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Neurodevelopment of Schizophrenia

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'Schizophrenia is a heterogeneous disorder that encompasses different phenotypic manifestations of the disease. Genetic, gene expression and animal model studies unequivocally suggest that the molecular pathophysiology of the disease is complex, perhaps even unique to each patient.'

1. Faluidi, G and Mirnics, K. *Int J Dev Neurosci*.. 2011 29:305-309.

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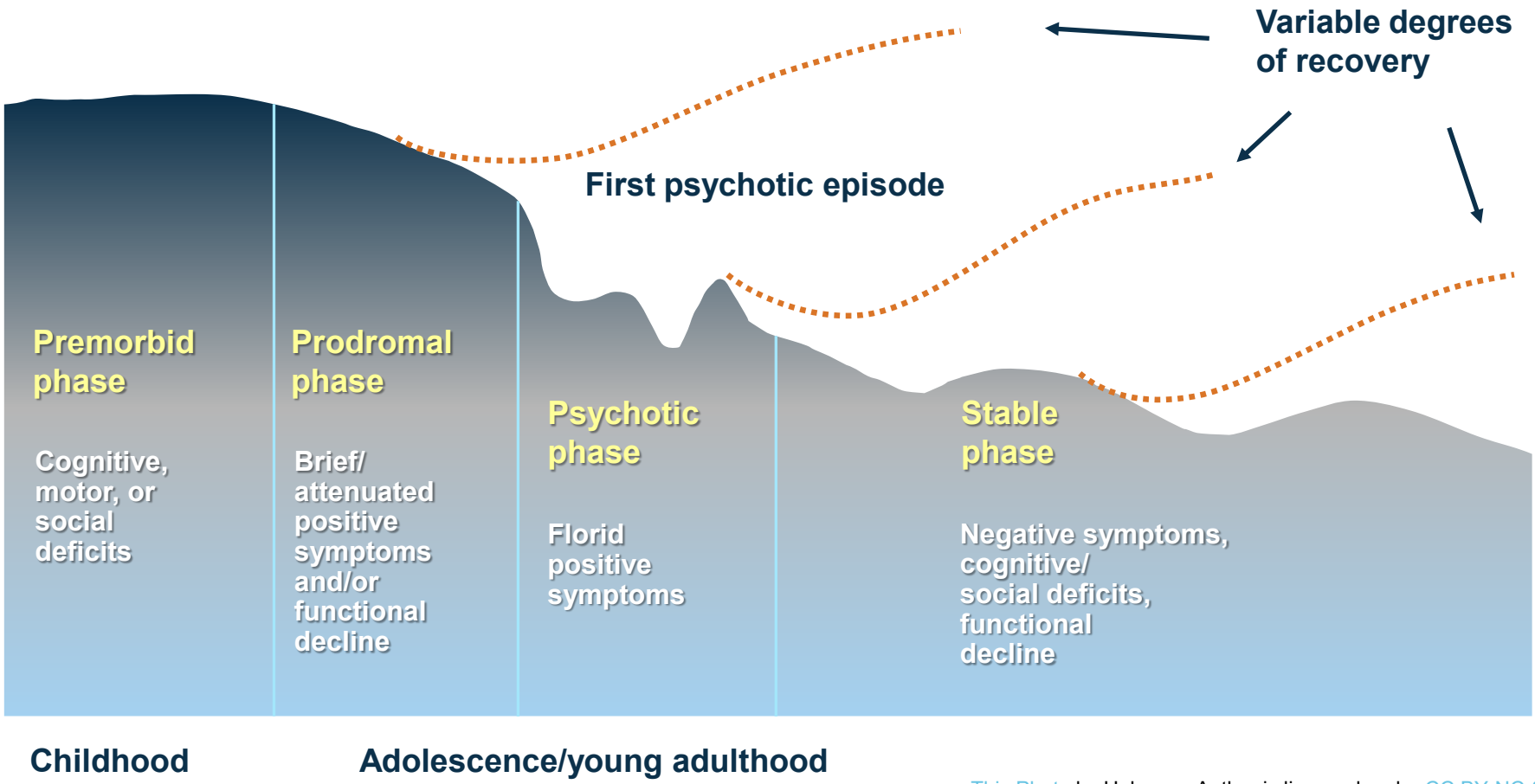
Theoretical Course of Illness for Schizophrenia



