

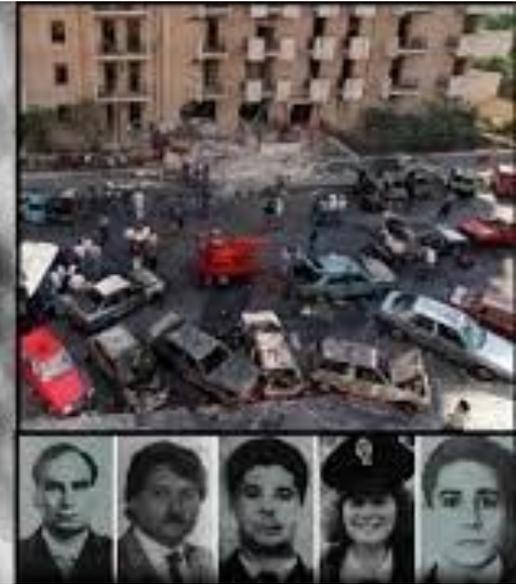
**30 years ago today at 17.58
Judge Giovanni Falcone was assassinated by
the Corleonesi Mafia**



Giovanni Falcone died together with his wife, Francesca, and three policemen from his escort, in an explosion caused by 30 tonnes of TNT buried under the motorway between the airport and Palermo



Paolo Borsellino was assassinated on July 19, 1992, in what is now known as “*The massacre of Via D’Amelio*”



“I believe it is necessary to realize that this is not a personal struggle between us and the mafia. If it were understood that this must be a commitment – extraordinary in the ordinary – of everyone towards a phenomenon that is unworthy of a civilized country, things would certainly be much better.”

G. Falcone



“It is nice to die for what you believe in; those who are afraid die every day, those who are not afraid die only once”

P. Borsellino

Two ways of looking at schizophrenia

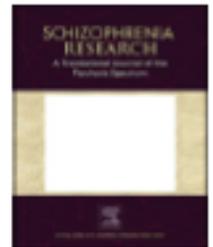
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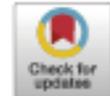
Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres



Point

Neurodegenerative model of schizophrenia: Growing evidence to support a revisit



Counter point

Schizophrenia: A developmental disorder with a risk of non-specific but avoidable decline



Invited commentary

Commentary on whether progressive brain change underlies the pathology of schizophrenia: Should this even be debated?





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William S. Stone^{a,*}, Michael R. Phillips^{b,c}, Lawrence H. Yang^{c,d}, Lawrence S. Kegeles^{e,f}, Ezra S. Susser^c, Jeffrey A. Lieberman^e

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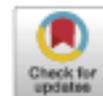
Schizophrenia: A developmental disorder with a risk of non-specific but avoidable decline

