PGC Worldwide Lab Call Details

DATE: Friday, September 12, 2014
PRESENTER: Robin M. Murray, Kings College-London
TITLE: “Deviant development, dopamine dysregulation and drug abuse- what schizophrenia genetics needs to explain”
START: We will begin promptly on the hour.
1000 EDT - US East Coast
0700 PDT - US West Coast
1500 BST - UK
1600 CEST - Central Europe
0000 AEST – Australia (Friday, September 12th into Saturday, September 13th, 2014)
DURATION: 1 hour

TELEPHONE:
- US Toll free: 1 866 515.2912
- International direct: +1 617 399.5126
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- This conference line can handle up to 300 participants.

PASSCODE: 275 694 38 then #

Lines are Muted **NOW**

Lines have been automatically muted by operators as it is possible for just one person to ruin the call for everyone due to background noise, electronic feedback, crying children, wind, typing, etc.

Operators announce callers one at a time during question and answer sessions.

Dial *1 if you would like to ask a question of the presenter. Presenter will respond to calls as time allows.

Dial *0 if you need operator assistance at any time during the duration of the call.

UPCOMING PGC Worldwide Lab

DATE: Friday, October 10, 2014
PRESENTER: Robert Yolken, MD
TITLE: To Be Announced
START: We will begin promptly on the hour.
1000 EDT - US East Coast
0700 PDT - US West Coast
1500 BST - UK
1600 CEST - Central Europe
0000 AEST – Australia (Saturday, October 11, 2014)
DURATION: 1 hour

TELEPHONE:
- US Toll free: 1 866 515.2912
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- Toll-free number? See http://www.btconferencing.com/globalaccess/?bid=75_public
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PASSCODE: 275 694 38 then #

Deviant development, dopamine dysregulation and drug abuse – *what schizophrenia genetics needs to explain*

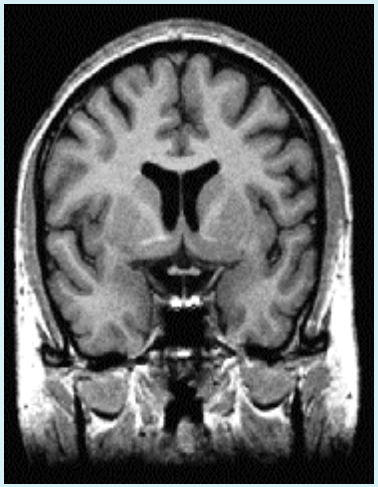
Robin M Murray, FRS

Department of Psychosis Studies

Institute of Psychiatry

robin.murray@kcl.ac.uk

Schizophrenia was originally conceptualised by Kraepelin in 1896 as a progressive deteriorating condition



When the brain structural abnormalities and cognitive impairment were demonstrated in the mid-1970s, these were taken as evidence of Kraepelin's progressive dementia

BRITISH MEDICAL JOURNAL

LONDON, SATURDAY 19 SEPTEMBER 1987

SW Lewis and RMMurray

Is schizophrenia a neurodevelopmental disorder?

A well established fact about schizophrenia is that first degree relatives have an increased risk of the disorder. Few now doubt that schizophrenia has a genetic basis, yet its mode of inheritance has to be explained. Even the identical twin of a schizophrenic stands a better than 50% chance of escaping the illness.[1] Genetic factors are not the whole story.

Kraepelin, who derived the concept of schizophrenia, considered that both heredity and organic brain disease were implicated, but somehow the organic aspects were neglected

graphy, and schizophrenia? The early development of the central nervous system is characterised not only by cellular proliferation and neuronal migration but also by cell death.[16] Complications during pregnancy and at birth can interfere with this neuronal fallout and impair the organisation of axonal connections, which leads to immature patterns of cells and their projections persisting.[16] Recent neuropathological findings in schizophrenia are suggestive of such neuronal damage early in life.[17,18]

Developmental not degenerative

Implications of Normal Brain Development for the Pathogenesis of Schizophrenia

Daniel R. Weinberger, MD

Arch Gen Psychiatry—Vol 44, July 1987

The Kraepelinians were buried but did not die!

However, in 2005, the Kraepelinians began to rise from the grave!

Annals of General Psychiatry

BioMed Central

Oral presentation

Open Access

Schizophrenia as a progressive brain disorder

Rene Kahn*

Address: Department of Psychiatry, Rudolf Magnus Institute of Neuroscience, University Medical Center Utrecht, The Netherlands
* Corresponding author

from International Society on Brain and Behaviour: 2nd International Congress on Brain and Behaviour
Thessaloniki, Greece. 17–20 November 2005

Published: 28 February 2006

Annals of General Psychiatry 2006, **5**(Suppl 1):S6 doi:10.11

Schizophrenia Bulletin vol. 34 no. 2 pp. 310–311, 2008
doi:10.1093/schbul/sbm166
Advance Access publication on January 22, 2008

Progressive Brain Changes in Schizophrenia

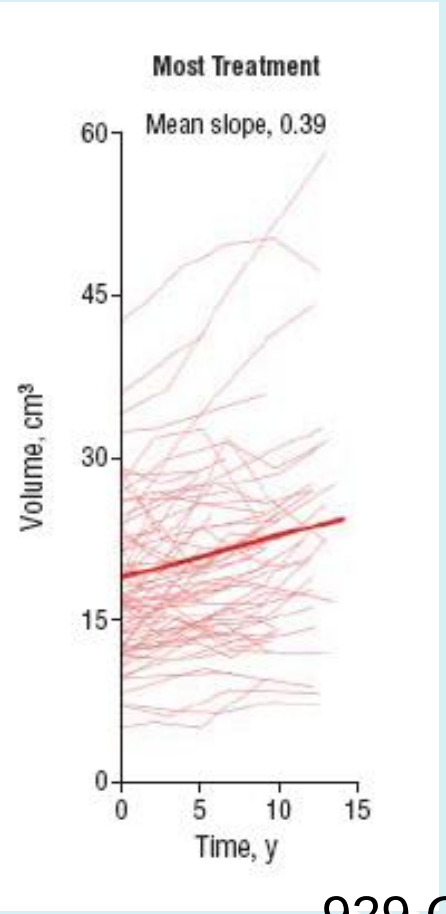
ORIGINAL ARTICLE

Long-term Antipsychotic Treatment and Brain Volumes

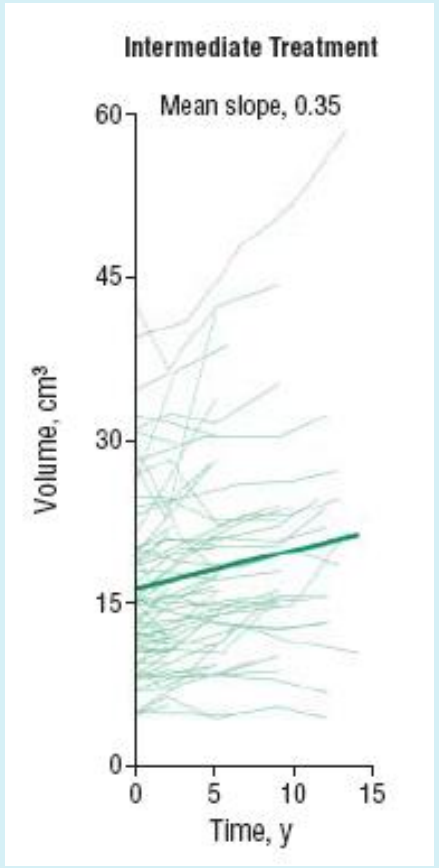
A Longitudinal Study of First-Episode Schizophrenia

Beng-Choon Ho, MRCPsych; Nancy C. Andreasen, MD, PhD; Steven Ziebell, BS; Ronald Pierson, MS; Vincent Magnotta, PhD

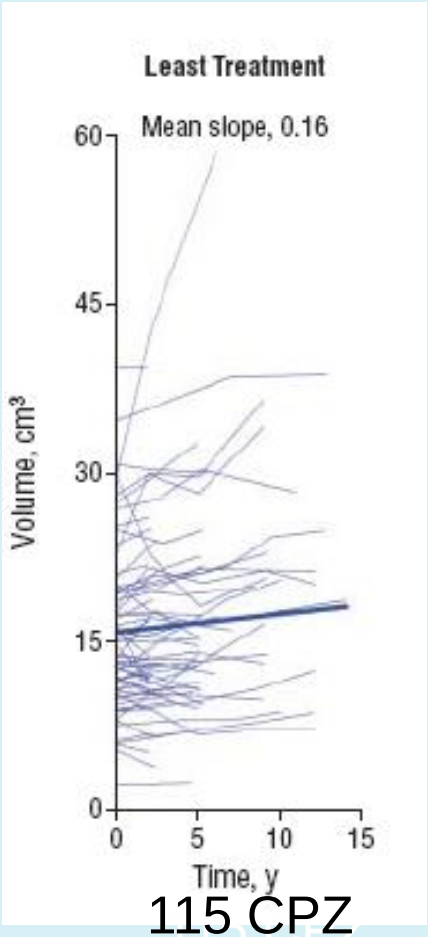
However, change in lateral ventricular volume over 7 years reflects the mean daily dose of antipsychotic.