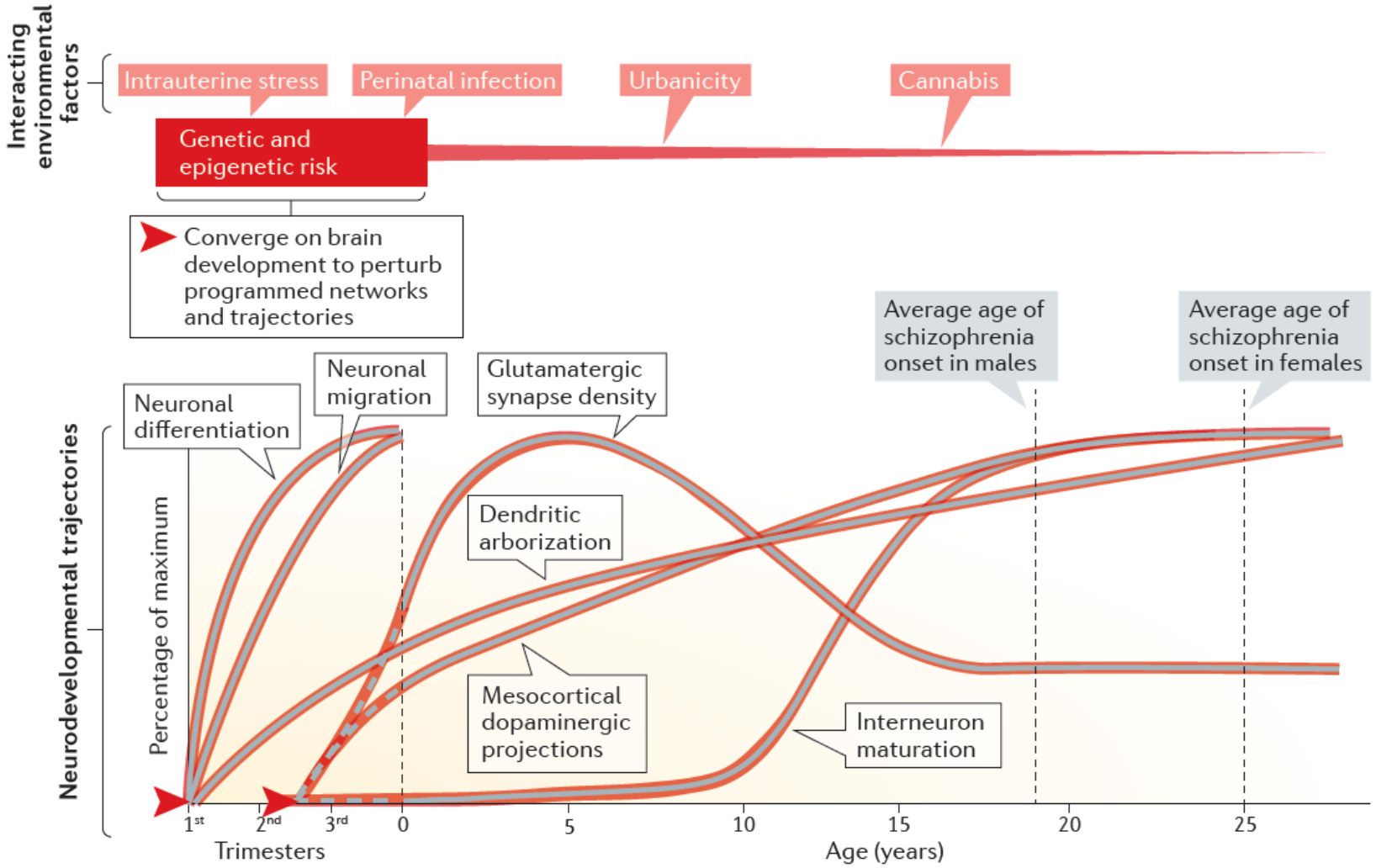
1. Tandon R, et al. *Schizophr Res*. 2009;110:1–23

Neurodevelopmental Model of Schizophrenia

- ***A risk-associated early developmental 'insult' occurs in the brain, prior to the onset of SCZ symptoms, with psychotic symptoms emerging in early adulthood, when normal maturational and environmental events impose increasing neural functional demands that reveal the brain abnormalities established earlier.***
- Theory Modifications:
  - Time of insult (prenatal, perinatal, childhood, adolescence)
  - Frequency of insults (one insult, a two-hit model, a multi-hit model or a stochastic continuum)
  - Nature of the insult
- Example Specific Potential Mechanisms:
  - Immune-mediated alterations
  - Excitatory–inhibitory imbalance in cortical tuning or connectivity *in utero*