R.M. Murray^{a,*}, E. Bora^b, G. Modinos^a, A. Vernon^a

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Lynn E. DeLisi



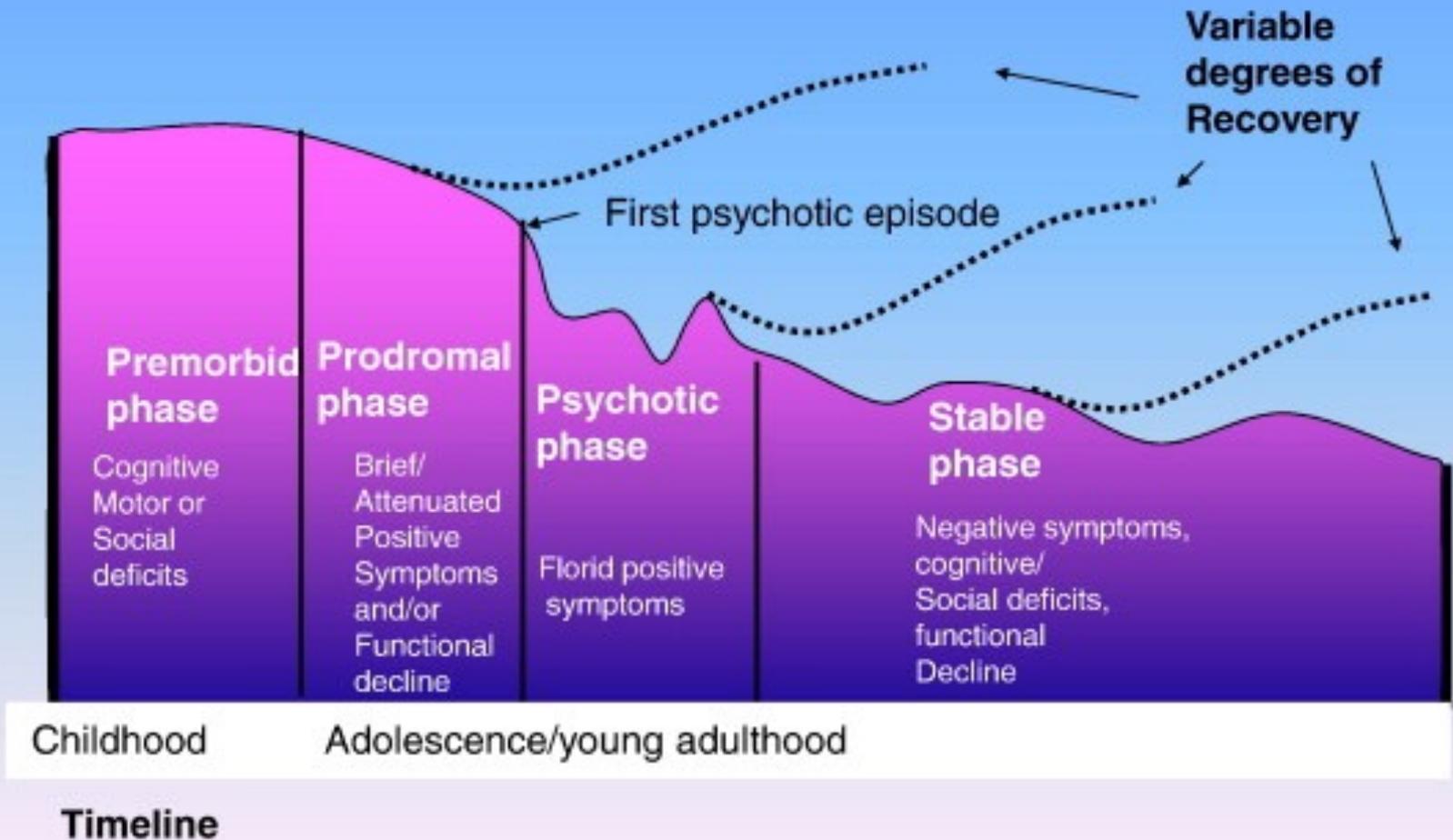


1. Deterioration in clinical function

Kraepelin considered that dementia praecox (schizophrenia) was a progressive disease



Natural history and course of Schizophrenia



Worsening brain abnormalities

Schizophrenia patients were found to have enlarged lateral ventricles and cognitive impairment