929 CPZ



392 CPZ



115 CPZ

There are subtle brain changes at first onset – abnormal gyrification, decreased cortical and hippocampal volume.

But the later so-called “progressive” brain changes are due to:-

1. Antipsychotics
2. Stress and cortisol damage
3. Substance abuse, lack of exercise, and metabolic syndrome

What about Cognition?

Chronic schizophrenic patients show poorer cognition than first onset patients

But there is no decline in cognition in follow-up studies of first onset psychosis

The findings in chronic patients are an artefact of selective loss of subjects – those who recover are not studied

E Bora and RM Murray Meta-analysis Schiz Bulletin 2014, 40,744-55

OUTCOME OF FIRST EPISODE PSYCHOSIS IN AESOP STUDY AT 10 YEARS

65% HAD NO PSYCHOTIC SYMPTOMS

46% (42% SZ) NONE FOR > 2 YEARS

12% NEVER HAD ANY AFTER FIRST EPISODE.

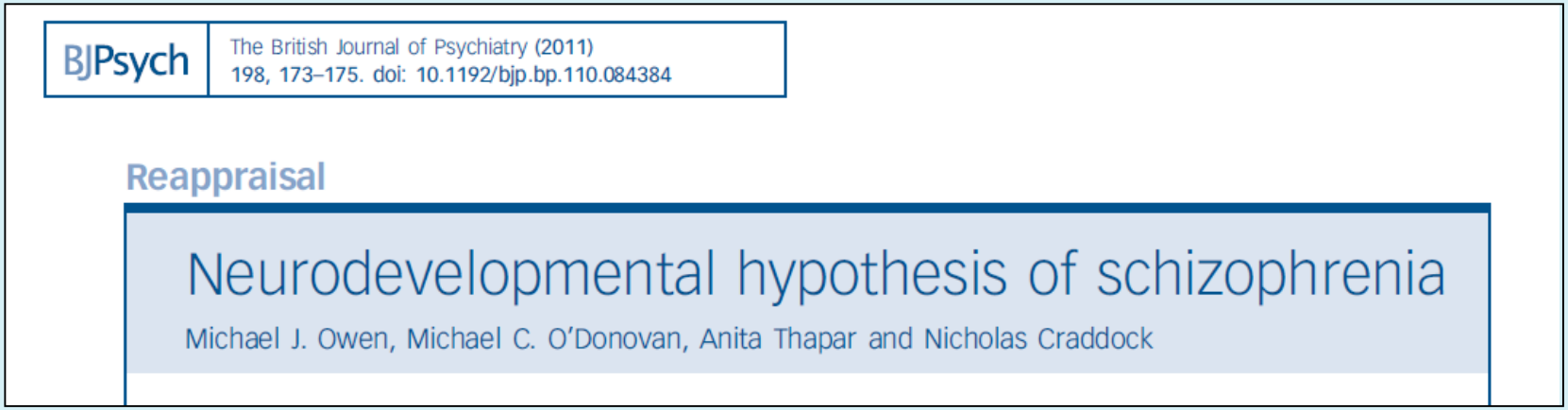
Morgan et al, Psychological Medicine, 2014 , 44, 2713-26

Schizophrenia is not a progressive deteriorating disease.

Neurodegeneration is not important

Look for genes involved in neurodevelopment rather than neurodegeneration!

The findings that there is an excess of Copy Number Variations (CNVs) in schizophrenia reinforces the Neurodevelopmental Hypothesis



A continuum of neurodevelopmental impairment from learning disability through autism to schizophrenia

Exposure to a variety of infections prenatally increases risk of later schizophrenia

This fits with evidence concerning HLA locus.* However, since immune response in pregnancy is mostly determined by mother's response, shouldn't the HLA association be stronger in mothers than in patients.

* Wright et al (1999) The teratogenic antibody hypothesis. In Psychiatry, Immunology and Viruses. Ed by N Muller Springer

The Dunedin Birth Cohort Study

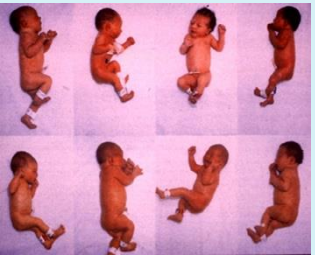
Those who met criteria for schizophreniform disorder at age 26 years showed:-

Higher overall obstetric complications (t=5.5; p<0.001)

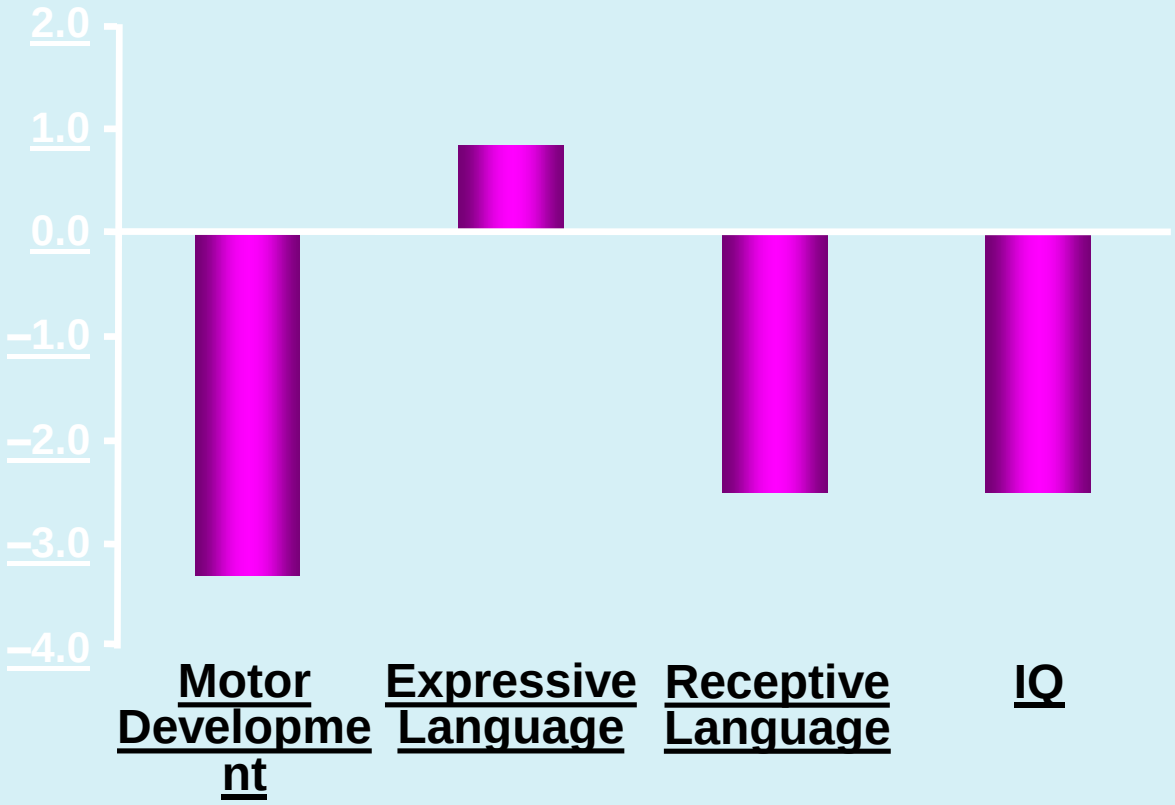
Higher neonatal insults (t=5.95; p<0.001)

Smaller for gestational age (0R=2.8; p<0.001)

More Hypoxia (OR=6.8; p<0.001)

