Computational modeling approaches to schizophrenia

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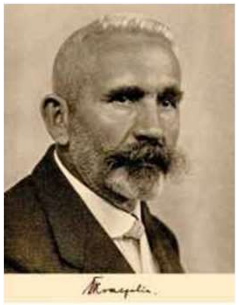
Historical concepts of schizophrenia and their problems

Schizophrenia: Concepts



Emil Kraepelin (1856-1926)

- „**Dementia praecox**“: endogenous, progressive psychosis
- Differentiation from „manic-depressive psychosis“
- Cognitive and emotional capacities deteriorate progressively, leading to severe changes in “personality”

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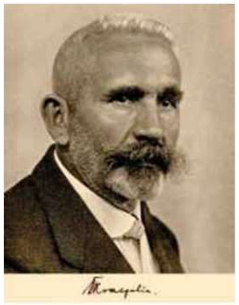

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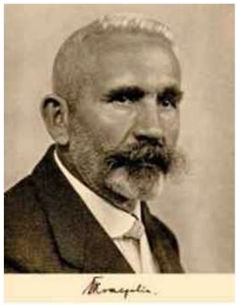
- created the term “schizophrenia”
- **Diagnostic symptoms**: impaired associations; affective disorders; “autism”; “ambivalence”
- **Accessory symptoms**: altered perception, negativism, manierism, stereotypical behavior, compulsions, changes in memory, speech and personality

Schizophrenia: Concepts



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Kurt Schneider (1857-1939)

- **1st rang symptoms**: “Ich-Störungen”; auditory verbal hallucination (comments and dialogue); delusional perception
- **2nd rang sypmtoms**: other hallucinations, affective symptoms (blunted/depressed mood), cognitive symptoms.

Schizophrenia: Concepts

ICD-10 (F20.9)	**DSM-5** (295.90)
1. Gedankenlautwerden, -eingebung, -entzug, -ausbreitung **2. Kontroll- u. Beeinflussungswahn, Gefühl d. Gemachten, Wahnwahrnehmung** **3. Kommentierende oder dialogisierende Stimmen** **4. Anhaltender deutlicher Wahn** **5. Anhaltende andere Halluzinationen** **6. Formale Denkstörungen** **7. Katatone Symptome** **8. Negative Symptome**	**1. Wahn** **2. Halluzinationen** **3. Desorganisierte Sprache** **4. Stark desorg./katatones Verhalten** **5. Negative Symptome** (z.B. red. emotionaler Ausdruck, Avolition)
Symptome: 1 von 1-4 *oder* **2 von 5-8**	**Symptome: 2 von 5** (inklusive 1., 2. o. 3.)
Zeitkriterium: > 1 Monat	**Zeitkriterium: > 1 bzw. 6 Monate**

Schizophrenia: Conceptual Problems

- Psychiatric diagnoses: descriptive categorizations with little predictive validity

- A set of positive and negative symptoms that often co-occur, but
  - heterogeneity between individuals
  - variability within individuals

• Multiple etiological factors at various levels of observation: molecular, cellular, systems-level, immunologic, psychological, social, environmental

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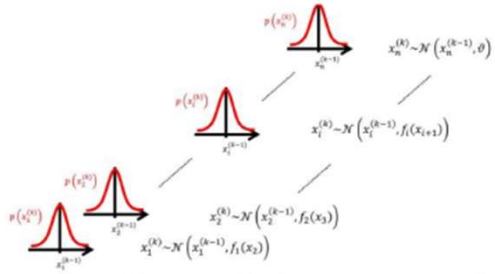
• Multiple etiological factors at various levels of observation: molecular, cellular, systems-level, immunologic, psychological, social, environmental

- **Powerful models** need to deal with
  - heterogeneous symptomatology
  - complex etiology
  - big data

Computational psychiatry

Computational Psychiatry



Cognitive Neuroscience | **Computational Neuroscience**

Computational Psychiatry

→ Link theoretical models with neurobiological findings in mathematical terms

→ Make precise quantitative predictions

→ Combine multiple levels of observation (and explanation)

→ Deal with multivariate datasets

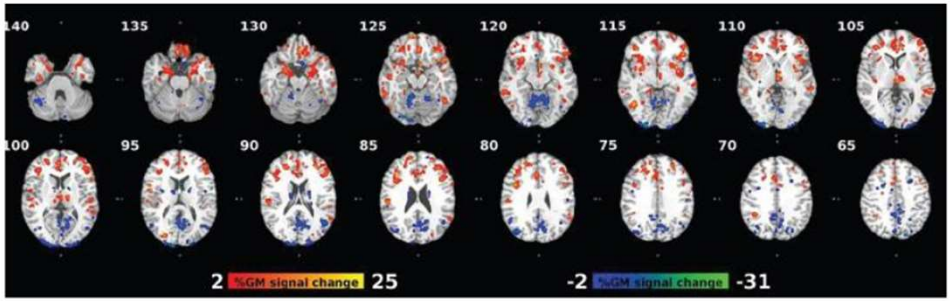
Stephan & Mathys, CONB 2014;
Krystal & Wang, Neuron 2014; Teufel & Fletcher, Brain 2016

Two approaches

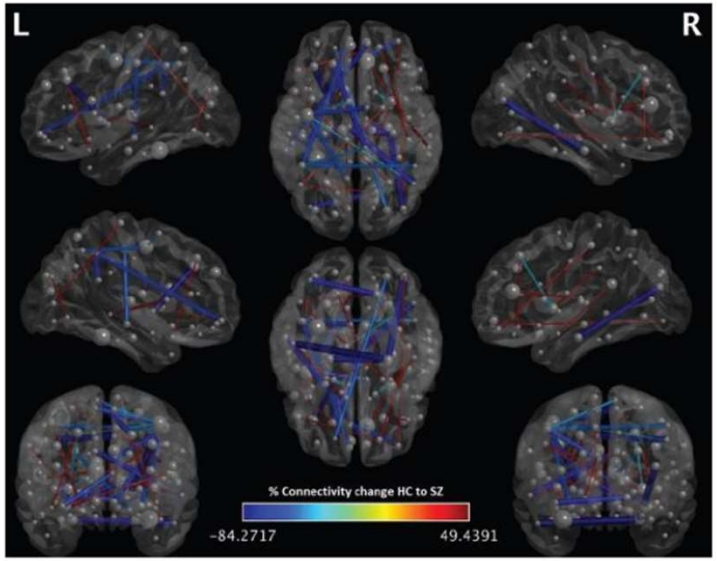
- **Data-driven approach**
  - Agnostic to theory
  - Machine learning (e.g., support-vector machines)
  - Multidimensional data
  - E.g., automatic diagnostic classification, prediction of treatment outcomes
- **Theory-driven approach**
  - based on conceptual models and prior evidence
  - Formal mathematical models of neurobiological or mental processes
  - Enforce precision in the formalization of conceptual models
  - Synthesizing disparate pieces of evidence and different levels of explanation

Klöppel et al., NeuroImage 2012
Teufel & Fletcher, Brain 2016
Huys et al., Nat. Neurosci 2016

Data-driven approach: diagnostics



T1 sMRI: 69.7%

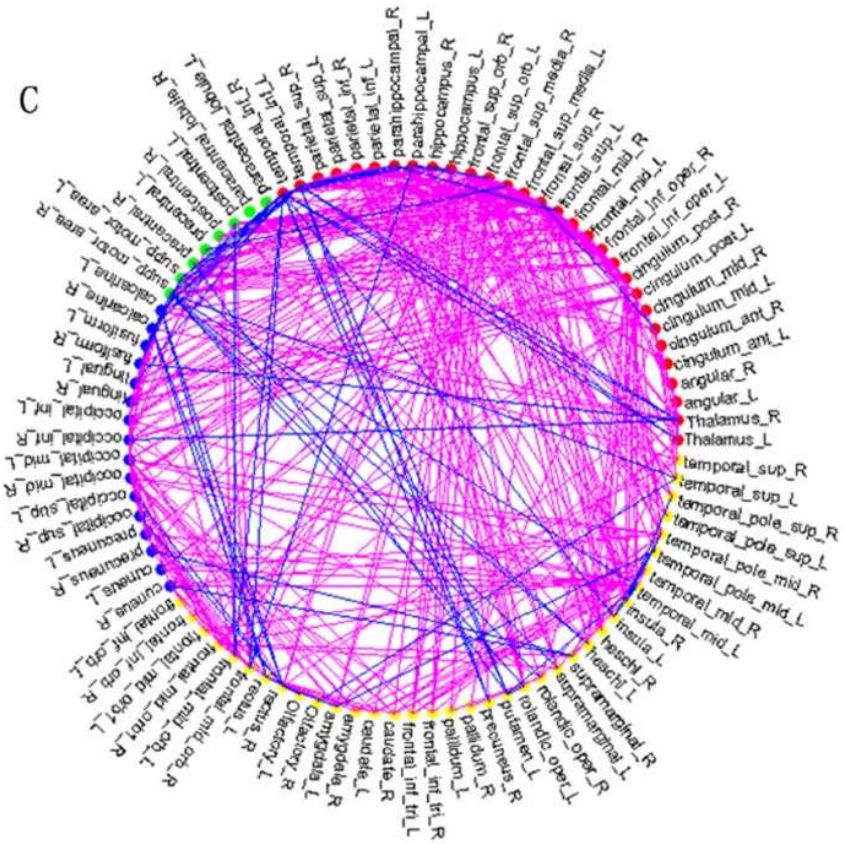


resting-state fMRI: 70.5%

combination: 75%

Cabral et al., Schiz Bull 2016

Data-driven approach: treatment



Tang, BMC Medical Engineering 2012

Prediction of treatment response to antipsychotics in schizophrenia (Metha et al., Schizophrenia Research 2013)

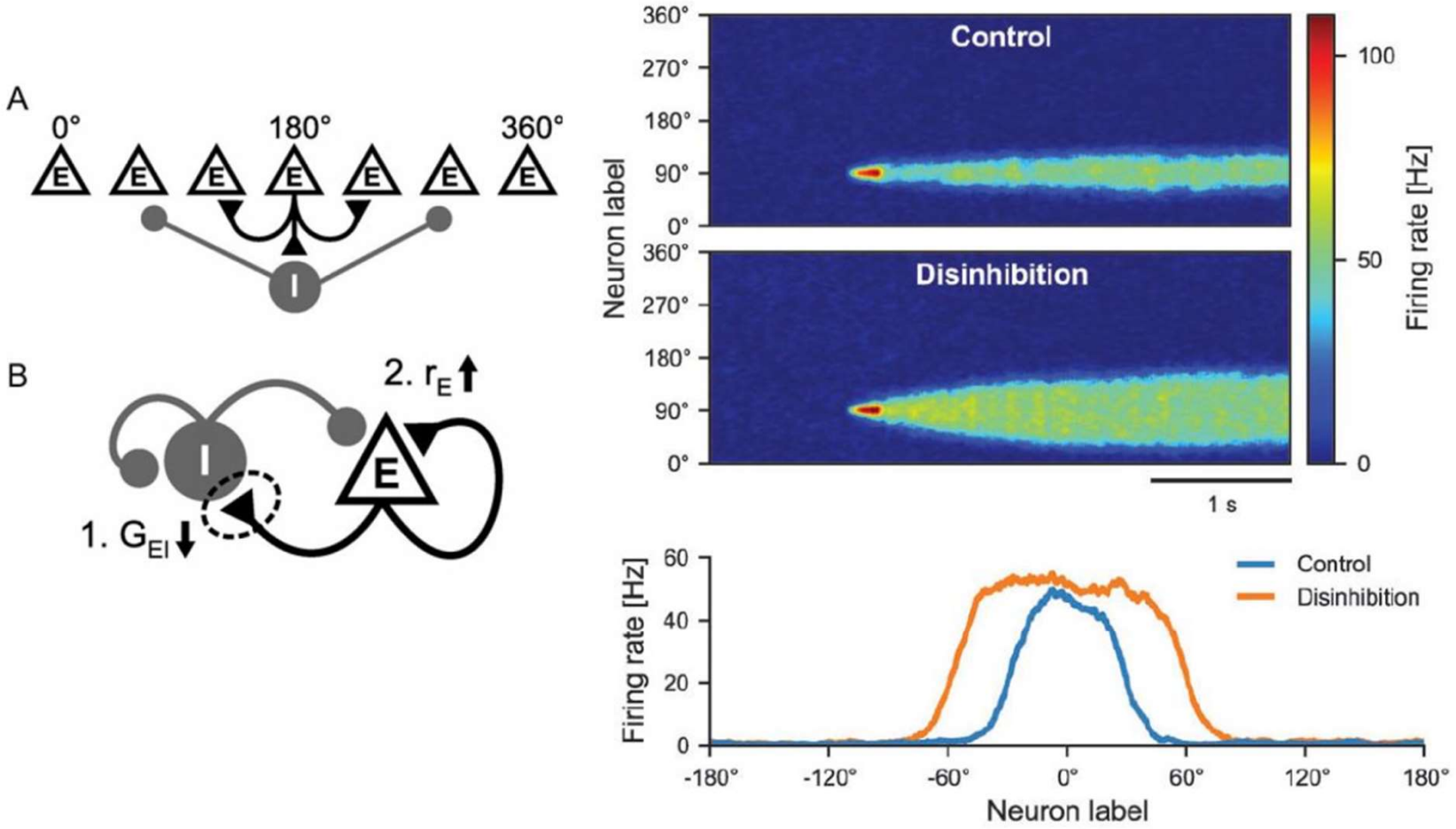
- categorically defined treatment response predicted at an odds ratio of 12.66 (CI: 7.91-20.29)
- 81% sensitivity and 76% specificity

