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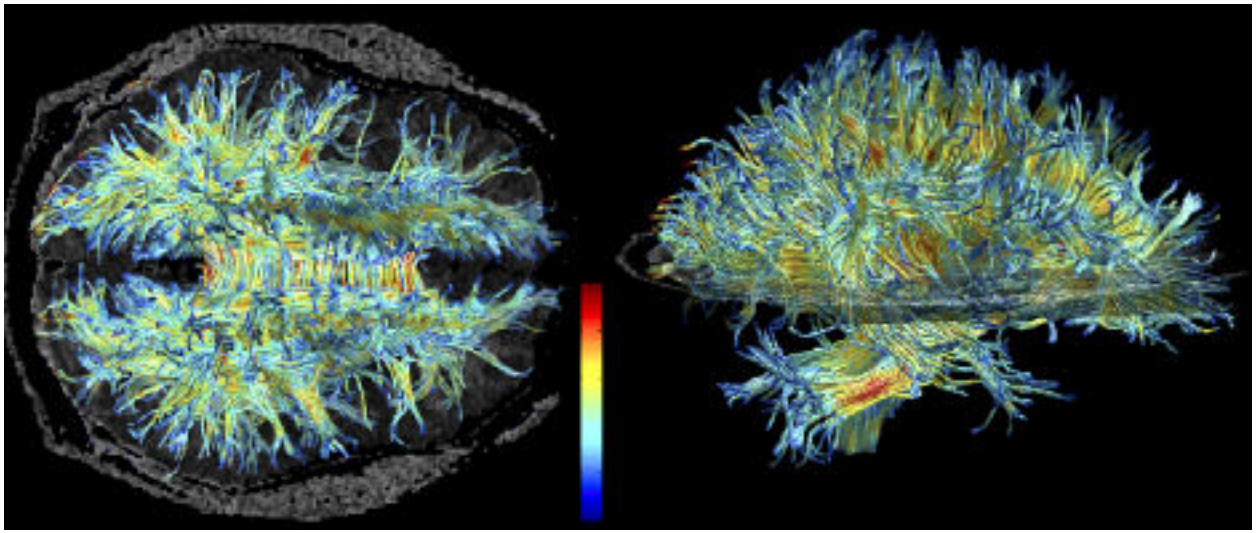
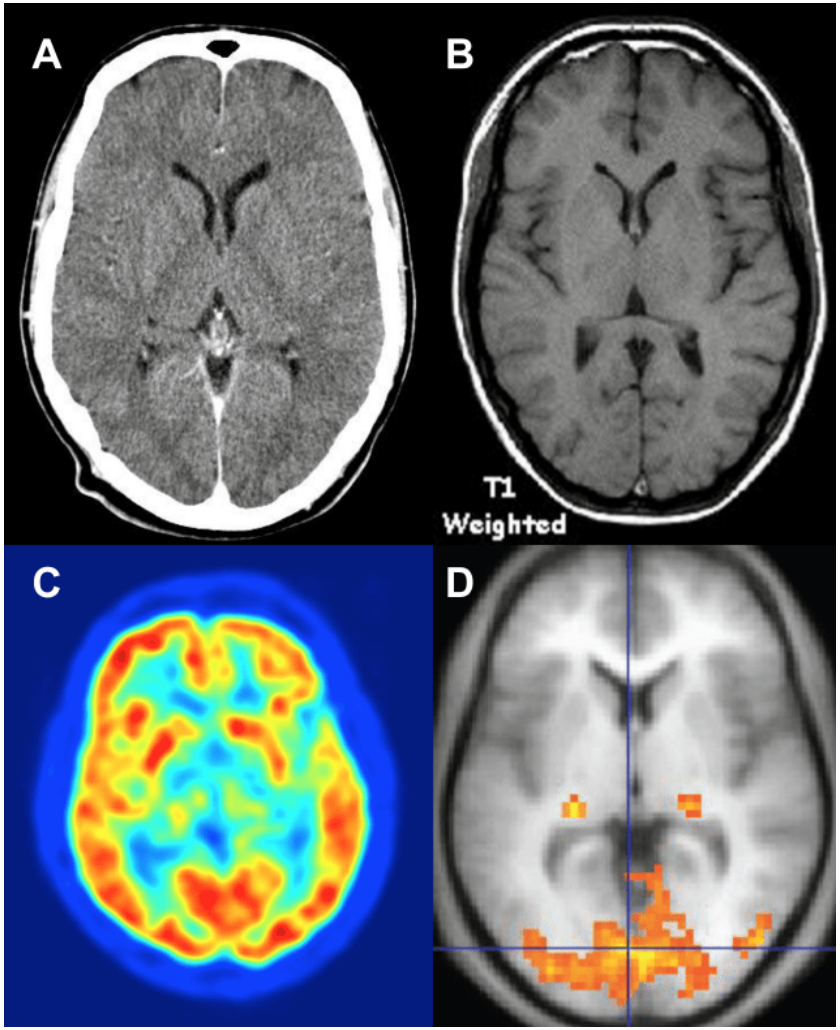
Neuroanatomical alterations in schizophrenia



