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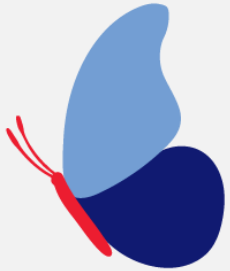
Brain-Behaviour Mapping: Are symptoms weak constructs?

Lena Palaniyappan

March 4, 2023



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Disclosures

Advisory Board	Otsuka Canada (2019)
Honorarium Recipient	Otsuka Canada (2023), Janssen Canada (2020)
Editorial Board Involvement	Canadian Journal of Psychiatry, Journal of Psychiatry & Neuroscience (Canadian CNP)

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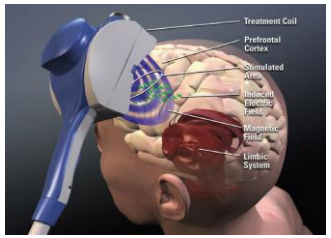
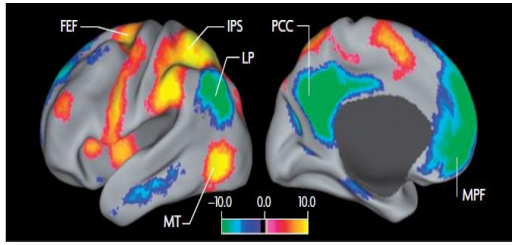
Symptoms to Circuits

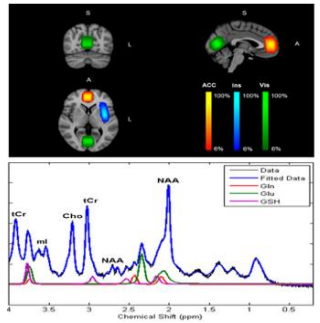
- Are symptoms natural kinds?
  - The role of linguistic semiology

- Non-causal mechanisms in brain-behaviour mapping
  - The role of compensation



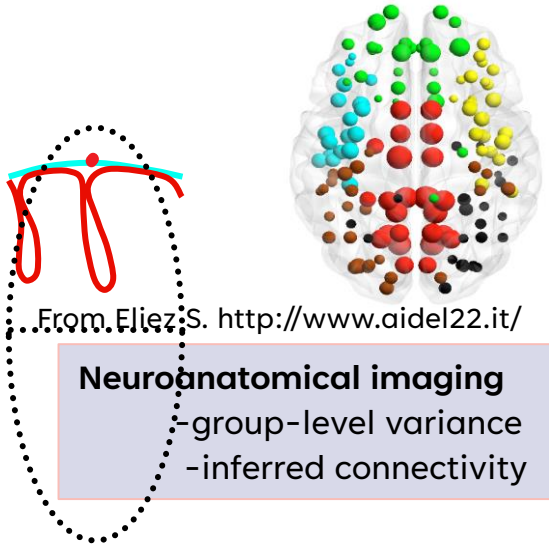


Functional MRI
-dynamic, time-varying measures



Perturb-and-measure / plasticity
e.g., induced connectivity
- TMS, tDCS

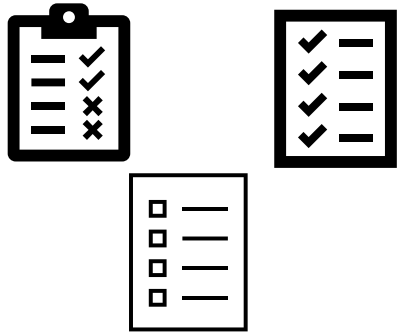
Neurochemical Imaging
-PET: receptors / release
-MRS: metabolites, time-course

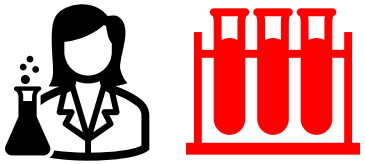


From Eliez S. http://www.aidel22.it/

Neuroanatomical imaging
-group-level variance
-inferred connectivity

Mapping biology to psychiatric constructs





Psychiatric constructs
- Clinician/patient-rated symptoms
- Diagnosis

Blood based markers
-inflammatory, genetic, protein measurements

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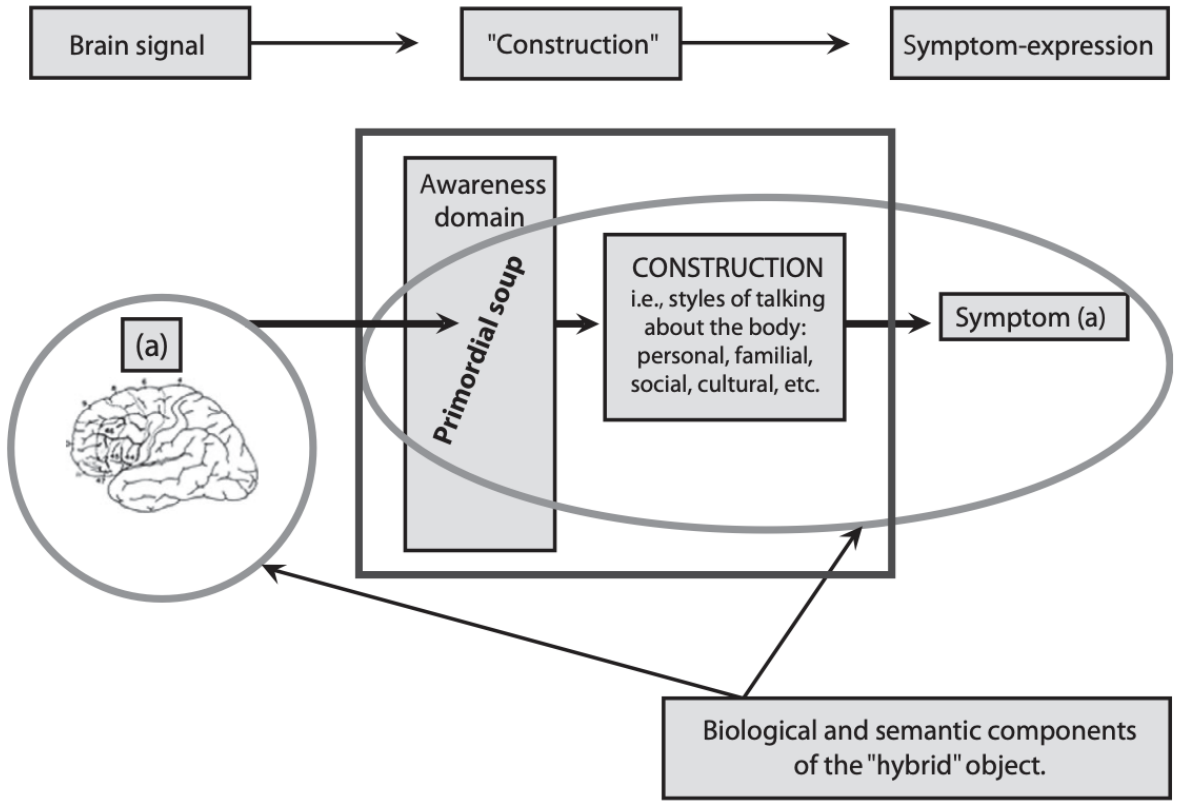
Symptoms are not ‘natural kinds’



Symptoms do not have natural (physical) dimensions.

They are ‘hybrid objects’ that emanate from the semantic envelope constructed by an individual who becomes aware of a ‘pre-conceptual’ brain signal.

Symptoms are equifinal as well as non-specific.

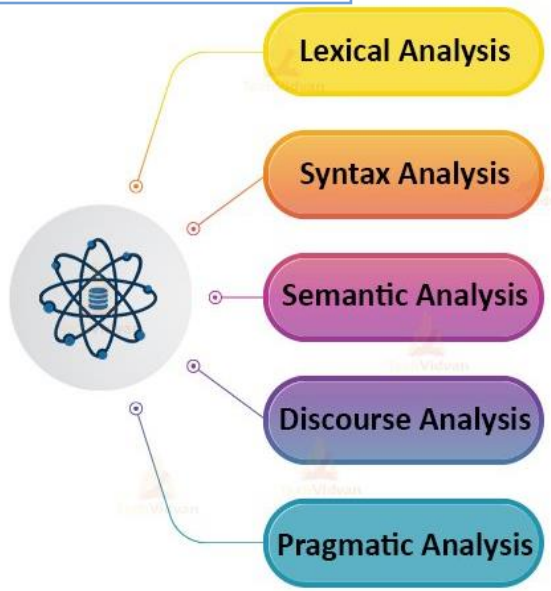
from Berrios & Markova 2015

DOI: 10.1017/CBO9781139424745.005

Natural Language Processing (NLP) provides a formal means to quantify language-based signs

- Speech has all three types of psychiatric signs in the semiotic sense
  - *icons* (sentiment words such as 'depressed' 'anxious')
  - *indices* (descriptions of voices, beliefs) and
  - *symbols* (incoherence, slowing)

  NLP of speech provides granular behavioural units of observation from the clinical dialogue process



