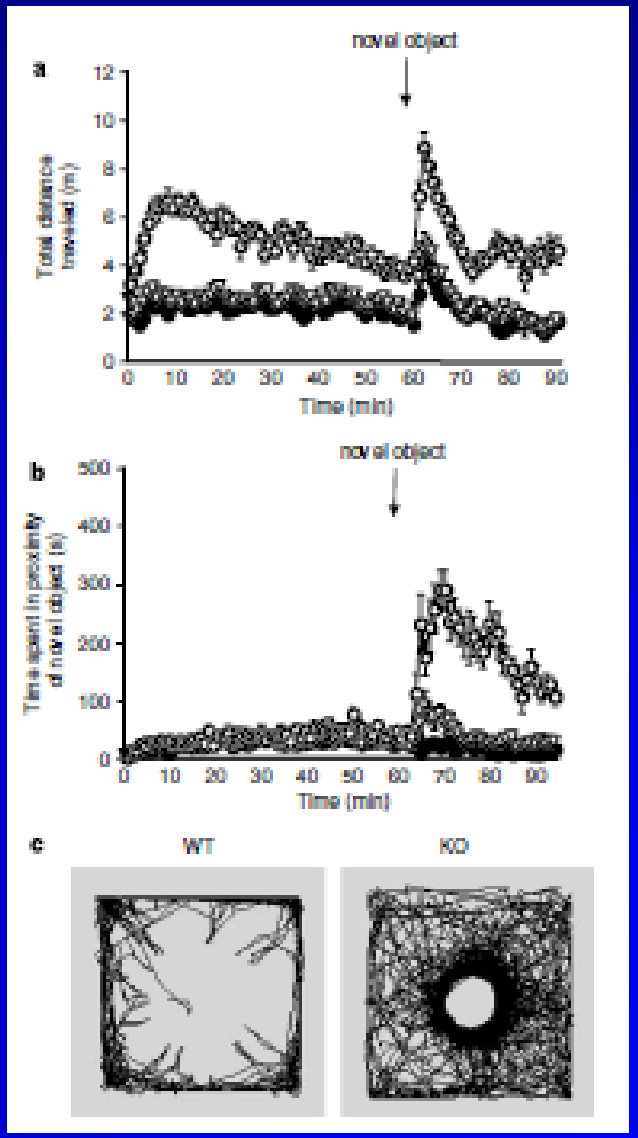


Figure 7 GluR1 knockout mice (KO) show reduced striatal dopamine (DA) clearance. KO exhibited (**a**) slower clearance of exogenously applied DA in the striatum across a range of DA concentrations as compared to WT ($n = 10–12$/genotype). Representative oxidation currents (converted to μM) (**b**). (Filled circles) WT; (open triangles) HET; (open circles) KO. $^{**}P < 0.01$.

…GLUTAMATE HYPOTESIS….





Cell, Vol. 98, 427–436, August 20, 1999, Copyright ©1999 by Cell Press

Mice with Reduced NMDA Receptor Expression Display Behaviors Related to Schizophrenia

Summary

N-methyl-D-aspartate receptors (NMDARs) represent a subclass of glutamate receptors that play a critical role in neuronal development and physiology. We report here the generation of mice expressing only 5% of normal levels of the essential NMDAR1 (NR1) subunit. Unlike NR1 null mice, these mice survive to adulthood and display behavioral abnormalities, including increased motor activity and stereotypy and deficits in social and sexual interactions. These behavioral alterations are similar to those observed in pharmacologically induced animal models of schizophrenia and can be ameliorated by treatment with haloperidol or clozapine, antipsychotic drugs that antagonize dopaminergic and serotonergic receptors. These findings support a model in which reduced NMDA receptor activity results in schizophrenic-like behavior and reveals how pharmacological manipulation of monoaminergic pathways can affect this phenotype.

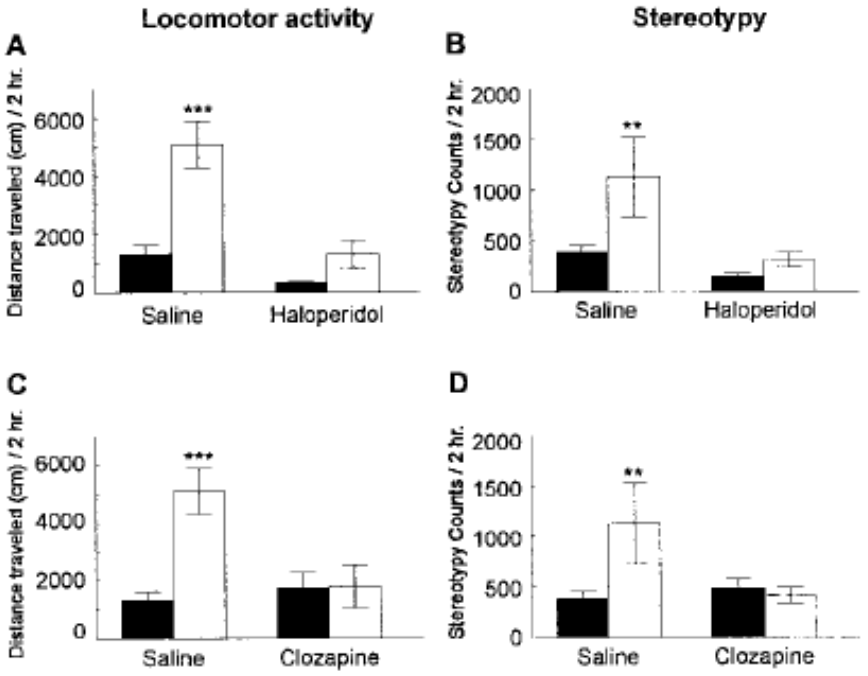


Figure 4. Administration of Haloperidol and Clozapine Attenuates Abnormal Behaviors of *Nr1*^{neo} −/− Mice

(A) Locomotor activity and (B) stereotypy of *Nr1*^{neo} −/− mice (open bars) and their wild-type littermates (filled bars) following administration of either saline or 0.5 mg/kg haloperidol, i.p. (C and D) Same as above, except that mice were treated with either saline or 0.5 mg/kg clozapine, i.p. For (A)–(D), *** = $p < 0.0005$, ** = $p < 0.005$, Student's two-tailed t test. n = 8 for all groups.

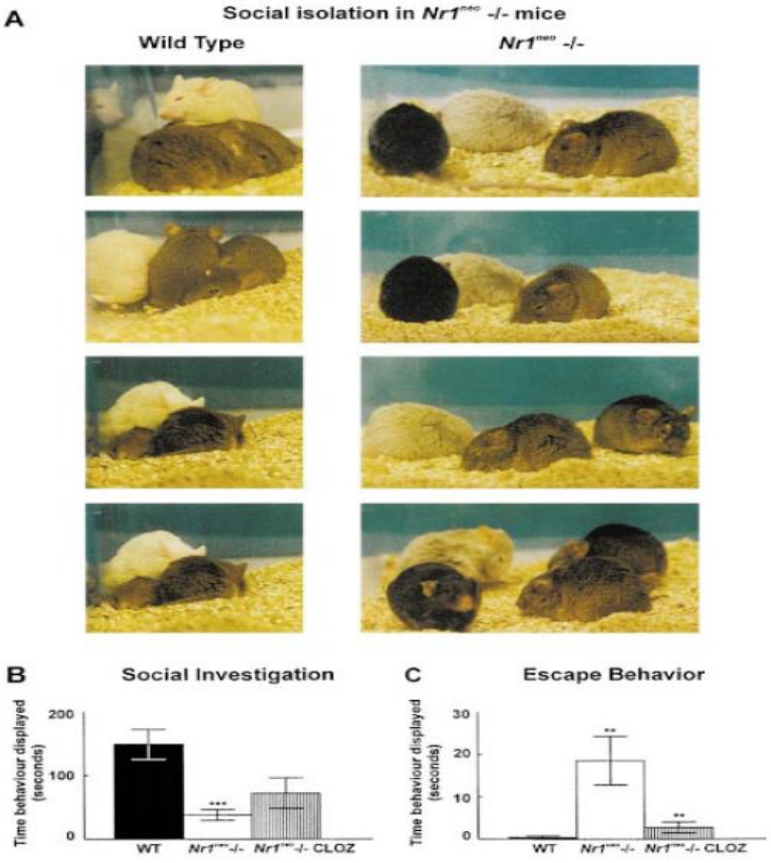


Figure 7. *Nr1*^{neo} −/− Mice Display Social Withdrawal that Can Be Quantified with the Resident–Intruder Behavioral Assay

(A) *Nr1*^{neo} −/− mice avoid contact with cagemates. Photographs of three wild-type mice housed together (left panel) and four *Nr1*^{neo} −/− mice housed together (right panel) were taken every half-hour for 2 hr. While wild-type mice typically prefer to nest, *Nr1*^{neo} −/− mice sleep isolated from other mice in the cage.

(B) Time spent by the resident male over a 6 min period actively pursuing social investigation of the intruder mouse, before and after treatment of *Nr1*^{neo} −/− mice with clozapine (0.5 mg/kg. i.p.).

(C) Time spent by the resident male over a 6 min period actively avoiding social interaction (escape behavior), before and after treatment of *Nr1*^{neo} −/− mice with clozapine (0.5 mg/kg. i.p.).