Theory-driven approaches

- **Synthetic models**
  - E.g., biophysically informed models
  - Model interaction between components through simulations and mathematical analysis
- **Algorithmic models**
  - E.g., reinforcement learning
  - Small number of parameters representing a specific process
  - Estimation through fitting model to data (e.g. behavioural)
- **Optimal models**
  - E.g., Bayesian models
  - Link observed behaviour to (Bayes-)optimal solution of a problem

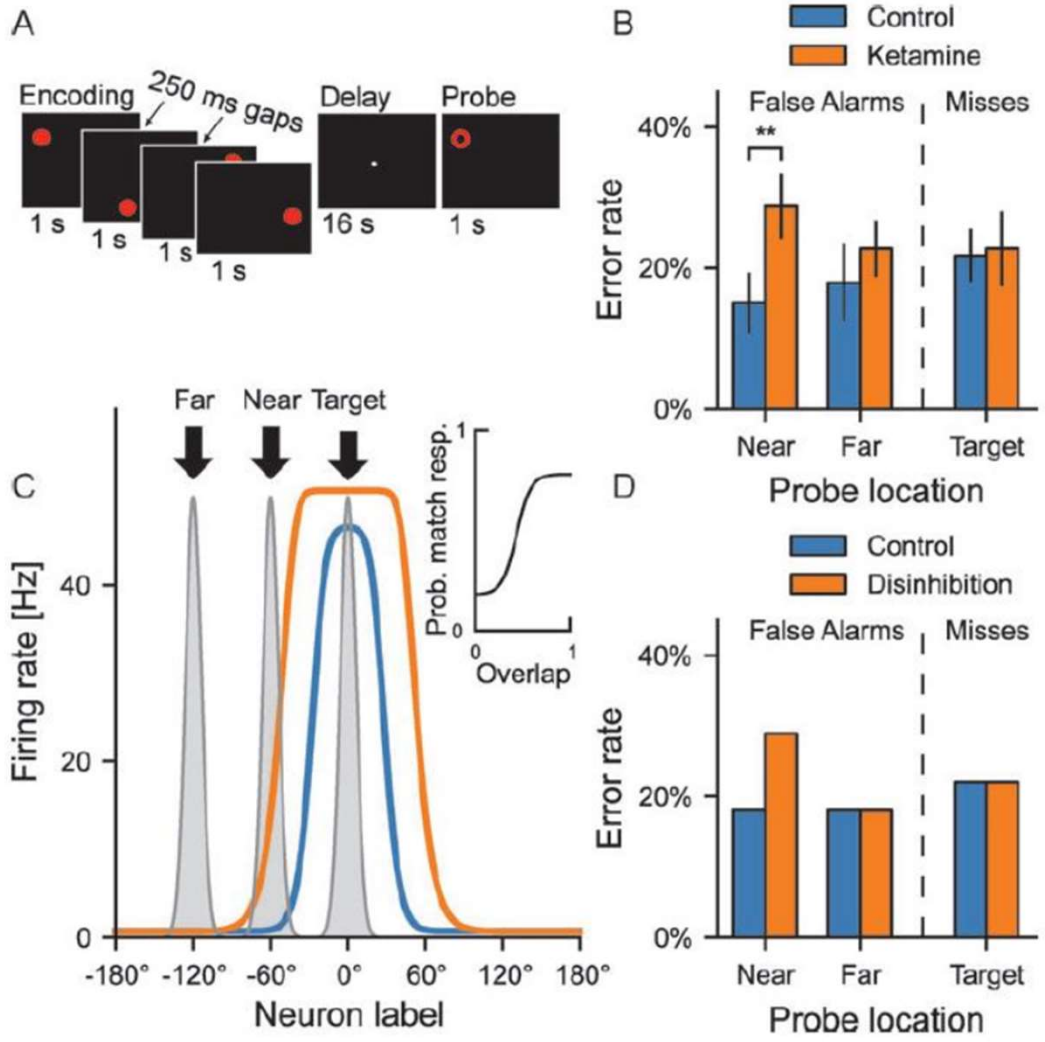
Huys et al., Nat Neurosci, 2016

Biophysical models



Murray et al., Cereb Cortex 2014

Biophysical models



Algorithmic models

- Patients diagnosed with schizophrenia show reduced learning from positive outcomes
- Most pronounced in patients with high-negative symptoms

- **Difficulty to learn from positive outcomes (dopaminergic neurotransmission) vs. deficit in representing the expected reward value of specific choices (working memory representation in OFC)**

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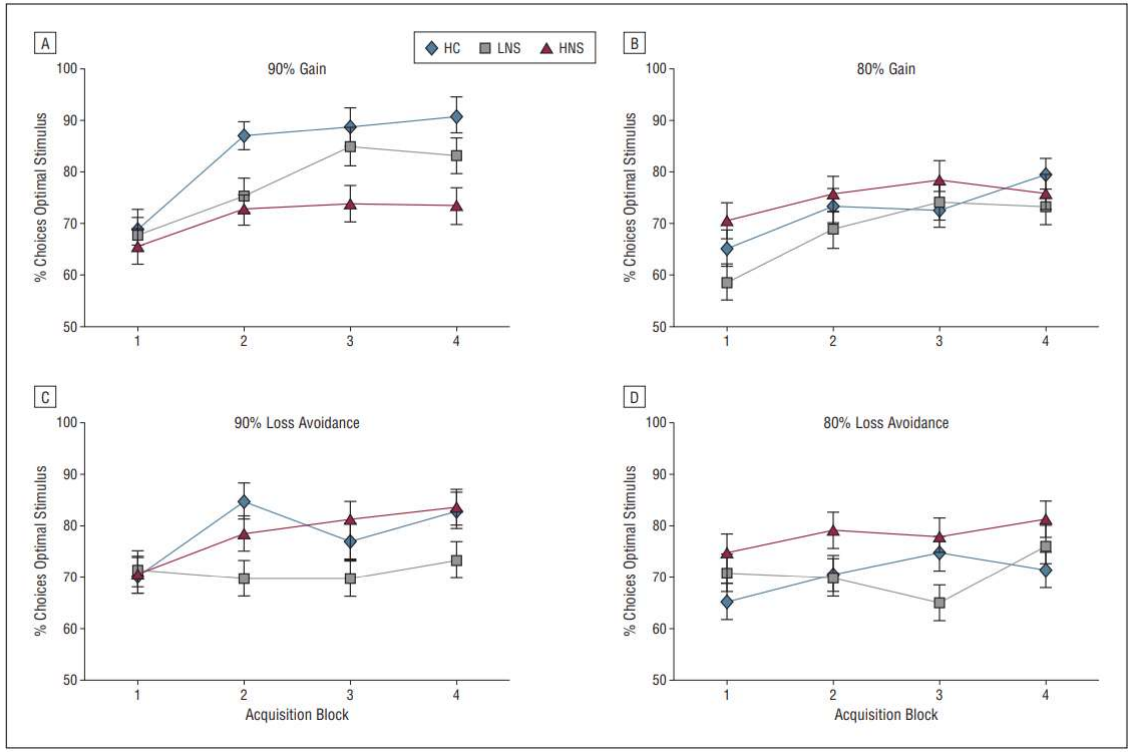
Two models:

- **Actor-Critic:**
  - "critic" evaluates the reward values of particular states
  - "actor" selects responses as a function of learned stimulus-response weights
- **Q-Learning:**
  - Agent learns the reward (Q-) value of specific decisions

Algorithmic models

Task: Learning between pairs of stimuli

- Stimulus + Reward vs. Stimulus + No Reward
- Stimulus + No-Reward vs. Stimulus + Loss



Negative symptoms are not associated with reduced learning from positive PEs per se, as previously suggested, but rather with impairment in the representation of positive expected value to guide decisions.

Algorithmic models

$$Q_a(t+1) = Q_a(t) + \alpha * PE(t)$$

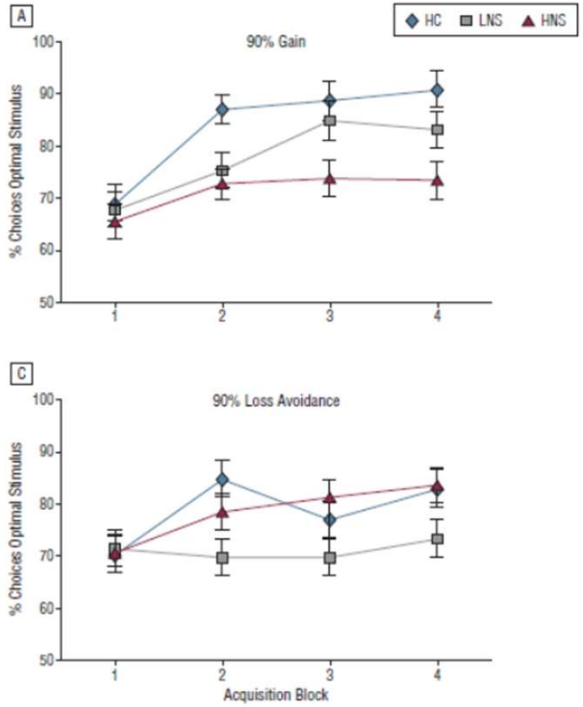
$$PE(t) = R(t) - Q_a(t)$$

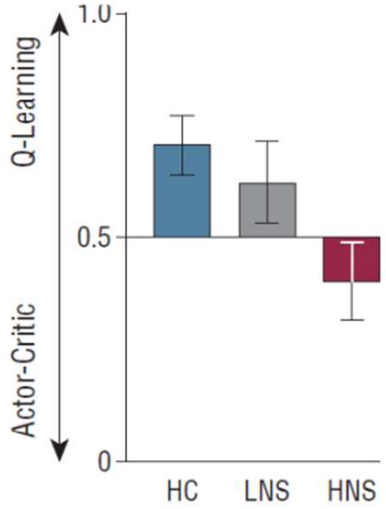
Q: expected value

α: learning rate

PE: prediction error

R: outcome





Gold et al., Arch Gen Psychiatr 2012

Optimal models

'We suggest that the positive symptoms of schizophrenia are caused by **an abnormality in the brains' inferencing mechanisms**, such that new evidence (including sensations) is not properly integrated, leading to **false predictions**.'