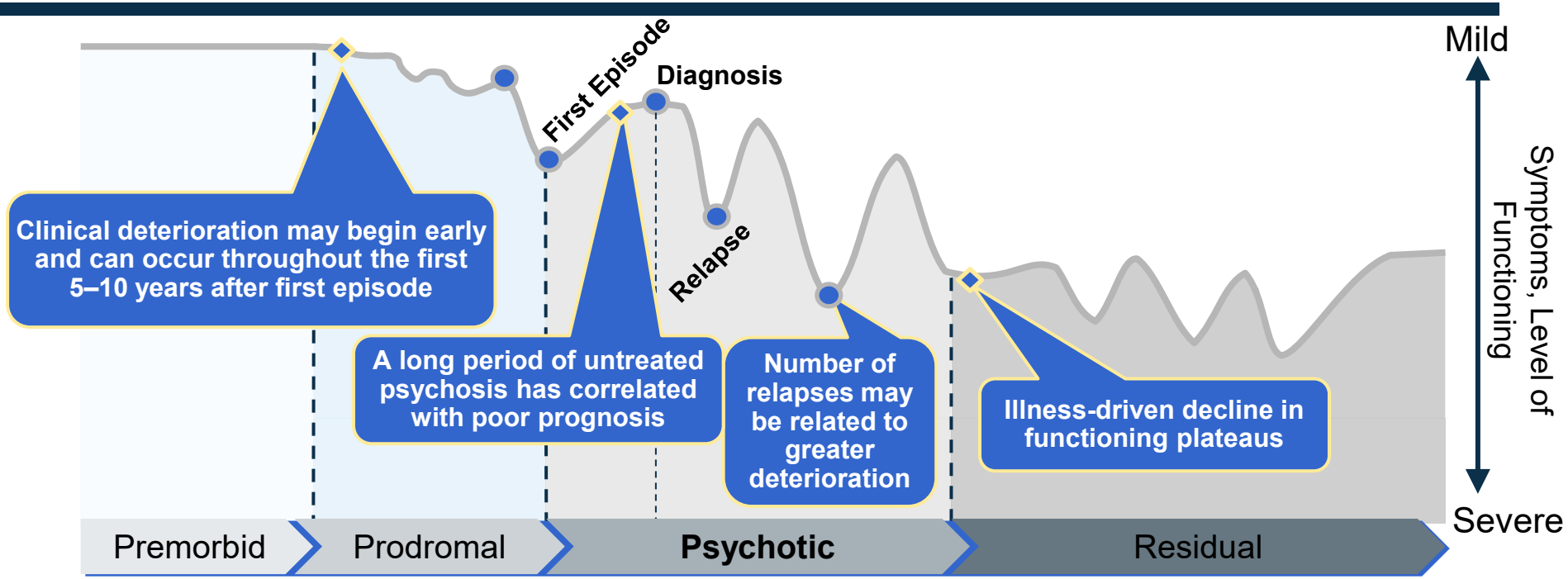
Objectives

- Describe the theoretical course of progression of schizophrenia that leads to functional decline
- Identify the neuroanatomical alterations observed in schizophrenia that may underlie the progressive nature of the disorder
- Describe the neurobiology of relapse and its impact on brain structure

Imaging tools to study progression of SZ



The Theoretical Course of Schizophrenia Progression May Lead to Functional Decline[1-4]



Childhood

- Functional impairment occurs and is difficult to distinguish from other causes
- Events may trigger disease development