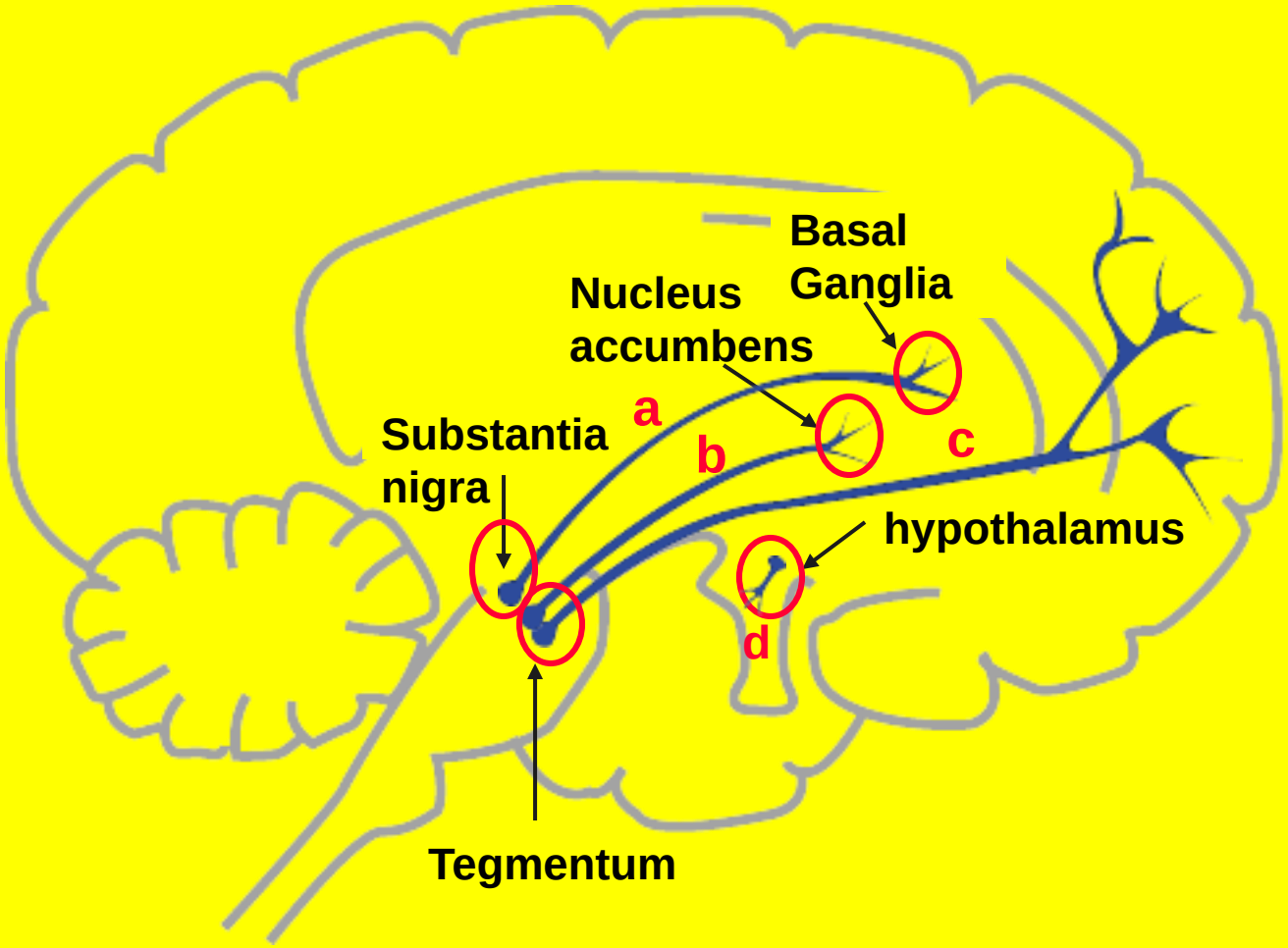
For (B) and (C), *** = $p < 0.0005$, ** = $p < 0.005$, Student's two-tailed t test. Error bars demonstrate the standard error of the mean (± SEM), n = 8 for all groups.

SEROTONIN HYPOTESIS

- **Hallucinogen agents, such as LSD, interact with 5-HT systems (agonists for 5-$HT_{2a/2c}$)**

- **The "atypical" antipsychotic drugs show an high affinity for 5-HT_{2A} receptor and a relatively low affinity for D2 receptor.**

Antipsicotici e vie



(Stahl, Ess. Psychopharmacol. 2000)

FARMACI ANTIPSICOTICI

I farmaci impiegati nella terapia della schizofrenia si dividono in due gruppi:

- **Antipsicotici tipici**

Bloccano specifici recettori per la dopamina (D2)

- **Antipsicotici atipici**

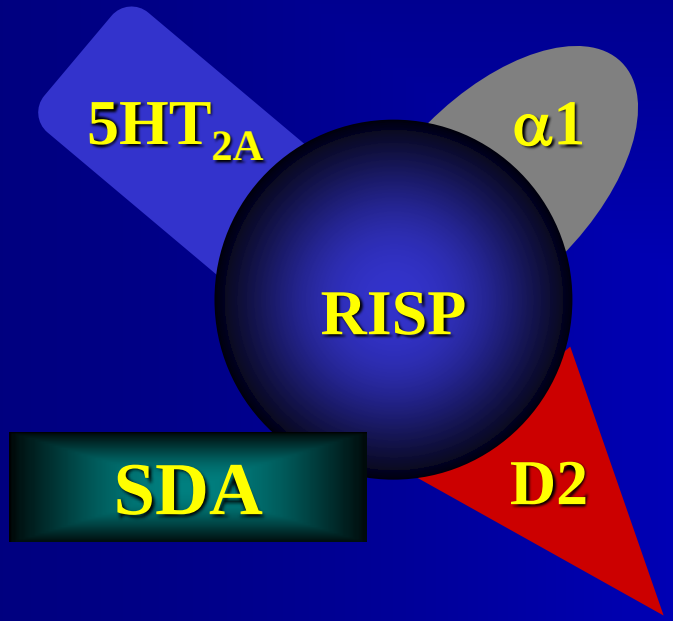
Bloccano specifici recettori per serotonina (5-HT2A) e dopamina (D2)

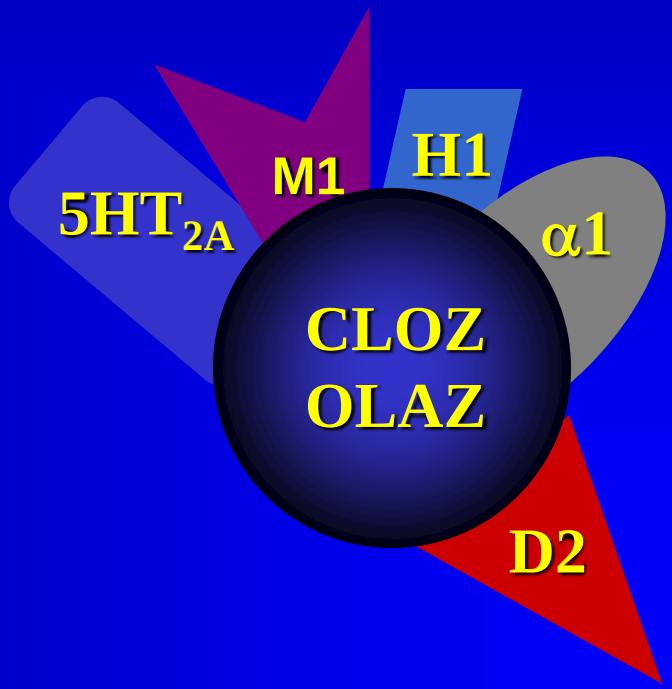
FARMACI ANTIPSICOTICI

Antipsicotici di prima generazione

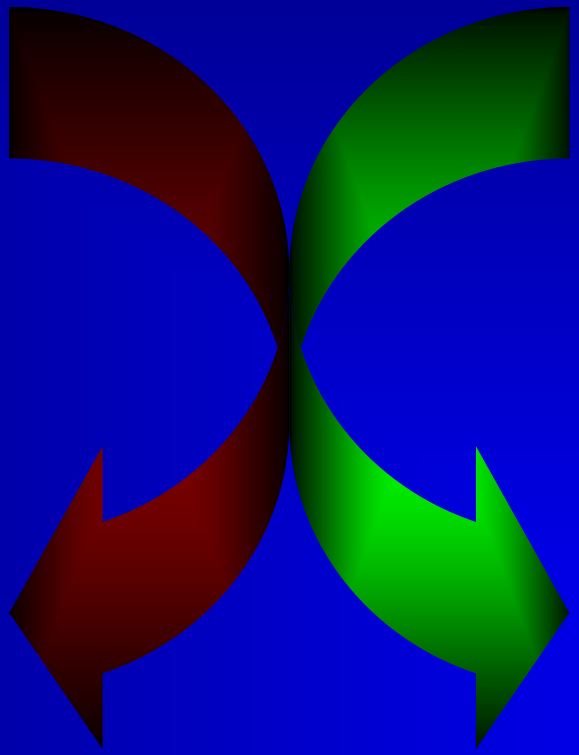
- Blocco recettori D-2
  - Migliorano i sintomi positivi
  - Determinano
    - EPS
    - Iperprolattinemia
    - Declino cognitivo
- Altri effetti recettoriali
  - Istaminergici
  - Alfa adrenergici
  - Muscarinici

Antipsicotici ATIPICI





Antipsicotici atipici: quali benefici?