Fletcher & Frith, Nat Rev Neurosci 2010

Optimal models

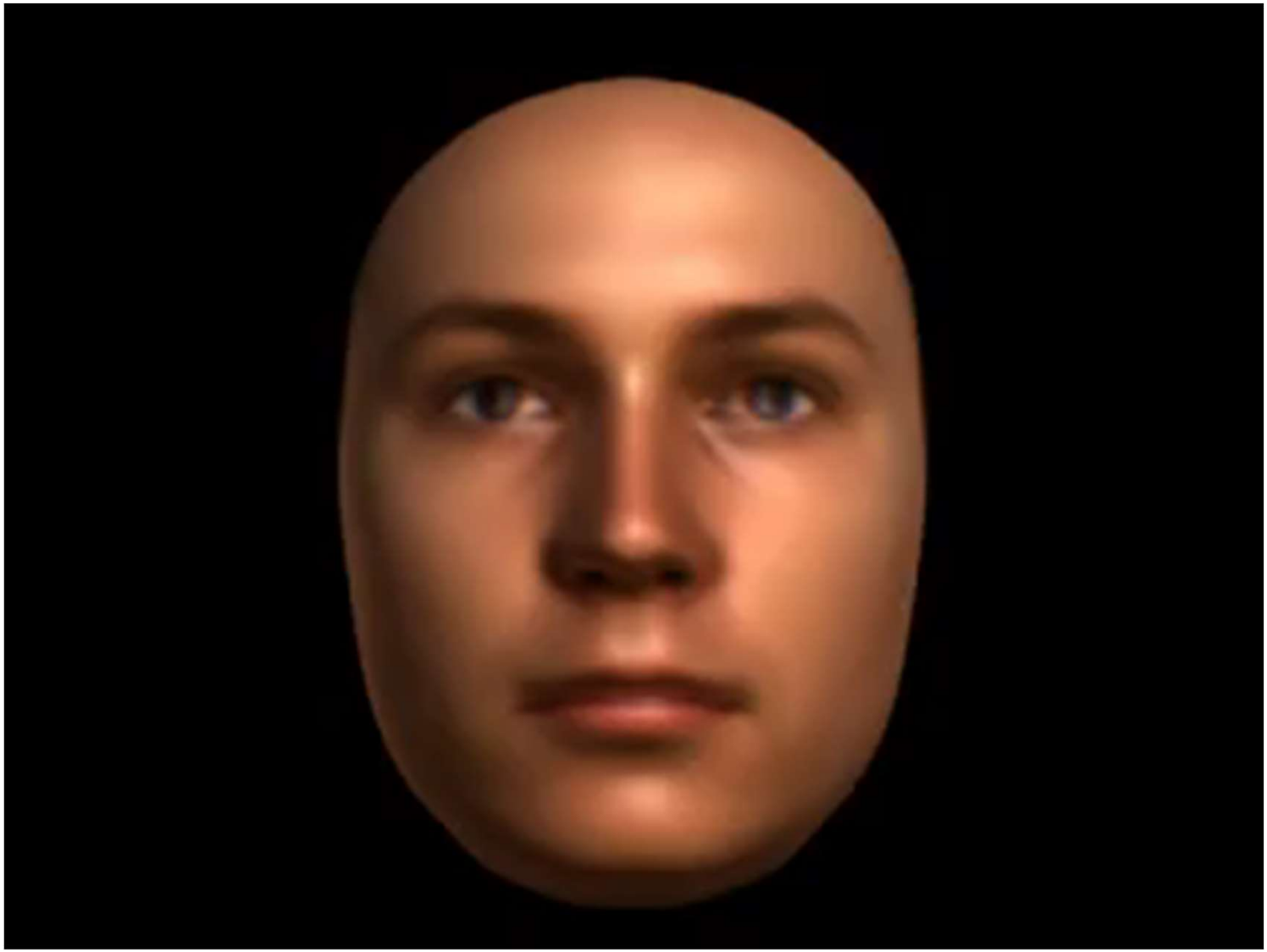
Hermann von Helmholtz (1821 – 1894)

Unconscious inference:
"The psychic activities that lead us to infer that there in front of us at a certain place there is a certain object of a certain character, are generally not conscious activities but unconscious ones. In their result they are equivalent to a conclusion, to the extent that the observed action on our senses enables us to form an idea as to the possible cause of this action."
(Handbuch der Physiologischen Optik, 1867)

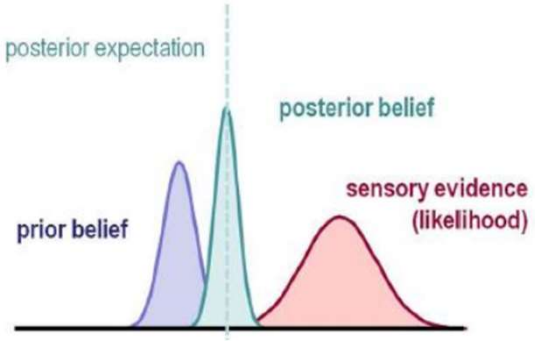
The **Helmholtz machine** (P. Dayan):

"The perceptual system is an inference engine whose function is to infer on the most probable cause of sensory input"

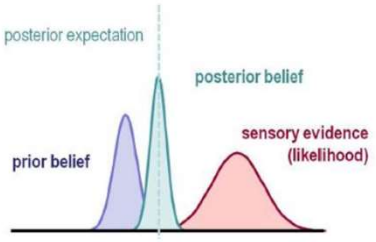
The hollow mask illusion



Bayesian perceptual inference

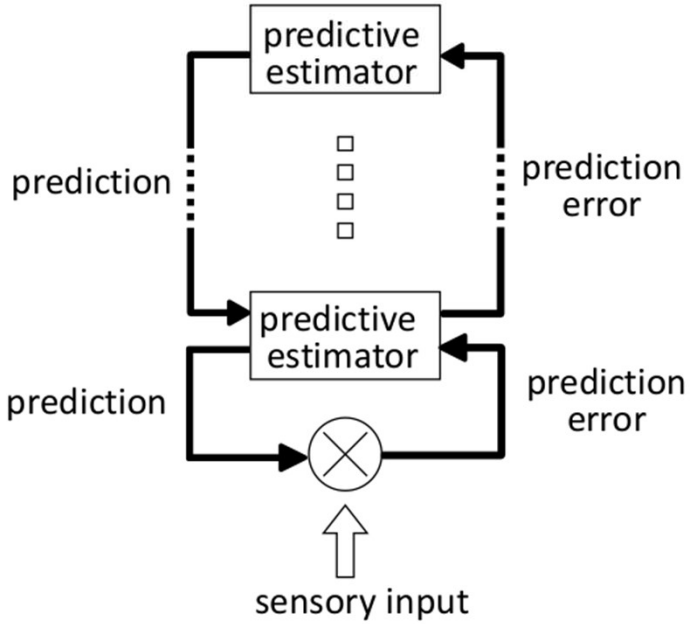


Predictive Coding



cognitive

sensory



prefrontal cortex

sensory cortices

Rao & Ballard, Nat Neurosci, 1999
Friston, Proc R Soc B, 2005

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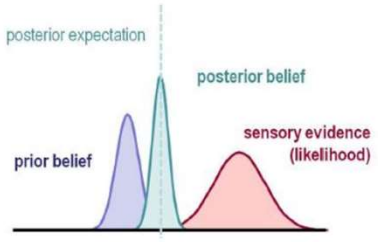

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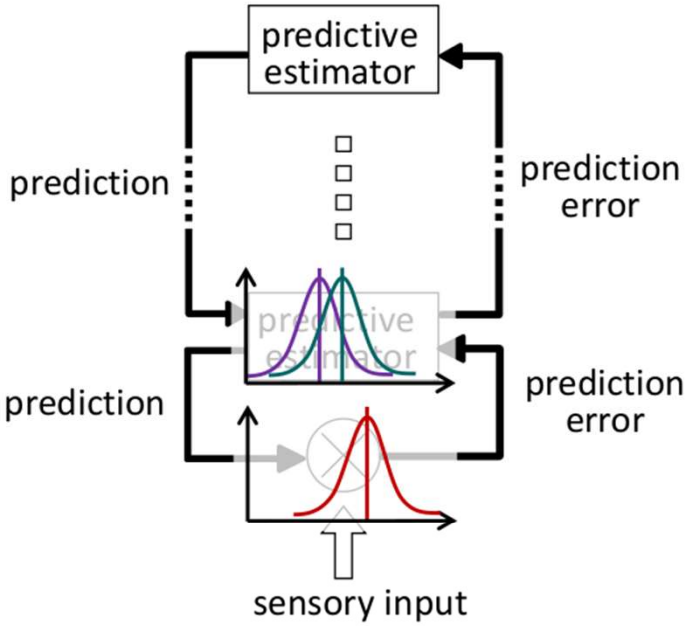

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Predictive Coding Models of Schizophrenia

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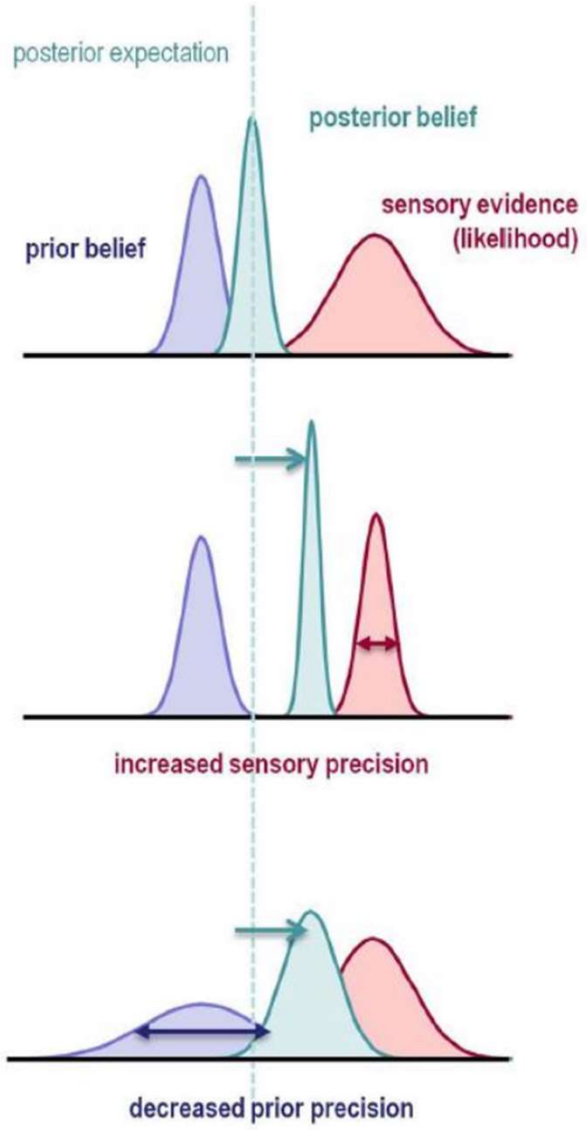
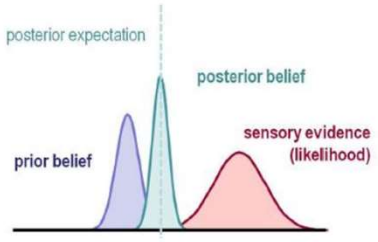


