



James S. McDonnell Foundation



Circular Inference in Schizophrenia

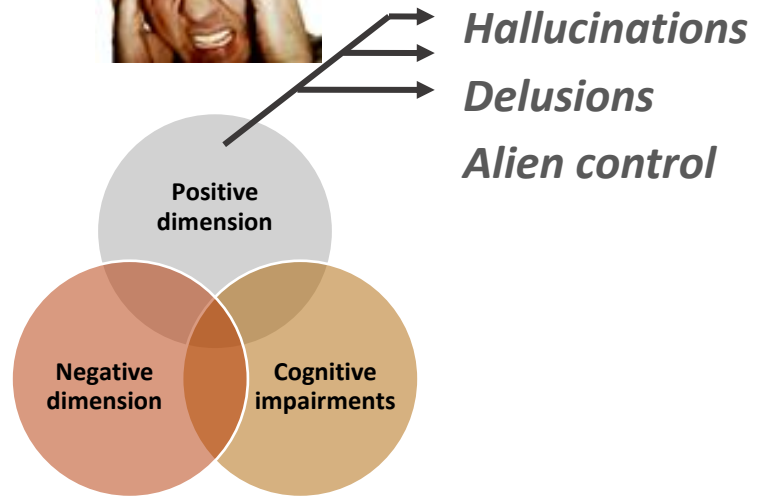
Sophie Deneve, Renaud Jardri, Sandrine Duverne

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Agence Nationale pour la Recherche (ANR)
James S. McDonnell Foundation
European research council (ERC)

Schizophrenia



- . 1% of the population.
- . Extremely disruptive.
- . Stigmatized.

Neural basis unknown, controversial

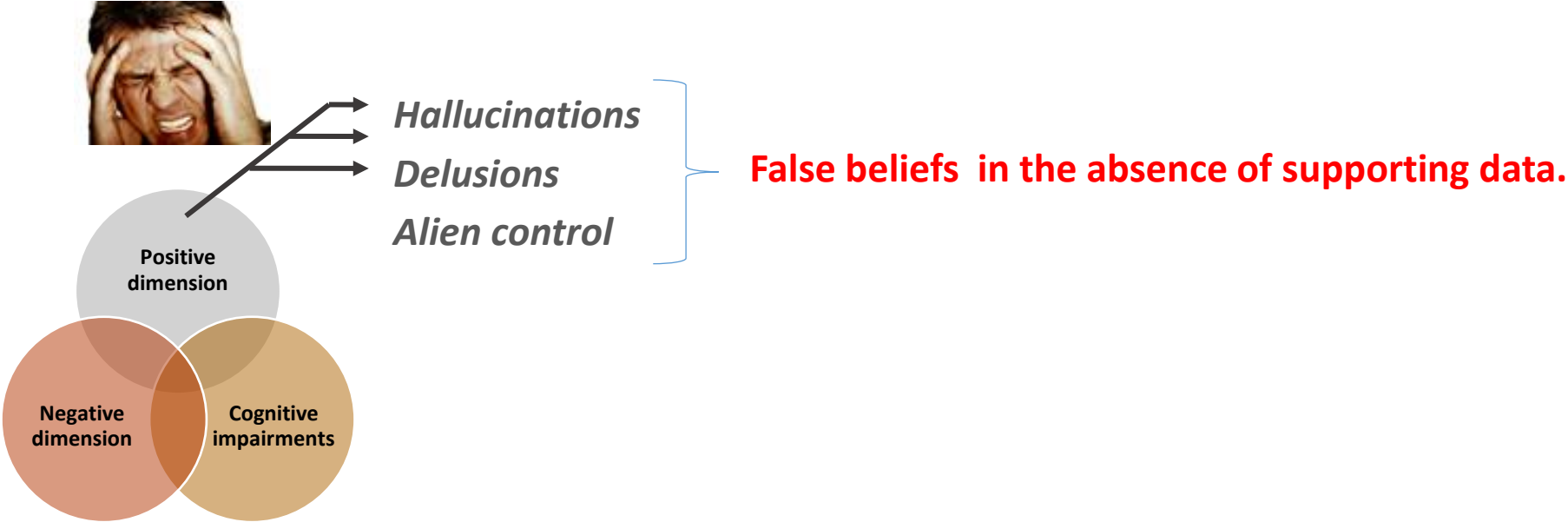
- Not resulting from focal brain lesions.
- Many neuromodulators involved (DA,NE,Ach,SE,Glu...).
- Affects “high level” but also “low level” functions.
- Large panel and heterogeneity of symptoms.

Neural basis unknown, controversial

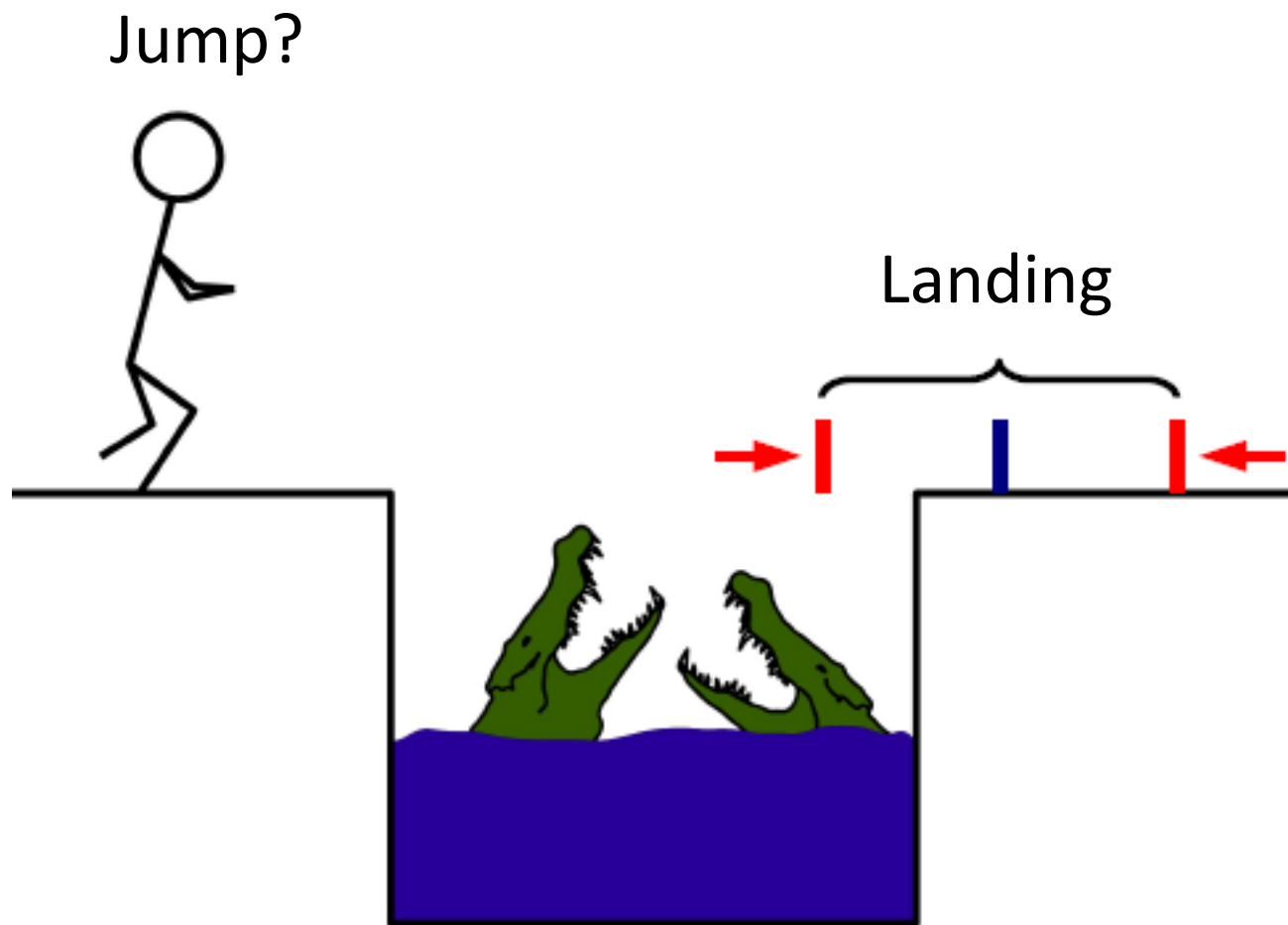
- Not resulting from focal brain lesions.
- Many neuromodulators involved (DA,NE,Ach,SE,Glu...).
- Affects “high level” but also “low level” functions.
- Large panel and heterogeneity of symptoms.

“Variety of dysfunctions similarly affecting global circuit functions”

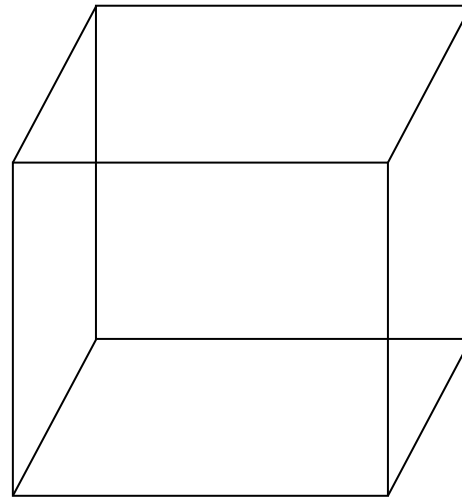
Schizophrenia: Normative approach



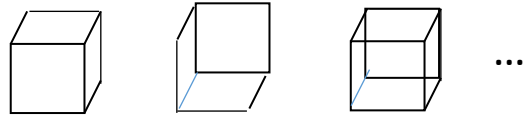
Uncertainty and decision



Uncertainty and perception



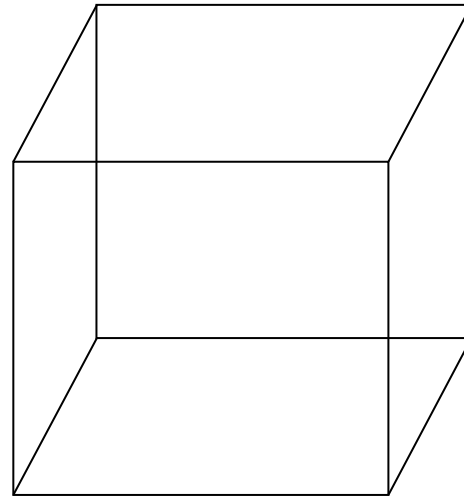
Uncertainty and perception



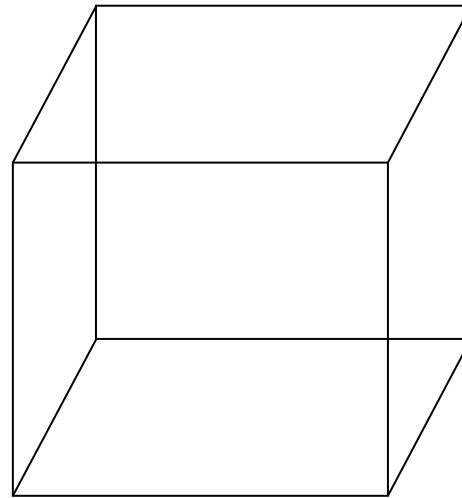
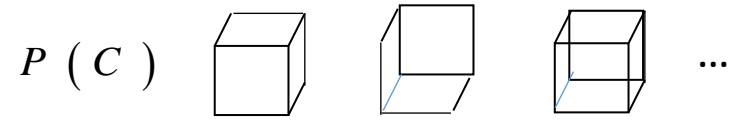
Cause



