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Fundamentals of functional and effective connectivity and their applications to neurodevelopmental and mental health conditions

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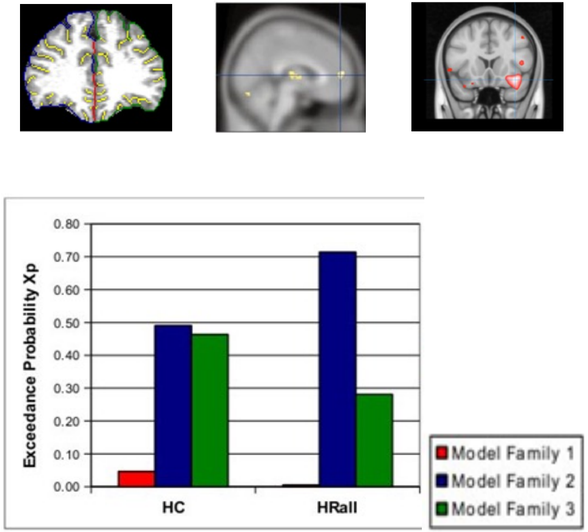
imh institute for mental health

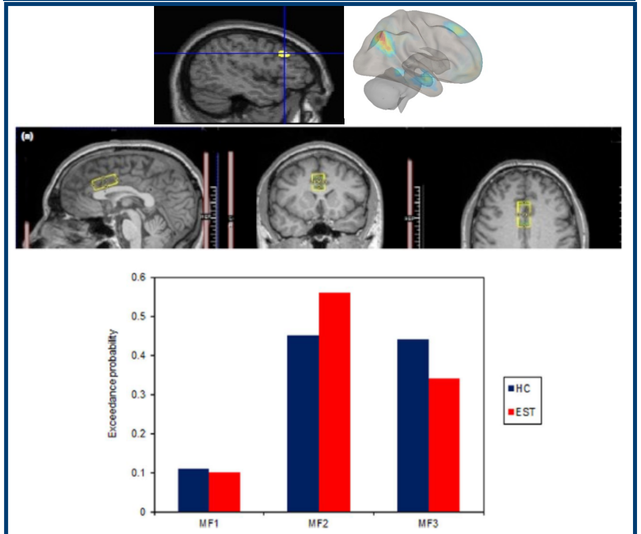
Research themes in schizophrenia

NEUROBIOLOGY - CONNECTIVITY



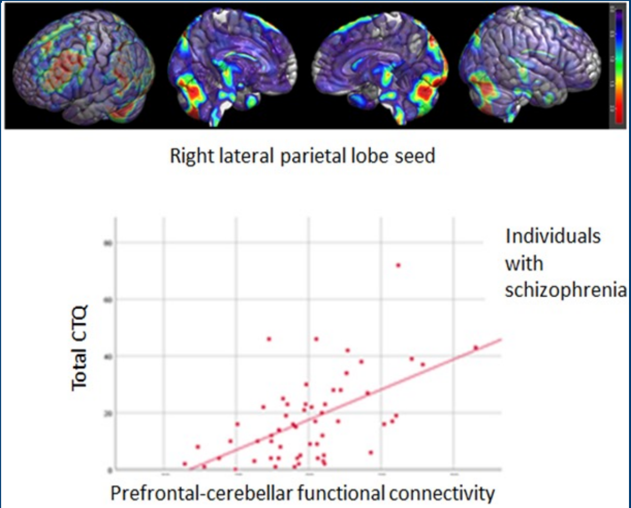
Dauvermann et al. 2012
Dauvermann et al. 2013

NEUROBIOLOGY – GLUTAMATE



Dauvermann et al. 2014; 2017a; 2017b
Corcoran, .., Dauvermann, 2020

NEUROBIOLOGY - ACUTE/CHRONIC STRESS



Dauvermann et al. 2021

Outline

- Relevance of cognitive function and functional large-scale networks
- Theoretical basis of functional connectivity
- Theoretical basis of effective connectivity
- Advantages and disadvantages of both approaches
- Discussion
- Summary

Learning objectives

By the end of this lecture, you will be able to:

- Understand the difference between functional and effective connectivity
- Consider the advantages and disadvantages of functional and effective connectivity approaches
- Critically appraise the potentials and limits of both approaches

- Is cognition important?
- Should we be worried if our cognitive performance is limited?
- Should we be worried if our cognitive performance is limited when we have a clinical diagnosis?

Relevance of cognitive function and functional large-scale networks in mental health conditions

- Psychosis
- Autism spectrum disorders

Psychosis - Background

- **Prevalence and diagnosis**
  - Approximately 0.5 - 1% or approximately 24 million people worldwide
  - Neurodevelopmental and neurobiological disorder
    - Onset typically during late adolescence or early adulthood
    - Onset tends to happen earlier among men than women

Ride et al. 2020

Psychosis - Background

- **Symptoms**
  - Positive symptoms (i.e., hallucination, delusions)
  - Negative symptoms (i.e., alogia)
  - Cognitive deficits (i.e., verbal memory, working memory, emotion recognition)
  - Some individuals are at ultra-high risk and about 22% of UHR individuals will transition to a psychotic disorder.
  - Already prior to diagnosis, cognitive deficits can occur, which are also prevalent with illness progression and are associated social disability.

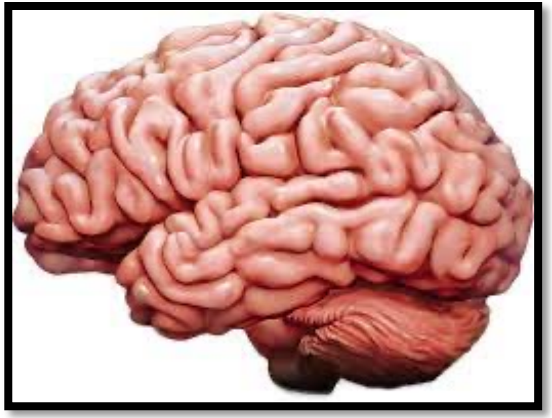
Dauvermann and Donohoe, 2019
Quidé et al. 2020
Fusar-Poli et al. 2020

Characteristics of cognitive function/deficits between individuals in schizophrenia and autism spectrum disorders

Clinical and cognitive symptoms

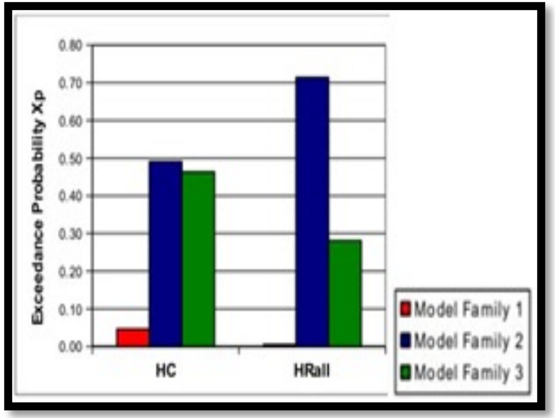
- Clinical symptoms
- Cognitive deficits

Neurobiological markers



- Lower surface area
- Lower cortical thickness
- Smaller volumes

Functional networks



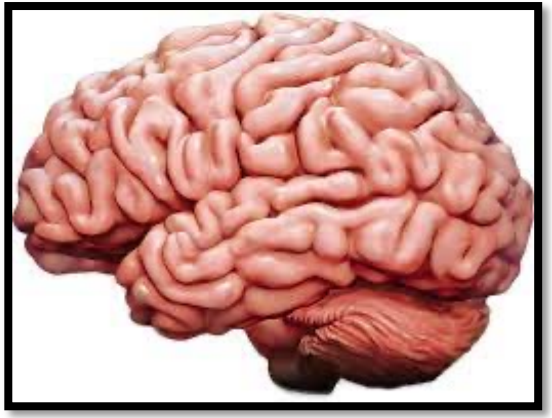
- Altered functional and effective connectivity

Characteristics of cognitive function/deficits between individuals in schizophrenia and autism spectrum disorders

Clinical and cognitive symptoms

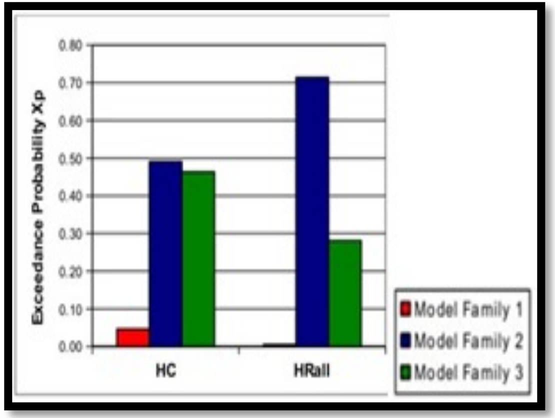
- Clinical symptoms
- Cognitive deficits

Neurobiological markers

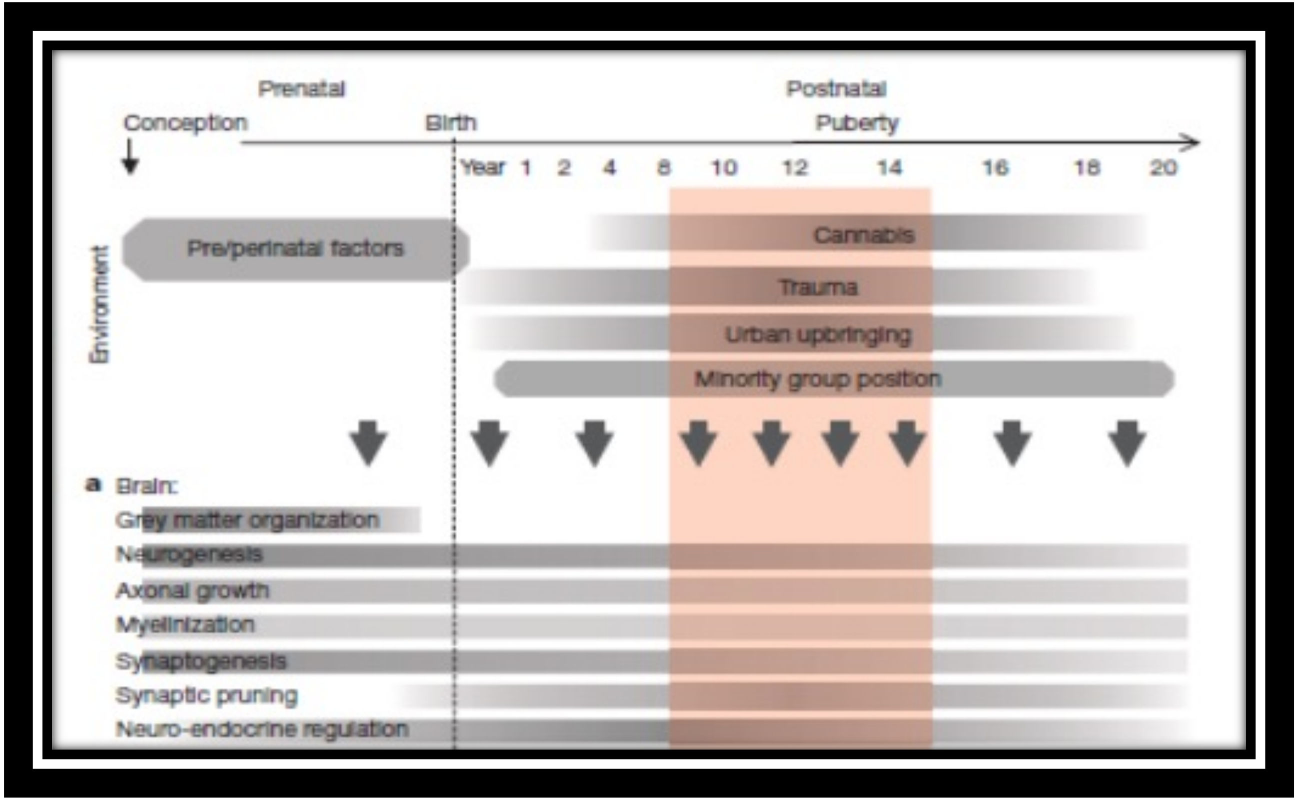


- **Lower** surface area
- **Lower** cortical thickness
- **Smaller** volumes

Functional networks



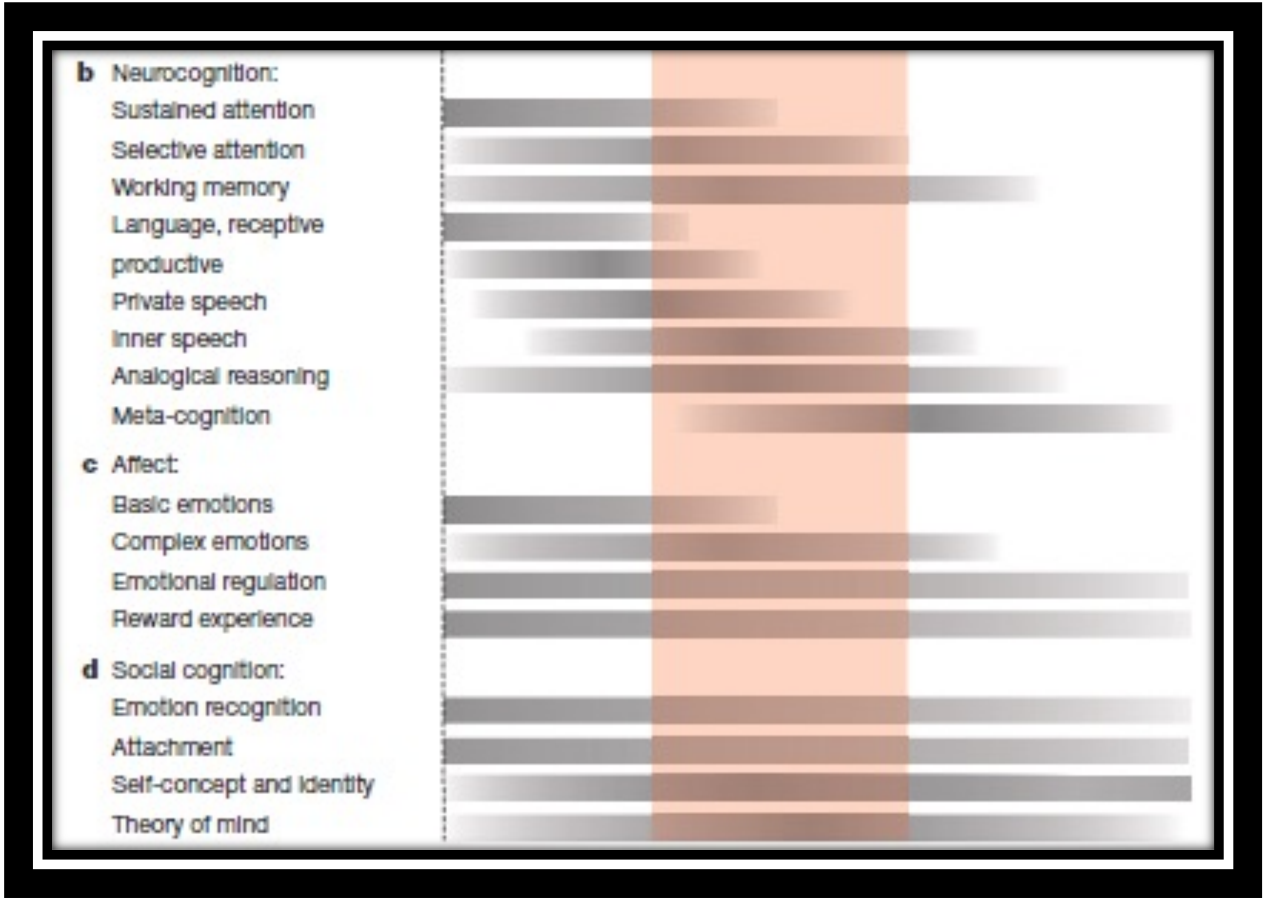
- **Altered** functional and effective connectivity



Environmental and biological risk factors in psychosis

Approximate timing of the development of the human brain, functional abilities, and impact of environmental exposures

van Os et al. 2010



Approximate timing of the development of the human brain, functional abilities, and impact of environmental exposures