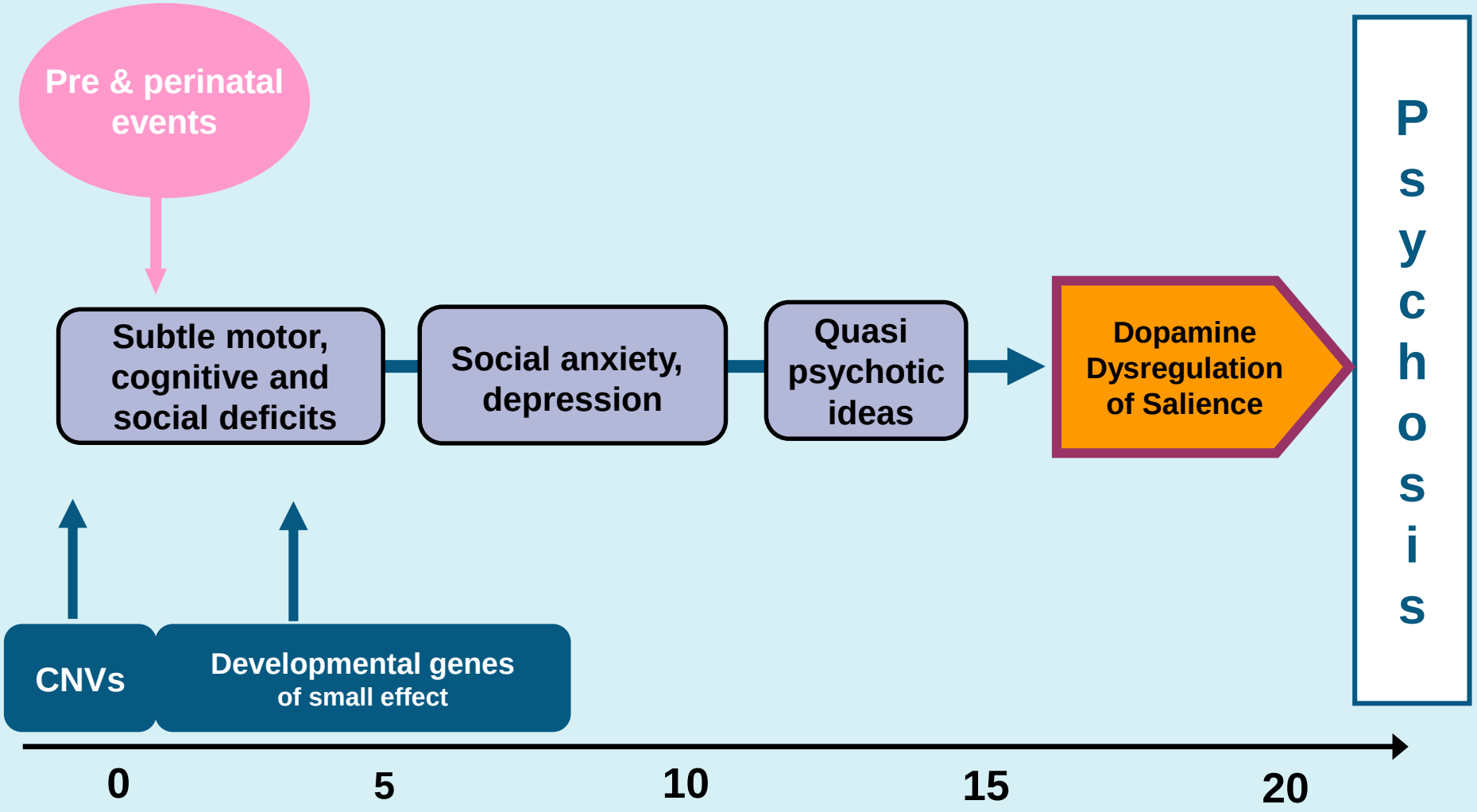


Motor and Language Development in Preschizophrenic Children

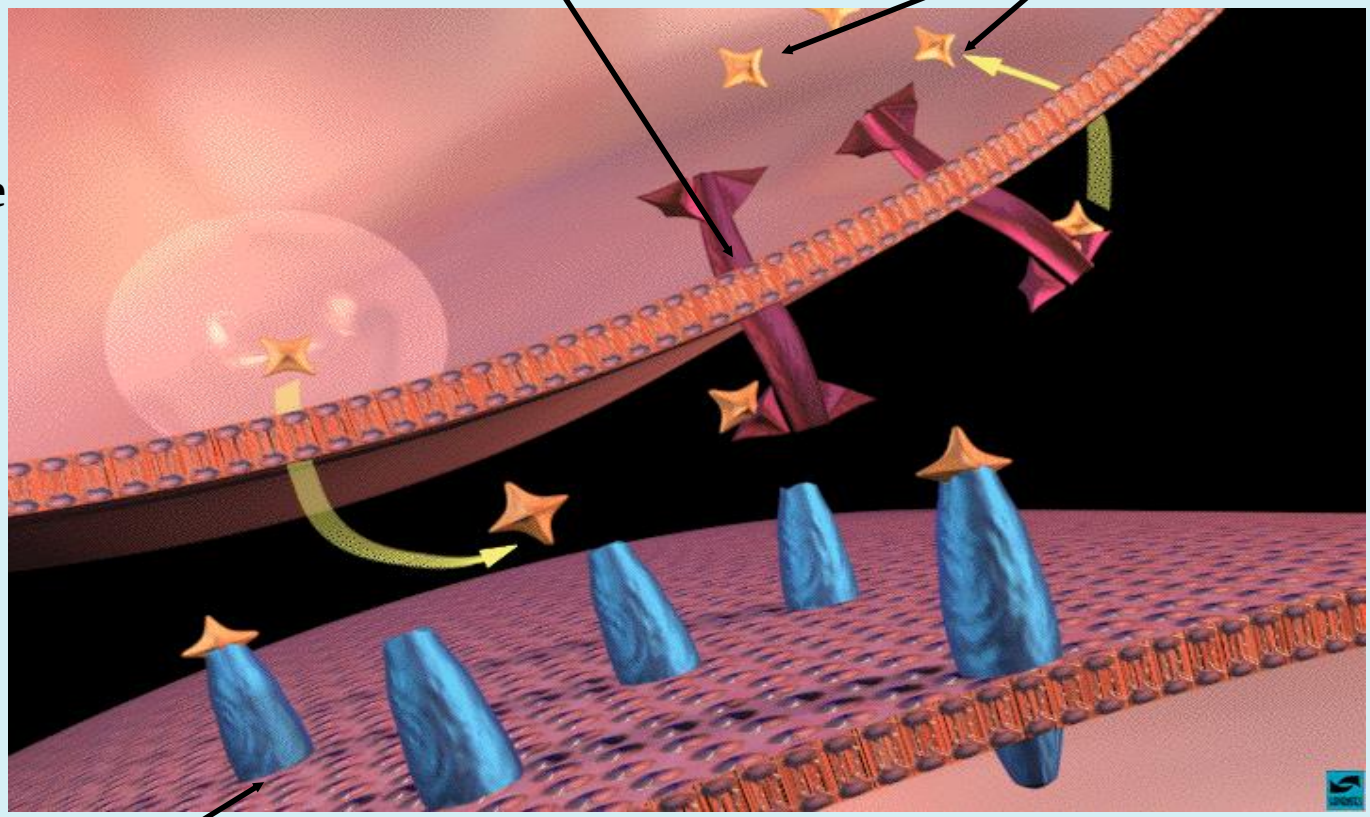


Cannon M et al. *Arch Gen Psychiatry*. 2002;59:449-456.