- Precision of prior beliefs ↓
- Precision of sensory data ↑

→ **Prediction error ↑**

Adams et al., Frontiers 2013

Predictive Coding



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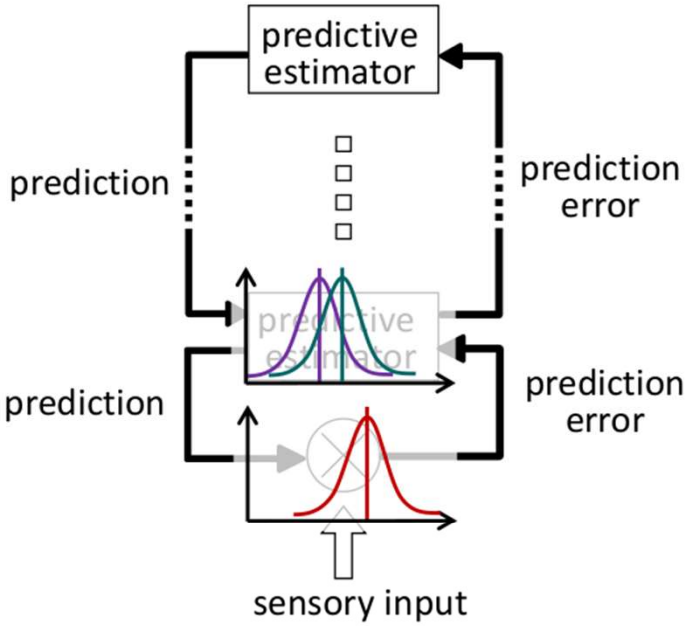

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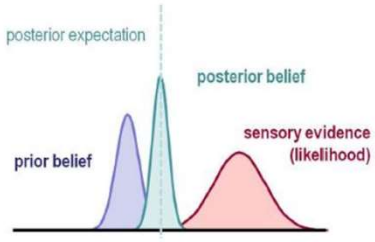

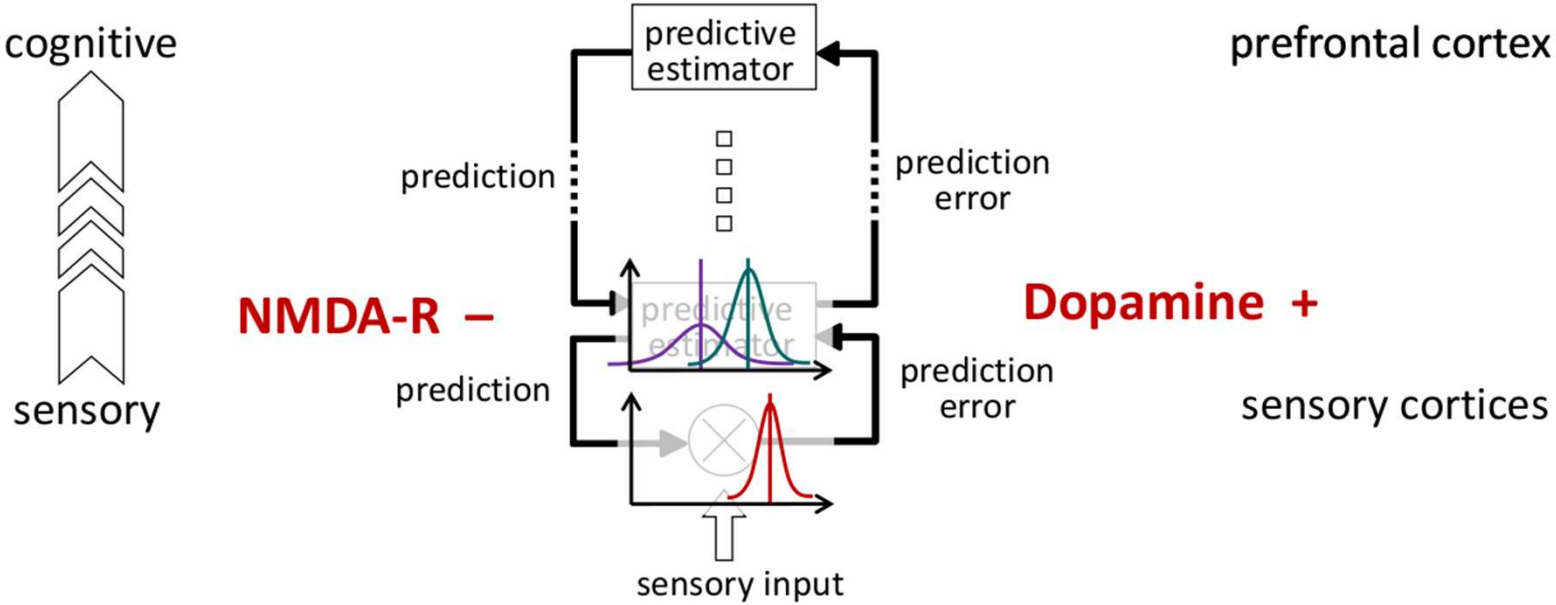

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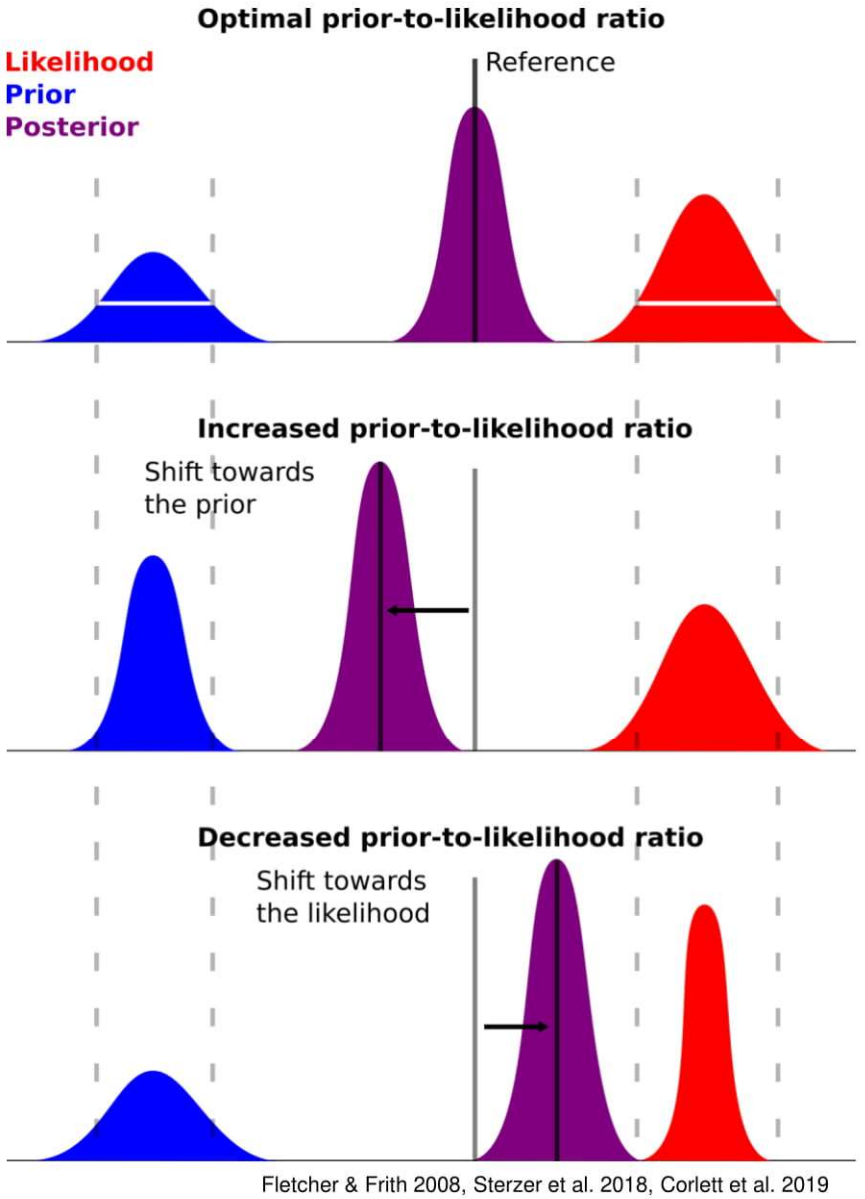
Empirical applications

Bayesian Perceptual Inference

Hypotheses

- Psychotic symptoms due to an alteration in perceptual inference.
- Prior-to-likelihood ratio: Shift in the relative precision of prior and likelihood



Fletcher & Frith 2008, Sterzer et al. 2018, Corlett et al. 2019

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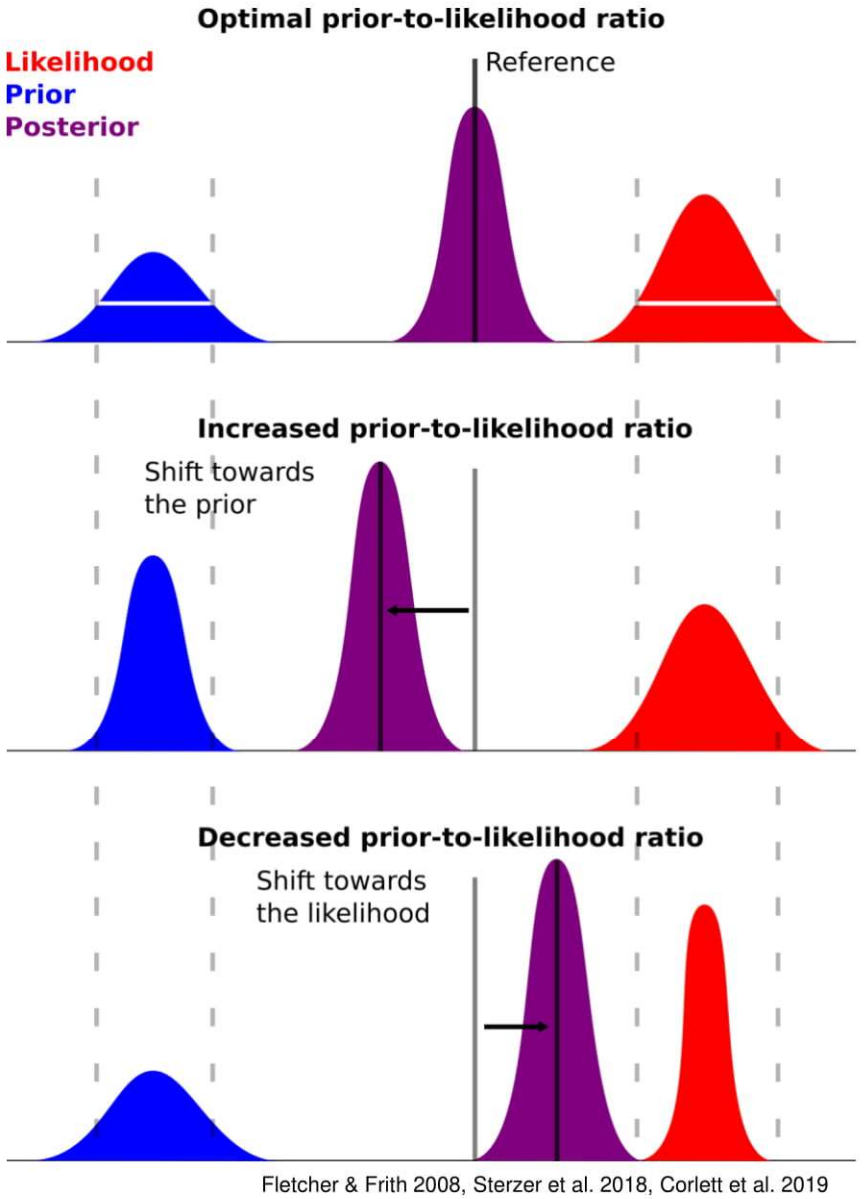
- Varying sensory evidence in ambiguous stimuli



