Psychotic Disorder

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Learning Objectives Stage 1

To obtain an In-Depth Knowledge in:

a. Types of psychotic disorders:

i. Primary (no clear secondary cause found) vs Secondary (due to substances or another medical condition) and concept of genetic predisposition. ICD 11 difference in concept

ii. First Episode Psychosis, brief or acute

iii. Schizophreniform

iv. Schizophrenia

v. Delusional Disorders and other sub-types

b. Symptoms & Signs, focusing on classification systems (ICD 10/11 vs DSM IVTR vs DSM 5)

c. Aetiology/ Pathophysiology and latest research

d. Epidemiology

e. Assessment

f. Management

g. Course & prognosis

Psychosis is:

Delusion-> fixed false belief not changeable with reason.
-> Bizarre, non-bizarre, referential, paranoid, thought extraction etc.

- An abnormal state of 'mind', where one's sense of reality is altered to various degrees.
- This alteration is characterized by changes in:

  a. Thought form -> disordered thought from, such as derailment, tangential thoughts, circumstantiality, grasshopper mind etc.

  b. Thought content -> illogical thoughts, delusions* (when severe) or overvalued ideas (when mild).

  c. Perceptual abnormality -> illusions (misinterpretation of external environment) & hallucinations (internally created abnormal perceptions). Both can appear in one or more of the 5 senses.

  d. Insight & Judgement -> diminished.

  e. Additional symptoms called 'negative symptoms' -> **a**volition, **a**nhedonia, **a**ffect (reduced to degrees), **a**logia (speech defect).

- Can have a secondary or primary cause:

  Secondary: due to a definite found 'external' cause such as other medical conditions or substances/ medications

  (note, ICD 11 categorizes substances as a 'primary cause'). This is debateable> as genetic predisposition triggered by substance can then be seen as a primary cause for psychosis.

  Primary: due to syndromes called mental and behavioural disorders in DSM and ICD:

  -> Schizophrenia and related disorders (including delusional disorder).

  -> Mood disorders (unipolar as well as bipolar)

Secondary causes:

a. **Normal states**
   -> hypnopompic/ hypnogogic hallucinations
   -> sleep deprivation
   -> bereavement
b. **Other medical conditions:**
   -> Endocrine disorders: hyper/ hypothyroidism, Cushing's, hypoparathyroidism, post-partum psychosis*
   -> Auto-immune disorders: SLE, anti-NMDA R encephalitis, Hashimoto's, Sarcoidosis
   -> Neurodegenerative disorders: Lewy-body, Alzheimer's, Parkinson's
   -> Other neurological disorders: neoplasms, CVA, EPILEPSY/ seizures, multiple sclerosis
   -> CNS infective disorders: HIV, viral encephalitis, malaria, syphilis
   -> Genetic disorders of metabolism such as porphyria.
   -> Nutritional abnormalities: B12 deficiency
   -> Poisons: heavy metals, fungal, industrial.
   -> Parasite infestations: neurocysticercosis.
   -> Para-neoplastic syndromes

First Episode Psychosis (FEP)

1. Can have any of the causes discussed above, thus:
2. Full comprehensive history and examination needed to determine cause for proper management.
3. Examination must include ALL systems, especially CNS.
4. Special Investigations: CBC, U&E, LFT, TFT, B12 and if needed, RPR, HIV, MRI, EEG, aNMDA.
   -> no current clear biomarkers, but in progress.
   -> Concept of endophenotyping: shared traits in families of psychotic disorders, state independent
      >> prepulse inhibition, lack of sensory gating, steady decline in working memory
   -> Genetics: RELN, FAB7, CHRNA7, COMPT, BDNF.
   -> fMRI: significant changes in under and over-activity in various regions (see schizophrenia)
   -> Different genetic areas, endophenotypal traits and fMRI findings in Bipolar Disorder.
5. FEP will in time – with proper investigation – show what underlying disorder is present.
6. Durations:
   * Less than a month -> Brief Psychotic Disorder
   * Up to 6 months -> Schizophreniform Disorder (schizophrenia-like disorder, but less in duration).
   * More than 6 months, with all inclusion and exclusion criteria for schizophrenia present -> Schizophrenia
   * If mood component is present, consider Schizoaffective Disorder, BUT, DSM criteria must be followed
     or diagnosis may be incorrect (vs MDD, severe with psychosis, or Bipolar Disorder, I, manic, severe with psychosis).

Management of FEP

With mild FEP, aim not to prescribe anti-psychotic for the first 24 – 48 hours if possible. Rather give benzodiazepines and actively search for underlying cause. If post ictal psychosis, will increase risk if seizure.

Acute setting

1. **With agitation/ aggression:**

-> Safety first for personnel & patient(s)

-> De-escalation techniques.

-> Skilled restrained by trained personnel only.

-> Sedation/ Tranquilization (make sure medically cleared!! QTc time very NB) Combination of APA and NICE guidelines

Agitation/ aggression can be due to multiple medical, substance and psychiatric conditions -> make sure which one!

REMEMBER: amount of agitation does NOT equal the dose; titrate according to weight and response.

a. Lorazepam 2-4mg po/imi stat 8 hourly (keep eye on respiratory effort)

then

b. Olanzapine 5 – 10mg oral dispersible or IMI (keep eye on BP): IMI not to be given within 2 hours of Lorazepam IMI

if unsuccessful, CAREFULLY consider

c. Haloperidol 5mg oral/ IMI & Promethazine 25mg oral/ 5 – 10mg IMI (monitor ECG, BP & respiratory effort)

d. Zuclopenthixol Acuphase: be cautious. 50 – 150mg IMI, preferably 2 – 3 days if repeat necessary. MAX 300mg 72 hours.

e. **Monitor vitals and for signs of:**

> Acute dystonic reaction -> Benztropine 2mg oral/ IMI

> Respiratory depression -> A/B/C & respiratory assistance

> Decreasing BP -> supine, feet raised, iv fluids, internal medicine if necessary

> Neurolept Malignant Syndrome: Fever, muscle rigidity (raised CK), autonomic instability, delirium

-> cessation of medication, iv fluids + urine output, Benztropine, refer to internal medicine (10% mortality)

> Akathisia (15% completed suicide): propranolol & benzodiazepine

In ward:

Option 1 (1st World Setting – NICE and APA)

* Start with 2nd generation/ atypical antipsychotic, lowest effective dose and titrate up to dose evidence based for effect.