924

CEREBRAL VENTRICULAR SIZE AND COGNITIVE IMPAIRMENT IN CHRONIC SCHIZOPHRENIA

EVE C. JOHNSTONE
C. D. FRITH

T. J. CROW
JANET HUSBAND

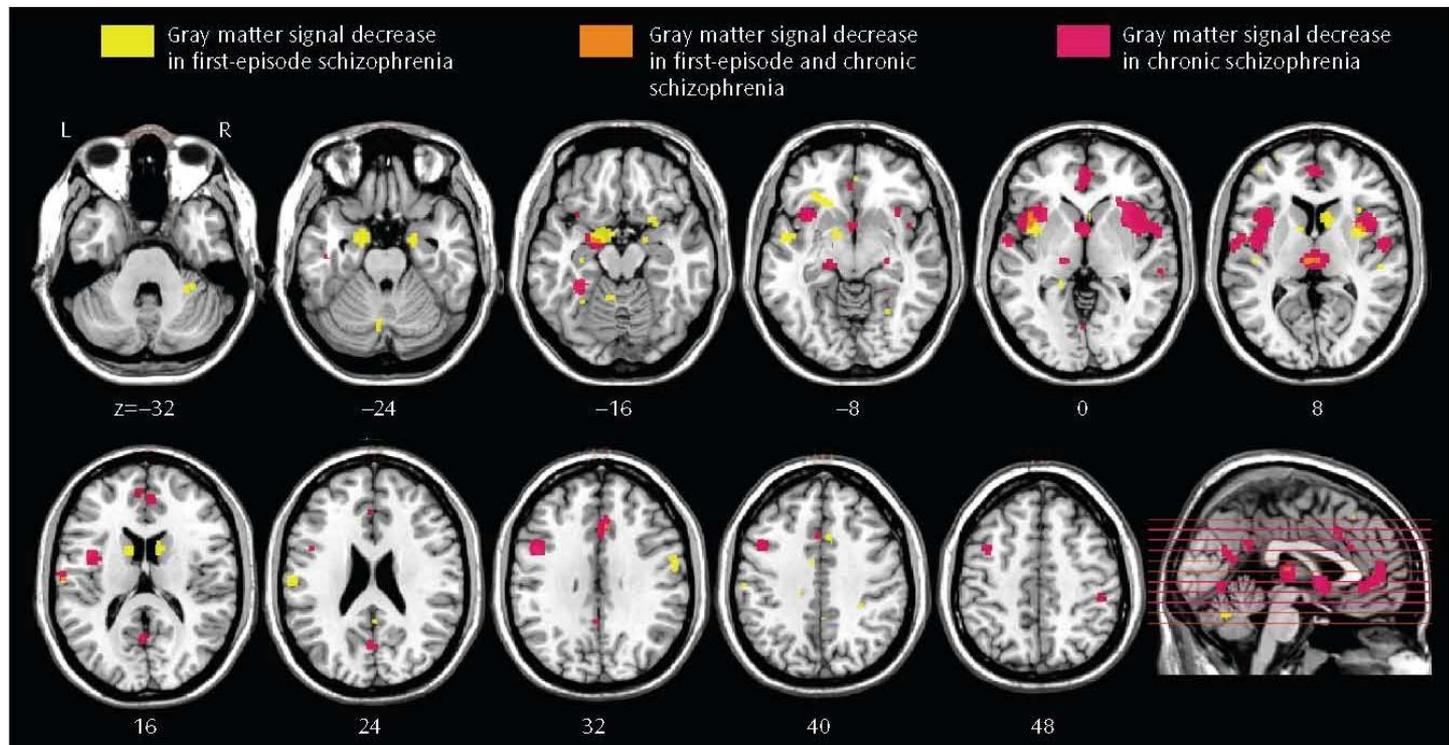
L. KREEL

*Divisions of Psychiatry and Radiology, Clinical Research
Centre, Watford Road, Harrow, Middlesex HA1 3UJ*