https://techvidvan.com/

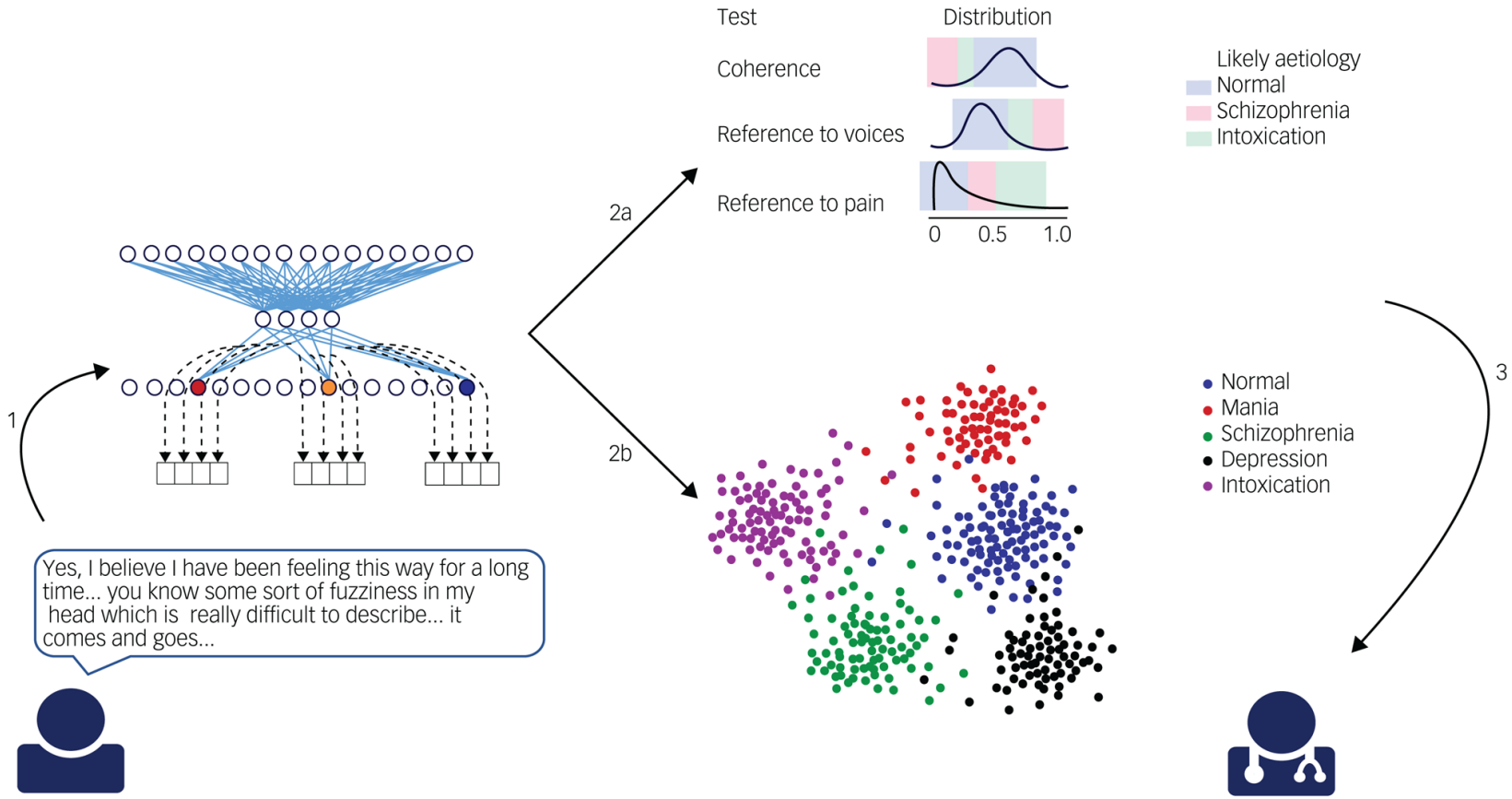
Limongi et al., Scz Bulletin, *in press.*

A trained NLP model (1) can provide

Quantitative readouts of signs (2a)

or

Used for identifying clusters of mental states (2b)



Rezaii et al., The British Journal of Psychiatry. 2022:251-3.

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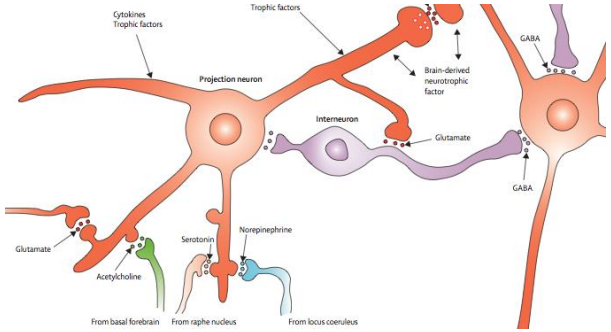
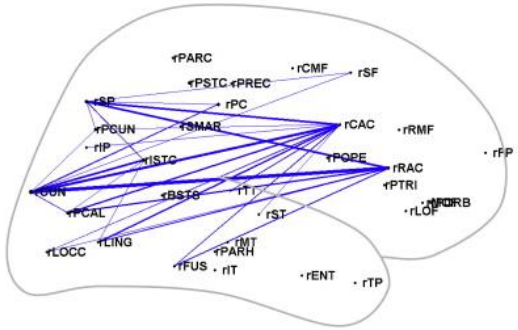
Psychosis and dysconnectivity in various units of analysis

MICRO-SCALE
synapses and circuits



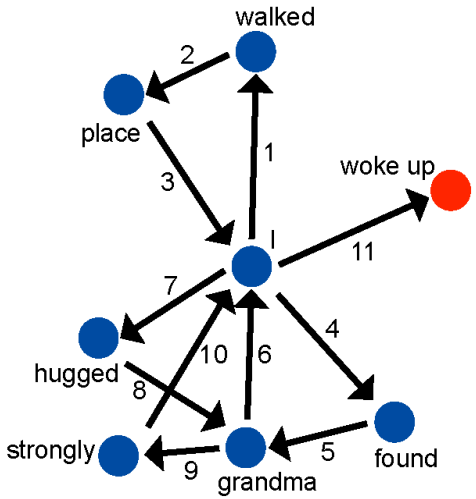
Kapogiannis & Mattson *Lancet Neurol*. 2011

MESO SCALE
Brain networks



Honey et al. *Neuroimage* 2010

MANIFEST-SCALE
Speech & behaviour



Mota et al. *Plos One* 2012

SOCIAL-SCALE
Interpersonal relations

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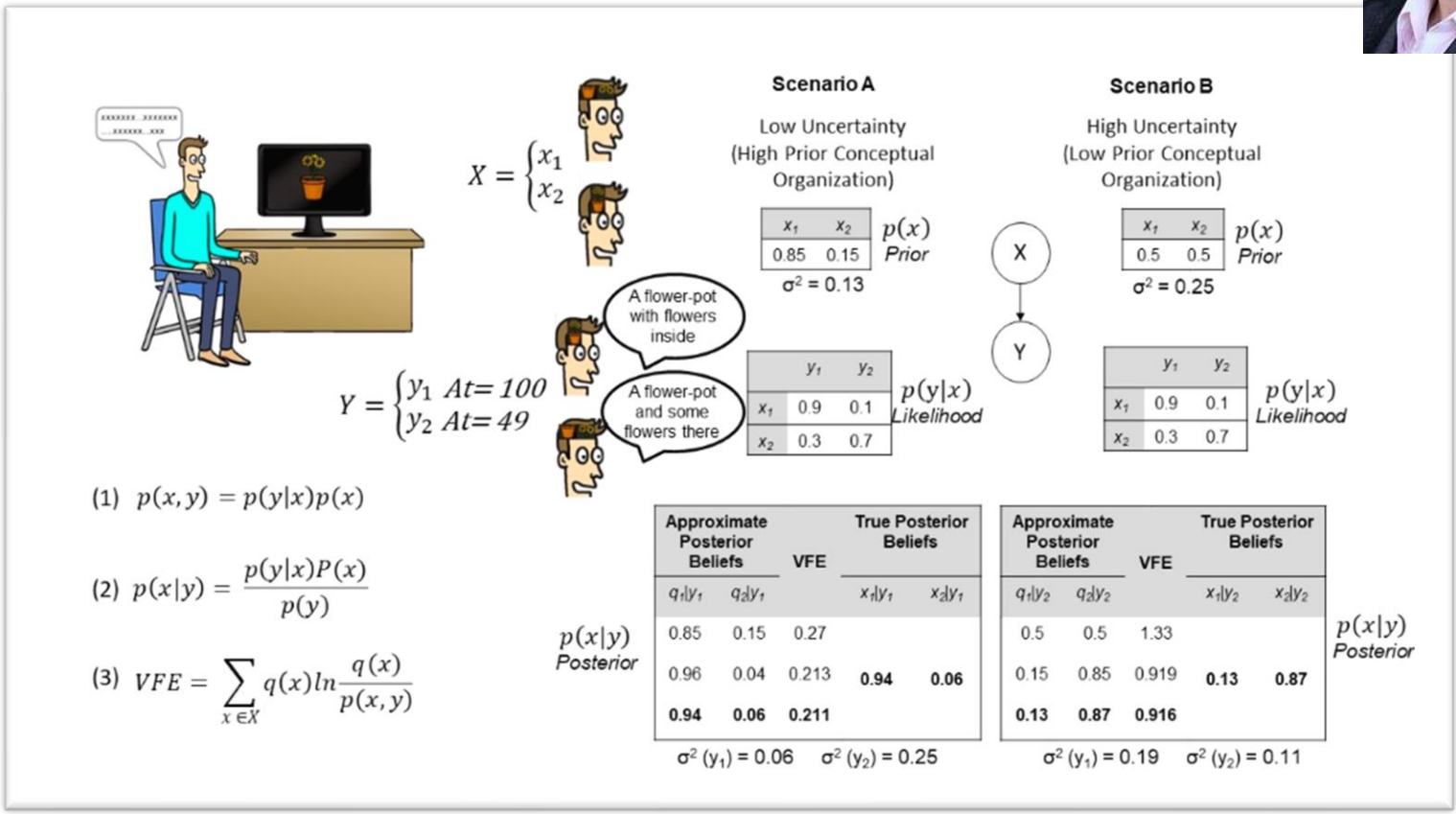
Lexical Analysis

Modelling Conceptual Disorganisation as a latent psychopathological construct

Conceptual (dis)organisation = a special case of uncertainty about ordered representations.

Language is employed to reduce this uncertainty (i.e., speech is an active process of making sense of the world)

A coherent speech production substantially minimizes uncertainty.



