

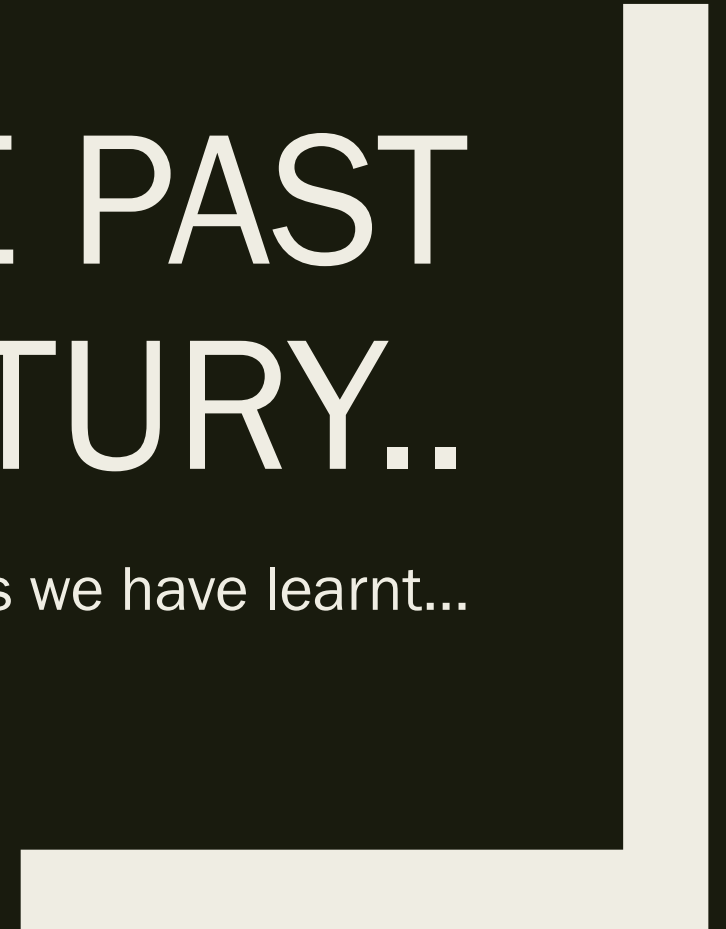
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RETHINKING TREATMENT APPROACH TO SCHIZOPHRENIA

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REVISITING THE PAST CENTURY..

The lessons we have learnt...



Asylums

Insulin Coma Therapy
1927

Frontal Lobotomy
1935

Serendipity in Psychiatry

■ Chlorpromazine

- *Discovered by Henri Labroit, French surgeon*
 - *Calming effect, reduced anesthetic doses*
- *First clinical trial by Pierre Deniker in 1952*
- *American company Smith Kline purchased rights in 1952*
- *FDA approved in 1954*