Adolescence to early adulthood

Approximately 2-5 y

- Negative symptoms usually develop first, followed by slight positive symptoms

Critical years

Approximately 5 y

- Majority of clinical deterioration occurs
- High risk of relapse

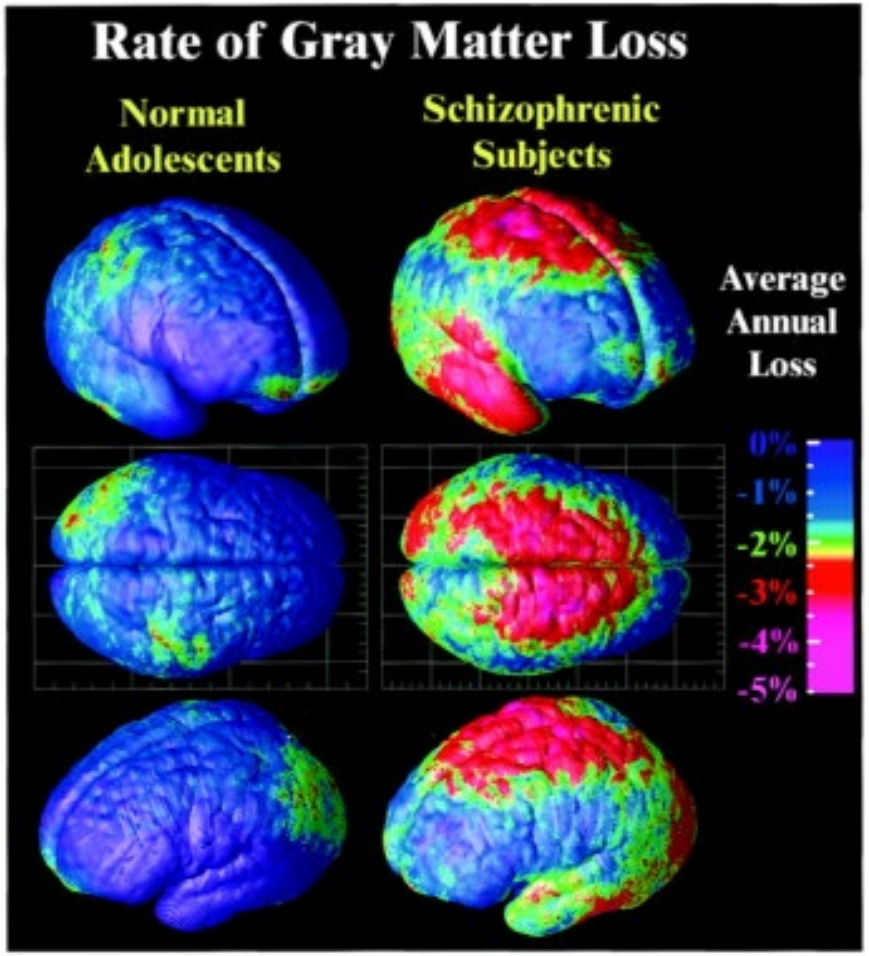
Remainder of life

- Disease severity and level of functioning vary; risk of relapse

1. Lieberman JA, et al. *CNS Spectr*. 2007;12(10)(suppl 18):1-16;
2. Emsley R, et al. *BMC Psychiatry*. 2013;13:50;
3. McGlashan TH. *Schizophr Bull*. 1988;14(4):515-542;
4. Lehman AF. *Am J Psychiatry*. 2004;161(suppl 2):1-56.

Reduced Gray Matter Volume (GMV)

- "Two-hit" hypothesis[1]
- Reduction in GM occurs early in disease course[2]
  - Parietal, motor and temporal cortices
- GM loss progresses with age[2]
  - Temporal and dorsolateral loss appears later in development (age 18)
- COMT variant may impact connectivity in first episode[3]



1. Koutselaris, et al, *Schizophrenia Bulletin*, 2014; 40(5): 1140-1153
2. Thompson, et al,, *PNAS*, 2001; 98(20): 11650-11655 (Figure)
3. Kang, et al,, *Neuroscience Letters*, 2018; epub ahead of print Sep 18 (Figure)

Abbreviations: GM: Gray matter; COMT: catechol-o-methyltransferase; STG: superior temporal gyrus; DLPFC: dorsolateral prefrontal cortex; HC: healthy controls; FES: First episode Schizophrenia; RSFC: Resting State Functional Connectivity; ACC: Anterior Cingulate Cortex

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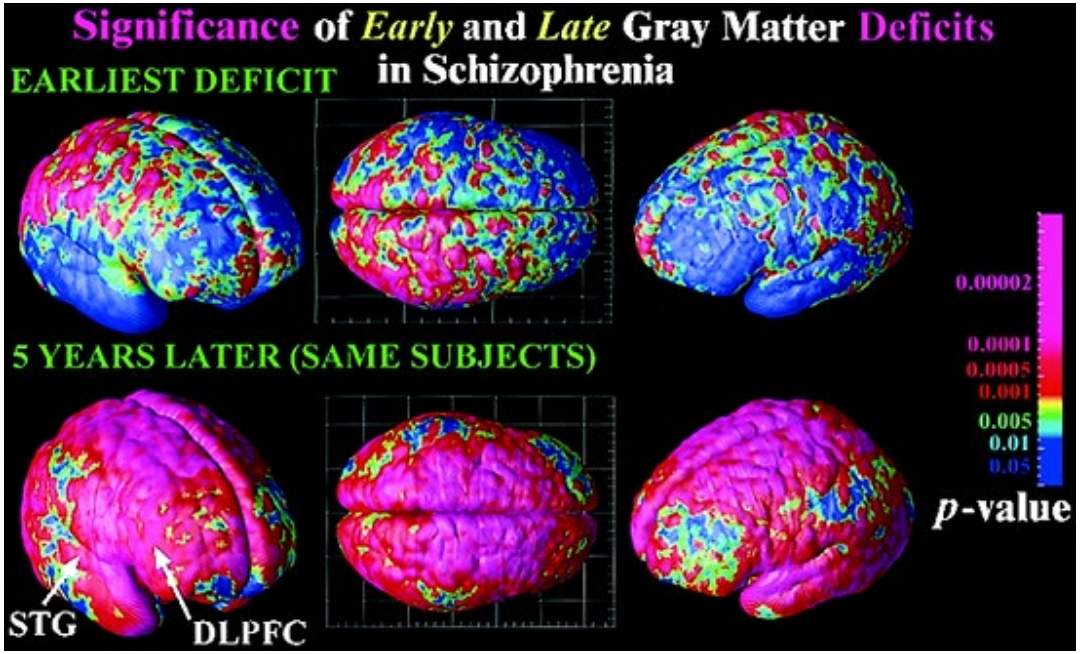