1. Risperidone

- 2nd Gen anti-psychotic,
- D1,5 receptor antagonists (main:536nM)
- D2,4 receptor antagonist, D3 inverse agonist.
- 5HT2A (420nM), 1D, 2C antagonists, 5HT7 irreversible antagonist.
- Some other receptors: alpha and histamine.
- Dose: 0.5 – 8 max, best evidence 1-6mg, EPS>8
- ½ life –> 20 hours.
- Hepatic (CYP2D6), renal (ex)
- Depot is *Risperdal Consta*.
- Adverse: Metabolic syndrome, EPS high doses, Tardive Dyskinesia, Akathisia
- NMS, hyperprolactinaemia, hypogonadism.
- Menstrual AN (D2 and 5HT2A).
- Black Box Dementia: sudden death -> Negated by 3 studies, best: CATIE AD = use safer than 1st gen.
- ? Depression due to high antagonism of 5HT?

Latest *Maudsley Prescribing Guidelines* is very helpful.

2. Olanzapine

- Thienobenzodiazepine (such as clozapine)
- D1, D2, D4, 5HT2A,3, M1, H1 antagonist
- ½ life: 21-54h, hepatic, P450, potentiates citalopram.
- 10 – 20mg/d, injectable im for sedation.
- AE: sedation, GIT, metabolic syndrome high (esp. weight gain), less QTC. EPS less likely.
- Combo with fluoxetine 20mg = *Symbax* for Bipolar Disorder depressed episode.

3. Quetiapine

- Dibenzothiazepine
- D1 (HIGH), D2, D3, D4, 5HT1A, 2A, alpha1,2, H1 antagonist
- Metabolite affinity for NA = ? anti-depressant property.
- Dose range from 150 – 800 mg nocte (dopaminergic with higher doses)
- Abuse: ‘Suzy Q’ (alt state producer) when snorted.
- AE: somnolence, fatigue, GIT, sedation, metabolic S., headache, dry mouth, QTc HIGHEST!
- Strong evidence as treatment for Bipolar depression.

4. Ziprasidone

- Atypical antipsychotic,
- D1, D5, D4, D3, D2, A2 adrenergic, 5HT1F, M1
- Peak 60 min (60% oral), 1/2L 7 hours.P450 3A4
- Schizophrenia, Mania, rest off label.
- Metabolic S, Chest pains, NB: Qtc prolongation, cases of death in Dementia. Cases of Dorsades de Pointes.

5. Amisulpride

- Benzamide
- 5-HT1A; 5-HT1B, D1, D4, D4, H1, H2, H4, M1, M2, M3, M4, Alpha 1A, Alpha 1D etc
- ½ life: 12h,
- Dose: 400mg-800mg
- AE: mostly EPS and galactorrhea, QTc prolongation (less than Quetiapine and Ziprasidone), seizures, less weight gain.

6. Aripiprazole

- Schizophrenia, Bipolar and unipolar (as augmentation)
- D2, D3, 5HT1A, 5HT2A, partial dopamine agonist.
- Dose: 5 – 20mg/d; most evidence for 10 – 15mg/d,
- ½ life: 75 hours, liver metabolism
- AE: GIT, dizziness, elderly should be voided due to hypotention, metabolic lower AE than others, EPS lower.

7. Haloperidol

- Butyrophenone
- Dose: 1,5mg – 10mg; 2,5mg – 6mg best evidence, see Emsley below.
- 1st gen antipsychotic: D5,4,2,3 inverse agonists, D1 silent antagonist; Sigma1,2; 5HT1A agonist, rest silent antagonists.
- 1/2L 10 – 30h,
- AE: EPSE, TD, NLMS, Qtc prl, galactorrhea, weight gain, brain volume loss (cortex)? Medication or schizophrenia or both?
- Acute psychosis, aggression, withdrawal, delirium, behavioural disorders.
- Oosthuizen , Emsley 2001 -> low doses haloperidol effective within 12 weeks with lower EPS, except
- TD and hyperprolactinaemia – still evident even at low doses.

8. Other 1st gens: Flupentixol, Zuclopenthixol (oral, acuphase, depot), Fluphenazine (Modcate)

US based **CATIE** trial (clinical antipsychotic trial for intervention effectiveness) as well as
UK based CutLASS trials, showed that 1st vs 2nd generation antipsychotics in a real world
scenario, showed now difference in effectiveness, and that **Clozapine** remained superior still.
NB: 74% of trial subjects dropped out early, due to AE intolerance -> compliance still biggest issue!

9. Clozapine

- Superior 2nd gen anti-psychotic (CATIE trial)
- Highest aff for D4, lower other D, inverse agonist 5HT2A,C, M1,2, strong anticholinergic,
- More active meso-limbic than striatal, lower EPSE = good for Parkinson's psychosis
- AE: metabolic, cardiomyopathy, agranulocytosis, hypersalivation, sedation, seizures.
- Indicated resistant schizophrenia or psychosis; BPAD, psychosis in Parkinson's disease.
- Precautions: metabolic screening and follow up; WCC screen and follow up (Finish study)
- Long term study, showed 10.3% contracted agranulocytosis in 2nd year, and some
- Even as long as 22 years! 40% non fatal , and 80% fatal had another medication
- Assoc with agranulocytosis (carbamazepine!), long term monitoring needed, beware of other adjunct treatment!.
- Dose: start with 12.5mg up titrate with 25mg increments to max of 450mg/d.
- With at highest 600mg/d for short period.
- Finish study AGCTS monitor: monthly for 1st 3/12; then 3/12, then 6/12. Check local protocol.
- Resistance to clozapine usually non compliance in up to 70% of patients; check levels.
- Compliance always an issue, check social circ (transport), support, and insight of patient & family.
- CIGARETTE SMOKING ALSO INDUSES METABOLISM, USUALLY HIGHER DOSES NEEDED.