Sensory observations

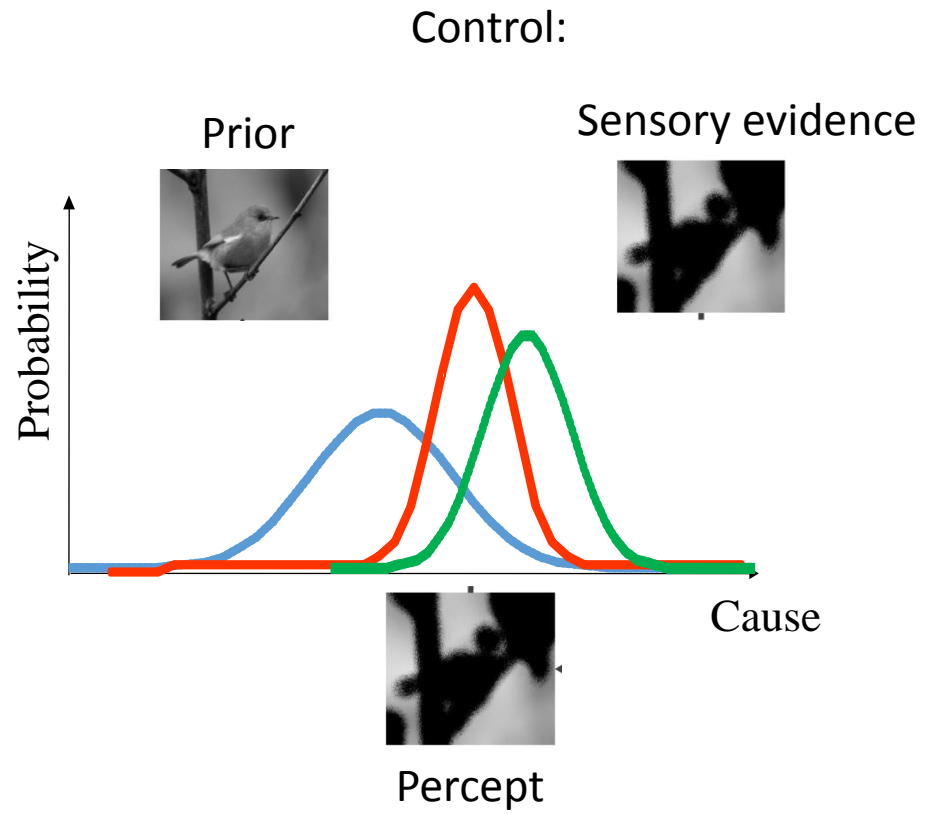


Uncertainty and perception

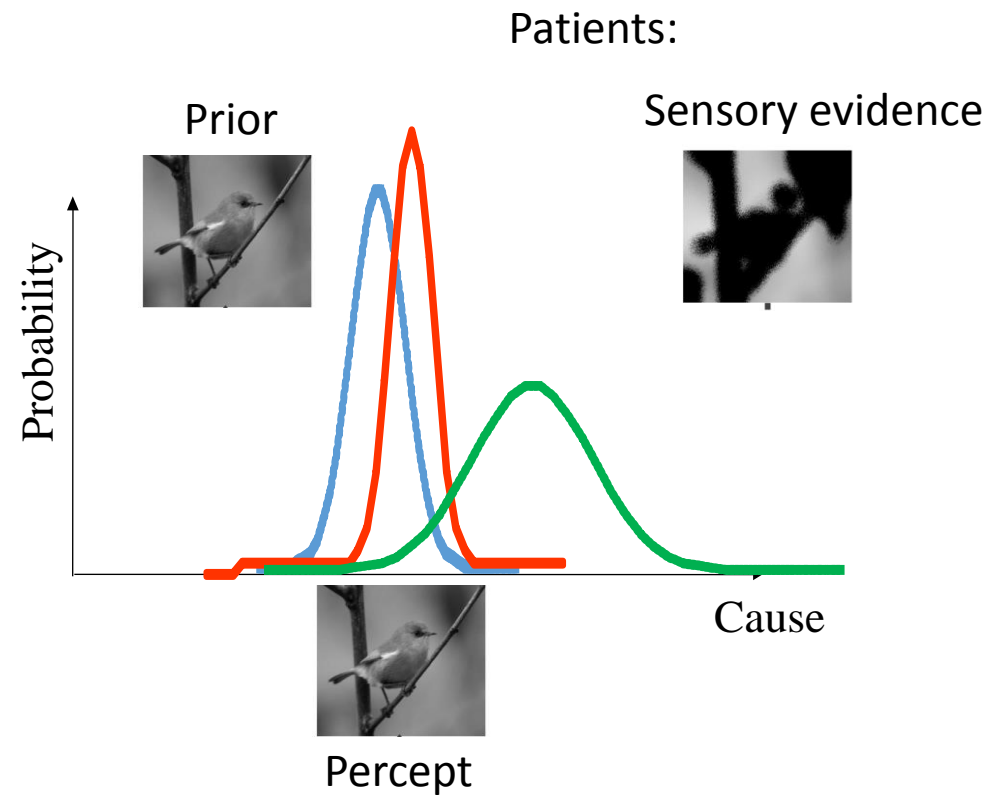
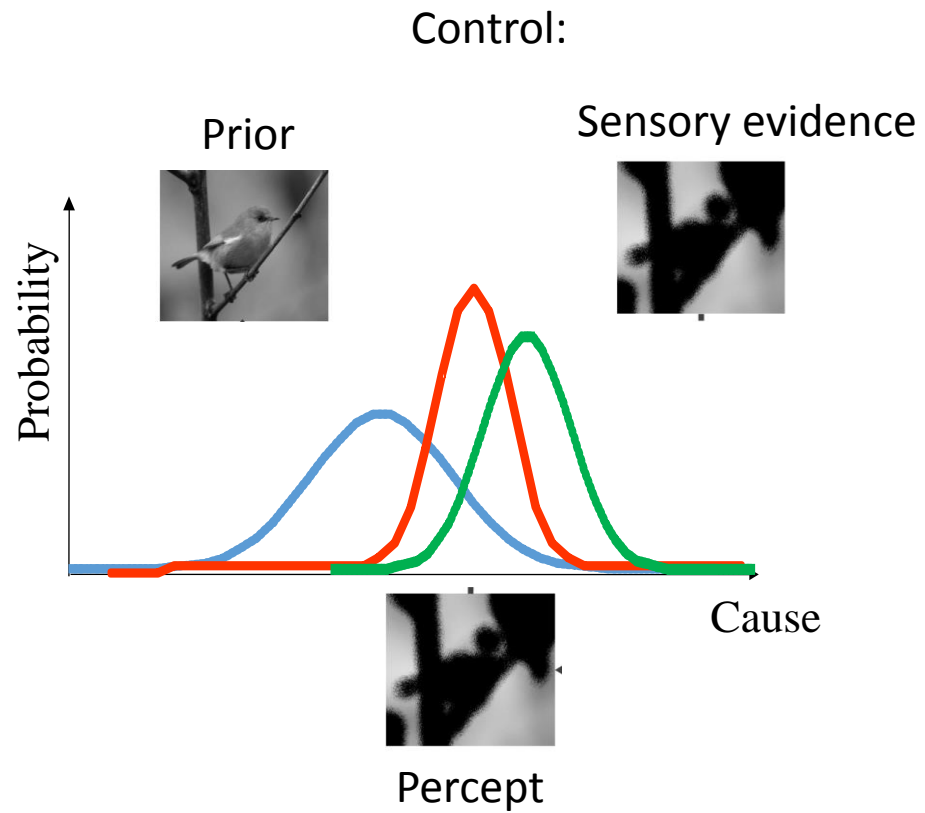


$$P(C|S) \sim P(S|C)P(C)$$

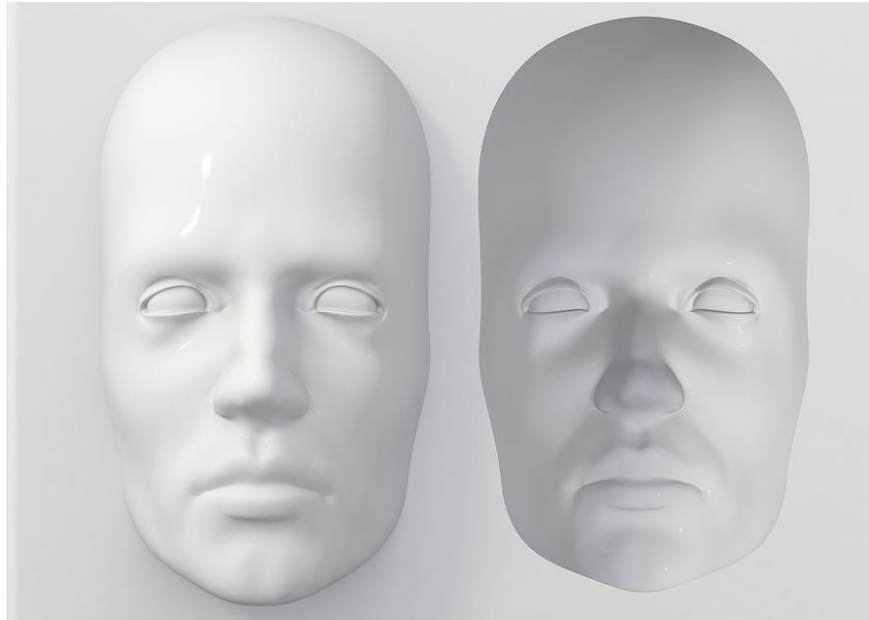
Are prior beliefs over-rated?



Are prior beliefs over-rated?

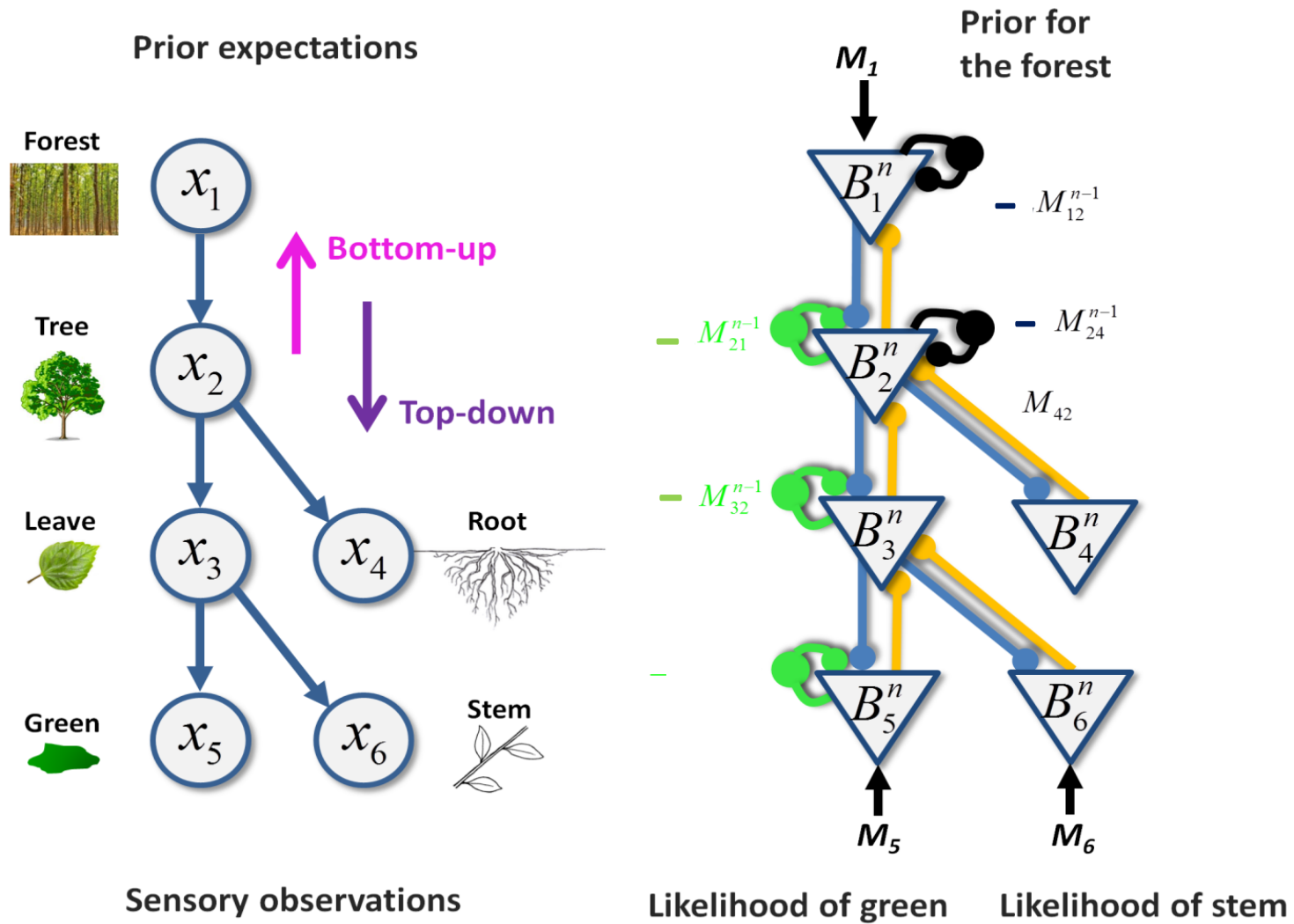


Patients are sensitive to perceptual illusions

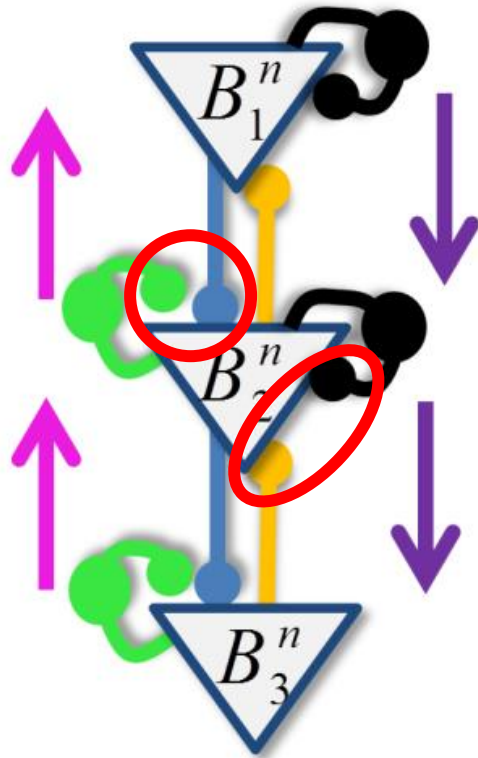


Schneider U, Borsutzky M, Seifert J, Leweke FM, Huber TJ, Rollnik JD et al. (2002).