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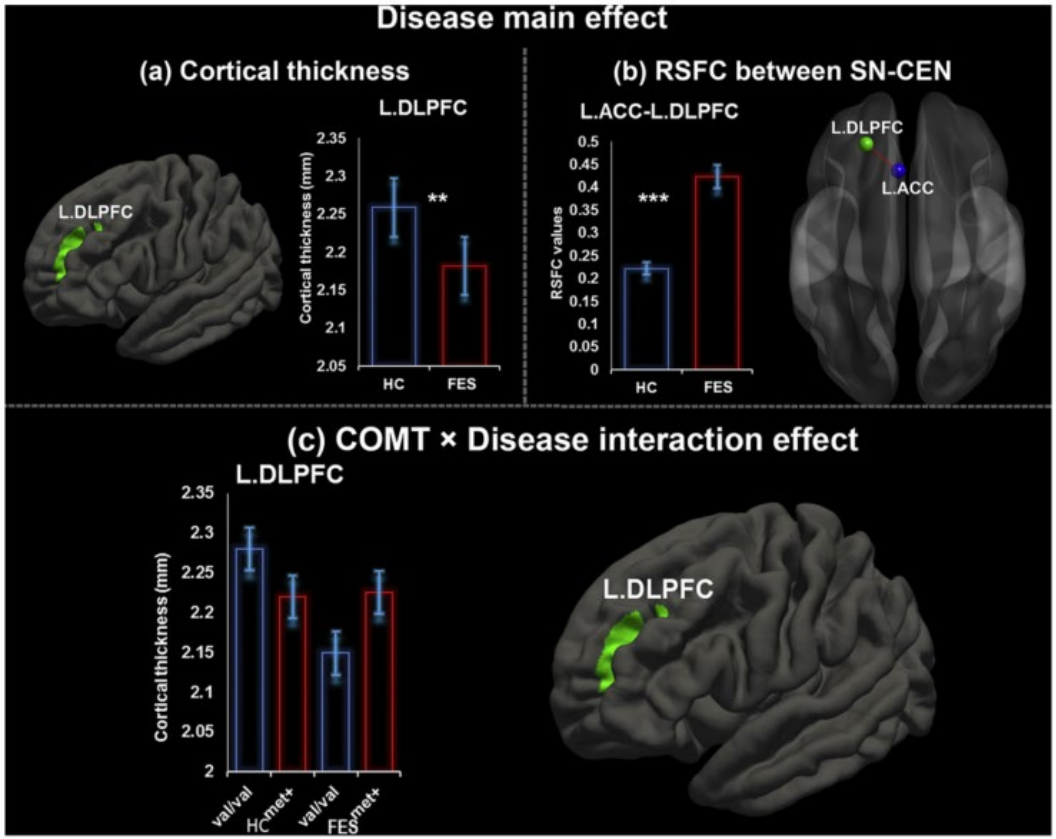

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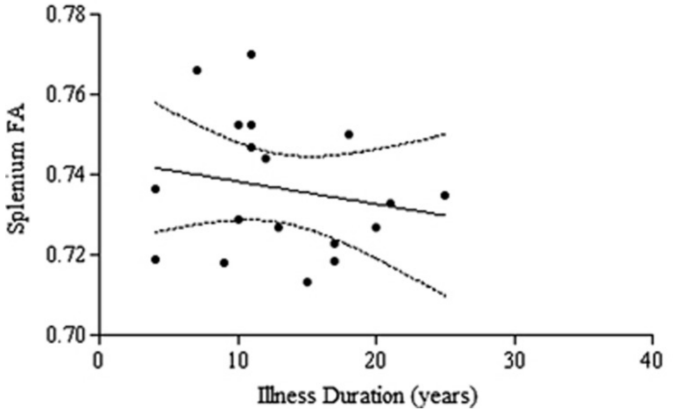
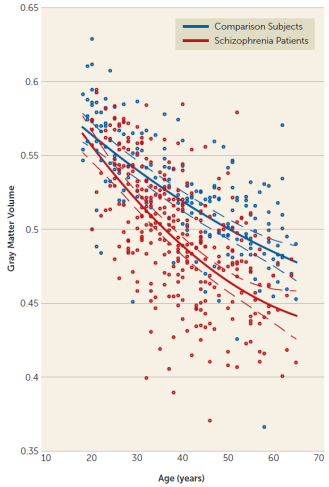
Structural changes over lifespan

- Decrease in WM is related to duration of illness[1]
  - Glial cell abnormalities
  - Myelination

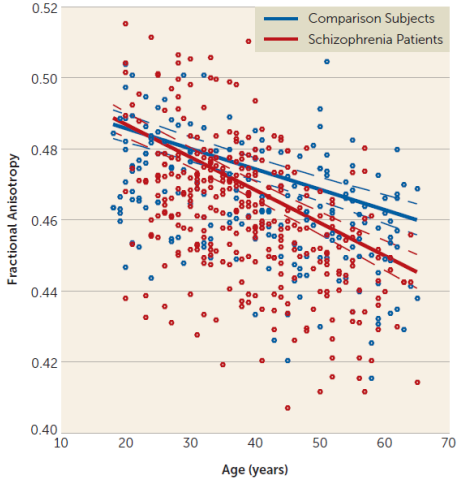


- Initial, rapid rate of GM loss, slows in middle life[2]
- Deficit in WM progressively worsens with age at a constant rate[2]