Schizophrenia

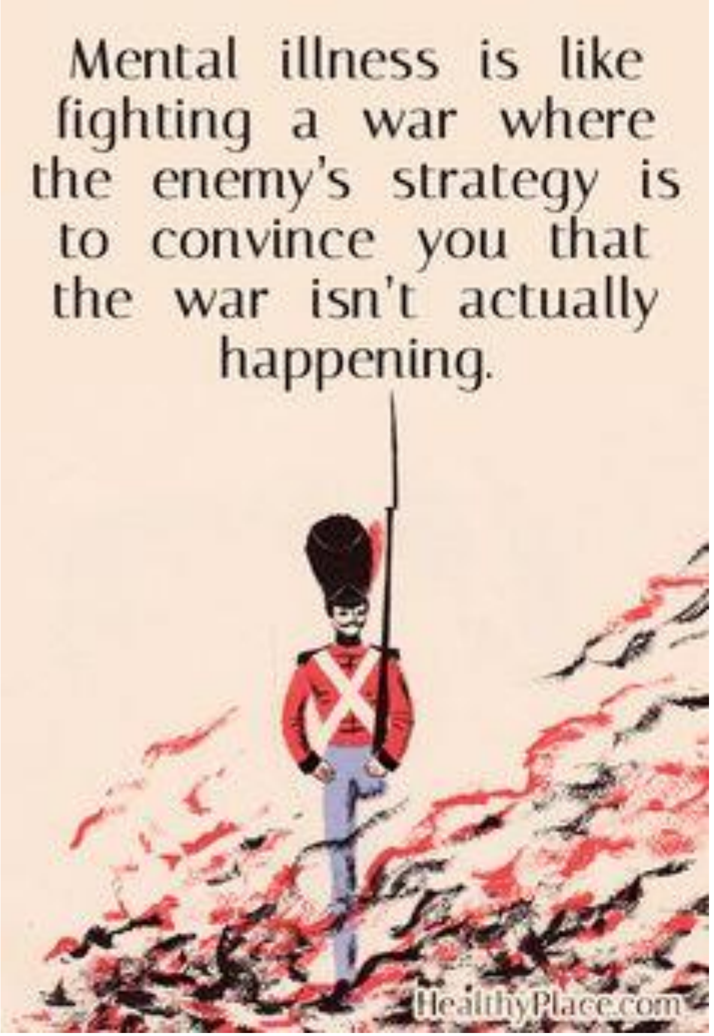
A Mental illness classified under psychotic disorders, presenting as a clinical syndrome, with a collection of mental and behavioural phenomena:

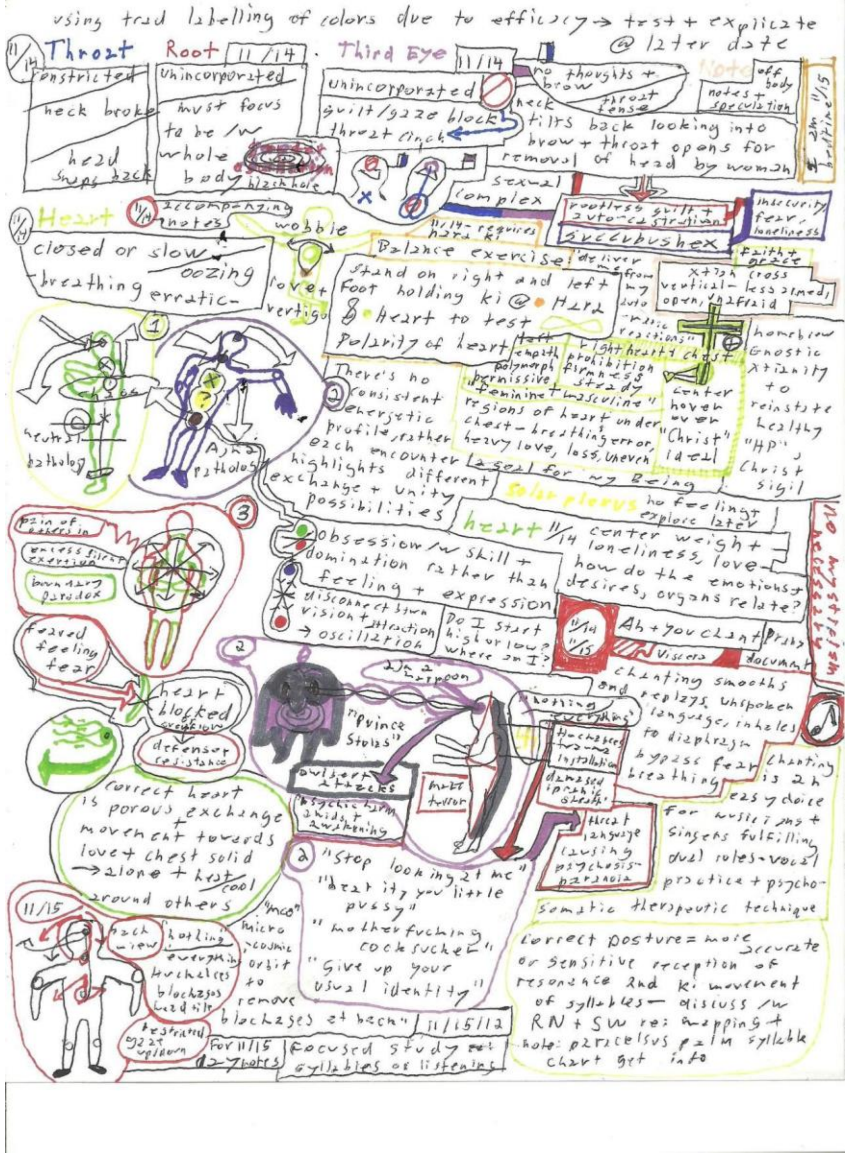
1. Abnormal perception with hallucinations and/or illusions
2. Abnormal beliefs and delusions.
3. Distorted thought construction, manifesting as disorganized speech/action
4. Unusual or restricted expression of emotion.
5. Cognitive decline
6. In some instances, catatonia.