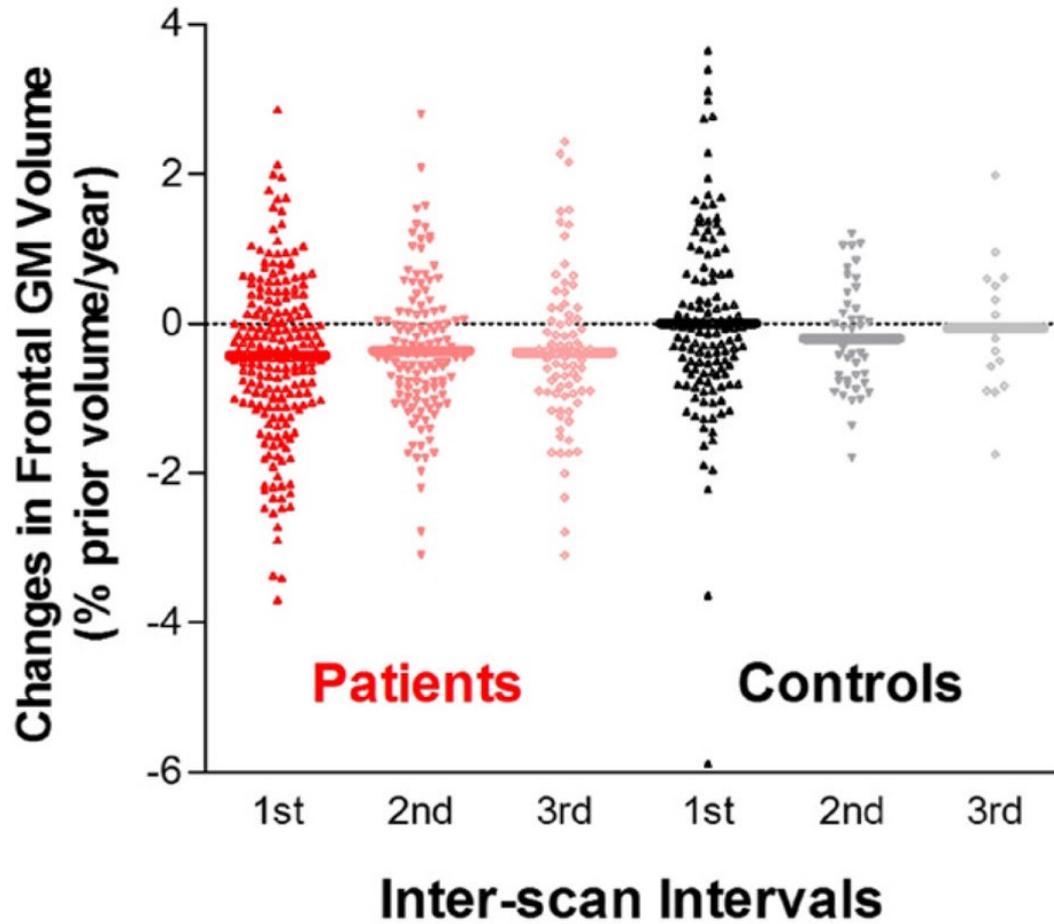
Summary By comparison with age-matched controls in employment, 17 institutionalised schizophrenic patients were shown by computerised axial tomography of the brain to have increased cerebral ventricular size. Within the group of schizophrenic patients increased ventricular size was highly significantly related to indices of cognitive impairment.

Changes in brain structure

FIGURE 1. Regional Overlap of Changes in First-Episode Schizophrenia and Chronic Schizophrenia^a



Nancy Andreassen et al, Biological Psychiatry, 2011



Decline in cognition

1. Bora and Murray meta-analysis showed no cognitive deterioration in first 5 years
2. The AESOP 10 year study showed a mean 2.9 decline in IQ (same as in mania)
3. Suffolk County study showed a moderate loss in cognitive function after 20 years
4. Several recent studies have shown an increased risk of dementia

These findings are best explained by accelerated brain ageing

Opposing View



Most people with schizophrenia don't show progressive decline in illness

Those who met criteria for schizophreniform disorder, compared to controls, showed:-

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

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

Smaller for gestational age ($OR=2.8$; $p<0.001$)

More Hypoxia ($OR=6.8$; $p<0.001$)



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

BJPsych

The British Journal of Psychiatry (2011)
198, 173–175. doi: 10.1192/bjp.bp.110.084384