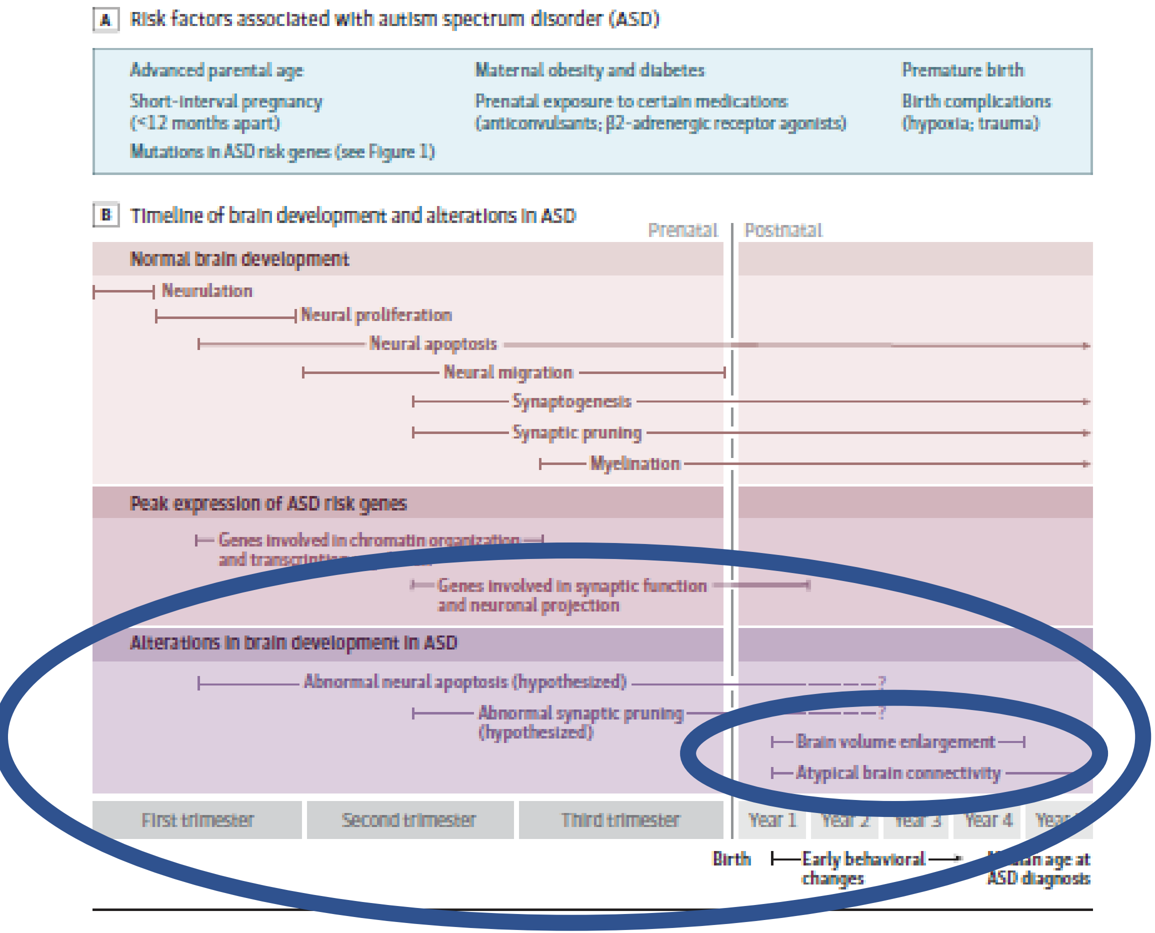
Impacting on psychological and cognitive factors

van Os et al. 2010

Autism spectrum disorders (ASD) - Background

- **Prevalence**
  - Approximately 1% or more than 5.5 million individuals in the EU
  - Occurs across all populations
  - Gender ratio: 4:1 – male to female
- **Diagnosis**
  - Neurodevelopmental diagnosis
    - Diagnosis at the age of two or three years of age -> adulthood
    - Symptoms linked to abnormalities during brain development
    - Expression of symptoms varies with age and developmental level of person
    - Neurobiological disorder

Masi et al. 2017
Shen and Piven, 2017
Lord et al. 2020



Neuro-development

Development of neurological and neurobiological pathways underlying typical functioning of motor, cognitive and social abilities

Deviations from typical development may lead to:

- Structural and functional brain alterations
- Behavioural changes

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Neurodevelopmental disorders

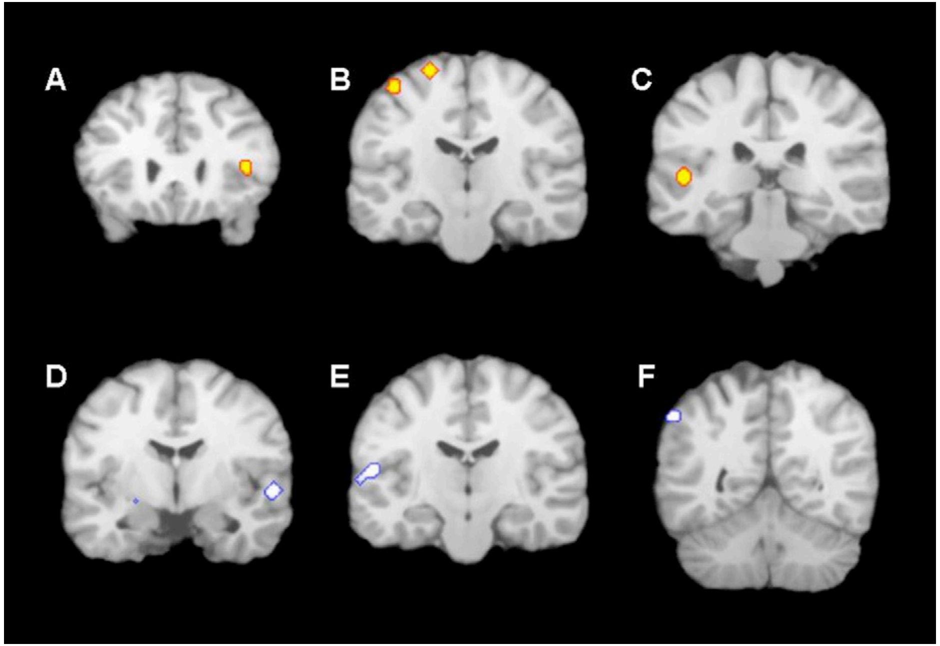
Muhle et al. 2018

Disrupted functional brain networks

- Disrupted functional networks may underlie clinical symptoms and cognitive impairments in neurodevelopmental disorders, including ASD
- Alterations of brain function and connectivity during social tasks, such as emotion recognition
- General finding across studies: Lack of preference for social stimuli in individuals with ASD

Dauvermann et al. 2014; 2017a/b
Corcoran, .. Dauvermann, 2020
Siegel-Ramsay, .., Dauvermann, 2020

‘Social brain network’



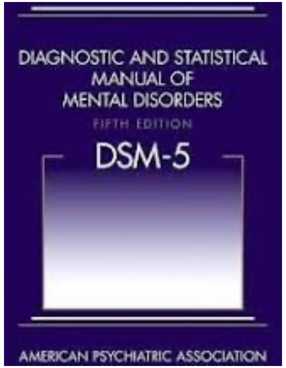
Top. Greater probability of activation (ASD > HC) in right IFG, left pre/post-central gyrus and left STG.
Bottom. Reduced probability of activation (ASD > HC) in right STS, left STG and left IPL.

Themes across task domains

- Influence of specific task and stimuli demands
- Lack of modulation in response to task/stimuli demands
- Age- and gender related changes

Philip, Dauvermann et al. 2012

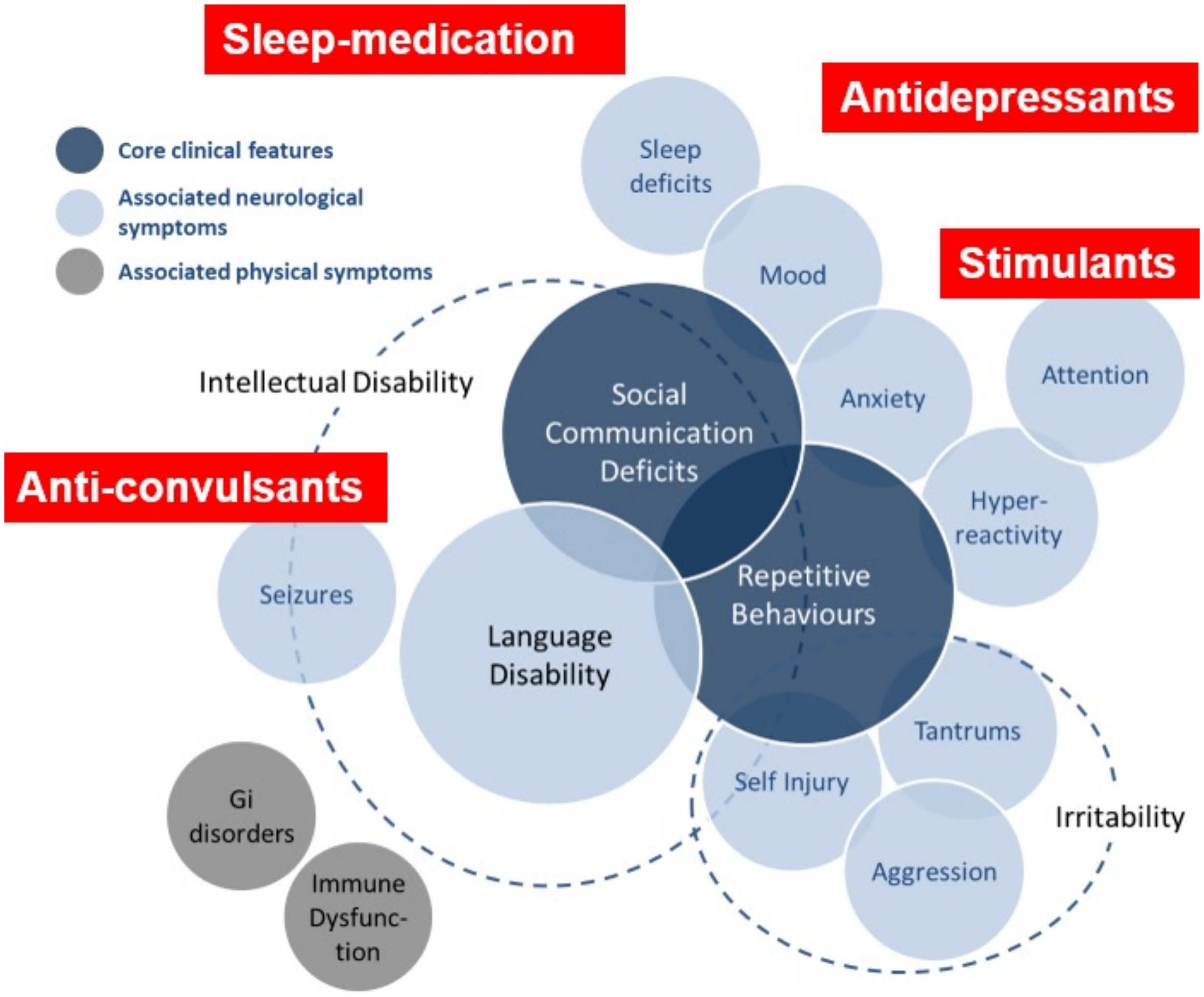
Diagnostic and Statistical Manual of Mental Disorders (DSM–5)



RRBIs - Restricted and repetitive behavioural interests

DSM-IV	DSM-5
<u>Three areas of impairment:</u> 1. Social interaction 2. Communication 3. RRBIs	<u>Reduced to two main areas:</u> 1. Social comm. & interaction 2. RRBIs
Sensory behaviours not included	Sensory behaviours included
Symptoms begin prior to 3 years of age	Symptoms begin in early childhood BUT symptoms may not manifest until social demands exceed capacity
No indication of severity as part of diagnosis	'Dimensional Levels of Severity' (level of support required)
No inclusion of 'specifiers'	Inclusion of 'specifiers' e.g. with/without intellectual impairment

American Psychiatric Association, 2013

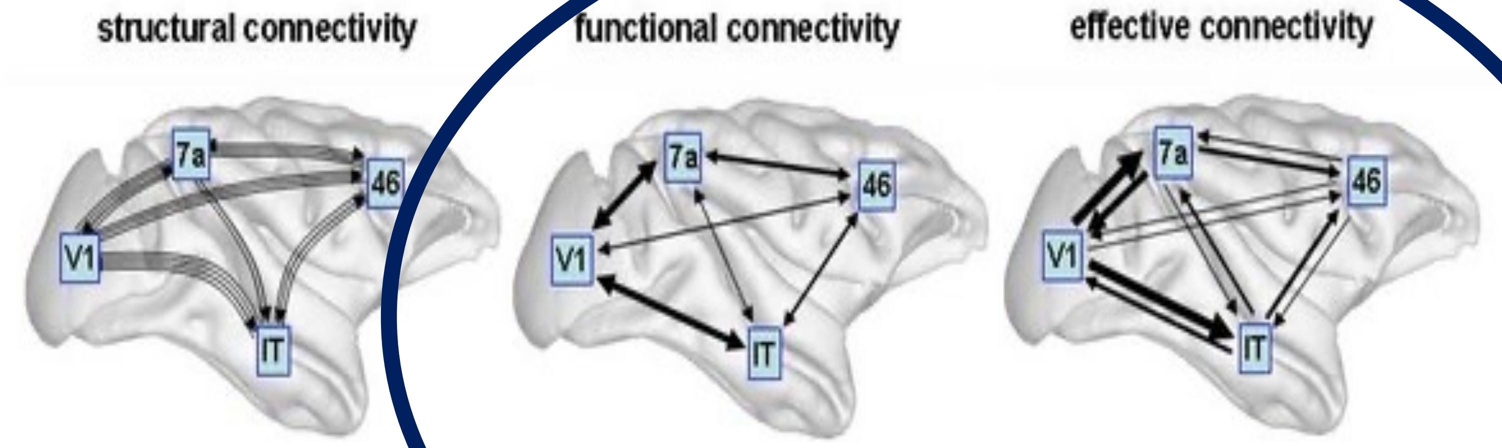


AIMS-2-Trials

Theoretical basis of functional connectivity
- Examples for application

- fMRI, EEG, MEG
- Psychosis
- Autism spectrum disorders

Functional neuroimaging with computational modelling



Structural (synaptic) connections linking sets of neurons or neuronal elements

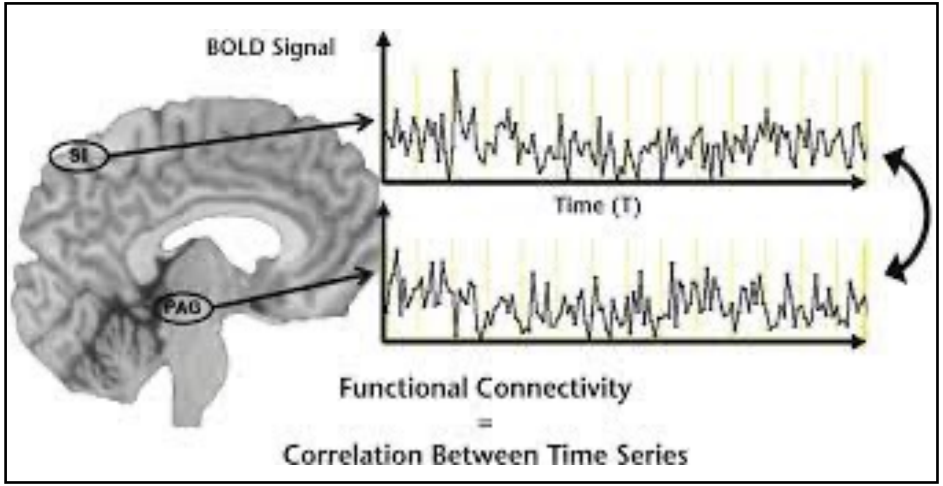
Statistical association or dependency between two or more anatomically distinct time-series

Causal (directed) influences between neurones or neuronal populations

Sporns, 2007

Functional connectivity

Definition: Statistical associations or dependencies between regional time series

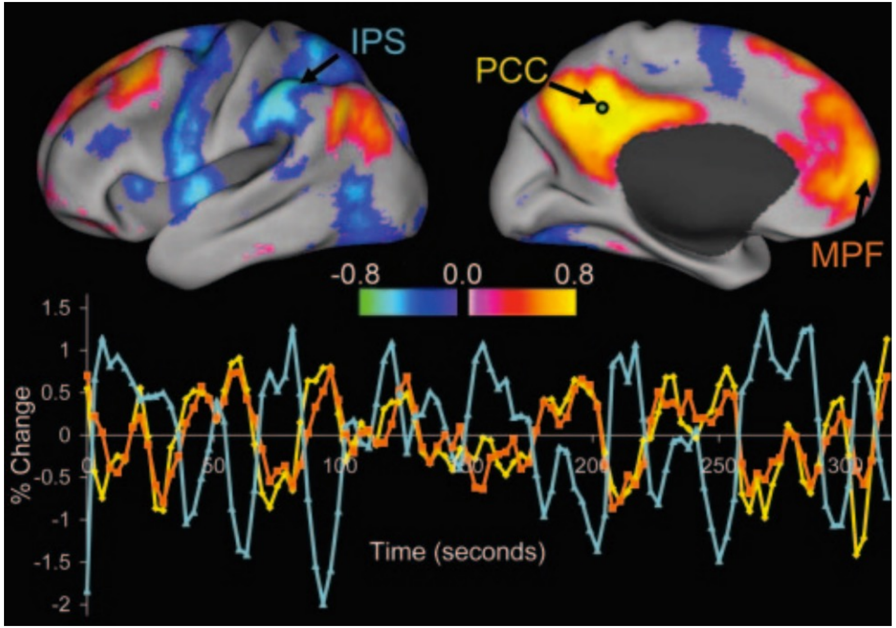


Extraction of reference of time series

Voxel-wise correlation with time series from other voxels in the brain

Friston, 2003
Fox, 2005

Functional connectivity



- Occurs during task and at rest
- Resting-state networks
  - Correlation between spontaneous BOLD signals of brain regions known to be functionally and/or structurally related
- Default mode network (DMN)
  - Decreased activity during cognitive tasks
  - Inversely related to regions activated by cognitive tasks
- Task-positive and task-negative networks