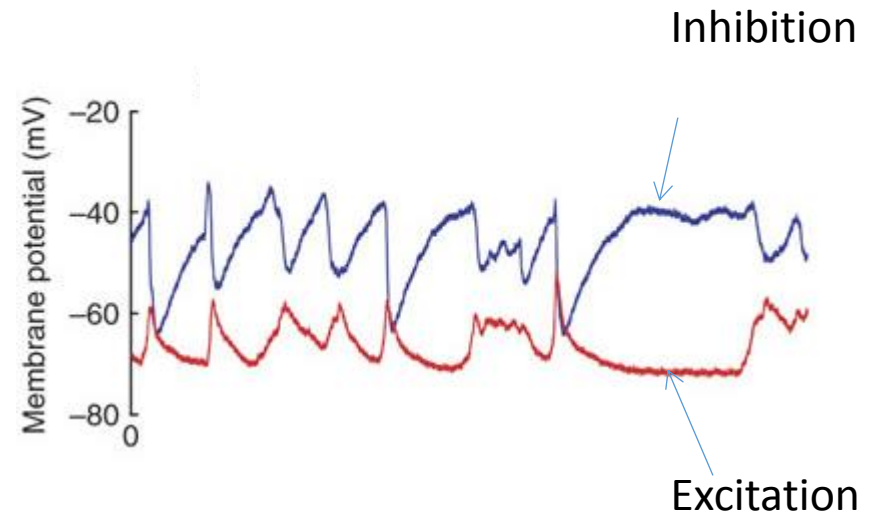
Belief propagation and inhibitory loops



Excitatory/inhibitory balance



- Tightly regulated.
- Shape dynamics of cortical circuits.
- Improves with maturation/learning/performance.
- Disrupted in other pathologies (autism, bipolar disorder, trauma ...)



Okun and Lampl, *Nat Neuro* 2008

Disruption in Excitatory/Inhibitory balance/regulation

Lower density of GABAergic synapses; Impaired Gamma oscillations; Animal models; Glutamateergic hypothesis: Ketamine and NMDA receptors...

Dalmau J, Gleichman AJ, Hughes EG, Rossi JE, Peng X, Lai M, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies.

Howes, O., McCutcheon, R. & Stone, J. Glutamate and dopamine in schizophrenia: an update for the 21st century. *J Psychopharmacol*, 1-19 (in press).

O'Donnell, P. Adolescent onset of cortical disinhibition in schizophrenia: insights from animal models. *Schizophr Bull* **37**, 484-492 (2011).

Lewis DA, Hashimoto T, Volk DW. Cortical inhibitory neurons and schizophrenia. *Nat Rev Neurosci*. 2005 Apr;6(4):312-24.

Lisman JE, Coyle JT, Green RW, Javitt DC, Benes FM, Heckers S, et al. Circuit-based framework for understanding neurotransmitter and risk gene interactions in schizophrenia. *Trends Neurosci*. 2008 May;31(5):234-42.

Lubow RE, Weiner L. Latent inhibition: Data, theories, and applications to schizophrenia. New-York: Cambridge University Press; 2010.

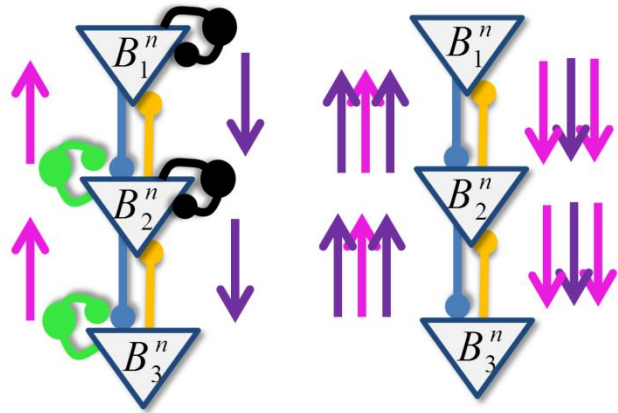
Mulert C, Kirsch V, Pascual-Marqui R, McCarley RW, Spencer KM. Long-range synchrony of gamma oscillations and auditory hallucination symptoms in schizophrenia. *Int J Psychophysiol*. 2011 Jan;79(1):55-63.

O'Donnell P. Adolescent onset of cortical disinhibition in schizophrenia: insights from animal models. *Schizophr Bull*. 2011 May;37(3):484-92.

Uhlhaas PJ, Singer W. Abnormal neural oscillations and synchrony in schizophrenia. *Nat Rev Neurosci*. 2010 Feb;11(2):100-13.

Yoon JH, Maddock RJ, Rokem A, Silver MA, Minzenberg MJ, Ragland JD, et al. GABA Concentration Is Reduced in Visual Cortex in Schizophrenia and Correlates with Orientation-Specific Surround Suppression. *Journal of Neuroscience*. 2010 Mar 10;30(10):3777-81.

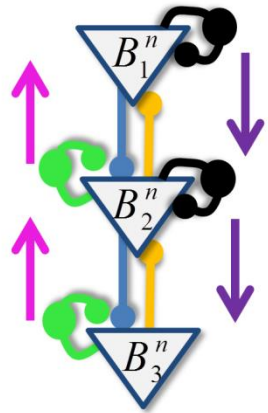
Why are inhibitory loops necessary?



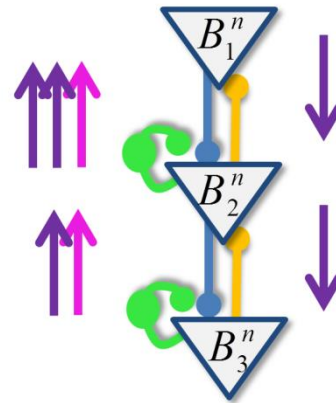
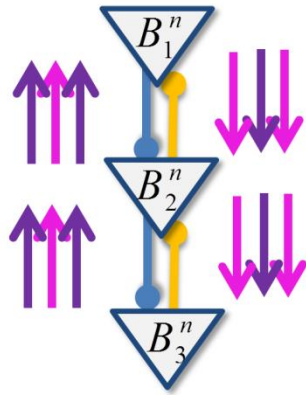
Over-confidence
Disorganized thoughts

Why are inhibitory loops necessary?

Descending loops:

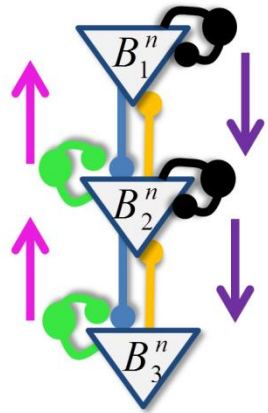


Over-confidence
Disorganized thoughts



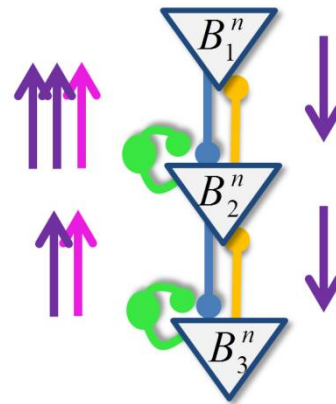
“See what you expect”
Prior expectation over-rated

Why are inhibitory loops necessary?



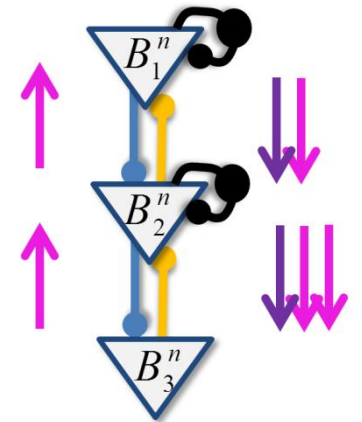
Over-confidence
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Descending loops:



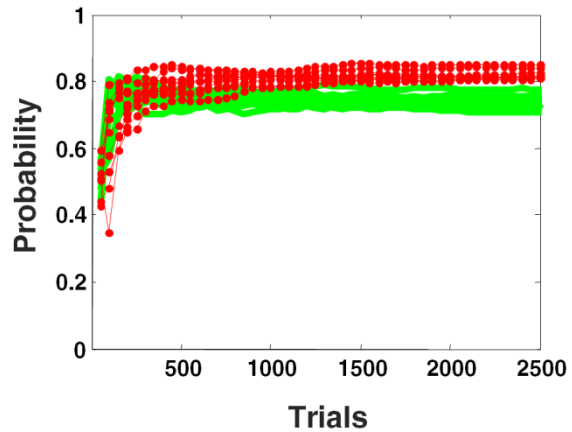
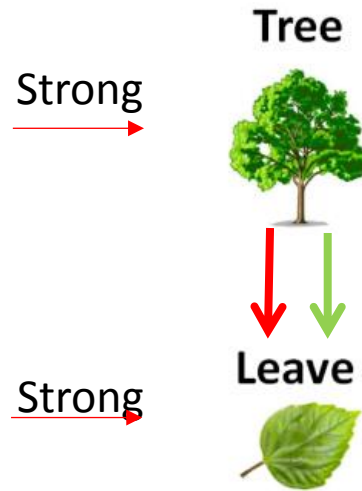
“See what you expect”
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Climbing Loops:

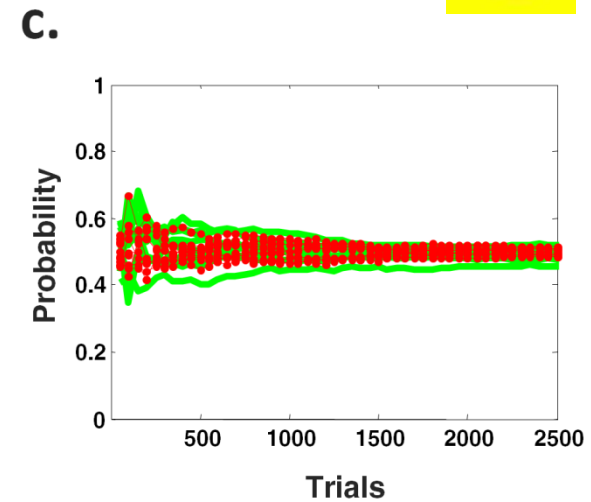
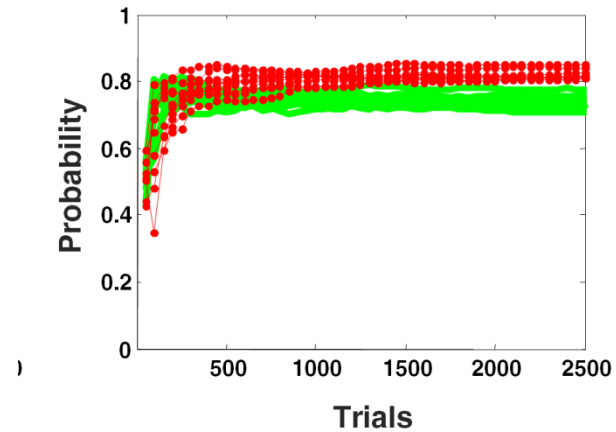
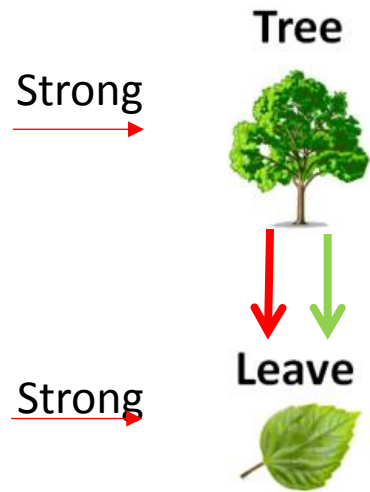


