

Misperceiving and Misbelieving Towards an understanding of psychosis

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*Bernard Wolfe Health
Neuroscience Fund*

welcometrust

Overview

- **What is psychosis?**
 - The features of psychosis – delusions and hallucinations
- **What is a delusion?**
 - Perception, inference and belief
 - Theories of delusions: abnormal perception or abnormal inference?
 - A different theory – denying the perception-inference distinction
- **Testing the theory**
 - Brain observations in mental illness and drug-induced psychosis

What is psychosis?

- A description
 - Delusions
 - Hallucinations
- A feature of severe mental illness

A delusion...

“All the time, they’re talking about me on the television...they’re talking about me and they’re talking to me...sending me messages, telling me what to do...I think that they think that I’m some sort of a political leader”

A Hallucination...

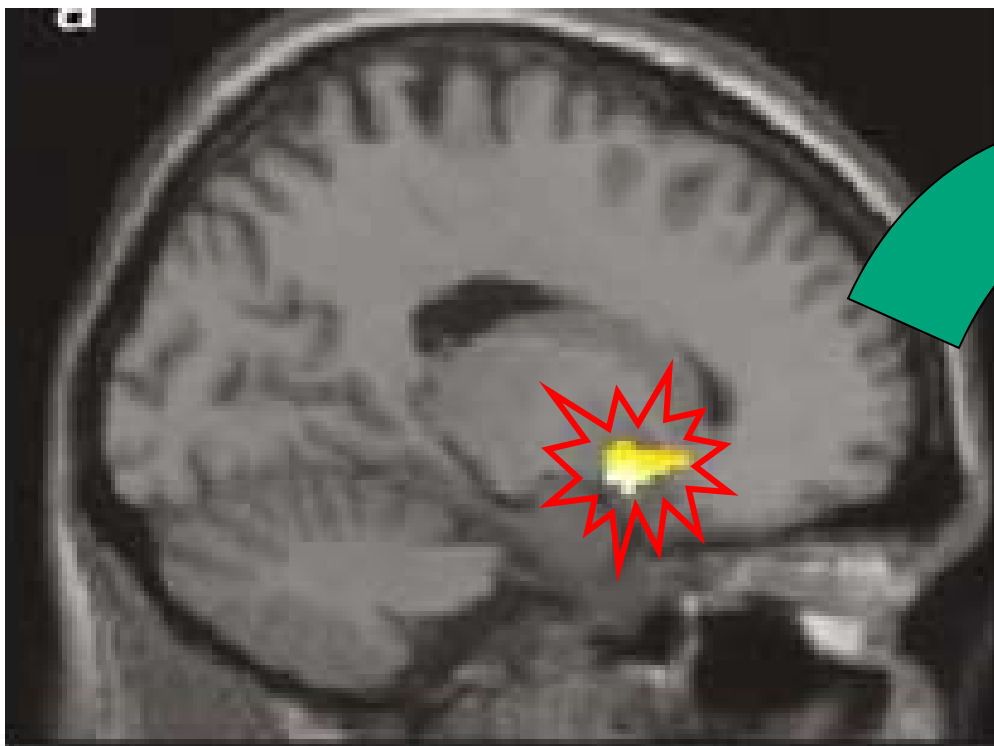
“If I have a fight with my sister and I run to my room, then I can still hear her whispering about me, calling me names, telling people lies about me”

Is she outside your room? Is that how you can hear her?

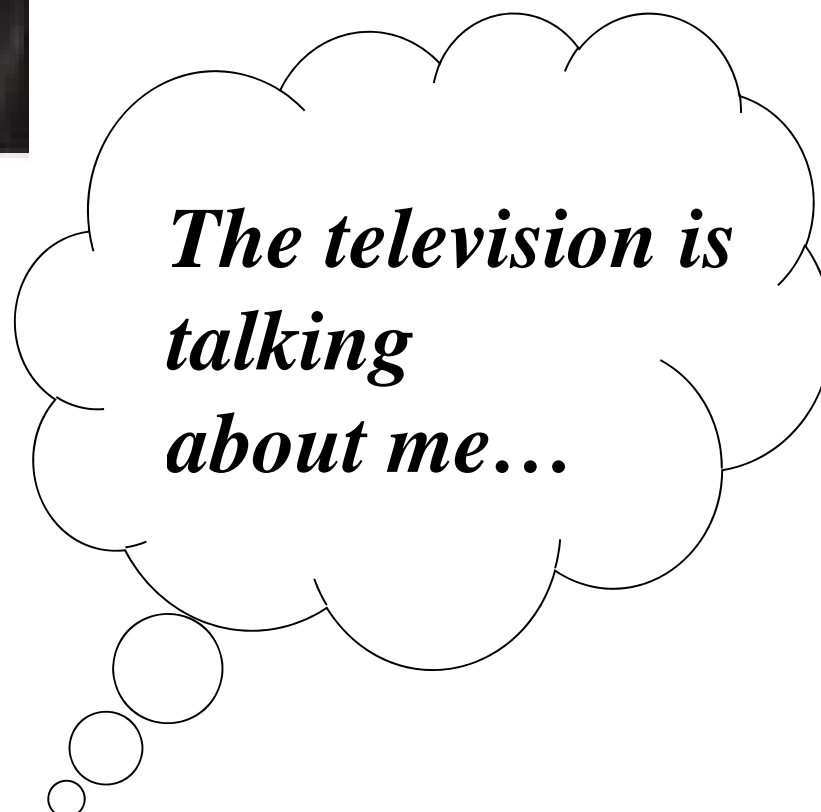
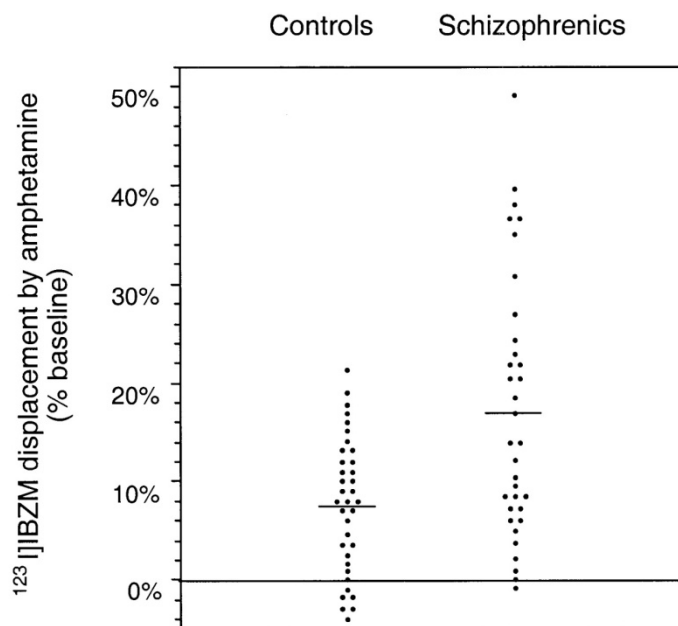
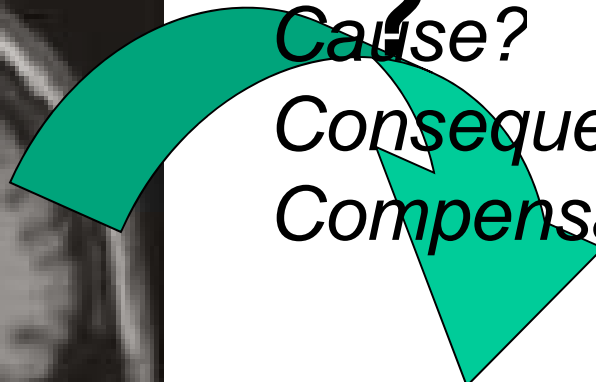
“No. She’s still downstairs and she is just whispering...I don’t know how she makes herself heard but I can hear her clearly”

Passivity – delusion or hallucination?

“They use the machine to make me move. They make me walk, they make me stagger. They control most of my movements...movements like walking, movements like running, movements of my face, making me smile when I don’t want to”



Three Cs:
~~Cause?~~
Consequence?
Compensation?



The logic of belief: deduction, induction or abduction?

- **Deduction**

- *“If P then Q”*
- *“P”*
- *Therefore “Q”*

- **Abduction**

- *“Q”*
- *Therefore “P”*



Previous explanations for delusions

- Delusions as rational inferences (abnormal experience)
- Delusions as irrational inferences (normal experience)
- Delusions as irrational inference acting on abnormal experiences

Delusions as rational inferences

- Brendan Maher:

“We find there arises in the patient certain primary sensations, vital feelings mood, awareness: something is going on. This general delusional atmosphere with all its vagueness of content must be unbearable...to reach some definite idea at last is like being relieved of some enormous burden”

Delusions as irrational inferences

- “Jumping to conclusions”
- Confirmation biases
- Self-serving biases

Delusions irrational inference acting on abnormal experiences

- Coltheart's two-factor model:
 - The perceptual change or anomaly of experience is a necessary prerequisite – **The content of the belief**
 - For the delusion to form this anomaly must be accompanied by a deficit in *reality evaluation* - **the reason that the belief is not rejected.**

See Coltheart QJEP 2007



Perception
as
unconscious
inference

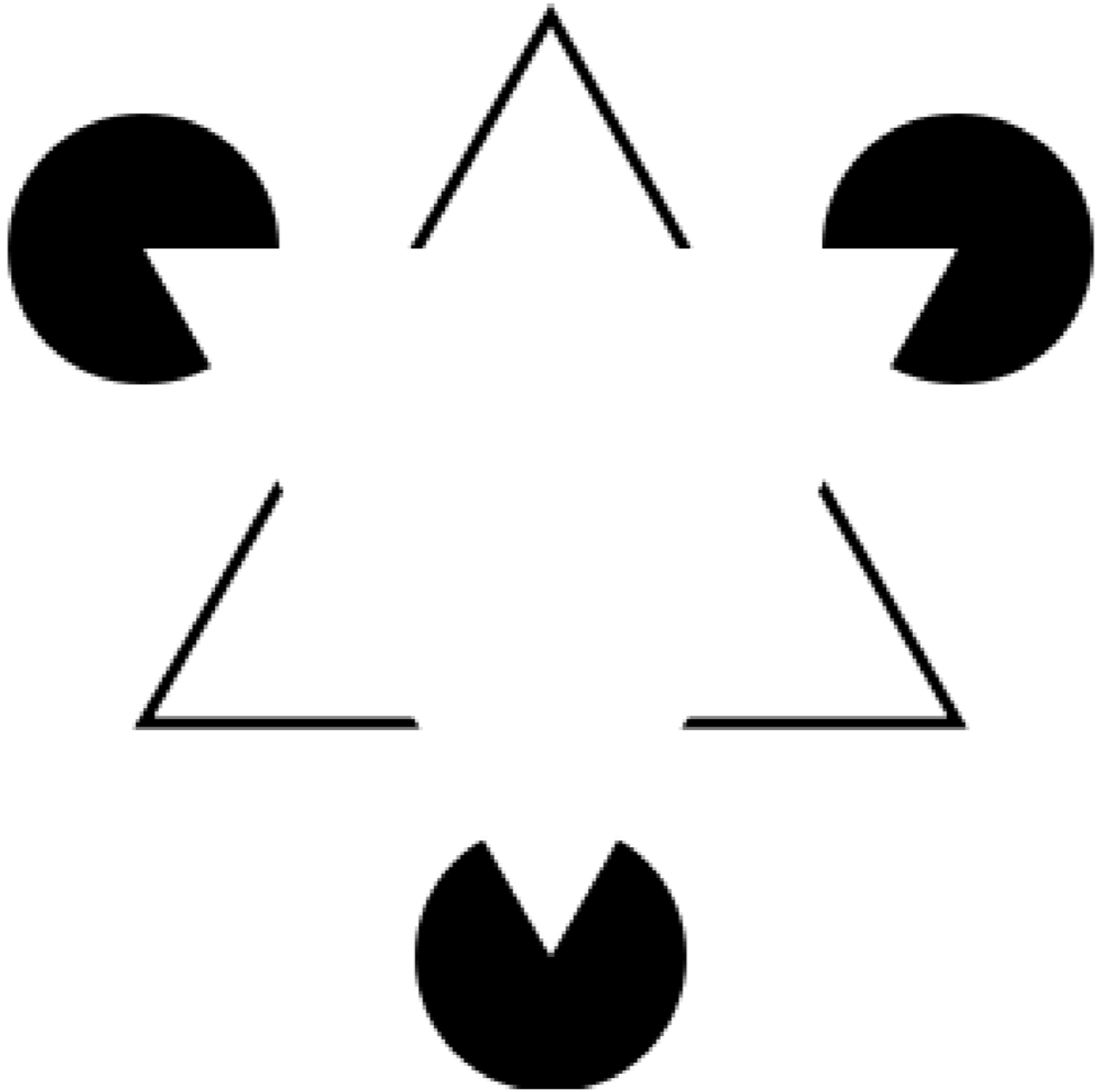


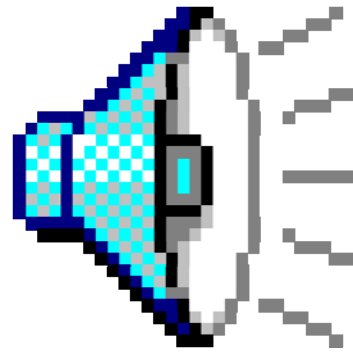
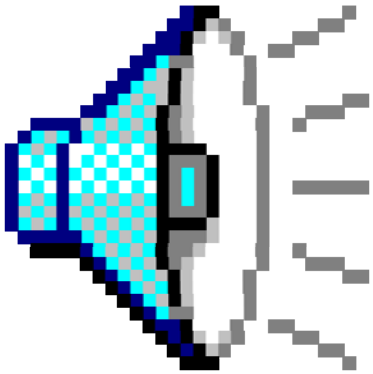
The world consists of causes of our sensations/percepts.
But we do not have direct access to these causes,

Perception is inference

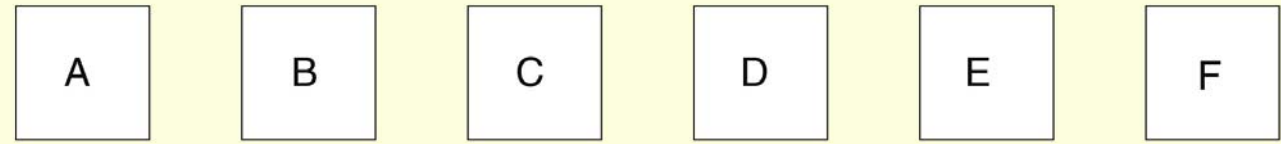
- Our senses represent causes in the world.
- These are inherently ambiguous
- Resolution of this ambiguity requires a best guess (an abduction)

The perceptual process involves inferring causes based on prior experience (“a matted felt of pure hypothesis”)

