

Computational models of schizophrenia

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CCN lecture
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Schizophrenia

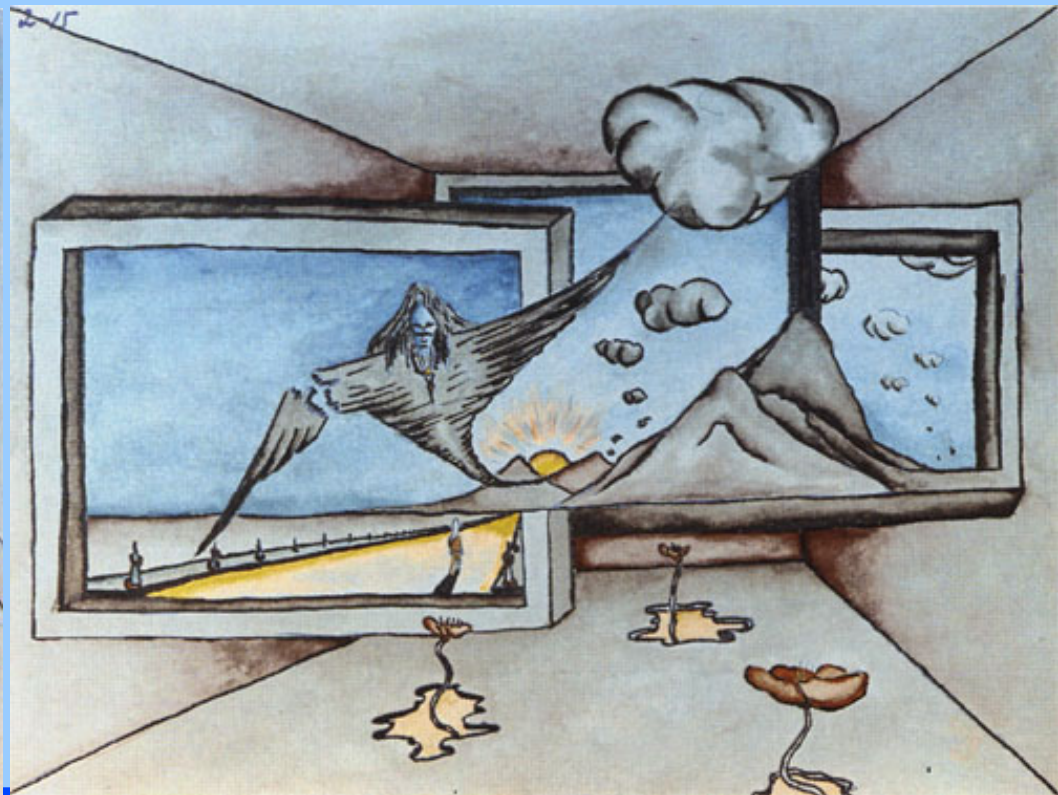
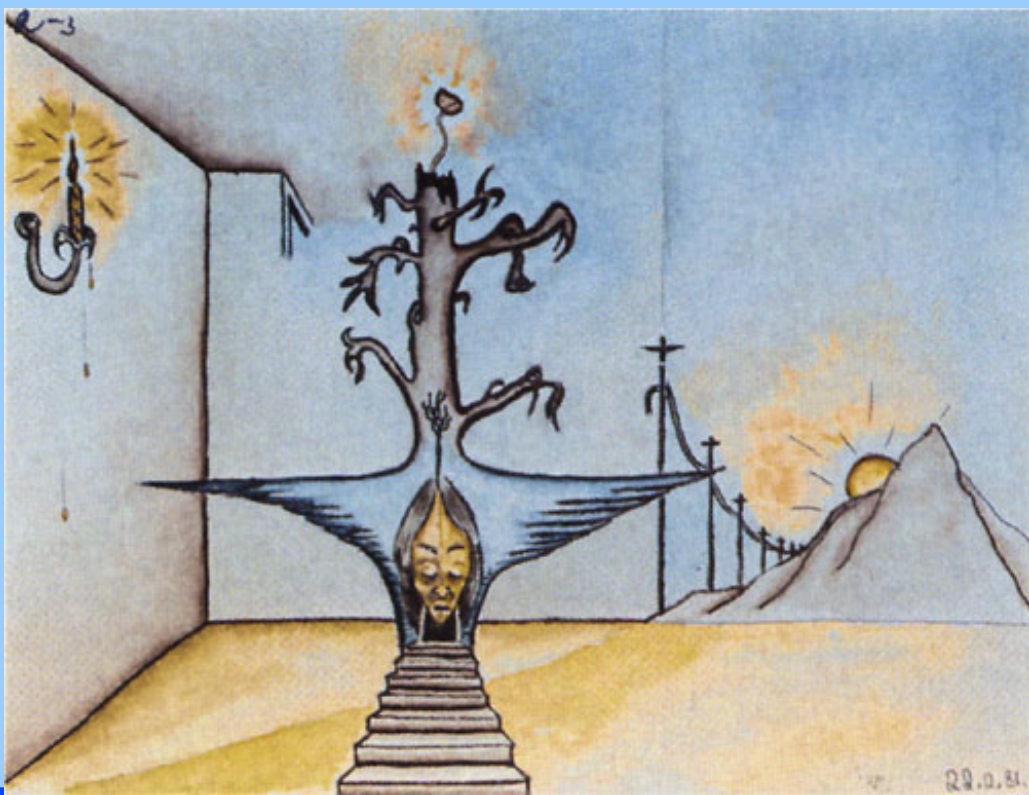
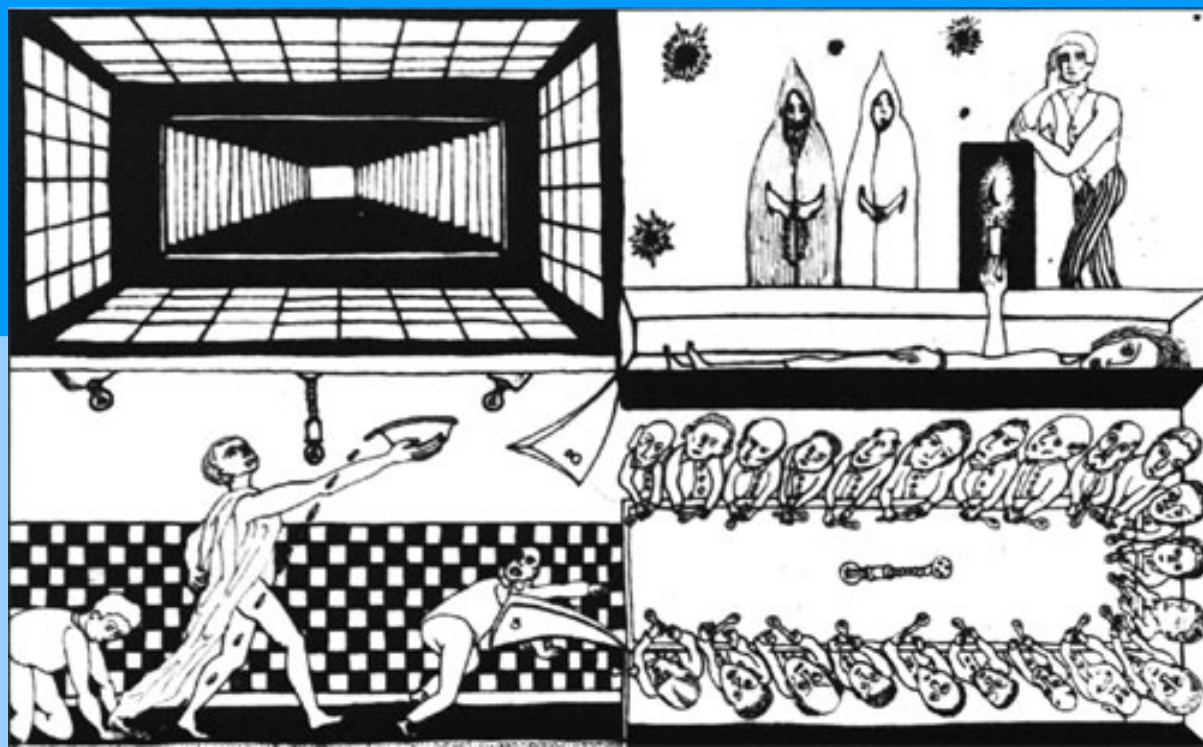
- Major neuropsychiatric disorder
- 1% lifetime risk, maybe increasing