Gray matter



White matter



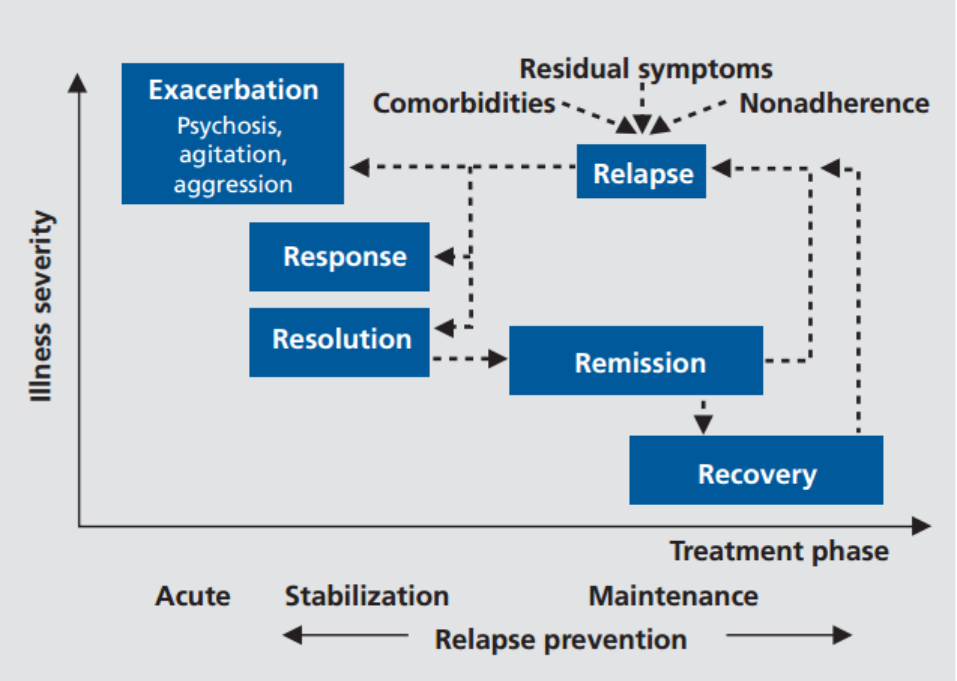
1. Holleran, et al, *Neuropsychopharm*, 2014;39; 944-954
2. Cropley, et al, *Am J Psychiatry,* 2017; 174;286-295

Abbreviations: WM: white matter; GM: gray matter; FA: Fractional Anisotropy

Relapse

Observations from the literature[1]

1. Relapse rates after treatment discontinuation are very high
2. Longer treatment period prior to discontinuation does not reduce risk
3. Many patients relapse very soon after discontinuation
4. The transition from remission to relapse may be abrupt
5. Severity rapidly returns
6. Response time is variable and treatment failure may emerge in some



1. Emsley, et al, *BMC Psychiatry*, 2013;13:50
2. Image: Kane and Correll, *Dialogues Clin Neurosci*; 2010; 12: 345-357

Hypotheses on neurobiology of relapse[1]

I. Neuroleptic-induced supersensitivity

II. Rapid onset psychosis

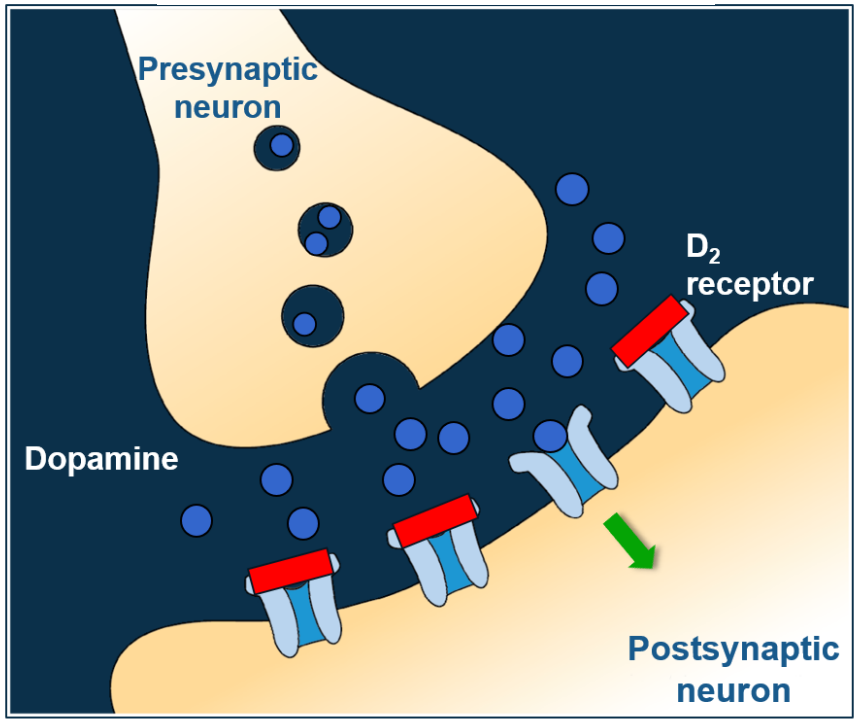
III. Neurotoxicity

IV. Dopamine/Glutamate hypotheses

V. Neuronal sensitization/"kindling"

VI. Inflammation

Mesolimbic Pathway[2,3]



The mechanism of action of antipsychotics in the treatment of schizophrenia is unknown.