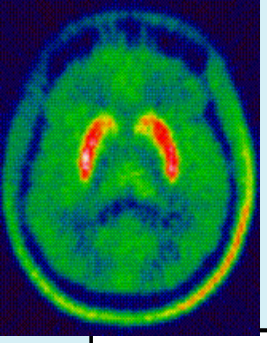
Developmental cascade towards schizophrenia



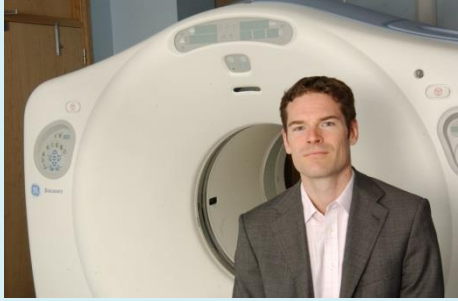
Dysregulation of the Dopamine System – the Final Common Pathway to Schizophrenia*

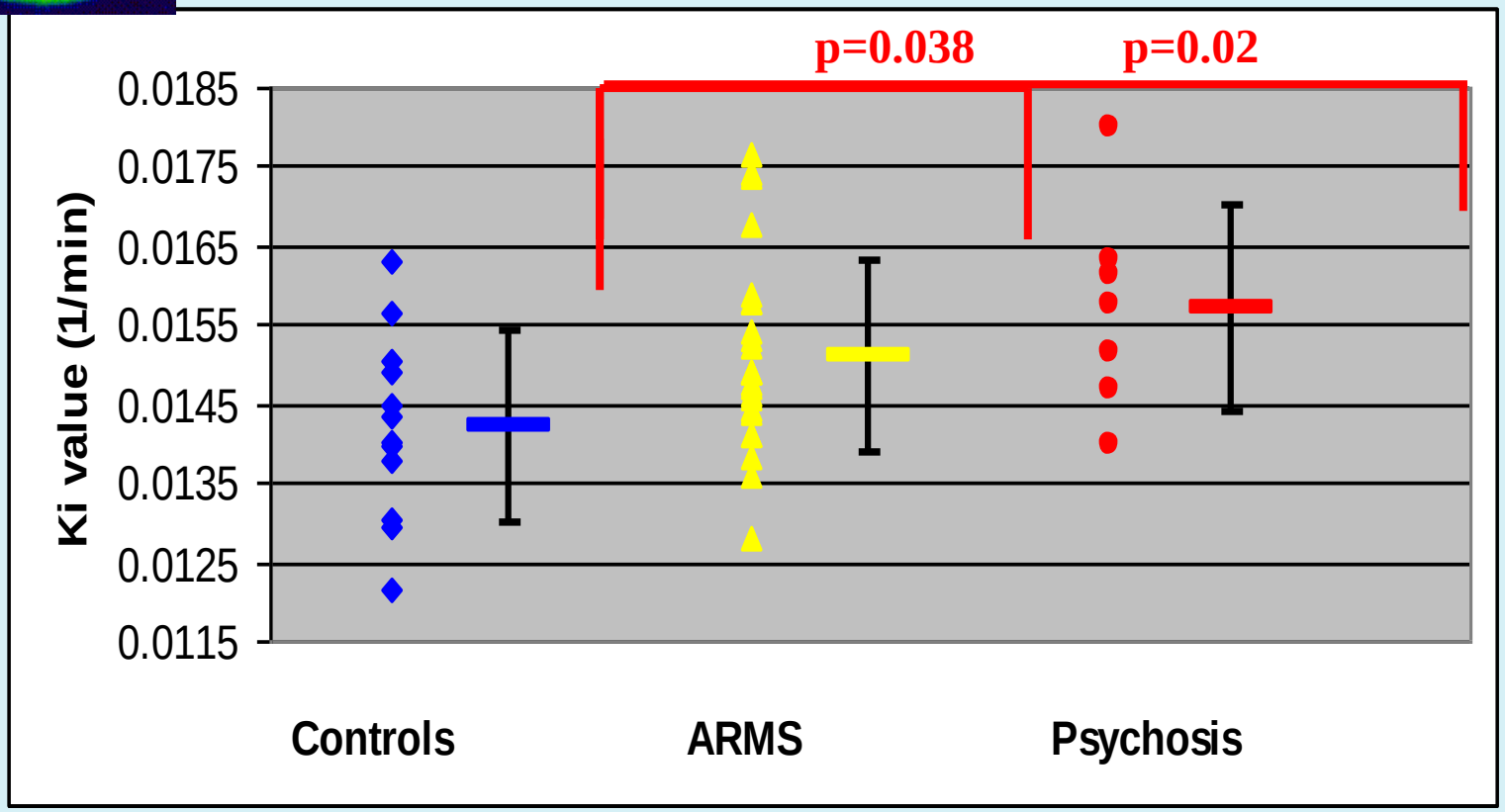


*Di Forti et al 2007 Risk Factors for Schizophrenia.:all roads lead to dopamine. European Neuropharmacology, 17,S101-S107



The Striatal DA abnormality arises in the Prodrome





18F-Dopa Uptake: presynaptic dopamine synthesis

Howes et al, Arch Gen Psych, 2009, 66. 13-20

Some Questions for Geneticists

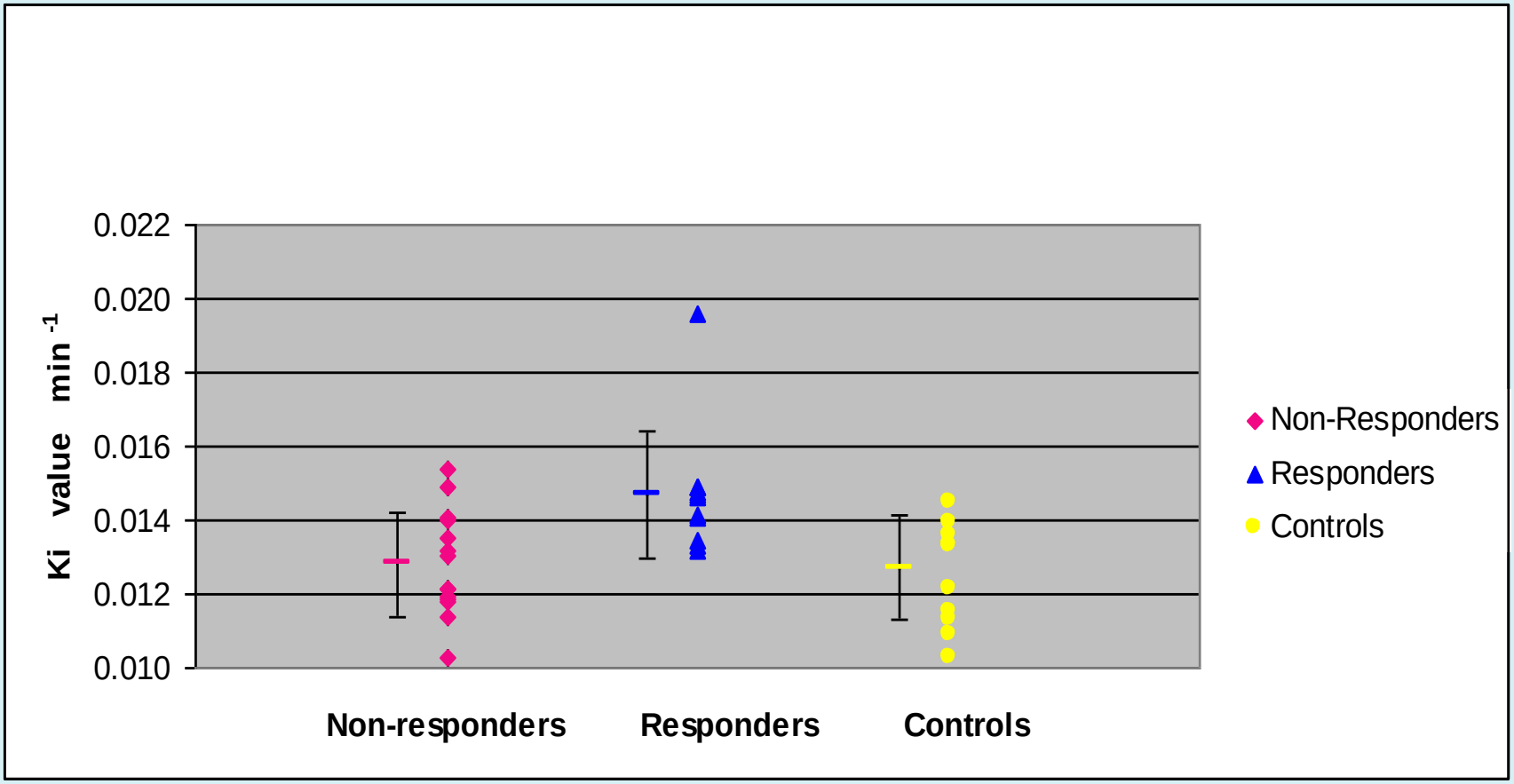
1. Why are DA genes not prominent in PGC GWAS – and DRD2 and AKT postsynaptic?