“Expect what you see”
Sensory evidence over-interpreted

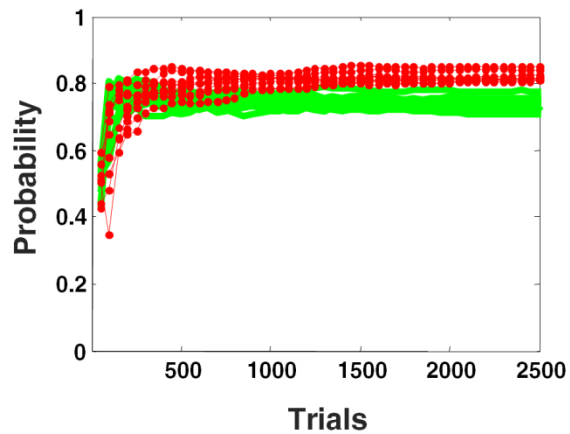
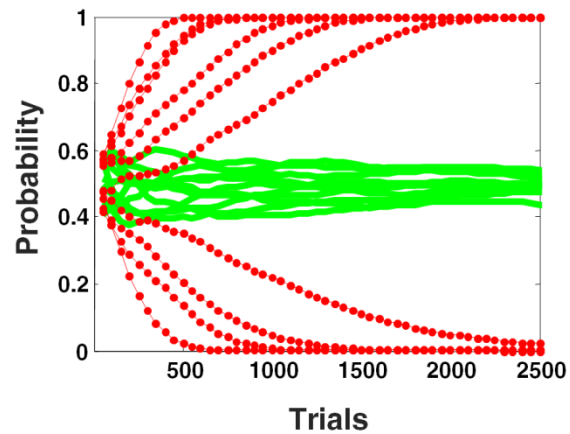
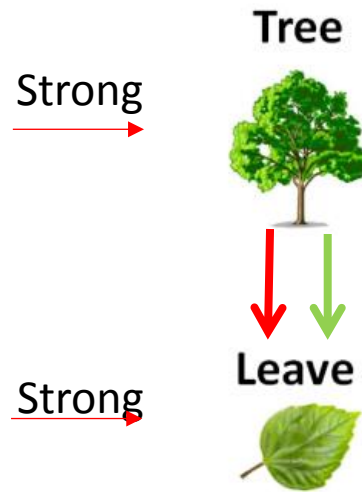
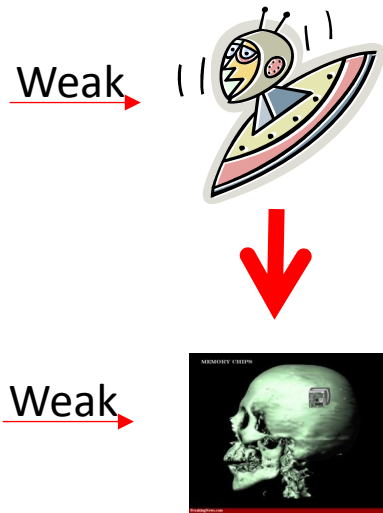
Learning of inexistent causal relationships (Delusions)



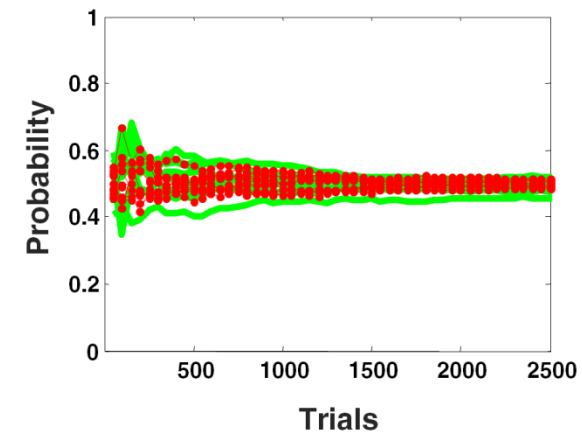
Learning of inexistent causal relationships (Delusions)



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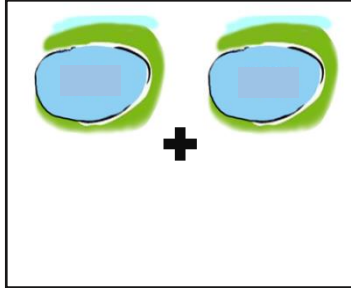


C.



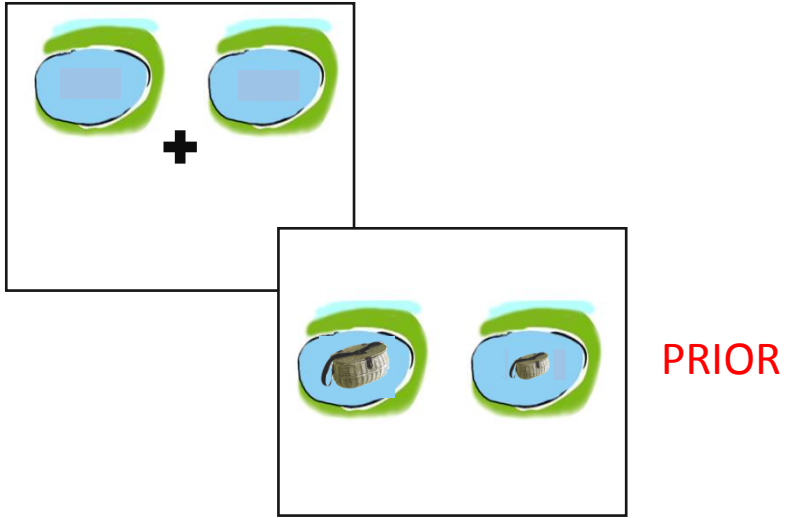
The Fisher Task

Renaud Jardri Alexandra Litvinova & Sandrine Duverne



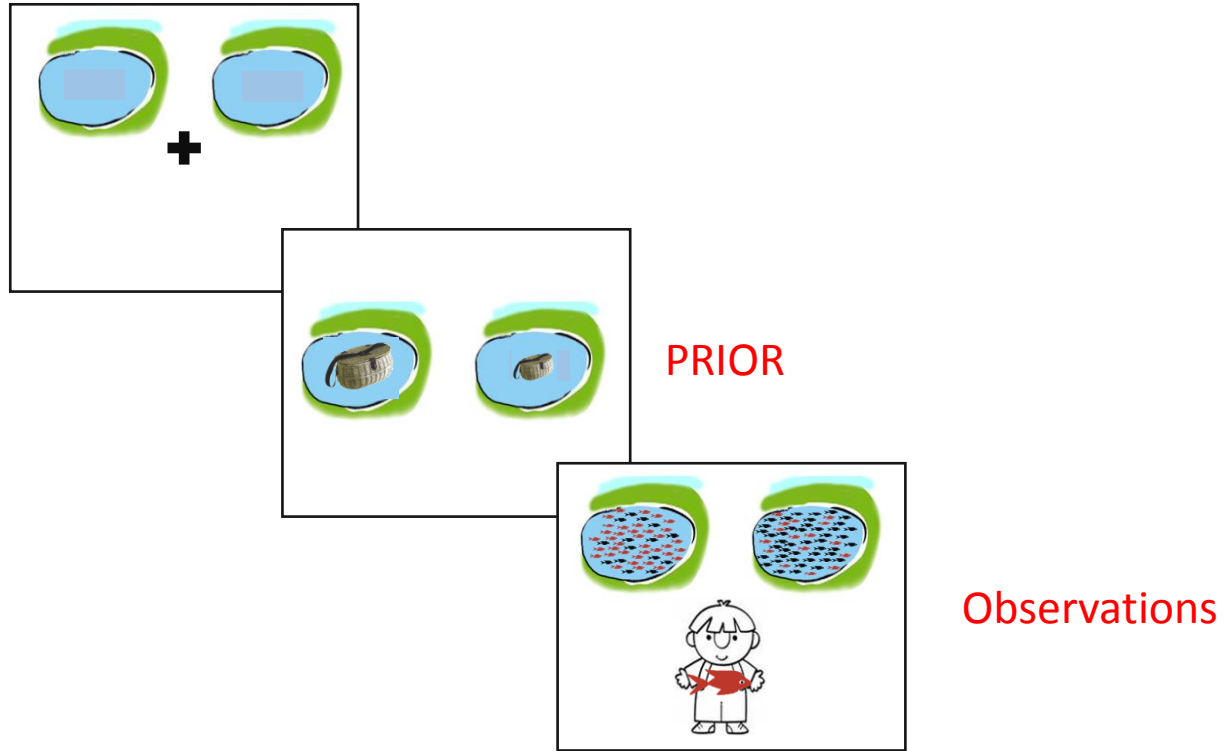
The Fisher Task

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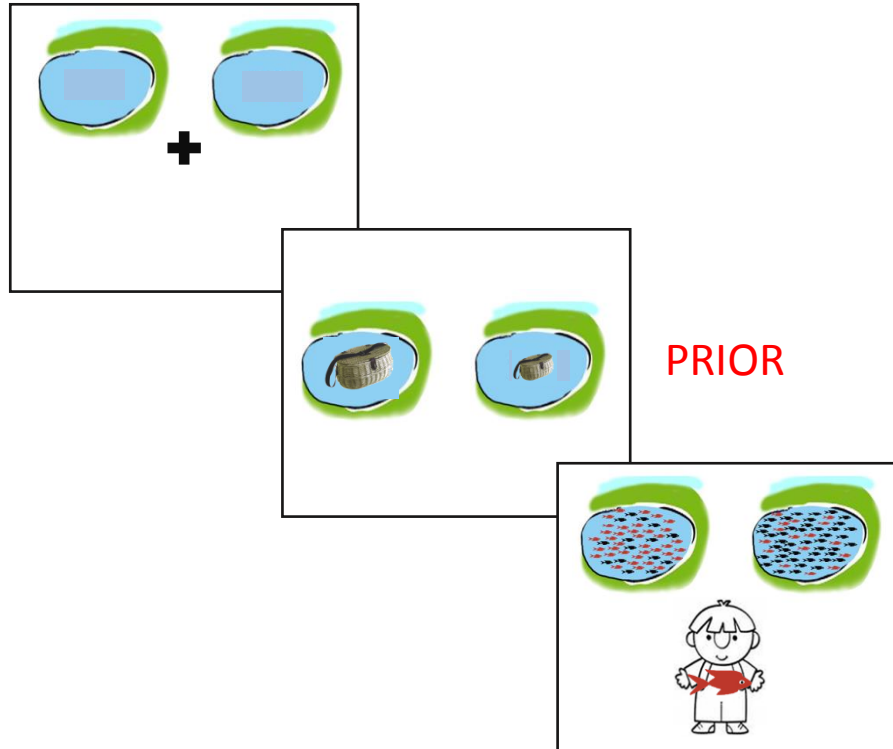
The Fisher Task

Renaud Jardri Alexandra Litvinova & Sandrine Duverne



The Fisher Task

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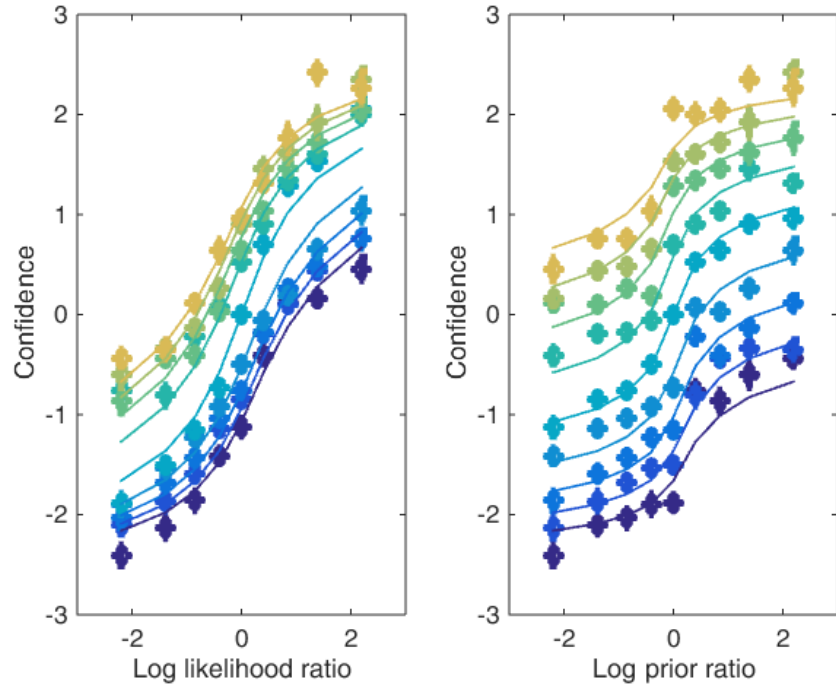


Observations

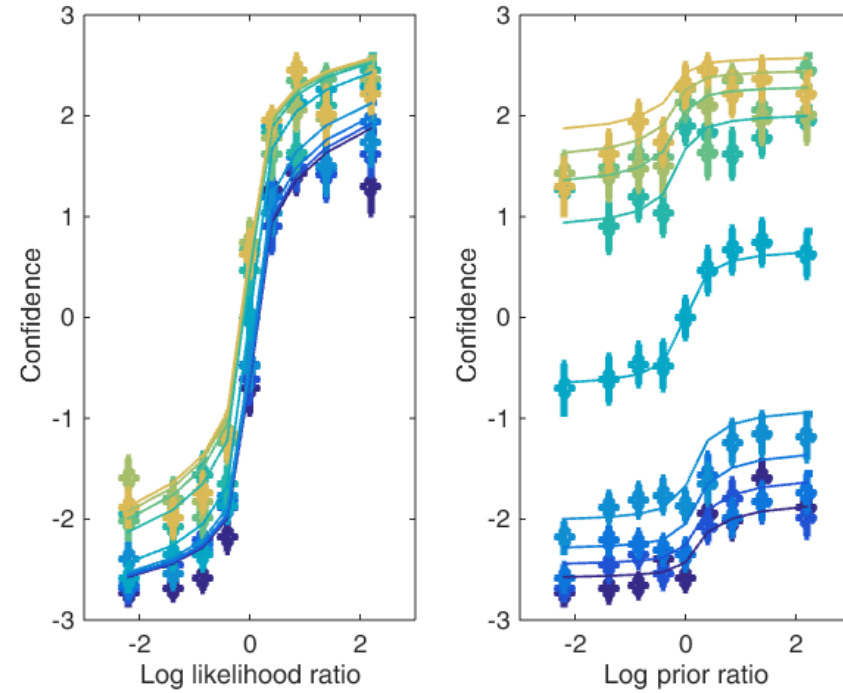


Mean group responses

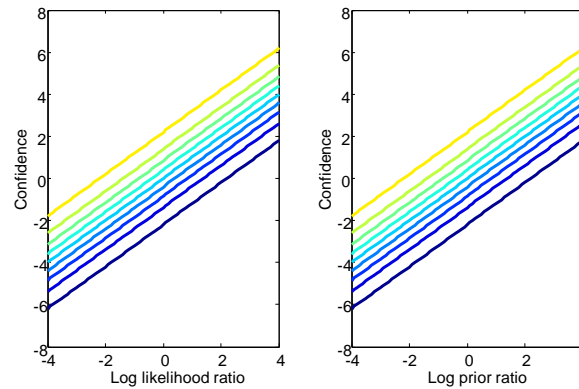
Controls:



Schizophrenes:

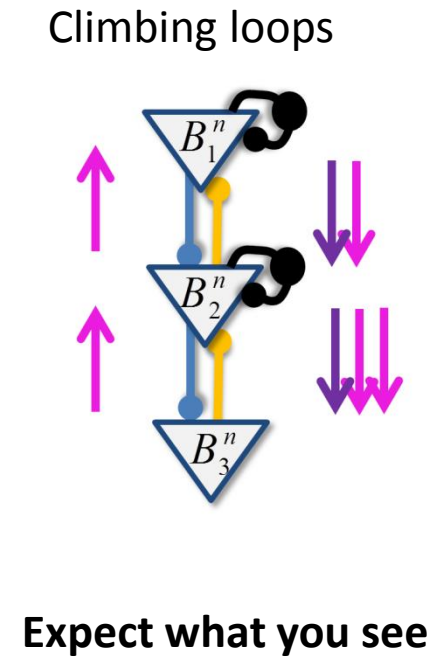
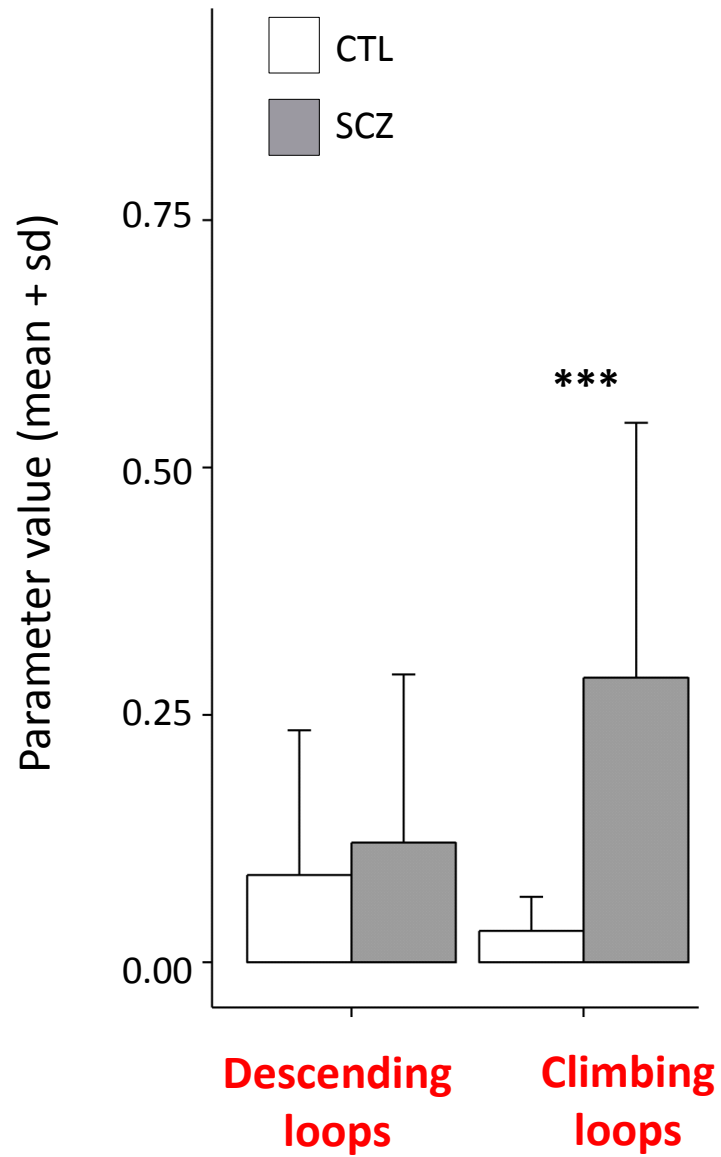


Without Loops:

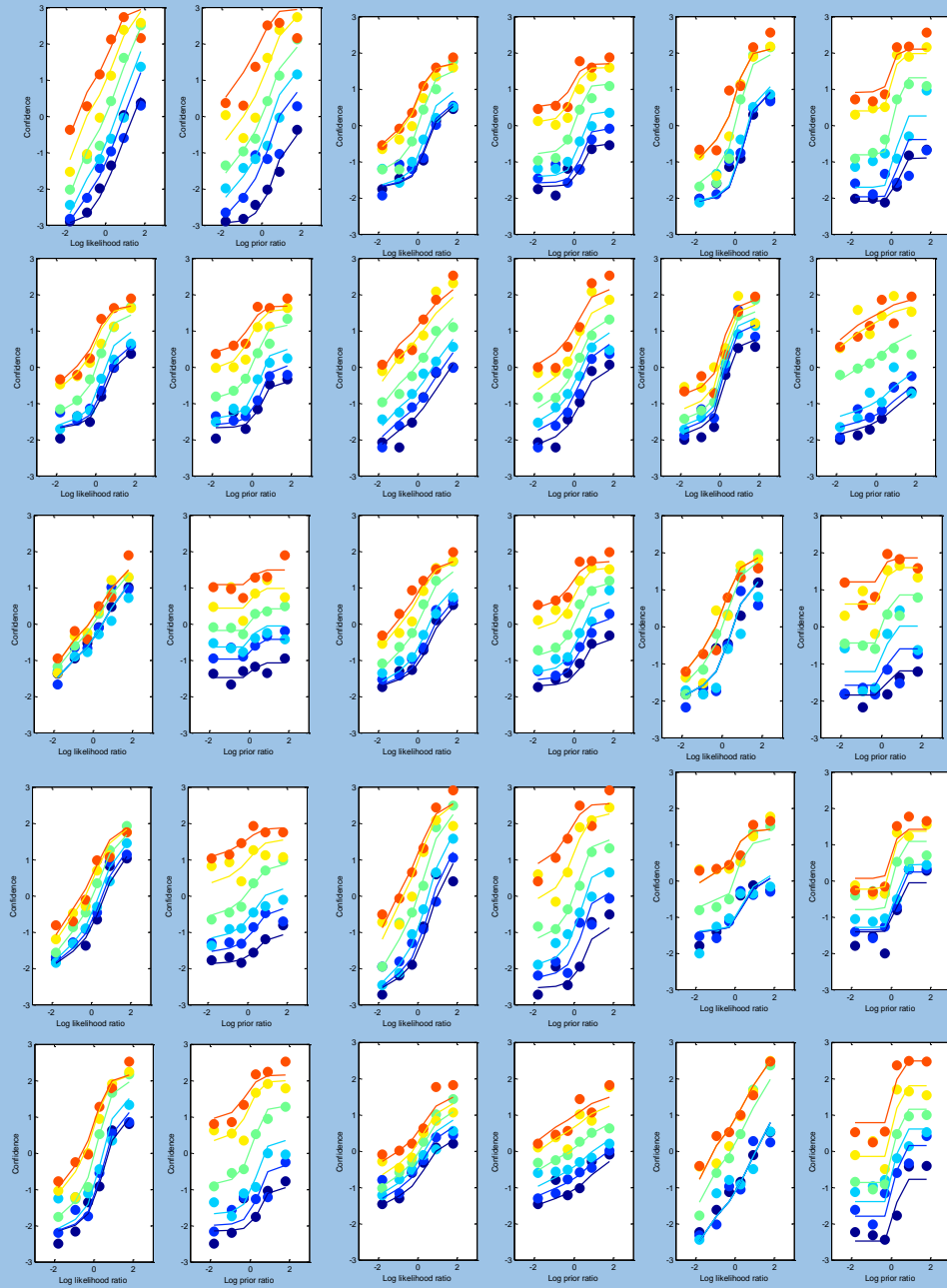


Jardri, Duverne and Deneve, in preparation

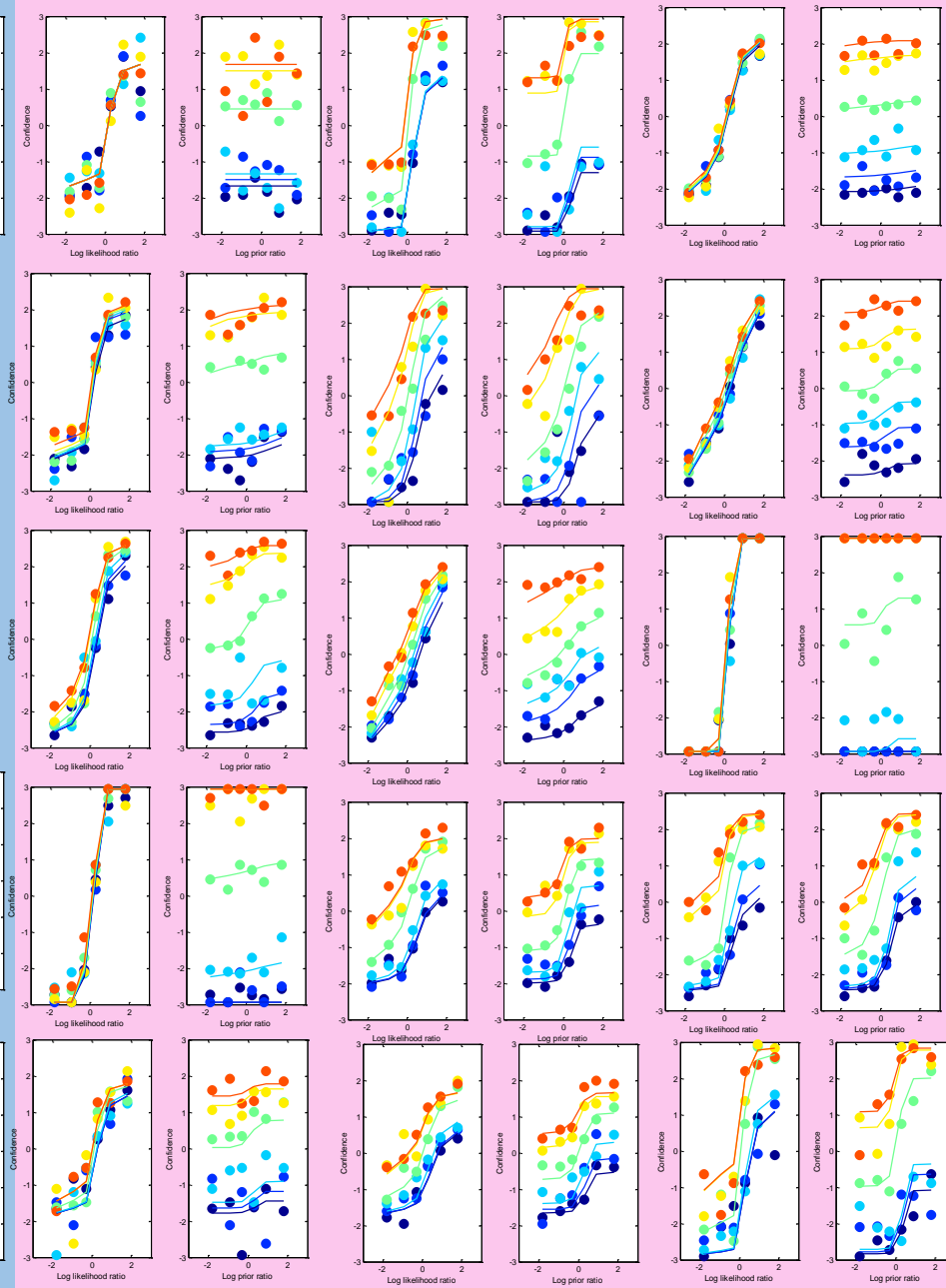
On average, patients over-interpret observations