■ Haloperidol

- *Discovered by Paul Janssen in 1958*
- *Synthesized from pethidine for pain*

■ Arvid Carlsson & Margit Lindqvist in 1963

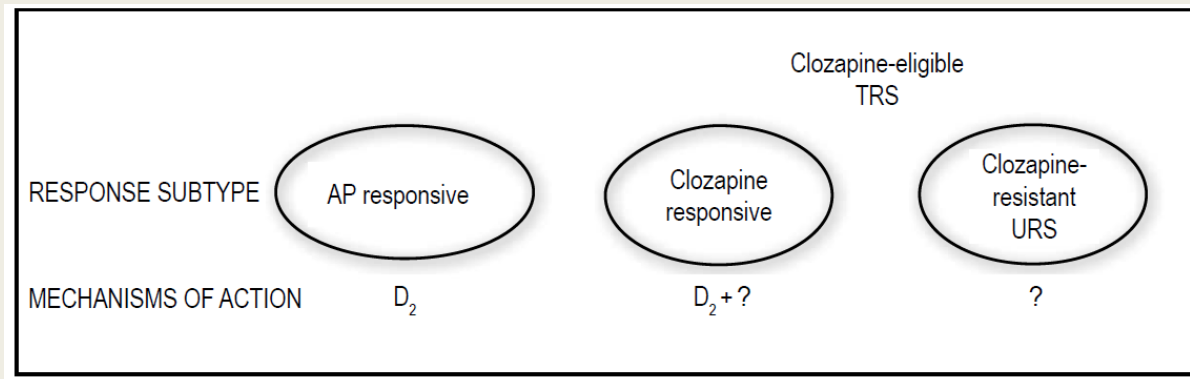
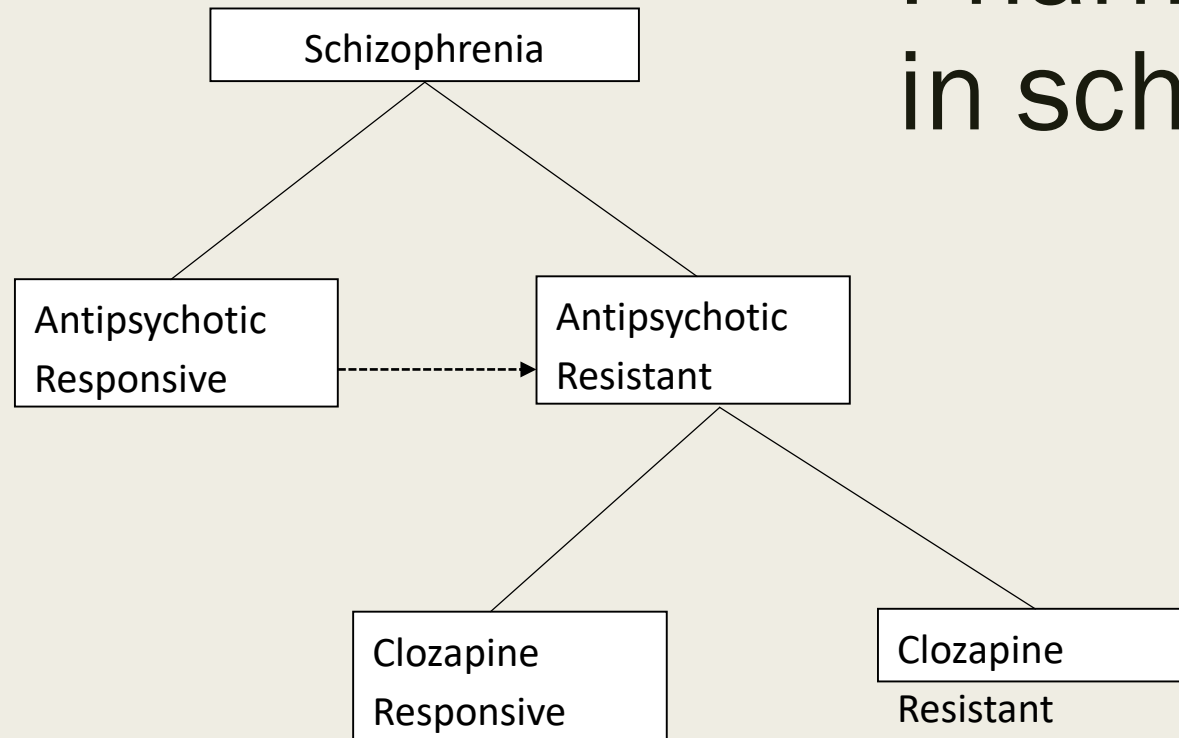
- *Chlorpromazine and haloperidol*
- *Increased metabolism of dopamine in mouse brains*
- *Sparked interest in dopamine in schizophrenia*

Clinical outcomes in Schizophrenia

	Definition	Cons
Response	20% reduction in total symptoms	Symptom-focus Non-specific symptoms Still symptomatic
Remission	Core symptoms below threshold (positive/negative/disorganisation)	Symptom-focus No good treatments for negative symptoms
Clinical Recovery	No symptoms and normal functioning over a period	High threshold Determinants of functioning are multiple and complex

Trajectories of response

Pharmacological subtypes in schizophrenia



PANSS RATING FORM

		absent	minimal	mild	moderate	<u>moderate</u> <u>severe</u>	severe	extreme
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P1	Delusions	1	2	3	4	5	6	7
P2	Conceptual disorganisation	1	2	3	4	5	6	7
P3	Hallucinatory behaviour	1	2	3	4	5	6	7
P4	Excitement	1	2	3	4	5	6	7
P5	Grandiosity	1	2	3	4	5	6	7
P6	Suspiciousness/persecution	1	2	3	4	5	6	7
P7	Hostility	1	2	3	4	5	6	7

N1	Blunted affect	1	2	3	4	5	6	7
N2	Emotional withdrawal	1	2	3	4	5	6	7
N3	Poor rapport	1	2	3	4	5	6	7
N4	Passive/apathetic social withdrawal	1	2	3	4	5	6	7
N5	Difficulty in abstract thinking	1	2	3	4	5	6	7
N6	Lack of spontaneity & flow of conversation	1	2	3	4	5	6	7
N7	Stereotyped thinking	1	2	3	4	5	6	7