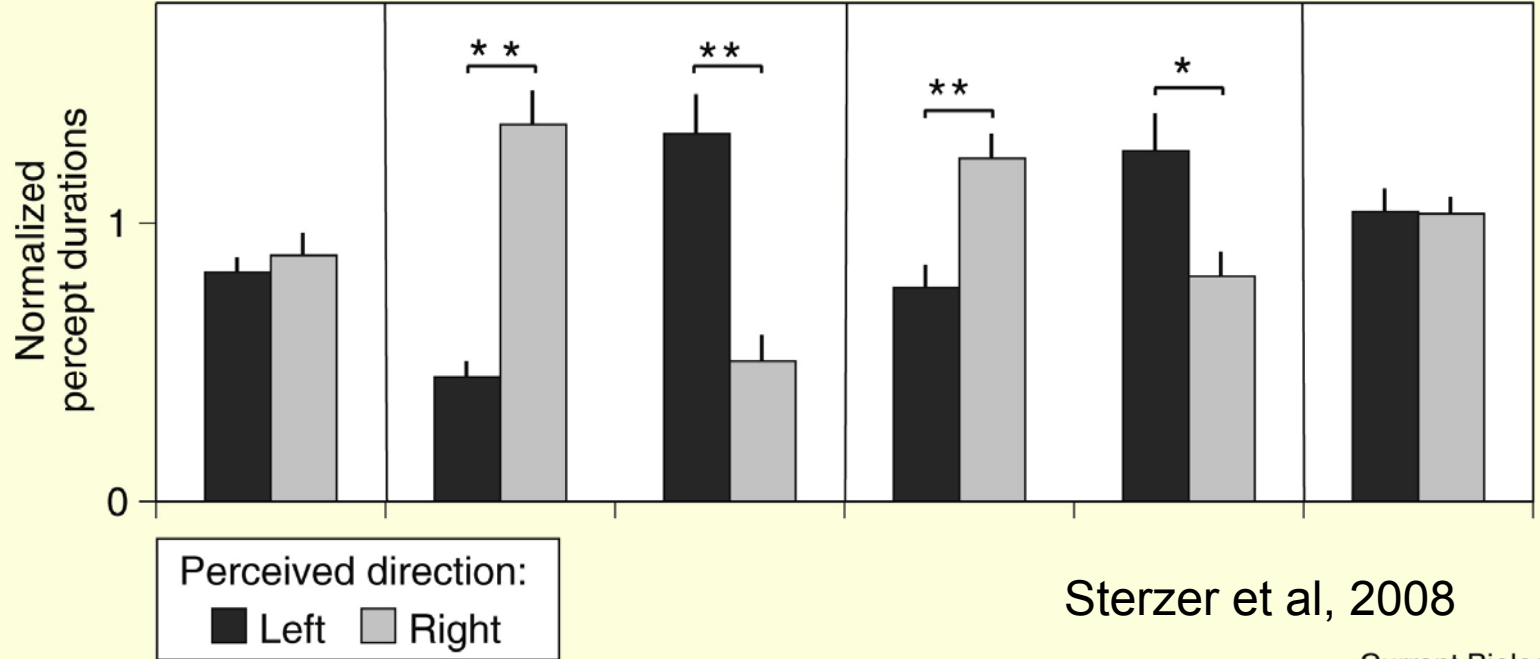
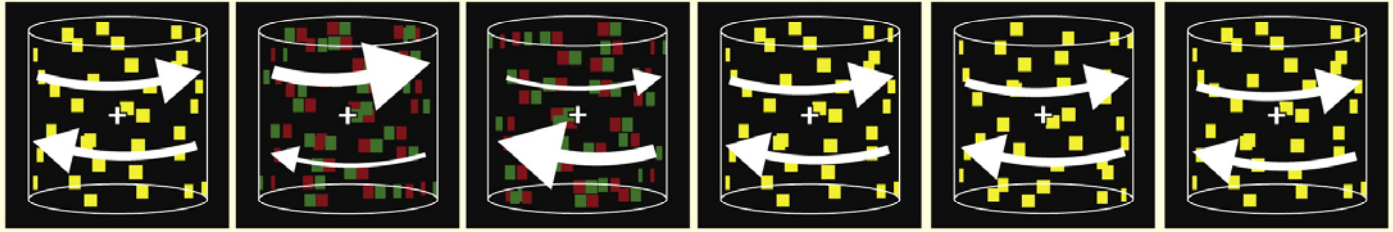








Baseline start Learning (Right, Left) Test (Right, Left) Baseline end



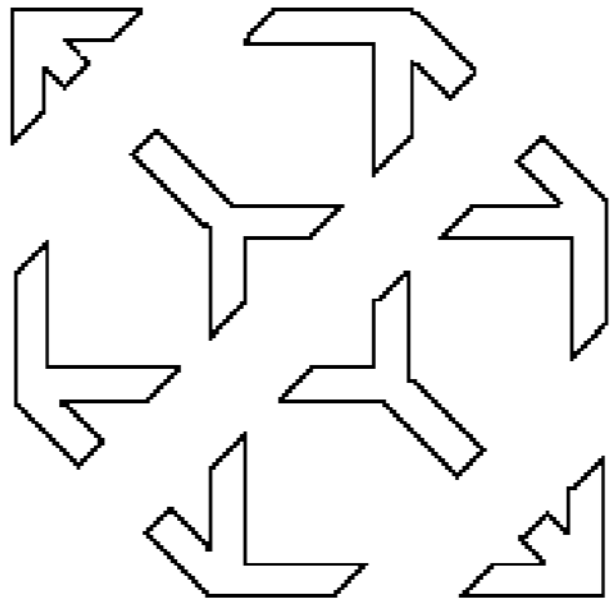
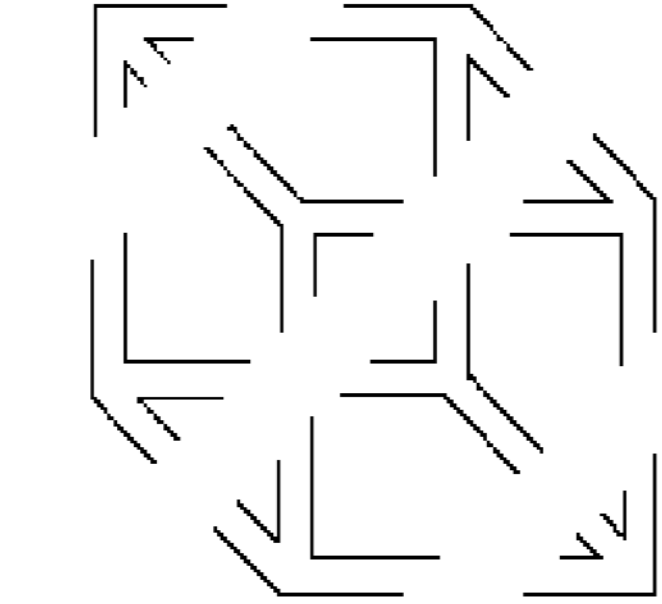
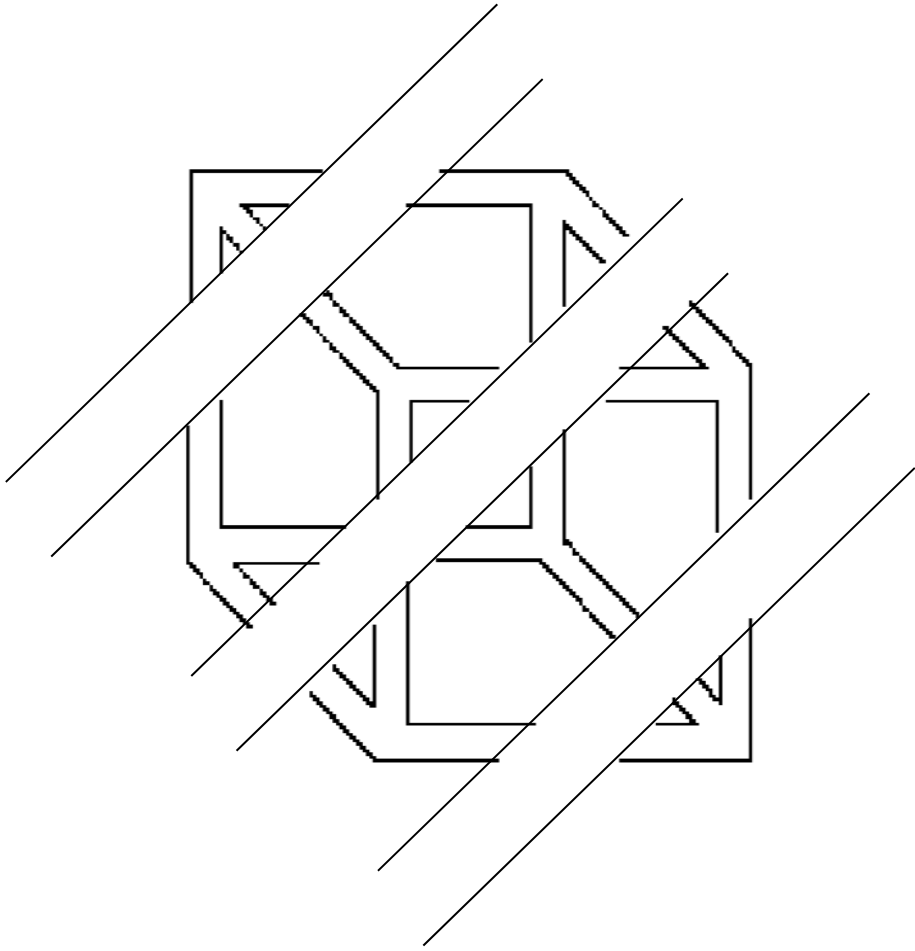
Sterzer et al, 2008

Interim summary

- A delusion is a belief, one that seems to be irrational.
- Like other beliefs it is an example of an abductive inference
 - the search for an explanatory cause of a sense input that is surprising or noteworthy.
- Previously, models of delusions have treated perception and inference as separable.
- But this is not the case.

Part II

- Perception is an inference based on previous experience
 - We are good at dealing with noisy and incomplete data
 - Sometimes, we experience what we expect rather than what is actually there
- How does the system avoid inflexibility?



Abduction and prediction error

- Learning is maximised in the setting of unpredictable events - “prediction error relates...to the very essence of learning...No learning occurs when the outcome is perfectly predicted”

–Schultz and Dickinson

Ann Rev Neurosci 2000

$$\Delta V = \alpha \beta (\lambda - \Sigma V)$$

Prediction

Attributes::

- A mismatch between current input and prior expectations
- A signal that our current model is wrong
- A drive to updating inference
- A drive to attentional allocation (and motivation?)
- A marker for distinguishing internally- from externally-generated sense data?

If μ

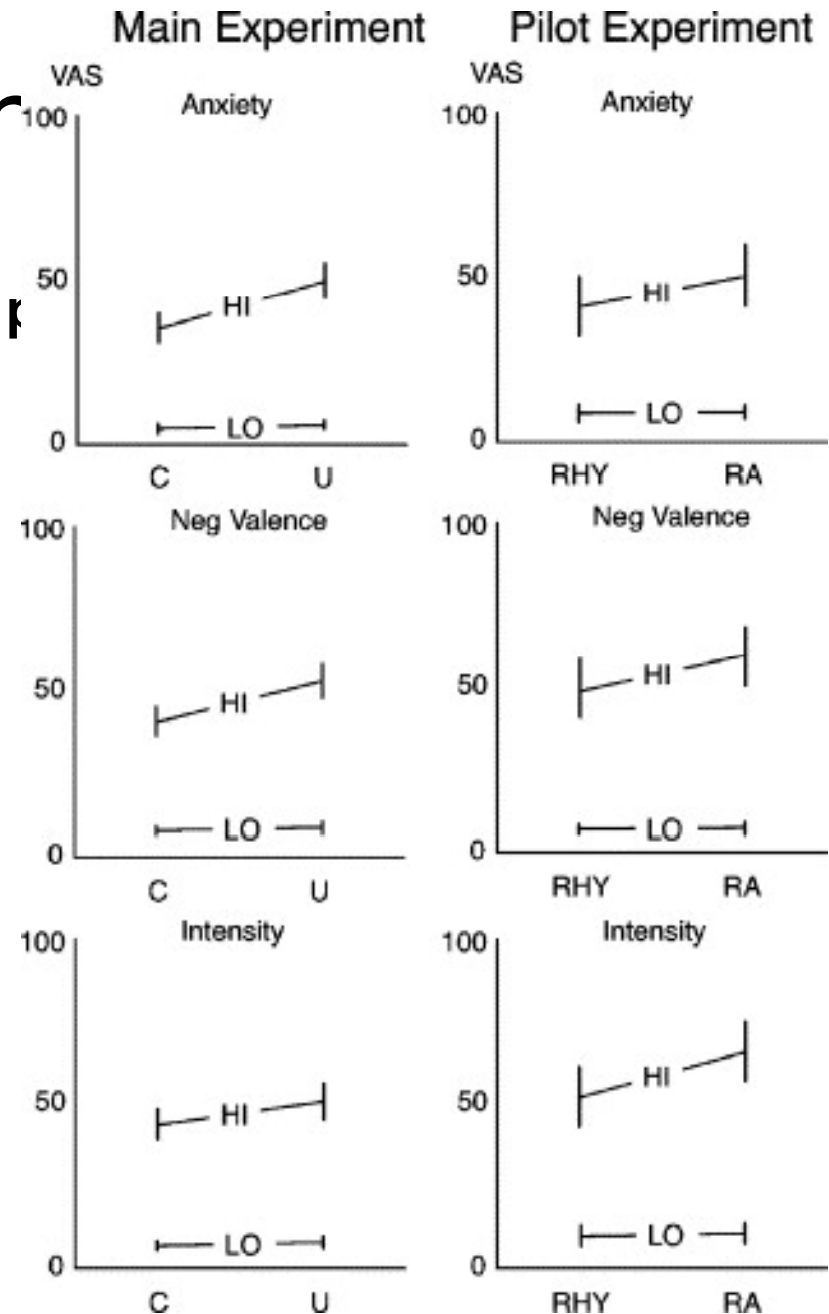
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Does a prediction error deficit explain the emergence of psychosis?

- Delusions are abnormal inferences
- Inference and perception are overlapping
- Our brains use a combination of prior expectations and current sensory data to try to make sense of the world in such a way that it becomes predictable.
- Such a system requires balance
 - efficiency of ignoring noise and irrelevant data versus rigidity produced by over-reliance on prior expectations
 - flexibility versus flimsiness produced by a tendency to change inference with each new piece of information.
- Prediction error controls this balance.
- Psychosis reflects an imbalance

Changing experience of things...

- "Colours seem to be brighter now, almost as if they are luminous"
- "Everything's brighter and louder and noisier"
- "I see things flat...There's no depth, but if I take times to look at things, I can pick out the pieces like a jigsaw puzzle"
- "...as if someone had turned up the volume...[background noises] seem to be just as loud as and sometimes louder than the main noises"
 - Chapman & McGhie, 1961; Chapman, 1966

Strange things begin to feel important...

- “...It was as if parts of my mind “awoke”...I became interested in a wide assortment of people, events, places and ideas which normally would make no impression on me...The walk of a stranger on the street could be a sign to me...Every face in the windows of a passing streetcar would be engraved on my mind...”

– ***Norma MacDonald, Living with schizophrenia, 1960***

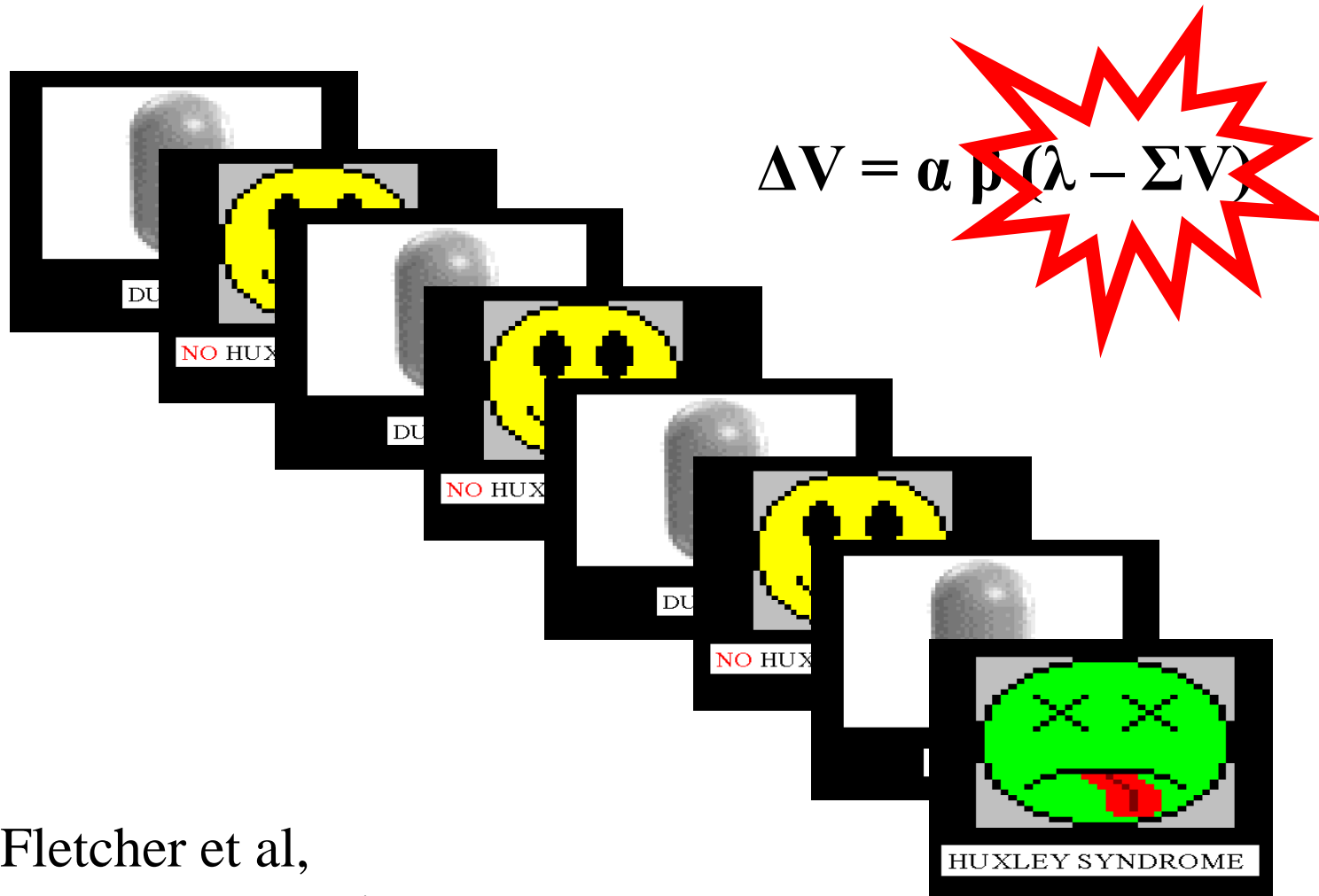
Changing associations...