2. However, Peter Holman's preliminary pathway analysis of PGC2 implicates "dopaminergic synaptic" pathway

3. Possibly other gene systems eg glutamatergic may modulate presynaptic DA synthesis?

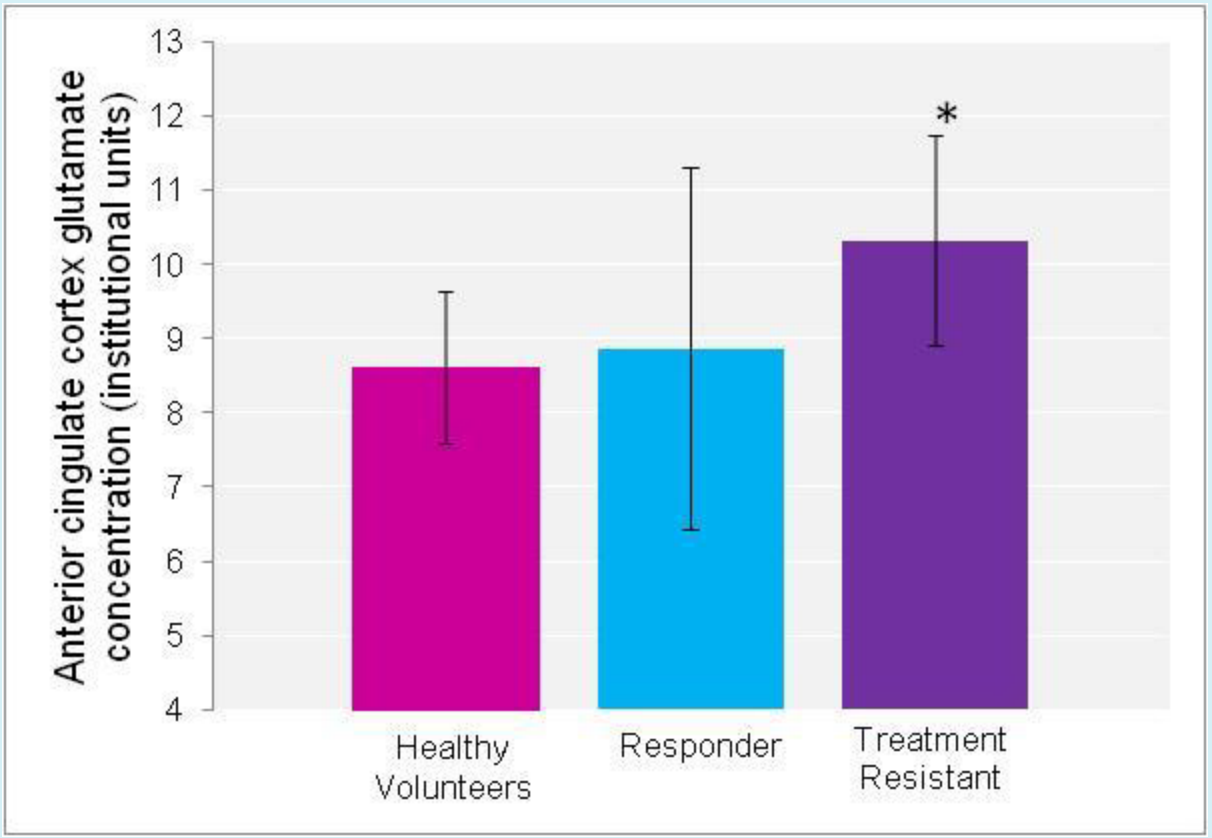
Why do some patients not respond to dopamine blockers?

Dopamine Synthesis is increased in Treatment-Responders (as expected) but not in Treatment-Resistant Patients



Demjaha et al, Arch Gen Psych 2012

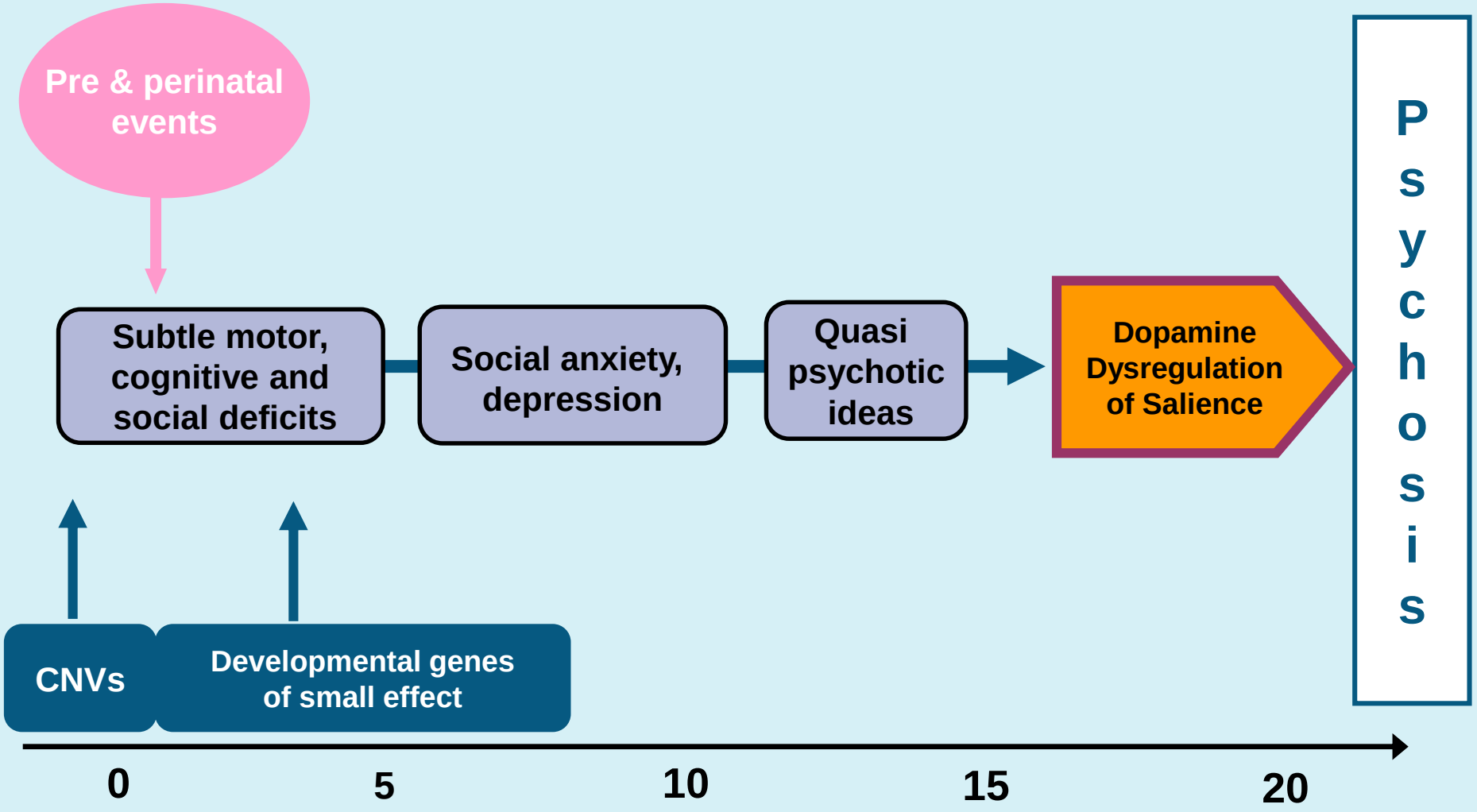
Glutamate levels in Anterior Cingulate are increased in Treatment-Resistant Patients but not in Treatment-Responders*



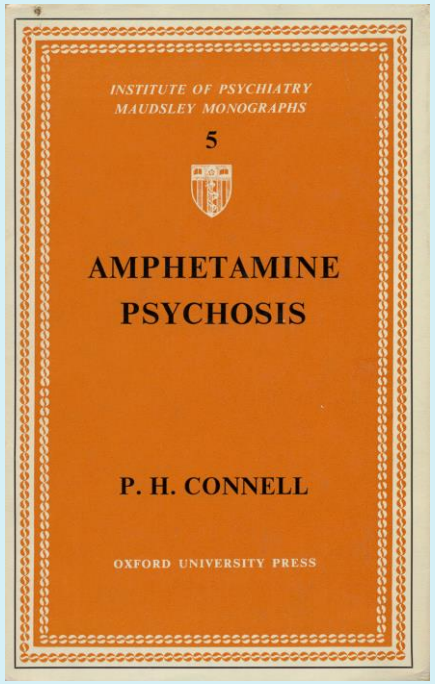
Egerton, Demjaha et al (2014) Biological Psychiatry

So should treatment resistant schizophrenic patients be more likley to show abnormalities in glutamate genes?