1. Emsley, et al *BMC Psychiatry*, 2013;13:50

2. Stahl SM. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*. 4th Edition. New York, NY: Cambridge University Press; 2013

3. Lieberman JA. *CNS Drugs*. 2004;18(4):251-267.

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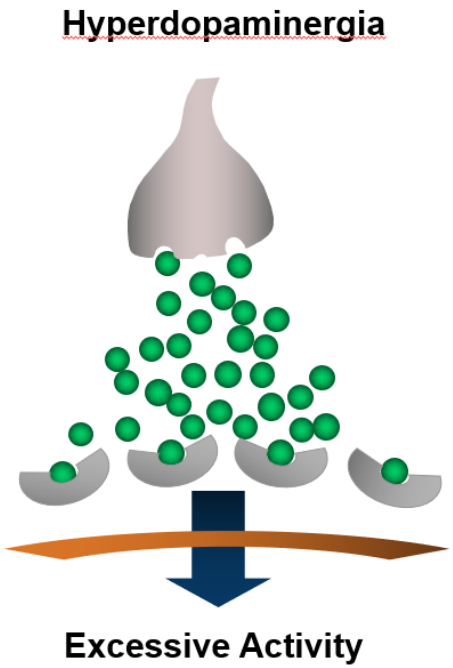

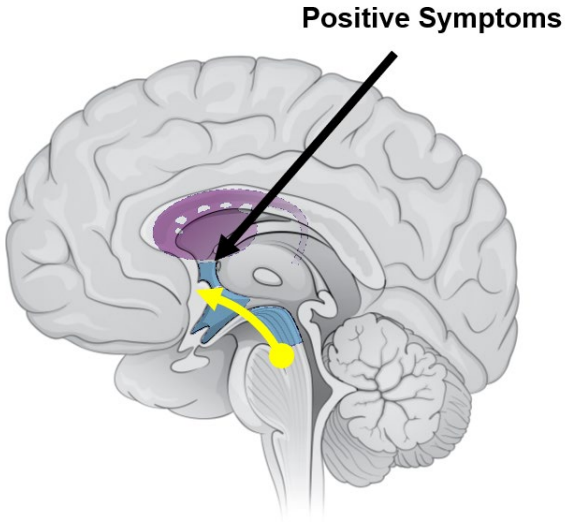

1. Emsley, et al *BMC Psychiatry*, 2013; 13:50

Adapted from:

4. Inoue and Naketa. *Jpn J Pharmacol*. 2001;86:376.
5. Kane et al. *J Clin Psychiatry*. 2002;63:763.
6. Gründer et al. *Arch Gen Psychiatry*. 2003 60: 974.

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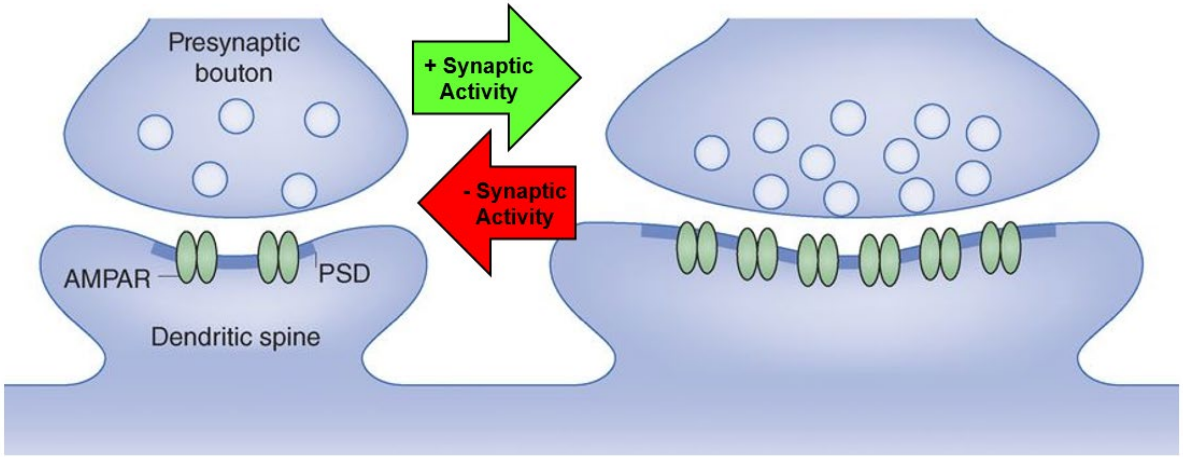

Synaptic plasticity: ongoing, adaptable structural changes involving glutamate receptors and underlying learning, memory, and cognitive changes[7-9]

1. Emsley, et al *BMC Psychiatry 2013;* 13:50

7. Purves D et al (eds). *Neuroscience*. 2nd Edition. Sinauer Associates, 2001
8. Bermúdez Rattoni F (Ed). Neural Plasticity and Memory: From Genes to Brain Imaging. Boca Raton (FL): CRC Press; 2007
9. Lesch & Waider. *Neuron*. 2012;76(1):175-191