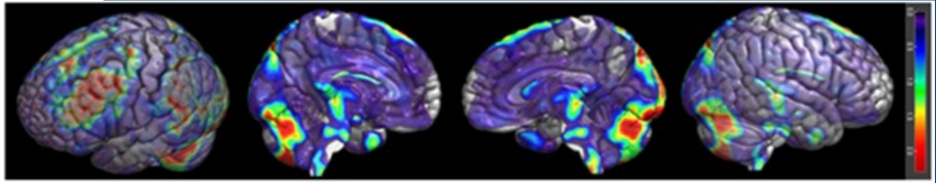
Fox et al. 2007

Functional connectivity approaches

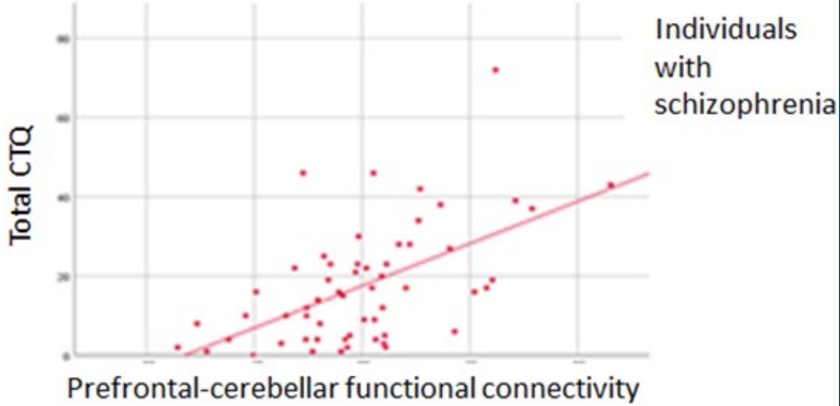
- Model-dependent method - *A priori* or hypothesis-driven from previous literature
- Model-free method – Data-driven method

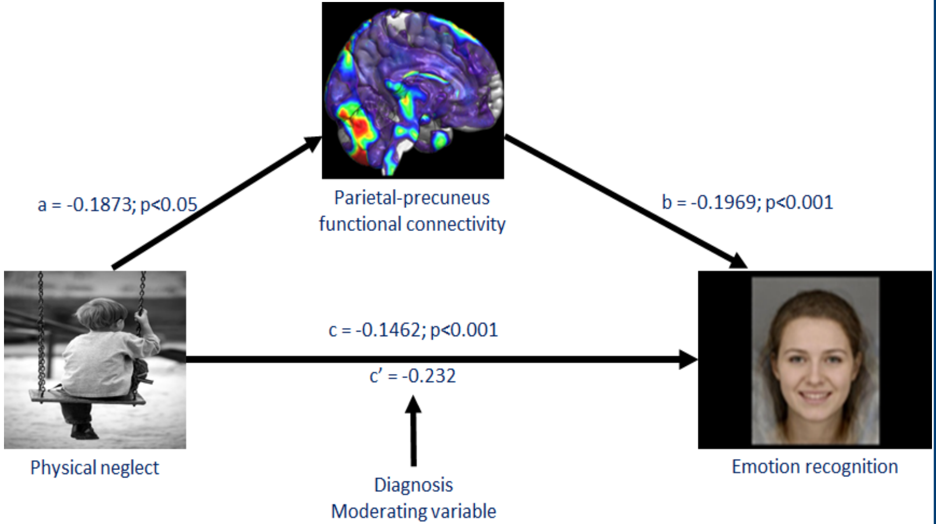
  - Seed-based functional connectivity analysis
  - Coherence analysis (EEG)
  - Eigen-composition (i.e., Principal Component Analysis)
  - Independent Component Analysis

CHILDHOOD ADVERSITY AND RESTING-STATE FUNCTIONAL CONNECTIVITY



Right lateral parietal lobe seed





Dauvermann et al. 2021

Combination of functional connectivity with glutamate levels

- It is not known of **how** altered glutamatergic systems may disrupt functional connectivity during resting-state fMRI in individuals with ASD

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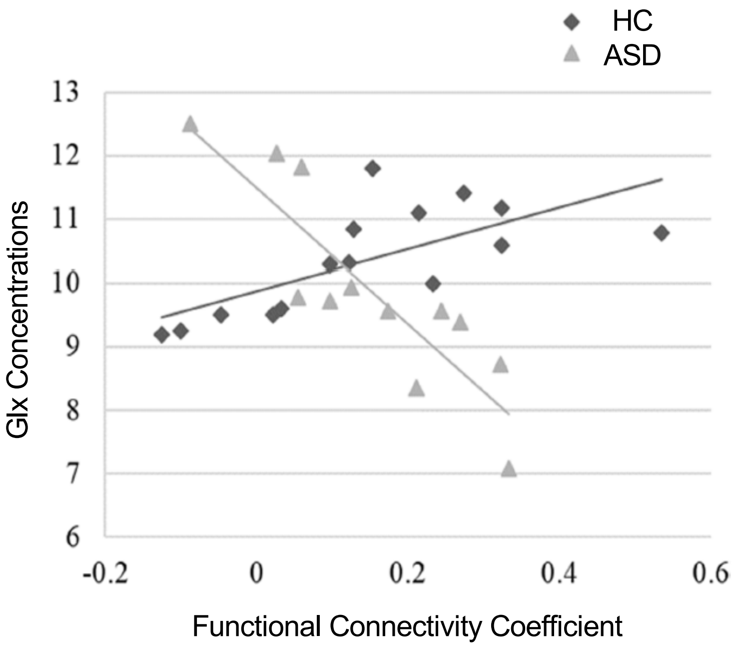
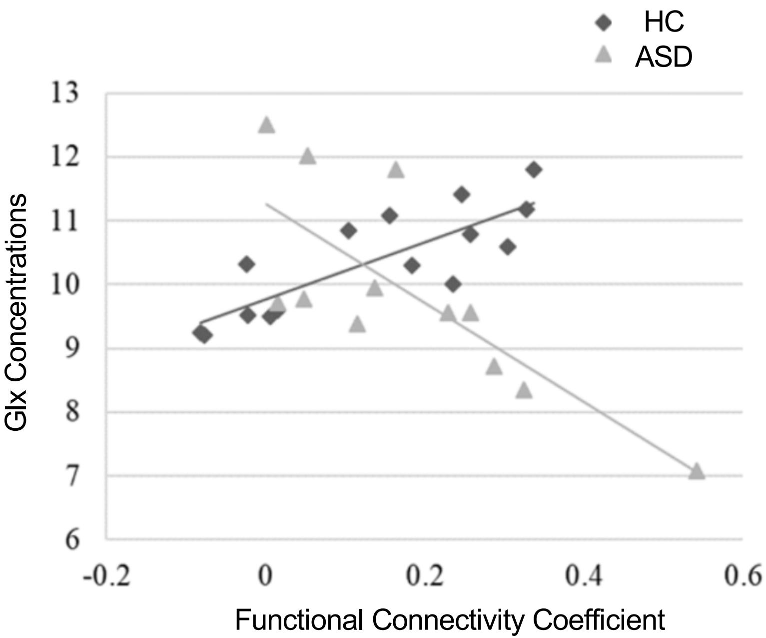
- Integration of studying glutamatergic dysregulation via the utilization of Proton Magnetic Resonance Spectroscopy (1H-MRS) and functional connectivity of resting-state fMRI data
- Study of the excitatory-inhibitory imbalance theory non-invasively and *in vivo* in humans

Glutamate levels and resting-state functional connectivity



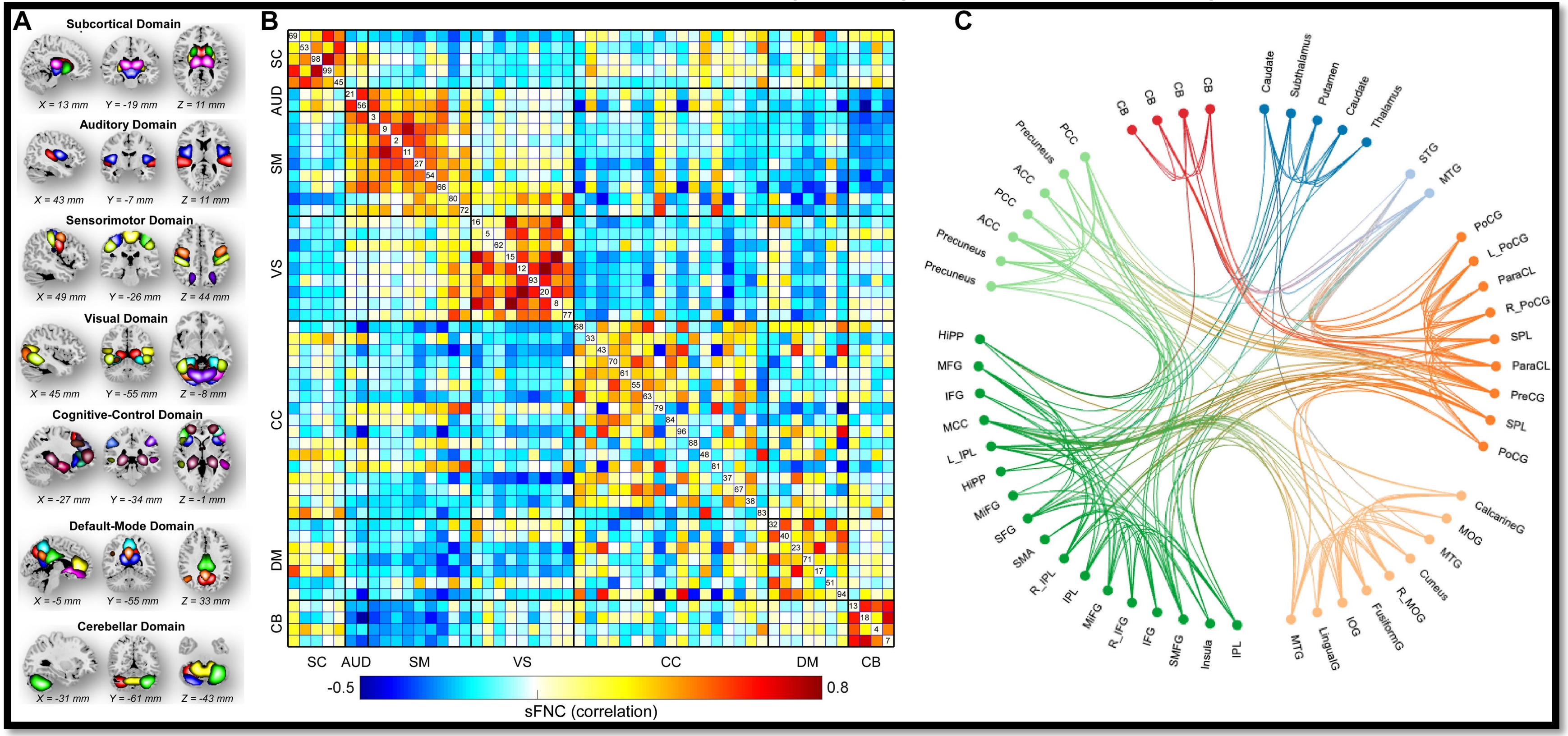
Right dorsal ACC and the right insular cortex (x = 34, y = -17, z = 20; k = 271, *T* =5.65; *Z* = 4.43; *p* < 0.001



Left dorsal ACC and the right insular cortex (x =28, y = -7, z = 20; k = 2420, *t* =6.31; *Z* = 4.76; *p* < 0.001

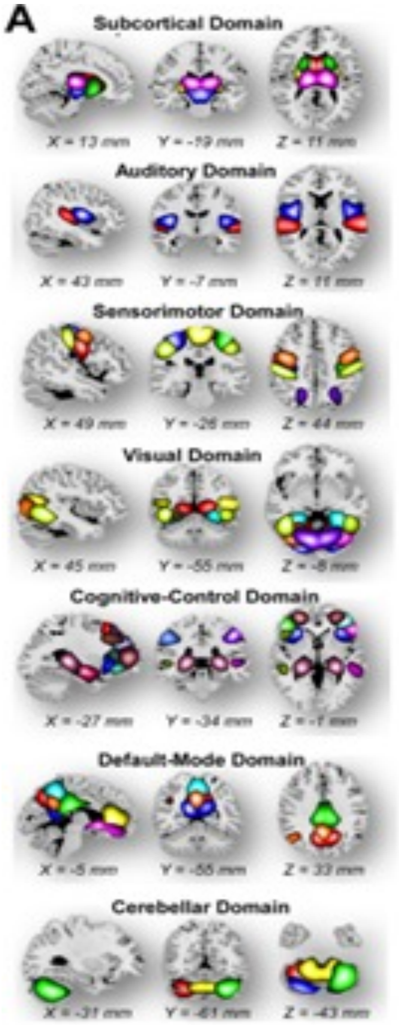
Siegel-Ramsay, .., Dauvermann, 2020

Functional connectivity (spatial maps) - EEG



Whole-Brain Functional Network Connectivity Abnormalities in Affective and Non-Affective Early Phase Psychosis

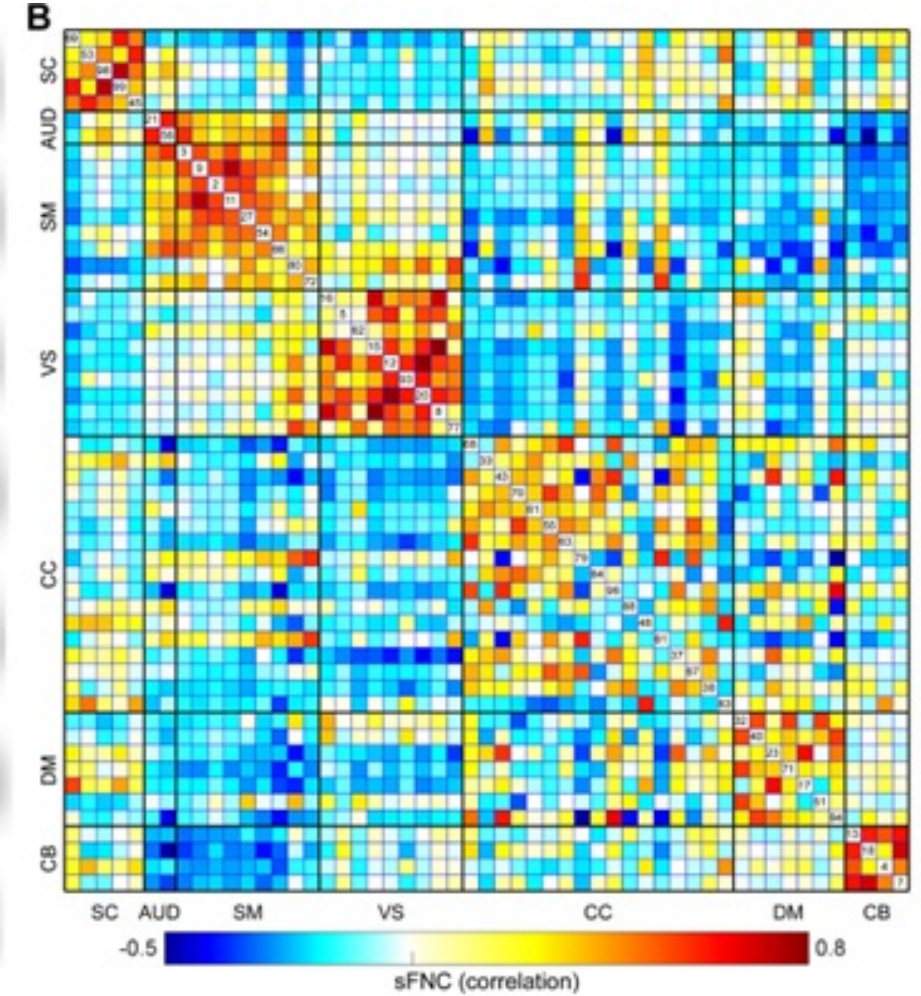
Fu et al. 2021



Spatial maps of the identified intrinsic connectivity networks and spatial functional network connectivity

53 ICNs were identified and sorted into seven resting-state functional domains. Each colour represents a single intrinsic connectivity network

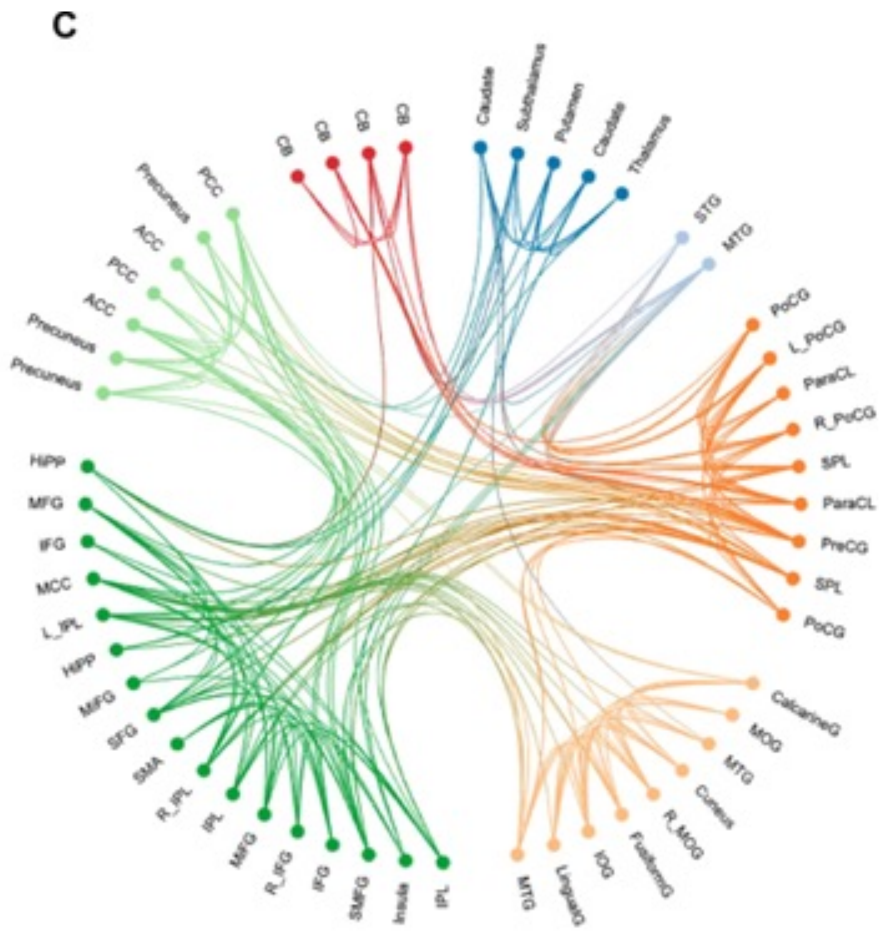
Fu et al. 2021



Spatial maps of the identified intrinsic connectivity networks and spatial functional network connectivity

Averaged spatial functional network connectivity matrix across participants.