Thus, Conceptual Disorganisation is a hidden construct that can be estimated (equation 2)

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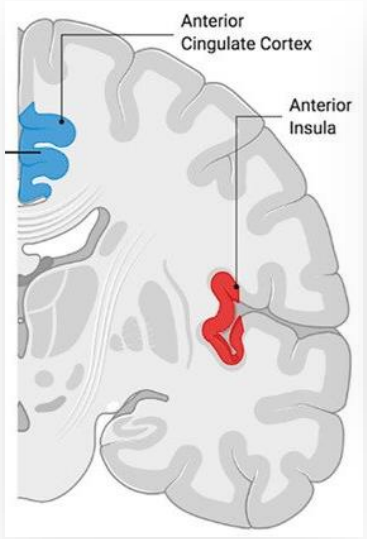
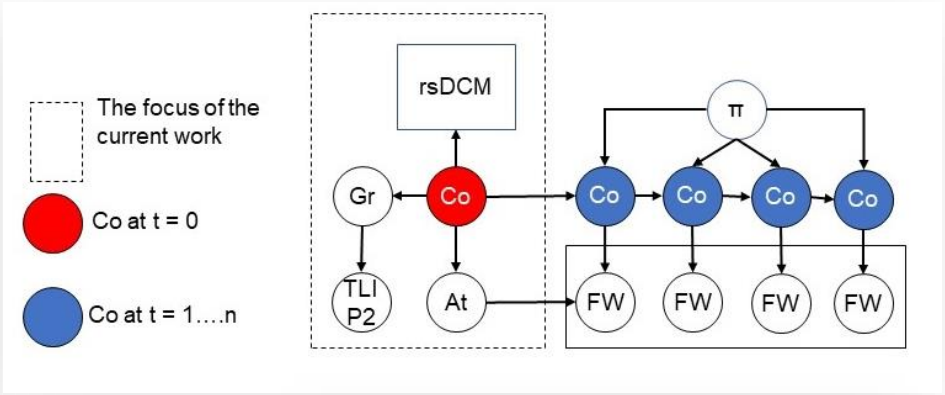
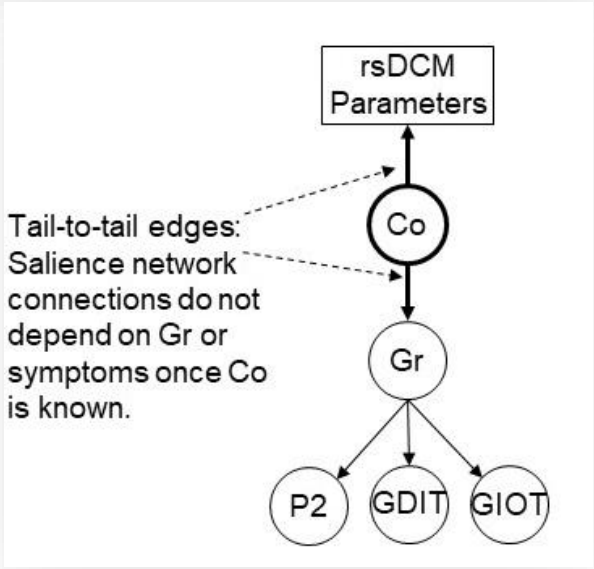
Analytic Thinking Index= articles + prepositions – pronouns – auxiliary verbs – conjunctions – negations – nonreferential adverbs.

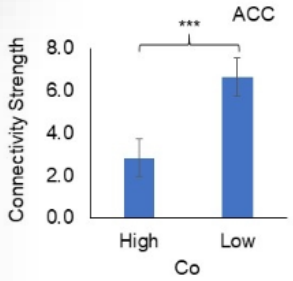
Limongi et al., in press Schizophrenia Bulletin
https://osf.io/jbtpd

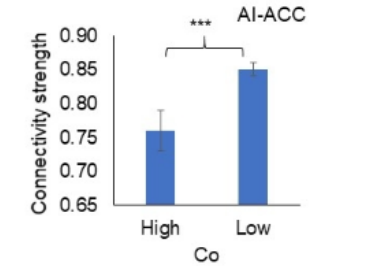
Higher inhibitory tone within the ACC and higher insula to ACC (Salience Network) excitatory drive relates to *computed* disorganization

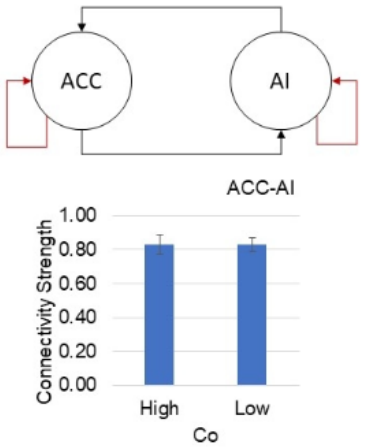


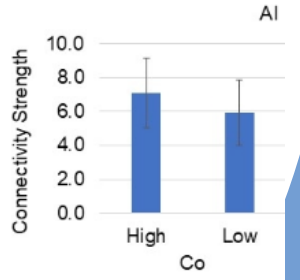












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Limongi et al., in press Schizophrenia Bulletin

Brain-Behaviour Mapping

Symptoms are weak constructs; semantic reconstruction is a ‘radar-jammer’

Speech is the “vital sign” of mental health

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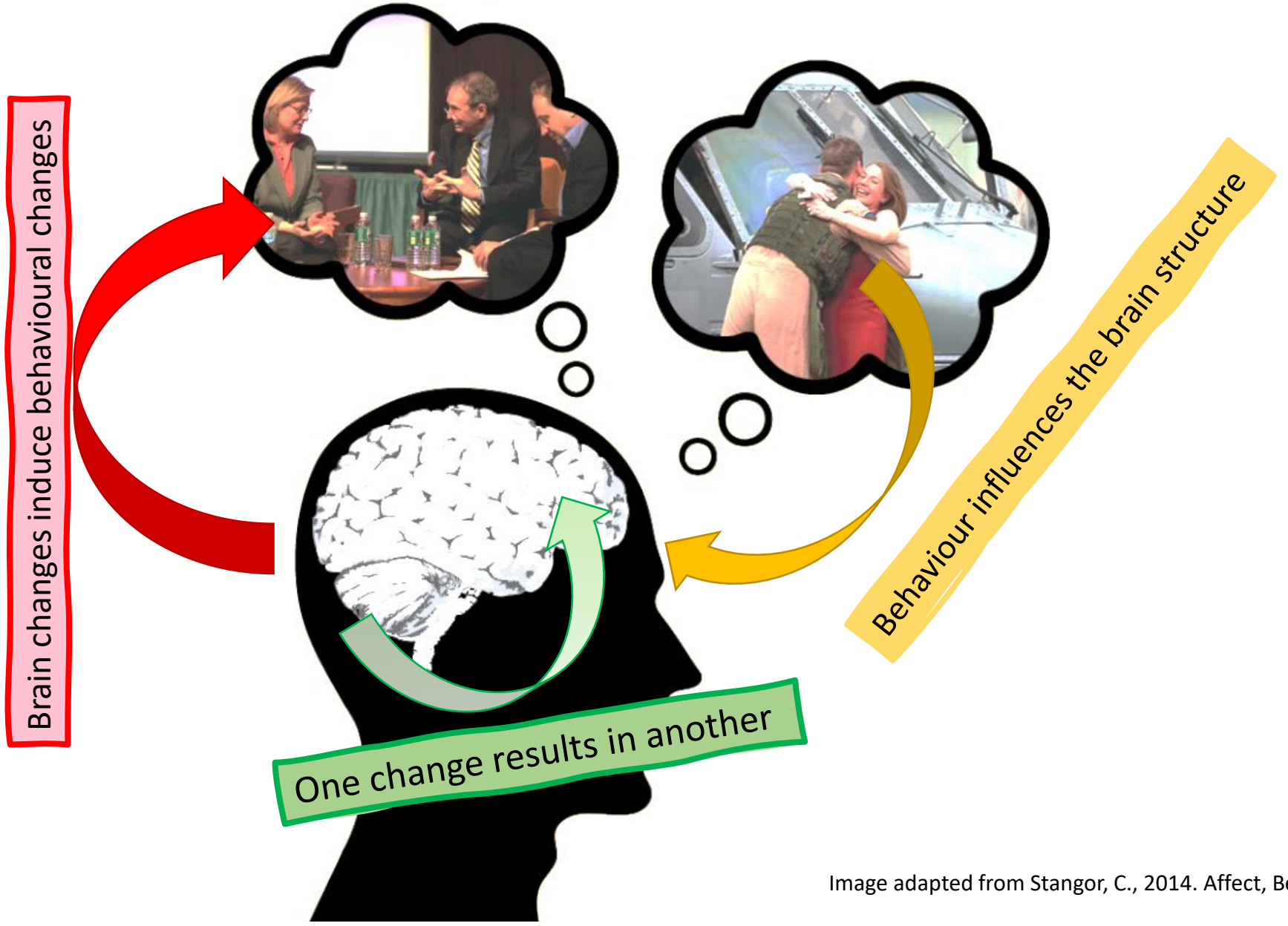
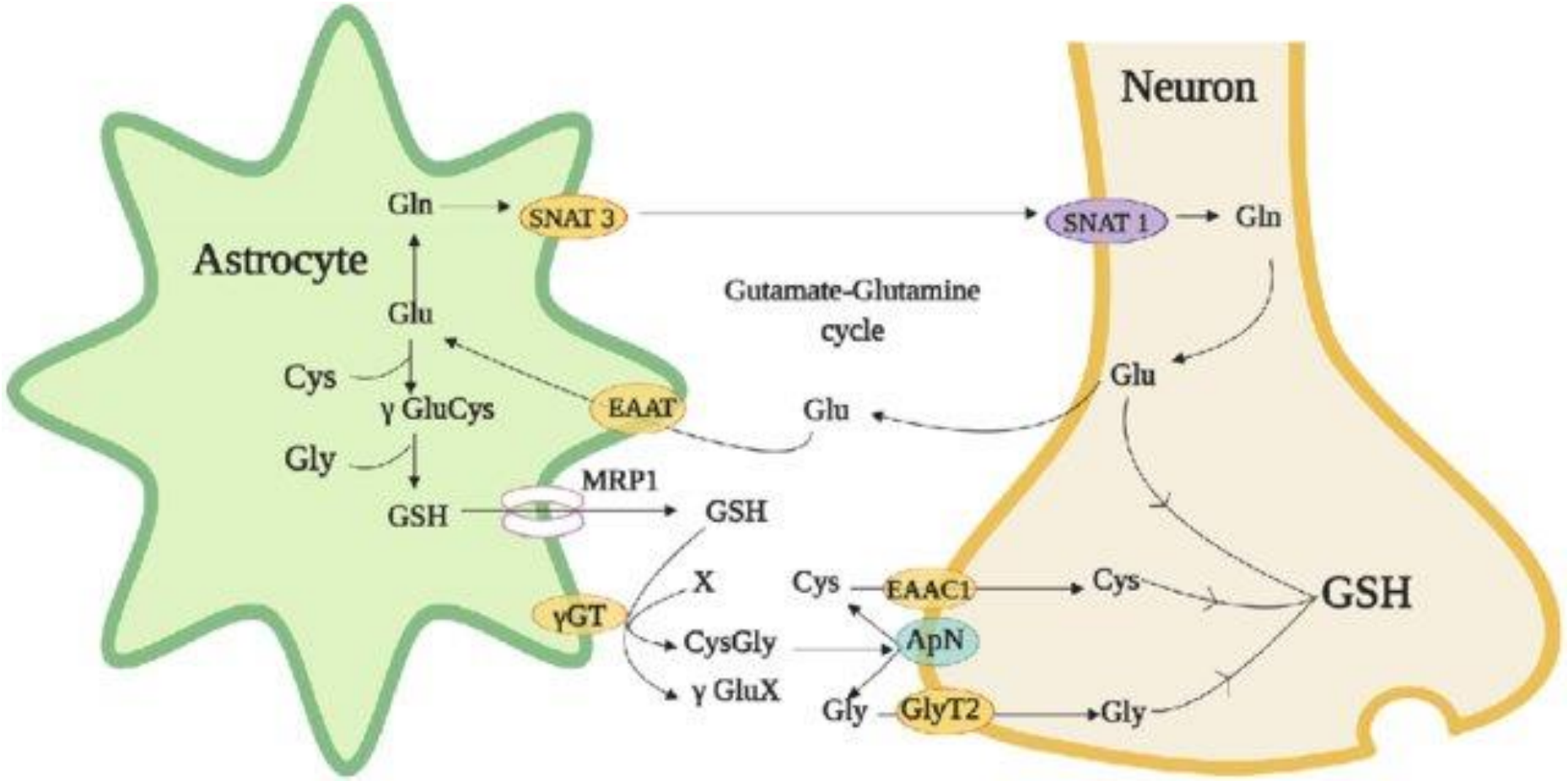


Non-causal Mechanisms

Image adapted from Stangor, C., 2014. Affect, Behavior, and Cognition. *Principles of Social Psychology*.