- Sudden psychotic episode...
- ...or a gradual withdrawal and decline

- Common to have several episodes
- Leaves you apathetic and emotionally-blunted

Positive symptoms

- Threatening voices
 - “Each mouthful is stolen...if only your foot had been chopped off”
- Thought echoing
 - “Whatever I think, the bells ring it, the wheels creak it, the dog barks it...”
- Visual hallucinations
 - “People float about him in the air, some of whom appear joyful, while others are crying. Angels no bigger than wasps fly around the patient”



Disorganisation

- Thought disorder
- Pressure of thought
 - “In my mind there ran like an endless clockwork a compulsive torturing, uninterrupted chain of ideas.”
- Incongruent behaviour
 - “A female patient approached one of the attendants whom she liked and told her in the friendliest manner 'I really would like to slap your face, people like you are usually called SOB's.'”

The Golden Age of Horticulture

At the time of the new moon, Venus stands in Egypt's August-sky and illuminates with her rays the commercial ports of Suez, Cairo and Alexandria. In this historically famous city of the Califs, there is a museum of Assyrian monuments from Macedonia. There flourish plantain trees, bananas, ... and olives. Olive oil is the Arabian liquor-sauce which the Afghans, Moors and Moslems use in ostrich farming. The Indian plantain-tree is the whiskey of the Parsees and Arabs. The Parsee possesses as much influence over his elephant as does the Moor over his dromedary.