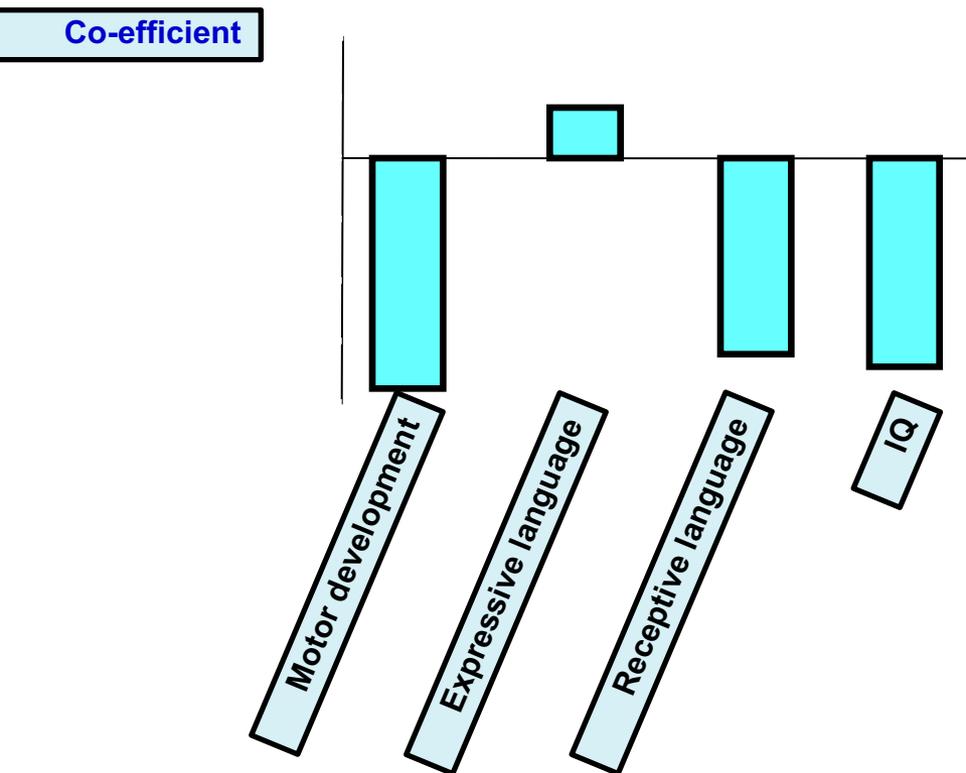
Reappraisal

Neurodevelopmental hypothesis of schizophrenia

Michael J. Owen, Michael C. O'Donovan, Anita Thapar and Nicholas Craddock

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

Motor and language development in pre-schizophreniform children



Reappraising the long-term course and outcome of psychotic disorders: the AESOP-10 study



C. Morgan^{1,2*}, J. Lappin^{2,3}, M. Heslin⁴, K. Donoghue⁵, B. Lomas⁶, U. Reininghaus¹, A. Onyejiaka¹, T. Croudace⁷, P. B. Jones⁸, R. M. Murray^{2,3}, P. Fearon⁹, G. A. Doody⁶ and P. Dazzan^{2,3}

HOW WERE 387 PATIENTS FUNCTIONING AT TEN YEARS?