Brain's primary antioxidant - GSH



Dringen et al., J Neurosci . 1999 Jan 15;19(2):562-9.
Dwivedi et al., Neurochemical Research 45(7):1461–1480

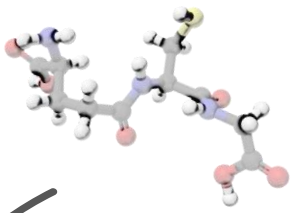
Two pathophysiological models of GSH aberration in schizophrenia

- A vicious circle model with primary GSH deficit

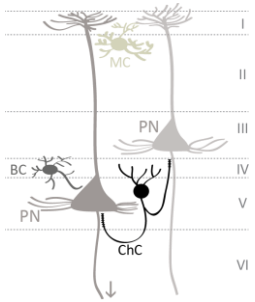
- An adaptive change model with secondary GSH changes

A: Primary GSH deficit

Primary glutathione deficit / redox imbalance

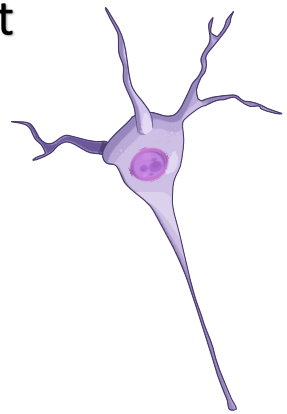


GABAergic dysfunction (NMDA)

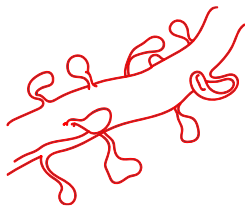


Glutamatergic excess

Progressive glutamatergic deficit



Uncompensated glutamatergic dysfunction

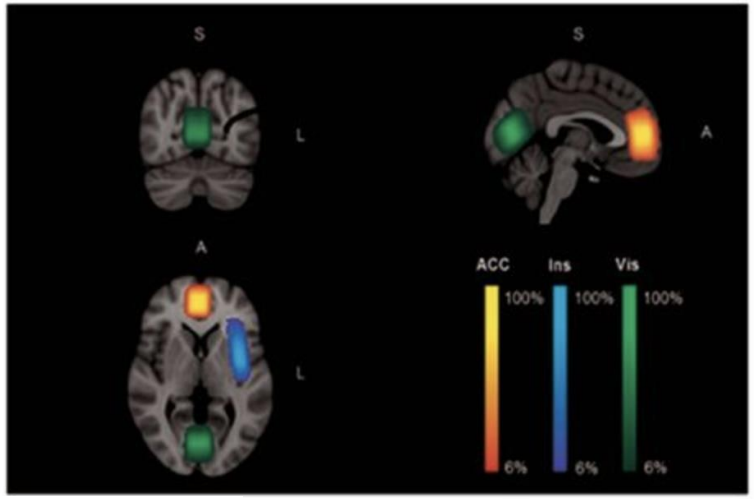


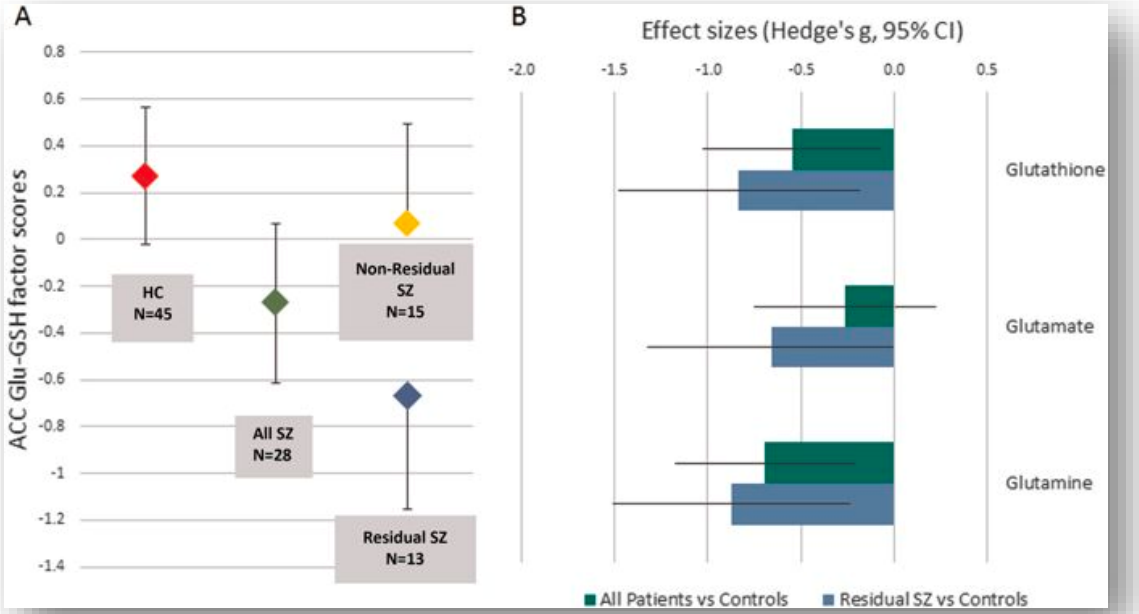
Stable cognitive deficits and negative symptoms

Palaniyappan et al., *Frontiers in Psychiatry* 2021

7T MRS GSH studies in schizophrenia

Short TE STEAM sequence (TE/TM/TR = 17/17/2000 ms)





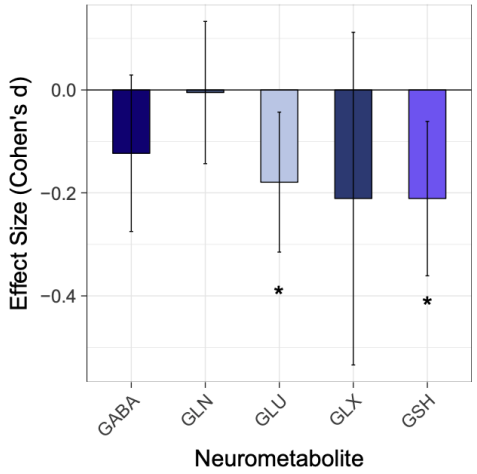
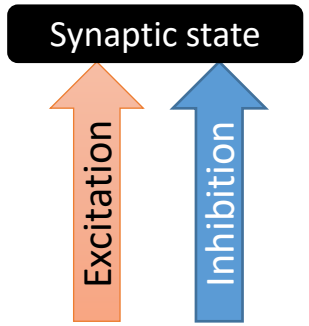
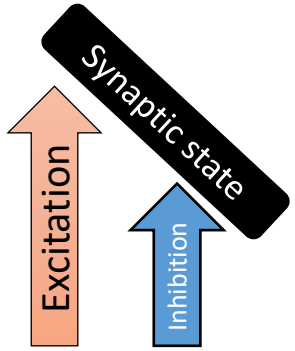


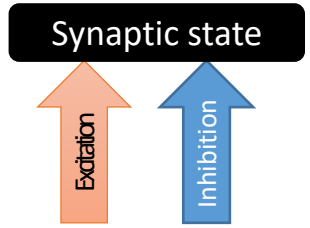
Fig. 2. The meta-analytic summary effect size (+/− 95% CI) for each neurometabolite. Gamma aminobutyric acid (GABA); Glutamine (Gln); Glutamate (Glu); Glutamate+Glutamine (Glx); Glutathione (GSH).