Negative symptoms

- Poverty of thought / perseverance
 - “...the rosary was 'A prayer multiplier and this in turn is a prayer for multiplying and as such is nothing else but a prayer mill, and is therefore a mill-prayer machine which is again a prayer-machine mill.....(several pages)”
- Blocking
 - “Obstacles to thinking...a tightness in his head as if my head were drawn together”
- Loss of initiative
 - “If one gives a patient a saw he will pull it back and forth until the wood is sawn through and remain standing apathetically till the attendant fixes a new piece under the saw”

Cognitive deficits

- Difficulty in maintaining context
- Disturbed ability to form associations
- Poor working memory

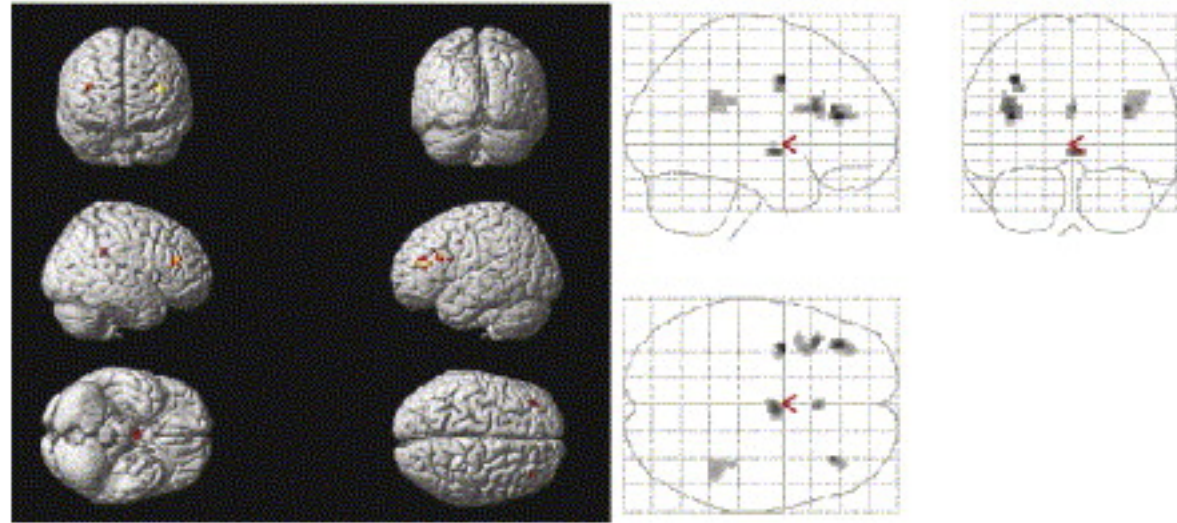
- Positives are fascinating...
- ...but negative/cognitive problems are more detrimental

- Medication alleviates positive symptoms
- Patient is left
 - Embarrassed
 - Confidence has taken a knock
 - Feeling of lost potential
 - 10% suicide rate