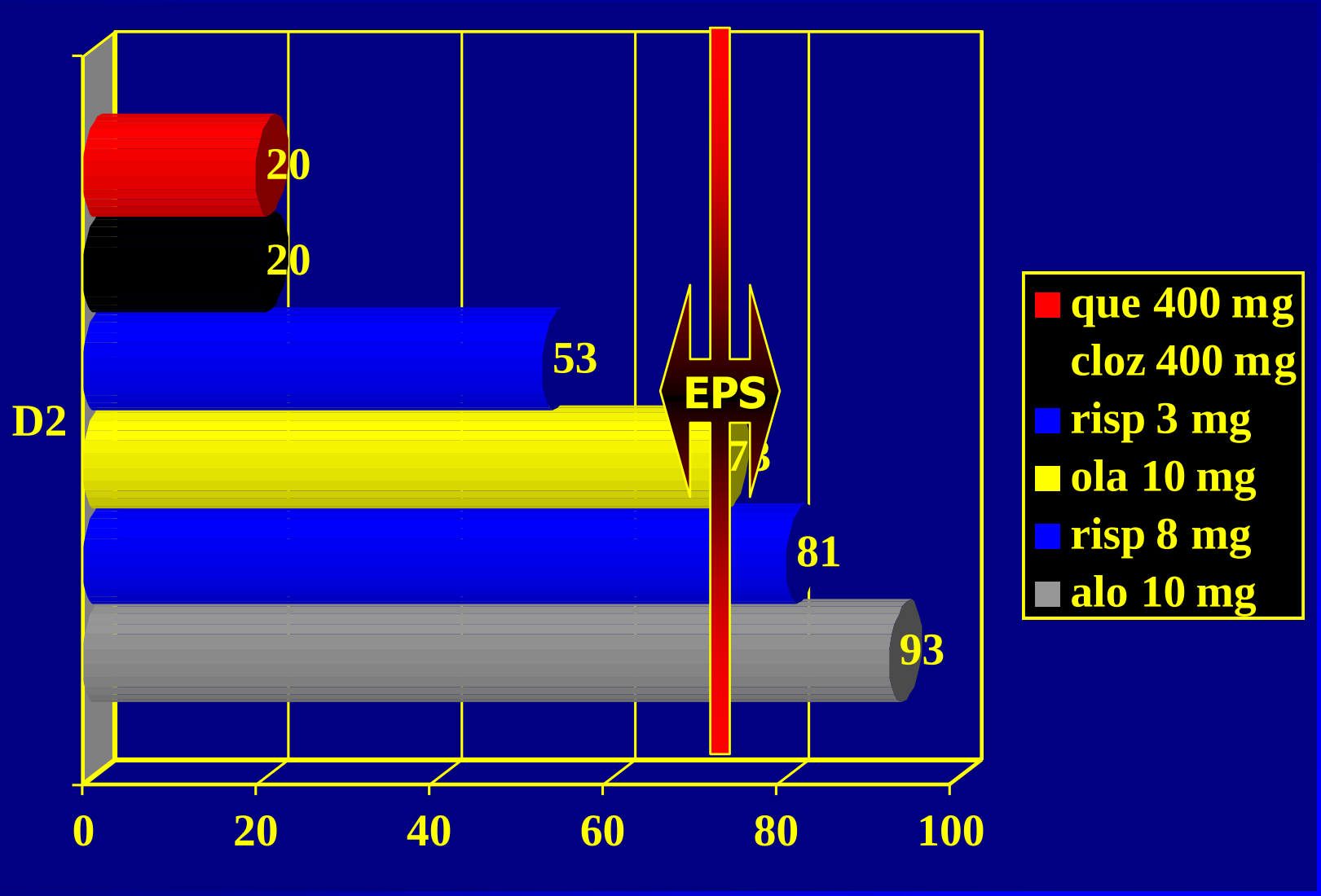
Minori effetti collaterali

Maggior efficacia sui sintomi negativi e cognitivi

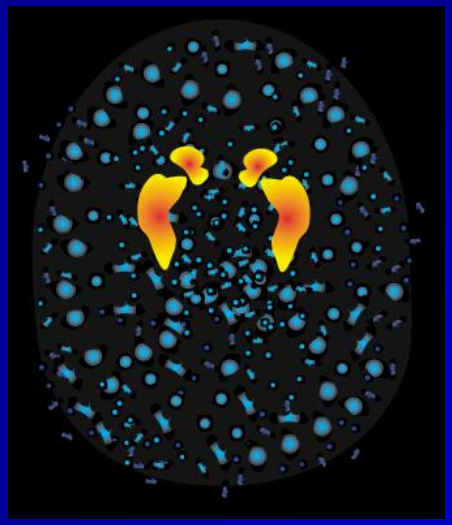
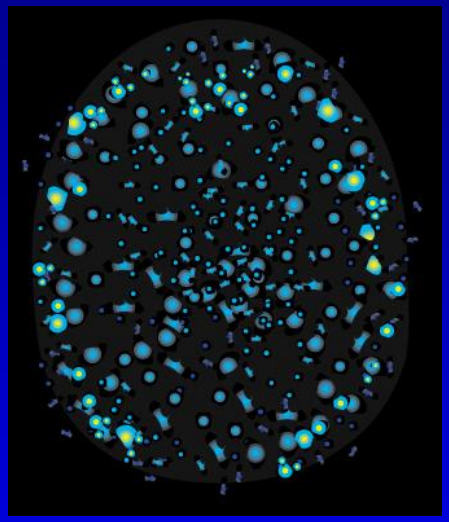
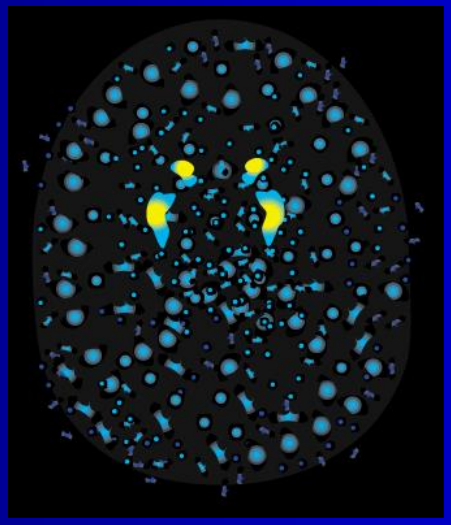
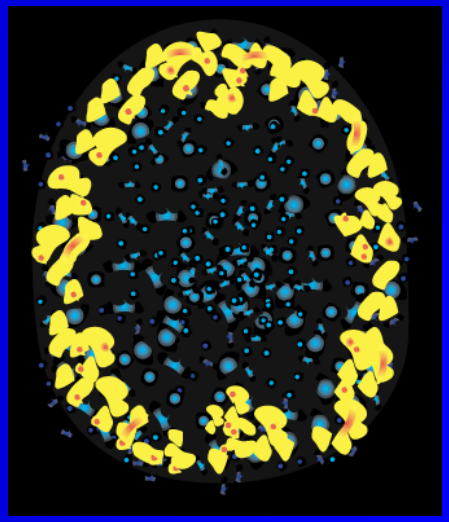
Antipsicotici atipici: basi farmacodinamiche e molecolari

- Ridotta affinità per il recettore D-2 e maggior selettività per il sistema dopaminergico mesolimbico
- Maggior potenza di blocco 5HT-2_a rispetto al blocco D-2
- Blocco multirecettoriale
  - (5-HT_{1A}, 5-HT_3, 5-HT_6, 5-HT_7, adrenergici α_1 e α_2, Ach-M, NMDA)
- Azioni modulatoria sul rilascio di monoamine e di altri neurotrasmettitori
- Attivazione di meccanismi di plasticità cellulare e di neuroprotezione

Tassi di occupazione recettoriale D2 in pazienti trattati con differenti antipsicotici



Antipsychotics and receptors

	D2 receptors	5-HT2A receptors
Typical		
Atypical		

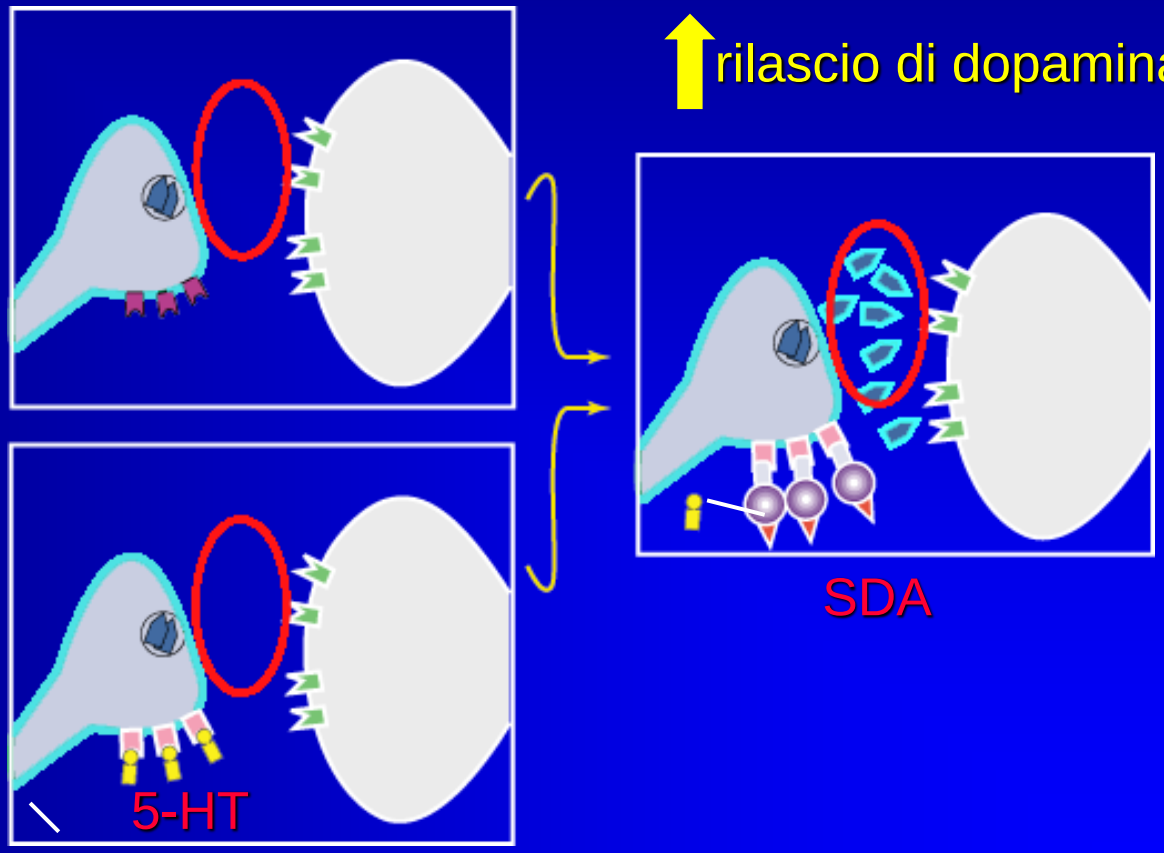
Cinetiche di dissociazione ed occupazione recettoriale

- La componente più rilevante nel determinare l'affinità dei farmaci antipsicotici per i recettori D-2 è rappresentata dalla K_{off} (costante di dissociazione).
- Gli antipsicotici atipici hanno una K_{off} più rapida rispetto ai neurolettici classici e conseguentemente presentano una minore affinità per i recettori dopaminergici D-2
- Una K_{off} rapida permette al farmaco di rispondere meglio al 'signalling' fisiologico

L’antagonismo dei recettori 5HT2A aumenta il rilascio di DA in PFC: effetti sul tono dell’umore e sulle funzioni cognitive

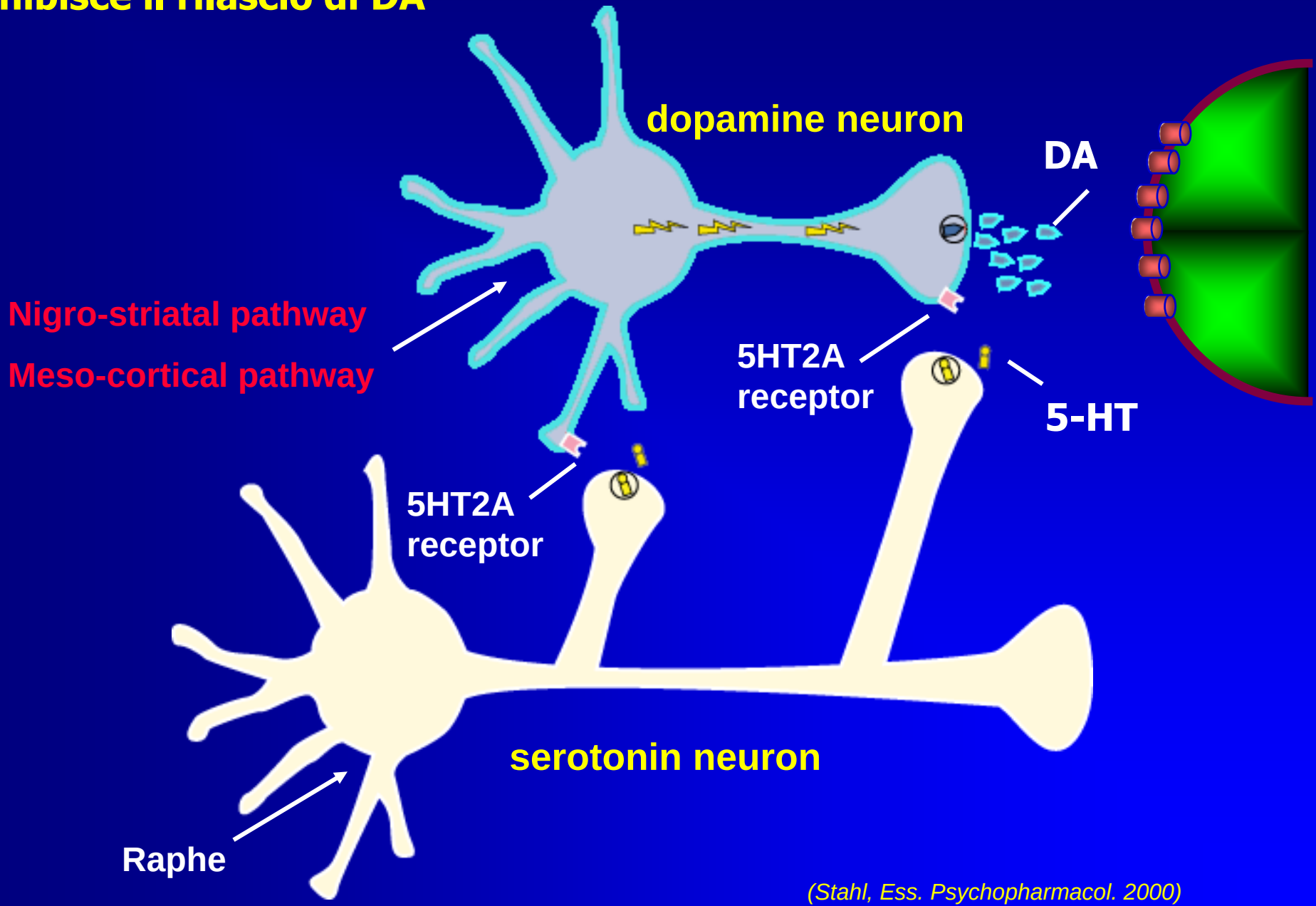
deficienza primaria di dopamina

deficienza secondaria di dopamina



(Stahl, Ess. Psychopharmacol. 2000)