Healthy system

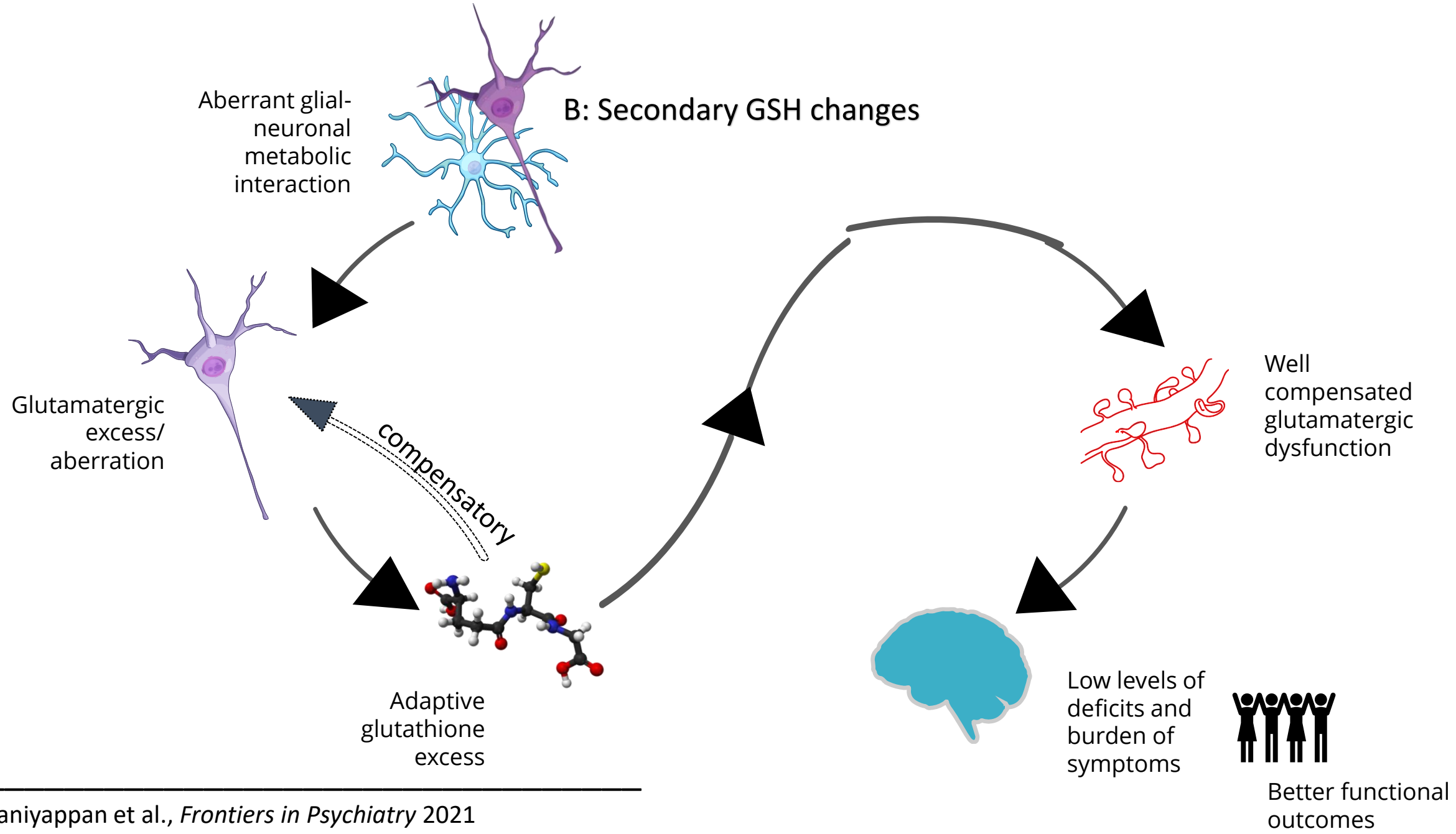


Excitotoxic mode



Deficit mode

Kumar et al., Molecular psychiatry. 2020 Apr;25(4):873-82.
Sydnor et al., Schizophr. Research 2020 Dec 226:61-69



Palaniyappan et al., *Frontiers in Psychiatry* 2021

Molecular Psychiatry
https://doi.org/10.1038/s41380-020-0704-x

IMMEDIATE COMMUNICATION

Early treatment response in first episode psychosis: a 7-T magnetic resonance spectroscopic study of glutathione and glutamate

Kara Dempster[1] · Peter Jeon[2] · Michael MacKinley[3] · Peter Williamson[3,4,5] · Jean Théberge[2,3,5,6] · Lena Palaniyappan[2,3,4,5]

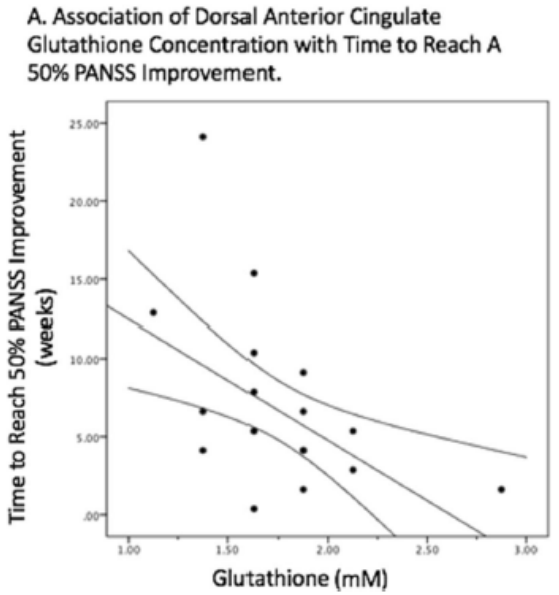
Kara Dempster

Dempster et al., Mol. Psychiatry, 2020

Higher antioxidant levels in prefrontal cortex relates to quicker and larger magnitude of treatment response in drug-naïve first episode psychosis

Higher glutamate was associated with more severe functional impairment

26 untreated FES; 27 HC
<3ds antipsychotic exposure



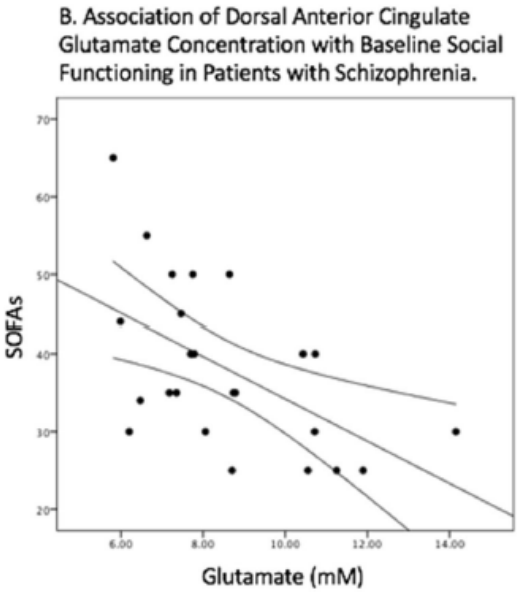


Fig. 2 Association of dorsal anterior cingulate metabolites with outcome measures. a Relationship between the estimated concentration of glutathione in millimolar units and the time taken to reach 50% reduction in the Positive and Negative Syndrome Scale (PANSS-8 items) score among patients with first-episode psychosis. b Relationship between estimated concentration of glutamate in millimolar units and baseline functioning assessed using Social and Occupational Functioning Assessment Scale (SOFAS) score among patients with first-episode psychosis.

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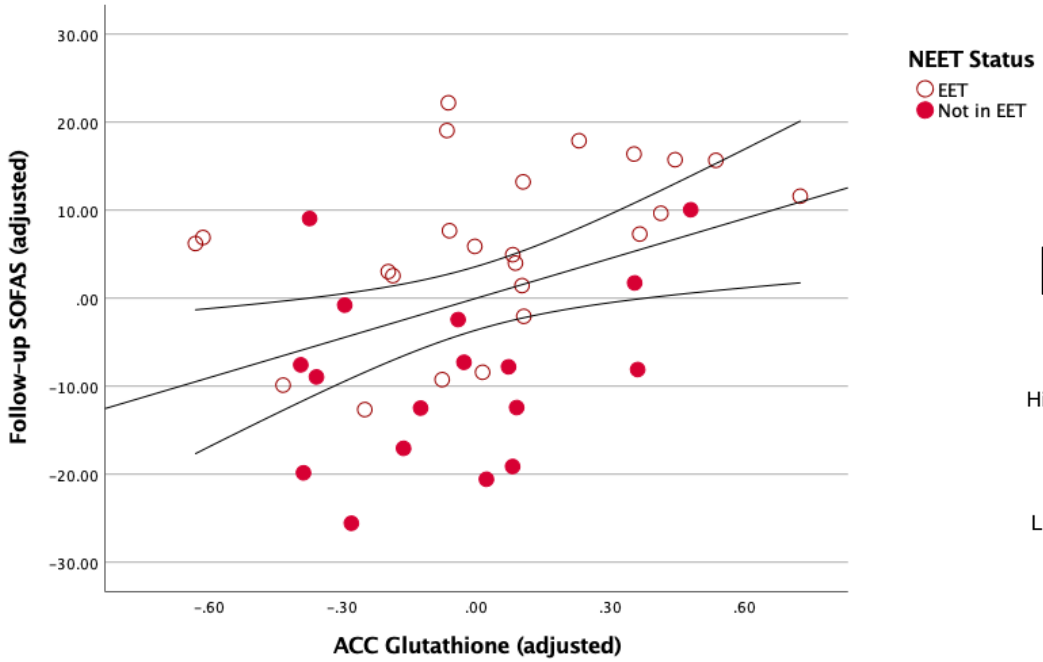
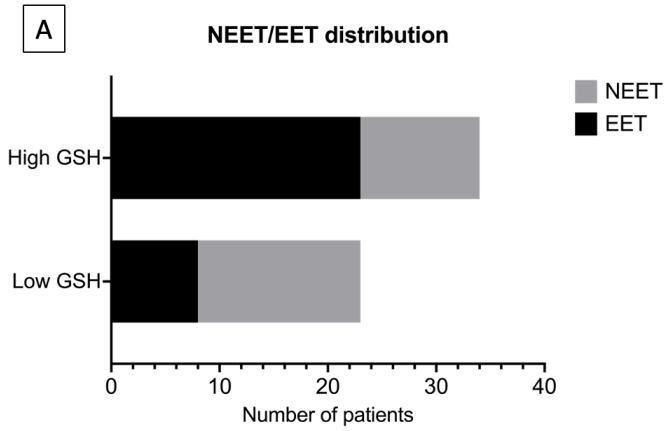
Central Oxidative Stress and Early Vocational Outcomes in First Episode Psychosis: A 7-Tesla Magnetic Resonance Spectroscopy Study of Glutathione

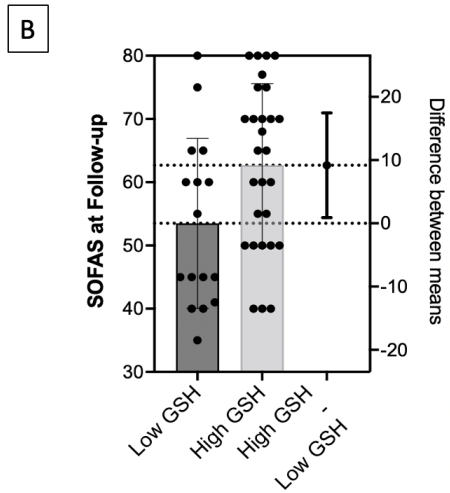
Michael MacKinley, Sabrina D Ford, Peter Jeon, Jean Théberge, Lena Palaniyappan ✉
Author Notes

Schizophrenia Bulletin, sbac012, https://doi.org/10.1093/schbul/sbac012
Published: 21 March 2022