Fu et al. 2021



Spatial maps of the identified intrinsic connectivity networks and spatial functional network connectivity

The functional connectivity profile of the averaged spatial functional network connectivity matrix.

Fu et al. 2021

Altered neural oscillations and synchrony in schizophrenia - MEG

Uhlhaas and Singer, 2010

Table 1 | **Neural oscillations in cortical networks**

Frequency band	Anatomy	Function
Theta (4–7 Hz)	Hippocampus[134], sensory cortex[140] and prefrontal cortex[141]	Memory[142,143], synaptic plasticity[18], top-down control[9] and long-range synchronization[9]
Alpha (8–12 Hz)	Thalamus[144], hippocampus[145], reticular formation[145], sensory cortex[146] and motor cortex[147]	Inhibition[148], attention[149], consciousness[150], top-down control[9] and long-range synchronization[151]
Beta (13–30 Hz)	All cortical structures, subthalamic nucleus[152], basal ganglia[152] and olfactory bulb[153]	Sensory gating[154], attention[155], motor control[156] and long-range synchronization[157]
Gamma (30–200 Hz)	All brain structures, retina[158] and olfactory bulb[159]	Perception[7], attention[160], memory[161], consciousness[162] and synaptic plasticity[16]

- Neural oscillations and their synchronisation may be core pathophysiological mechanisms in schizophrenia

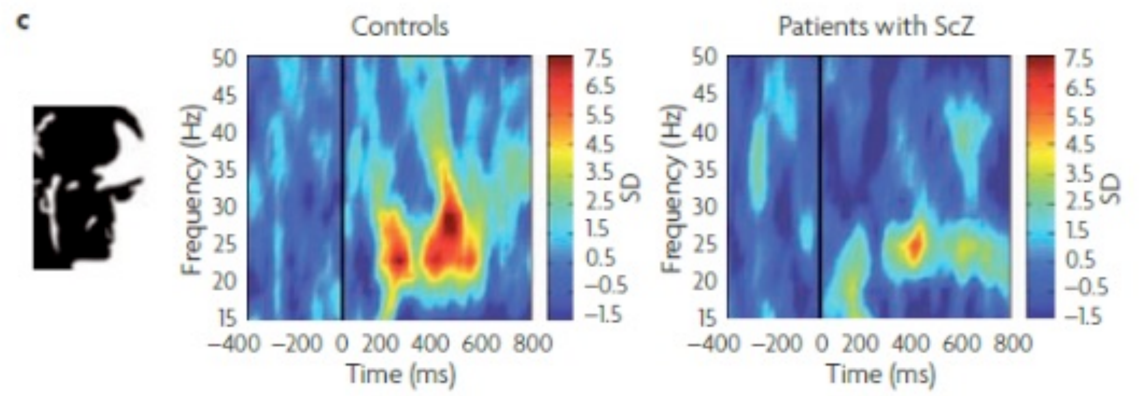
Altered neural oscillations and synchrony in schizophrenia - MEG

Uhlhaas and Singer, 2010

Beta (13–30 Hz)	All cortical structures, subthalamic nucleus[152], basal ganglia[152] and olfactory bulb[153]	Sensory gating[154], attention[155], motor control[156] and long-range synchronization[157]
Gamma (30–200 Hz)	All brain structures, retina[158] and olfactory bulb[159]	Perception[7], attention[160], memory[161], consciousness[162] and synaptic plasticity[18]

- Associated with deficits in neural oscillations, especially in the beta- and gamma-band frequencies
- Dysfunctions in neural synchrony could result from deficits in GABA (γ-aminobutyric acid)-ergic neurotransmission and the reduced integrity of cortico-cortical connections
- Neural oscillations are involved in the maturation of cortical networks during early and late critical periods

Altered neural oscillations and synchrony in schizophrenia -MEG



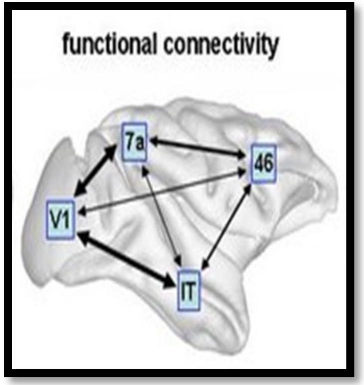
Dysfunctional phase synchrony during Gestalt perception in schizophrenia

- Mooney faces presented in an upright and inverted orientation
- Participants indicate whether a face was perceived
- Average phase synchrony (indicated by the coloured scale) over time for all electrodes
- In individuals with schizophrenia, phase synchrony between 200-300 ms was significantly reduced relative to controls.

Uhlhaas and Singer, 2010


TIME FOR A
BREAK

Functional connectivity



Advantages

- No experimental control (i.e., resting-state but also useful for tasks)
  - Free from experimental confounds
  - Possible to scan participants who would find it difficult to complete a task
  - No model of what caused the data (i.e., sleep or hallucinations)

Disadvantages

- Interpretation of findings is based on correlations; descriptive
- No mechanistic insight
- Typically, dissatisfying for experimental tasks
- Typically, suboptimal for experiments with *a priori* knowledge

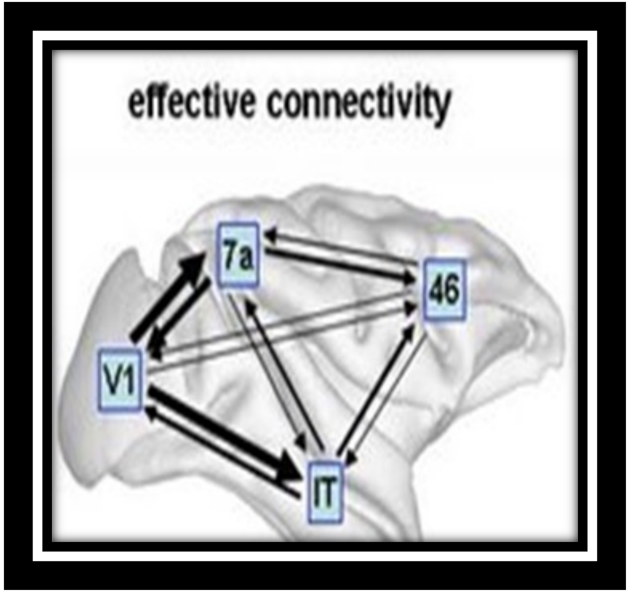
Theoretical basis of effective connectivity
- Examples for application

- fMRI, EEG, MEG
- Psychosis

Effective connectivity

- Definition: Causal (directed) influences between neurons or neuronal populations

- Models of causal interactions among neuronal populations with the aim of indirectly inferring on regional effects of inter-regional connectivity



Objectives for effective connectivity

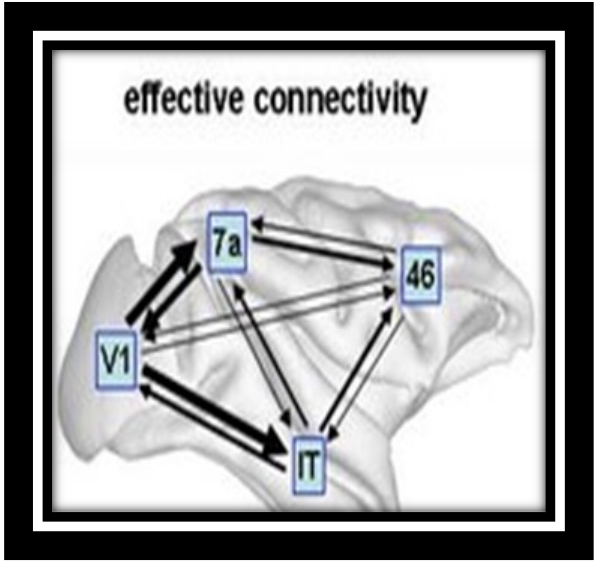
Disadvantages from functional connectivity

- Interpretation of findings is based on correlations; descriptive
- No mechanistic insight
- Typically, dissatisfying for experimental tasks
- Typically, suboptimal for experiments with *a priori* knowledge

Advantages to effective connectivity

- To analyse neural function on a network level
- To infer neurobiological mechanisms underlying cognitive function
- To infer causal or mechanistic function
- To infer experimental modulation
- To bridge the gap between rodent work and human work

Effective connectivity approaches



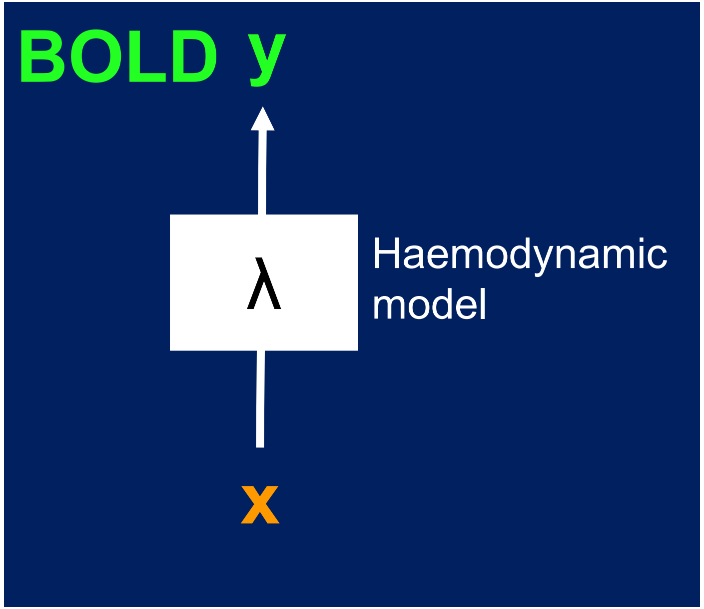
- Structural Equation Modelling
  - (McIntosh et al., 1994; Büchel and Friston, 1997)
- Regression models (Psychophysiological models)
  - (Friston et al., 1997)
- Volterra kernels
- (Friston et al., 2000) Time series models (Granger causality)
  - (Goebel et al., 2003)
- Dynamic Causal Modelling (DCM)
  - (Friston et al., 2003; Stephan et al., 2008)

Dynamic Causal Modelling (DCM)

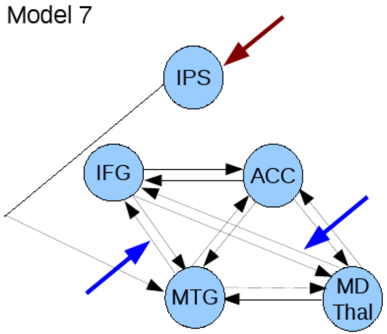
- fMRI, EEG, MEG
- Psychosis

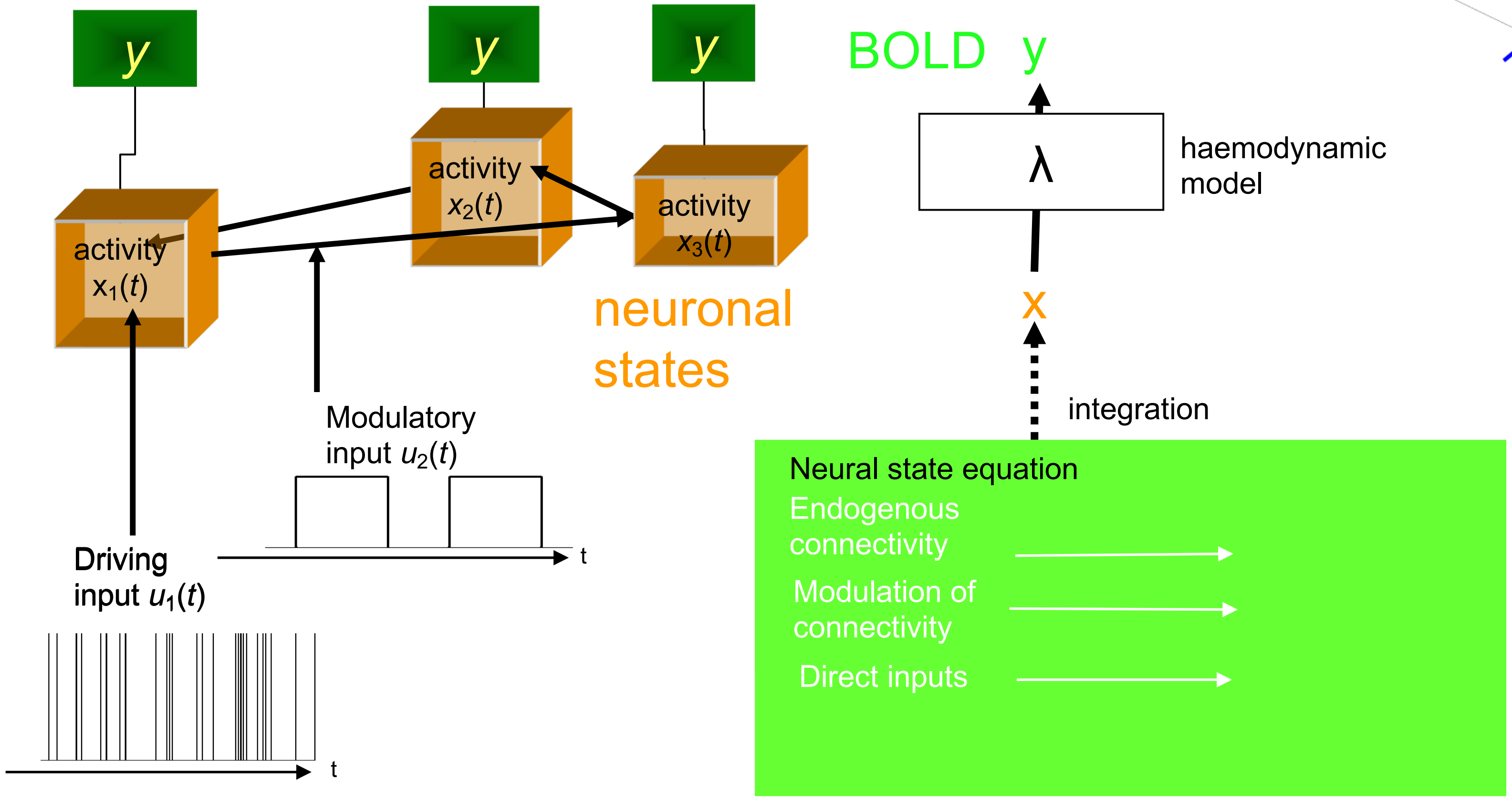
Basic Idea of DCM

- Cognitive function is measured and modelled at the neural level.
- The modelled neural dynamics (x) are transformed into area-specific BOLD signals (y) by a haemodynamic forward model (λ).
- Aim: To estimate the parameters of a neural model, such that the predicted/modelled BOLD responses correspond as closely as possible to the observed/measured BOLD responses



Activity-dependent changes of neural function





Edinburgh High Risk Study (EHRS)

- Familial risk of schizophrenia
  - At least two first-degree relatives with schizophrenia
- Healthy controls
  - No family history of schizophrenia or personal history of a serious psychiatric disorder
- Age between 16 and 25 years

HC	Healthy controls
HR	High risk subjects
HR-	High risk subjects without symptoms
HR+	High risk subjects with symptoms
4 ill	Four ill subjects with schizophrenia

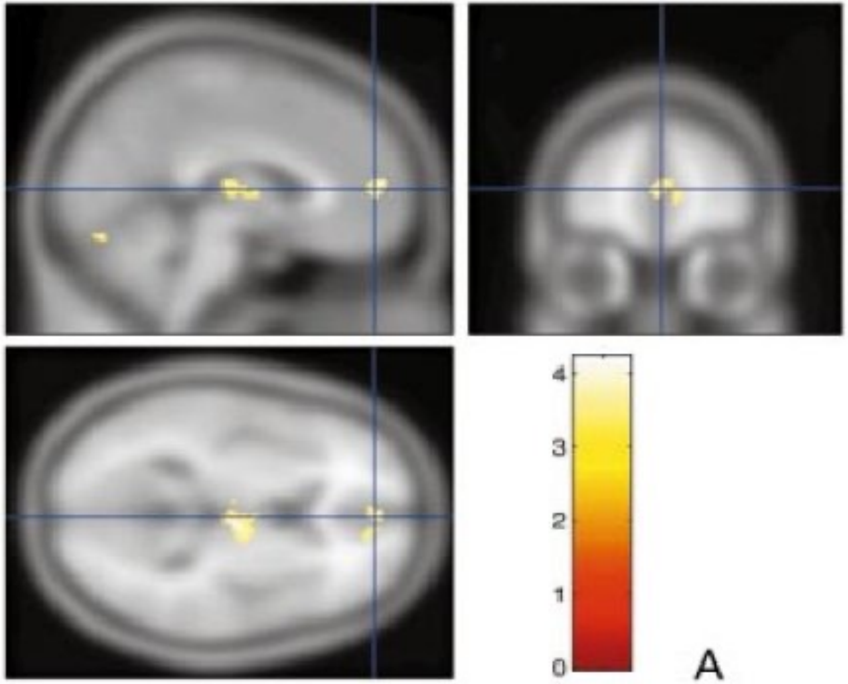
Byrne et al. 1999
Johnstone et al. 2000

Verbal fluency task – Hayling Sentence Completion Task

<u>Examples</u>

‘He mailed the letter without a … .’