La stimolazione dei recettori 5HT2A inibisce il rilascio di DA



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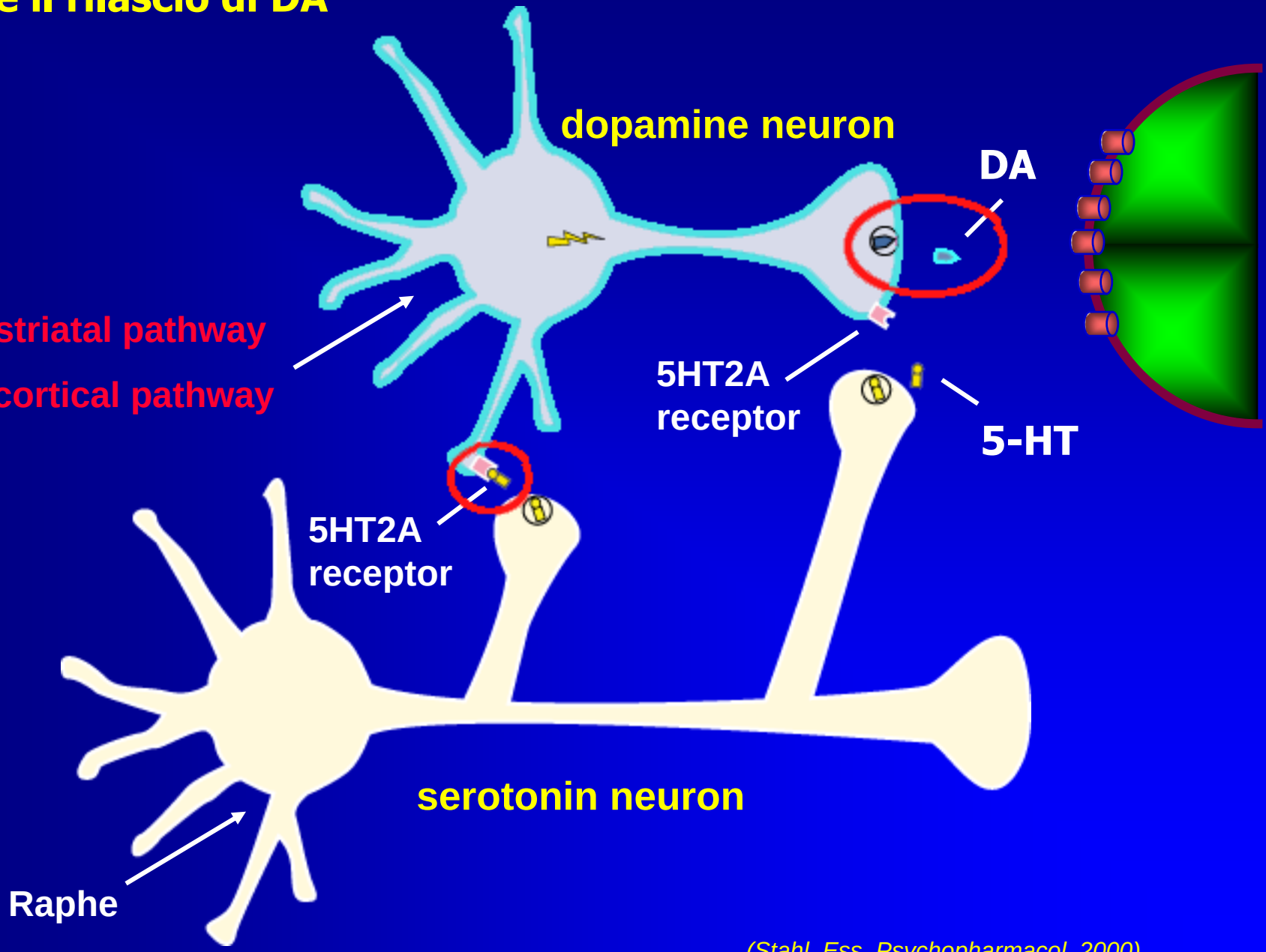

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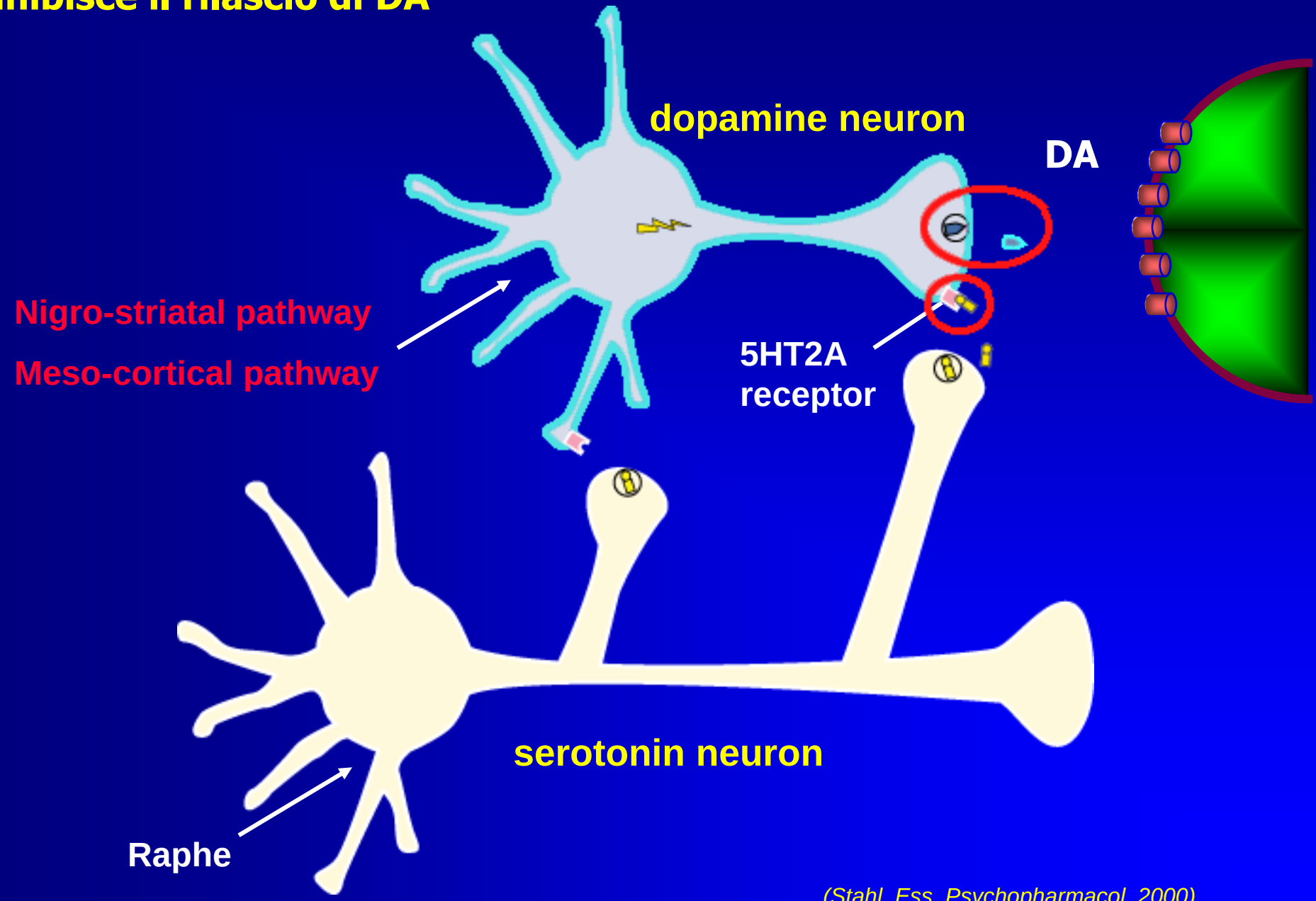
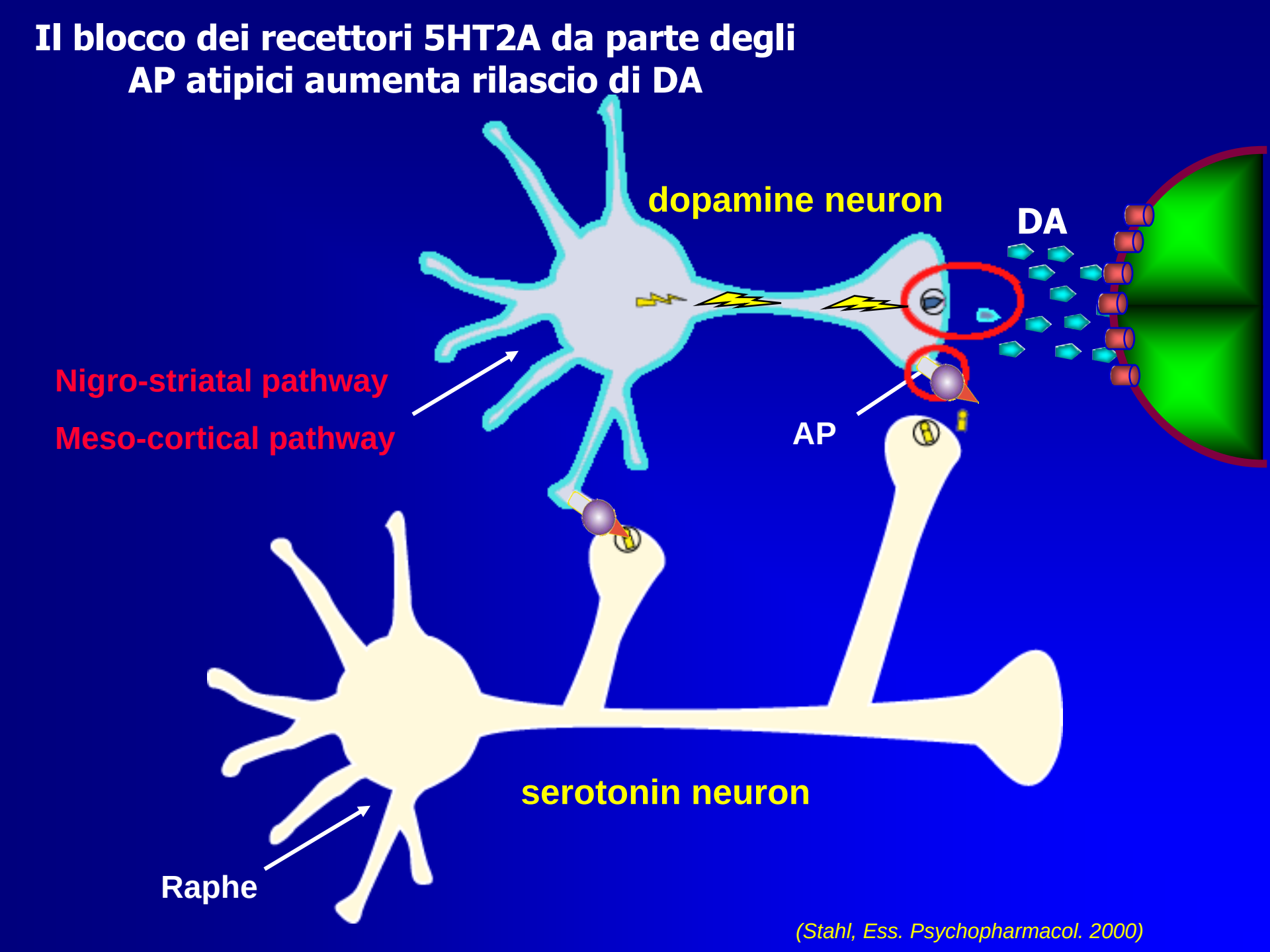