Neuropathology of schizophrenia

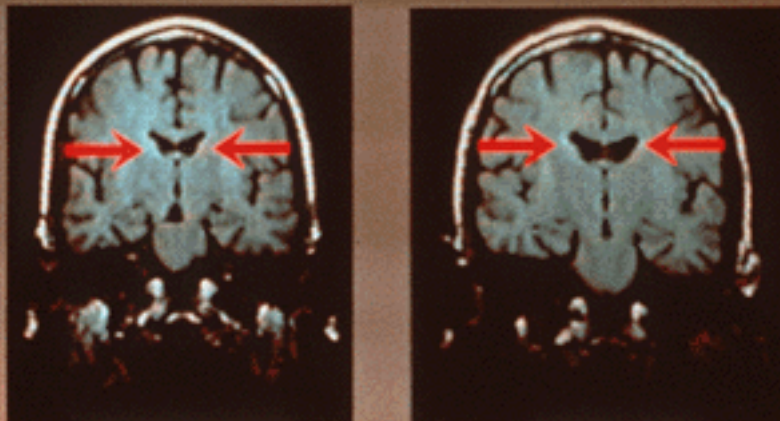
Underactive frontal lobes

Comparison subjects minus patients



SCHIZOPHRENIA IN MONOZYGOTIC TWINS

Pair no. 2: 44 year old males



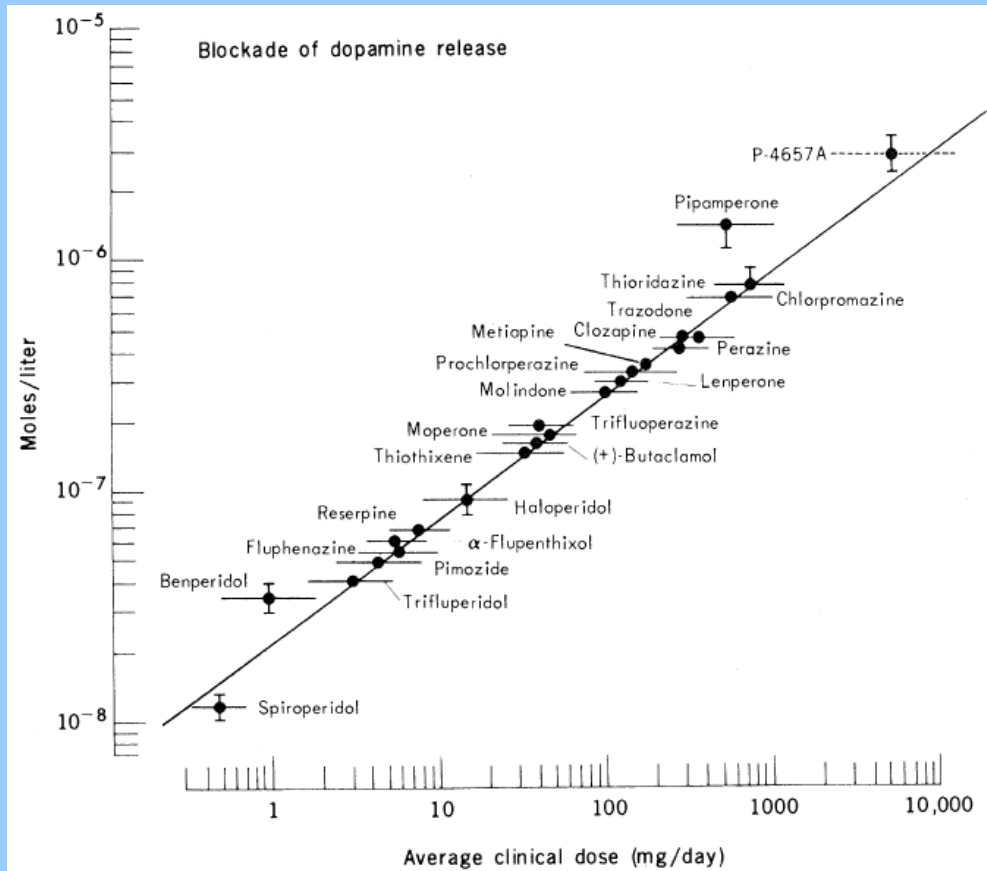
UNAFFECTED

AFFECTED

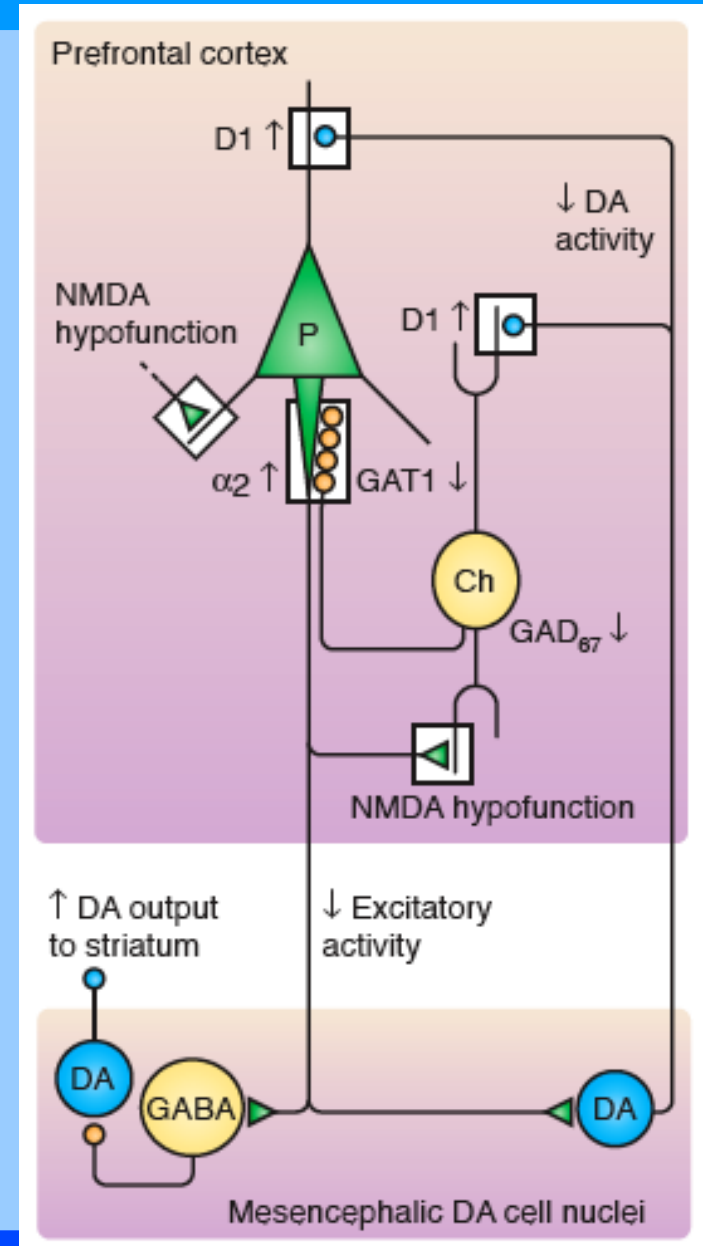
Enlargement of the ventricles

Neuropathology of schizophrenia

Dopamine imbalance...?