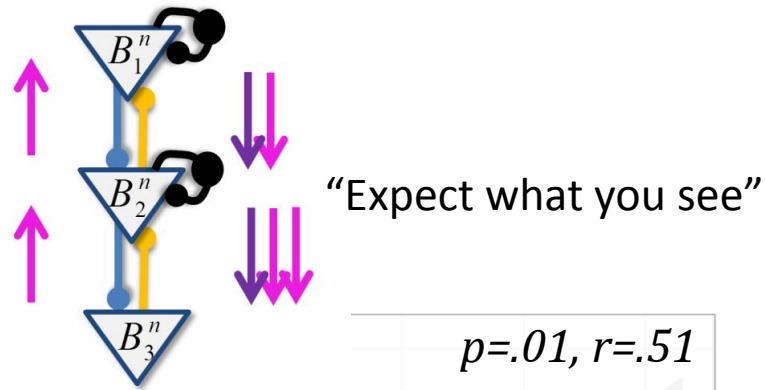
Control



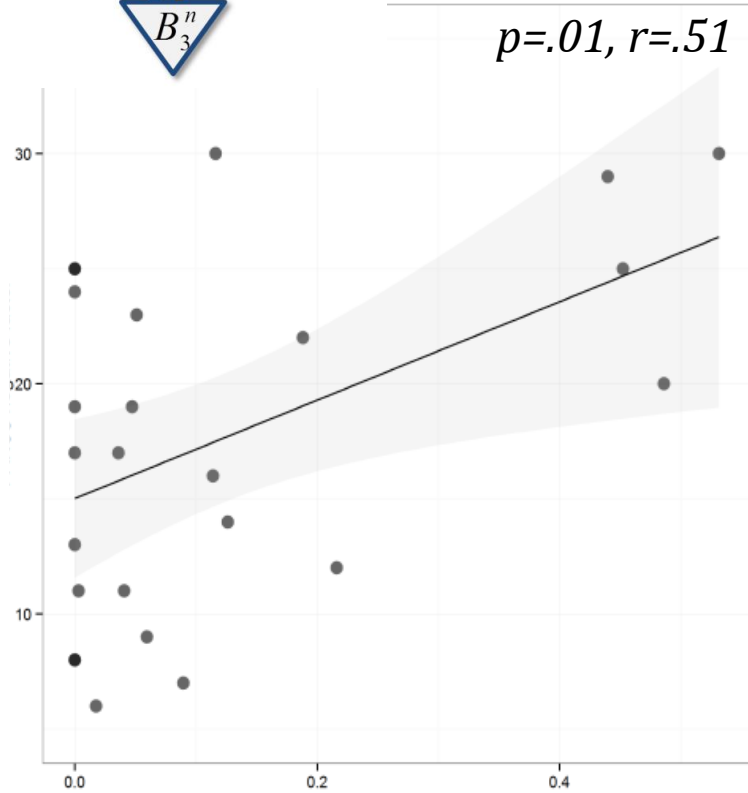
Patients



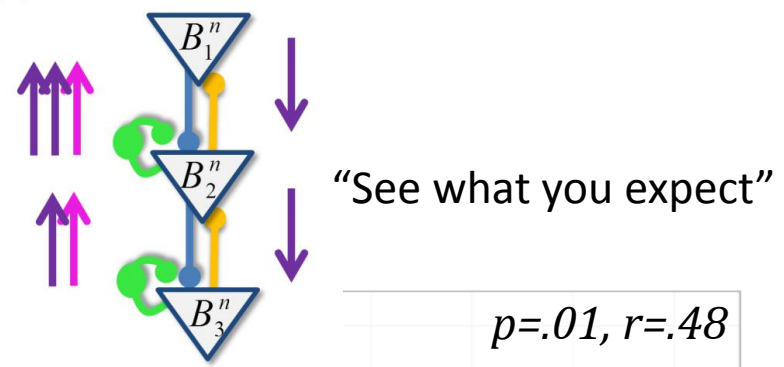
Positive dimension associated with ascending loops, negative dimension with descending loops



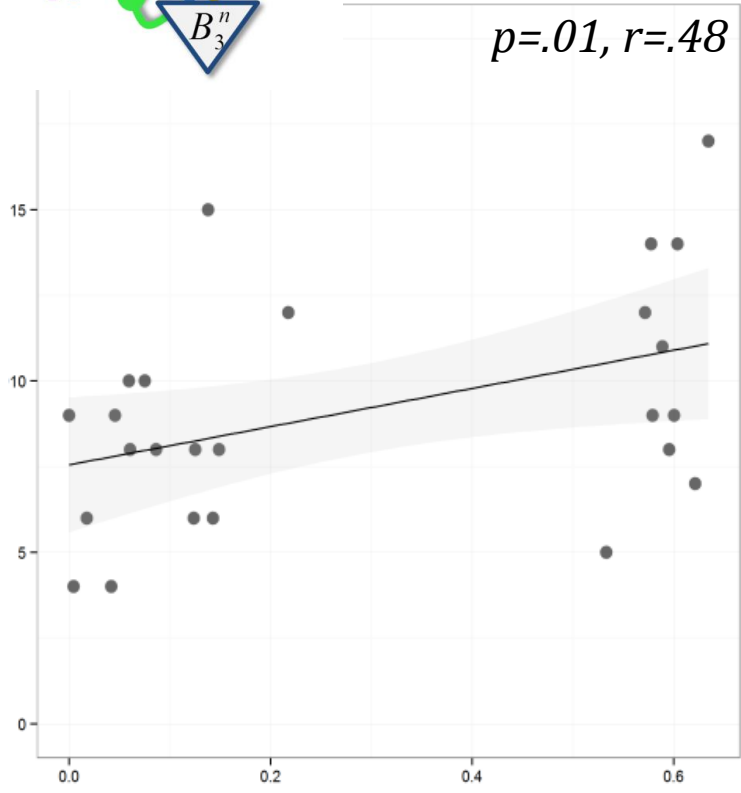
PANSS positive factor



Climbing loops



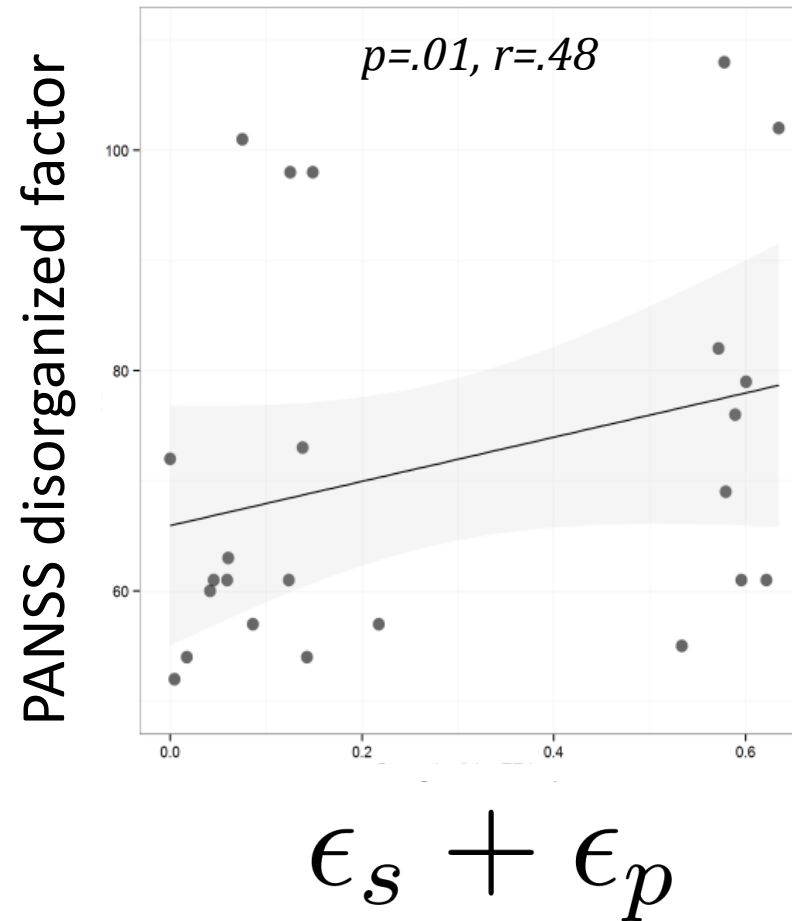
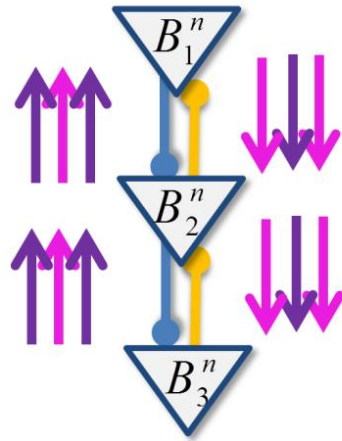
PANSS negative factor



Descending loops

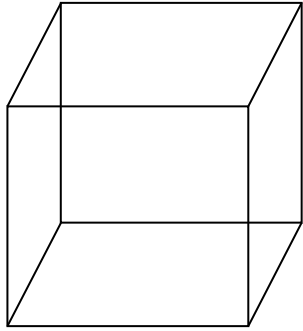
Total loops (ascending + descending) associated with disorganized thoughts

Ascending + Descending loops

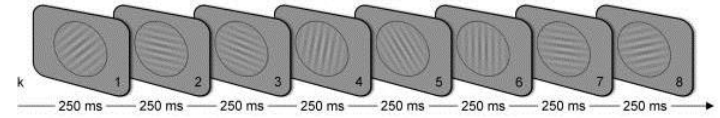


Future Directions

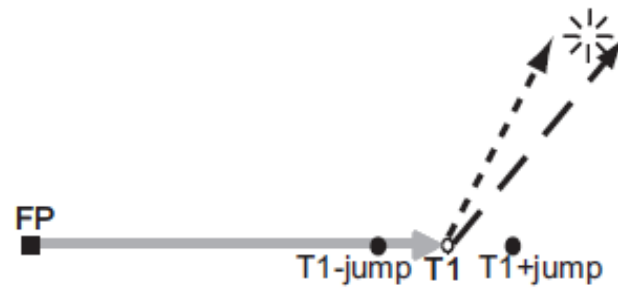
BISTABLE PERCEPTION



DECISION FROM SEQUENTIAL DATA



EYE MOVEMENT SEQUENCES



Thanks to

Renaud Jardri, Sandrine Duverne, Pantelis Leptourgos



James S. McDonnell Foundation



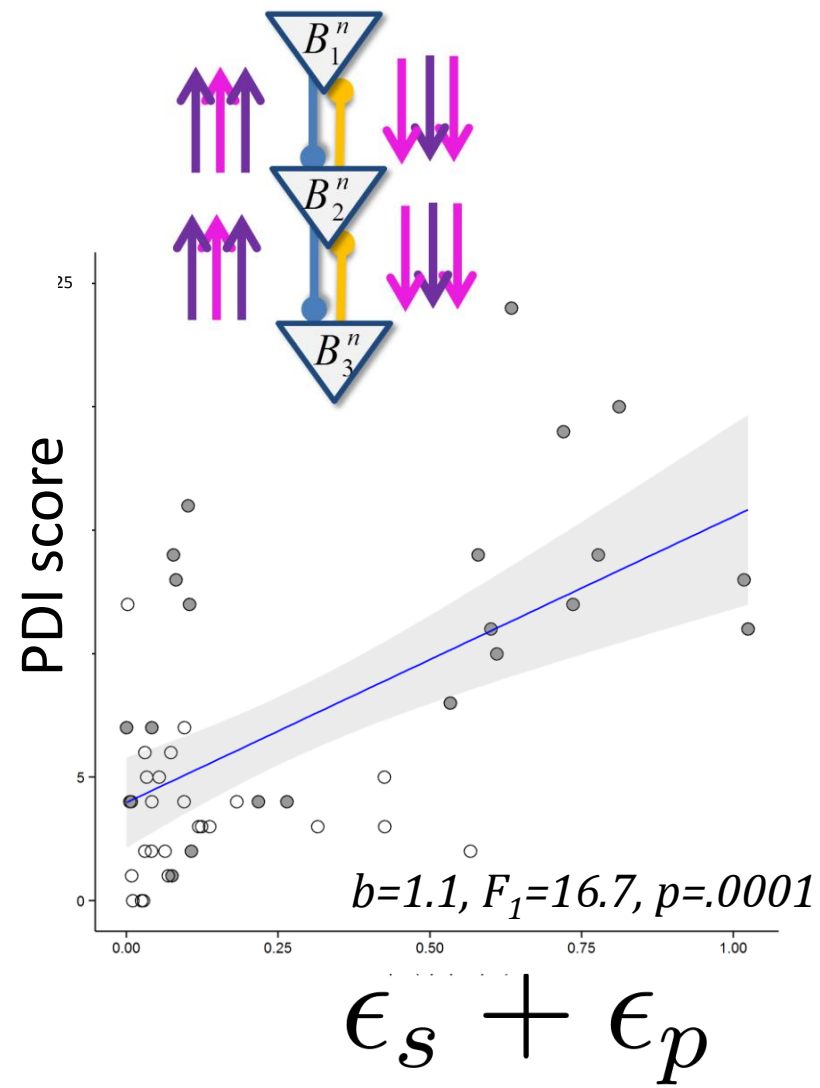
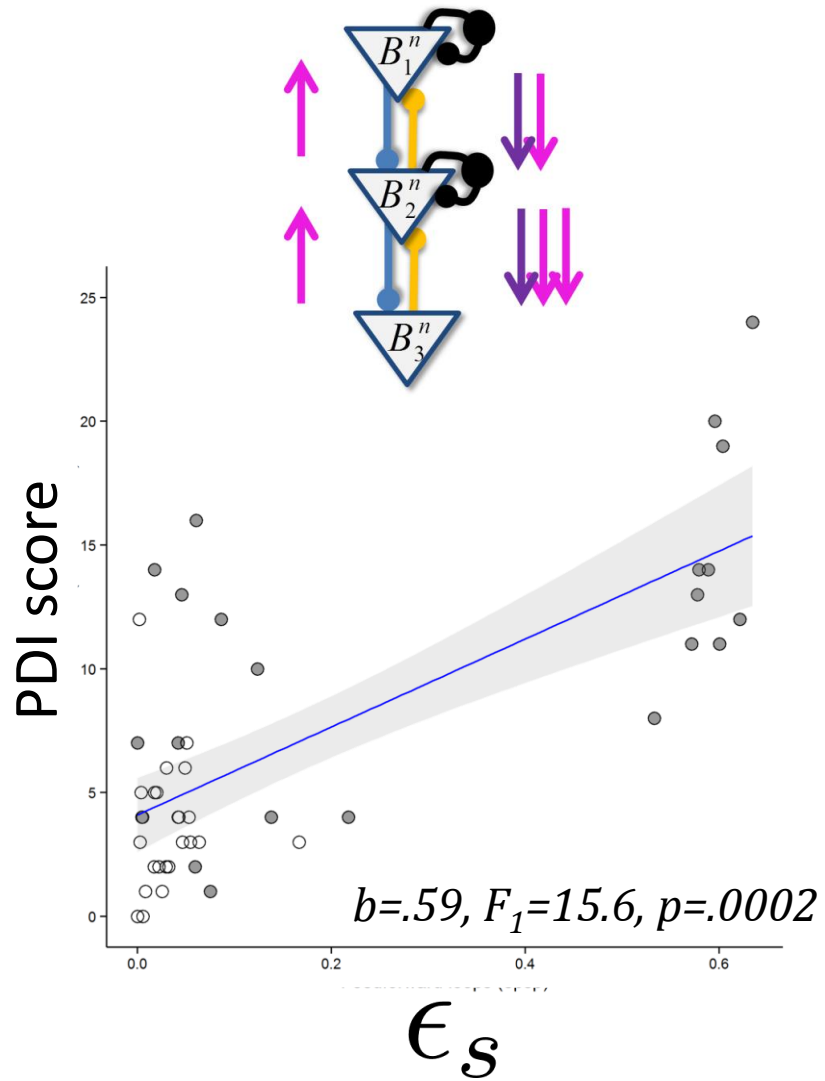
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Agence Nationale de la Recherche
ANR