1, Birnbaum, R and Weinberger, DR, 2017. Nat Rev Neurosci (12):727-740

Neurodevelopmental Model of Schizophrenia



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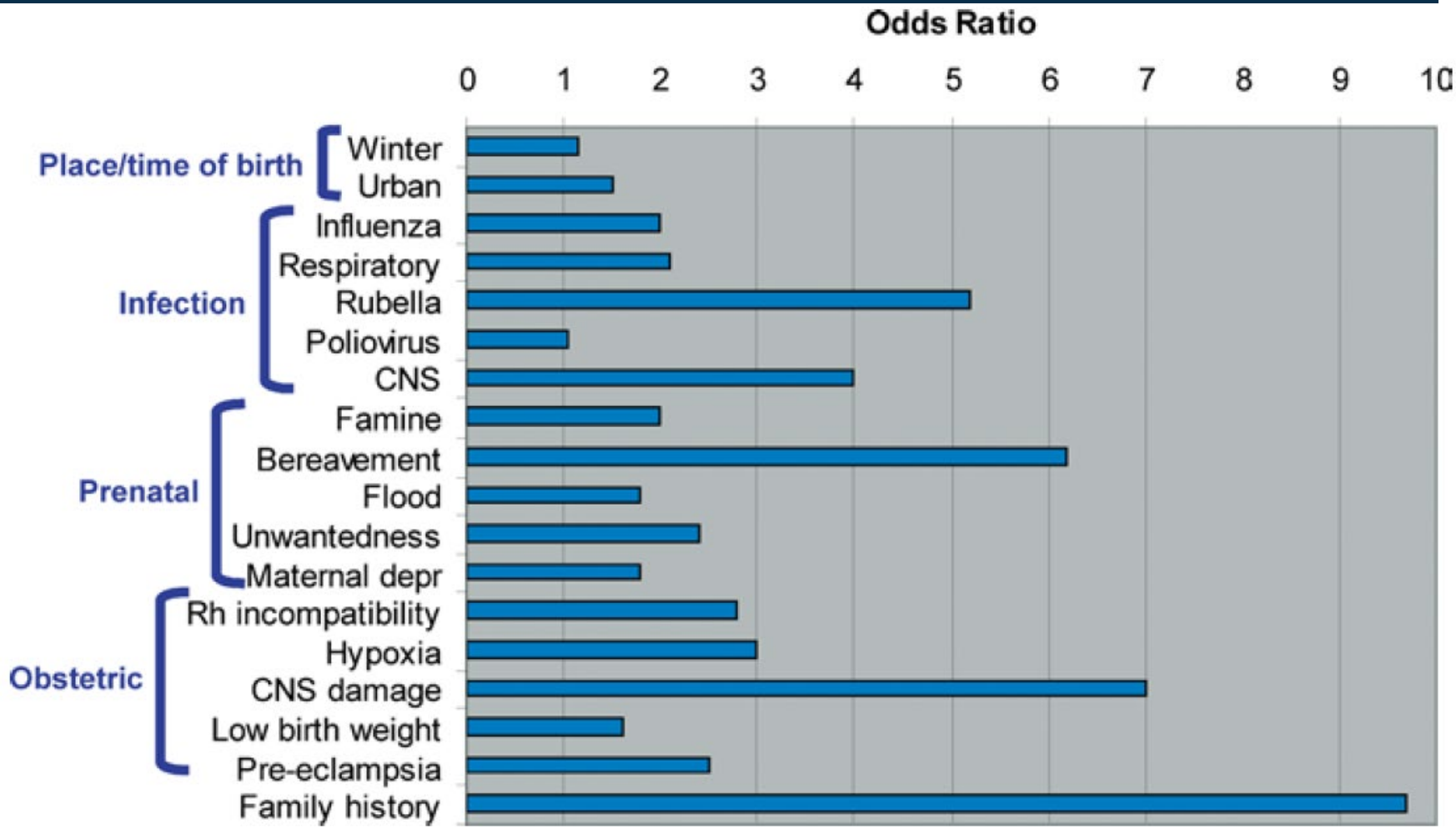
Risk: Genetic Vulnerability

- 50% concordance rate of SCZ in homozygous twins[1]
  - Rare, highly penetrant mutations *DISC1* and 22q11 microdeletion
- *DISC1*[2]
  - Mutations found in SCZ can alter gene expression patterns during fetal brain development.
  - Mutations have been associated with neuroanatomical abnormalities like alterations in neuronal structure in the hippocampus and cortex.
- 22q11 microdeletion – strongest known risk factor for SCZ[3]
  - 1-2% of sporadic cases of SCZ
  - 1/3 pf carriers develop SCZ or schizoaffective disorder (25-31 times the rate of general population).
  - Wide range of abnormalities reported in brain structure and function
- Currently, at least 43 candidate genes have been identified, but individual effect sizes are consistently modest, especially relative to the evidence for high heritability.[1]