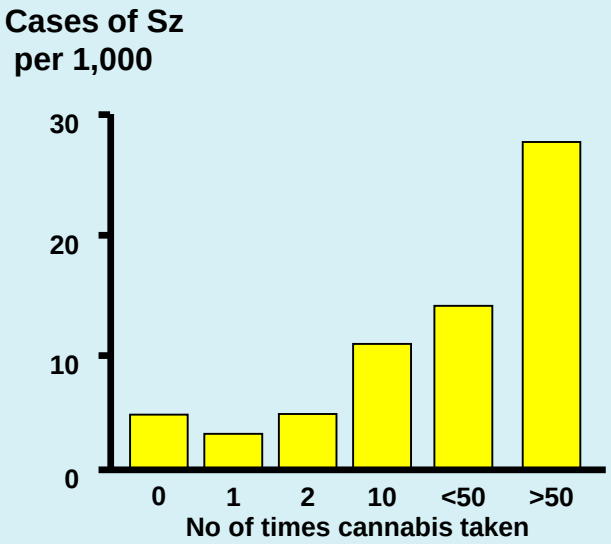
Developmental cascade towards schizophrenia



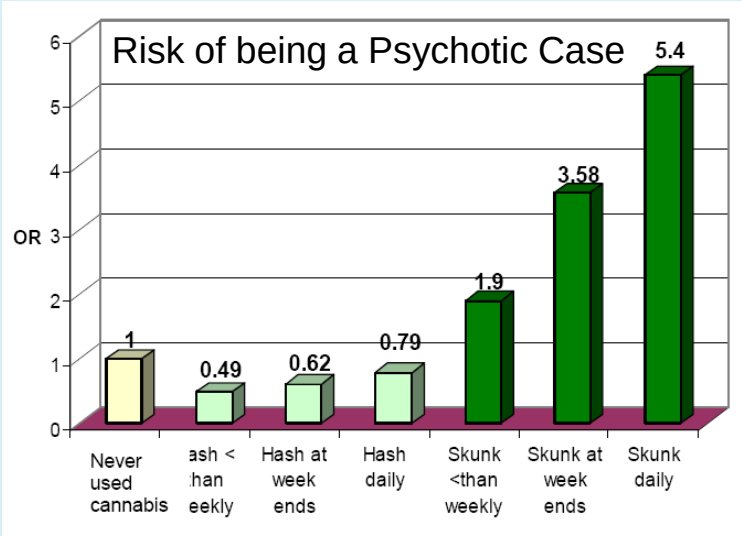
Drug Use can increase risk of Schizoprenia



Swedish Army Study of Andréasson et al 1987



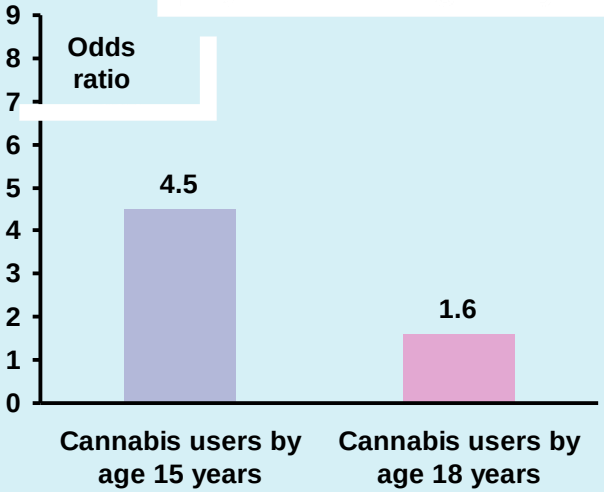
Di Forti et al, 2014



Cohort Studies

Country	n	FU	OR
Sweden	50,053	25 yrs	3.1
NL	4,045	3 yrs	2.8
NL	4,045	3 yrs	12.0
NL	18,000	Retro	3.2
NZ (Chr)	1,265	3 yrs	1.8
NZ (Dun)	1,253	15 yrs	3.1
Germany	2,436	4 yrs	1.7
UK	8,500	18 mths	1.5
Australia	3,800	14 yrs	2.2

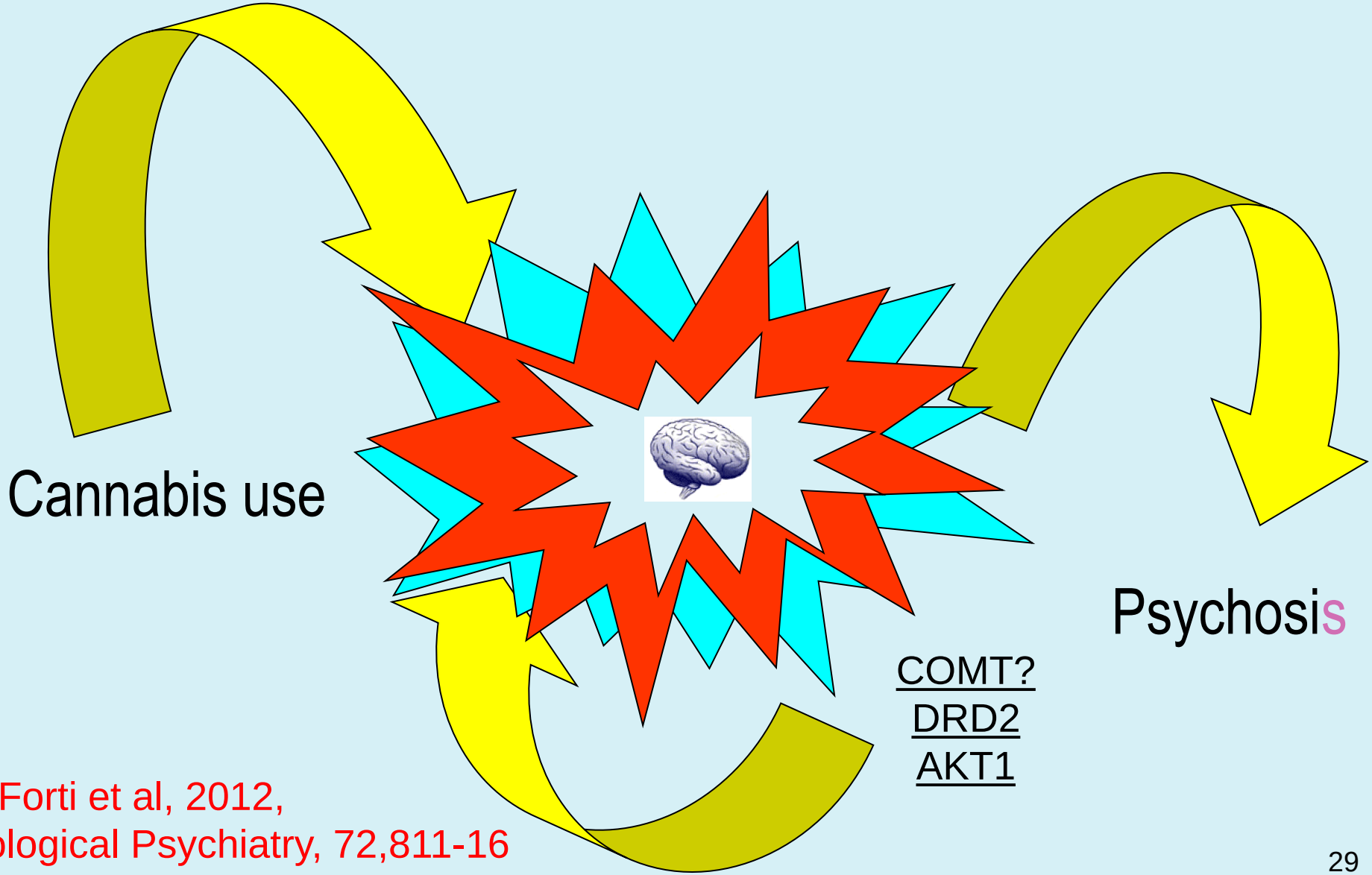
Risk of schizophreniform psychosis at age 26 years



Arseneault et al 2002 BMJ, 325.1212

However, still only a minority of those adolescents who use high potency cannabis daily will develop psychosis.

Gene-Environment Interaction?