- "I've got too many thoughts. You might think about...that ashtray and just think, oh! Yes that's for putting my cigarette in, but I would think of it and then think of a dozen different things connected with it"
- "I try to read...but it takes me ages because each bit I read starts me thinking in ten different directions at once".
 - Chapman and McGhie 1961
- "I had to make sense, any sense, out of all these uncanny coincidences. I did it by radically changing my conception of reality"
– *Peter Chadwick*

- “The Sensitivity”
- “At ordinary times I might have taken pleasure in watching the dog, but [previously] would never have been so captivated by it.”
- “out of these perceptions came the absolute awareness that my abilities to see connections had been multiplied many times over”.
 - (Matussek, 1987)

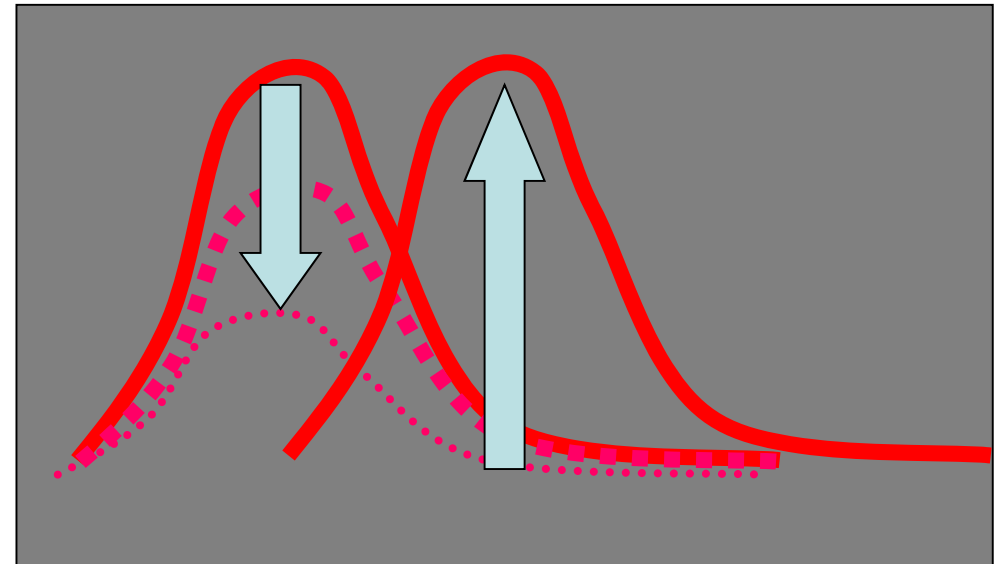
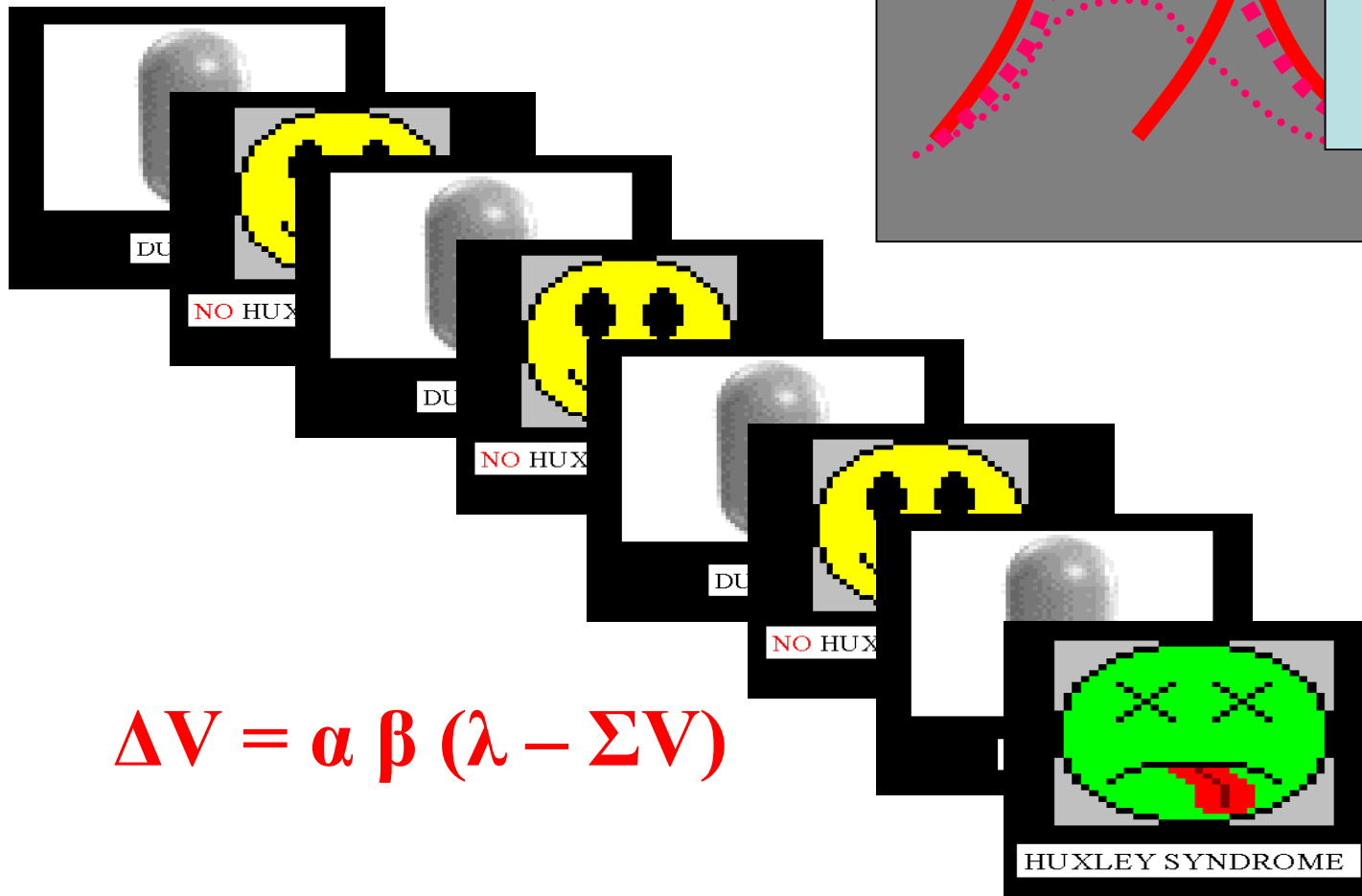
Part III - Testing the PE model...

- Evidence of altered prediction error signal in people with psychosis?
- Prediction error and a drug model of psychosis - ketamine



Fletcher et al,
Nature Neuroscience 2001

Fletcher et al,
Nature Neuroscience 2001



$$\Delta V = \alpha \beta (\lambda - \Sigma V)$$

The allergist game...

Imagine that you are an allergist, someone who tries to discover the cause of allergic reactions in people.

You have just been presented with a new patient, “Mr X”, who suffers from allergic reactions following some meals but not others. In an attempt to discover which foods cause Mr X to have allergic reactions, you arrange for him to eat various foods for a meal on each day, and observe if he has an allergic reaction or not.

Trial structure



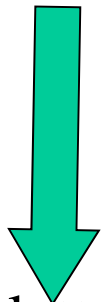
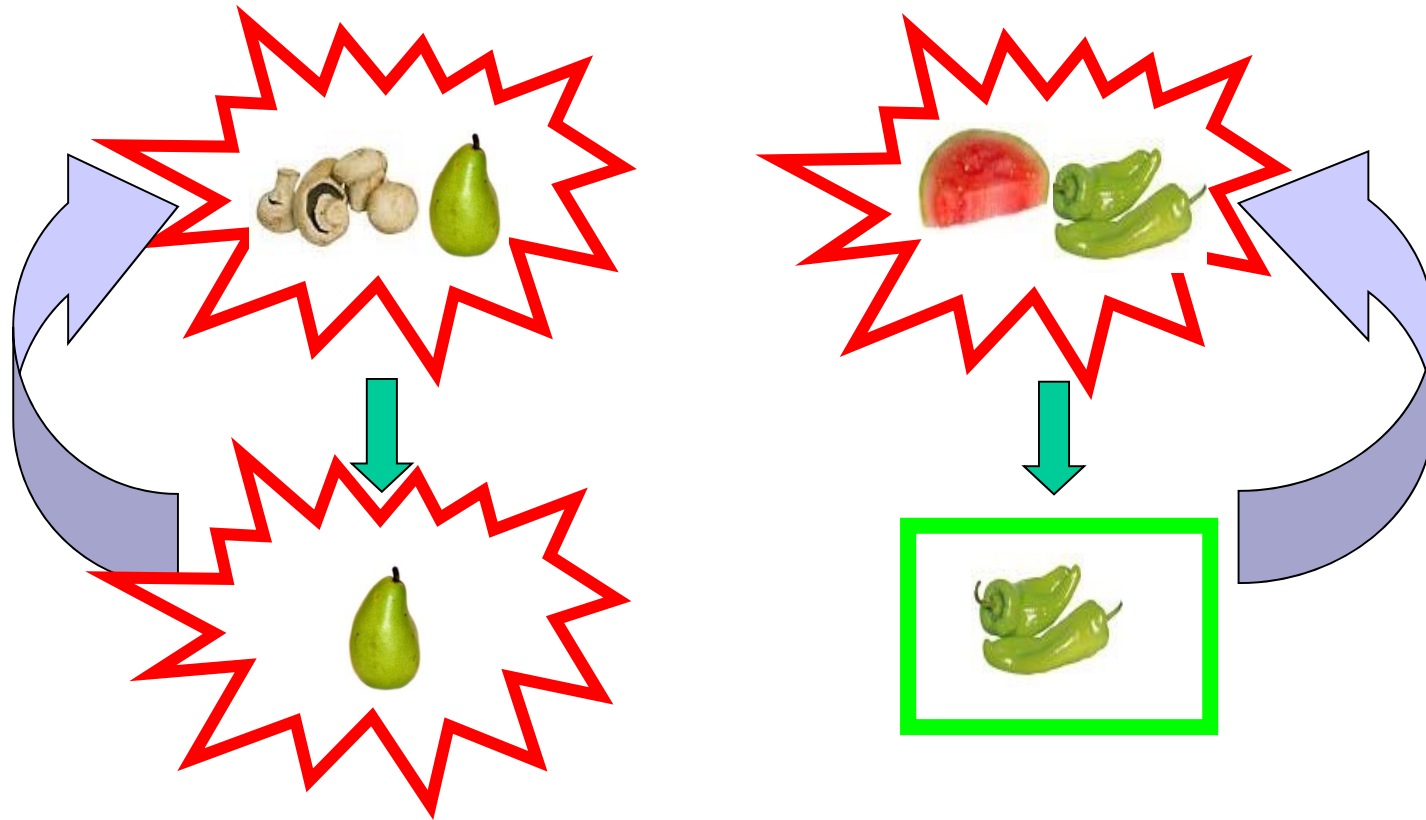
or...

NO REACTION

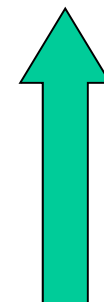
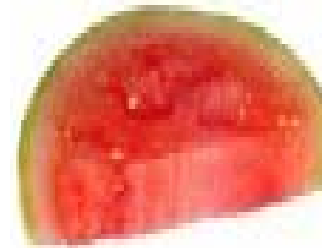
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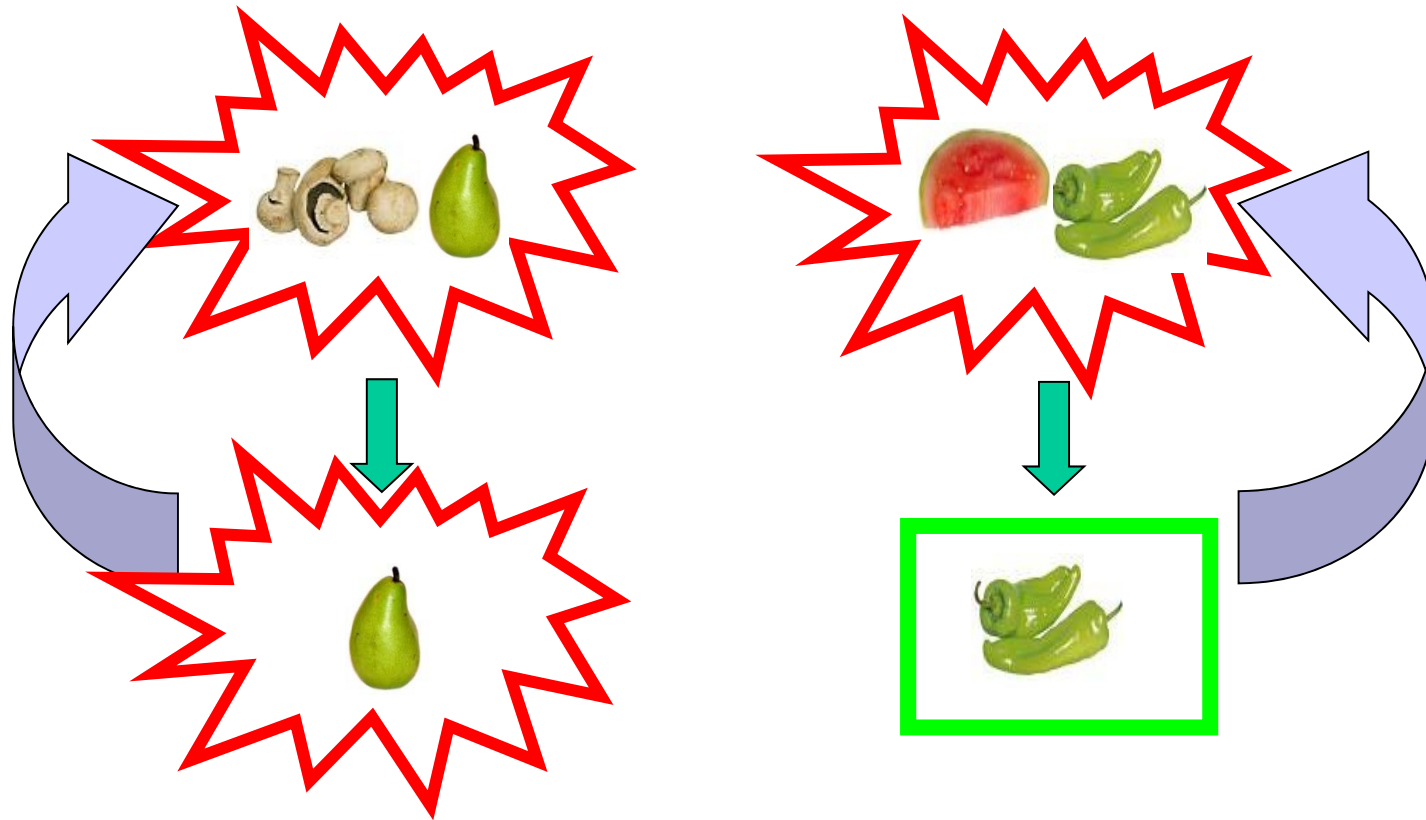