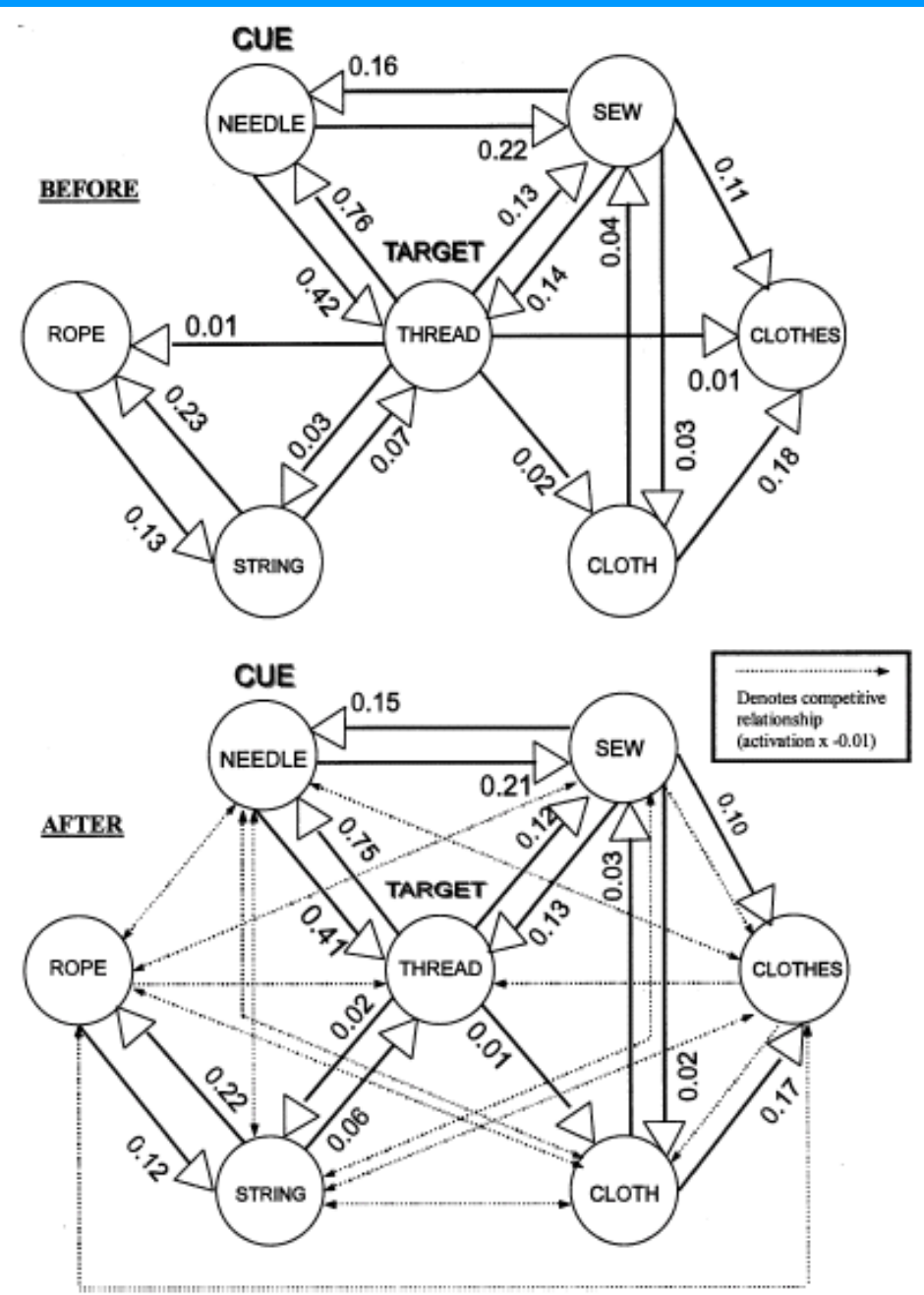
...or deficient glutamate transmission?