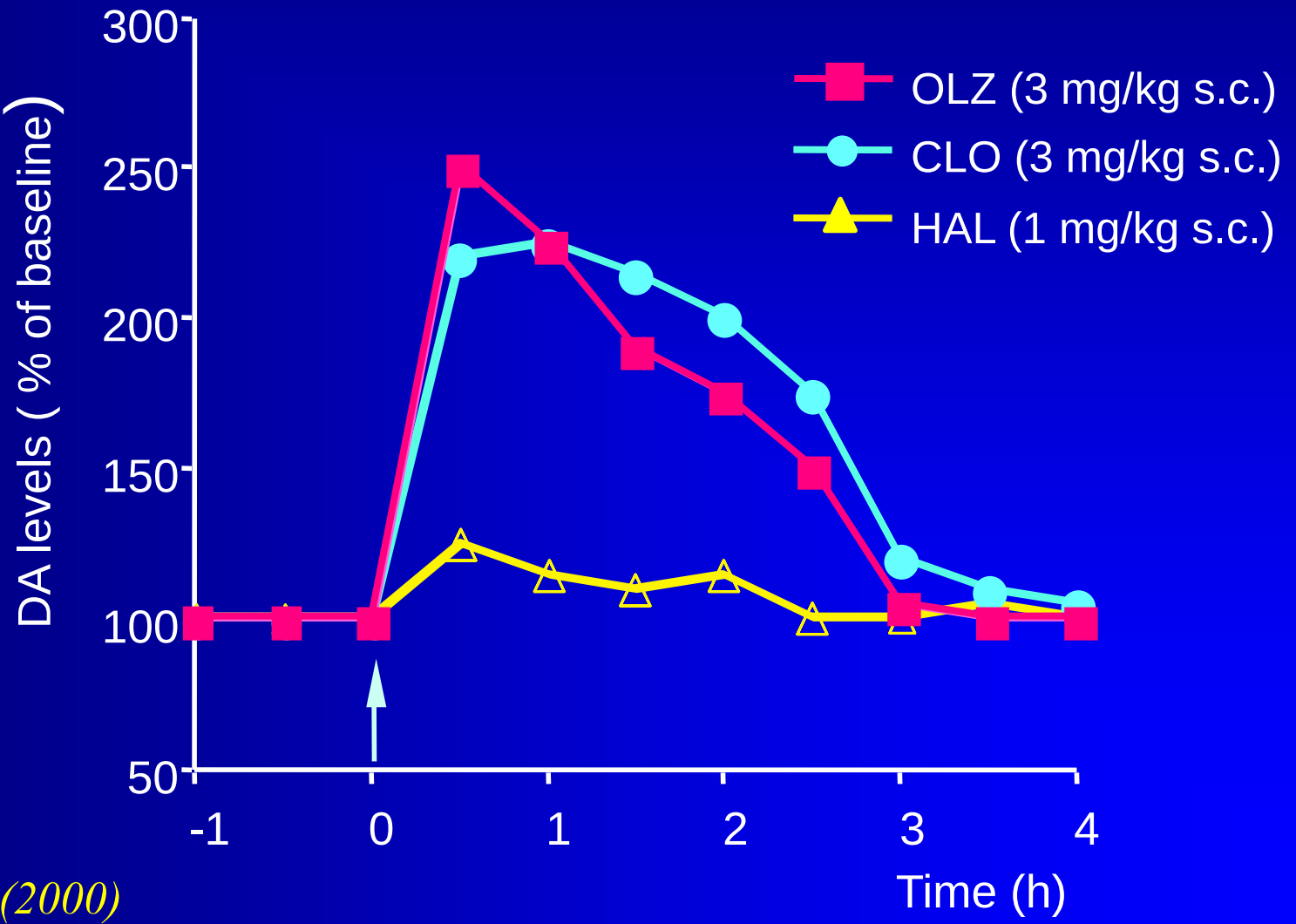
(Stahl, Ess. Psychopharmacol. 2000)

Il blocco dei recettori 5HT2A da parte degli AP atipici aumenta rilascio di DA



(Stahl, Ess. Psychopharmacol. 2000)

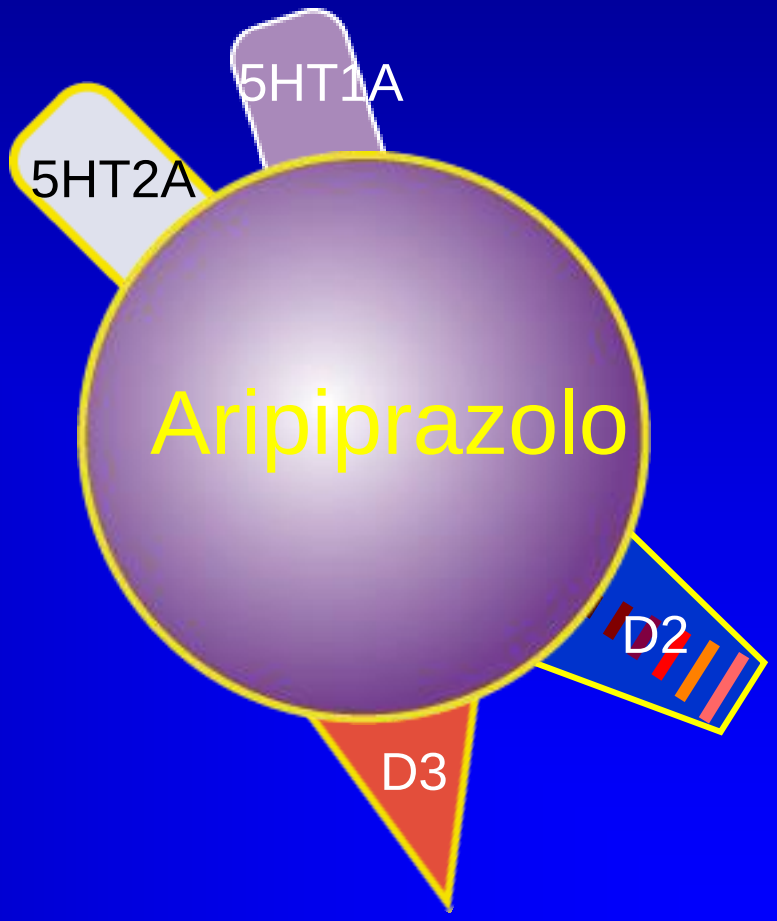
Effect of olanzapine and clozapine on dopamine efflux in rat prefrontal cortex



Zhang et al. (2000)

Stabilizzatori dopaminergici: una nuova classe di farmaci antipsicotici?

- Si comportanto come agonisti parziali
- Riducono l'eccessiva attività dopaminergica
- Aumentano la trasmissione dopaminergica, quando è deficitaria
- Il legame del farmaco induce modificazioni conformazionali nel recettore D-2, una situazione intermedia tra stimolazione e blocco



Gli AP atipici aumentano i livelli di monoamine in PFC: meccanismi molecolari

- DOPAMINA:
  - Antagonismo 5-HT2a — CLO, OLA
  - Antagonismo $\alpha 2$ — CLO, QUE, RIS

- NORADRENALINA:
  - Antagonismo 5-HT2a — CLO, OLA
  - Antagonismo $\alpha 2$ — CLO, OLA
  - Inibizione reuptake NA — ZIP

- SEROTONINA:
  - Agonismo 5-HT1a (indiretto?) — CLO
  - Antagonismo $\alpha 2$ — RIS
  - Inibizione reuptake 5-HT — ZIP

Effetti collaterali dei farmaci antipsicotici: meccanismi recettoriali

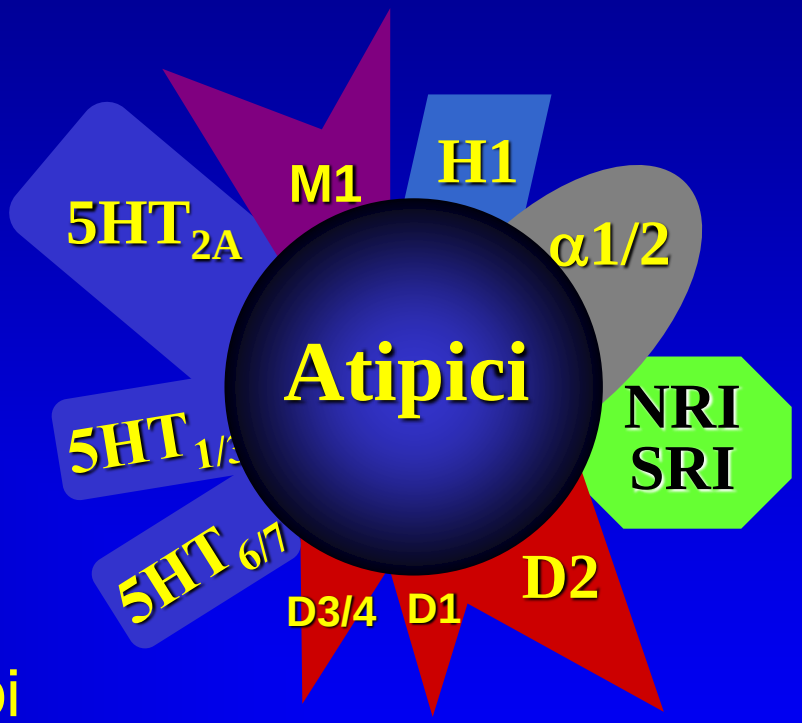
- Recettori dopaminergici:
  - Blocco D-2 — Effetti extrapiramidali, Iperprolattinemia
- Recettori serotoninergici:
  - Blocco 5-HT2c — Aumento di peso
- Recettori colinergici:
  - Blocco M-1 — Disturbi accomodazione, xerostomia, stipsi ritenzione urinaria, disturbi cognitivi
- Recettori istaminergici:
  - Blocco H-1 — Aumento di peso, Sedazione
- Recettori adrenergici:
  - Blocco alfa-1 — Ipotensione, tachicardia riflessa potenziamento azione prazosina
  - Blocco alfa-2 — Blocco attività antiipertensiva di clonidina