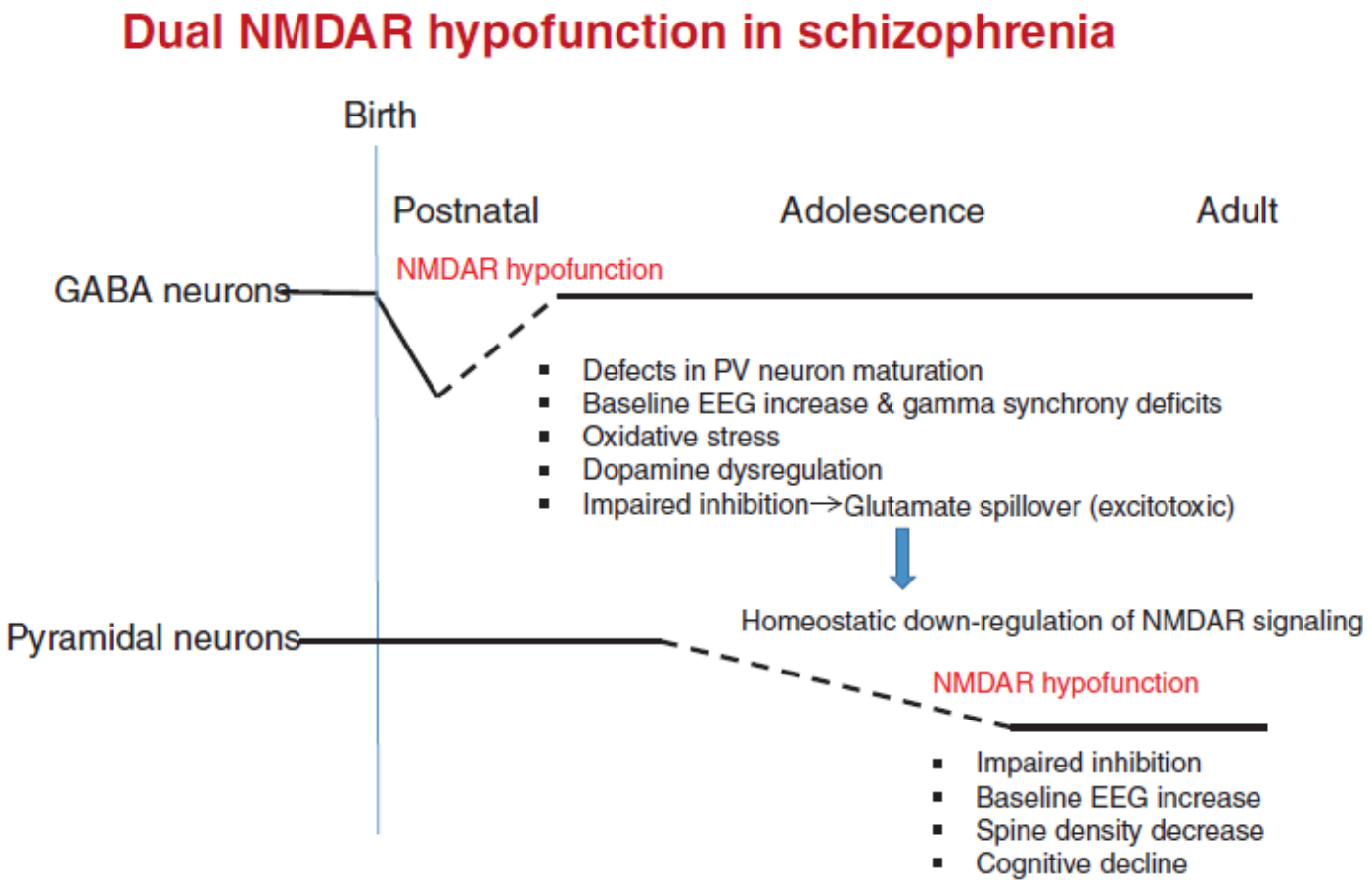
1. Insel, T. Nature. 2010; 468:187-193.
2. Nakata, K et al., PNAS. 2009; 106(37):15873-15878.
3. Drew, LJ et al., Int J Dev Neurosci. .2011; 29(3): 259–281.

Risk: Environmental Exposure



1. Sullivan, PF. The genetics of schizophrenia. *PLOS*. 2005; 2(7):614-618.

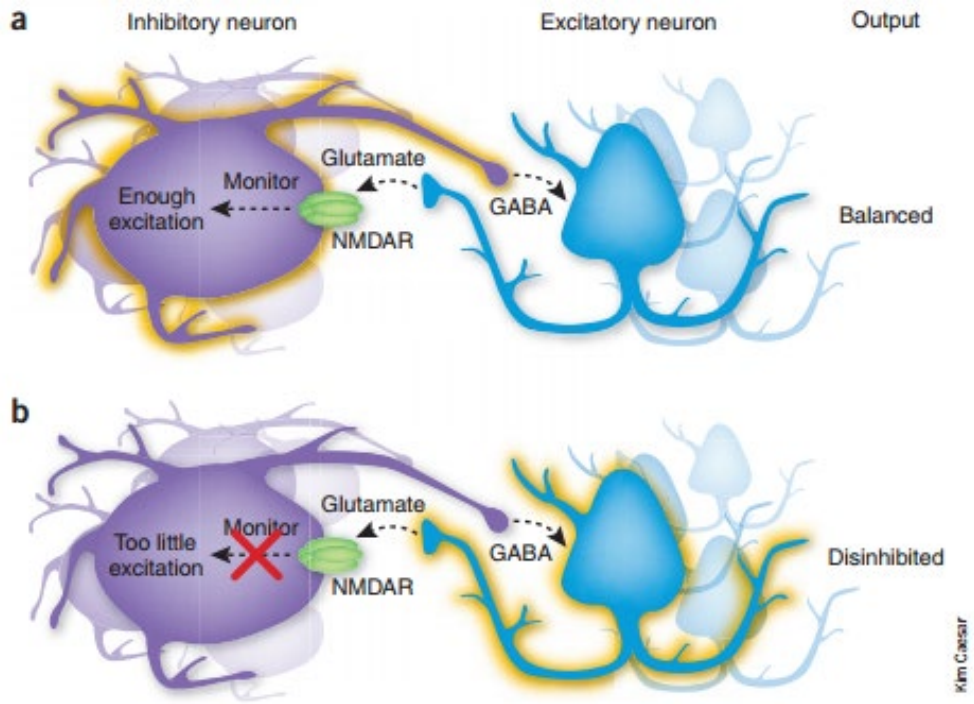
Prodromal: Neurodevelopmental NMDAR hypofunction



NMDAR, n-Methyl-D-aspartate receptor; PV, parvalbumin; EEG, electroencephalogram

1. Nakazawa, K et al., Spatial and temporal boundaries of NMDA receptor hypofunction leading to schizophrenia. Schizophrenia. 2017; 7:1-11.