Higher baseline GSH in FES relates to better vocational outcomes by 1 year





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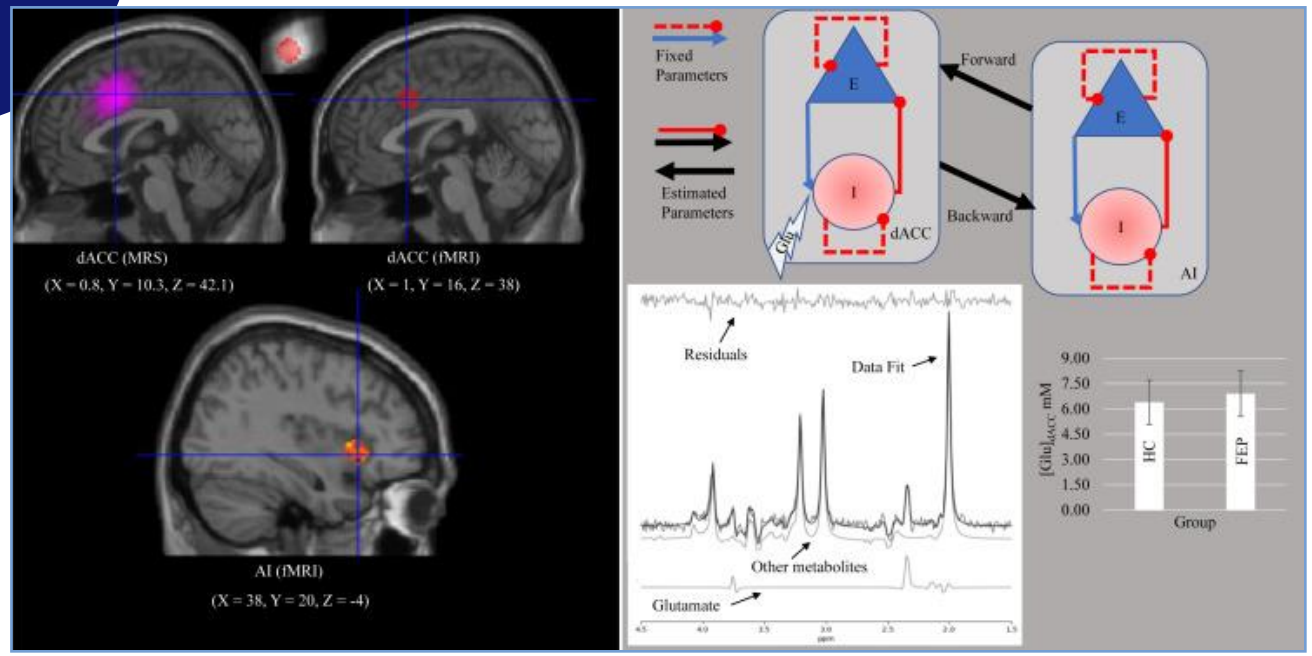


Archival Report

Biological Psychiatry

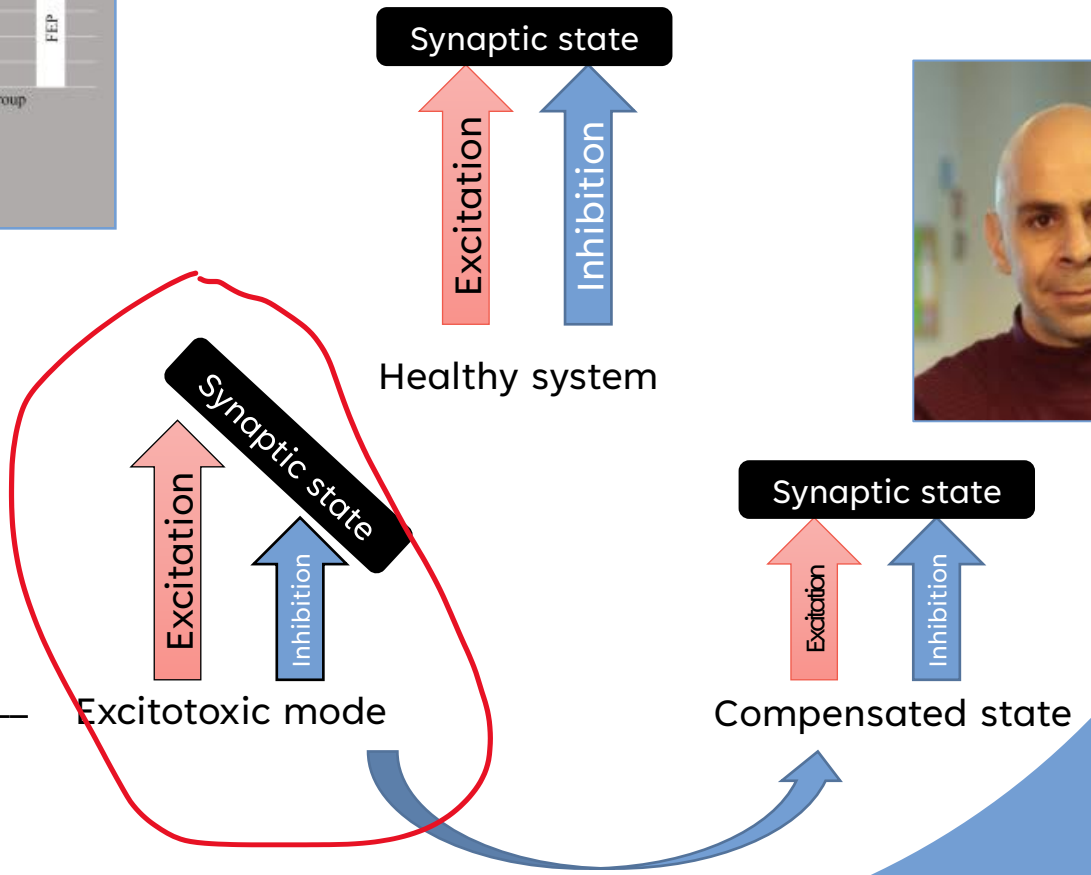
Article

Counteracting Effects of Glutathione on the Glutamate-Driven Excitation/Inhibition Imbalance in First-Episode Schizophrenia: A 7T MRS and Dynamic Causal Modeling Study

Roberto Limongi [1,*], Peter Jeon [2,3], Jean Théberge [2,3,4,5] and Lena Palaniyappan [1,2,4]

Higher levels of 'excitotoxic' glutamate relates to circuit-level disconnection

Higher antioxidant levels may attenuate the glutamate induced disinhibition



Limongi et al., Biol. Psychiatry, 2020
Limongi et al., Antioxidants, 2021

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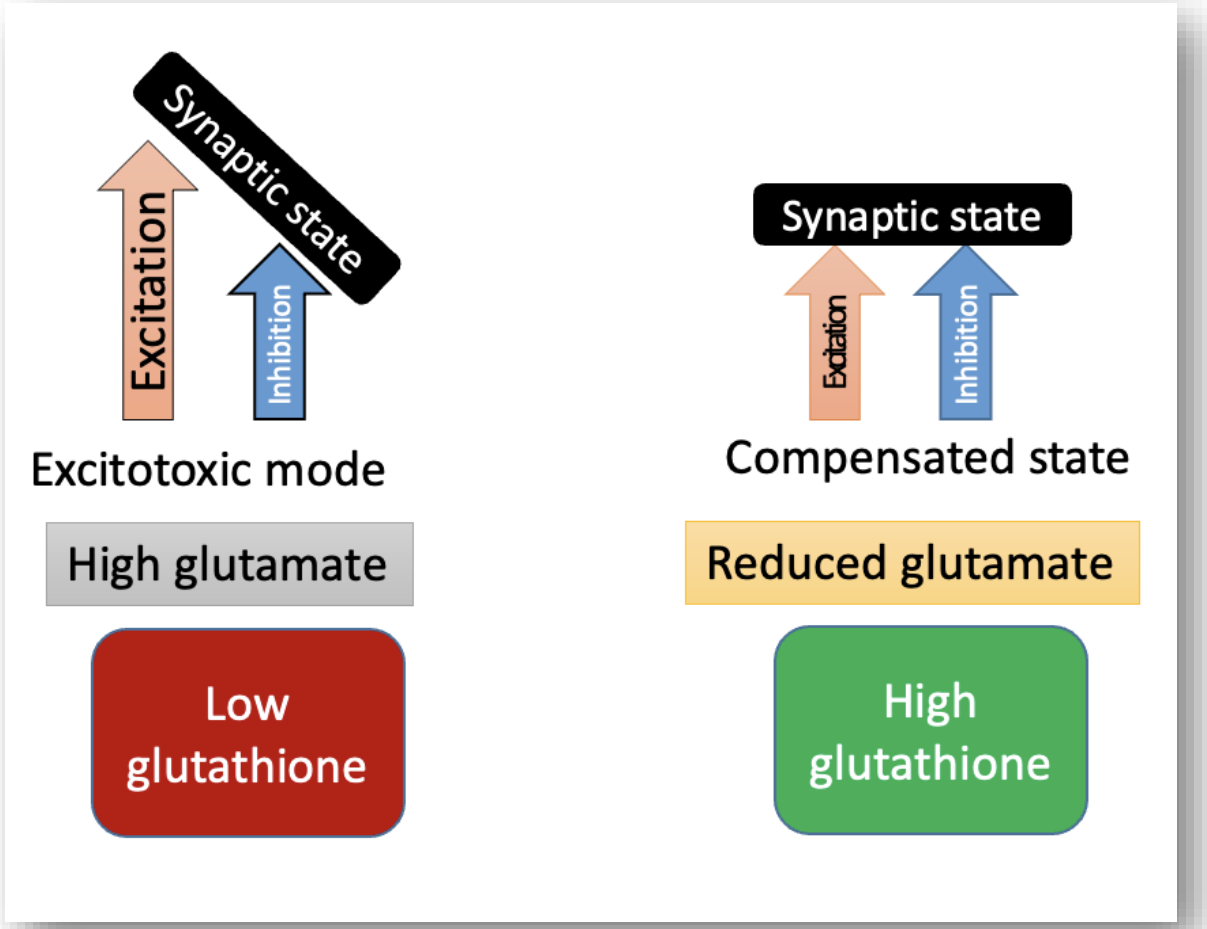
MRS dorsal ACC glutathione may mark the state of ‘compensation’ in cortical microcircuits