A computational approach

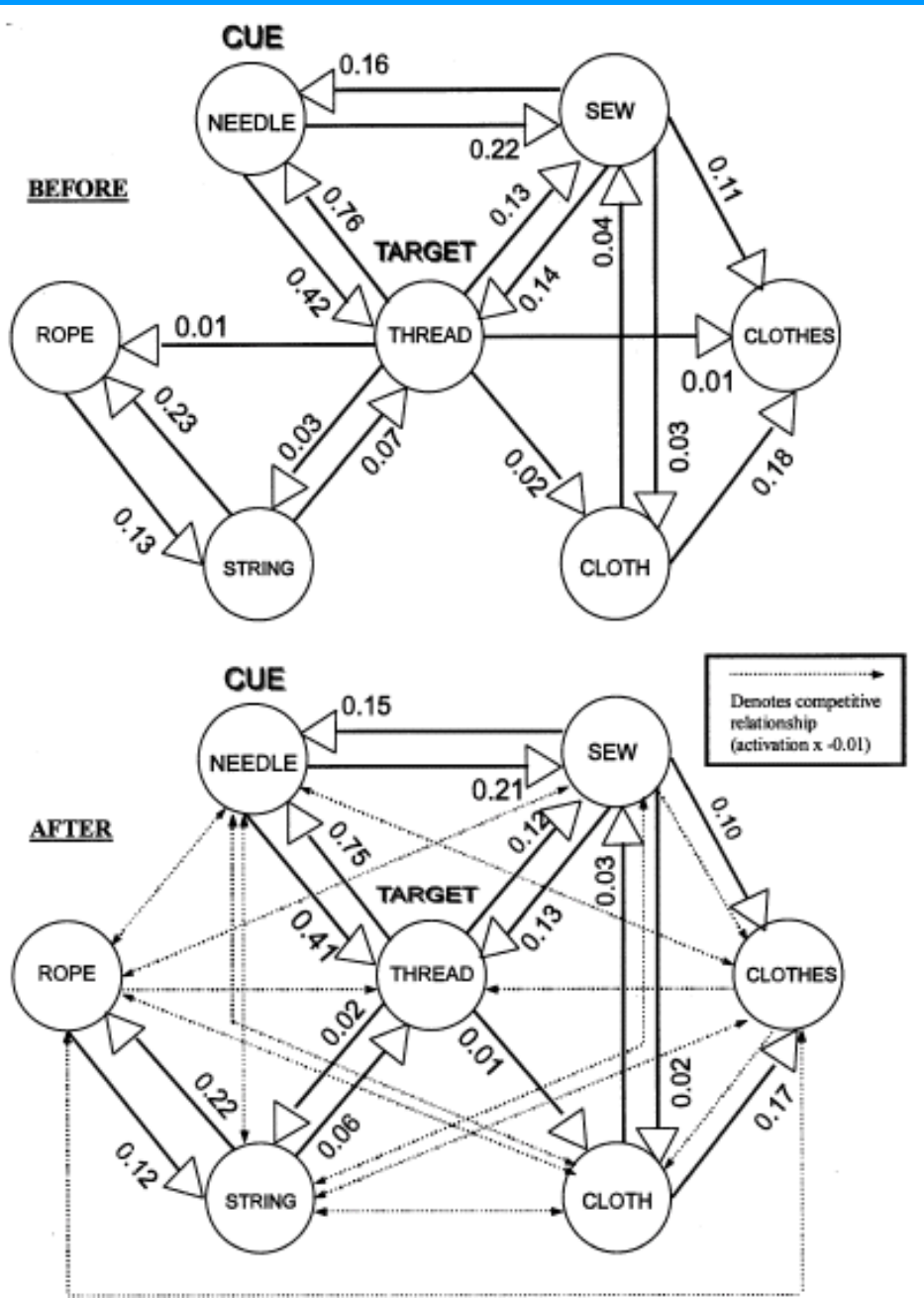
- A lot of factors, interacting over several levels
- From genetic, to cellular, up to neural circuits and behaviour
- Biophysical to biologically-inspired
- Networks, mathematical, abstract cognitive
- As of yet, no cohesive concerted effort

High-level, cognitive modelling

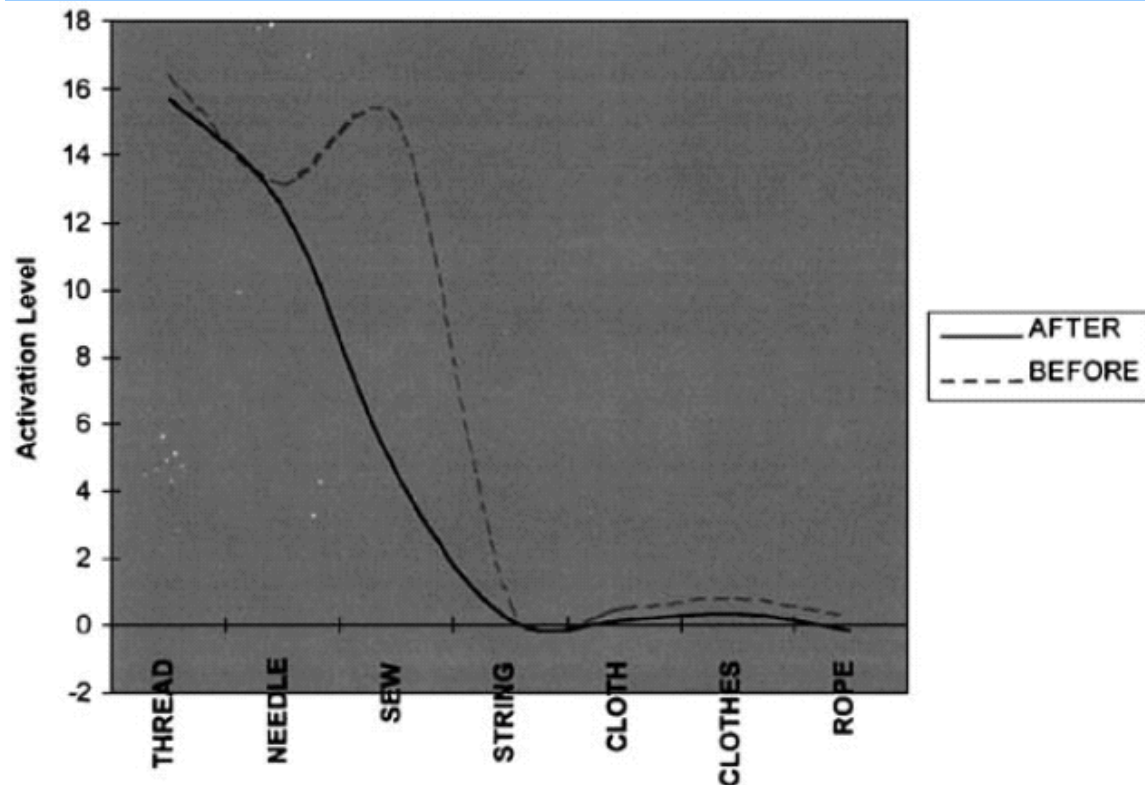


- Han et al., 2003
- Associative memory
- Abstracted, behaviourally-based
- Connectivity
 - Associative strength
- Network size
 - Number of associations
- Controls:
 - HCSN>LCSN>HCLN>LCLN
- Patients:
 - HCSN>HCLN>LCSN>LCLN