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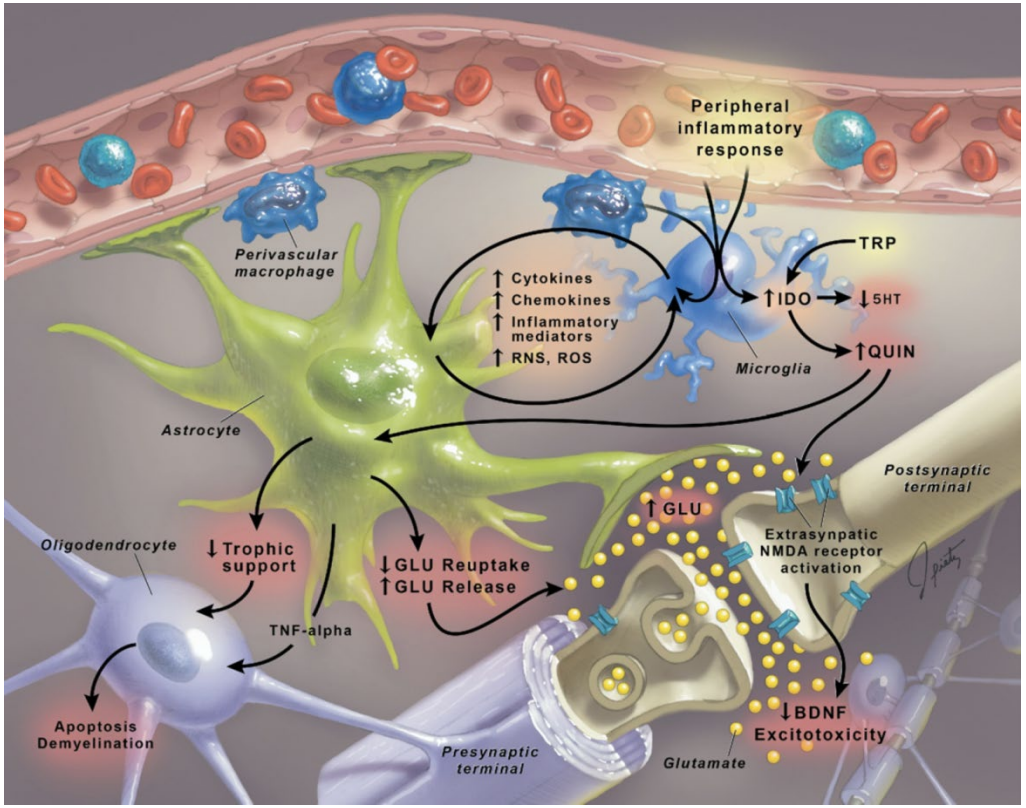
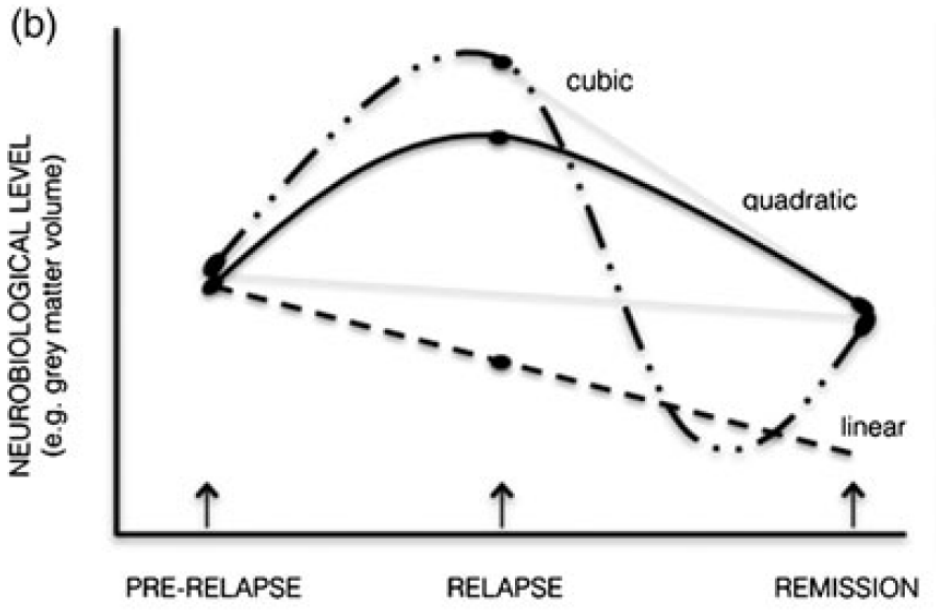


1. Emsley, et al *BMC Psychiatry. 2013;*13:50

10. Image: Miller AH et al. *Biol Psychiatry*. 2009;65(9):732-741.

Structural changes: Relapse

- Illness Progression follows relapse[1]
- "Relapse signature"[2]
- Duration of relapse, not number of relapses is related to White Matter loss in cortical regions[3]



1. Emsley, et al, *Schizophrenia Research*, 2013: 148; 117-121
2. Cropley and Pantelis, *Epidemiology and Psychiatric Sciences*, 2014; 23: 219-225
3. Andreasen et al, *Am J Psych*, 2013; 170:609-615