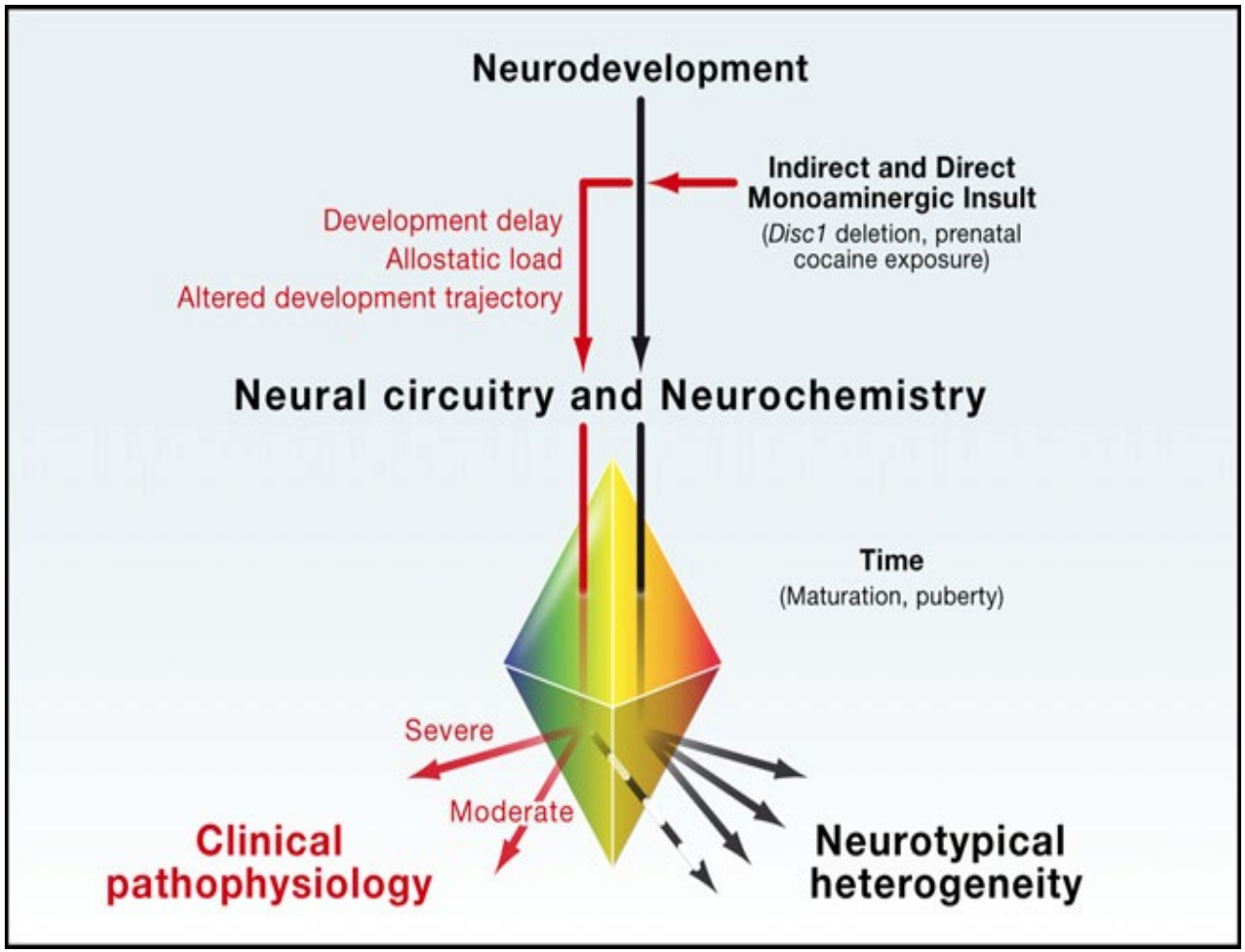
Prodromal: Inhibition/Excitation Imbalance



- The prodrome is hypothesized to be associated with aberrant neuronal dynamics
  - Specifically an impairment in both amplitude & precision of synchronized rhythmic activity.
- **A crucial variable for precise rhythmic activity is the balance between excitation and inhibition.**
- Current theory highlighted:
  - One reason for emergence of psychosis & associated perceptual & cognitive deficits is to be found in the disruption of neural dynamics coordinating brain activity in large-scale networks.