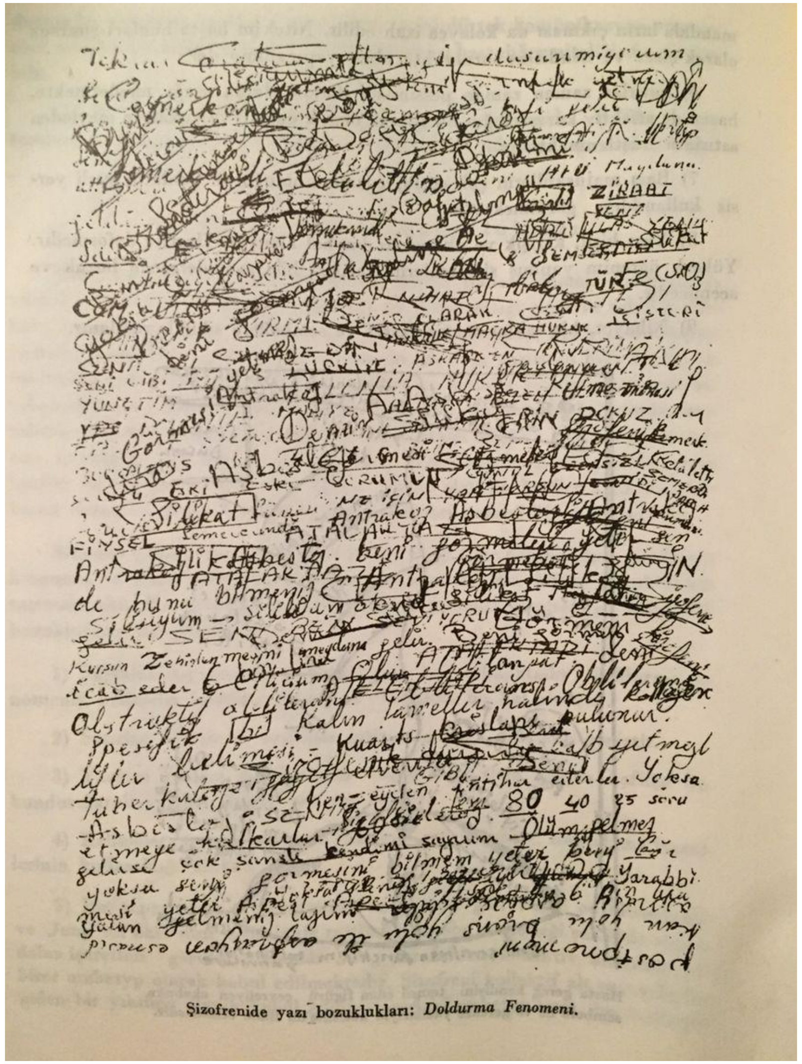
> A complex illness with different manifestations in different individuals.
> Unknown definitive aetiology; diagnosis based on clinical judgement using DSM or ICD criteria.

DSM 5

- The presence of 2 (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated), with at least 1 of them being (1), (2), or (3):
    1. delusions,
    2. hallucinations,
    3. disorganized speech,
    4. grossly disorganized or catatonic behaviour, and
    5. negative symptoms
- Must cause significant disruption in level of function
- Must not be due to another medical condition
- Continuous signs of disturbance must persist for at least 6 months, with at least one month of symptoms.


Mental illness is like fighting a war where the enemy's strategy is to convince you that the war isn't actually happening.
HealthyPlace.com

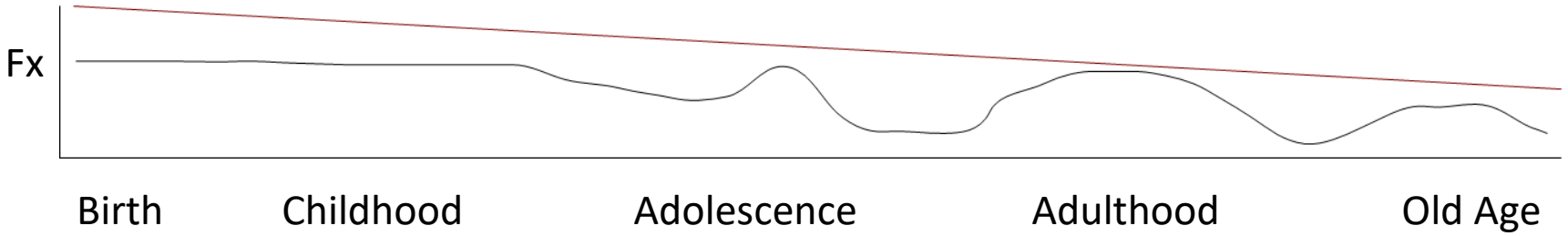

using trad labelling of colors due to efficacy → test + explicate @ later date
Throat
Root
Third Eye
Heart
Balance exercise
Solar plexus


Şizofrenide yazı bozuklukları: Doldurma Fenomeni.

Differential diagnosis:

a. Other psychotic disorders
b. Another medical condition causing psychosis -> watch out for delirium and epilepsy!
c. Anxiety disorders (decompensating)
d. OCD and related disorders (decompensating)
e. PSTD and related disorders
f. Dissociative disorder
g. Personality disorders (Borderline -> micro-psychotic events, Schizotypal, Paranoid type)
h. Malingering
i. Factitious Disorder
j. Neurodevelopmental disorders such as ASD

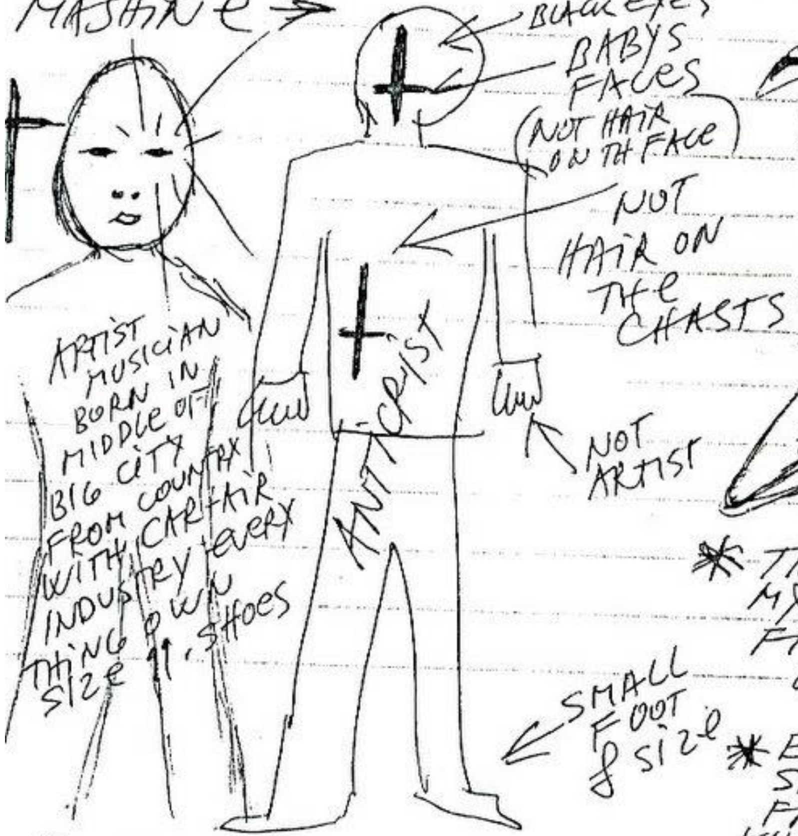
Course:

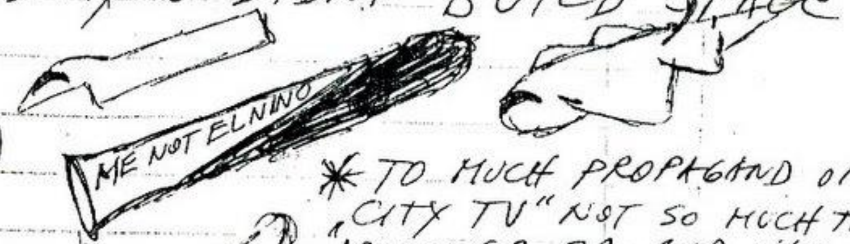


Duration of untreated psychosis suggests decrease in function, hence Early Intervention in Psychosis Services
Studies have shown steady decrease in cortical density fronto-temporal areas as well as thalamic areas of the brain

- *Changes in cortical thickness during the course of illness in schizophrenia.*
  van Haren NE1, Schnack HG, Cahn W, van den Heuvel MP, Lepage C, Collins L, Evans AC, Hulshoff Pol HE, Kahn RS. 2011
- *Cortical Brain Abnormalities in 4474 Individuals With Schizophrenia and 5098 Control Subjects via the Enhancing Neuro Imaging Genetics Through Meta Analysis (ENIGMA) Consortium. van Erp TGM1, Walton E2, Hibar DP3, Schmaal L4, Jiang W5, Glahn DC6, Pearlson GD6, Yao N6, Fukunaga M7, Hashimoto R8, Okada N9, Yamamori H10, 2018*

... I W.W. AND YOU ARE GOING BACK TO OCEANS — AND
95% BLACK EYES DO KILL 5% BLONDES (NEXT YEAR 3...
IT MEENS END HUMANS YOU DIDNT BUILD SPACE
MASHINE →





* TO MUCH PROPAGAND ON T...
„CITY TV" NOT SO MUCH TALK
ABOUT GB-FR-GER-YUG-CR...
SKEEDEN ETC. USA
ALL IS TALK ABOUT CHINA-
AFRICA-PORTUGAL-GREEK-S...
MOST POOR BLACK EYES PLACES
ARONDE WORLD — THEY DO
KILL BLONDES — BECAUSE
NOONE LAFT IN TORONTO (ONL...
6-7 PEOPLE ON THE STREETS

* THEY DO KILL SLAVICS LIKE ADOLPH H.
MY GOD — AGEINST CAN. LAW NOW THEY DO
FINISH 5%. 6-7 LAFT IN THE CITY
ON BRITISH TERITORY MY GOD
HOW TO HELP HUMANS MY GOD 95% STUP...

* EMPTY VILLAGE HEAD DOESNT KNOW TO DRAW
SING NOT ENOUGH FAST AND ARTIST-MUSICIA...
FROM MIDDLE OF BIG CITY FAST — FROM COUNT...
WITH CAR-AIR INDUSTRY EVERYTHING OWN-EURO...

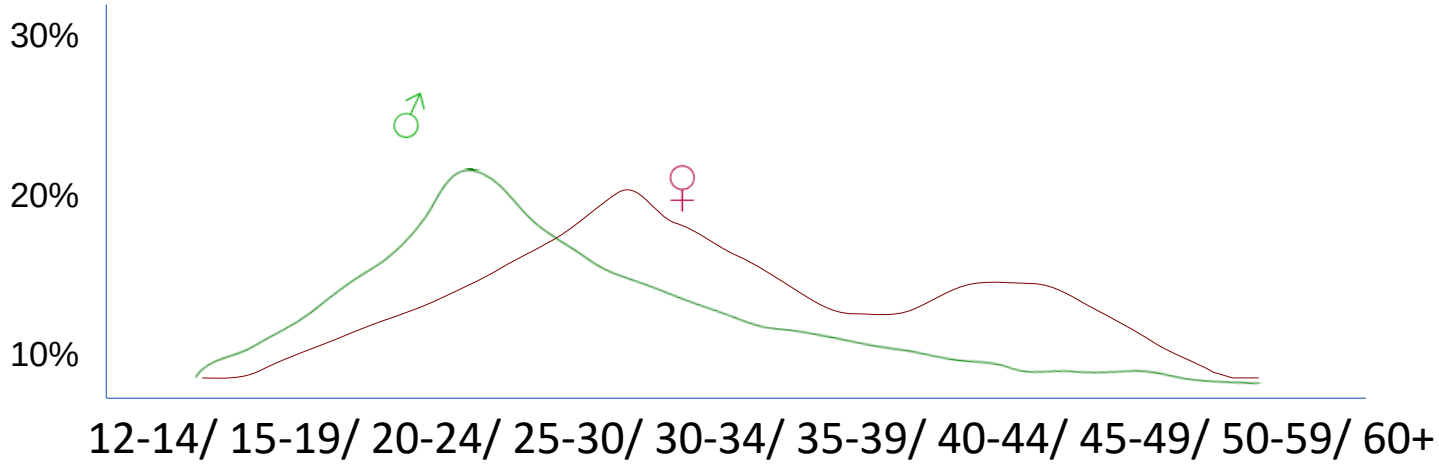
- KEEPS BLONDES IN THE BASEMANTS LIKE SEX SLAVES ON CRACK COCAIN 7D...
„GO MAKE SOME $ FOR SOME COCAIN"

...5% STUPID DO HAVE BIG CHANCE TO MAKE TERMONUCLEAR WAR (AND CRAZY GERMANY IS PUSH...
...SA IN EUROPE) BECAUSE J DID HIT NATO IN EUROPE AND J AM RADY TO HIT GREEK-ITA...
...ND ADRIATIC CITY (J DID ORDER IT) DID YOU REMMEMBER FRANCE FIRST N. CARIER
... BLOVE UP ENGINES (ON THE COORS TO YUGOSLAVIA — NOW KILL TILD WAVES 300
...RAZY STORMS WATCH TV — J AM GOING TO HELP HUMANS (DID YOU SEE CRAZY CL...

Good Prognostics:

- Female
- Later onset
- Acute onset vs. insidious
- Precipitating factors
- Normal pre-morbid personality/ function
- Good social support/ educational
- No negative symptoms or cognitive impairment
- No family history and good treatment effect with little to no side effects

Epidemiology



Usually, traits can be seen in early childhood (mostly retrospectively); high risk factors being:

- Hypo-active
- Hypotonia, poor 'cuddliness'
- Unusual pattern or slow milestones achievement
- Soft CNS signs, especially clumsiness or poor coordination.
- Deficits in attention and information processing *(National Child Developmental Study; Canon et al, Crow et al)*

Dichotomy exists regarding schizophrenia being:

1. Developmental disorder (evidence for low IQ before psychotic symptoms)
2. Degenerative disorder; but exceptions in literature and media:
   John Nash, John Ogden, Katherine Routledge etc.