Retrospective revaluation



Corlett et al *Neuron* 2004

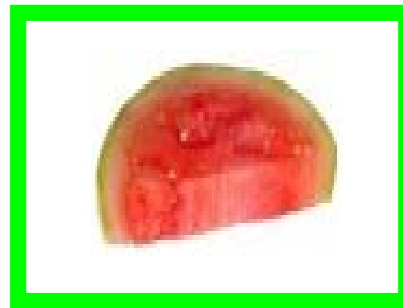




Prediction Error:

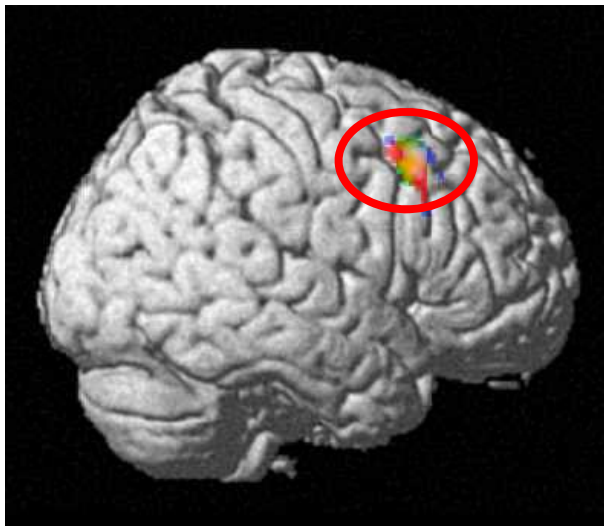


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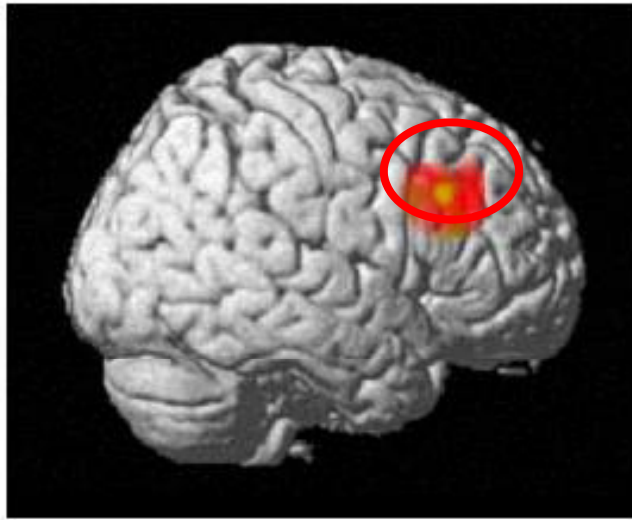


Corlett et al *Neuron* 2004

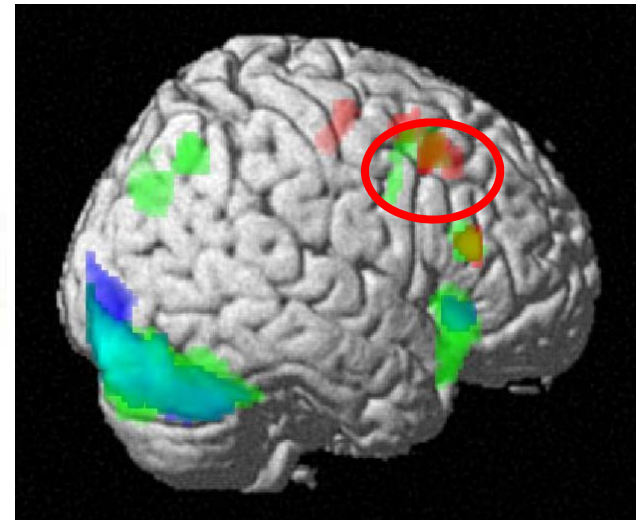
Brain marker for PE-dependent learning



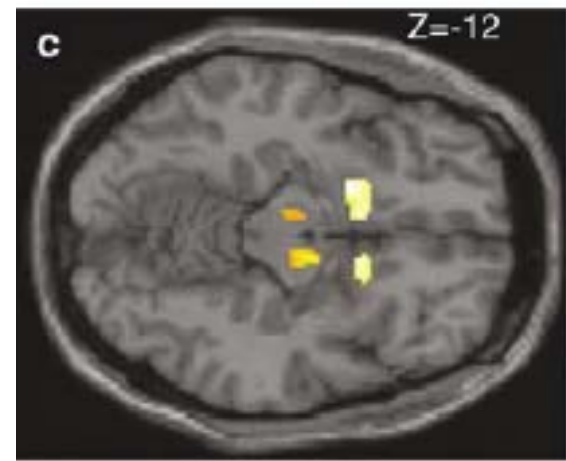
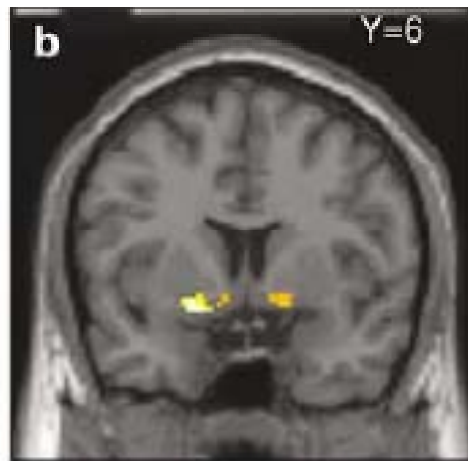
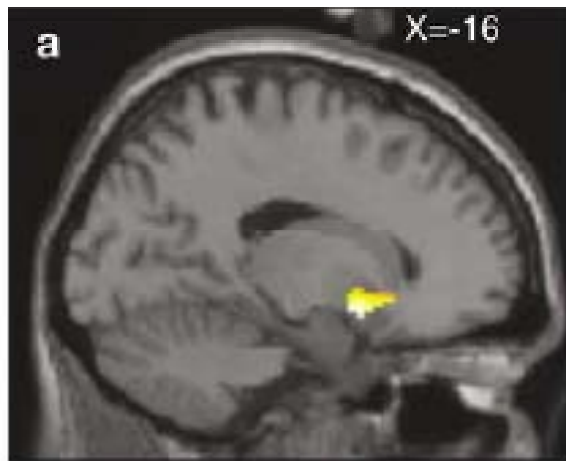
Fletcher et al
Nature Neurosci, 2001



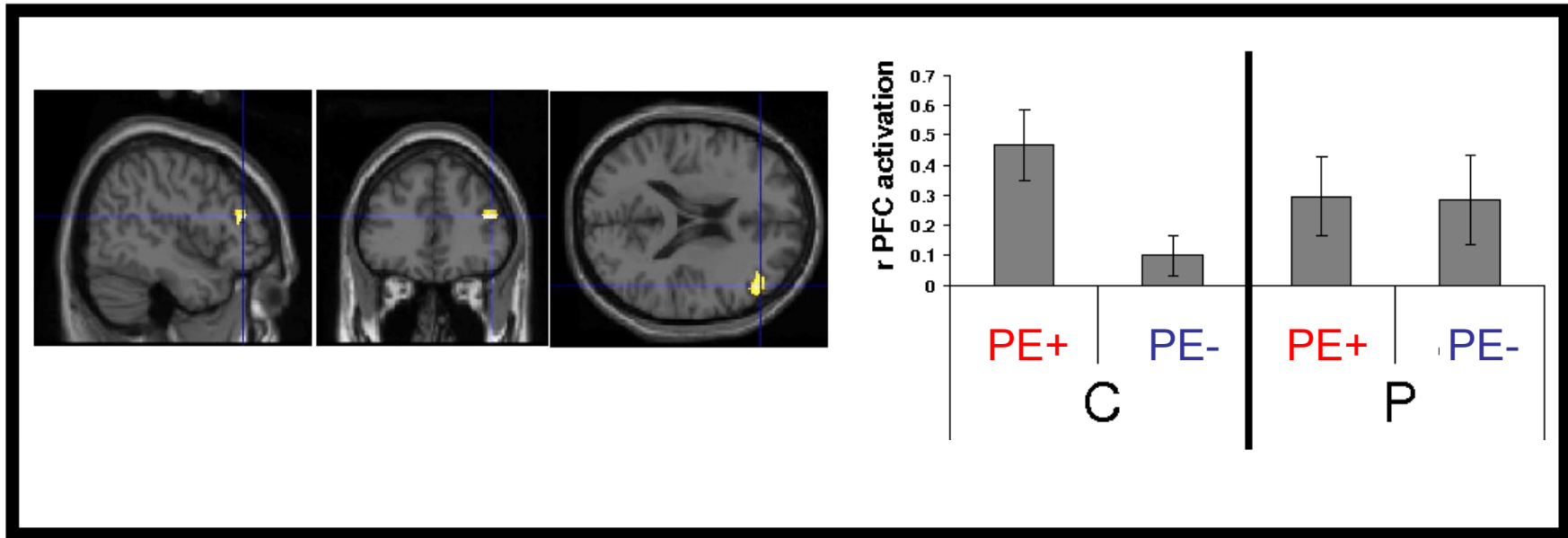
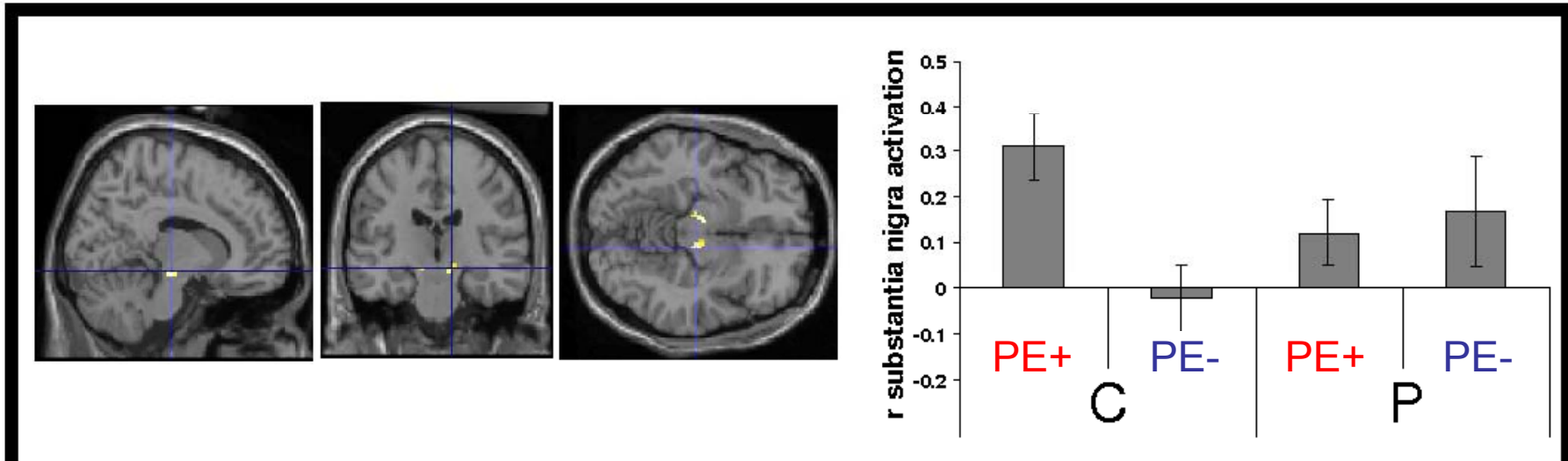
Corlett et al
Neuron, 2004



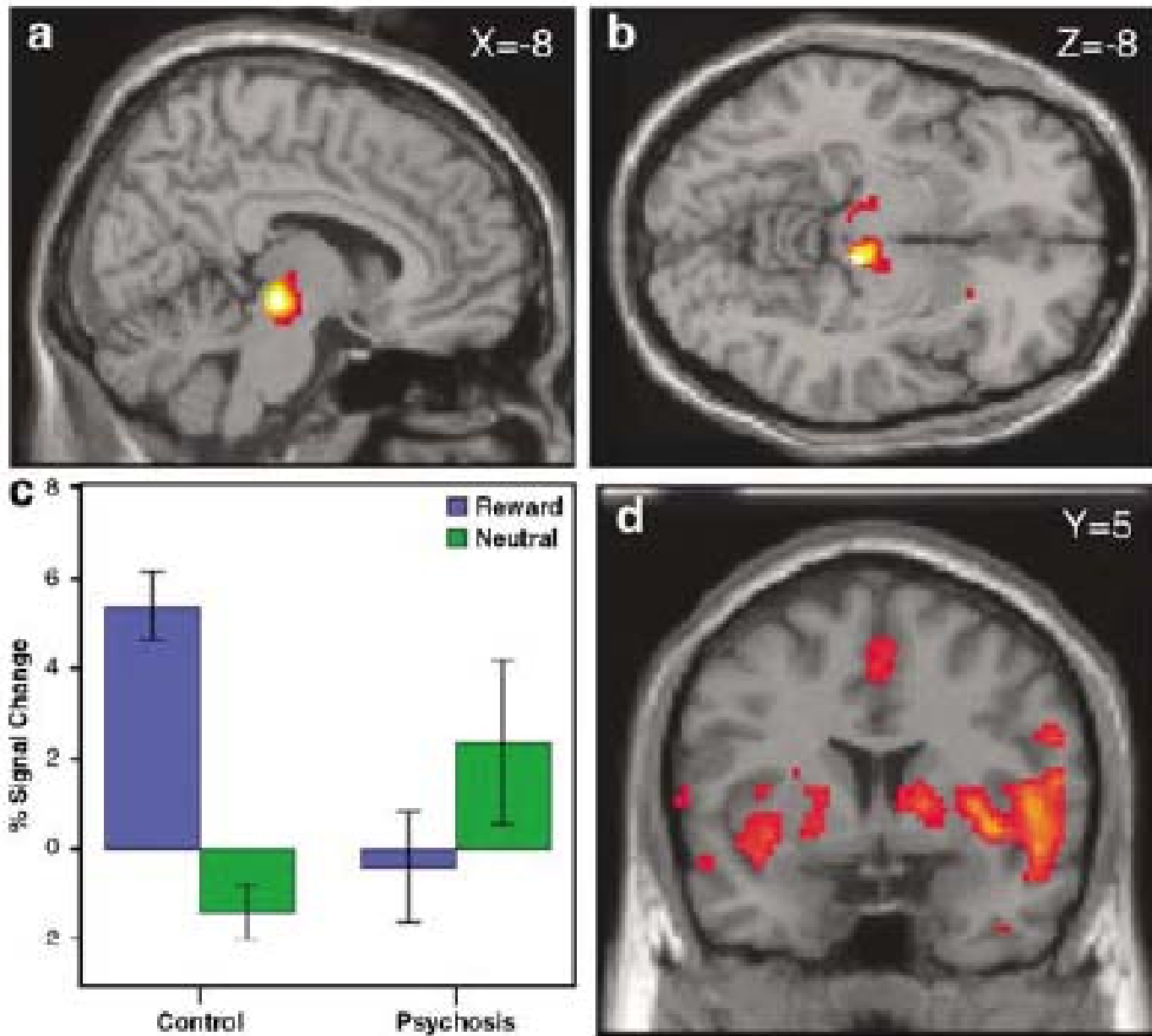
Turner et al
Cereb Cortex, 2004



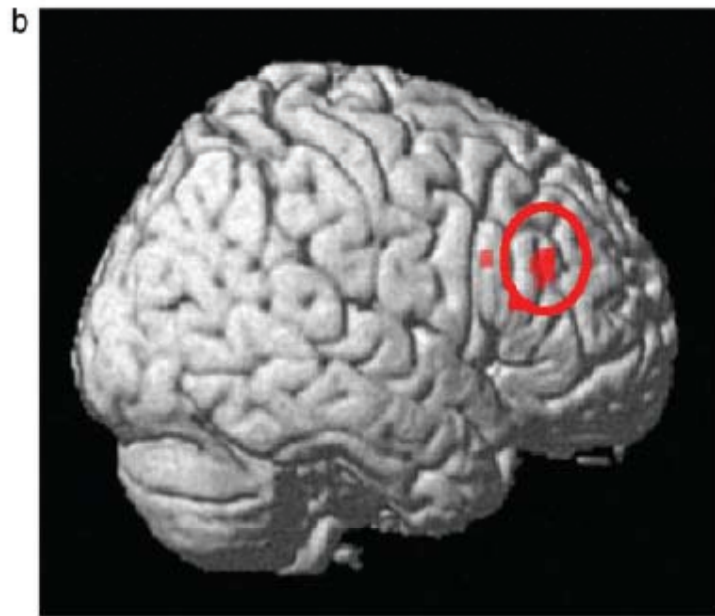
Murray et al, Molecular Psych, 2007; Corlett et al, Arch Gen Psych 2006; Brain 2007