1. Mikanmaa, E et al., 2017. NeuroImage. 1-10.

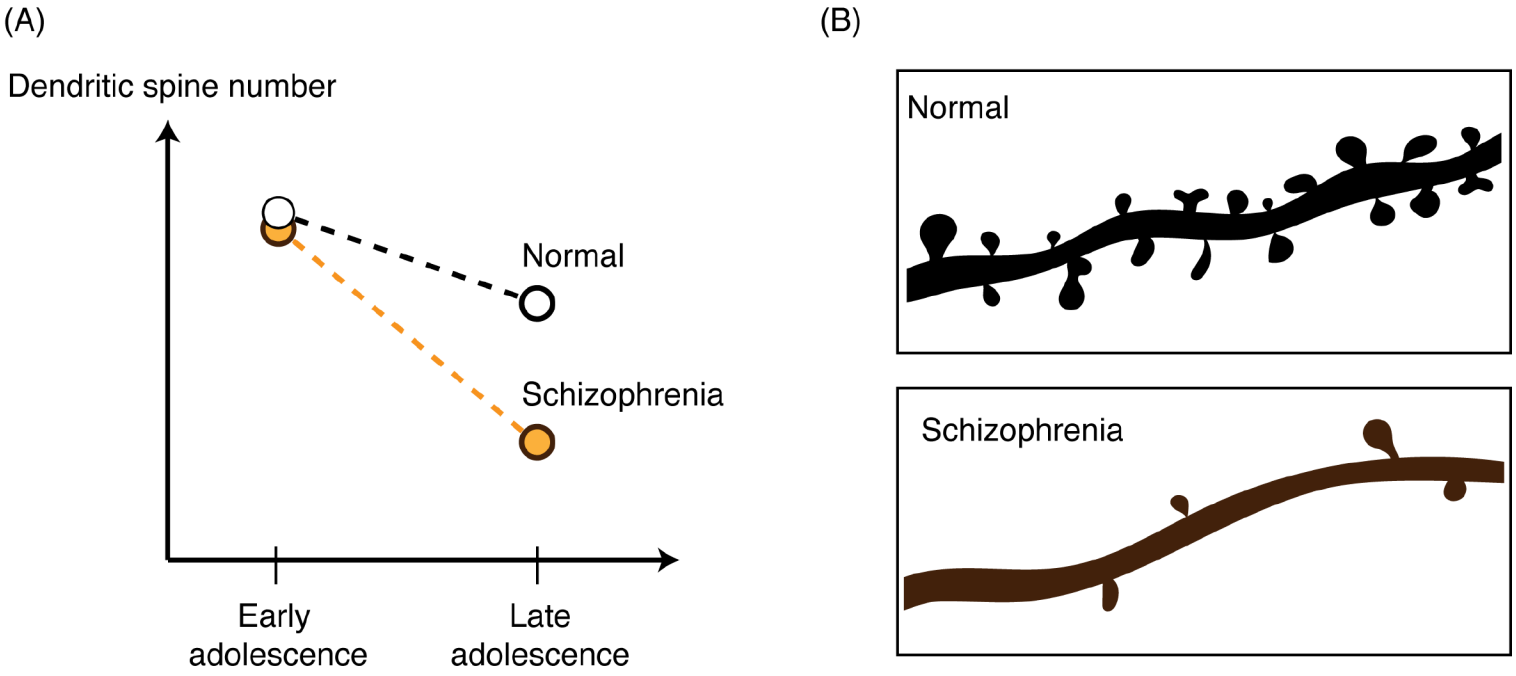
Allostatic Load and the Developmental Trajectory to Psychosis



Reprinted by permission from Elsevier Neuron,Thompson, BL and Levitt P. 2010; 65: 437-439 License 4478751464758