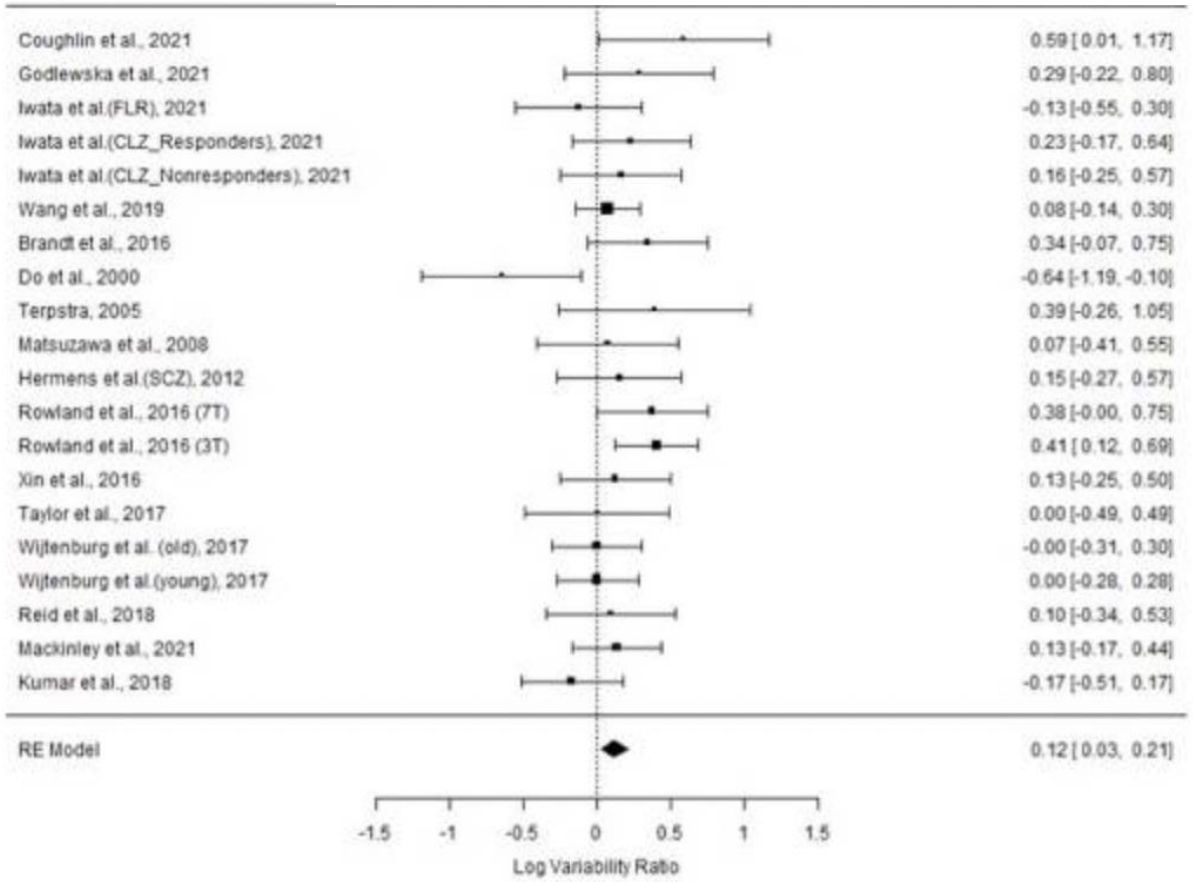


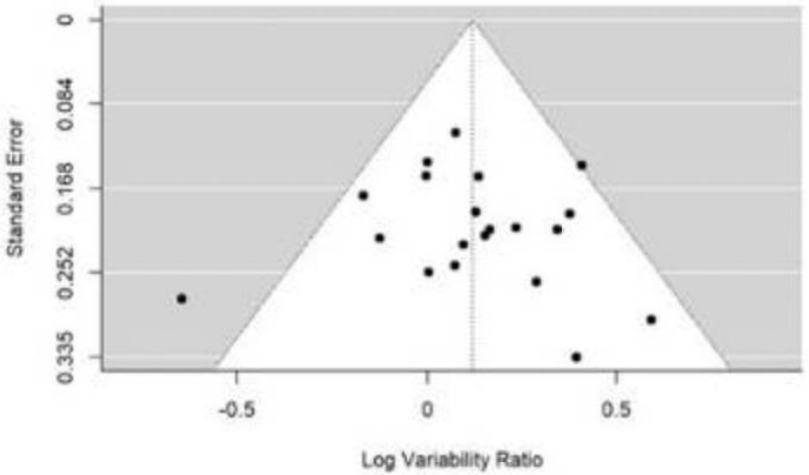
Limongi et al., *Antioxidants* 2021

Front Psychiatry. 2021; 12: 796466.
Published online 2021 Nov 30. doi: 10.3389/fpsyt.2021.796466
PMCID: PMC8669304
PMID: 34916980

Schizophrenia Increases Variability of the Central Antioxidant System: A Meta-Analysis of Variance From MRS Studies of Glutathione

Lena Palaniyappan, [1,2,3,4,*] Priyadharshini Sabesan, [1] Xuan Li, [5] and Qiang Luo [5,6]





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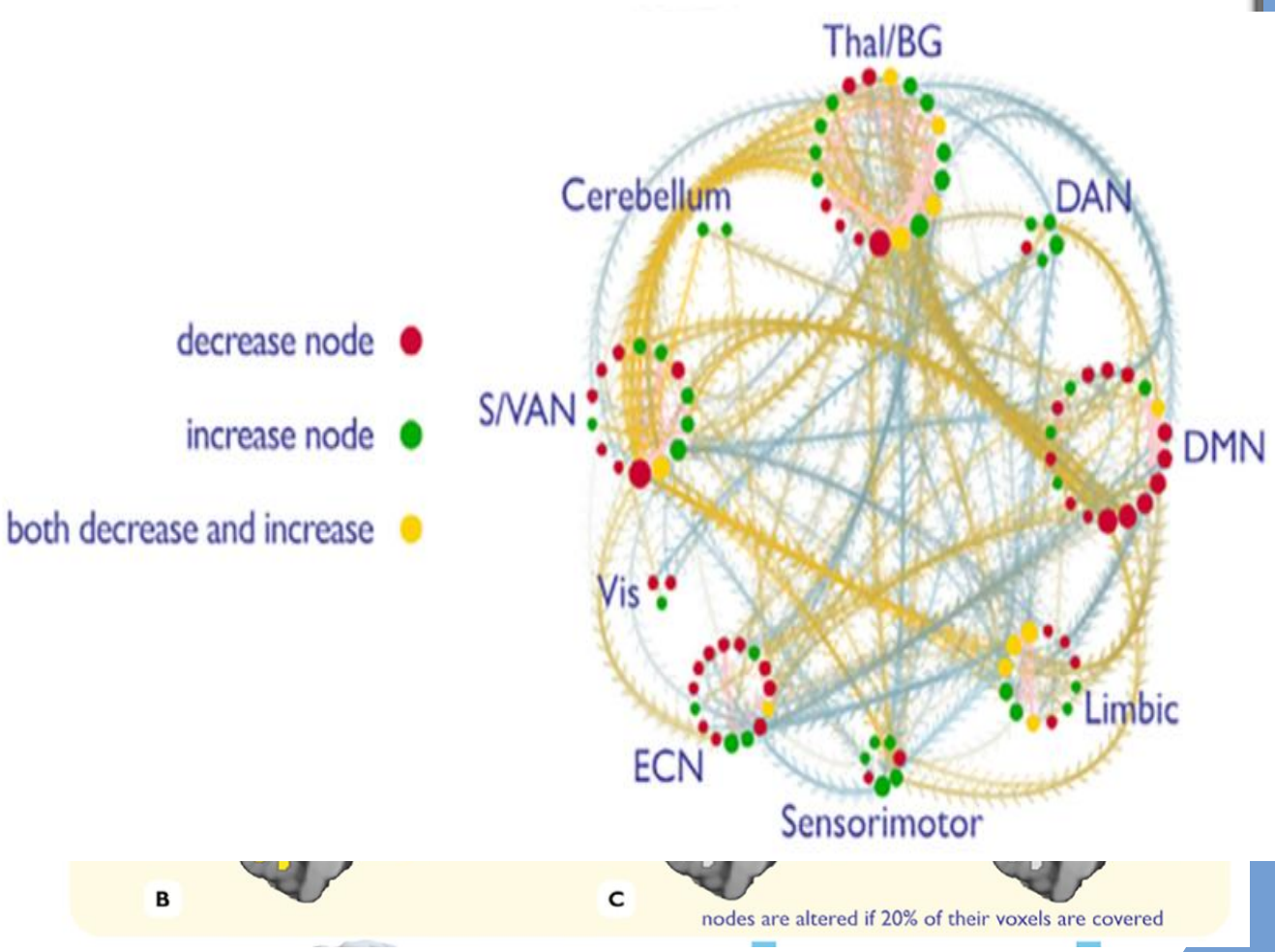
In psychiatric disorders grey mat increases and decreases are not independent

- A coordinate-based meta-analysis of 64 VBM studies in various disorders
- Estimate the probability of finding a grey matter increase or decrease in one region given an observed change in the opposite direction in another region.



Mancuso et al. Neuroimage, 2020

- **Concomitant brain changes of opposing nature occur as a rule, not exception, in psychiatric disorders**