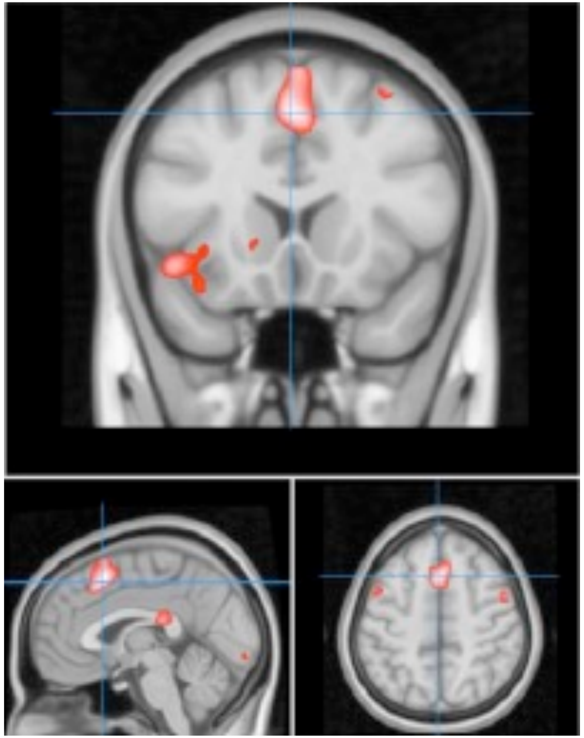
‘Rushing out he forgot to take his … .’

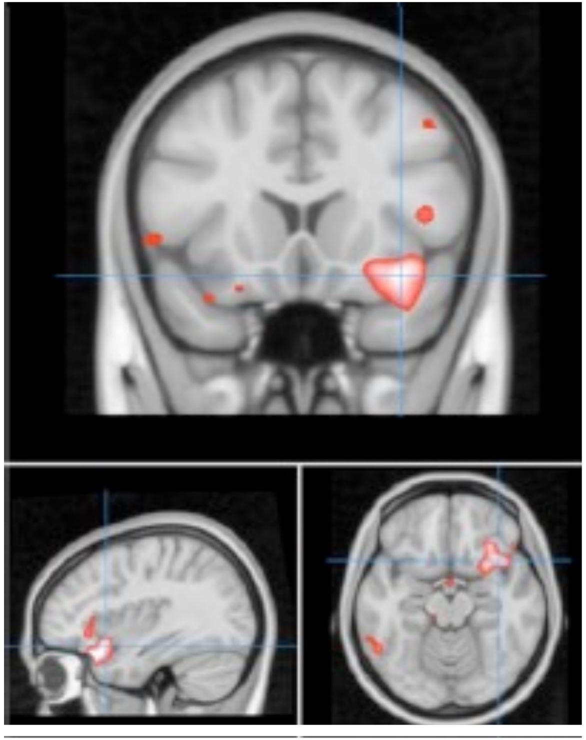


Maps thresholded at $P < 0.001$ uncorrected voxel level, extent threshold 100 voxels.

Whalley et al. 2004

Functional Connectivity





Left:
Reduced lateral-medial prefrontal FC in HR in contrast to HC

Right:
Reduced prefrontal-thalamic FC in HR in contrast to HC

HC	Healthy controls
HR	High risk subjects
HR-	High risk subjects without symptoms
HR+	High risk subjects with symptoms
4 ill	Four ill subjects with schizophrenia

Maps thresholded at *T* >=2.5, *P*<0.05 corrected for multiple comparison, minimum cluster size 50 voxels.

Whalley et al. 2005

Prefrontal Gyrification Index

Cortical folding

- Developmental process by which outgrowth of the cortex leads to sulcal and gyral patterning

Gyrification Index

- Measurement of cortical folding
- Ratio of the entire cortical contour of the brain to the superficially exposed contour

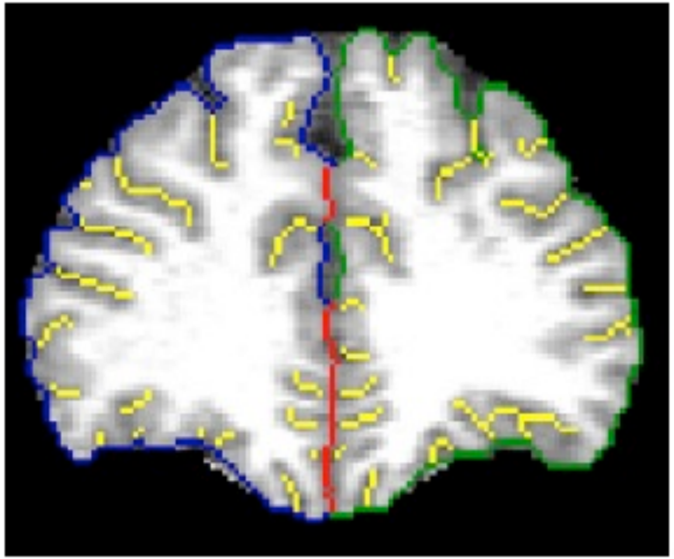
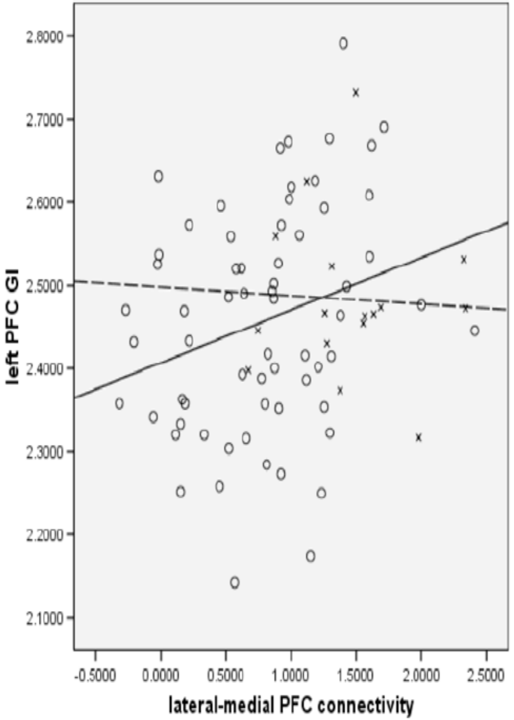
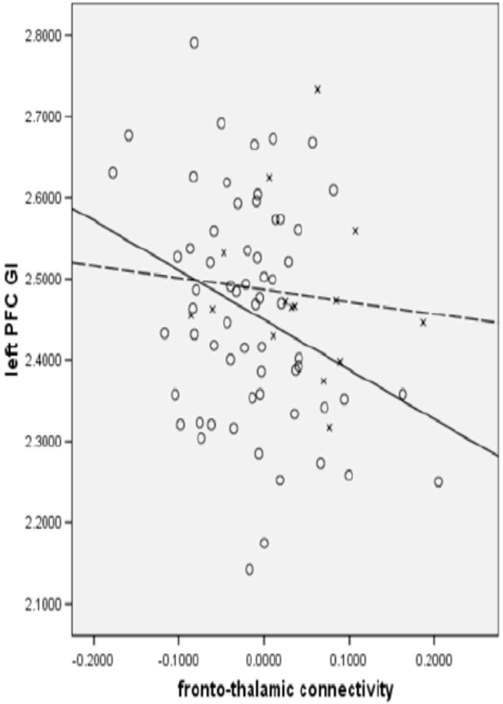


Fig. 3. A-GI total inner contour trace on a coronal slice of a control subject. Colors: blue=exposed inner contour right; green=exposed inner contour left: yellow=buried inners.

Bonnici et al. 2007

Functional connectivity and Prefrontal Gyrification Index





<u>Lateral-prefrontal PFC FC and left PFC GI</u>

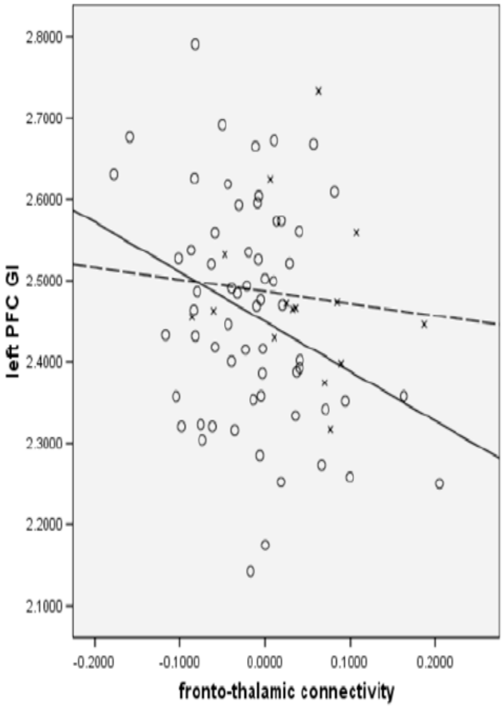
- HR – r= 0.228; *p*=0.017
- HC – r= -0.21; *p*=0.403

<u>Fronto-thalamic FC and left PFC GI</u>

- HR – r= -0.293; *p*=0.016
- HC – r= -0.023; *p*=0.9

Whalley et al. 2005
Dauvermann et al. 2012

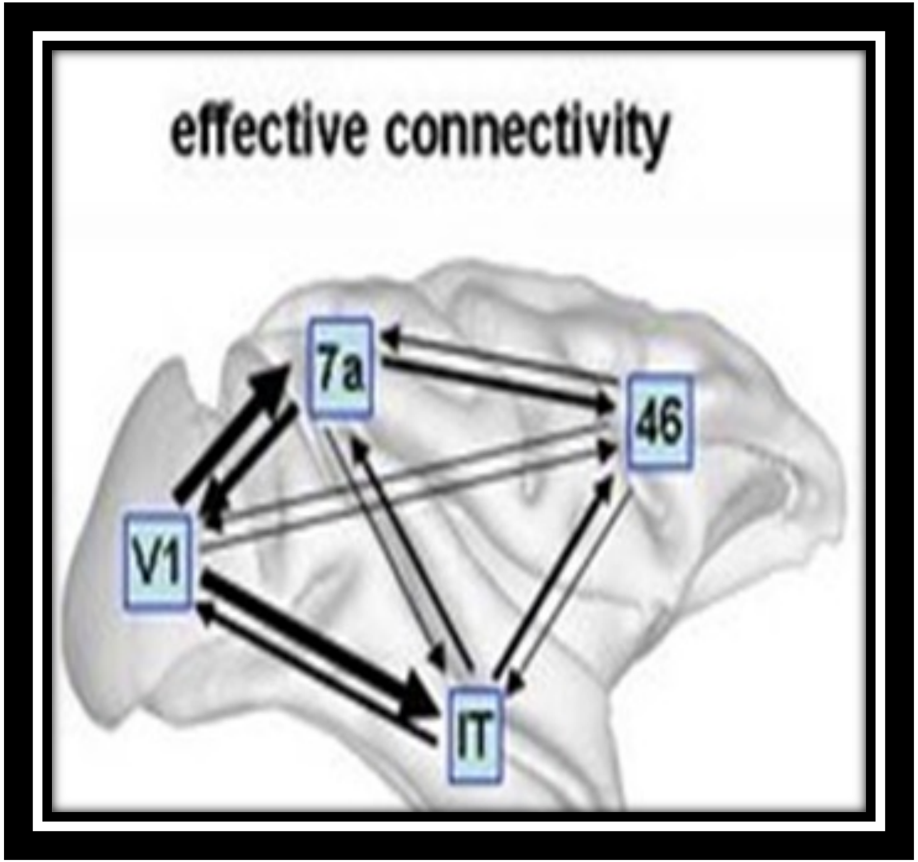
Functional connectivity and Prefrontal Gyrification Index



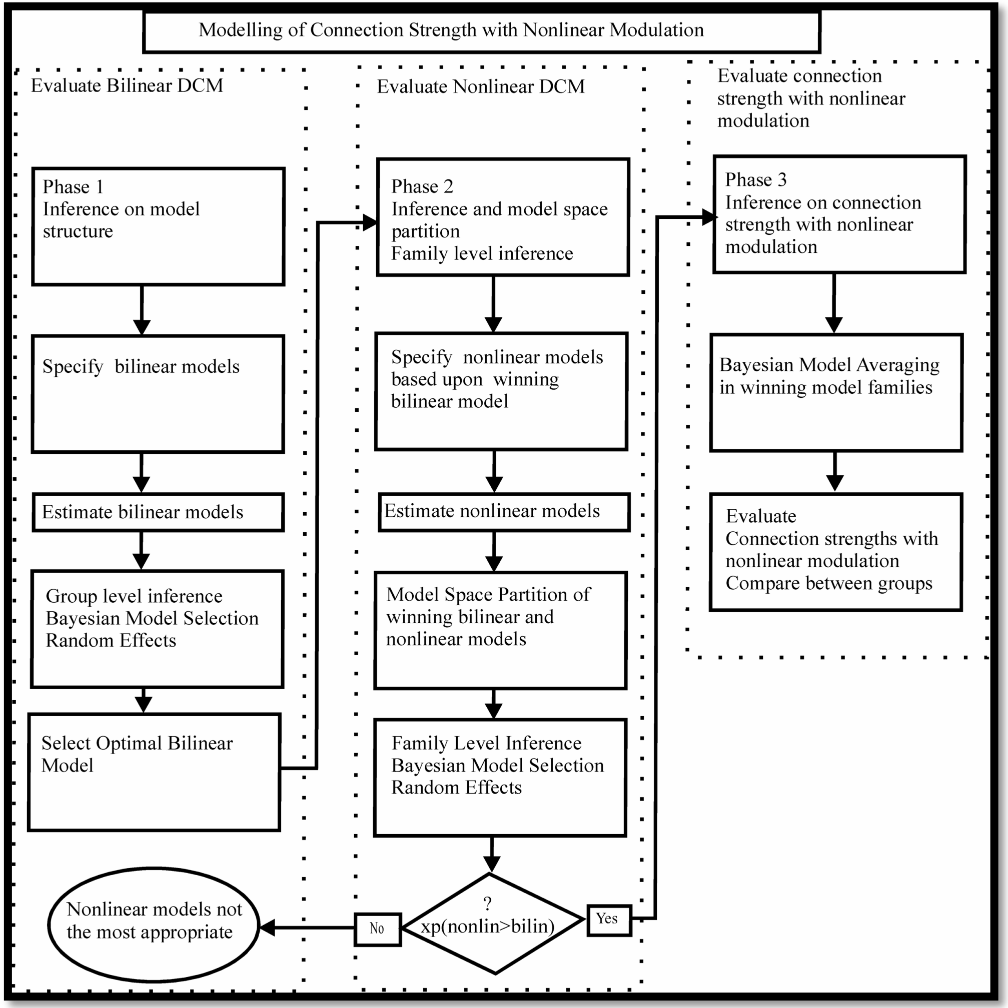
<u>Fronto-thalamic FC and left PFC GI</u>

- **HR – r= -0.293; *p*=0.016**
- HC – r= -0.023; *p*=0.9

Whalley et al. 2005
Dauvermann et al. 2012



Bayesian estimations of how the rate of change of neuronal activity in one region influences neuronal activity in other regions