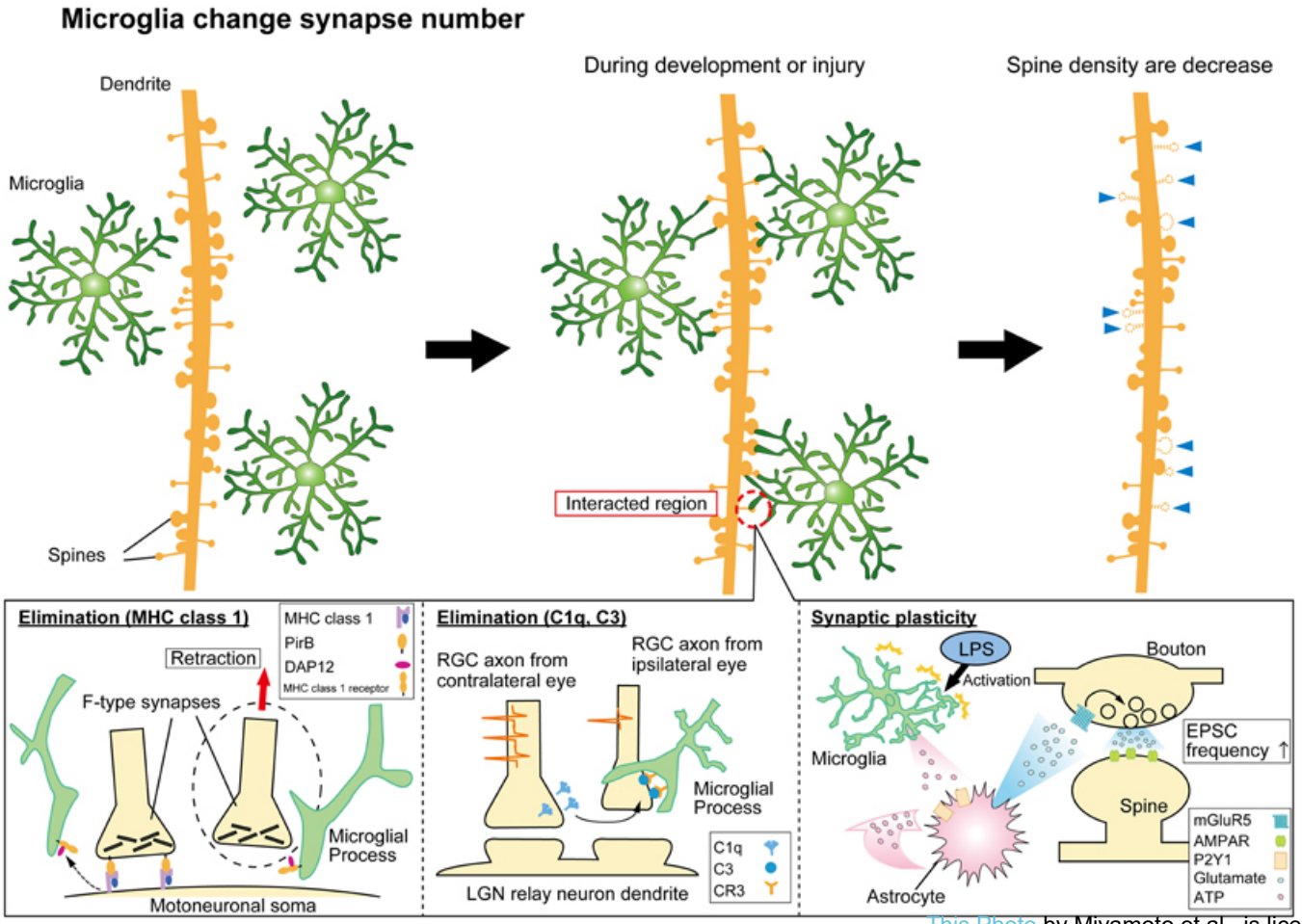
Psychosis: Synaptic Pruning Hypothesis

- **Hypothesis: disease presentation might arise from abnormal synaptic pruning in the affected individuals**



1. Boska, P. Abnormal synaptic pruning in schizophrenia: Urban myth or reality?. *J Psychiatry Neurosci*. 2011; 32(2): 75-77.
2. http://sitn.hms.harvard.edu/flash/2016/using-genetics-to-understand-schizophrenia-and-more/

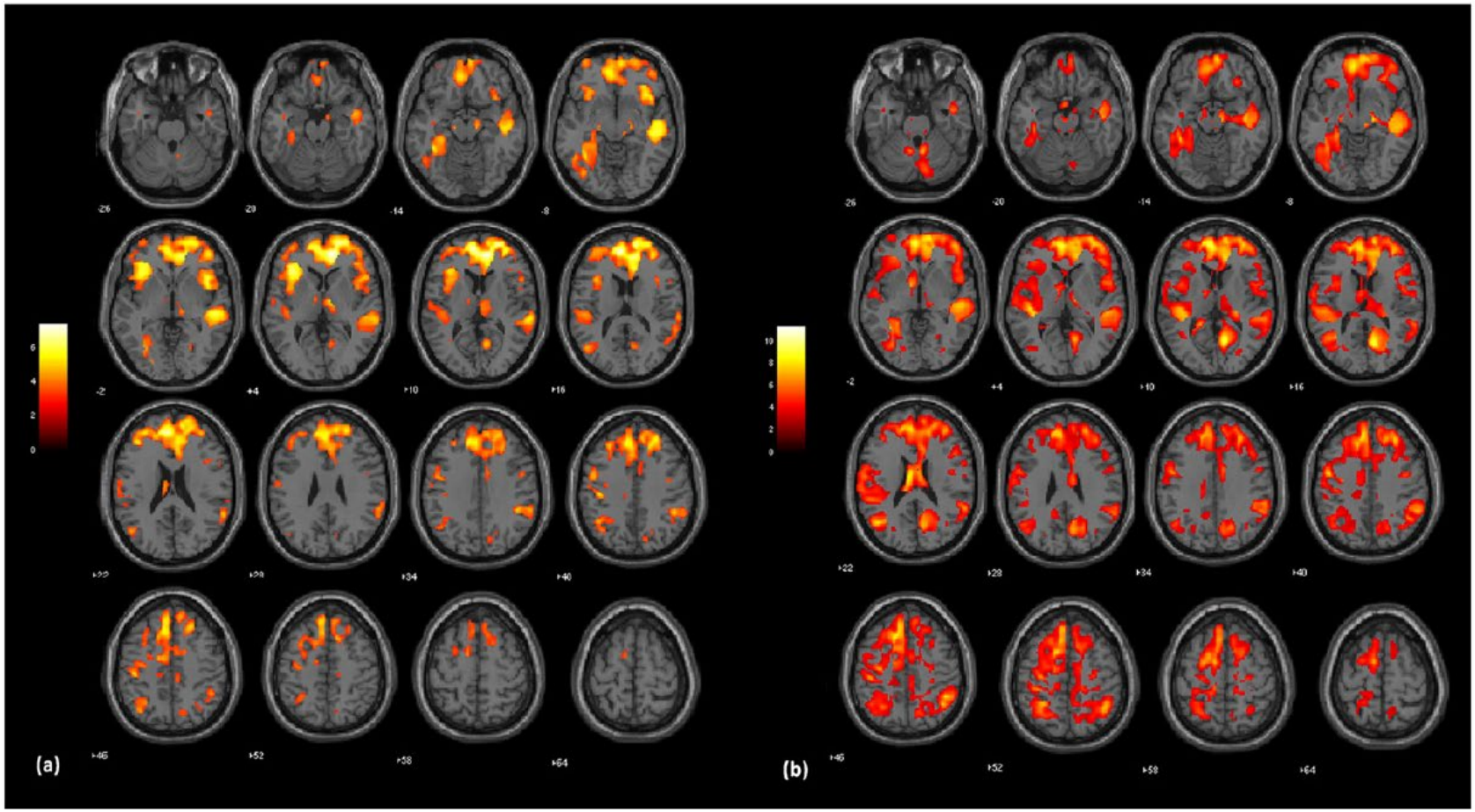
Psychosis: Microglia-mediated Synaptic Pruning