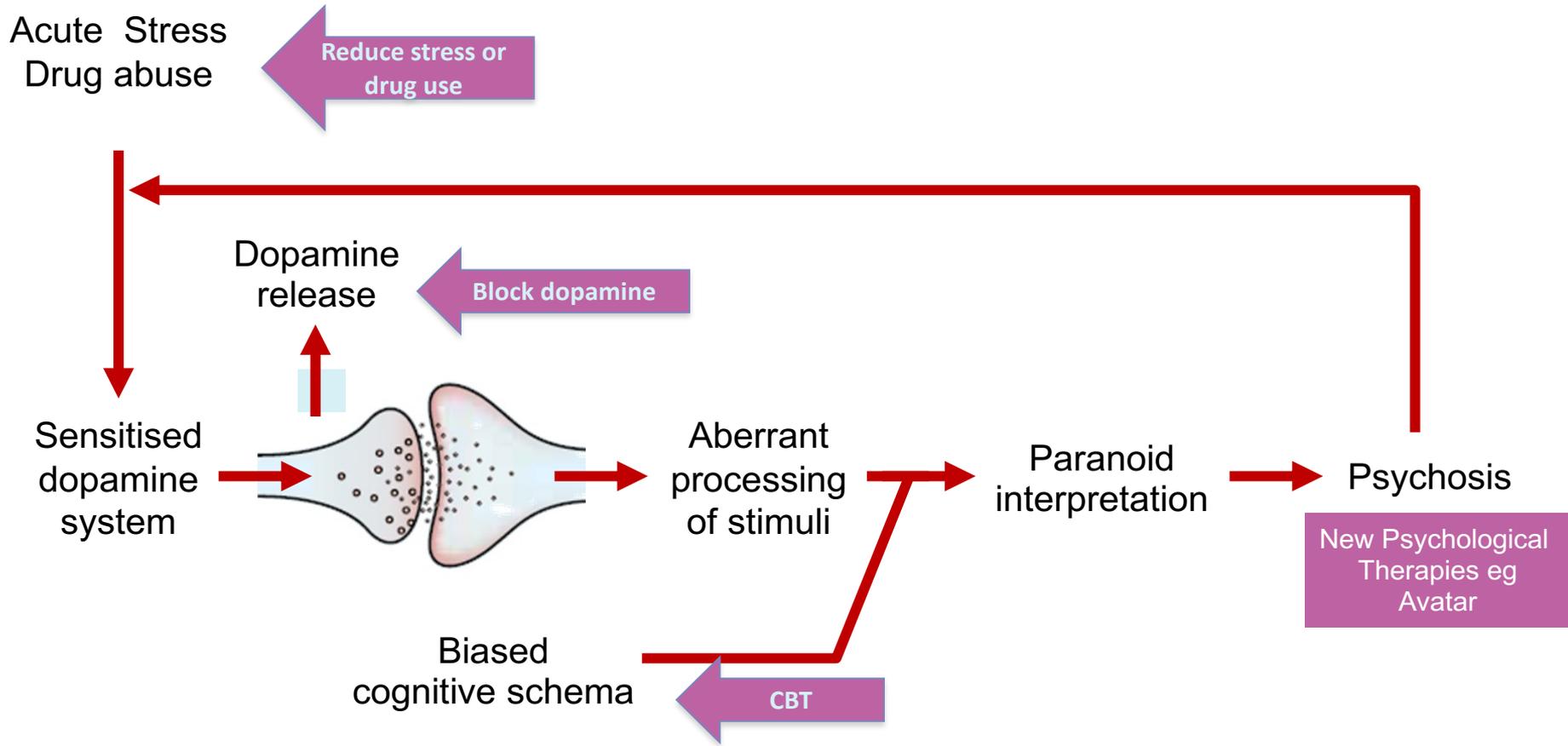
65% had no psychotic symptoms at 10 years;

46% had had none for >2 years (40% of those with a diagnosis of Schizophrenia)

21% overall and 19% of people with schizophrenia had no psychotic symptoms and were not taking antipsychotics

Do people with schizophrenia inherit a predisposition to continuing cognitive decline through life?

However, stress may lead to dopamine release and a vicious cycle of decline



In 1987 we proposed the neurodevelopmental theory of schizophrenia



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

graph, 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.² 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.³ Recent neuropathological findings in schizophrenia are suggestive of such neuronal damage early in life.⁴

Excess exposure to pre- and peri-natal hazards

In the USA, Dan Weinberger independently made a similar proposal

Over the next two decades from 1987, it became accepted there was a developmental component to schizophrenia.