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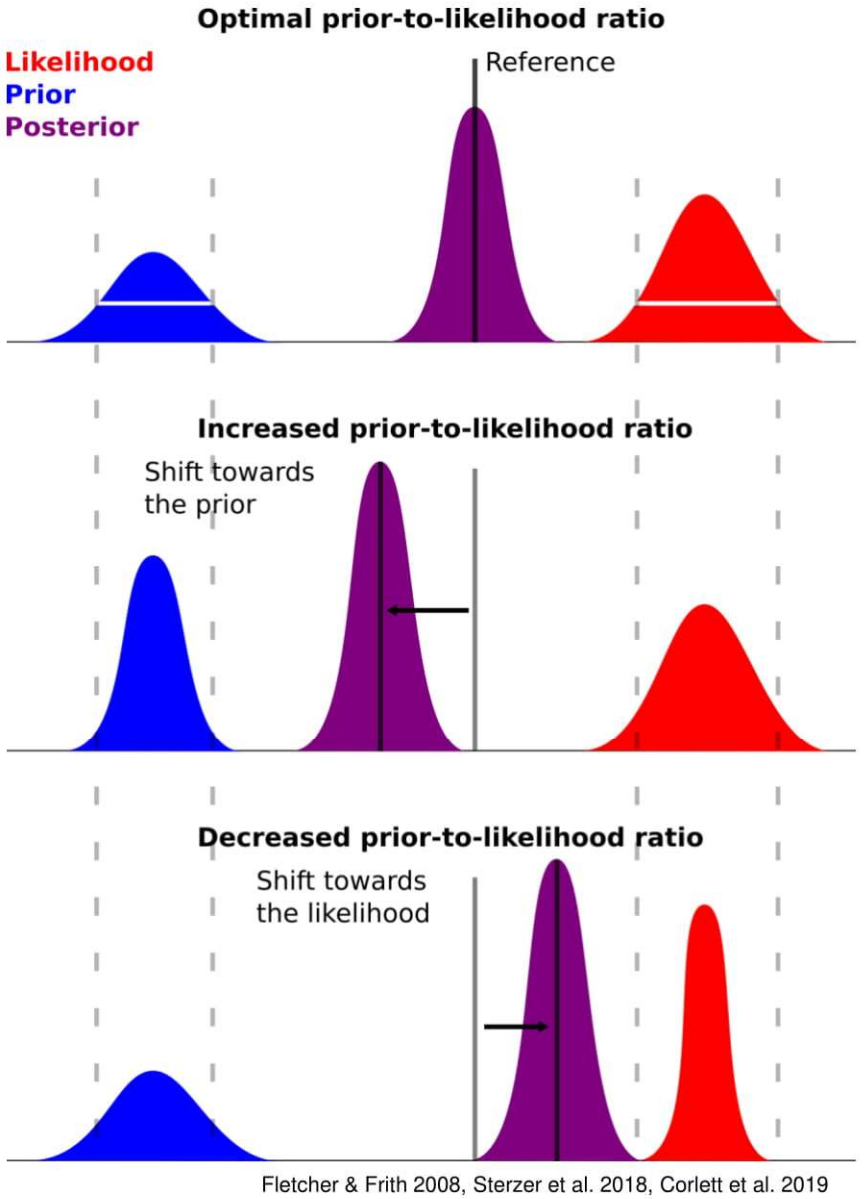
- Differences in PLR between schizophrenia (**Scz**) patients and controls?
- Correlation to symptom severity?



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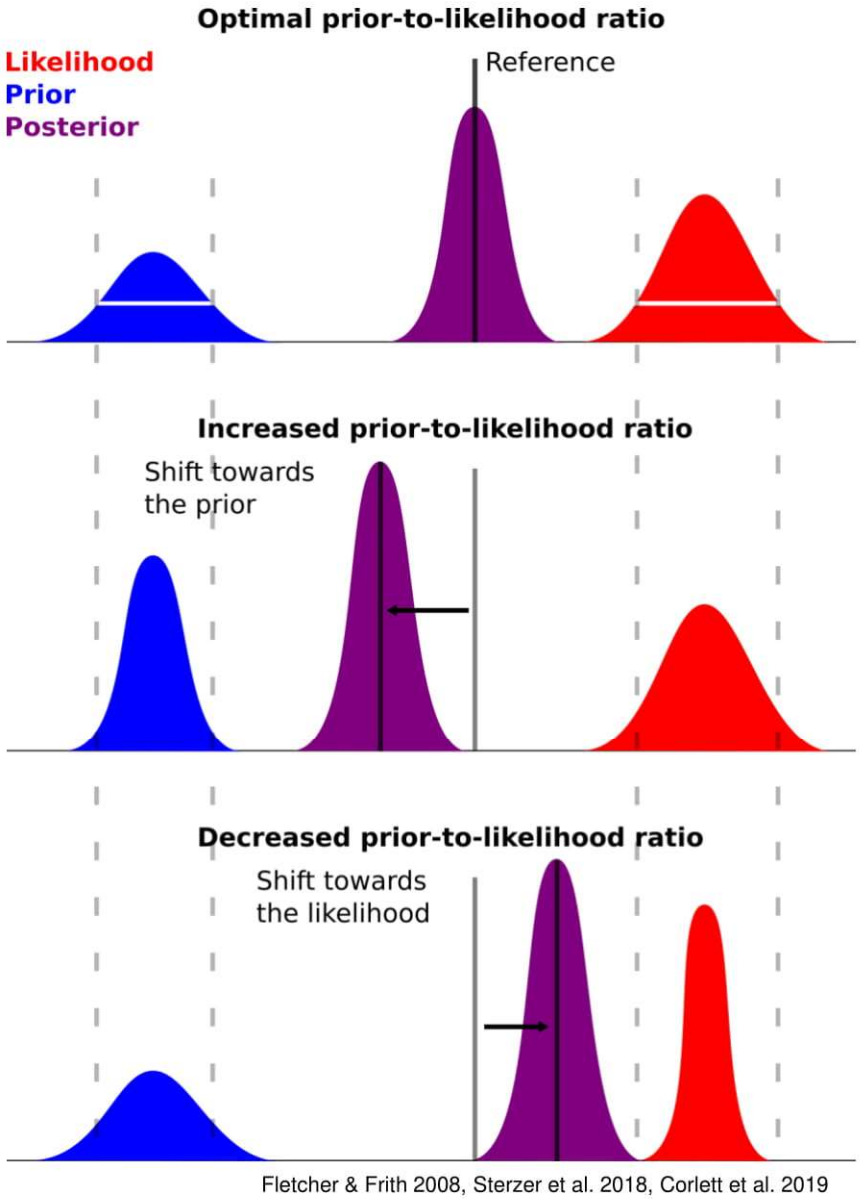