- Substance abuse common; up to 50% abuses substance, linked to violence, suicide, incarceration.
- Population density: higher prevalence in denser populated areas, thus more prevalent in urban areas; almost non existent in pop <10 000, even if high family history. Reason unclear.
- Lifetime prevalence: 1.4%
- WHO *Teen Court Study* shows psychotic illness on the rise (excluding SIP).
- Geographical: As mentioned, highly populated cities higher incidence (confounders taken into account)
  (Farris & Dunken, Chicago 60's; replicated by Croudace & Nottingham)
- Also more prevalent in lower socio-economic groups.

Aetiology/ Pathophysiology

Theories only currently:
A. Neuro-chemical
1. Dopaminergic hypothesis
Theorized that overactivity of dopamine system in meso-limbic and meso-cortical pathways responsible for sx of schizophrenia (pos. sx associated with meso-limbic, neg. sx with meso-cortical).
Further theorized that this leads to erroneous LTD & LTP in combined pathways, and thus follows atrophy of certain areas of brain such as cortices.

Evidence for theory:

- Anti-psychotics = DA antagonists (especially D2)
- Dopamine agonists can lead to psychosis (cocaine, amphetamine)
- Correlation between DA metabolite HVA and severity of illness
- Genetic evidence that may prove: COMT, DRD4, AKT1

Evidence against theory:

- PET scans examining drug action in living pt's, challenged idea that amount of DA blocking correlated with clinical benefit (some studies showed 90% blockage, with little effect). Correlates with Emsley & Oosthuizen 2001 Haloperidol study.
- DA antagonists has effect in minutes, but effect takes days to weeks, and not similar in all.

- Atypicals lower affinity for claimed DA receptors; plethora of other receptors as well, equally effective.
- Drugs like psilocybin and DMT mostly acts upon 5HT (2A) receptors, very low affinity DA receptors; most potent hallucinogenics.

2. Glutamate hypo-activity (NMDA receptors)
3. 5-HT over-activity
4. GABA hypo-activity in hippocampi

B. Neuro-developmental

- Evidence for delayed milestones in childhood.
- Abnormal cerebral studies at 1st presentation psychosis
- Absence of gliosis against theory in full.

C. Disconnection hypothesis

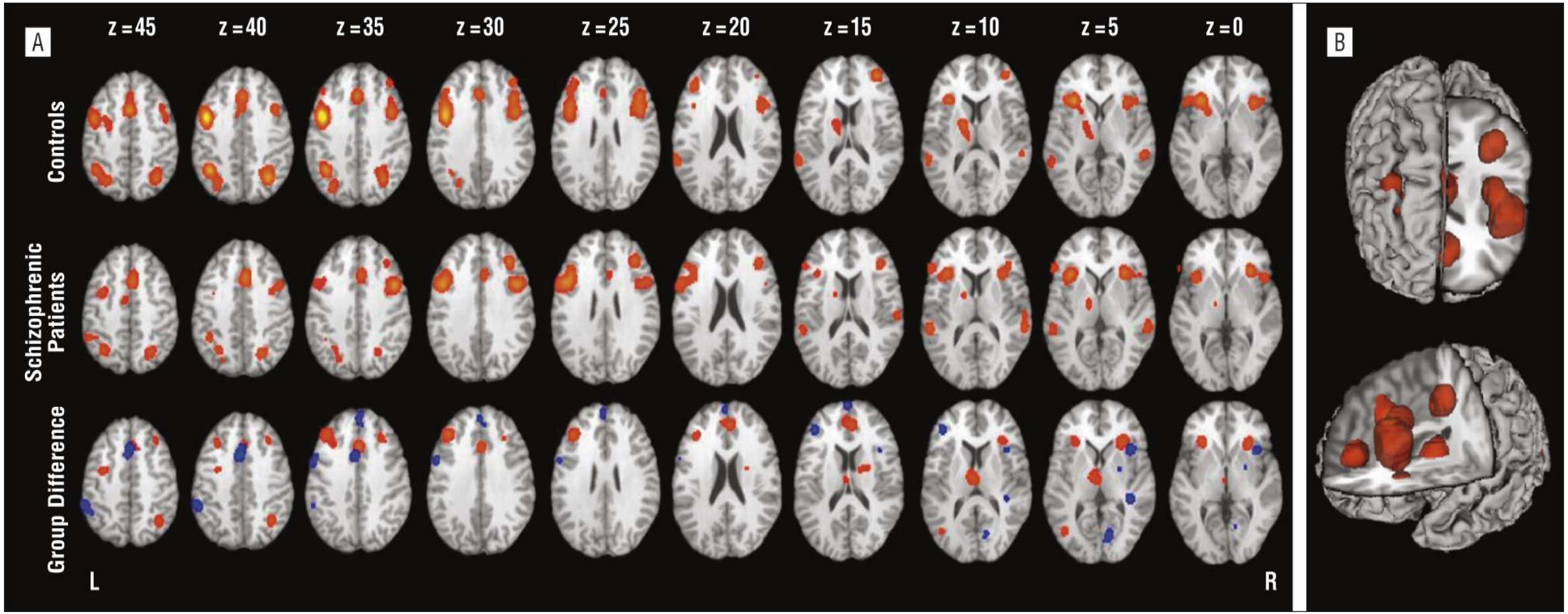
- fMRI/ SPECT showed:
  ^ Widespread reduced grey matter (could be hypotrophy only due to action of other pathways.
  ^ Reduction in white matter integrity.
  ^ Reduced fronto-temporal blood flow.