The advocates of degeneration were

buried

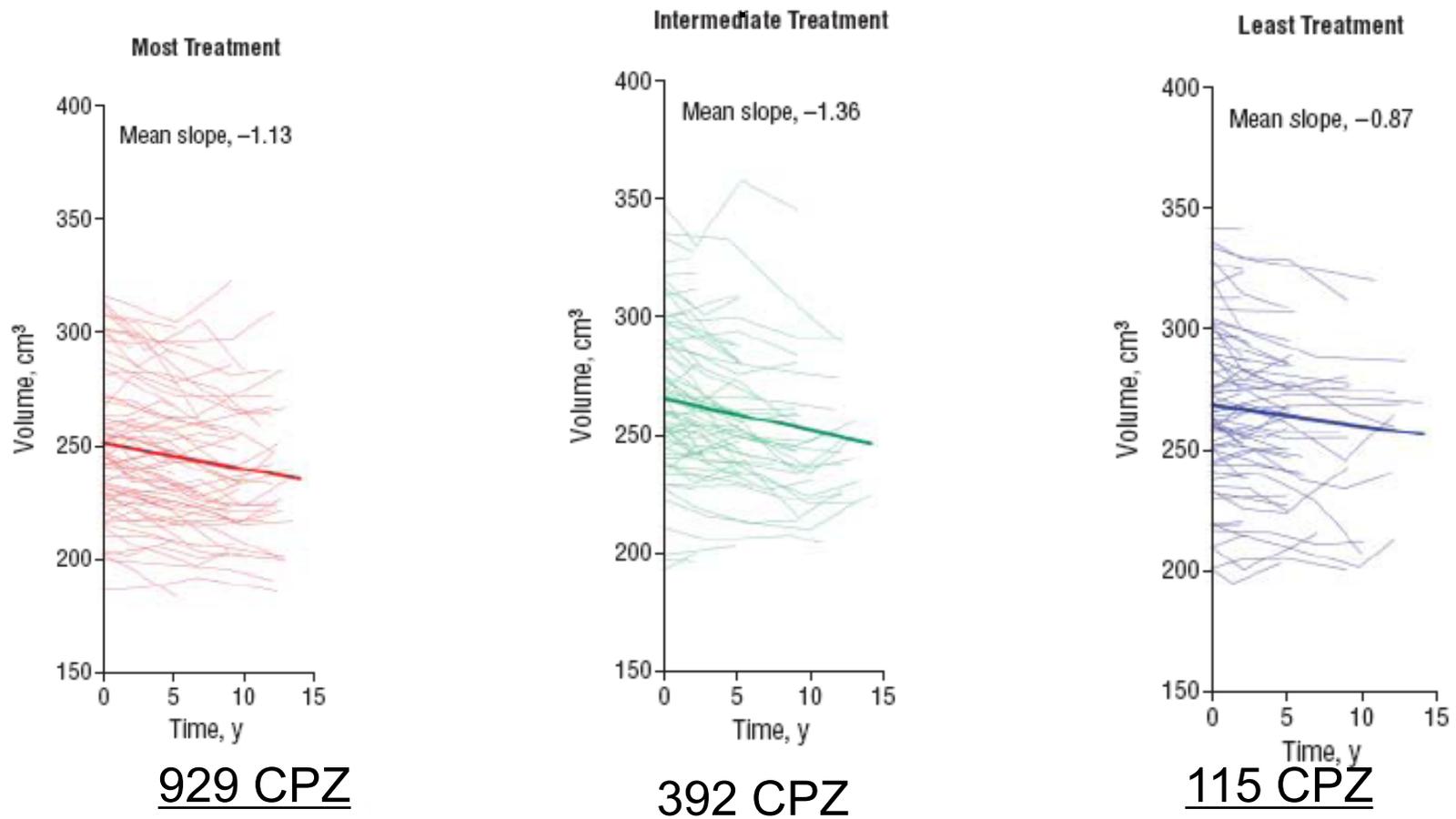
- but they did not die!



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



Brain may be abnormally impacted by antipsychotics, anticholinergics, cannabis, tobacco, metabolic syndrome, hypertension, diabetes, poverty, homelessness, poor diet



Ageing in the Normal Dunedin Population

Greater brain age at age 45 was associated with measures of poor brain health at age 3 and with worse childhood cognition

Participants who had experienced more psychopathology exhibited increased pace of aging in general, increased epigenetic ageing and more cognitive difficulties.

1.7 million New Zealanders over 50, those who had received a diagnosis of any psychiatric disorder were 4 times more likely to develop dementia than the remainder of the population

There is nothing specific about accelerated ageing in relation to schizophrenia; sadly it is a general characteristic of people with psychiatric illness

Schizophrenia polygenic risk predicts general cognitive deficit but not cognitive decline in healthy older adults

Adrianna P. Kępińska¹, James H. MacCabe¹, Dorina Cadar², Andrew Steptoe², Robin M. Murray¹ and Olesya Ajnakina^{2,3}

6,817 older adults (> 50 years) were followed up for ten years. Polygenic risk score for schizophrenic predicted low score at baseline but no further decline.

Genetic predisposition to schizophrenia is associated with stable IQ deficit.

The Kraepelinian model of degeneration provides a convenient alibi for poor care and poor funding of services – therefore popular in USA

Lynn Delisi - Stop arguing, this will lead nowhere

Genes for neuronal health operate through life causing developmental impairment but ultimately progressive changes and dementia

Inflammation

Brain Organoids





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