Antipsicotici e aumento di peso

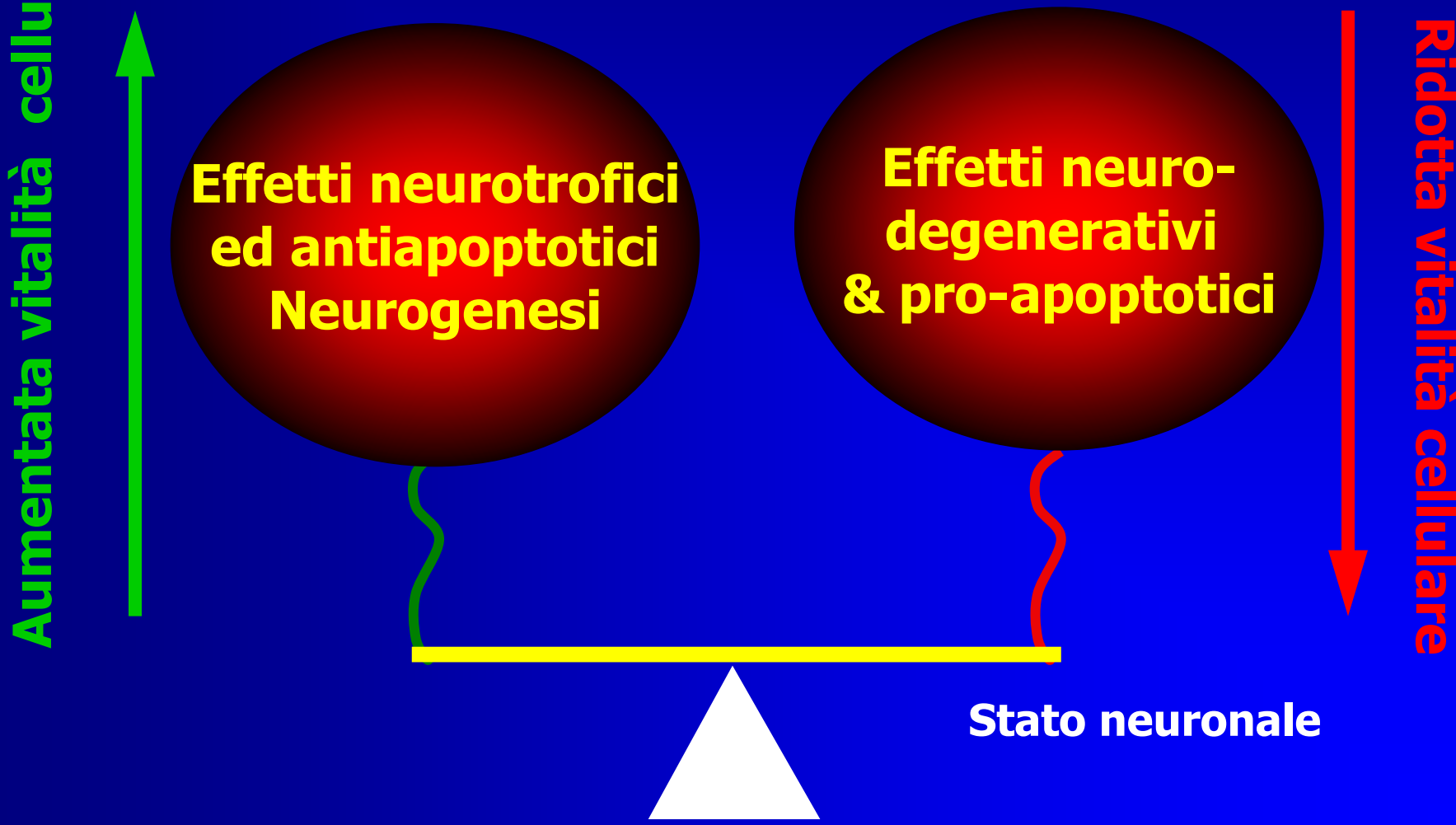
- L'aumento di peso è un fenomeno comunemente associato alla terapia antipsicotica
- Il meccanismo dell'aumento di peso è tuttora sconosciuto
  - Fenomeno complesso influenzato da molteplici fattori
  - L'antagonismo dei recettori 5HT-2c e H1 è un possibile candidato
- L'aumento di peso è spesso correlato alla risposta clinica e ai valori basali dell'indice di massa corporea (BMI)

Farmaci antipsicotici: quali sviluppi?

- Farmaci selettivi per specifici sottotipi recettoriali
- Farmaci attivi su nuovi bersagli
  - –Sistema glutammatergico
    - Inibitori Trasportatore della glicina
    - Modulatori recettori NMDA
    - Ampakine
    - Agonisti recettori metabotropi
  - –Modulazione signalling e meccanismi intracellulari



Vulnerabilità cellulare e patologie psichiatriche



Modelli animali per la Schizofrenia

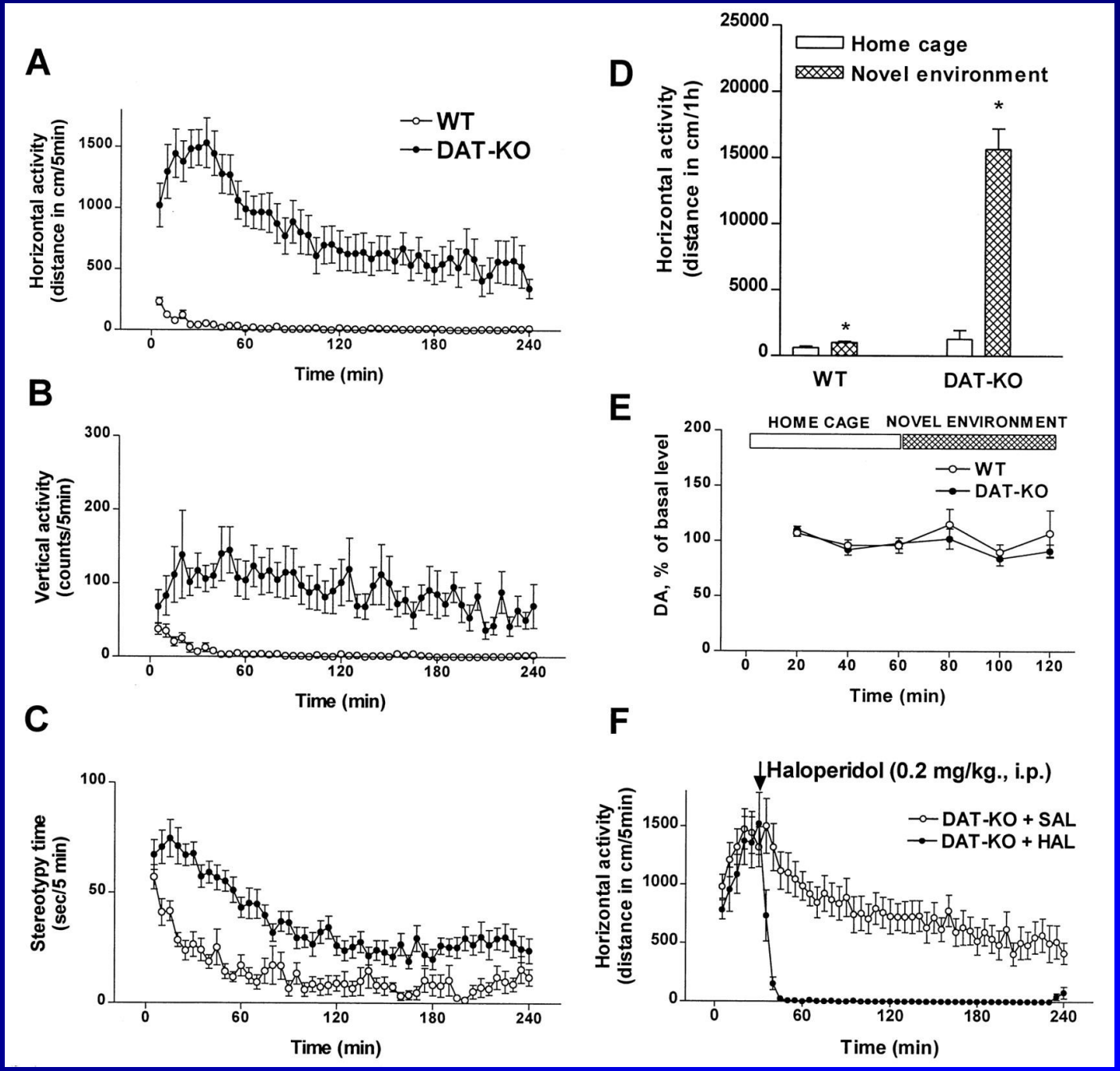
Neurotrasmettitori

- **Dopamine**
  - DAT knock-out mice
- **Glutamate**
  - PCP treated rats
  - NMDA-R1 KD mice
  - NMDA-R2A knock-out
  - AMPA GluR1 knock-out

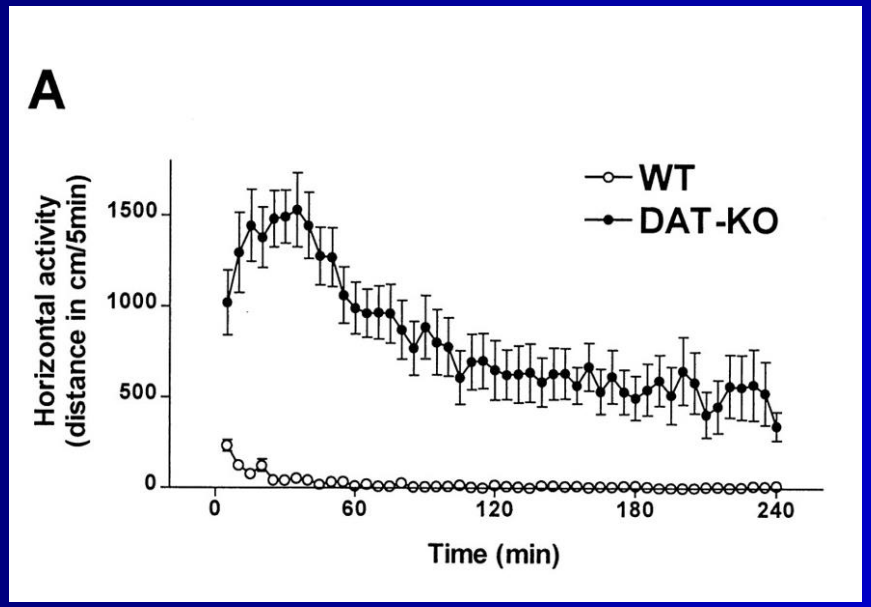
Neurosviluppo

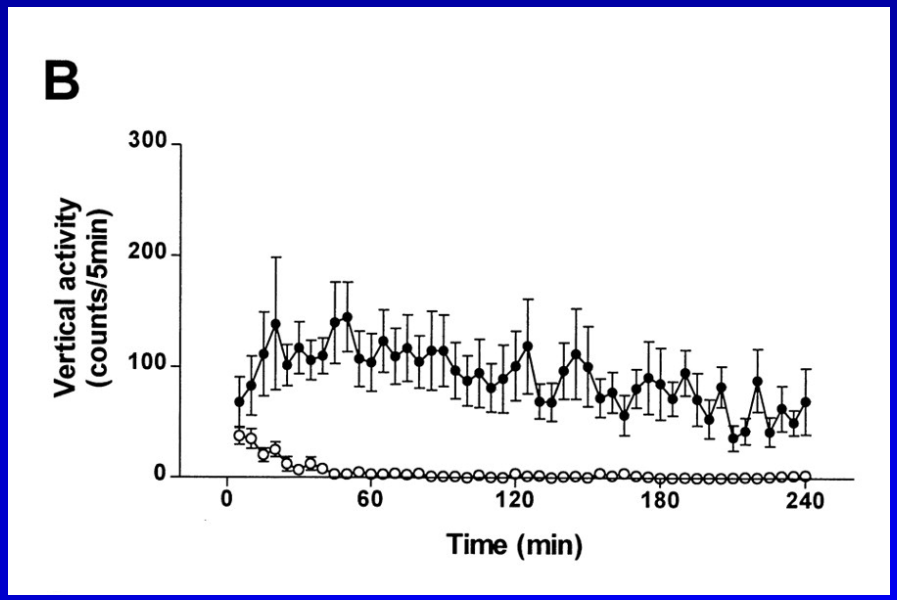
- **Etiological factors**
  - Prenatal stress or MD
  - Fetal hypoxia
  - Malnutrition
  - Viral infection
- **Neuronal maturation**
  - Reeler mice
  - Methylazoxymethanol
  - Neonatal lesion