- Neuroimaging of schizophrenia: structuralabnormalities and pathophysiologicalimplications, Peter F BuckleyDepartment of Psychiatry, MedicalCollege of Georgia, Augusta, GA, USA

- Neuro-imaging studies by Paum M Thompson et al 2001 & 2009

** Newer molecular imaging techniques a promising future.*

D. Others: AN information processing/ neuro-degenerative sans gliosis ect.


A
z = 45
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Controls
Schizophrenic Patients
Group Difference
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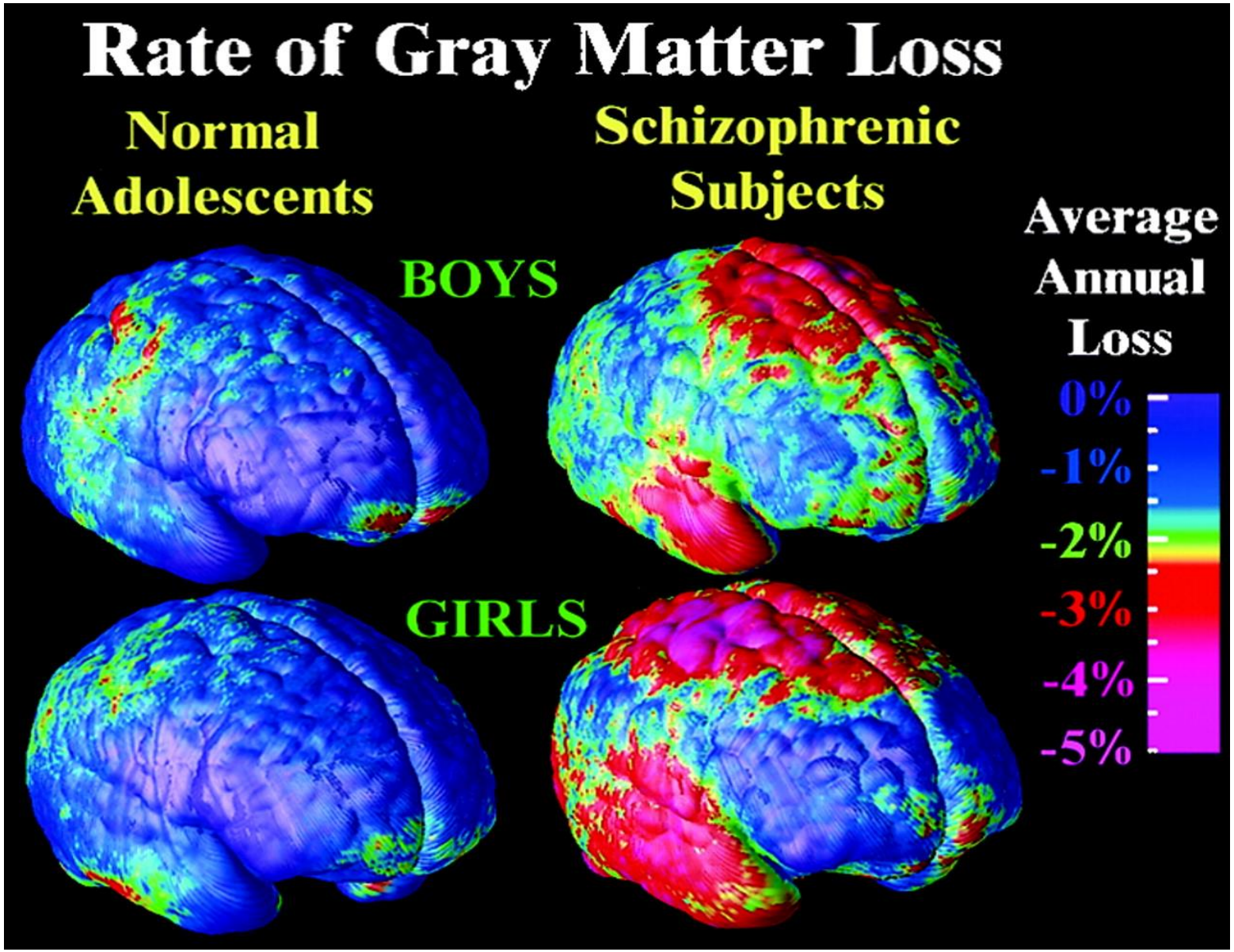
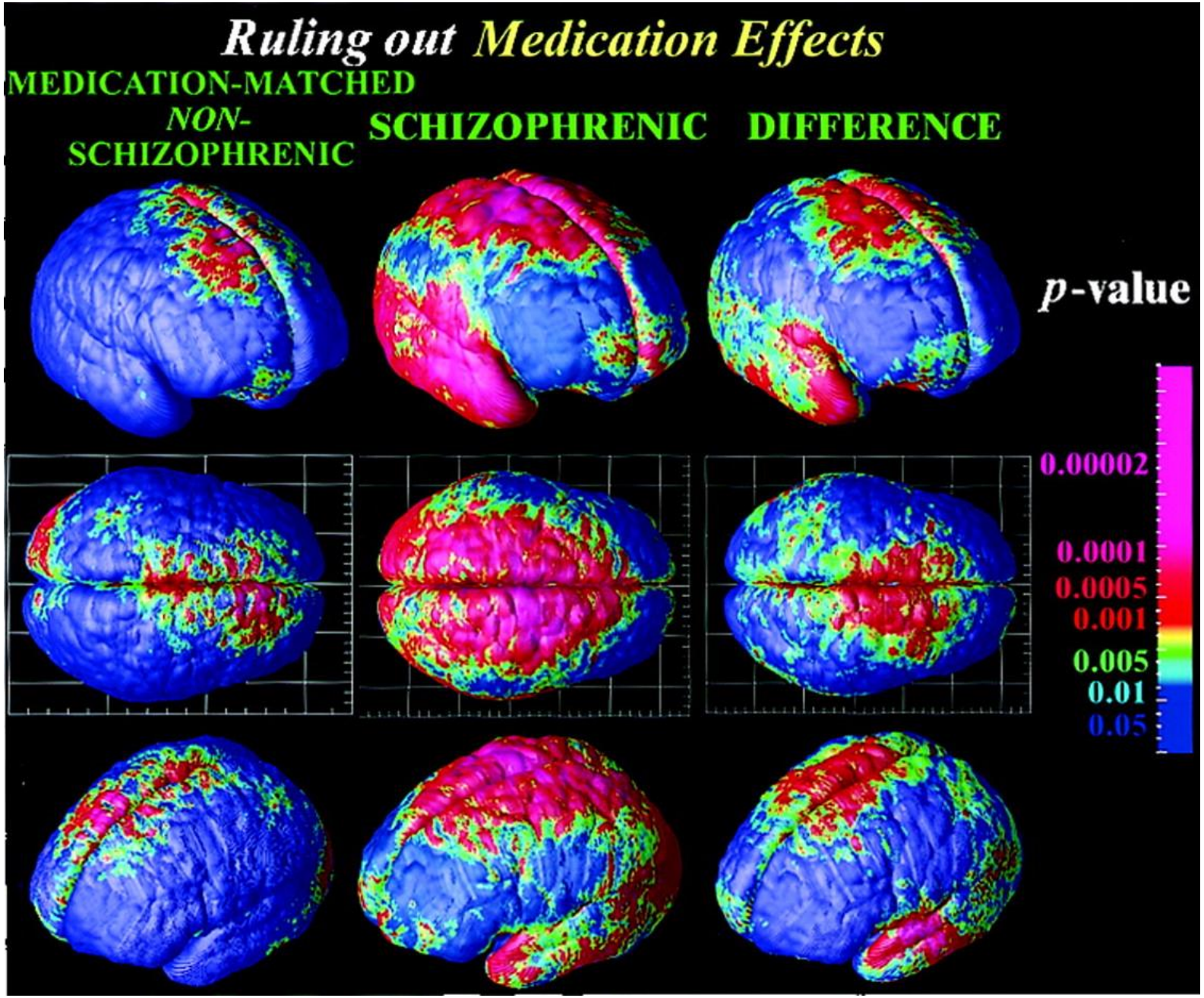
B