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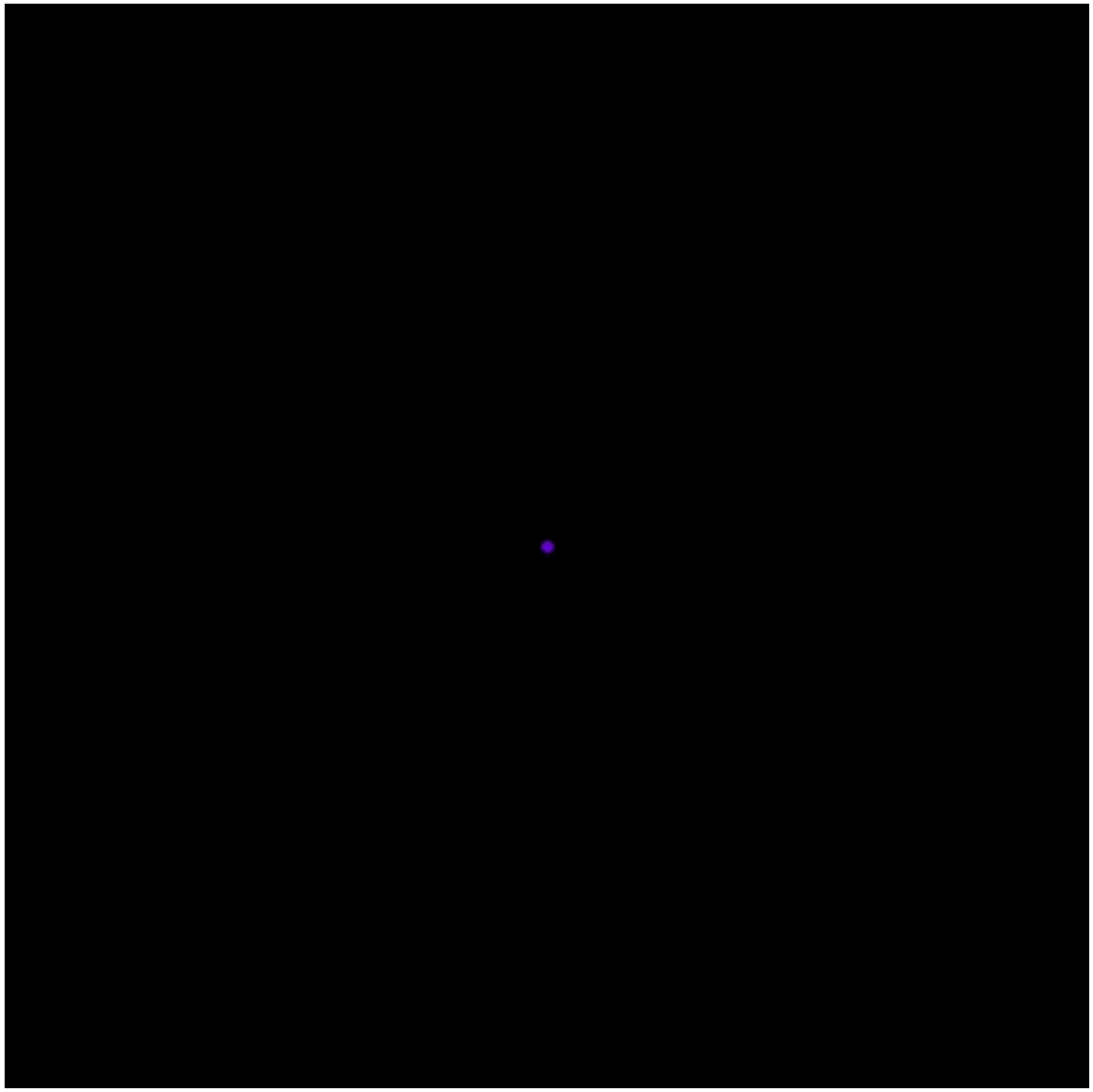
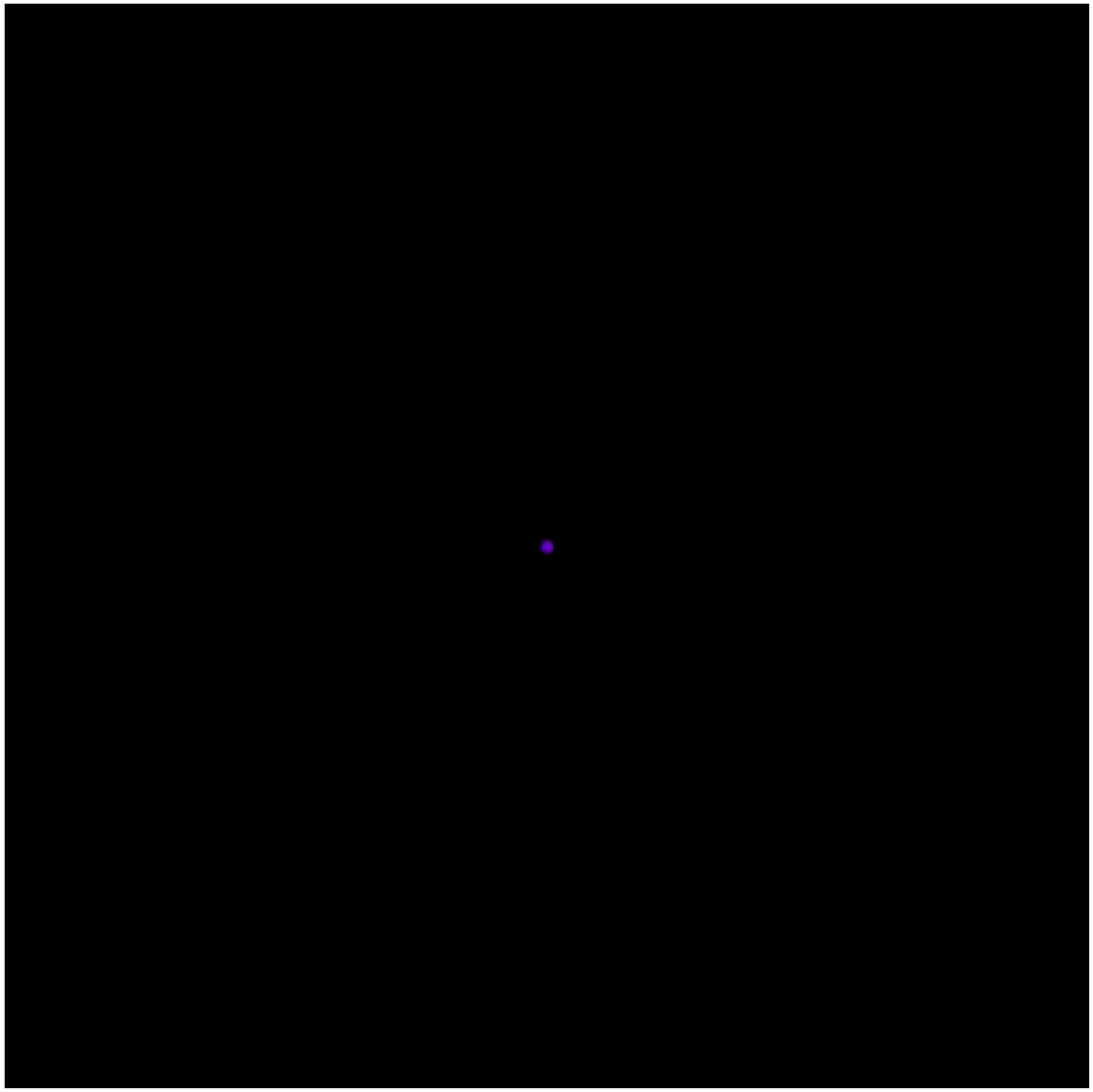
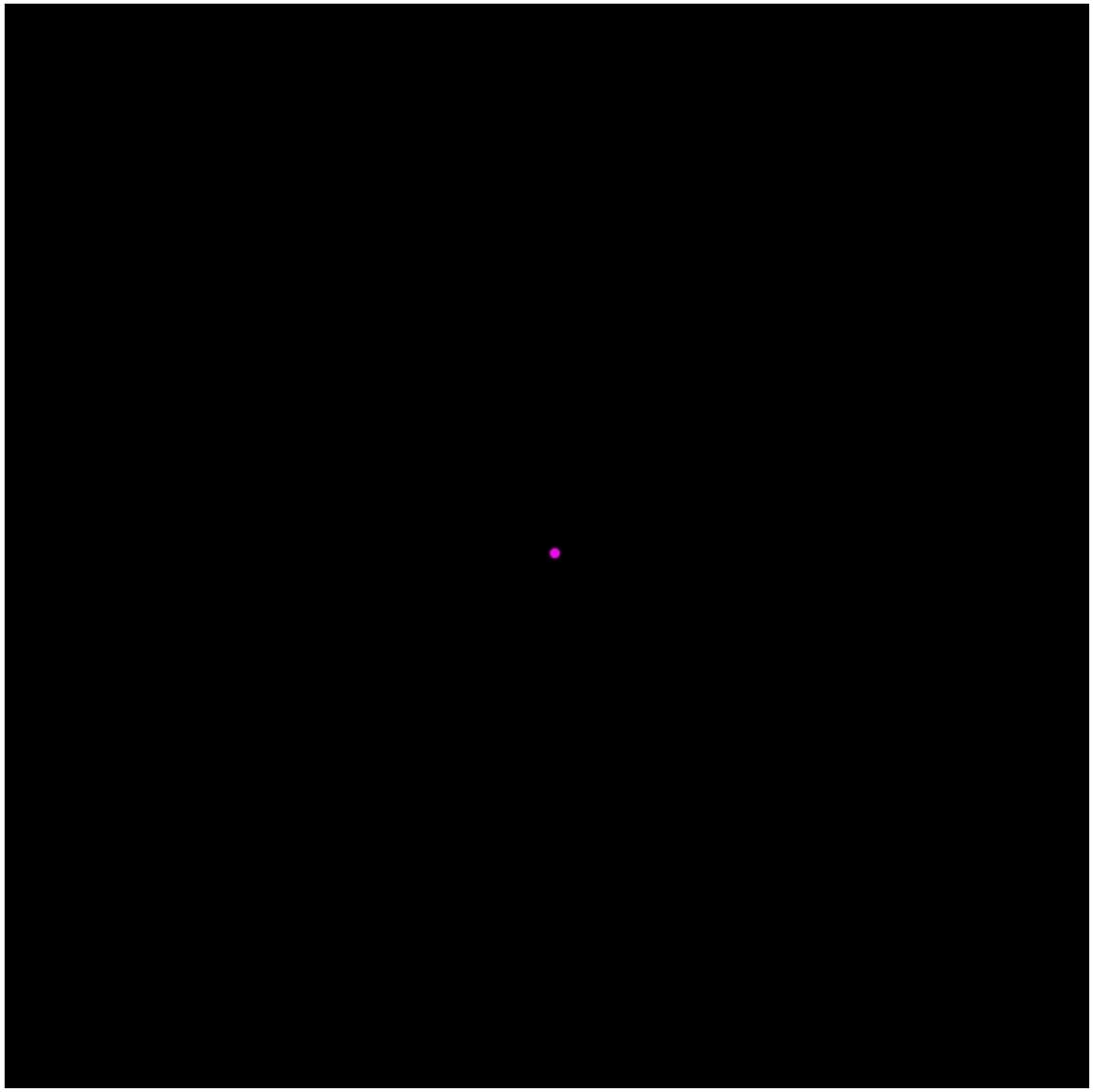


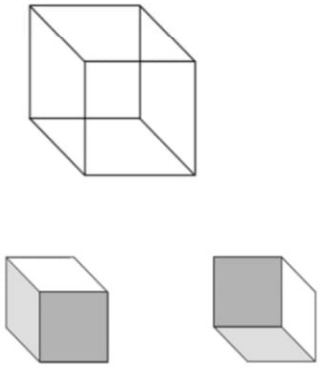




Models of Bistable Perception

Perceptual Bistability

- Constant ambiguous sensory: Transitions between two alternative, mutually exclusive interpretations.



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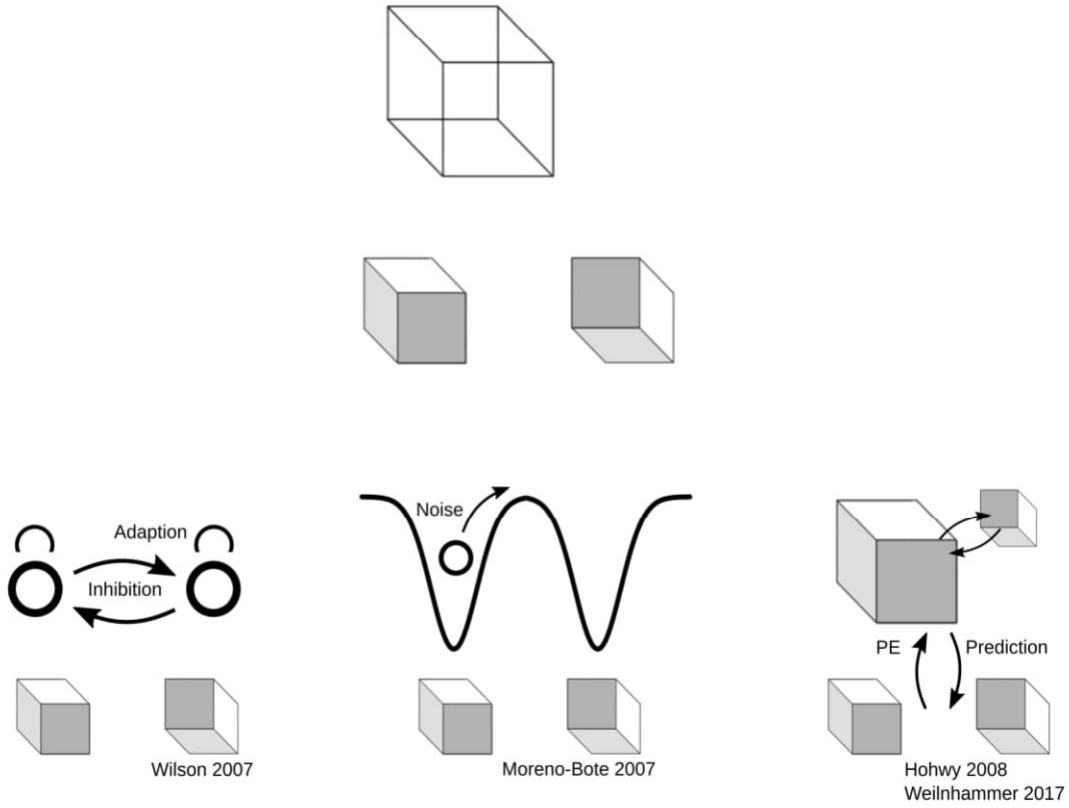


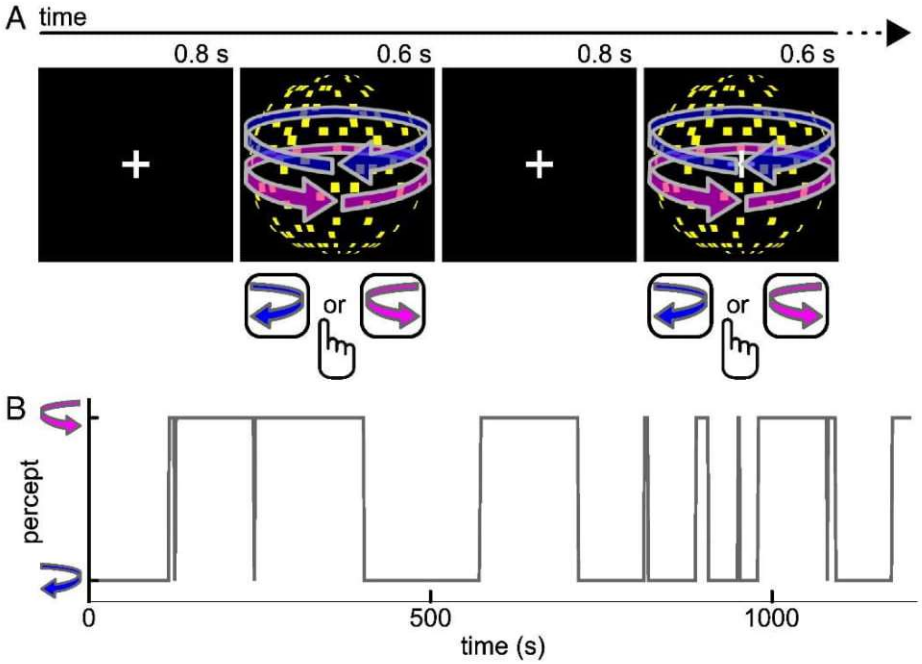
Predictive Coding

- Bistable perception arises from the interplay of perceptual predictions (prior) and sensory evidence (likelihood).