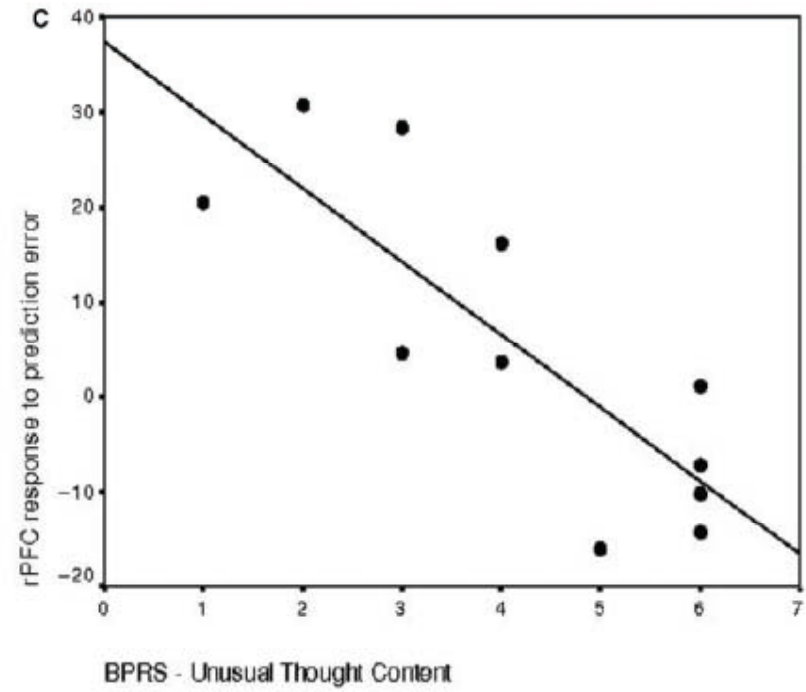
Corlett et al, Brain 2007



Murray et al, Molecular psychiatry 2008



Corlett et al Brain 2007



- In early psychosis, the brain marker for PE has changed
 - Cause?
 - Consequence?
 - Compensation?
 - Medication effects?

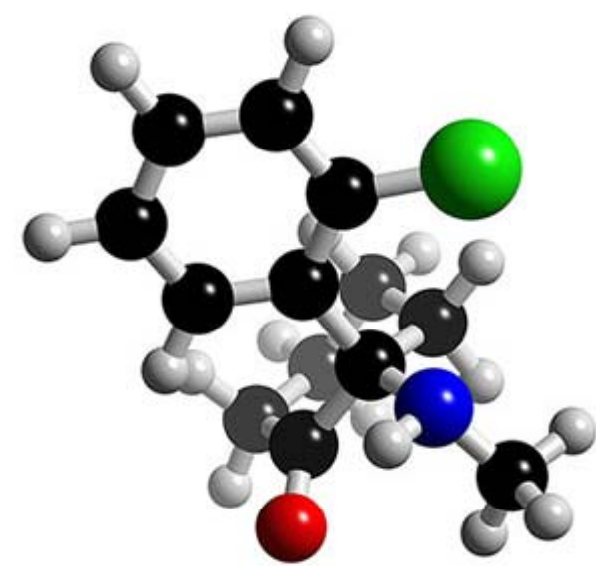
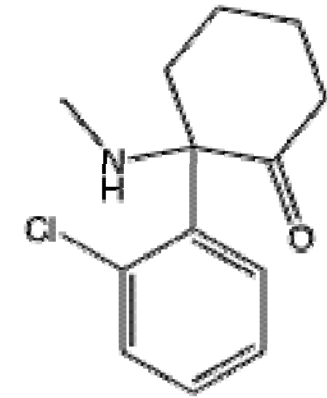
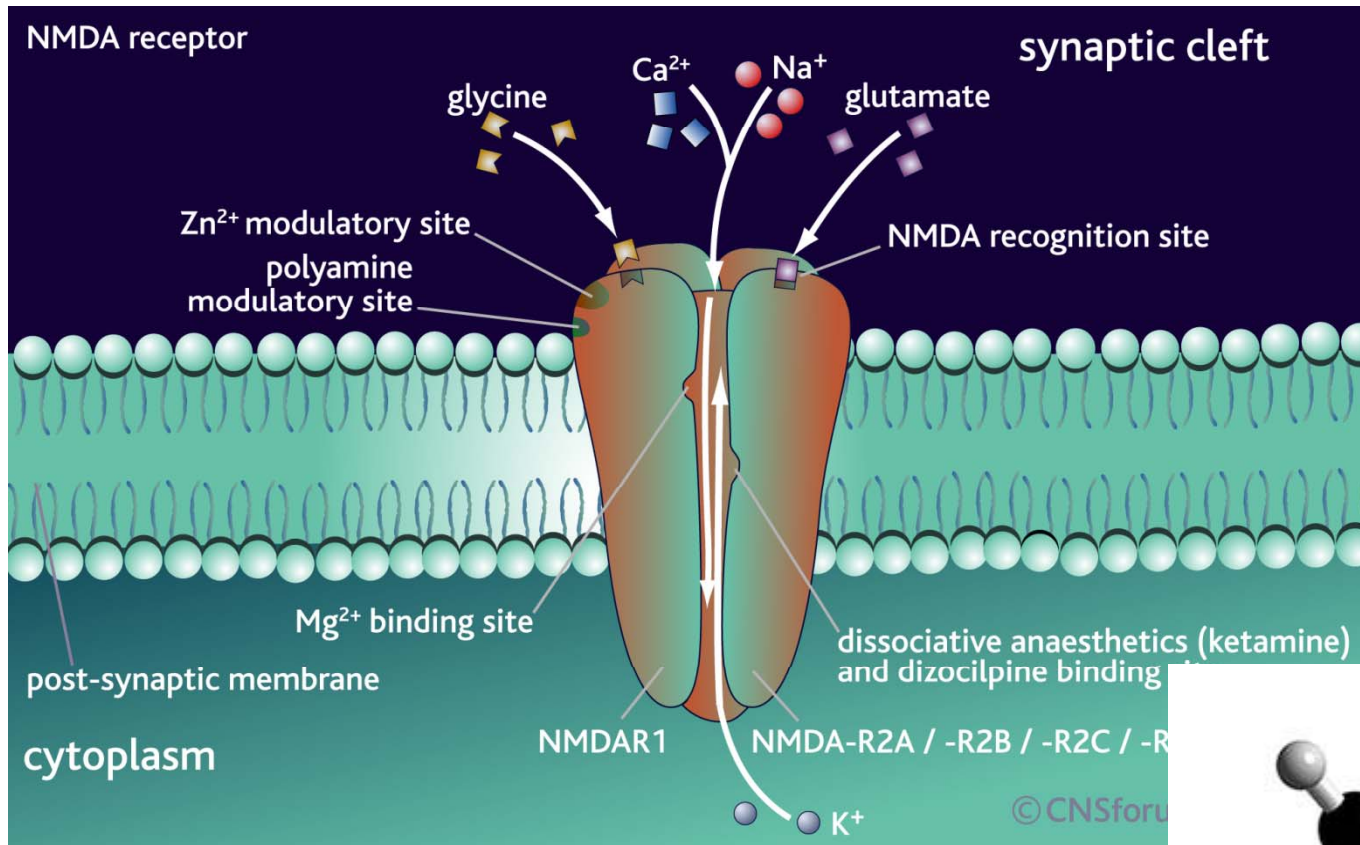
Drug models of mental illness

We can:

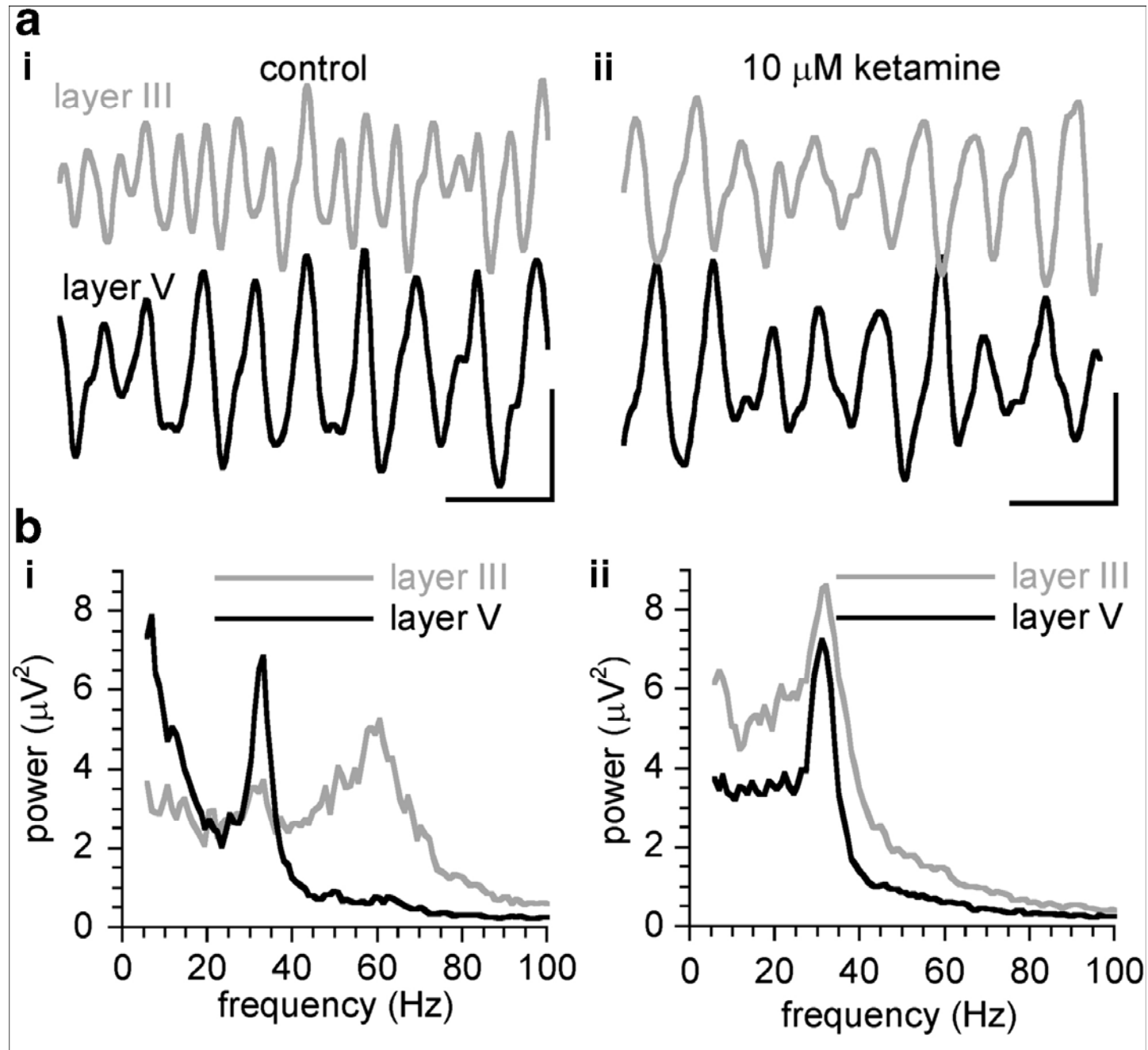
- Make planned controlled manipulations of particular symptoms
- Relate symptoms to neurochemical manipulations
- Relate these symptoms to particular psychological processes and their neural underpinnings
 - During drug administration
 - Before drug administration

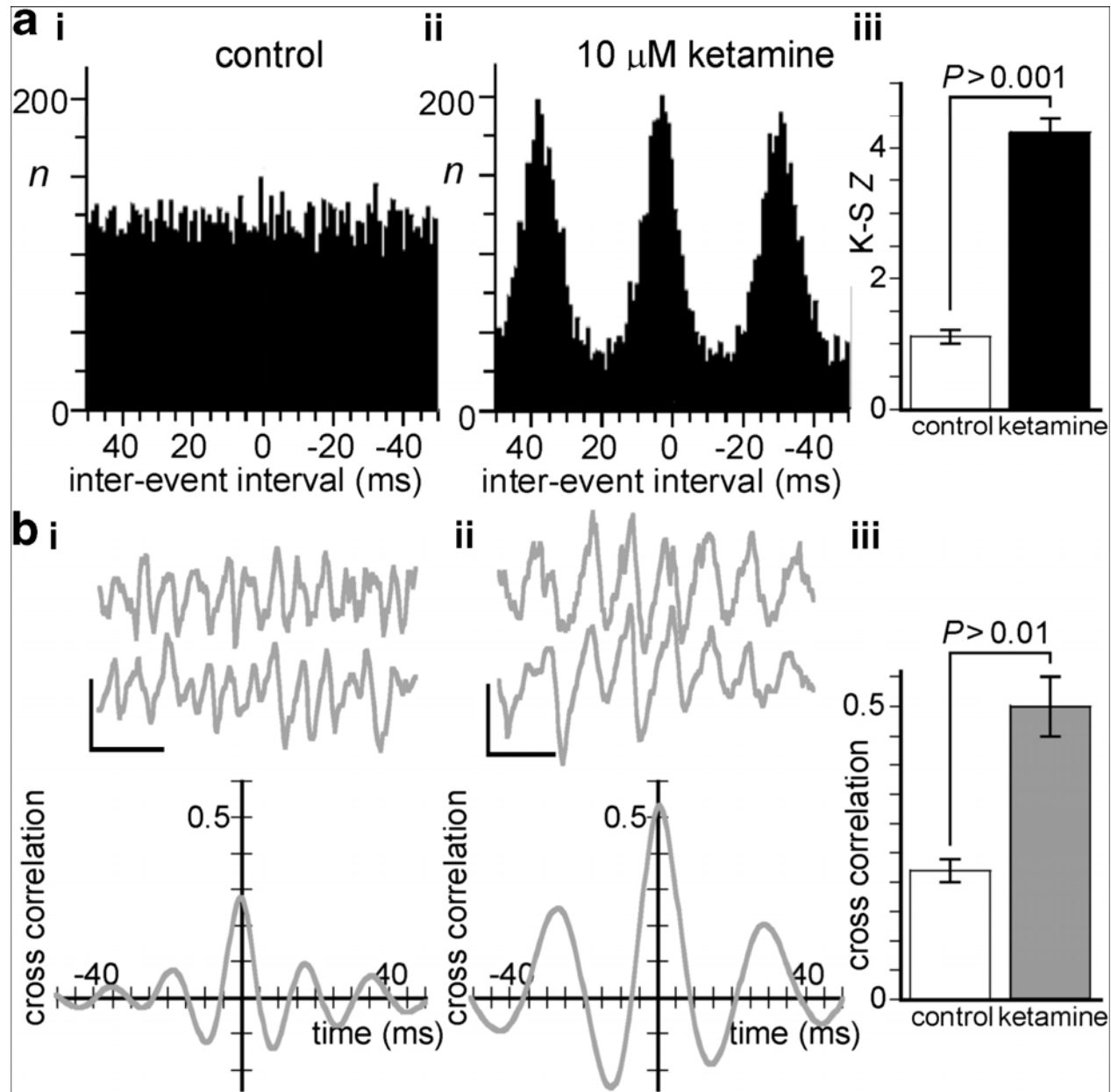
We cannot:

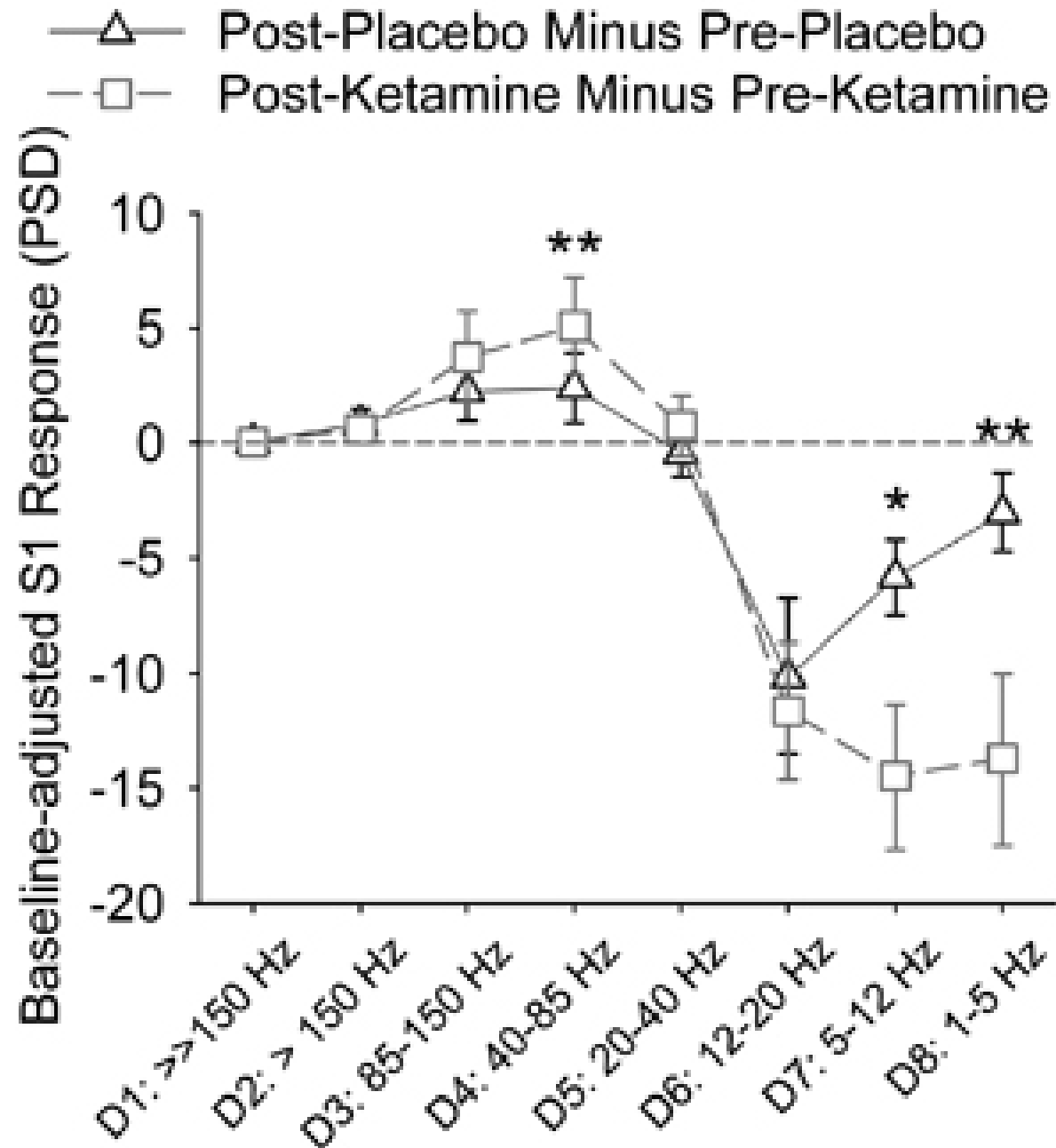
- Replicate the disease in its entirety



Scatton B 1993







Effects of ketamine

- Negative symptoms
- Thought disorder
- Odd “beliefs”
- Perceptual changes and strange associations

- *Given intra-venously to healthy controls using a target-controlled infusion pump*

Odd beliefs

- I feel paranoid that people are [looking at me] but I know that they're not, 'cause I'm in an experiment, so I know that they're not. I feel like I've not got control over what I'm saying, so I feel like what I am saying is not right, and then people are just looking at me and ...OK. I feel as if peoples' reactions are different to me, reacting differently to me, but I don't feel people are gossiping about me. They just seem to be giving me a lot more attention, a lot more time, everything seems a lot slower. It's like that film [the Truman Show].

Odd perception and attention

Ketamine

- “I seemed to lose my experience of 3D space...The computer screen seemed to be in the same plane as the wall behind it...I ceased to have any sense of the relative positions of objects in space”
- “you appear like a 2D image”

Psychosis

- “I see things flat, whenever there is a sudden change, I see it flat...There's no depth, but if I take times to look at things, I can pick out the pieces like a jigsaw puzzle”
 - Chapman 1966

Odd perception and attention

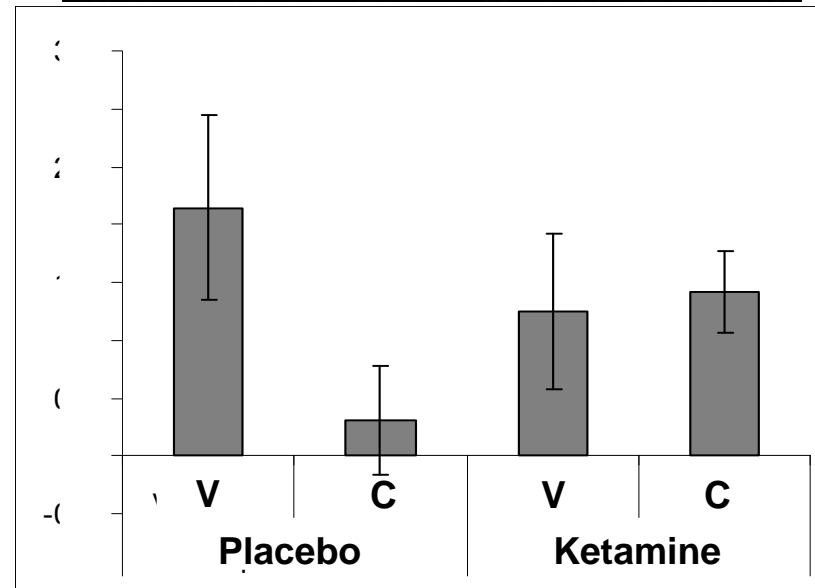
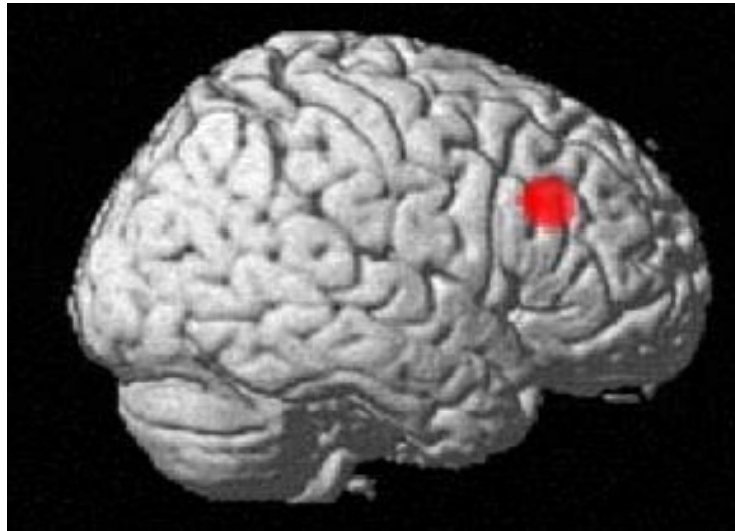
Ketamine

- ‘The object of my gaze was very bright’
- “I felt that my hearing had changed in that background noises became clearer”
- “I couldn’t make out the outline of things.”

Psychosis

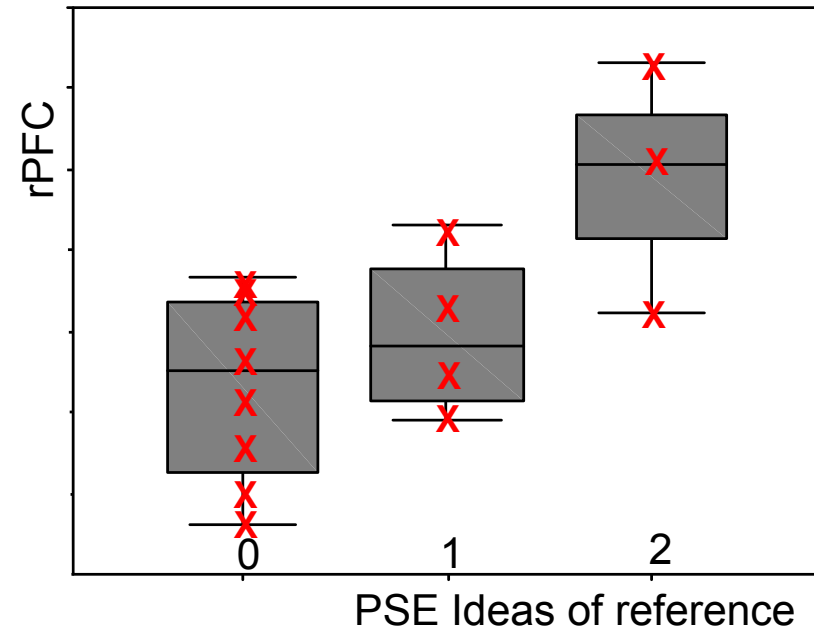
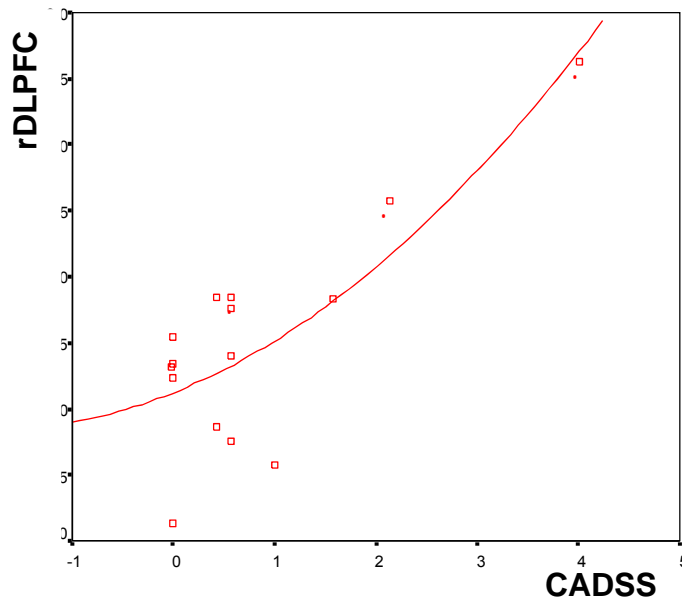
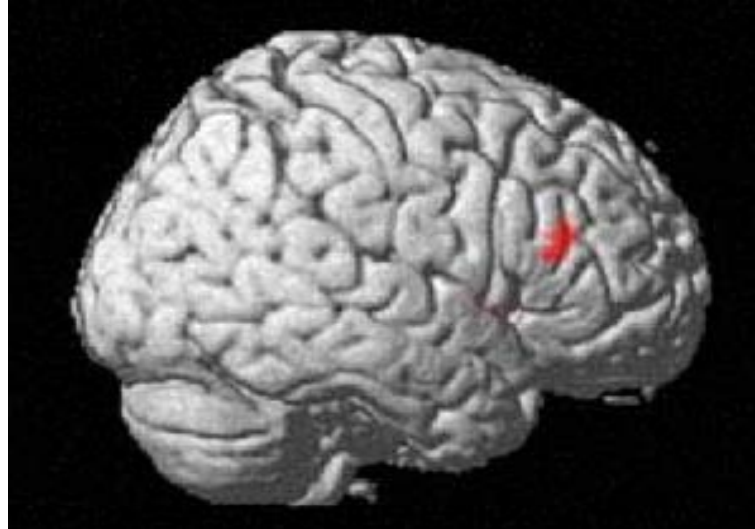
- "Colours seem to be brighter now, almost as if they are luminous"
- "Everything's brighter and louder and noisier"
- "...as if someone had turned up the volume...[background noises] seem to be just as loud as and sometimes louder than the main noises"
 - McGhie & Chapman, 1961

Post-revaluation surprise under low dose ketamine...



Corlett et al
Arch Gen Psych, 2007

At high dose ketamine:

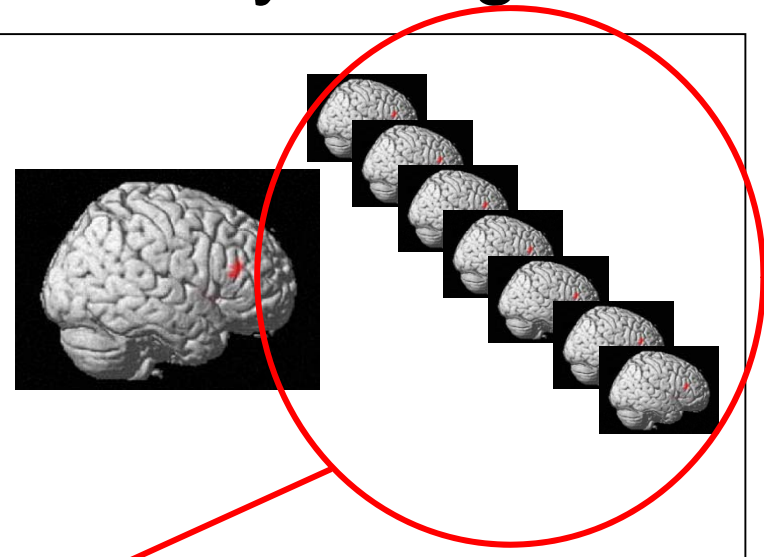


Replication and extension - study design

18 healthy
volunteers
(8 female)