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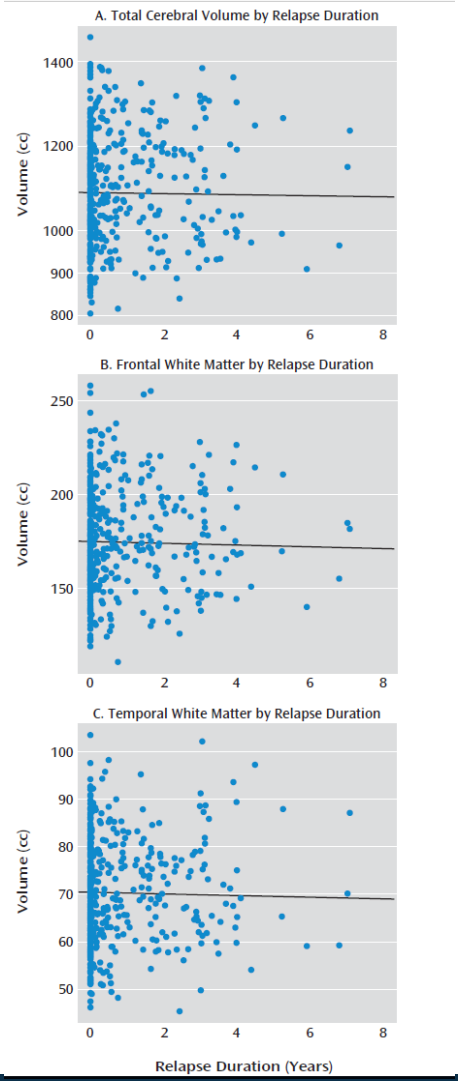

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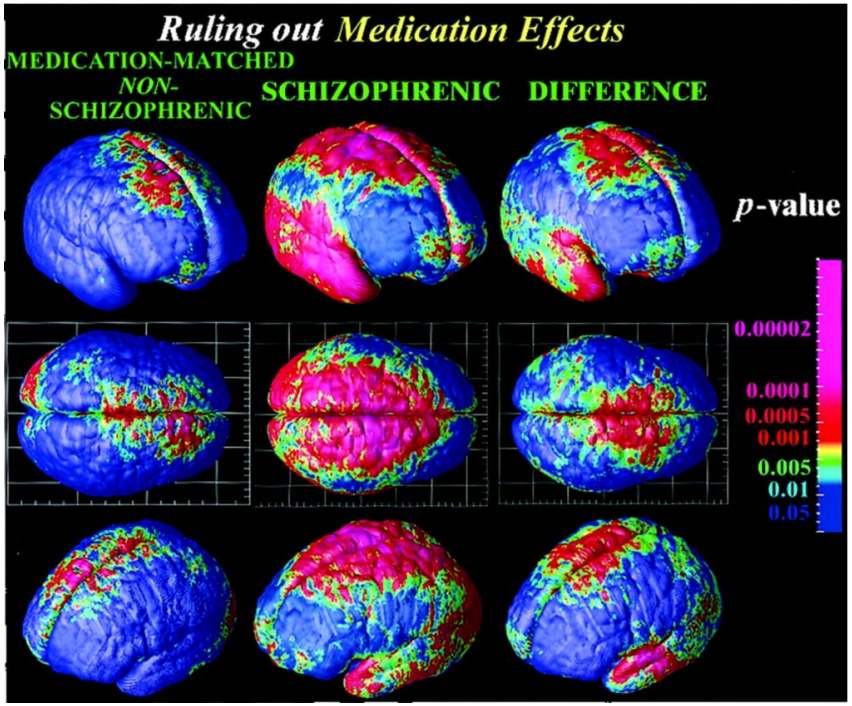
Effects of Antipsychotics on brain structure

- GM deficit in temporal lobe is specific to schizophrenia and not medication[1]
- Overall GMV decrease is associated with higher exposure to antipsychotics and is in line with enlargement of lateral ventricles[2]
- First episode studies
  - Edinburgh High Risk Study of Schizophrenia: Changes in volume correlated with symptom severity, not medication[3]
  - WM changes related to pathophysiology of schizophrenia[4]



1. Thompson et al, *PNAS*, 2001:98(20): 11650-11655
2. Fusar-Poli et al, *Neuroscience and Biobehavioral Reviews*, 2013; 37:1680-1691
3. Lawrie, *Ther Adv Psychopharmacol*, 2018; 8(11): 319-326.
4. Holleran, et al, *Neuropsychopharm*, 2014; 39: 944-954

Abbreviations: GM: Gray Matter; GMV: Gray Matter Volume; WM: White Matter

Summary

- The progression of schizophrenia that leads to functional decline begins in late adolescence and is accompanied by changes in brain structure and connectivity that contribute to symptom severity and worsening of outcomes.
- Relapse is a complex but common aspect of the disorder and results in further perturbations of brain structure and less favorable outcomes for patients.
- While antipsychotics reduce the likelihood of relapse and may offer some protection against structural alterations associated with schizophrenia, at higher doses they may contribute to these structural changes.

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