G1	Somatic concern	1	2	3	4	5	6	7
G2	Anxiety	1	2	3	4	5	6	7
G3	Guilt feelings	1	2	3	4	5	6	7
G4	Tension	1	2	3	4	5	6	7
G5	Mannerisms & posturing	1	2	3	4	5	6	7
G6	Depression	1	2	3	4	5	6	7
G7	Motor retardation	1	2	3	4	5	6	7
G8	Uncooperativeness	1	2	3	4	5	6	7
G9	Unusual thought content	1	2	3	4	5	6	7
G10	Disorientation	1	2	3	4	5	6	7
G11	Poor attention	1	2	3	4	5	6	7
G12	Lack of judgement & insight	1	2	3	4	5	6	7
G13	Disturbance of volition	1	2	3	4	5	6	7
G14	Poor impulse control	1	2	3	4	5	6	7
G15	Preoccupation	1	2	3	4	5	6	7
G16	Active social avoidance	1	2	3	4	5	6	7

Schizophrenia is a complex phenotype



**Are they all dopamine related?
Do they have a common aetiology?**

Antipsychotics as “magic bullets”

Tranquilizer to Antipsychotic

- Imply disease specific treatment
- Altering underlying biological processes
- Over-marketing

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Magic Bullets for Mental Disorders: The Emergence of the Concept of an “Antipsychotic” Drug

JOANNA MONCRIEFF

CanJ Psychiatry 2015;60(3 Suppl 2):S14–S18

Chapter 2

What Does Schizophrenia Teach Us About Antipsychotics?

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Jimmy Lee, MBBS, MMed⁶; Margaret Hahn, MD, PhD, FRCPC³

Schizophrenia is complex

- Antipsychotics target mainly positive symptoms
- Precision in drug evaluation
- Basis for “polypharmacy”
- Opportunity to study neurobiology

Cognitive Architecture of Schizophrenia

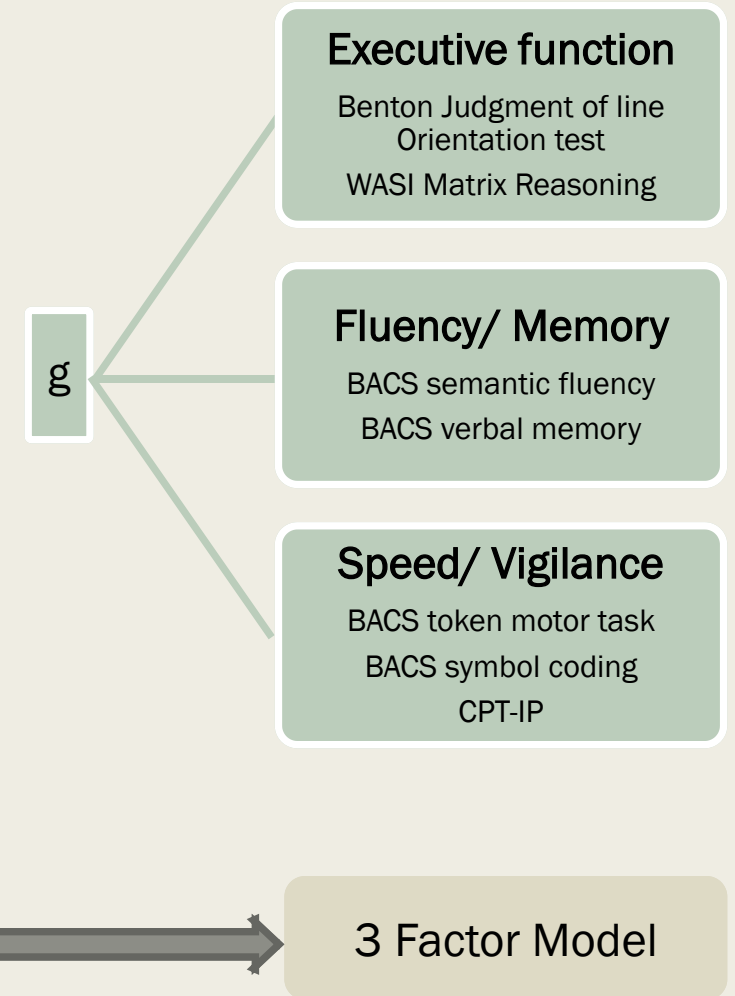
10 Neuropsychological tests; 32 subtests

(No. in parenthesis indicates contributing subtest)

- WASI Matrix Reasoning (1)
 - CPT-IP (16)
 - WCST-64 (5)
 - Benton Judgment of Line Orientation Test (1)
 - Verbal memory (1)
 - Digit sequencing (1)
 - Token motor task (1)
 - Semantic fluency (4)
 - Symbol coding (1)
 - Tower of London (1)
- BACS