MHC, Major histocompatibility complex; PirB, Paired Ig-like receptor B; DAP12, DNAX activation protein of 12kDa; C1q, Complement component 1q; C3, Complement component 3, CR3, Complement receptor 3; RGC, Retinal ganglion cell; LGN, Lateral geniculate nucleus; LPS, Lippopolysaccharide; EPSC, Excitatory postsynaptic current; mGluR5, Metabotropic glutamate receptor 5; P2Y1, Purinoreceptor 1; ATP, Adenosine Triphosphate

1. Sekar, A et al., Schizophrenia risk from complex variation of complement component 4. Nature. 2016; 530(7589): 177-183

Chronic Illness: Grey Matter Deficits



1. Torres, UF et al., Neuroimage:Clin. 2016

Chronic Illness: White Matter Deficits

Abnormalities of these WM structures provide evidence supporting the hypothesis of cerebral dysconnectivity in schizophrenia

Group comparison	Cluster size	*T*-value (voxel)	Anatomical region	Assigned white matter structure
C > FEP	251	4.25	Frontal lobe, medial orbital gyrus R	
C < FEP	209	4.37	Parietal lobe, region of gyrus Andrei Retzii L	Subcallosal white matter, Posterior cingulum bundle
C > REP	3606*	7.08	Occipital lobe, median area L	Inferior fronto-occipital fasciculus
	615	4.77	Cuneus L/R	
	194	4.03	Frontal lateral white matter compartment R	Corona radiata, Corticothalamic tract
	519	3.49	Frontal lobe, F1 region L	
C < REP	299	4.00	Temporal lobe, superior temporal gyrus, Angular gyrus R	Inferior longitudinal fasciculus, Arcuate fasciculus
	711	3.97	Cerebellum L	
FEP > REP	1033	5.40	Occiptal lobe, median and basal parts L	Inferior fronto-occipital fasciculus
	2064	4.82	Middle and upper pontine area, lateral circumference, cerebellar peduncle L	Corticospinal tract
	209	4.57	Parahippocampal area T4/T5 L	Fornix
	519	4.04	Middle and upper pontine area, lateral circumference, cerebellar peduncle R	Corticospinal tract
	265	3.78	Frontal lobe, F1 region, middle part R	
FEP < REP	n.s.	n.s.	n.s.	n.s.

*Between-group differences in white matter structure were found in reported clusters. Only clusters showing group differences at a significance level of $p < 0.001$ and exceeding the expected number of voxels per cluster according to the Gaussian Random Field theory are reported. *$p < 0.001$ (cluster-level, FWE corrected for multiple comparisons). Anatomic labeling, corresponding cluster size and T-value are shown for each cluster. The type of group comparison is indicated in the form A < / > B, where A > B indicates lower white matter in group B compared to A and vice versa. Lateralization is marked with L for left and R for right hemisphere. Anatomical names of white matter structures were assigned using Mori: MRI Atlas of Human White Matter (Mori et al., 2005). C, control; FEP, first episode patients; REP, recurrent episode patients. C, control; FEP, first episode patients; REP, recurrent episode patients.*

1. Milliet, B et al., Serum S100B Protein is Specifically Related to White Matter Changes in Schizophrenia. Front Cell Neurosci. 2016; 10(33): 1-14.

Summary

- The disease course of schizophrenia typically progresses through multiple phases, each hypothesized to have underlying abnormal neurodevelopment, which ultimately results in psychosis and chronic illness.
- The neurodevelopmental model of schizophrenia proposes that genetic and environmental risk factors combine to significantly alter the trajectory of normal brain development.
- The prodromal phase of schizophrenia has been noted to have altered cellular excitatory/inhibitory activity that can critically disrupt functioning of neural networks.
- Increasing allostatic load on neural circuitry, during the prodrome, increases the likelihood of clinical pathophysiology resulting in psychosis.
- The synaptic pruning hypothesis is hypothesized to be a reason for the protracted time observed to reach psychosis, and may be the result of abnormal microglia activity.
- Abnormal neurodevelopment and degeneration due to altered functioning can result in increasing brain volume deficits during chronic illness.