DAT KO mice


A
Horizontal activity (distance in cm/5min)
WT
DAT-KO
Time (min)
B
Vertical activity (counts/5min)
Time (min)
C
Stereotypy time (sec/5 min)
Time (min)
D
Home cage
Novel environment
Horizontal activity (distance in cm/1h)
WT
DAT-KO
E
HOME CAGE
NOVEL ENVIRONMENT
WT
DAT-KO
DA, % of basal level
Time (min)
F
Haloperidol (0.2 mg/kg., i.p.)
DAT-KO + SAL
DAT-KO + HAL
Horizontal activity (distance in cm/5min)
Time (min)

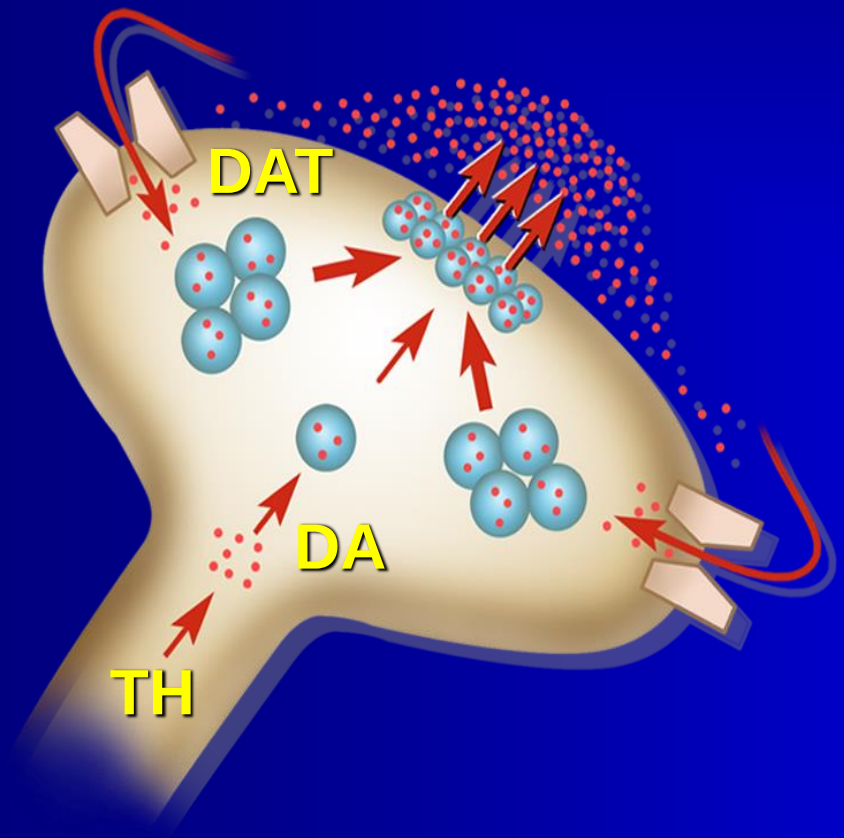
Characterization of Locomotion



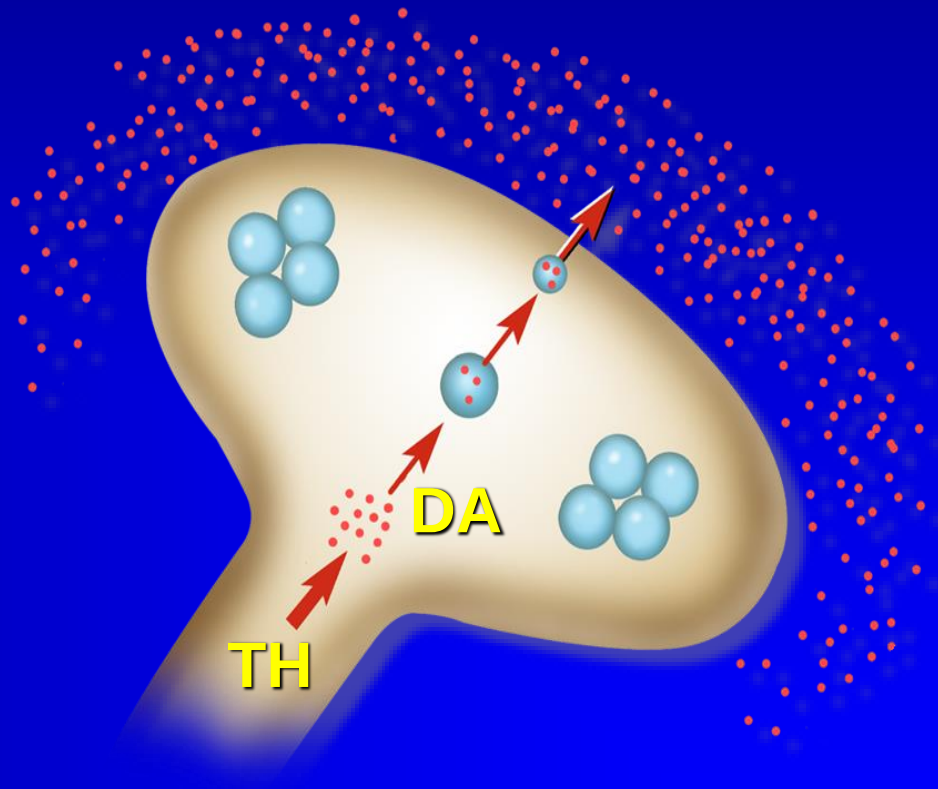


Look at that knock-out go go go!!

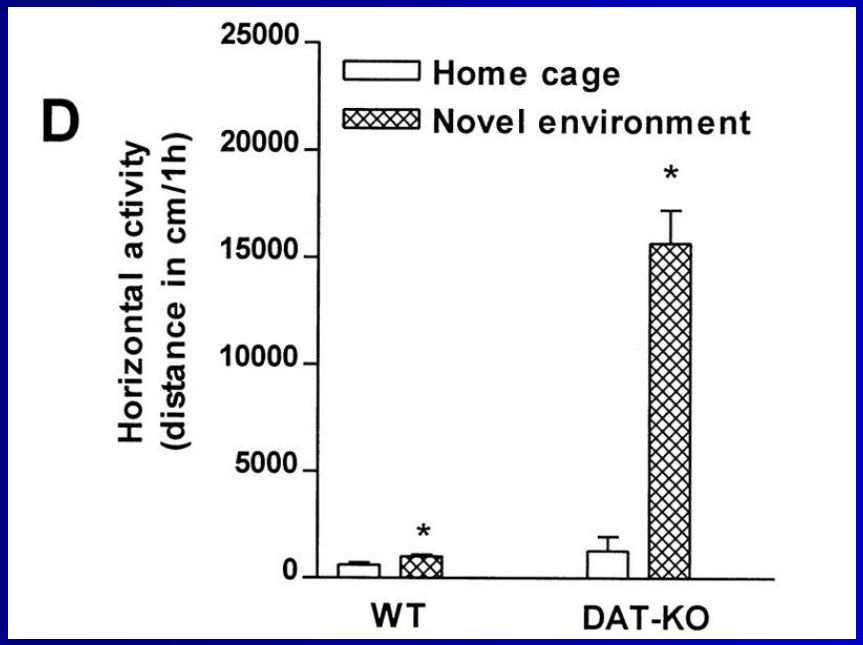
Normal Neurotransmission (WT mice)

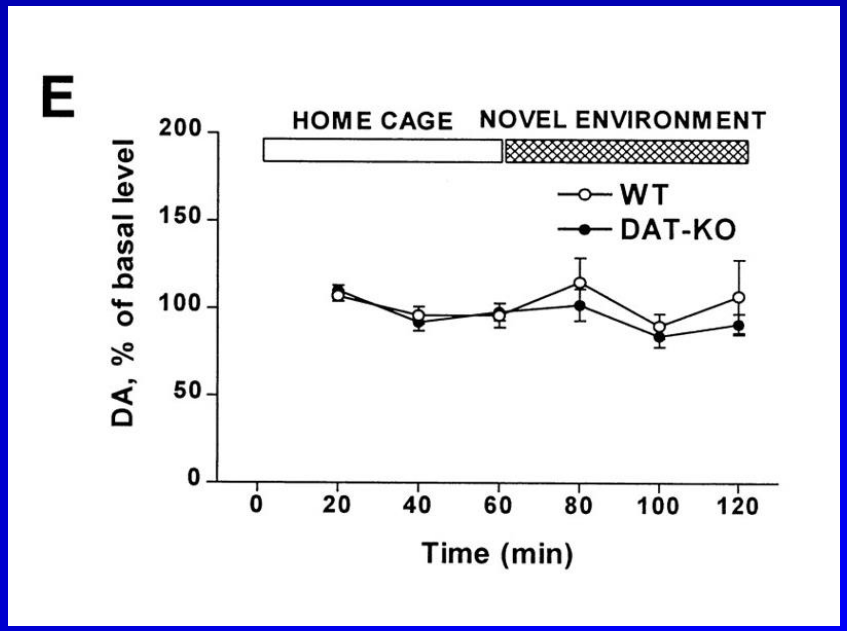


Lack of Dopamine Transporter (DAT-KO mice)