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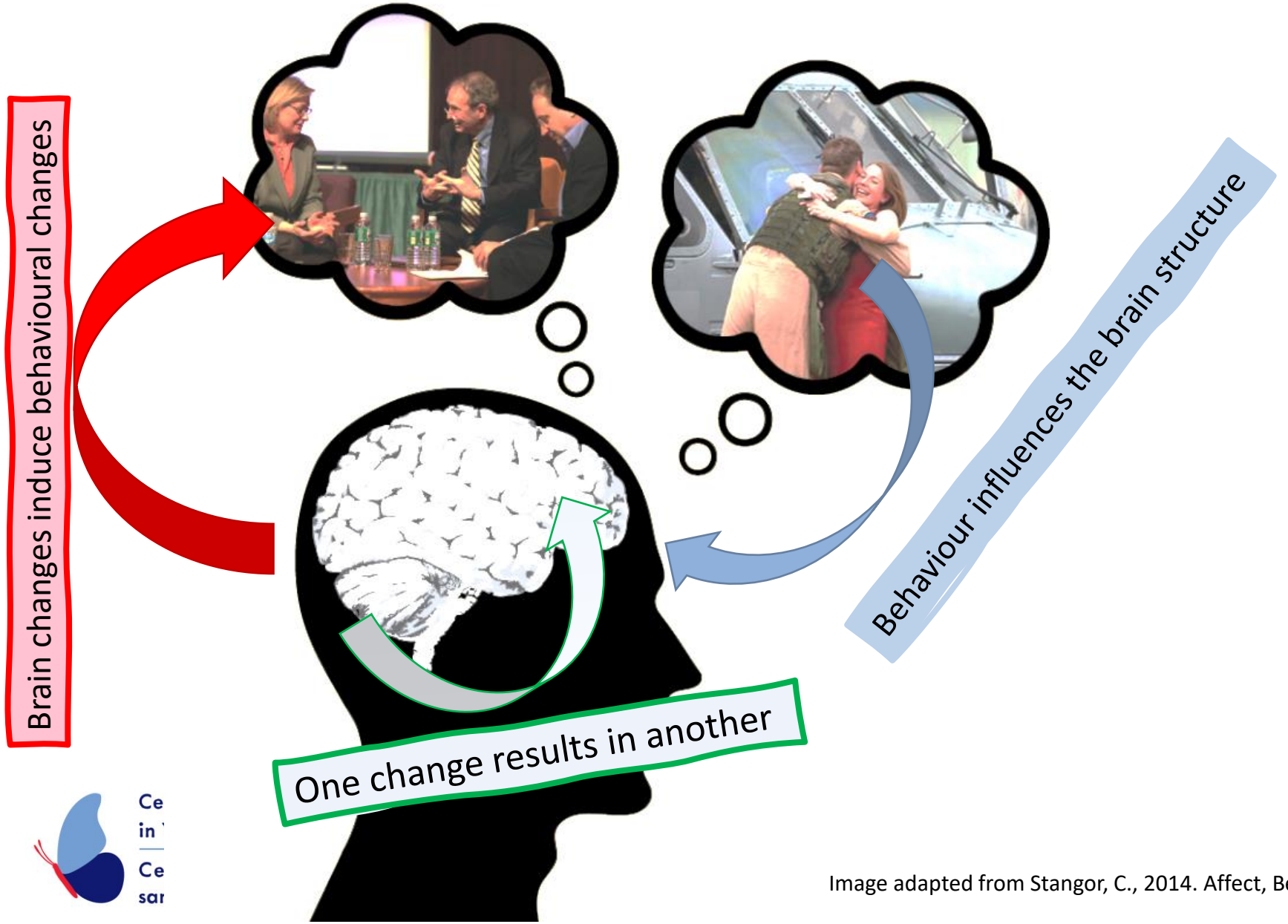
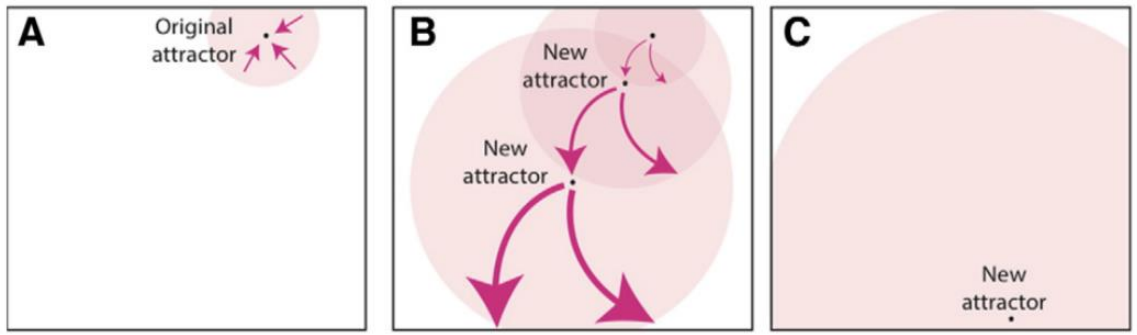


Non-causal Mechanisms

Image adapted from Stangor, C., 2014. Affect, Behavior, and Cognition. *Principles of Social Psychology*.

Physiological/neurochemical/structural changes that occur after psychosis may be an adaptive process in search of the “new normal”



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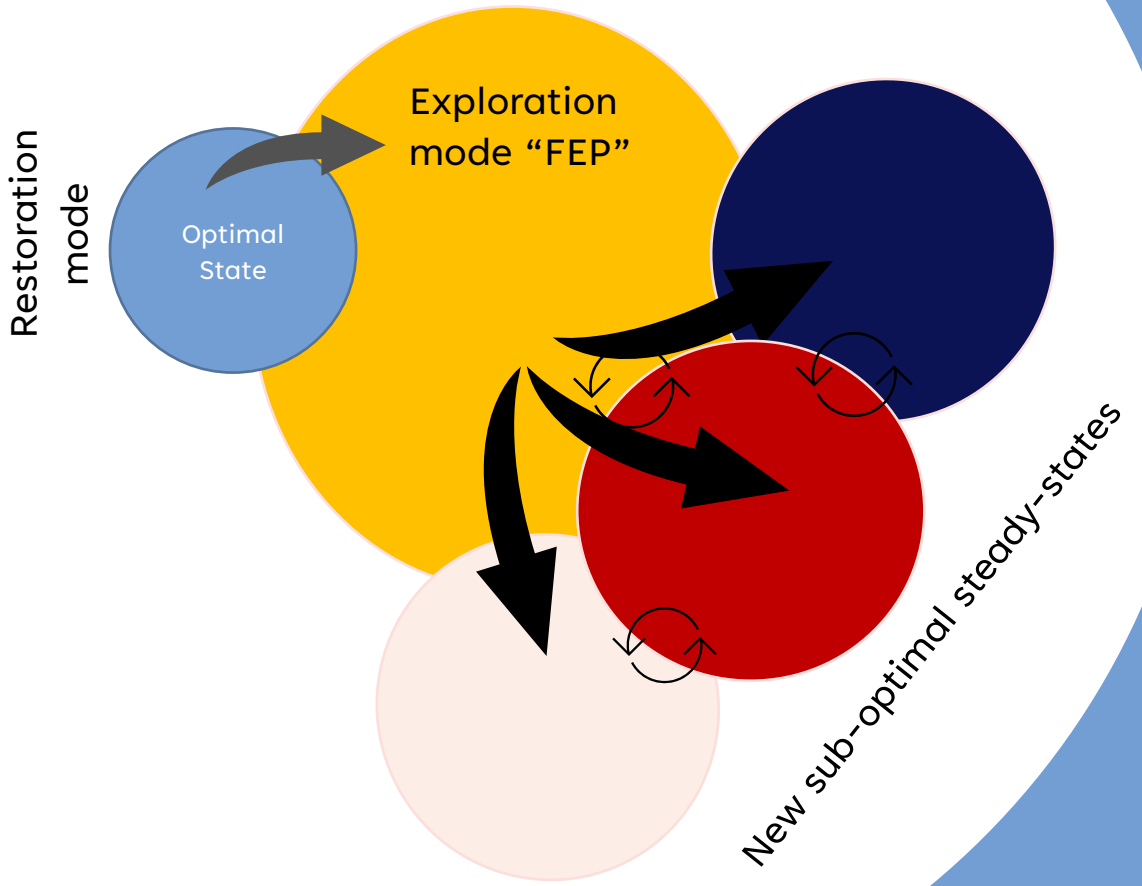
Physiology & Behavior

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

Complexity and network dynamics in physiological adaptation: An integrated view

György Baffy [a,b,*], Joseph Loscalzo [b]

[a] Department of Medicine, VA Boston Healthcare System, Boston, MA, United States
[b] Department of Medicine, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA, United States



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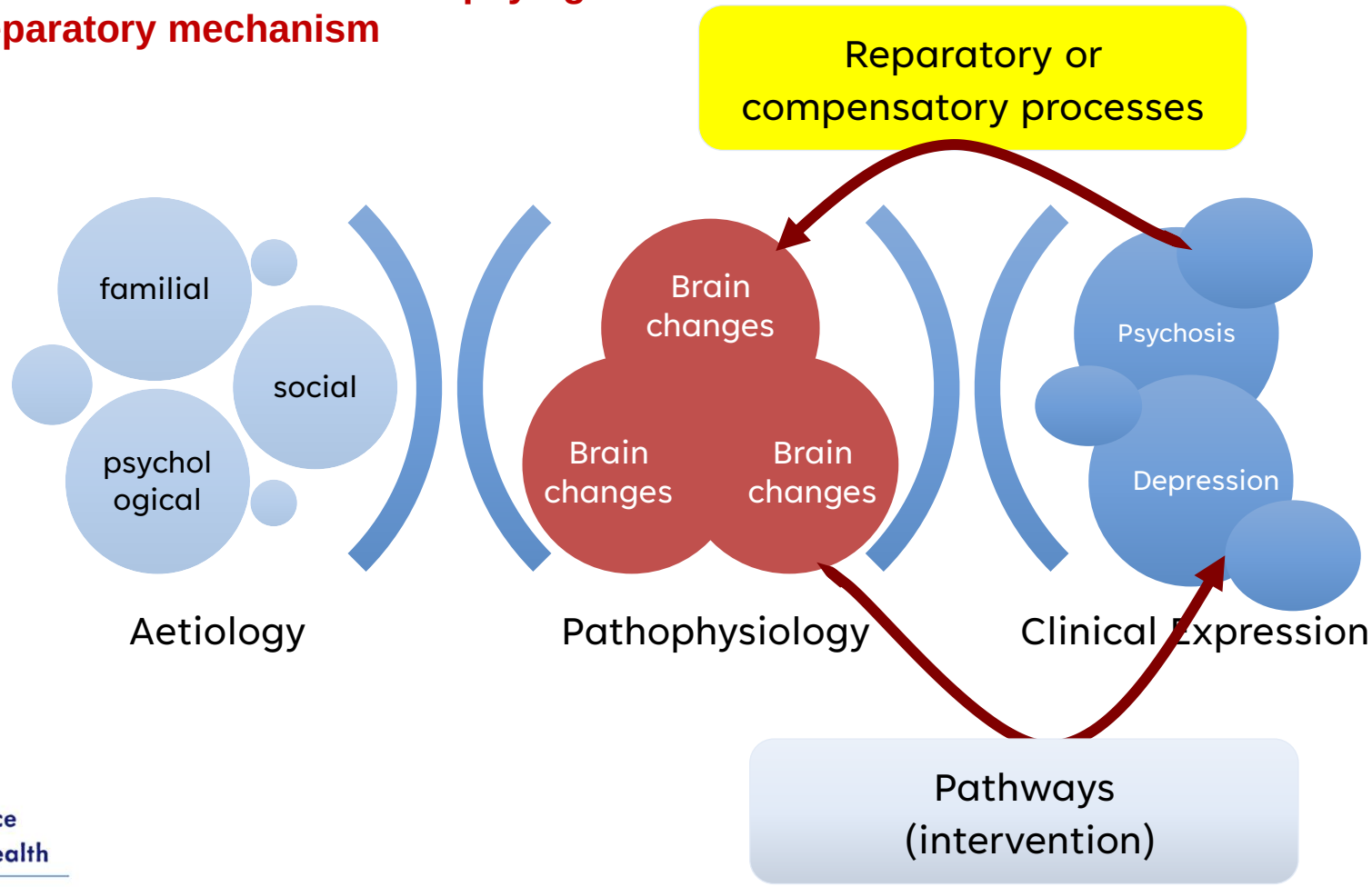
There are intrinsic compensatory defences operating for every deficit

We cannot map brain-to-behaviour without paying closer attention to this reparatory mechanism



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Brain-Behaviour Mapping

Symptoms are weak constructs; semiotic reconstruction is a ‘radar-jammer’

Speech is the “vital sign” of mental health

Adaptive changes introduce complexity in brain-behaviour mapping

Heterogeneity is best understood in the context of compensation

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