Prediction
Error



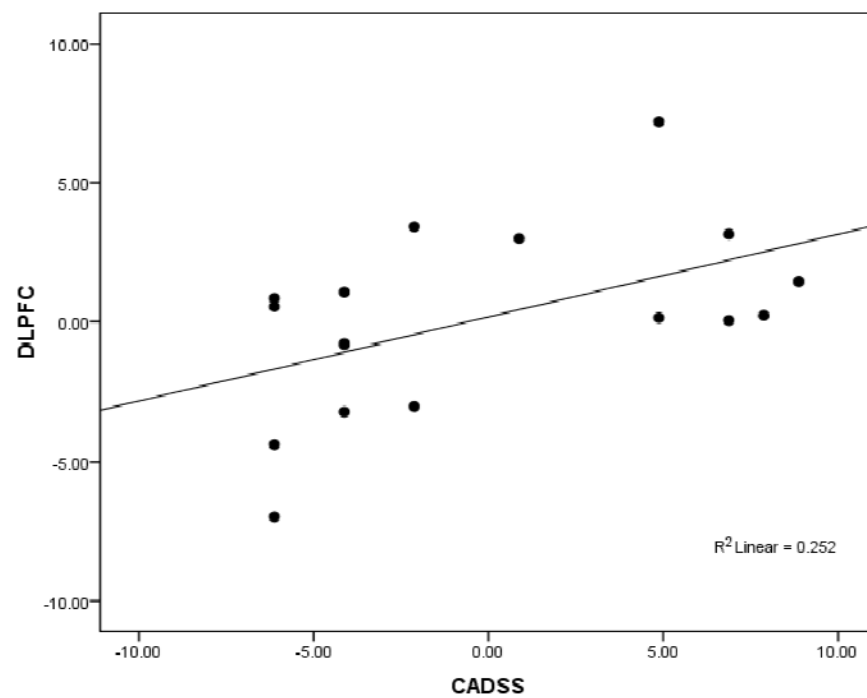
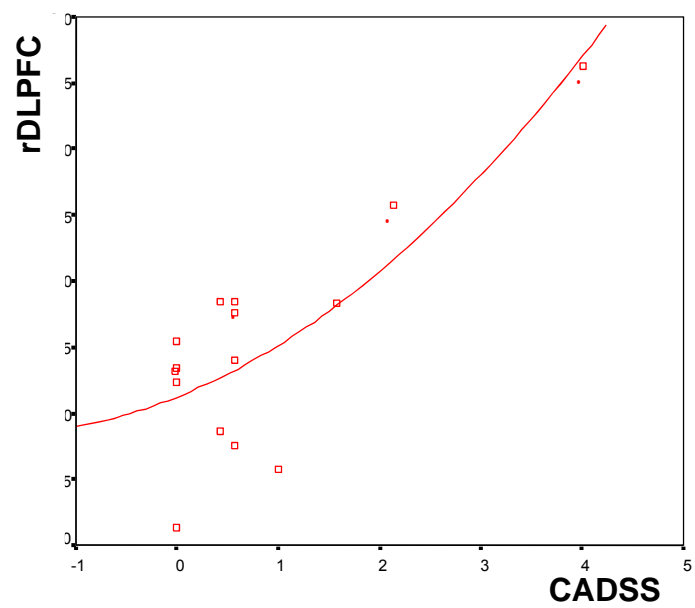
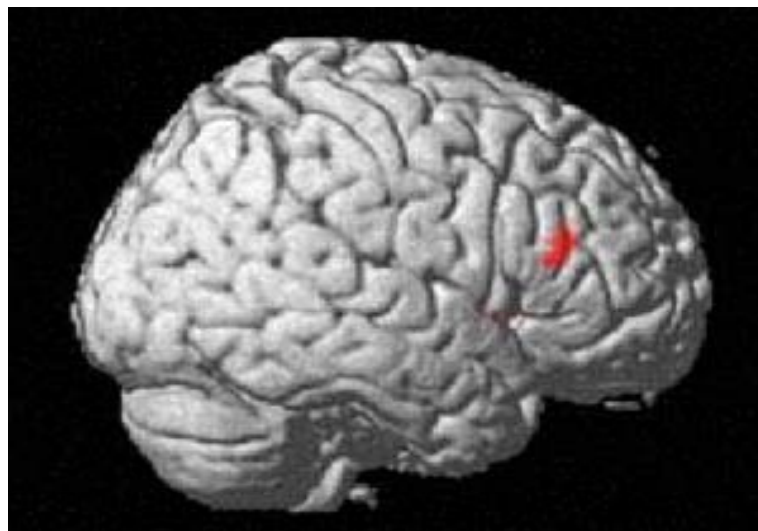
Stage 1

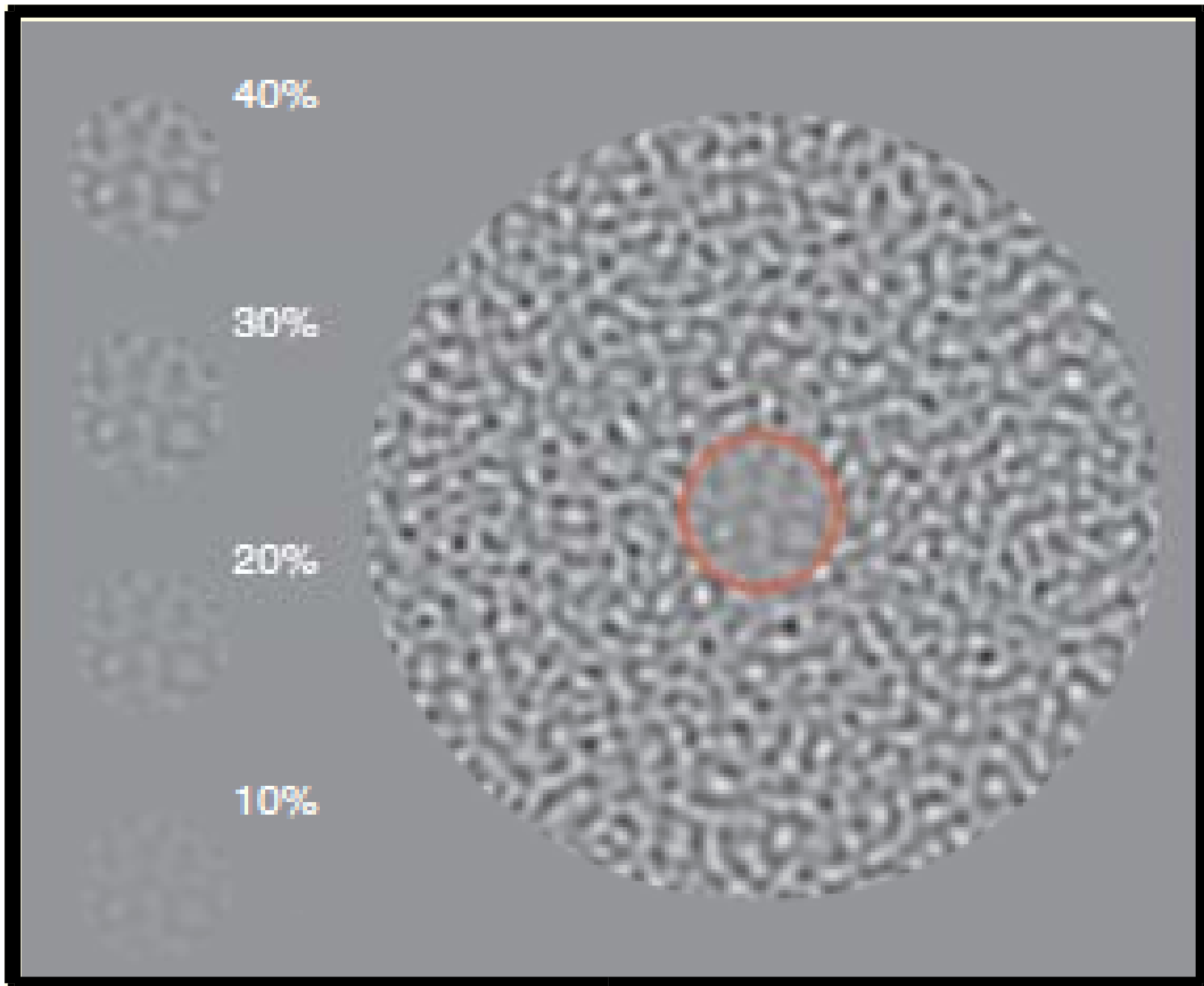
> 28 days

Stage 2

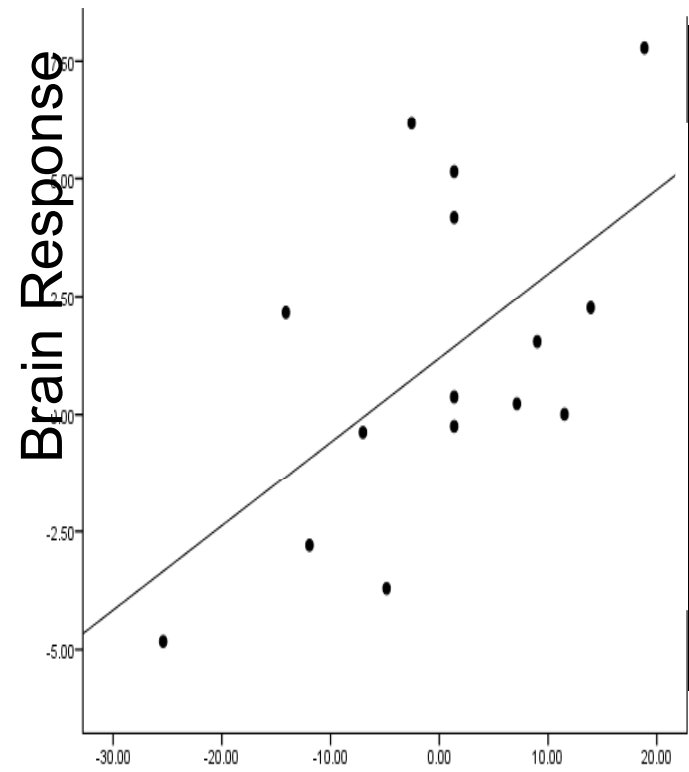
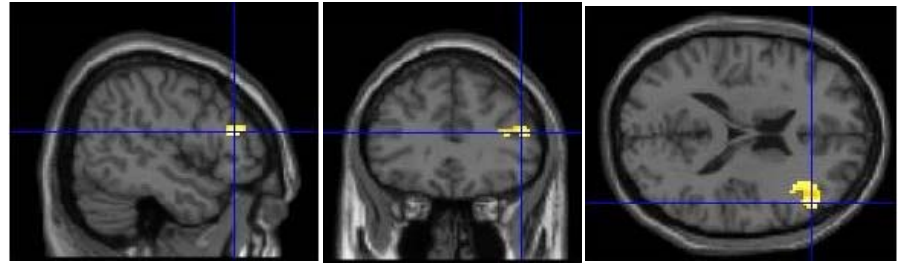
Perceptual changes
Symptoms scores
"Specific" cognitive changes



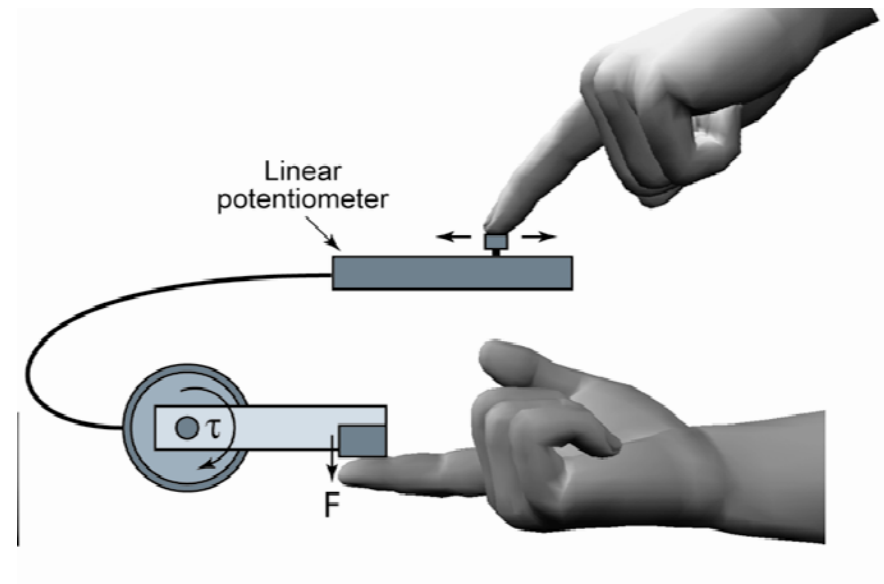
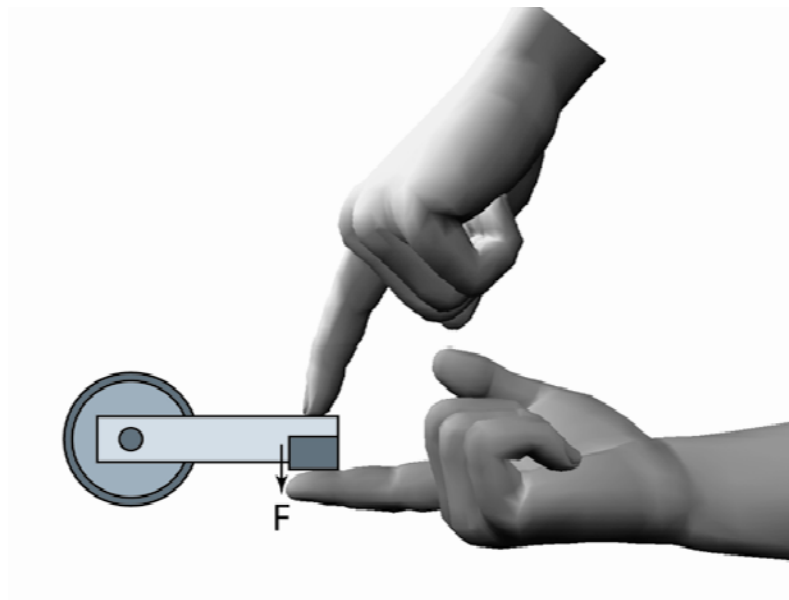
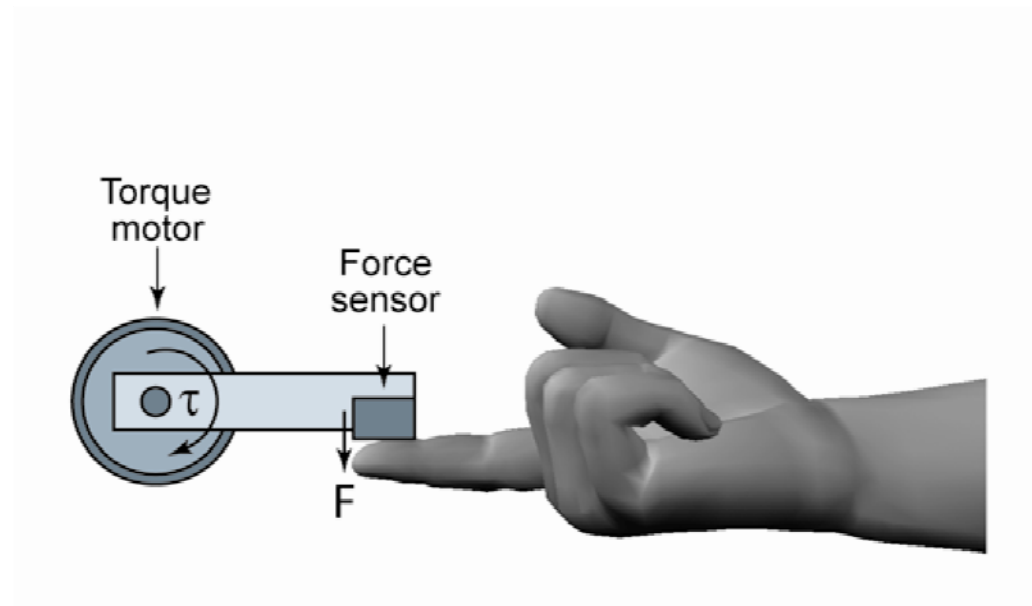