High-level, cognitive modelling

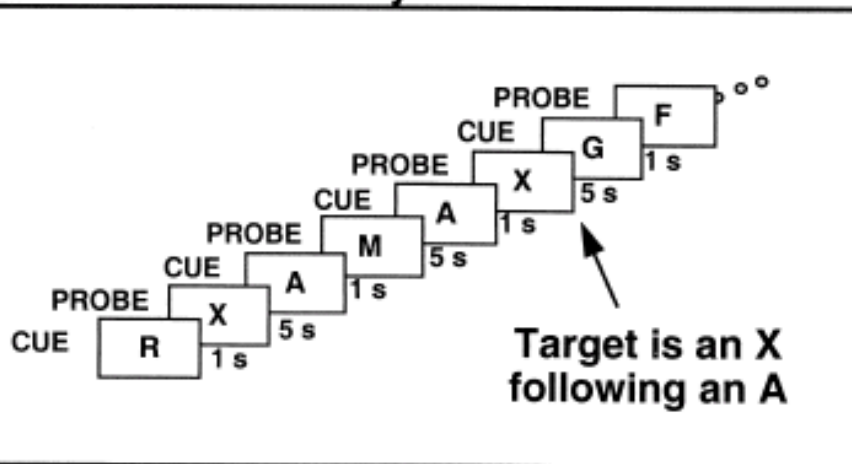


- Lowering connectivity did
- Weakened or distracted?
- Noise didn't replicate data