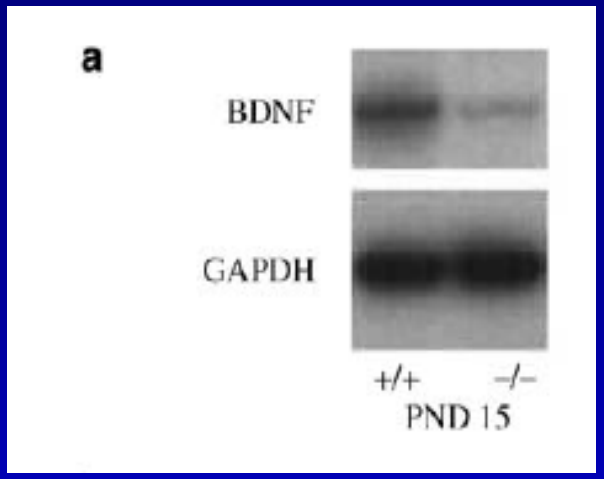


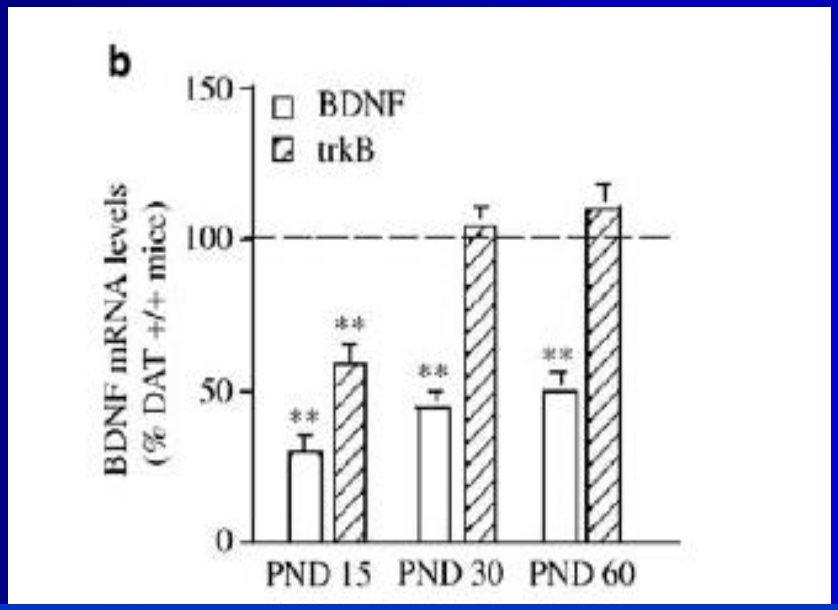
Hyperactivity Is Dependent on Novel Environment

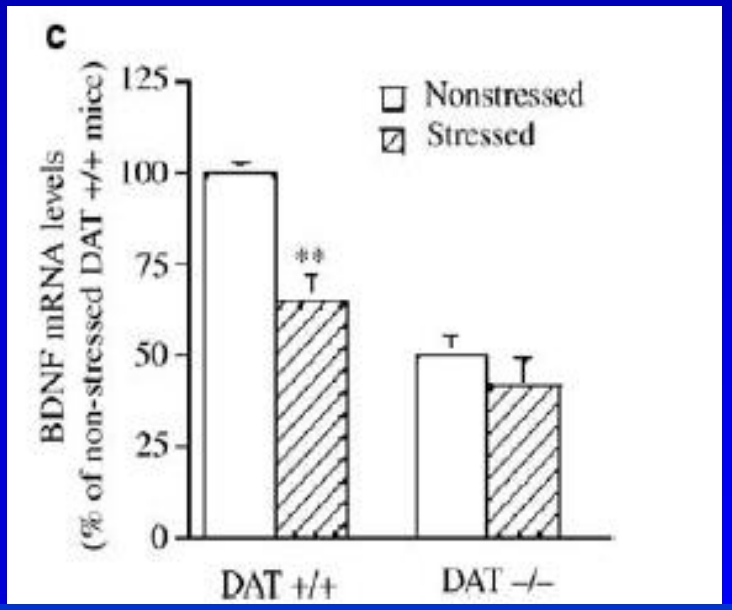




BDNF gene expression is reduced in the frontal cortex of dopamine transporter knockout mice

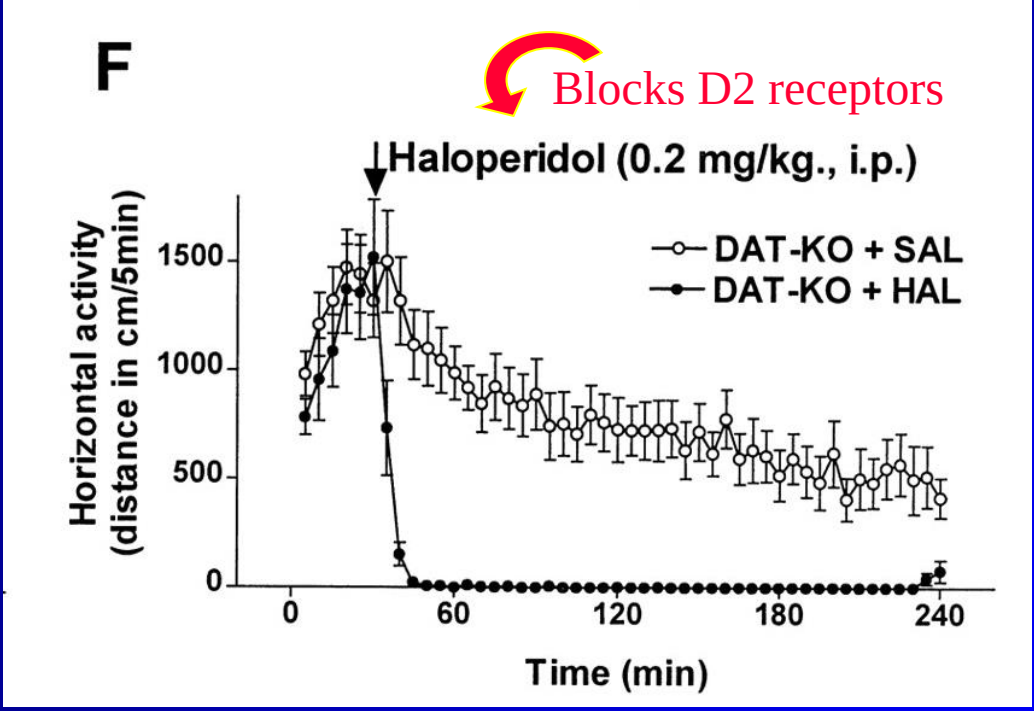






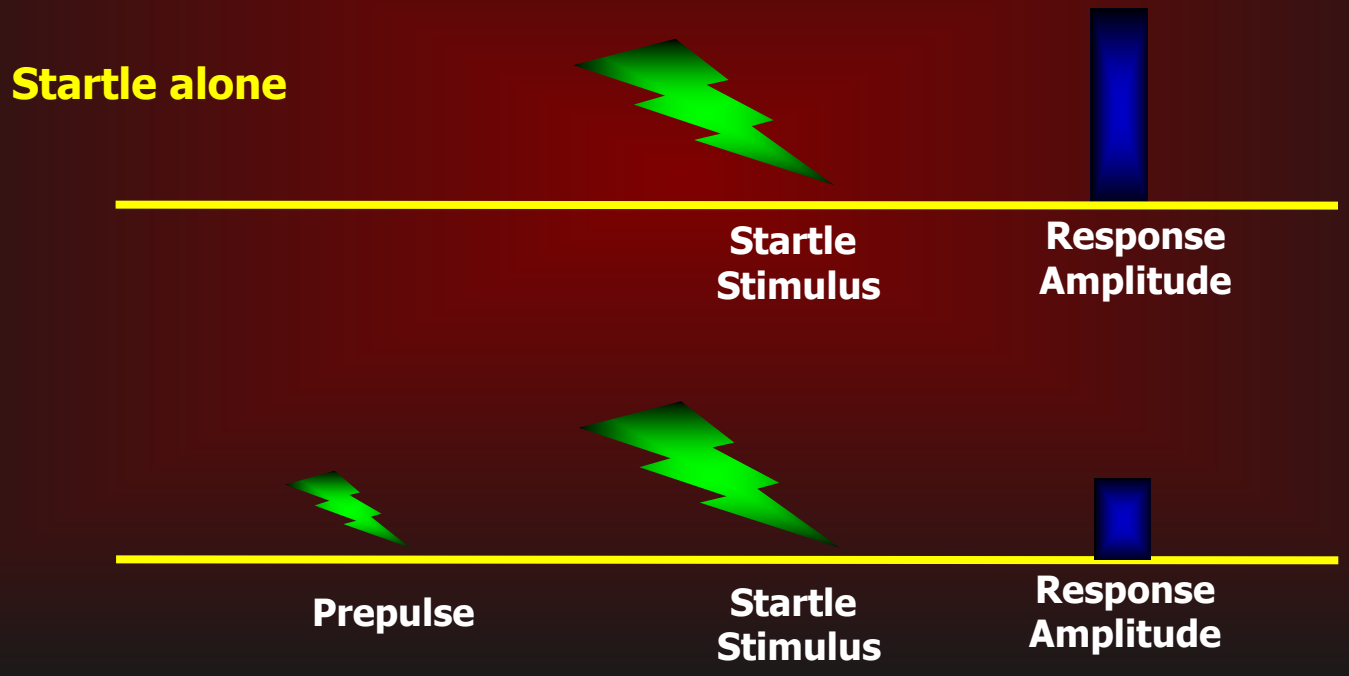
Fumagalli et al. (2003), Mol. Psychiatry 8:898-899

Hyperactivity is associated with activation of postsynaptic DA receptors



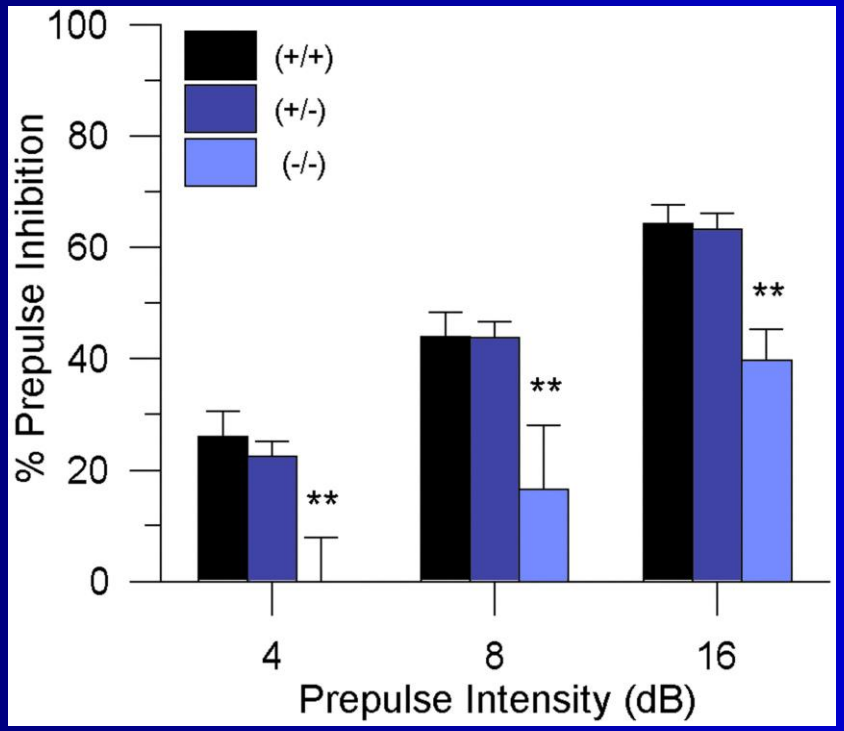
Caratteristiche degli AP atipici: Inibizione da pre-impulso (PPI)

La PPI è un meccanismo secondo il quale la risposta ad uno stimolo è ridotta quando tale stimolo è preceduto da un pre-impulso.



PPI is used as a model of attentional processes, and disruptions in PPI:

- Have been observed in schizophrenic patients,
- Can be induced by NMDA antagonists, such as MK-801 and PCP;
- Is prevented by atypical APDs, including clozapine, risperidone, quetiapine, and olanzapine



Prepulse Inhibition in DAT Knock Out Mice