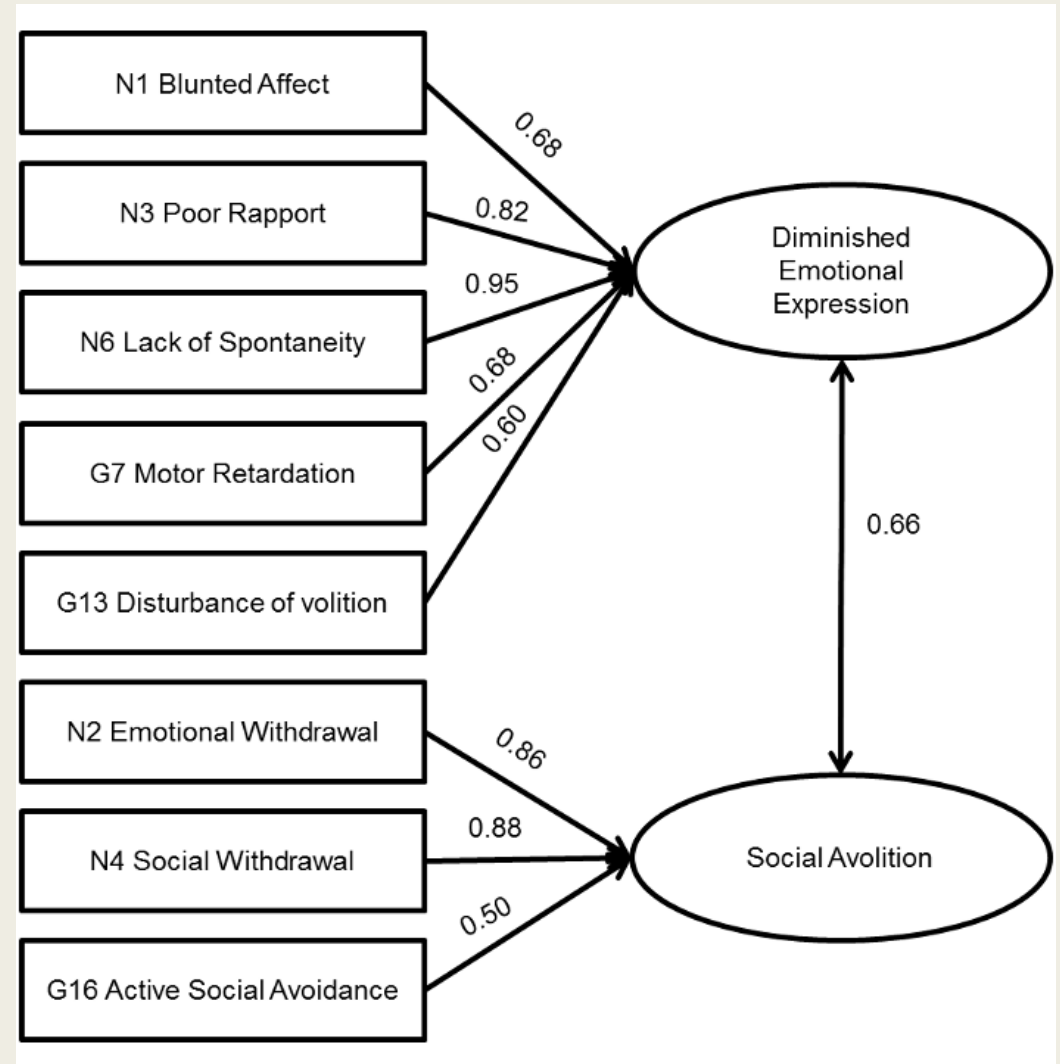
n=707

- (1) PCA subtest reduction: CPT-IP, WCST-64, Semantic fluency
- (2) EFA on reduced components + remaining subtests



The relationship between negative symptom subdomains and cognition

- Validating 2-factor model (n=687)
 - Positive and Negative Syndrome Scale (PANSS)
- Fit indices
 - CFI 0.995
 - TLI 0.993
 - RMSEA 0.033



Negative symptoms & Cognition

- Differential effects between 2 factors and cognition
 - DEE had significant associations with cognition

The **Common Substrates Model** depicts the relationship between DEE, SA, the three cognitive domains and a common substrate.

Transdiagnostic approach

Social amotivation seen in individuals at risk of psychosis

- Similar negative symptom structures between schizophrenia and Ultra-High Risk (UHR) groups
 - *Suggesting that negative symptoms predate onset of frank psychosis*
- Social amotivation in UHR predicts functioning in 1 year

Conclusion

- Schizophrenia is not a single disease entity
 - *Approach schizophrenia as a complex multifaceted condition*
- There is no “magic bullet” antipsychotic
 - *Be precise in defining treatment outcomes*
 - *Antipsychotics act primarily on positive symptoms*
 - *Due to inter-relatedness of symptoms, antipsychotics might have secondary effects on other symptom domains*
- Deconstruct schizophrenia
 - *Opportunity to study biology and tailor treatments*
 - *Harness observations over decades, i.e. pharmacological subtypes*
 - *Transdiagnostic treatments*