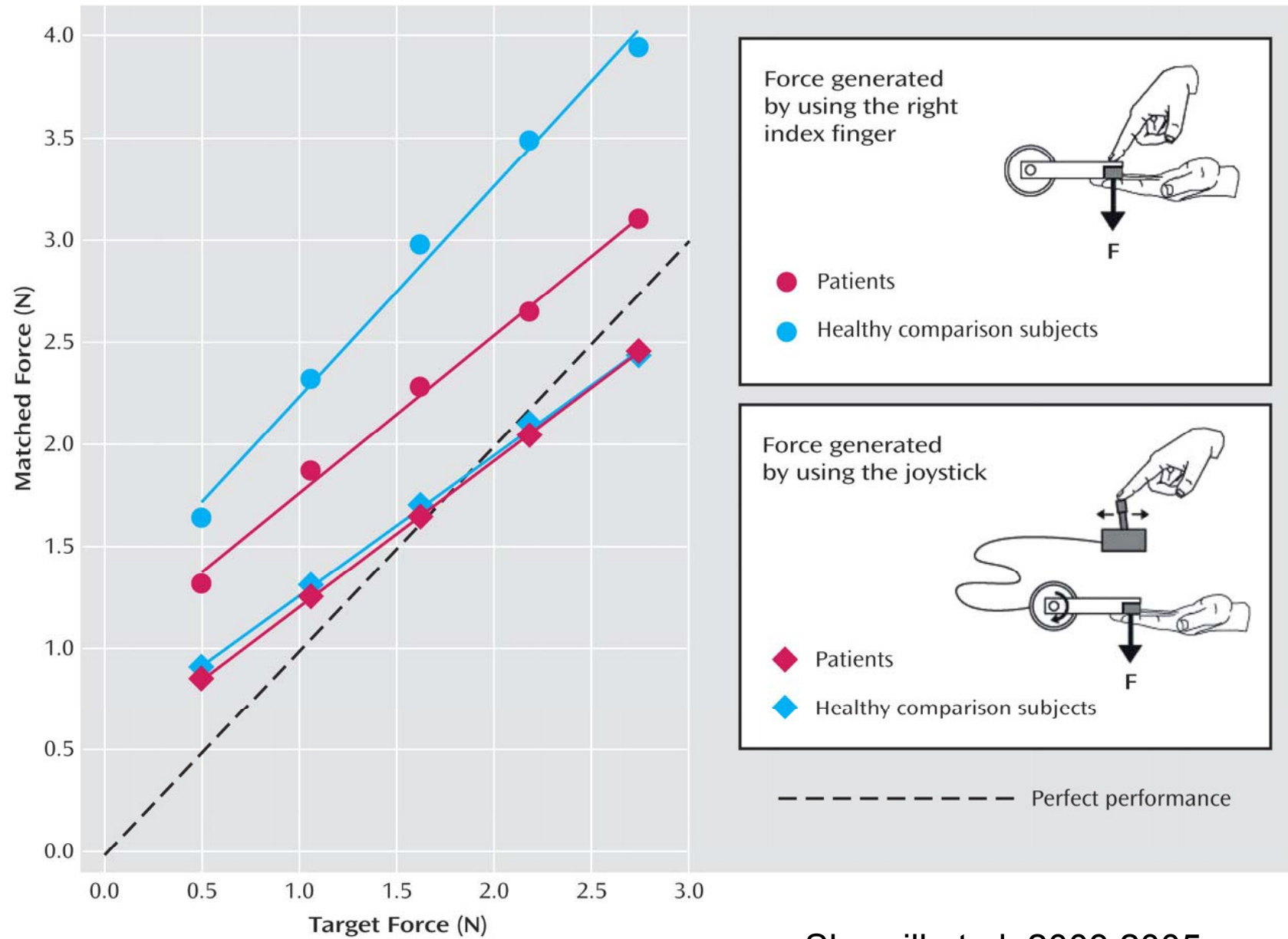


Dakin et al 2005

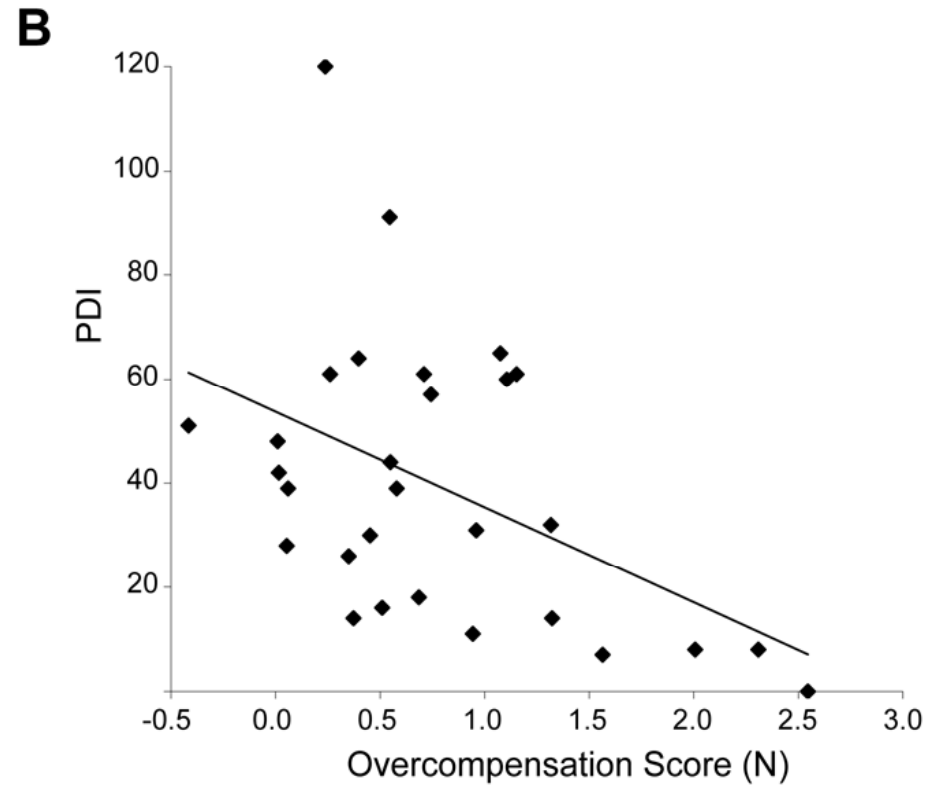
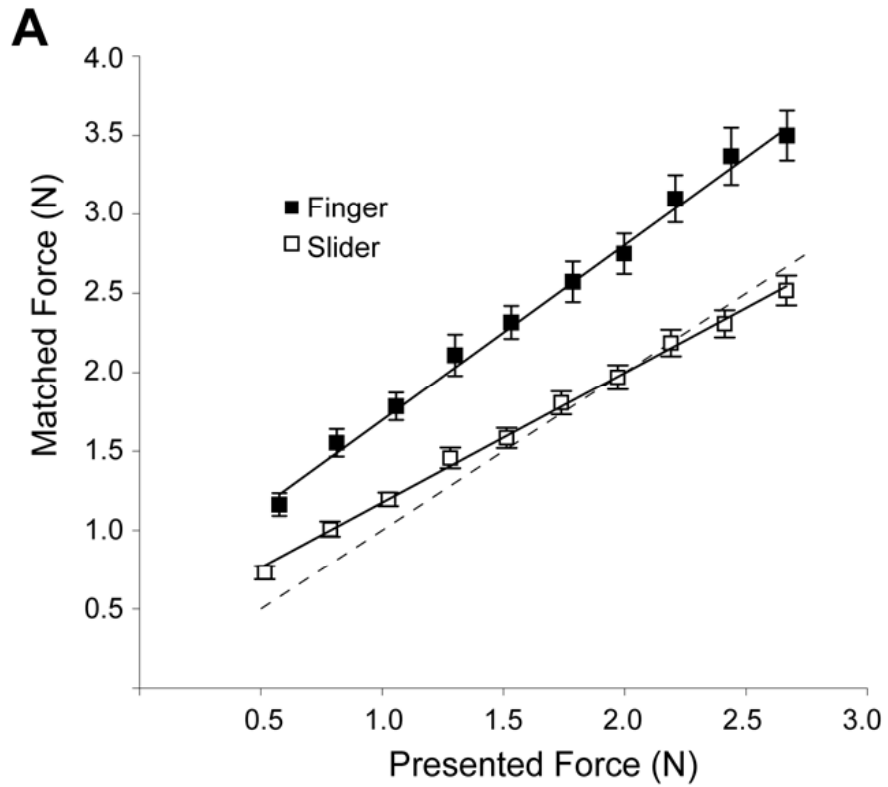


Release from Suppression

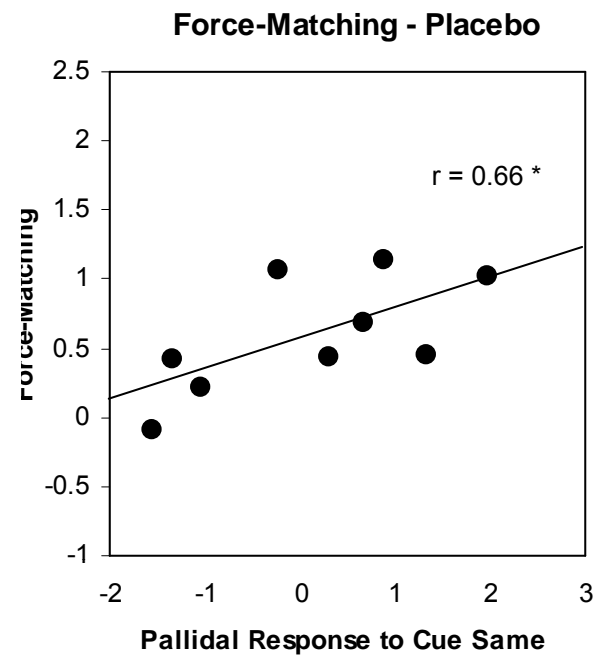
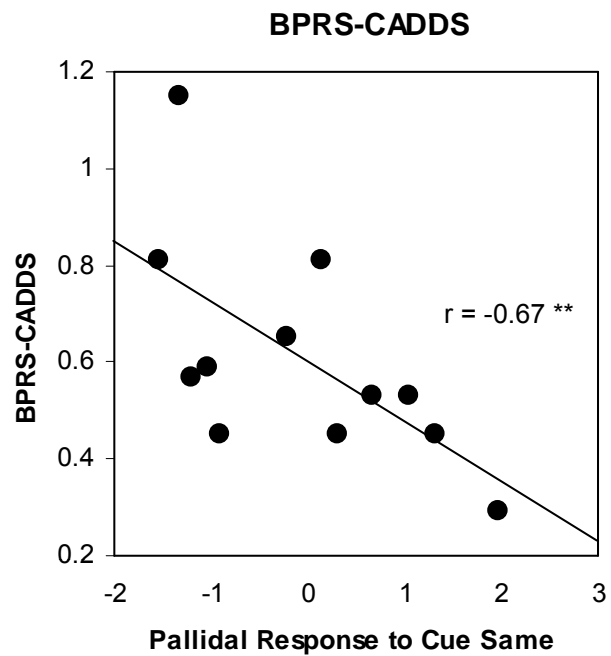
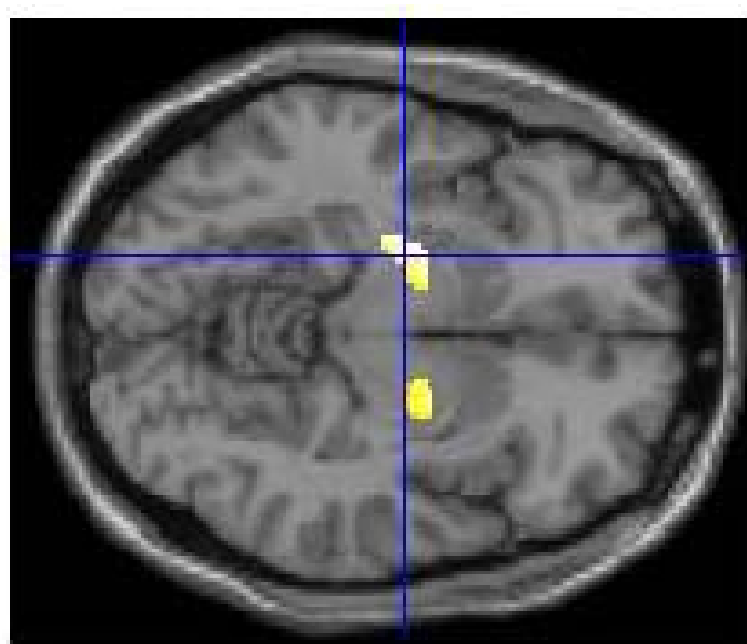




Shergill et al, 2003;2005



Teufel et al, 2011 Neuropsychologia



* $p \leq 0.05$; ** $p \leq 0.01$

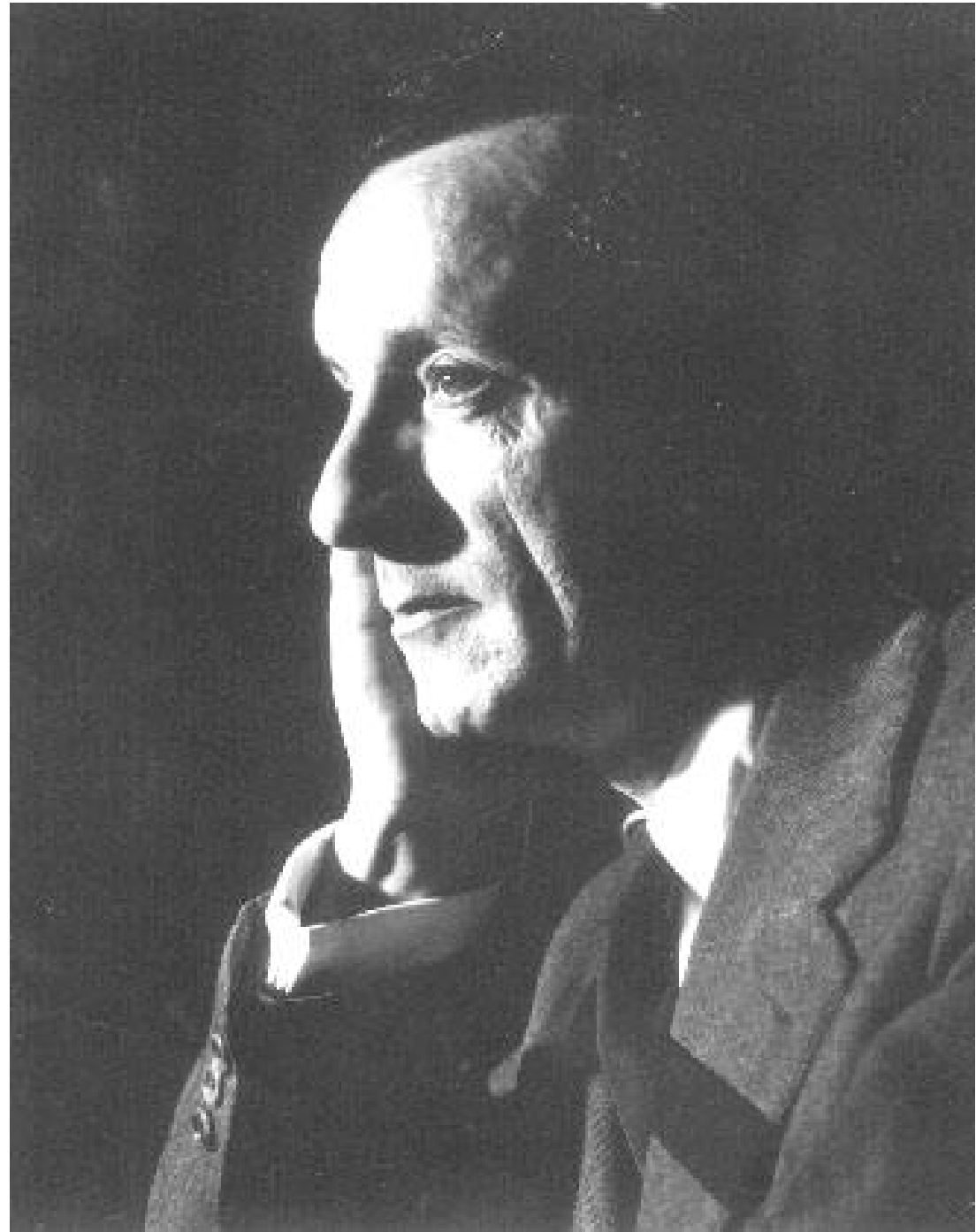
Summary.

- We do not need to invoke distinct perceptual and/or inferential problems to try to explain delusions
- The brain makes predictions which may over-write incoming data
- If those predictions are violated to a sufficient degree (*prediction error*) it must engage in new inferential processes (abduction)

Summary

- I suggest that perturbed prediction error signal can account for many of the early symptoms of emerging psychosis
 - Brain imaging studies of mental illness are consistent with this
 - A drug that produces comparable symptoms is also associated with an apparent disturbance in prediction error.
 - In healthy people, variations in the brain sensitivity to prediction error are predictive of the cognitive, perceptual and inferential effects of a subsequent drug challenge.

Strictly speaking, we are all deluded, making up the world to fit with what we already believe.



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