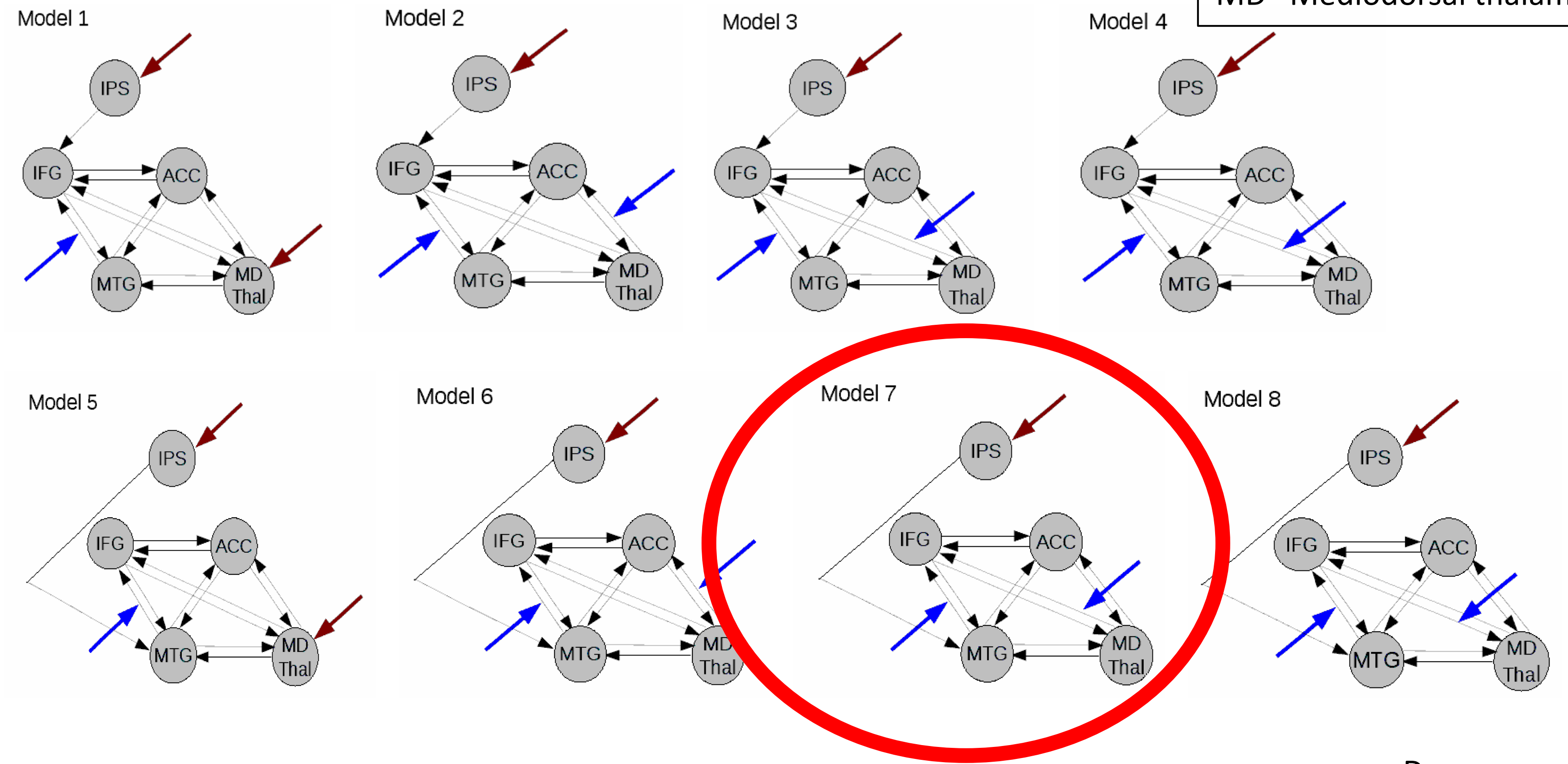


Dauvermann et al. 2013

Endogenous connection
Modulatory input
Driving input

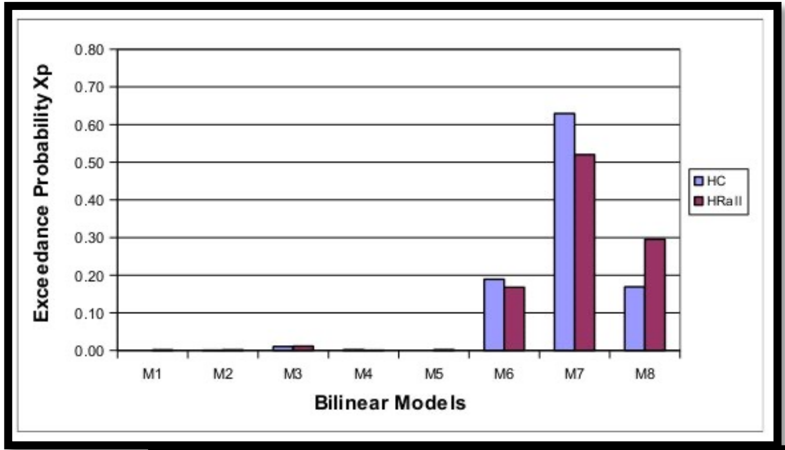
Linear Models

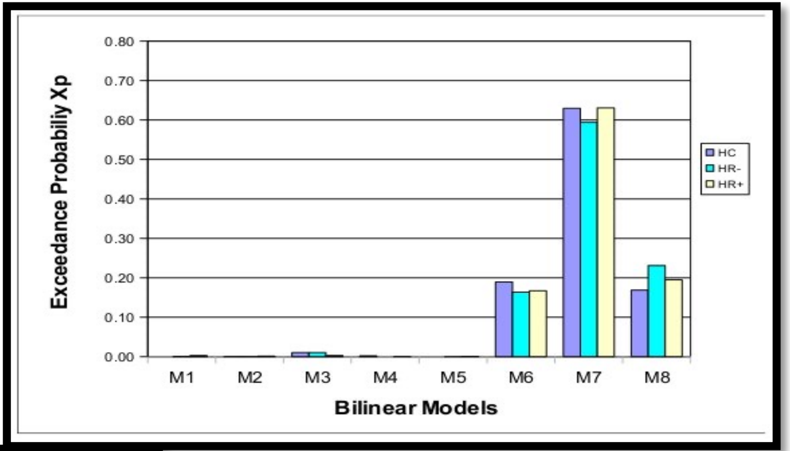
IPS Intra-parietal sulcus
IFG Inferior frontal gyrus
ACC Anterior cingulate cortex
MTG Middle temporal gyrus
MD Mediodorsal thalamus

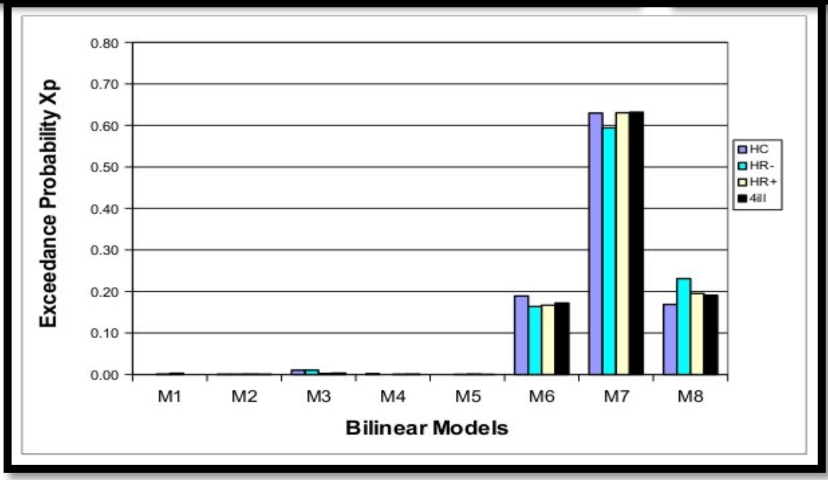


Dauvermann et al. 2013

Optimal linear model

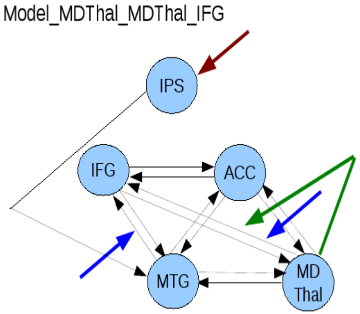


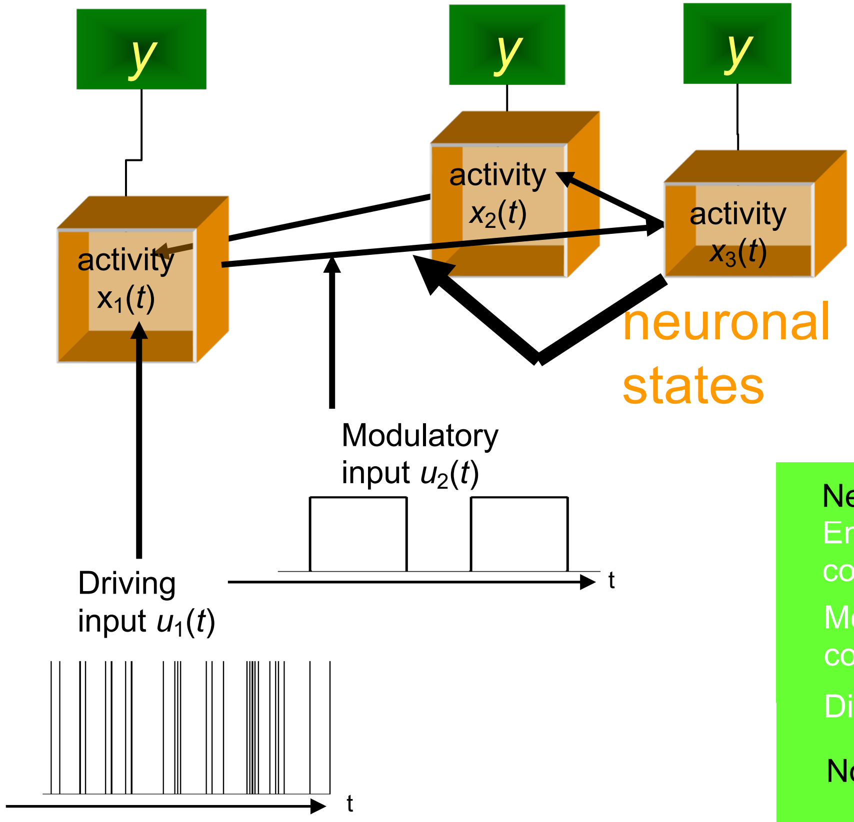


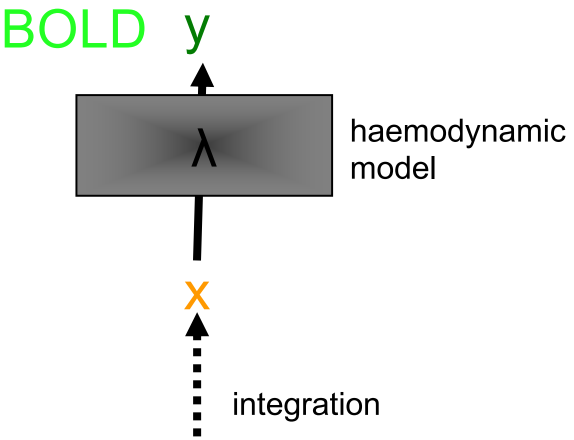


Dauvermann et al. 2013

Activity-dependent changes of neural function







Neural state equation

Endogenous connectivity

Modulation of connectivity

Direct inputs

Nonlinear input $D^{(j)} = to\Theta \left| \frac{1}{2} \frac{\partial^2 f}{\partial x_j^2} \right|_{u=0} \quad (1 \leq j \leq n)$

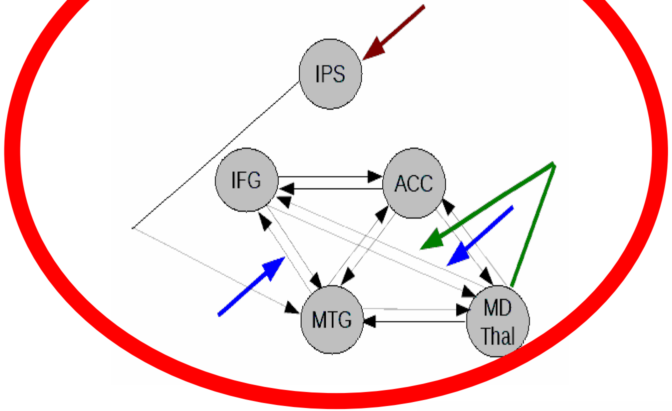
Dauvermann et al. 2013

Nonlinear models

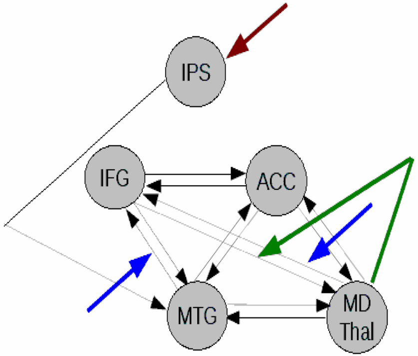
IPS Intra-parietal sulcus
IFG Inferior frontal gyrus
ACC Anterior cingulate cortex
MTG Middle temporal gyrus
MD Thalamus Mediodorsal thalamus