Mapping adolescent brain change reveals dynamic wave of accelerated gray matter loss in very early-onset schizophrenia, *Paul M. Thompson et al Sept 2001*


Ruling out Medication Effects
MEDICATION-MATCHED
NON-SCHIZOPHRENIC
SCHIZOPHRENIC
DIFFERENCE
p-value
0.00002
0.0001
0.0005
0.001
0.005
0.01
0.05

E. Genetics/ epigenetics:

- MZT: 46% vs DZT: 12 – 15%.
- One parent: 12 – 15%; 2 parents: 40%; Grand Parent: 6%; no relatives: 0.5 – 1%

> [Of note: schizophrenia spectrum with continuum approach not in use as outcomes so different:50% show good outcome on treatment, and 2% full recovery after 1 episode
>
> - PR Jones '97.]

- Best evidence in genes (yet sketchy): COMT, DRD4, AKT1RGS4, PPP3CC, ZDHHC8, DISC1; but answers not why only
- 46% MZT get disorder; epigenetics may prove the answer as J Mills (below).
- Weinberger & Harrison: gene expression analysis = abnormality in mRNA & protein expression.
- Jonathan Mills et al (Kings College 2011): epigenetic abnormality = 20% variation in methylation of area ST6GALNAC1 linked to schizophrenia. NB is overmeth of ZNF659 = schizophrenia, but undermethylation of same area = Bipolar Disorder.

Environmental stressors linked are:

- Birth complications.
- Childhood brain damage (esp post infection – see 28 year Finnish study; 7x more prone).
- Winter birth
- Heavy cannabis use esp with COMT gene AN; (still controversial, Swedish and NZ study
- challenges this idea). But cannabis now showed to reduce adolescent neurocognitive
- ability by up to 8 IQ points. NZ 10 year study followed 1000 teens into adulthood.

Thus multiple-hit hypothesis seem to be nearest to ‘truth’ about pathophysiology:

- Genetic predisposition (COMT genes etc) with,
- epigenetic undermethylation of ZNF659 due to,
- multiple environmental stressors throughout life which can lead to schizophrenia.

Preventative measures:

- ID at risk genetics with,
- Better peri-natal care.
- Prodromal: Psychotherapy, Omega 3, SSRI, monitor early warning signs
- 1st onset: Anti-psychotics (low dose as possible), social support and education, esp HEE families.

Co-Morbid Medical Illness in Schizophrenia

- Up to 80% have a medical illness, up to 50% may be undiagnosed
- Co-Morbid substance use/ misuse is high: nicotine 90%, alcohol 40%, use as
- Self medication especially for EPS.

Management

- As with FEP -> anti-psychotics are currently the only (albeit crude) way of managing the symptoms.
- Up to 78% of patients with Schizophrenia will relapse in first year without medication. Up to 90% relapse in second year.
- Monitor for early warning signs. PANSS, CAARMS (very limited) etc.
- CATIE showed us the high percentage of patients not being treatment compliant.
- Insight generally a problem with non-adherence to treatment.
- LAI medication has shown to be the current best affective treatment against relapse (latest research).
- Continued psych education (patient and family) is very important.

Delusional Disorder

A mental disorder (rare), characterized by a person having a fixed delusion without experiencing other symptoms of psychosis (no perceptual, affect changes or thought from disorder). They can – apart from social relationships, be relatively functional in society. It must be present for more than 1 month.

Delusions can be either bizarre or non bizarre (and is usually non-bizarre, as bizarre delusions are mostly found in schizophrenia). Other causes for psychotic disorders as previously discussed, MUST be excluded.

Types:

1. Erotomaniac type (another person in love with the person assessed).
2. Grandiose type (believing to be exceptional but unrecognized).
3. Jealous type (theme is that of a belief that the partner is unfaithful in absence of any proof).
4. Persecutory type (theme of being persecuted in various ways without any proof).
5. Somatic type (theme of bodily functions and/ or sensations).
6. Mixed type (multiple above-mentioned present) -> make sure it is not schizophrenia.
7. Unspecified type (not clearly the above stated)
8. Specify with bizarre content if present -> yet again, make sure not schizophrenia.

Management and prognosis

Quite rare, but non-responsive to anti-psychotics. Last mentioned can be used to manage agitation.

Psych education best, but insight almost always remain a problem. This can be challenged with Socratic-based therapy techniques.

References/ recommended reading

Time-Lapse Mapping of Cortical Changes in Schizophrenia with Different Treatments Cerebral Cortex
May 2009;19:1107--1123 doi:10.1093/cercor/bhn152

Functional magnetic resonance imaging in schizophrenia Raquel E. Gur, MD, PhD; Ruben C. Gur, PhD 2010

Abnormal neural connectivity in schizophrenia and fMRI-brain-computer interface as a potential therapeutic approach
Sergio Ruiz1,2*, Niels Birbaumer2,3 and Ranganatha Sitaram2,4,5* 2013

DiagnosticClassificationofSchizophrenia PatientsontheBasisofRegionalRewardRelatedfMRISignalPatterns
StefanP.Koch1*,ClaudiaHägele1,John-DylanHaynes2,AndreasHeinz1, FlorianSchlagenhauf1,3,PhilippSterzer1 2014

CATIE & Cutlass trials. DOI: 10.1192/bjp.bp.107.037218

Kaplan & Sadock's Comprehensive Textbook of Psychiatry, 10th edition, Walters Kluwer 2017

The Maudsley Prescribing Guidelines in Psychiatry, 13th Edition
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