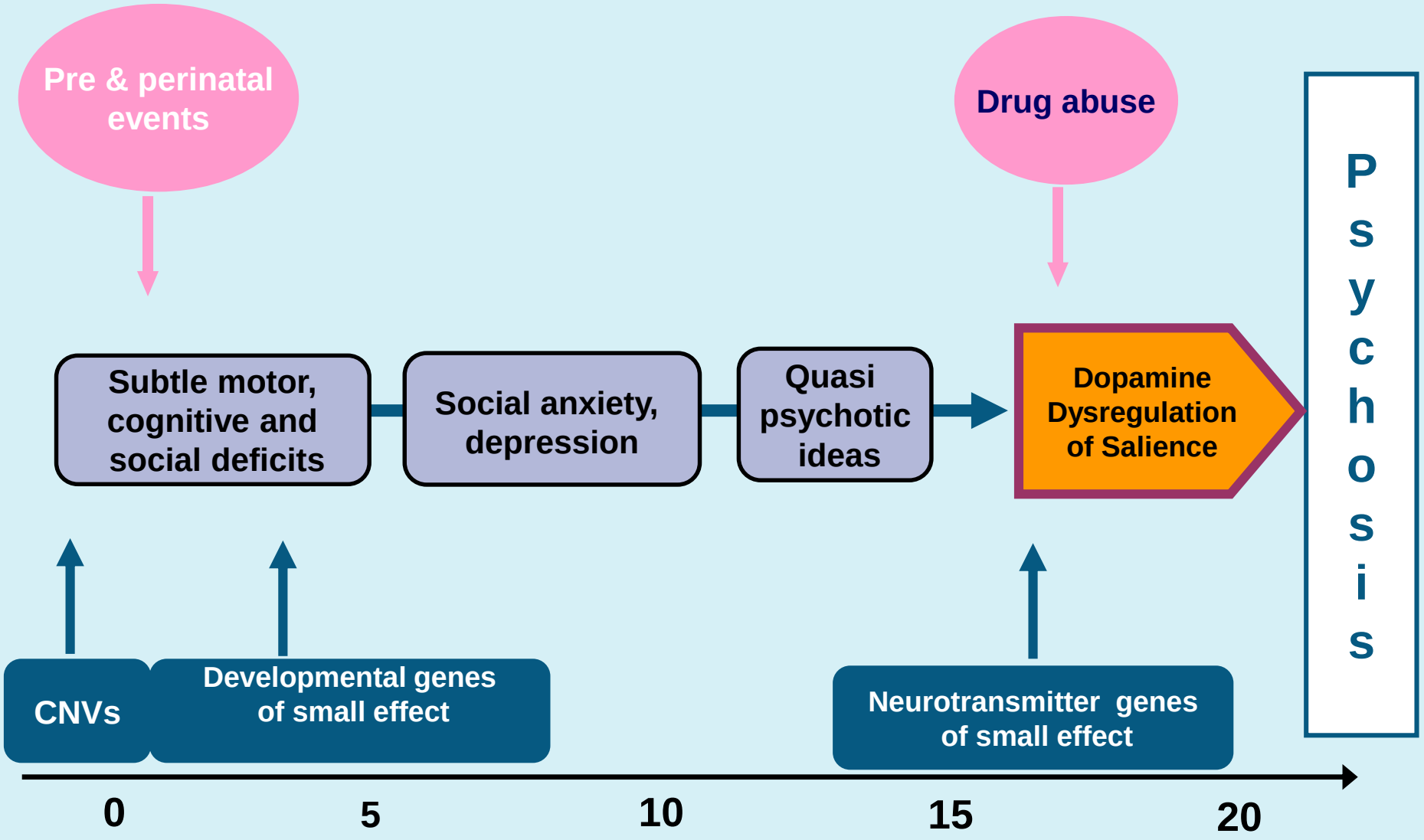


Di Forti et al, 2012,
Biological Psychiatry, 72,811-16

Might cannabis use be a reflection of predisposition to Schizophrenia?

However, since many schizophrenic patients use cannabis, is the polygenic risk score for Sz contaminated by genes which increase cannabis use?

Power R et al Biological Psychiatry 2014

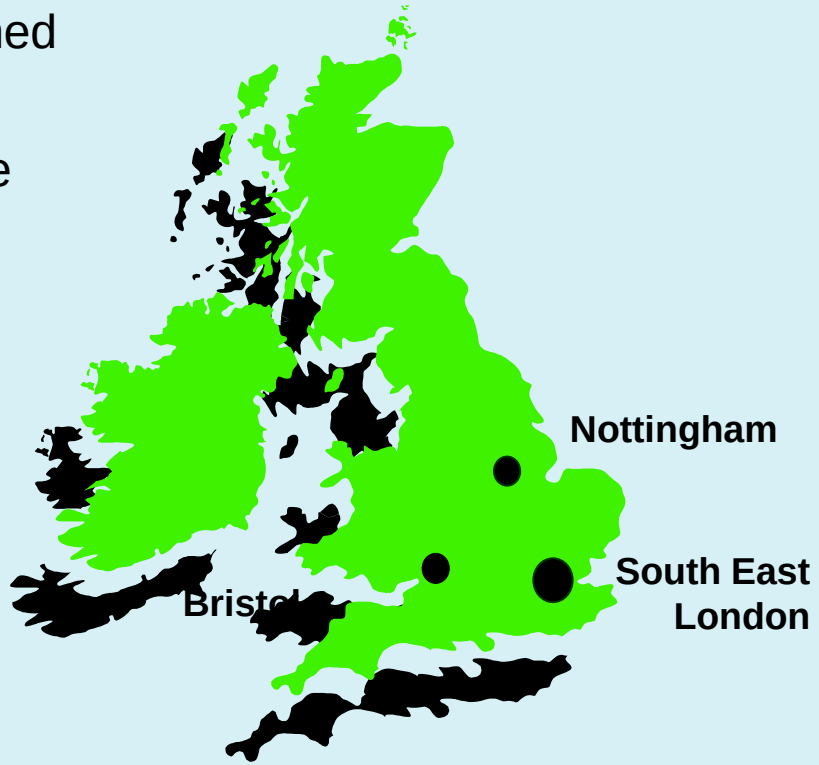

Pre & perinatal events
Drug abuse
Psychosis
Subtle motor, cognitive and social deficits
Social anxiety, depression
Quasi psychotic ideas
Dopamine Dysregulation of Salience
CNVs
Developmental genes of small effect
Neurotransmitter genes of small effect
0
5
10
15
20

Are social factors themselves component causes?

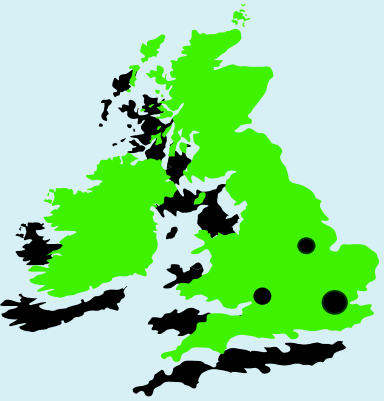
ÆSOP – epidemiological study of first-episode psychosis in three English Cities

All individuals 16-65 years living in three defined city areas who presented to psychiatric services with their first psychotic episode

	Incidence rate for schizophrenia per 100,000
London	**20.1**
Nottingham	**7.7**
Bristol	**7.2**



Kirkbride et al 2006, Arch Gen Psychiatry, 63, 250-258



AESOP Study – Incidence of Schizophrenia by Ethnicity

	Rate Ratios
British Whites	1
Non-British Whites	2.5
South Asians	1.4
Africans	5.8
African-Caribbeans	9.1

Fearon et al, Psychological Medicine, 2006, 36, 1541-1550

Risk in siblings of African-Caribbean people with schizophrenia - who live in the Carribean - is about 5% (i.e. same as whites).

Risk in siblings of African-Caribbean patients - who live in UK - is about 25%

Some environmental factor operating in UK is increasing risk in A-C migrants

Hutchinson et al, British J Psychiatry, 169. 777-780

What causes the high rates in black migrants?

Most of the evidence implicates social factors – deprivation, poor education, discrimination, hostility, etc

Is psychosis in black migrants more psychosocial and less genetic?