Endogenous connection
Modulatory input
Driving input
Nonlinear modulation

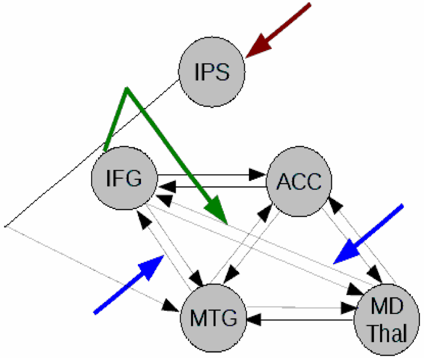
Model_MDThal_MDThal_IFG



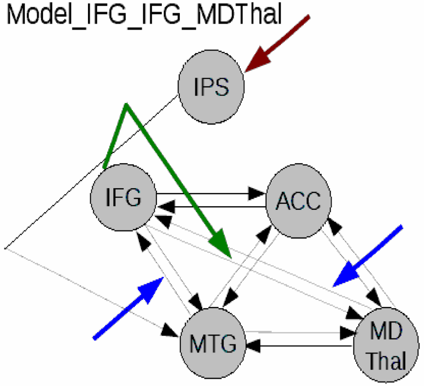
Model_MDThal_IFG_MDThal



Model_IFG_MDThal_IFG

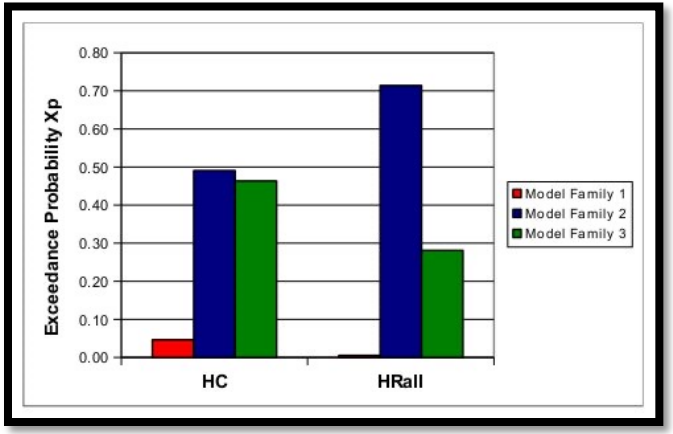


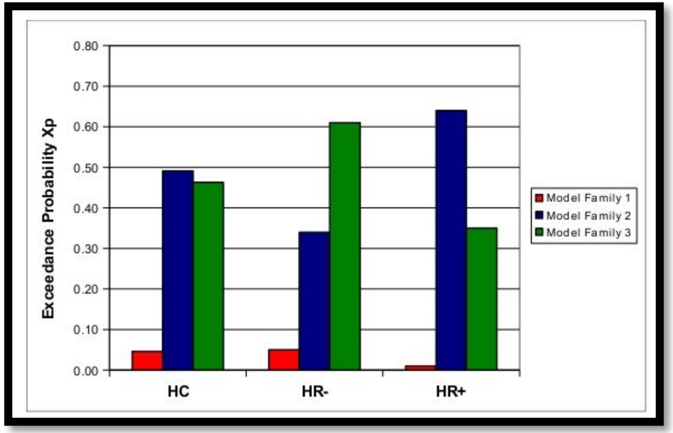
Model_IFG_IFG_MDThal

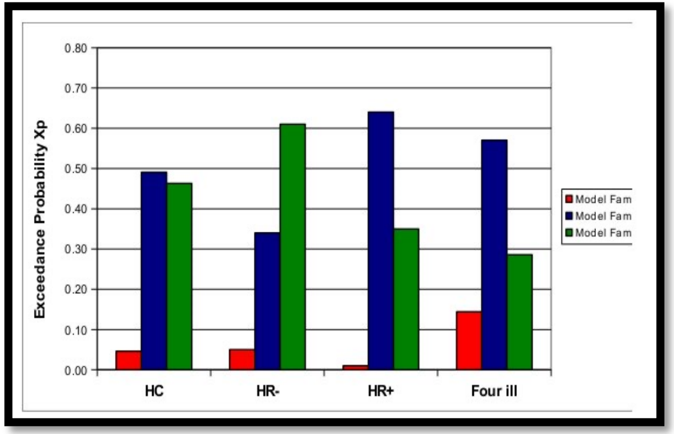


Dauvermann et al. 2013

Optimal nonlinear model family

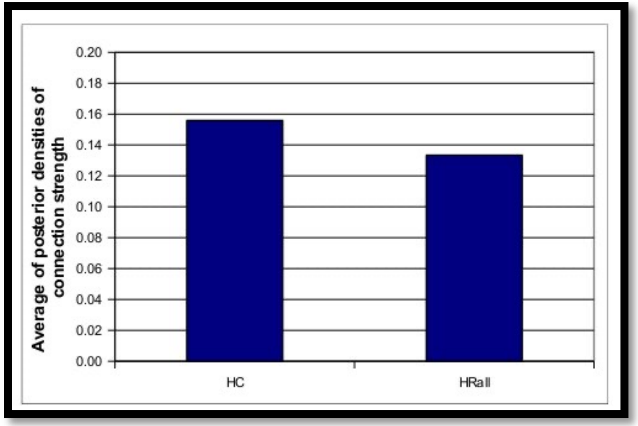


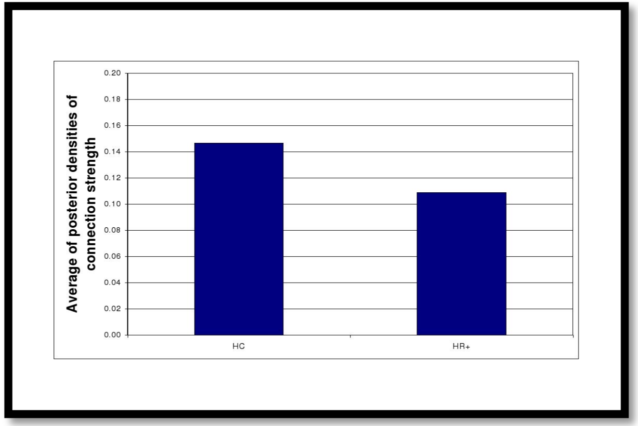


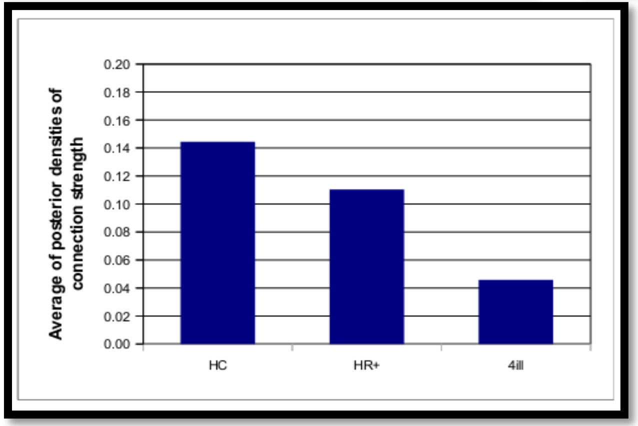


Dauvermann et al. 2013

Differentiation between HC and HR+







Model_MDTHal_MDTHal_IFG and symptom 'delusion' in HR+

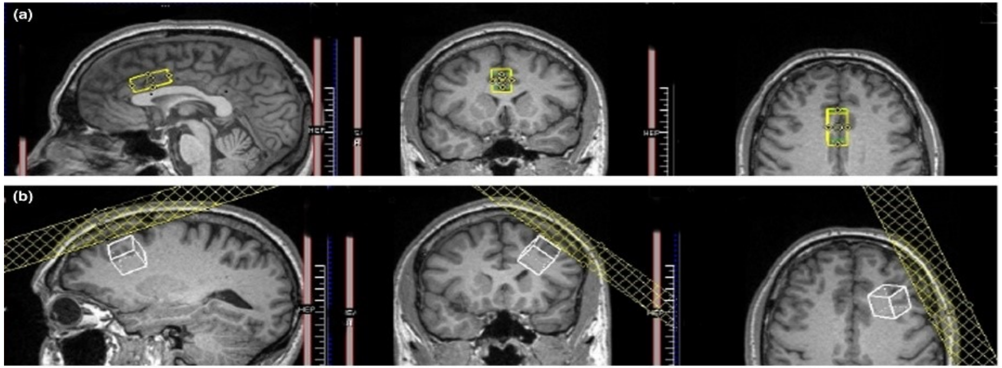
r = -.246; *p* = 0.041; 95% CI (-0.543; -.0.024)

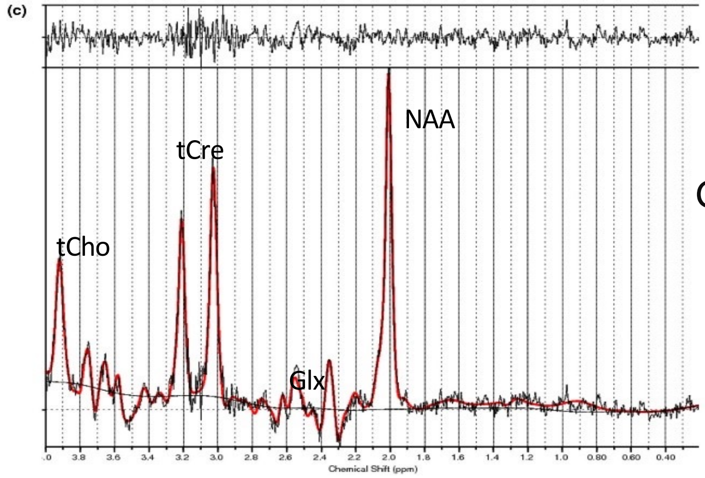
Model_MDTHal_MDTHal_IFG and symptom 'delusion' in HRall

r = -.201; *p* = 0.05; 95% CI (-0.446; -.0.02)

Dauvermann et al. 2013

Childhood adversity and Glutamate



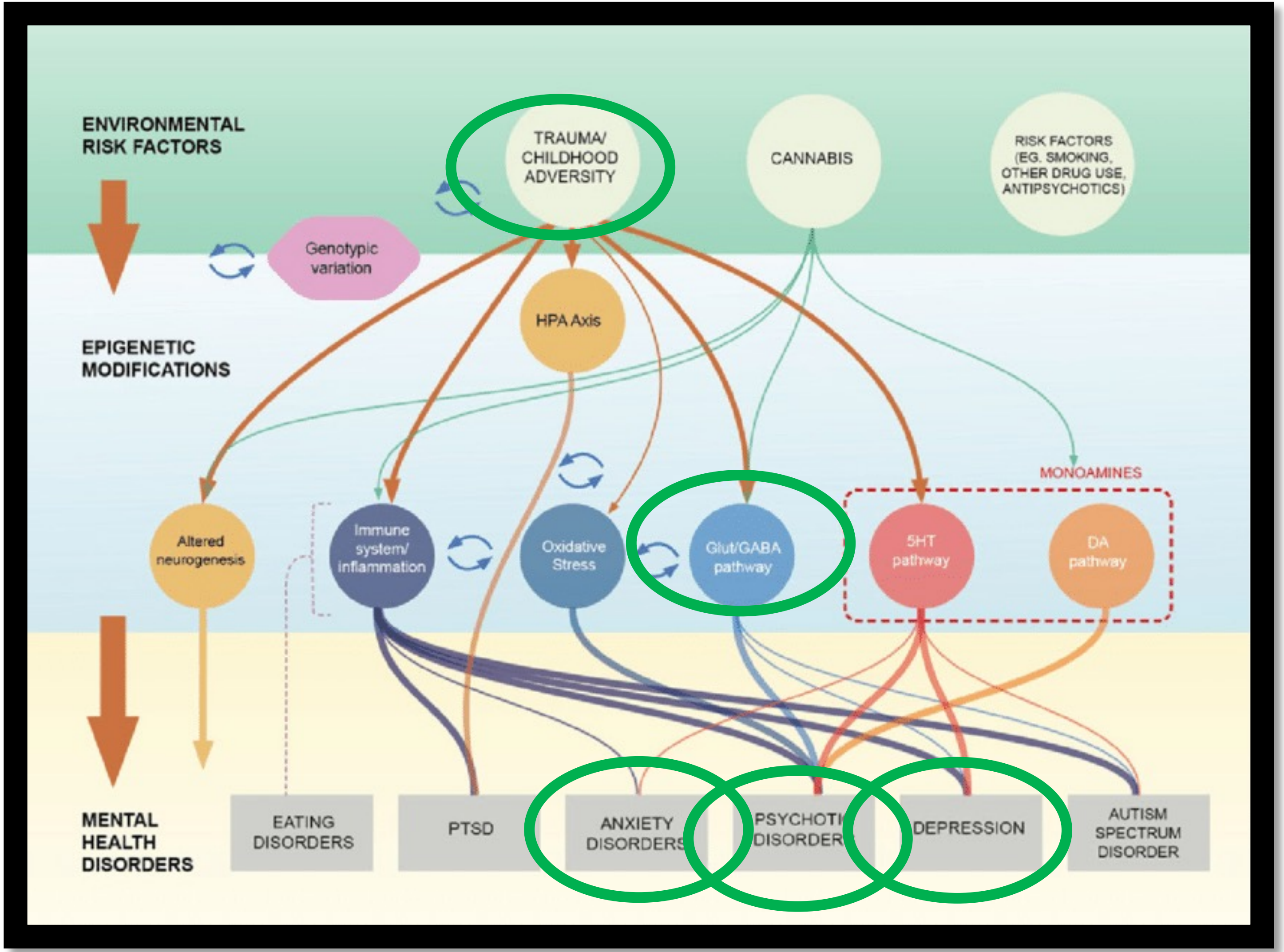


Glutamate+ Glutamine (Glx) in the dorsolateral PFC (DLPFC)

Novel finding in humans

- Replicating *post-mortem* and preclinical studies demonstrating that childhood adversity may change glutamatergic regulation

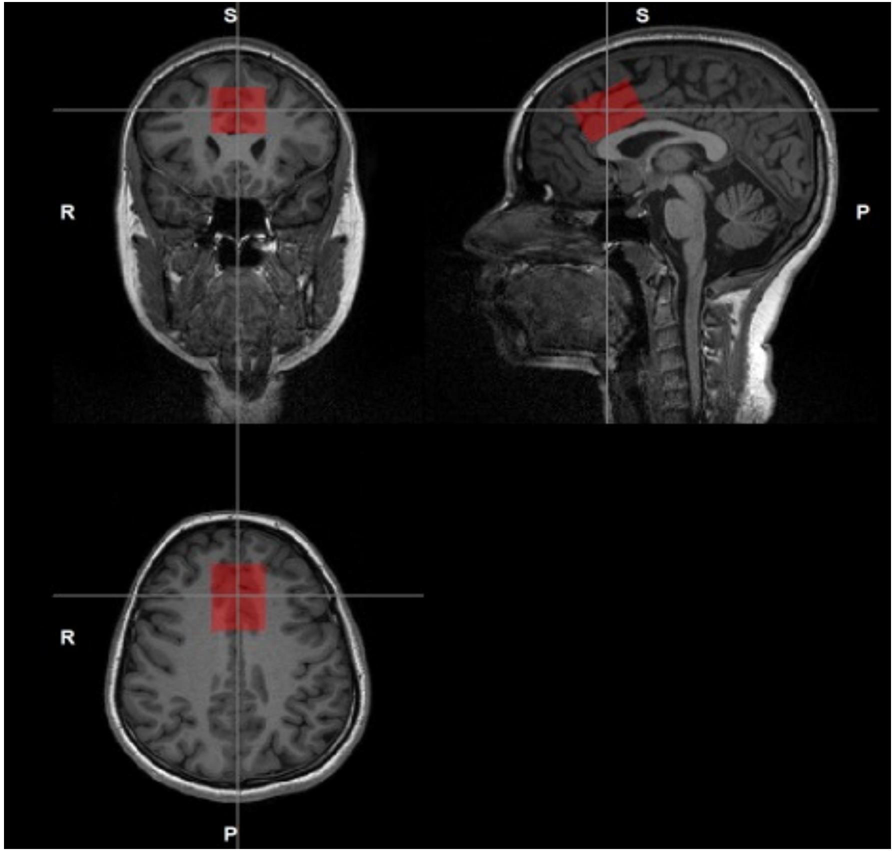
Corcoran, … Dauvermann, 2020

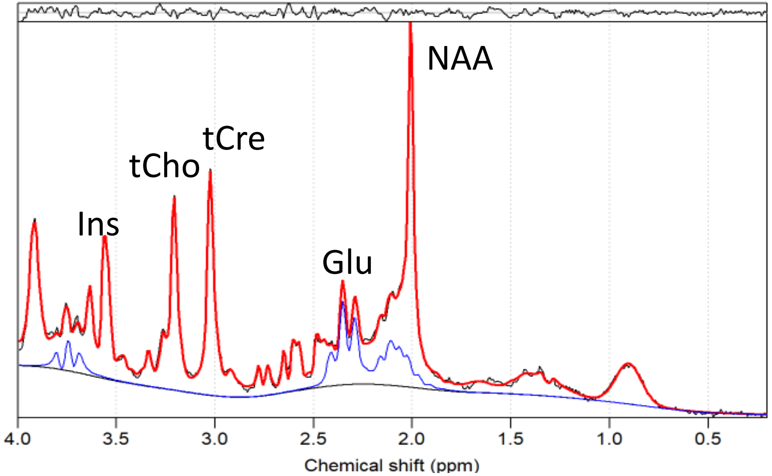


Alameda et al. 2022

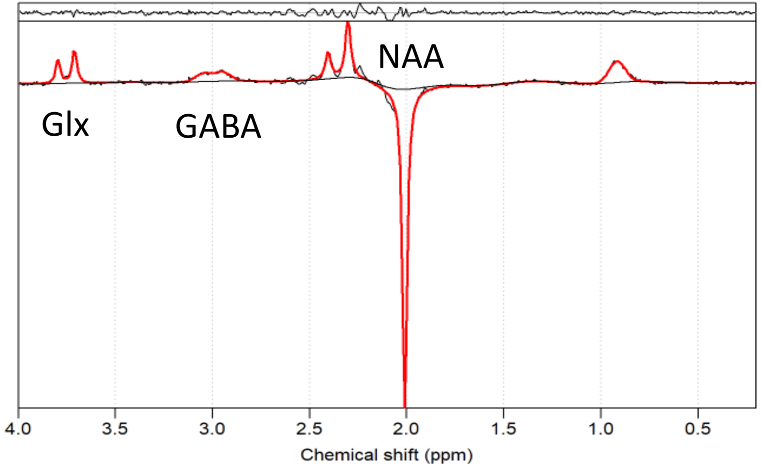
Glutamate and GABA concentrations

dorsal anterior cingulate cortex (dACC)





Glu

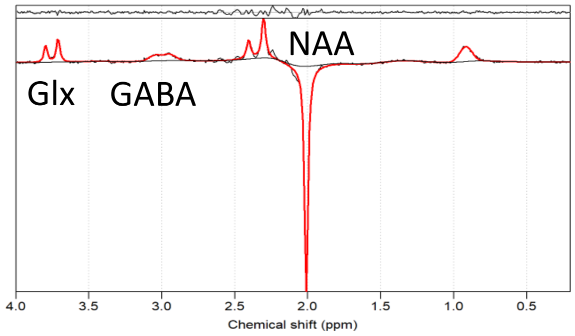


GABA

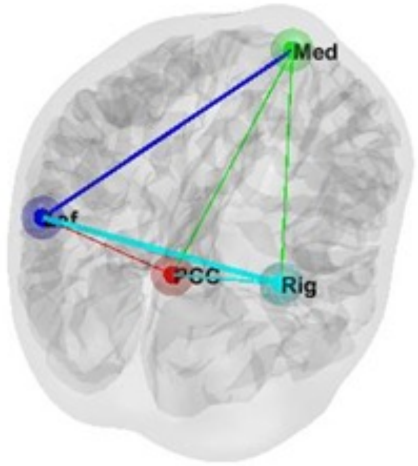
Corcoran, … Dauvermann, 2020; Siegel-Ramsay, … Dauvermann, 2020

Towards a more mechanistic understanding: GABA concentrations, Default-mode network connectivity and Childhood adversity

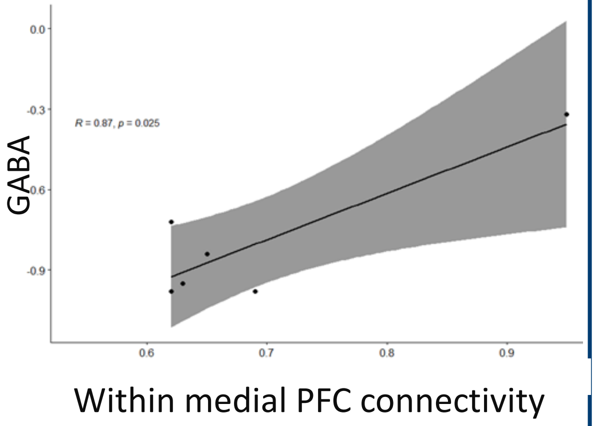
GABA in the dACC



Default-mode network - DCM



GABA and inhibitory connection strength with CA



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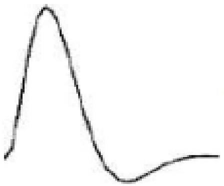
Basic Idea of DCM for EEG/MEG