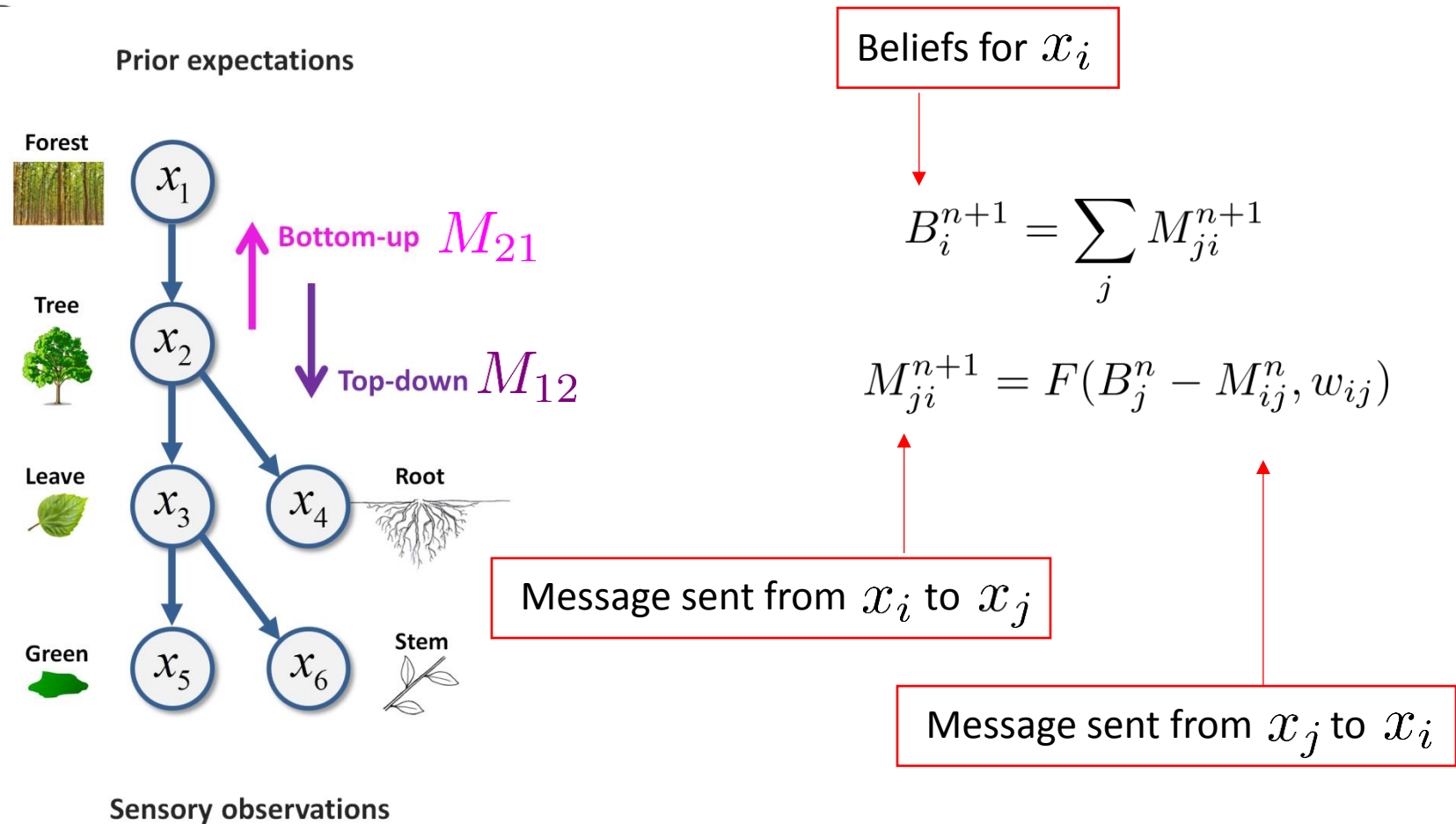


European Research Council

Ascending loops correlated with non-clinical beliefs

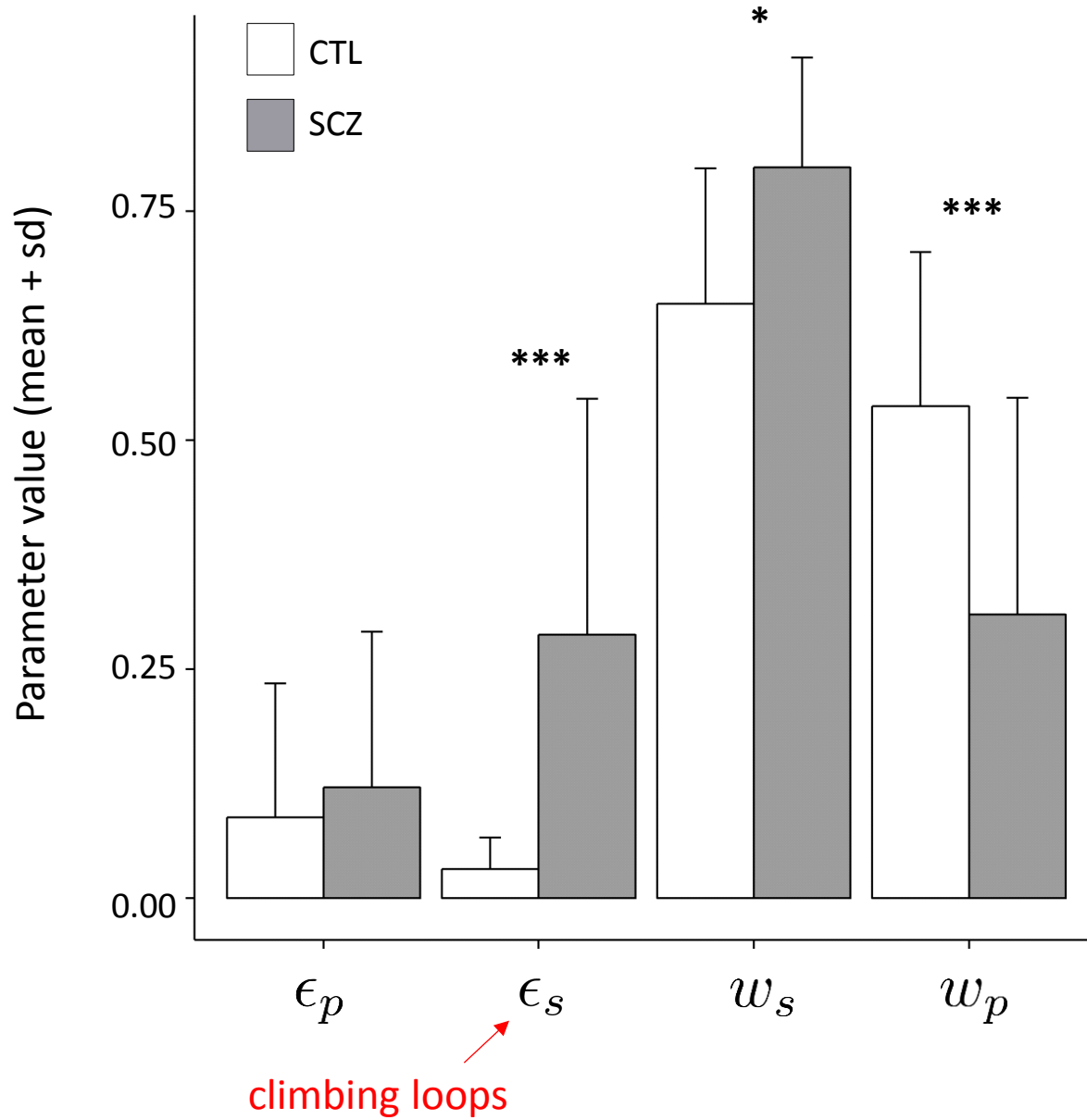


Hierarchical inference with belief propagation

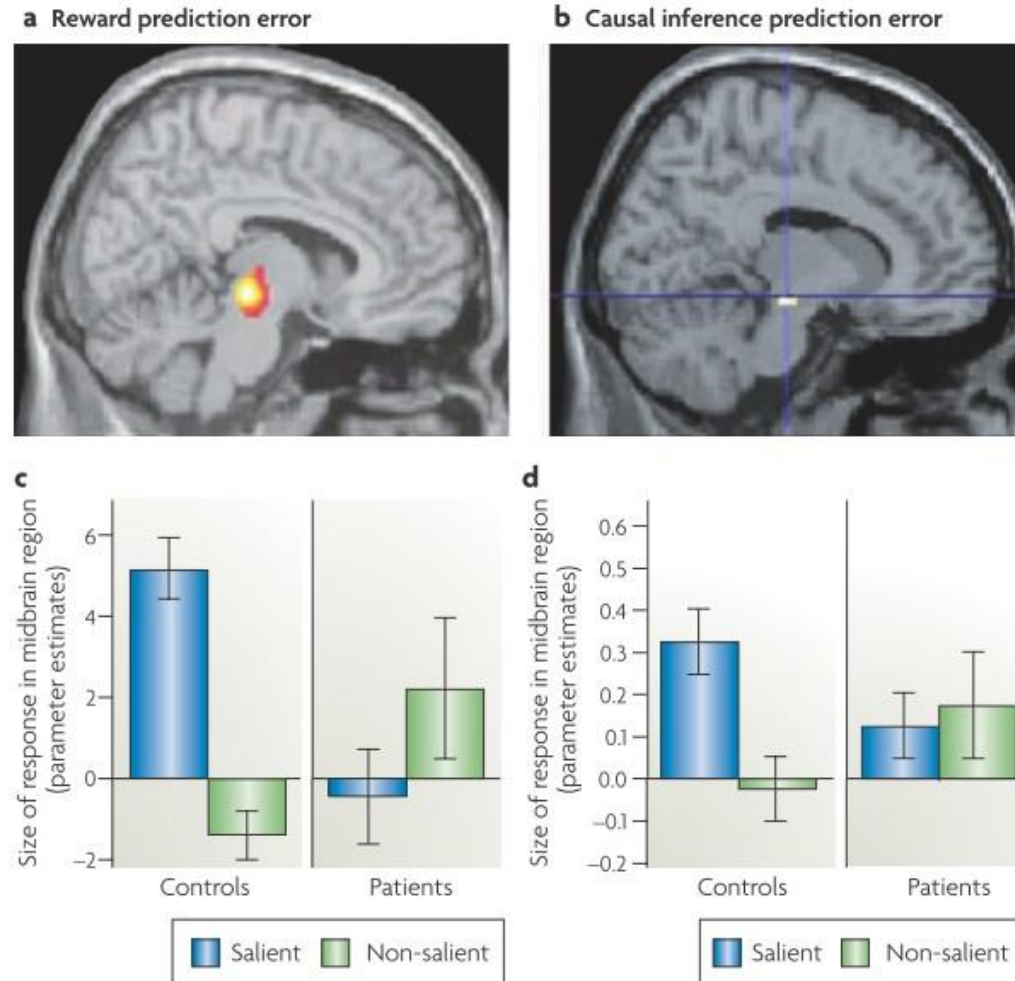


Messages are corrected by message sent previously in the opposite direction

Mean parameter values



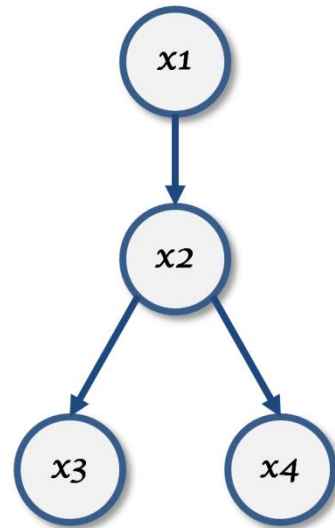
Impaired prediction errors in schizophrenia?