Prior Predictions in Bistability

Implicit priors

- Intermittent presentation leads to a stabilization of perception (“priming”)



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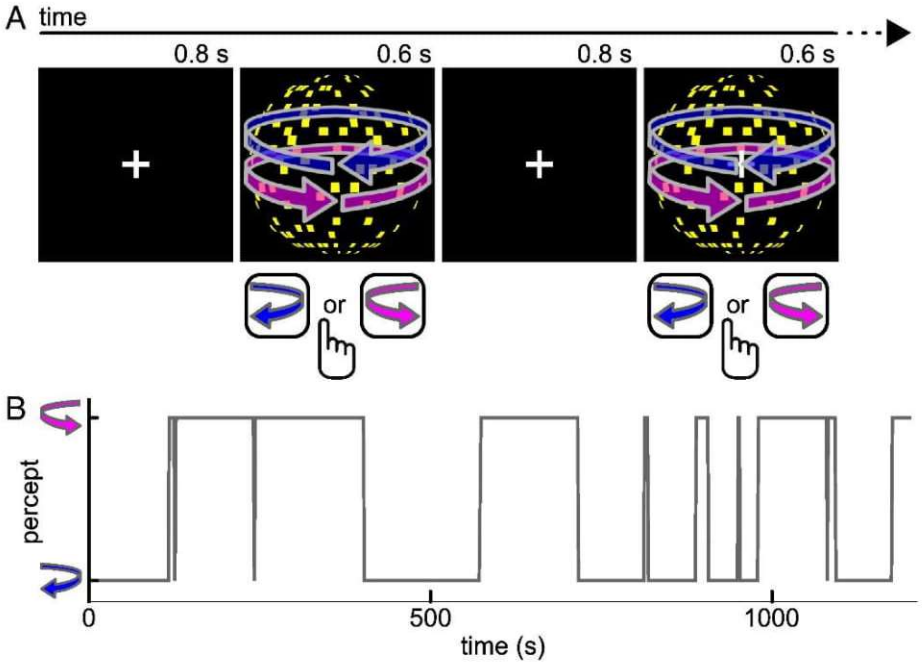

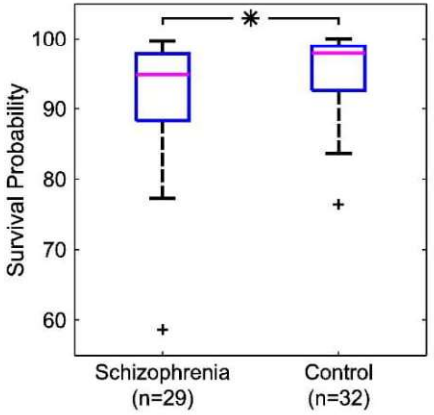

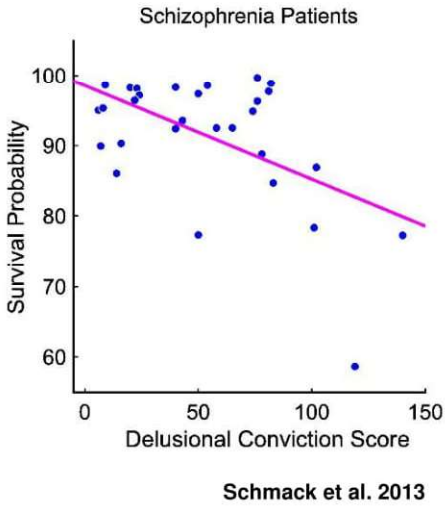

Schmack et al. 2013

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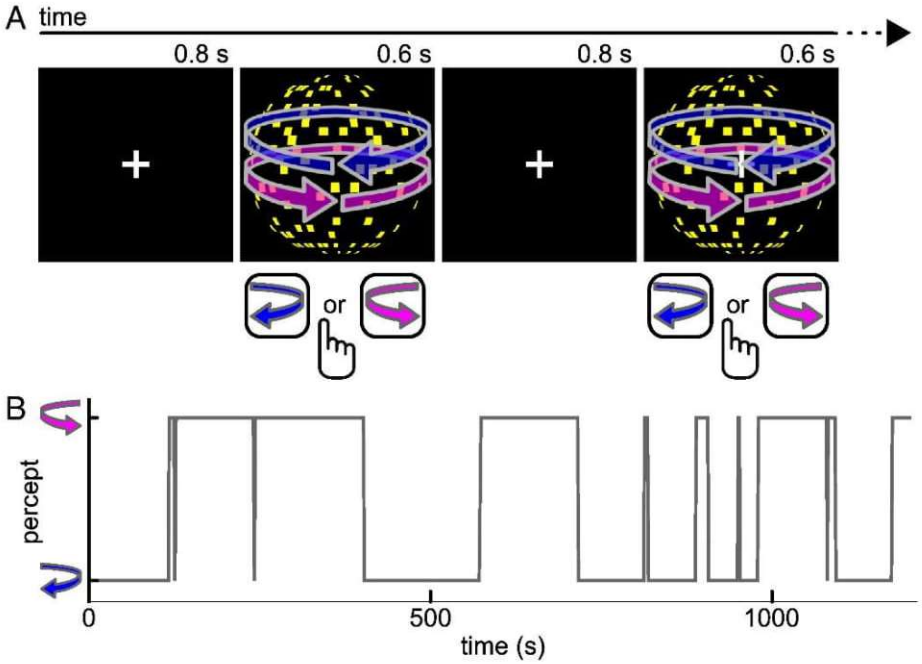
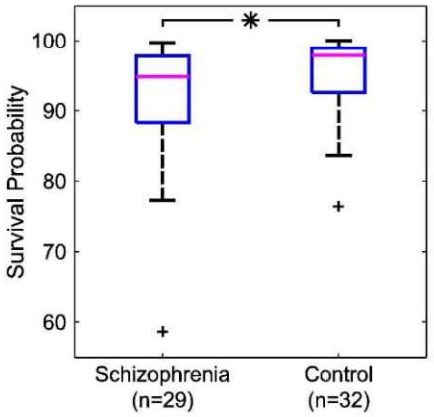
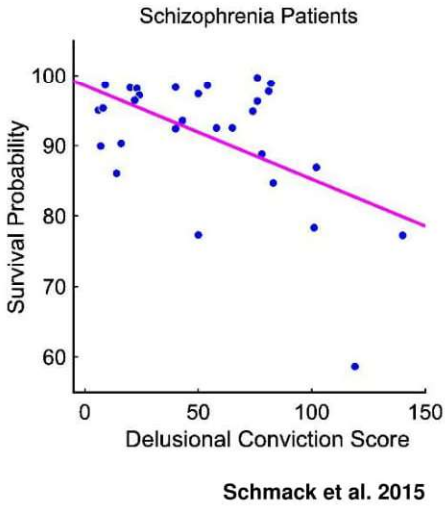
Implicit priors

- Intermittent presentation leads to a stabilization of perception (“priming”)







Schmack et al. 2015

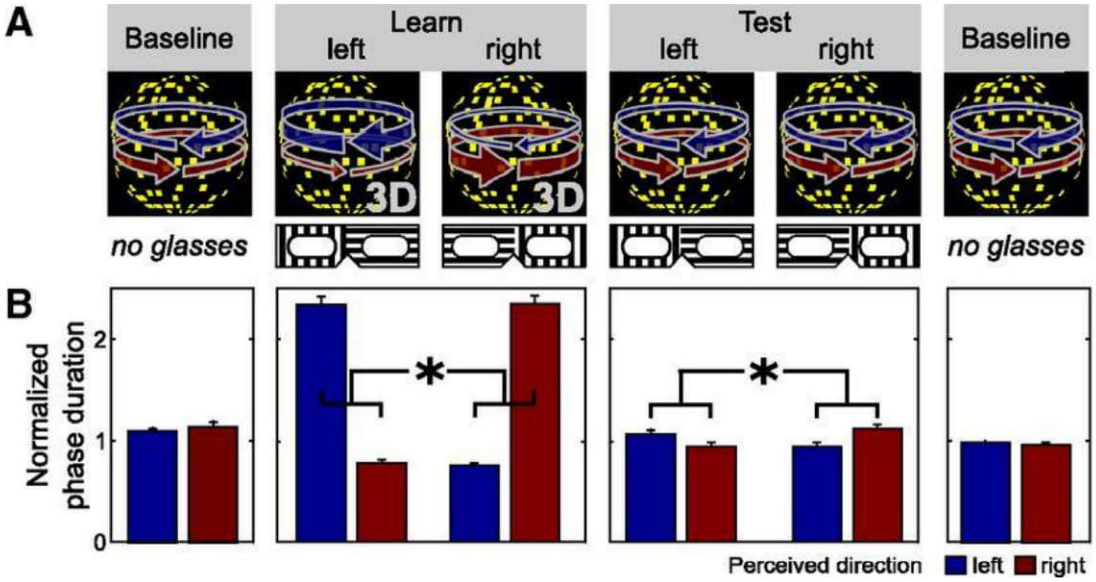
Scz: Reduced prior-to-likelihood ratio at sensory levels

- Reduced stabilization of perceptual time-courses
- Negative correlation of perceptual stability to delusional conviction

Prior Predictions in Bistability

Explicit Priors

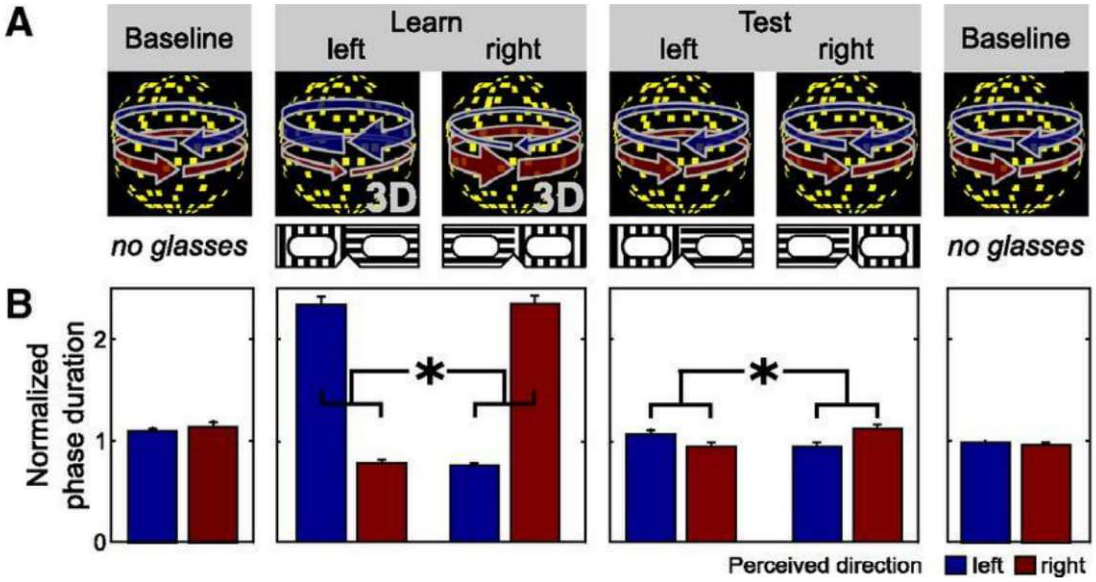
- Cognitive manipulations modulate perceptual time-courses in bistability (“biases”)

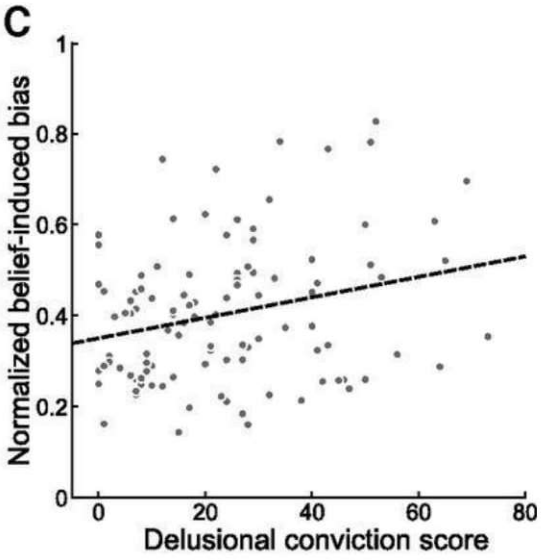


Prior Predictions in Bistability

Explicit Priors

- Cognitive manipulations modulate perceptual time-courses in bistability (“biases”)