- C [illegible]
- DC [illegible] (E [illegible] /E [illegible] F)
- [illegible] B [illegible]

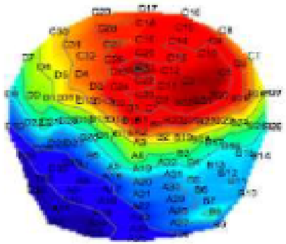
David et al. 2006
David and Friston, 2003
Kiebel et al. 2007

Evolution and observation mappings



Hemodynamic
observation model:
temporal convolution

Electromagnetic
observation model:
spatial convolution



neural states dynamics

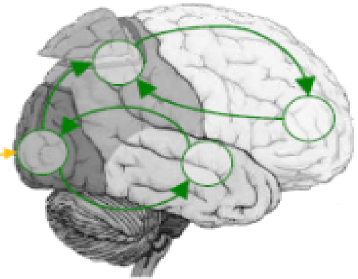
$$\dot{x} = f(x, u, \theta)$$

High
spatial
resolution

fMRI

EEG/MEG

High
temporal
resolution



inputs

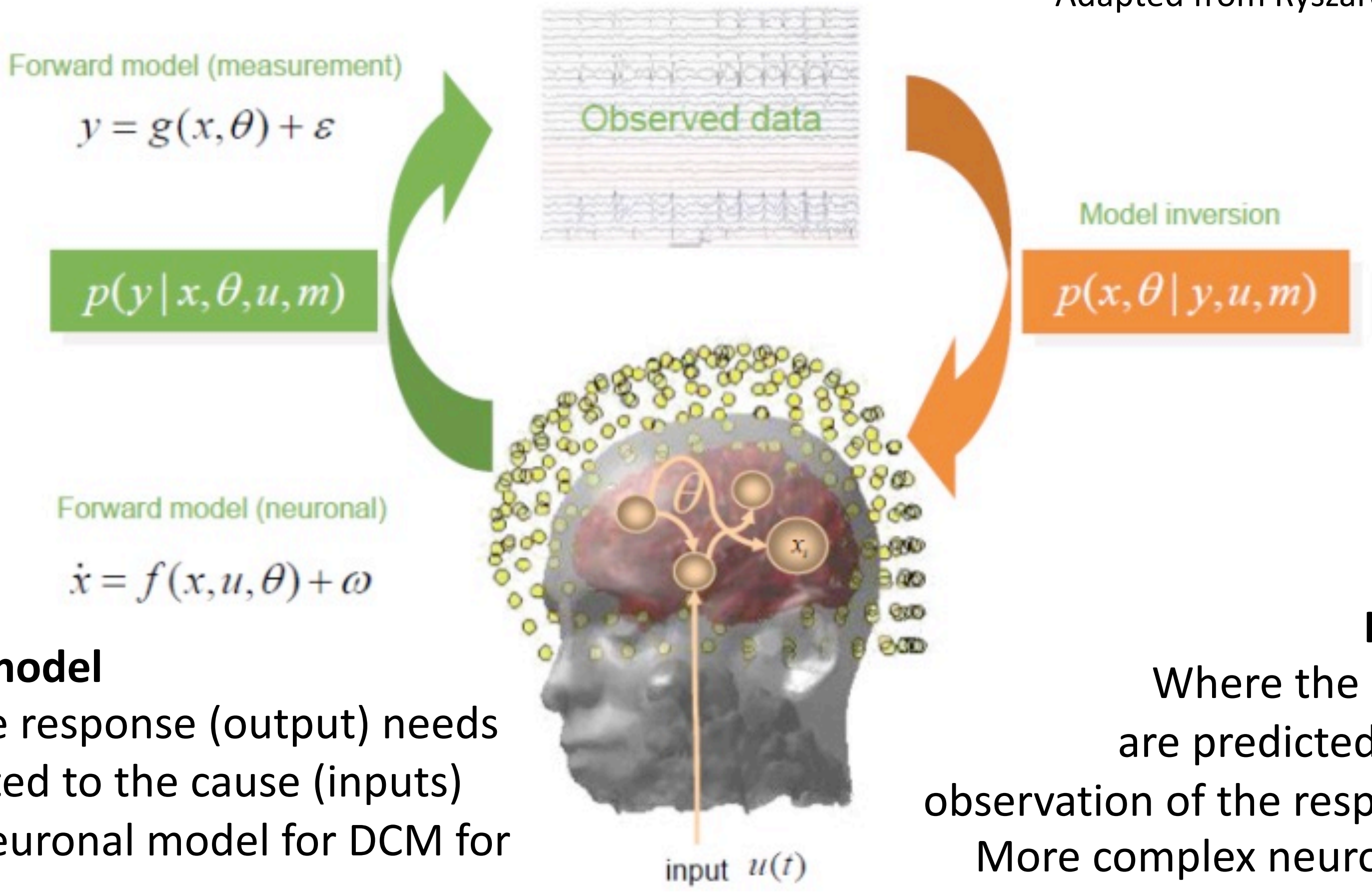
- simple neuronal model
- realistic observation model

- realistic neuronal model
- simple observation model

Adapted from Ryszard Auksztulewicz

Forward models and their inversion

Adapted from Ryszard Auksztulewicz



Forward model
Where the response (output) needs to be related to the cause (inputs)
Simpler neuronal model for DCM for fMRI

Inverse model
Where the cause (inputs) are predicted based on the observation of the response (output)
More complex neuronal model for DCM for EEG/MEG

Model specification and inversion

$$u(t)$$
$$\downarrow$$

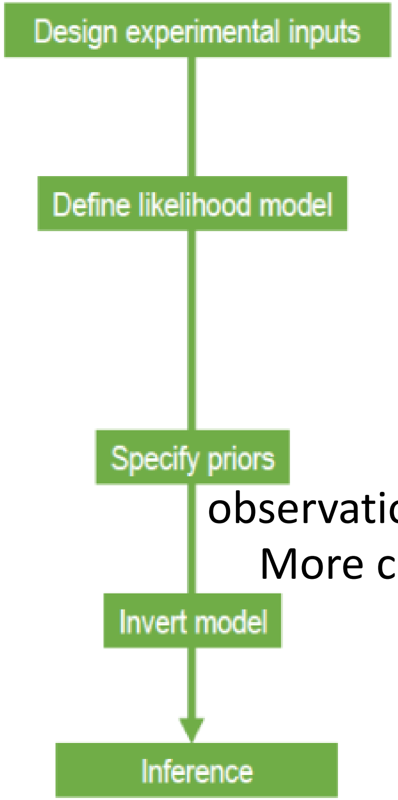
Neural dynamics $\dot{x} = f(x, u, \theta)$

Observer function $y = g(x, \theta) + \varepsilon$

$$p(y \mid \theta, m) = \mathrm{N}\,(g(\theta), \Sigma(\theta))$$
$$p(\theta, m) = \mathrm{N}\,(\mu_\theta, \Sigma_\theta)$$

Inference on models $p(y \mid m) = \int p(y \mid \theta, m)\, p(\theta)\, d\theta$

Inference on parameters $p(\theta \mid y, m) = \dfrac{p(y \mid \theta, m)\, p(\theta, m)}{p(y \mid m)}$



Inverse model

Where the cause (inputs) are predicted based on the observation of the response (output)

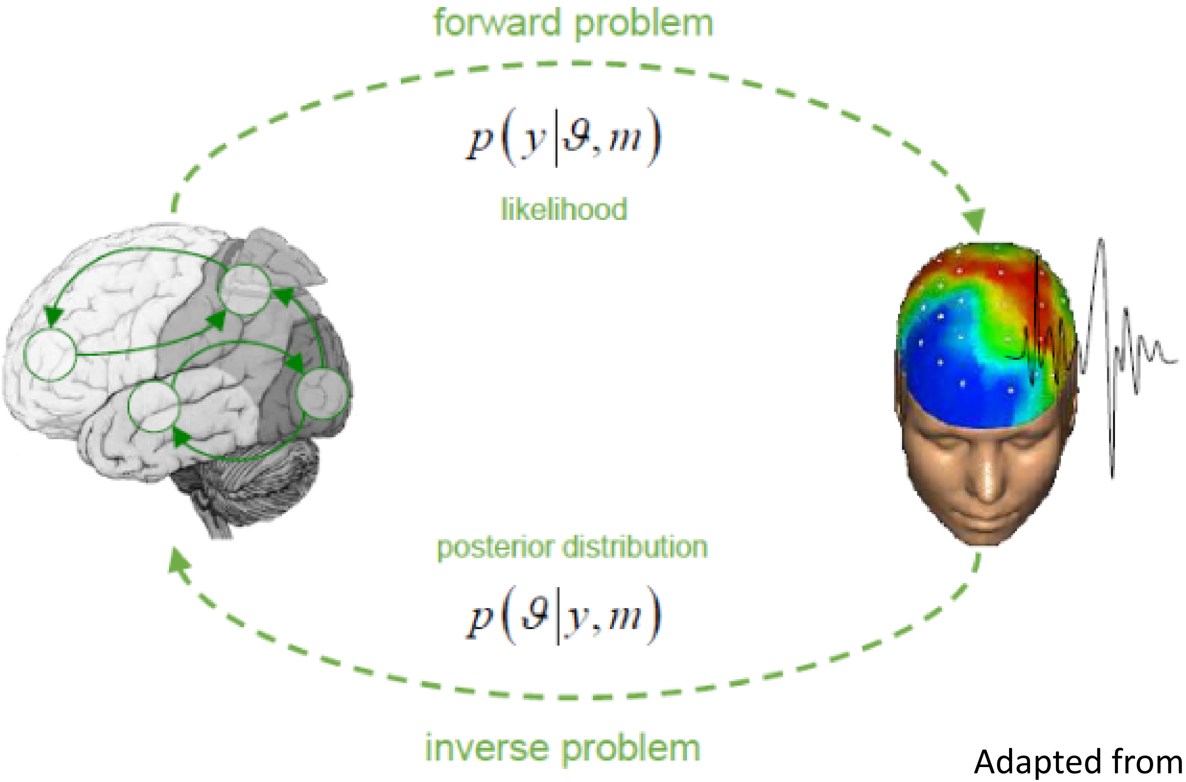
More complex neuronal model for DCM for EEG/MEG

Adapted from Ryszard Auksztulewicz

Bayesian inference

forward and inverse problems

High
spatial
resolution



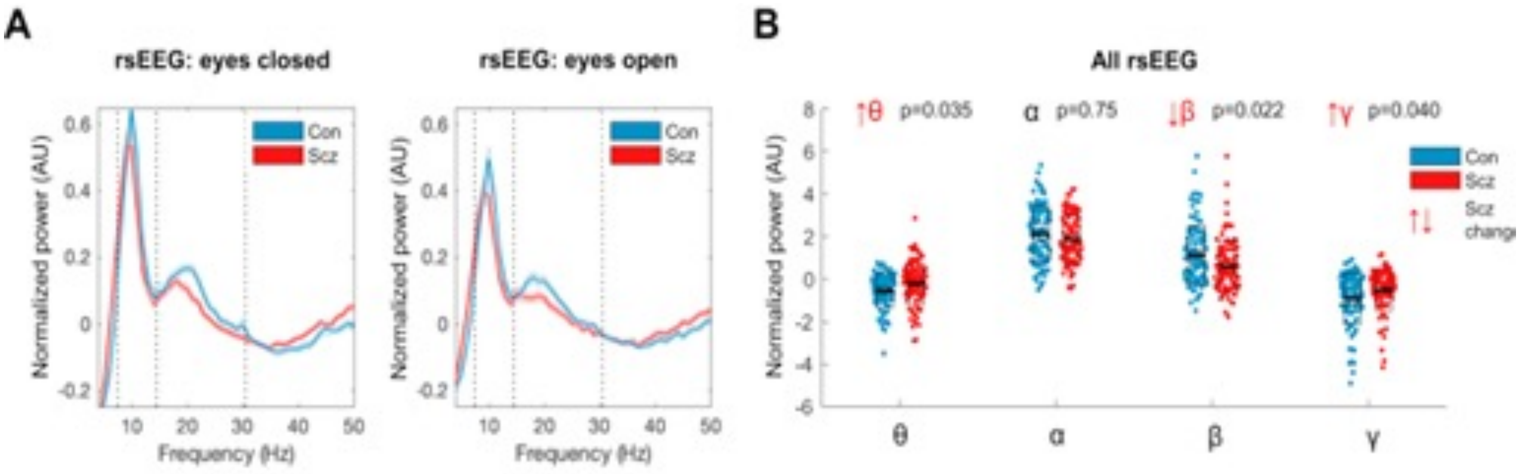
High
temporal
resolution

Adapted from Ryszard Auksztulewicz

Computational Modelling of EEG and fMRI Paradigms Indicates a Consistent Loss of Pyramidal Cell Synaptic Gain in Schizophrenia

Adams et al. 2022

Resting-state electroencephalography (rsEEG)



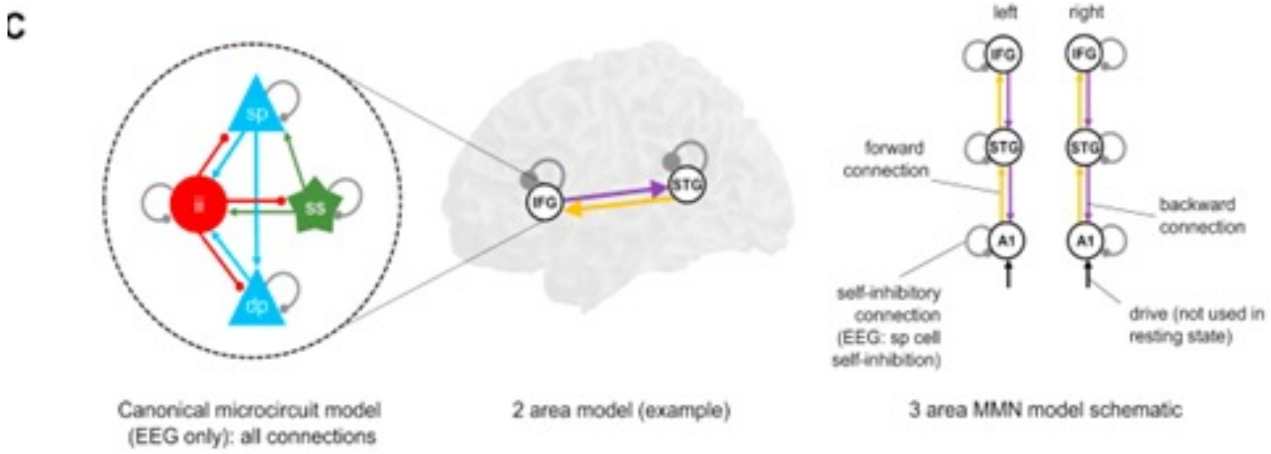
(A) Mean normalised eyes closed and eyes open rsEEG power spectra (± SEM) across all channels for control subjects (Con) (*n* = 98; blue) and people with schizophrenia diagnoses (PScz) (*n* = 95; red) groups, divided into four frequency bands (dotted lines): θ (3–7 Hz), α (8–14 Hz), β (15–30 Hz), and γ (>31 Hz).

(B) Group comparisons in mean power across both eyes closed and eyes open conditions in the θ, α, β, and γ bands are shown. The box plots show the mean, SEM, and SD. *p* values are Bonferroni-corrected for four comparisons.

Adams et al. 2022

EEG Dynamic causal modelling (DCM) model structure - Canonical microcircuit model

Adams et al., 2022



This microcircuit (left) consists of superficial pyramidal (sp) and deep pyramidal (dp) cells, inhibitory interneuron (ii), and spiny stellate (ss) cells. They are interconnected with excitatory (arrowheads) and inhibitory (beads) connections; their self-inhibitory connections parameterise their responsiveness to their inputs, i.e., synaptic gain.

In EEG DCM, each modelled cortical area contains a microcircuit (middle); functional magnetic resonance imaging DCM uses a much simpler neuronal model. Both DCMs have self-inhibition parameters (round gray beads), which—in EEG—inhibit superficial pyramidal cells specifically. A schematic DCM diagram is explained on the right.

D

Can the application of functional and/or effective connectivity to brain imaging contribute to clinical and cognitive diagnostic, predictive and treatment interventions in the future?


Summary

Summary

- Main principle of functional connectivity:
  - Analyse data between two brain regions with temporal correlations
- Main principle of DCM for effective connectivity:
  - Analyse data and generative models in a Bayesian framework to infer parameters and compare models
- Advantages and disadvantages dependent on available data and hypothesis

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imh institute for mental health

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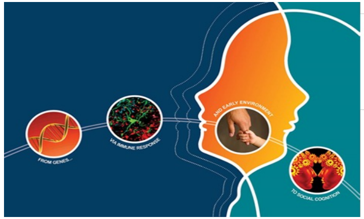
With help from Alex Murray and Martin Wilson



erc European Research Council

NICOG

CogGene

Immune Response and Social Cognition in Schizophrenia (iRELATE)
Gary Donohoe
John Kelly
Colm McDonald
Declan McKernan
Derek Morris
Tom Burke
Sinead King

Scottish Family Mental Health Study and Edinburgh High Risk Study
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