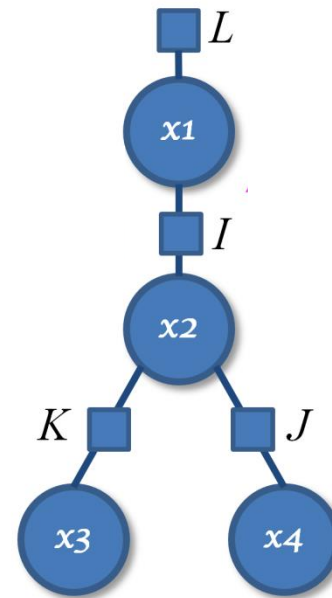
Murray GK et al.,
Mol Psychiatry 2007
Corlett PR et al., *Brain* 2007
See also: Fletcher P & Frith CD,
Nat Rev Neurosci 2009

Bayesian network and factor graph

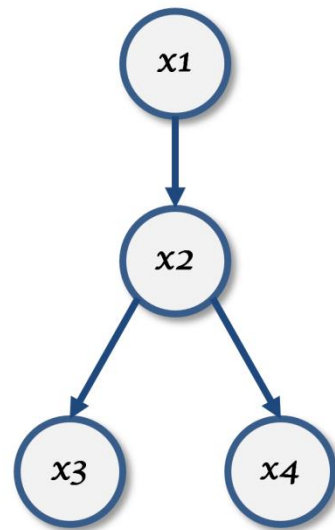
Causal model



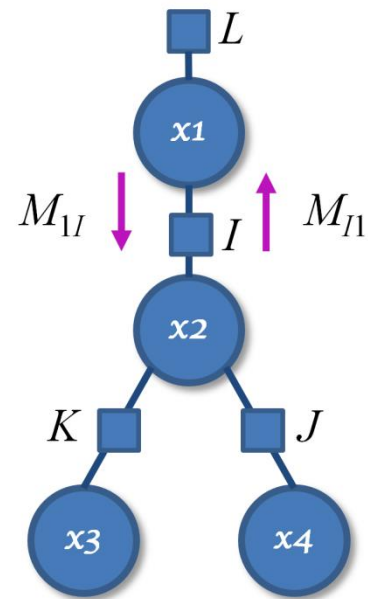
Pairwise factor graph



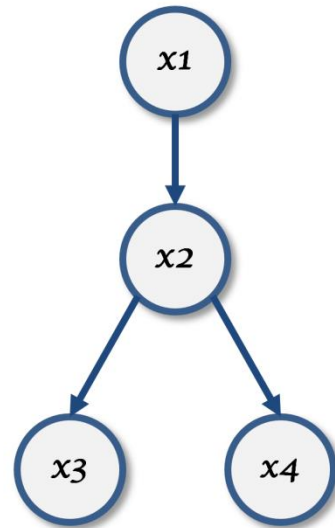
Causal model



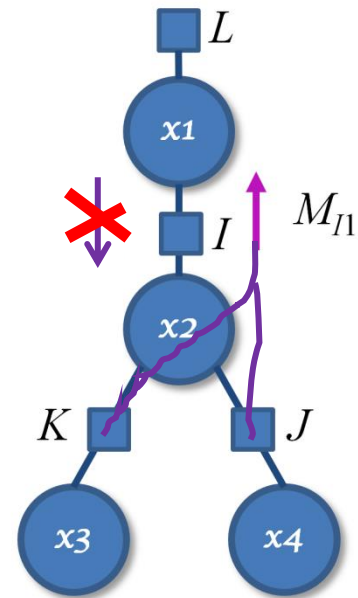
Pairwise factor graph



Causal model



Pairwise factor graph



Belief propagation

$$p(\mathbf{x}) = \prod_I f_I(\mathbf{x}_{N_I})$$

Belief propagation iterates:

Message from nodes to factors: $\mu'_{j \rightarrow I}(x_j) = \prod_{J \in N_j \setminus \{I\}} \mu_{J \rightarrow j}(x_j)$

Message from factor to nodes: $\mu'_{I \rightarrow i}(x_i) = \sum_{\mathbf{x}_{N_I \setminus \{i\}}} f_I(\mathbf{x}_{N_I}) \prod_{j \in N_I \setminus \{i\}} \mu_{j \rightarrow I}$

Beliefs are product of messages:

$$b_i(x_i) = \frac{1}{Z} \prod_{I \in N_i} \mu_{I \rightarrow i}(x_i)$$

Belief propagation

$$p(\mathbf{x}) = \prod_I f_I(\mathbf{x}_{N_I})$$

Belief propagation iterates:

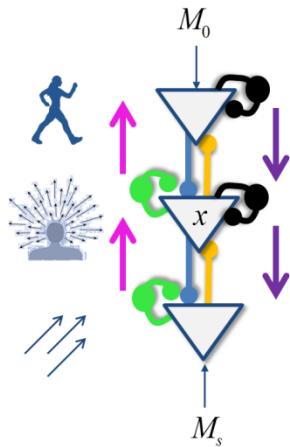
Message from nodes to factors: $\mu'_{j \rightarrow I}(x_j) = \prod_{J \in N_j \setminus \{I\}} \mu_{J \rightarrow j}(x_j)$

Message from factor to nodes: $\mu'_{I \rightarrow i}(x_i) = \sum_{\mathbf{x}_{N_I \setminus \{i\}}} f_I(\mathbf{x}_{N_I}) \prod_{j \in N_I \setminus \{i\}} \mu_{j \rightarrow I}$

Beliefs are product of messages:

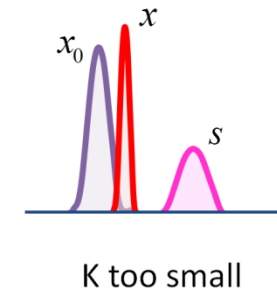
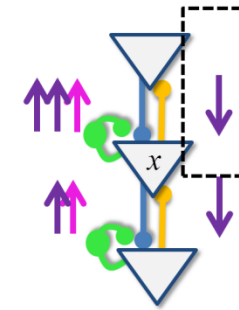
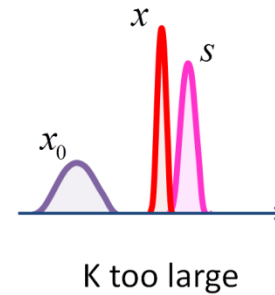
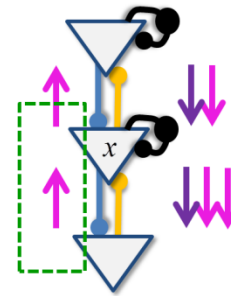
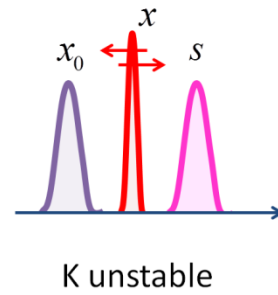
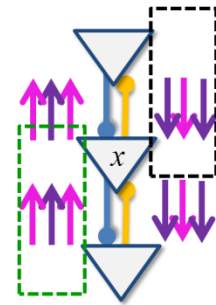
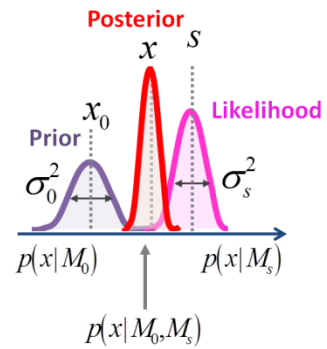
$$b_i(x_i) = \frac{1}{Z} \prod_{I \in N_i} \mu_{I \rightarrow i}(x_i)$$

Continuous, gaussian-distributed variables



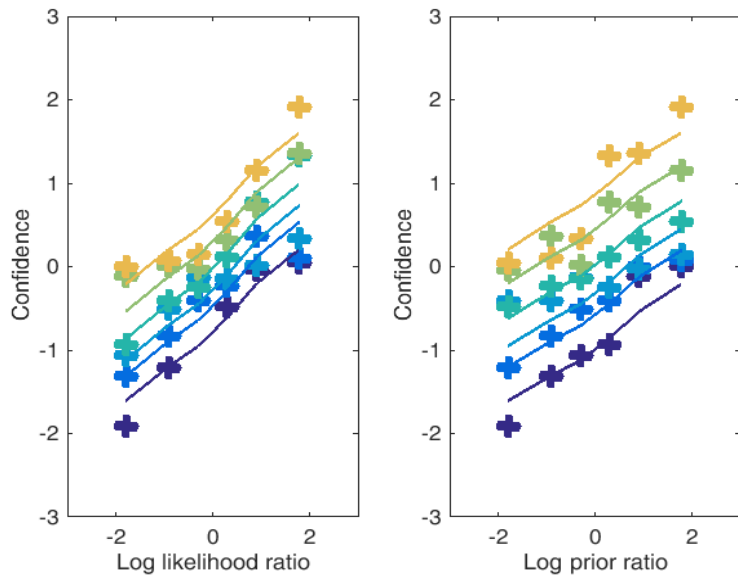
$$x = x_0 + K(s - x_0)$$

$$\text{with } K = \frac{\sigma_0^2}{\sigma_s^2 + \sigma_0^2}$$

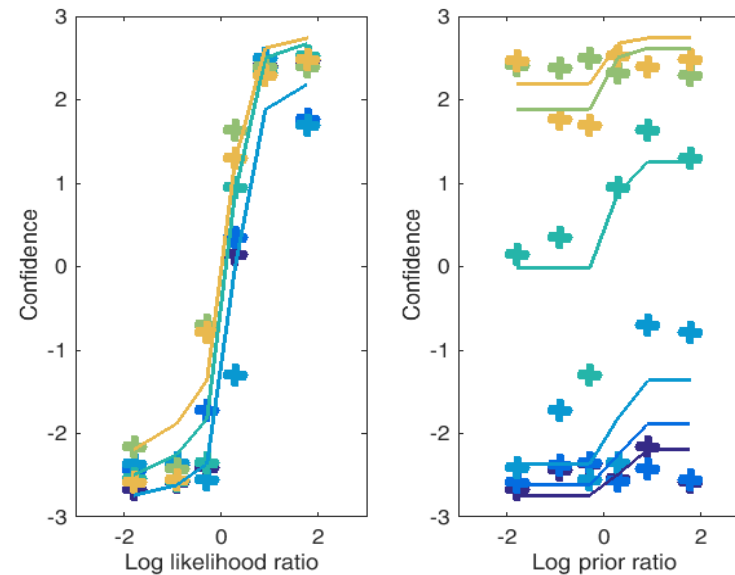


Individual subjects

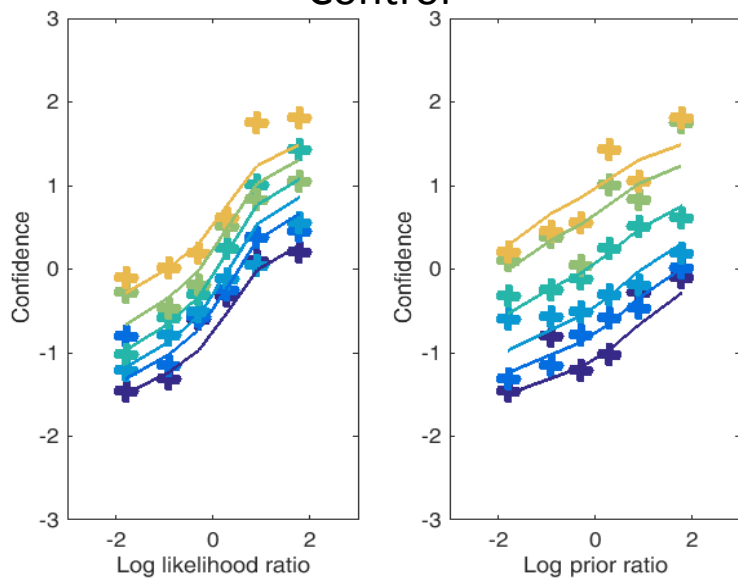
Control



Patient



Control



Patient