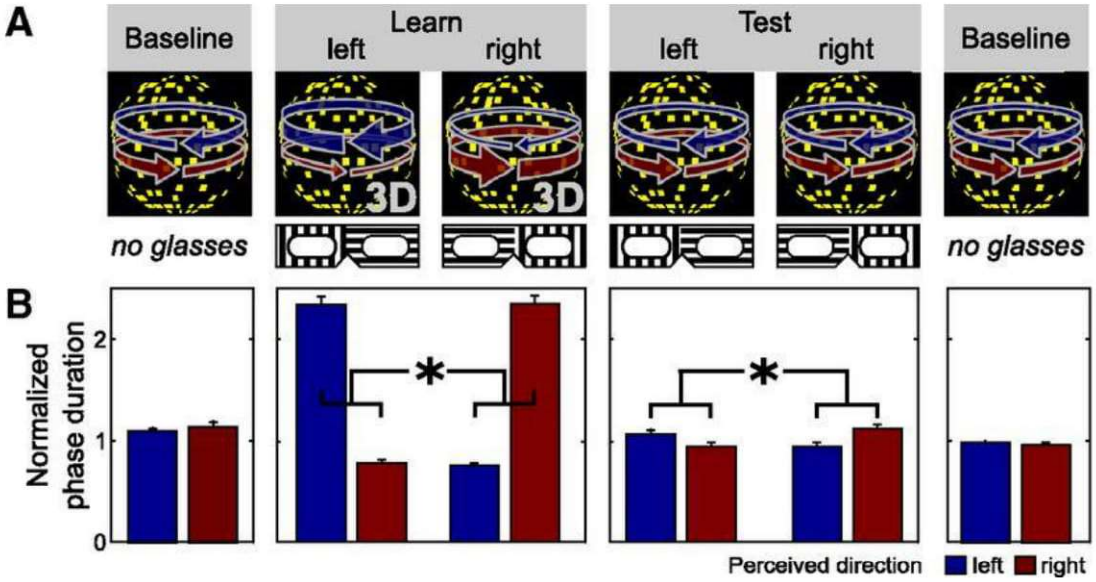


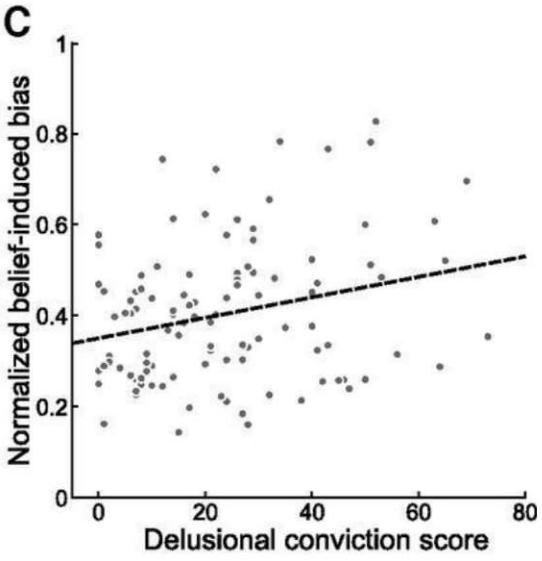
Schmack et al. 2013

Prior Predictions in Bistability

Explicit Priors

- Cognitive manipulations modulate perceptual time-courses in bistability (“biases”)





Schmack et al. 2013

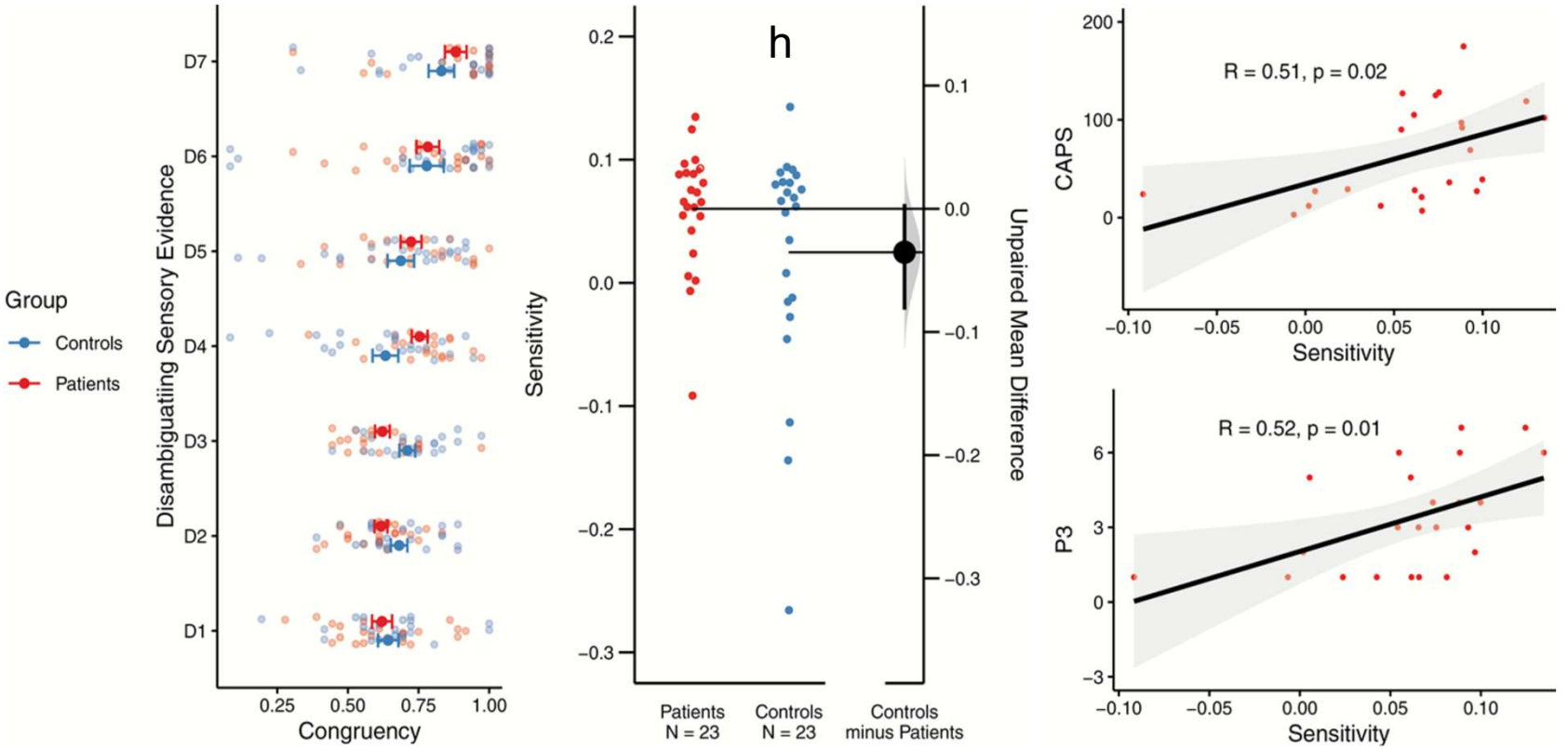
Delusions: Increased prior-to-likelihood ratio at higher levels

- Positive correlation of high-level biases to delusional conviction
- Compensation for reduced perceptual stability at sensory levels

Generative Models of Bistability

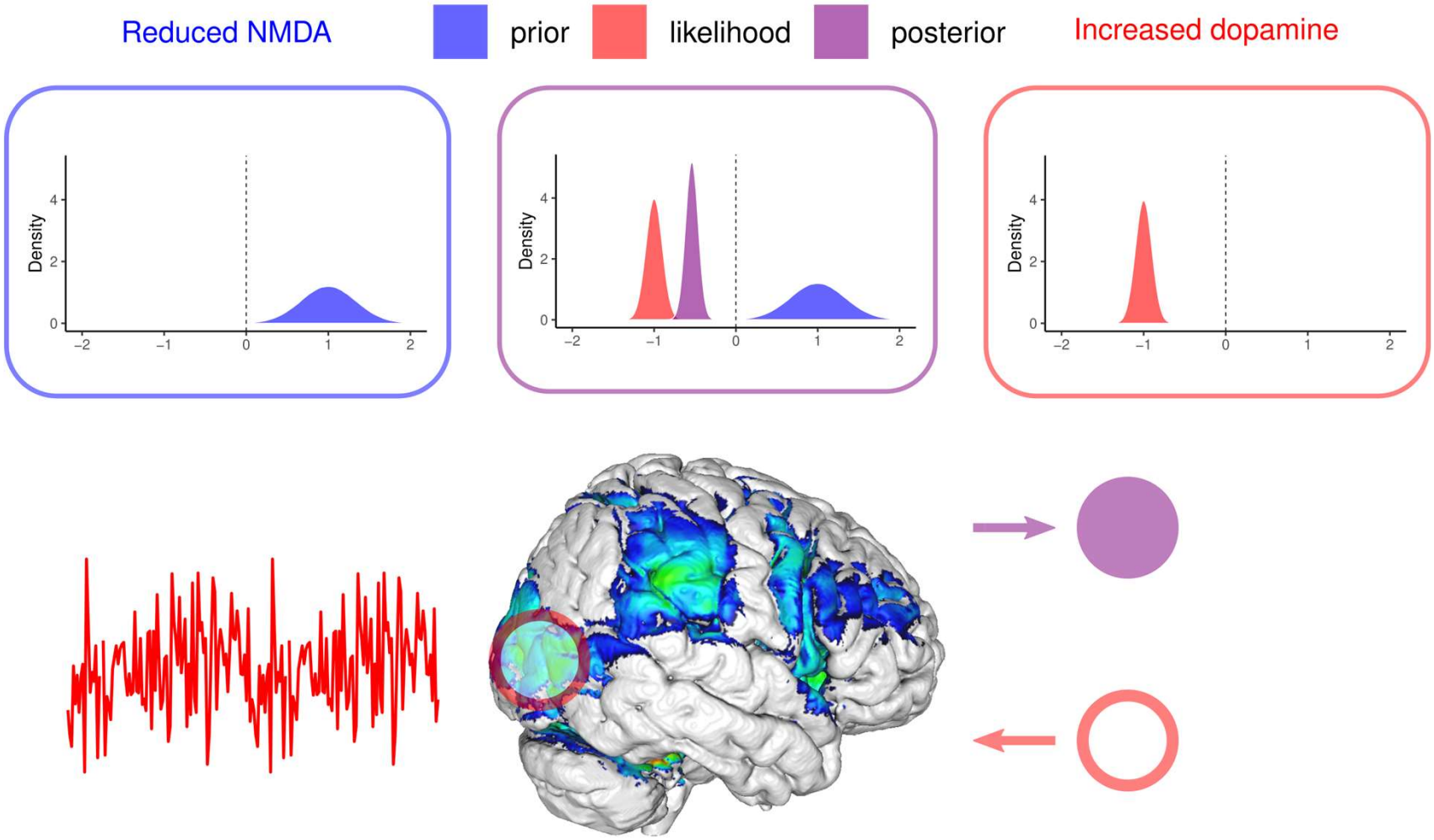
Predictive Coding

- Remaining evidence for the alternative stimulus interpretation constitutes a prediction error.



Weilnhammer,…, Sterzer (2020), ***Schizophrenia Bulletin***

Summary


Reduced NMDA
prior
likelihood
posterior
Increased dopamine
Density
4
2
0
−2
−1
0
1
2

Questions and Discussion