We could look at this if there were a polygenic risk score for black subjects

AESOP Study - Risk of Schizophrenia is increased by:-

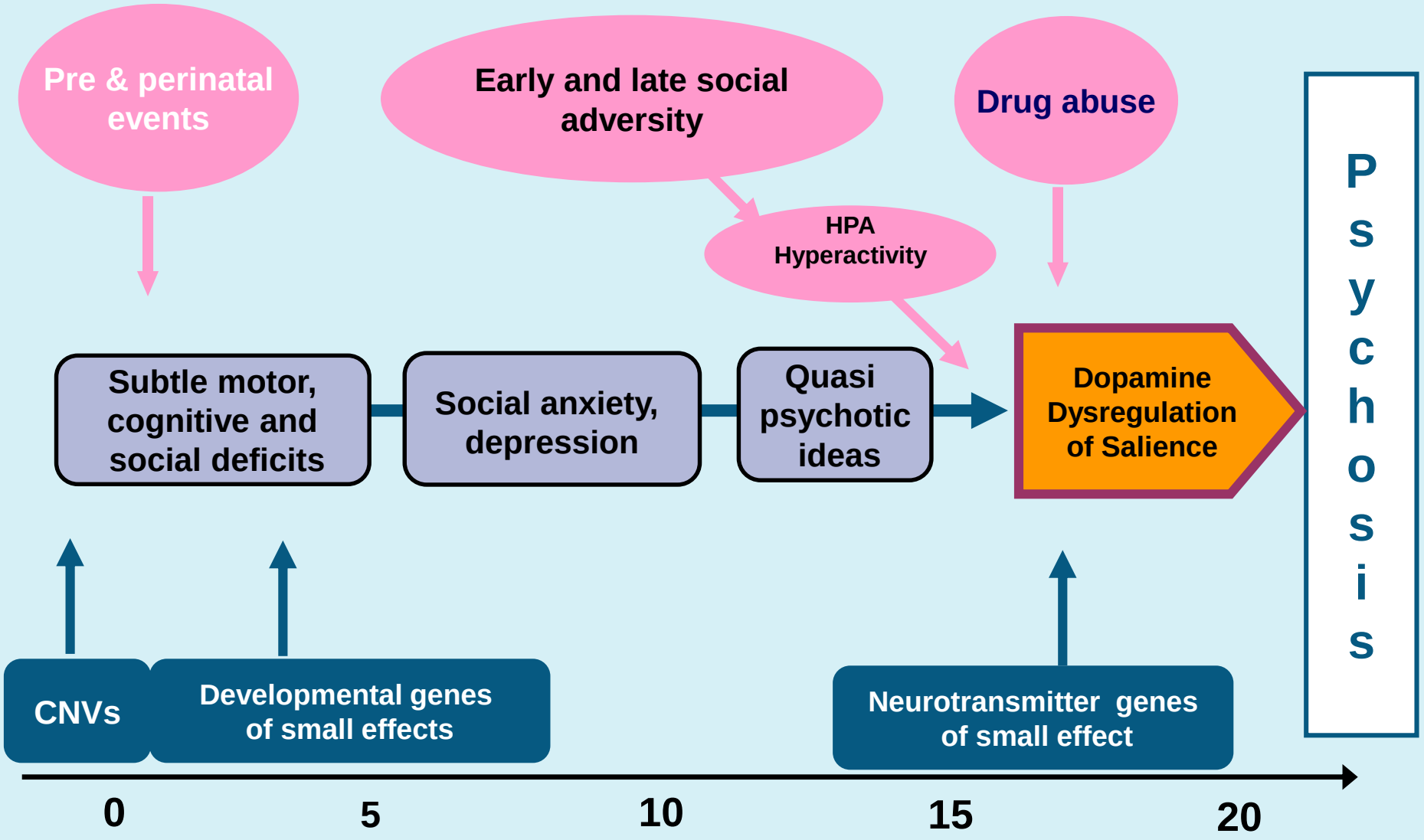
Urban effect

Migration/ethnic minorities

Childhood adversity

What is the nature of the relationship between childhood abuse and Family History?

1. Childhood abuse is not explained away by Family History
2. Indeed, childhood abuse is commoner in those psychotic patients with no family history
3. Two separate pathways?
4. What will molecular studies show?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Quasi psychotic ideas
Dopamine Dysregulation of Salience
Psychosis
CNVs
Developmental genes of small effects
Neurotransmitter genes of small effect
0
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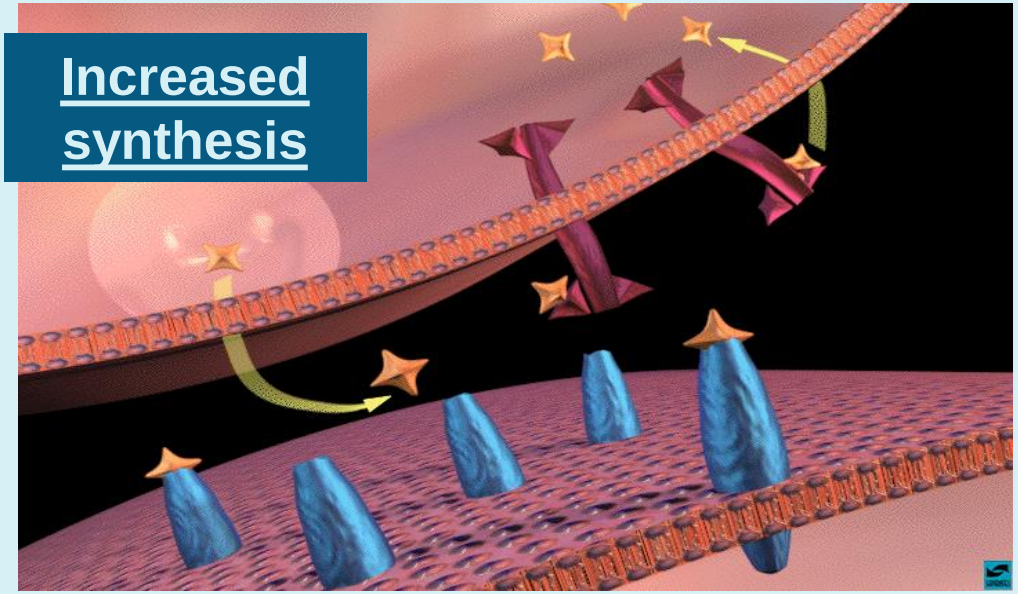
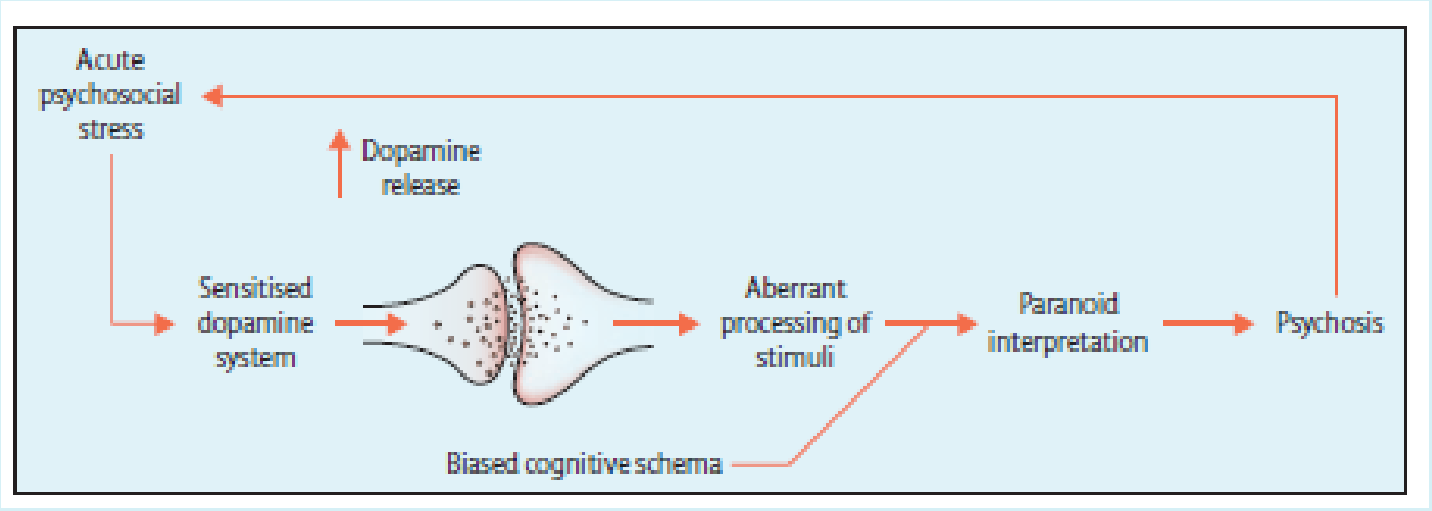
15
20

If the Final Common Pathway to Psychosis is Dopamine Dysregulation, can Social Factors Cause this?



Stress, childhood abuse, Migration, drug abuse all increase striatal DA (Mizrahi etal, 2011, Egerton et al 2014)



Howes and Murray, Lancet, On-line Dec 6 2013

Conclusions

Schizophrenia is not a degenerative disease but rather a syndrome with a number of different environmental risk factors

What is the nature of the gene-environment interplay?

For example, are the genes which make people vulnerable to cannabis-induced psychosis quite different to those which make people vulnerable to obstetric insult or child abuse?

Thanks to Many Colleagues