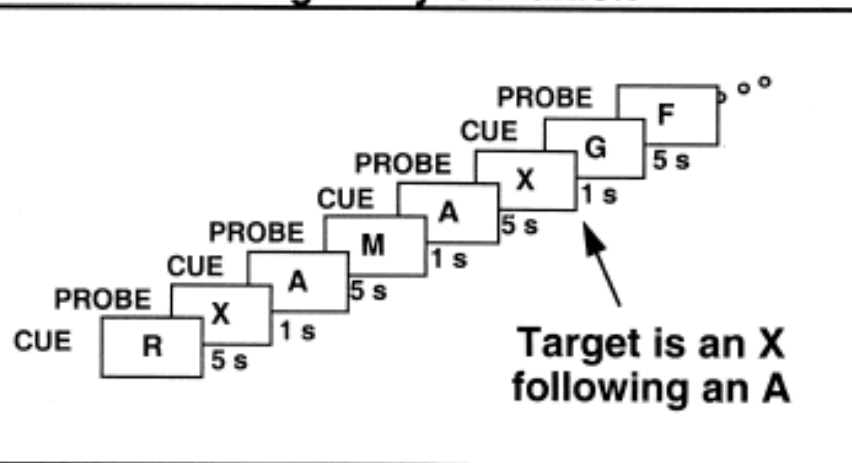


Still connectionist, more biological

Short Delay Condition



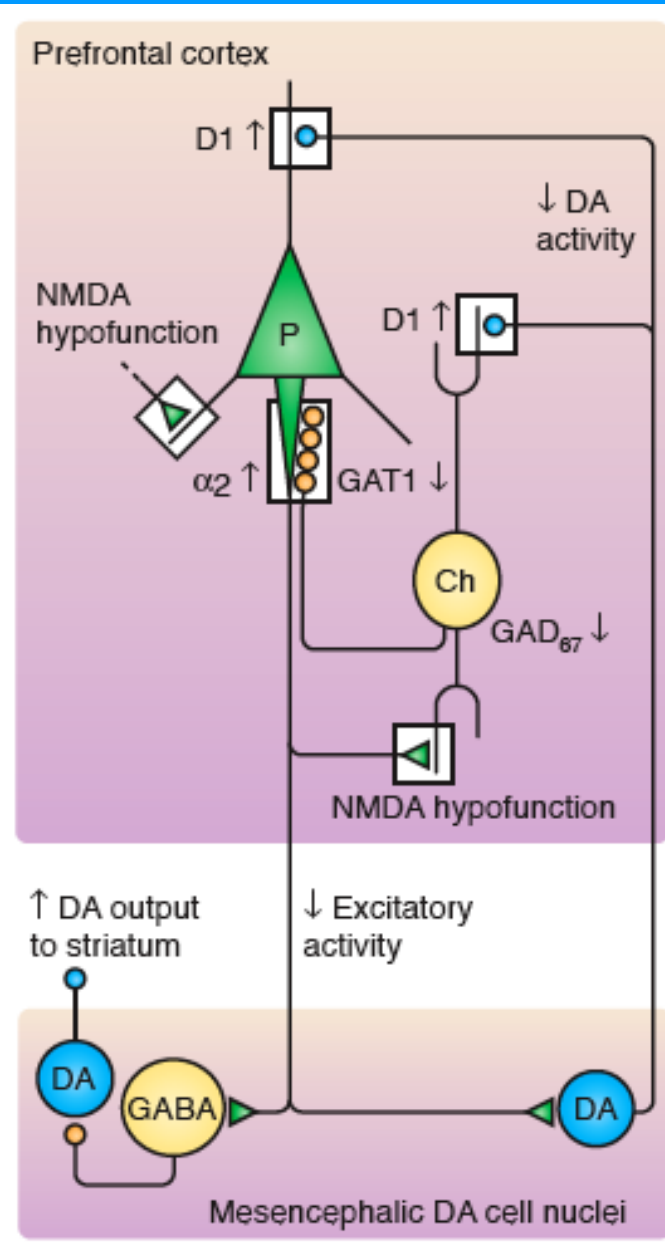
Long Delay Condition



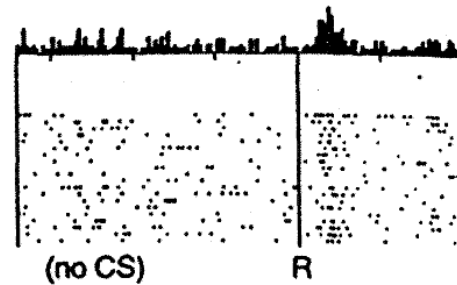
		CUE	
		VALID	INVALID
TARGET	PROBE	A-X (70%)	"B-X" (10%)
	NONTARGET	"A-Y" (10%)	"B-Y" (10%)

- Braver et al., 1999
- Short-term, dynamically-updating associations
 - AX-CPT
- 2 key measures
 - Context sensitivity: ratio of AX hits to BX false alarms
 - Context cost: slowing of AY relative to BY trials

Interlude: the role of dopamine

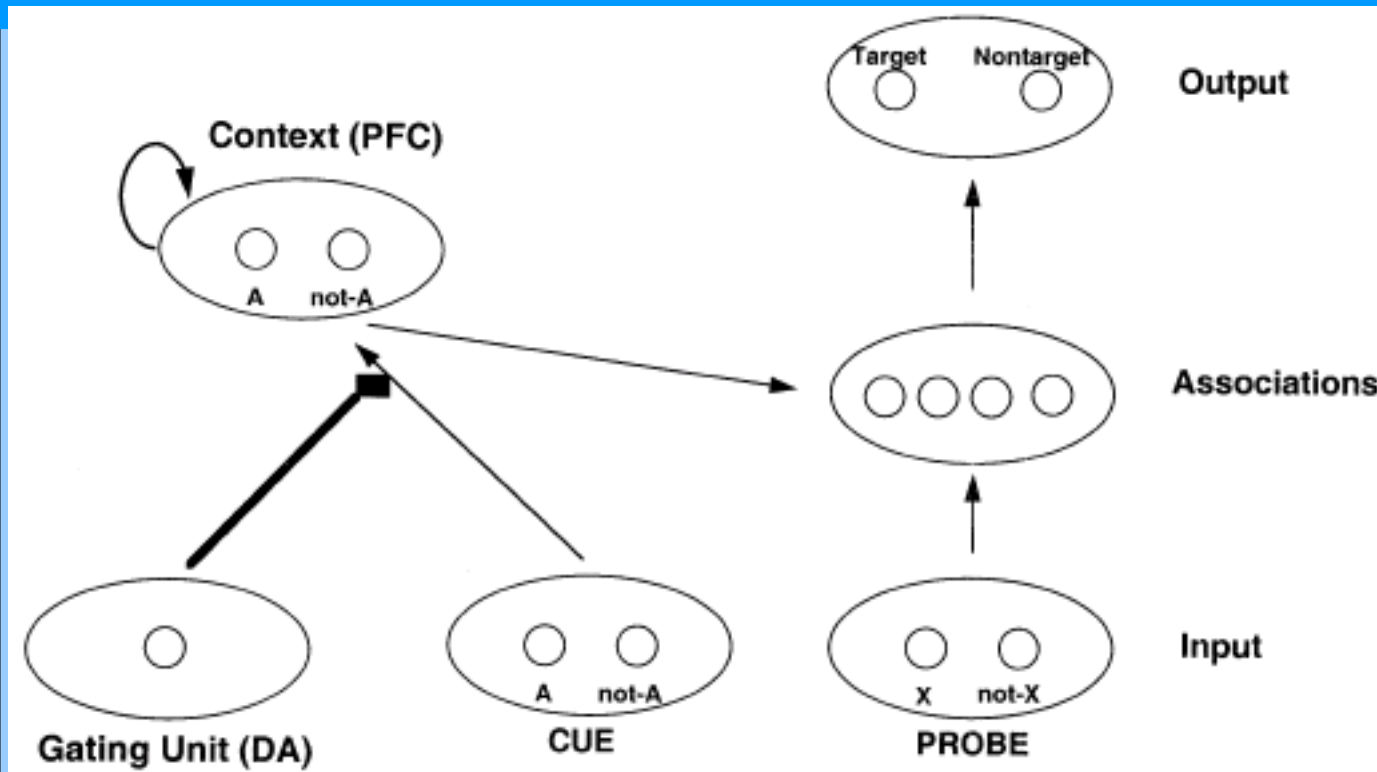


No prediction
Reward occurs



- Generally potentiates glutamate
- Augments Hebbian processes
- Dependent on significance of the context/stimulus

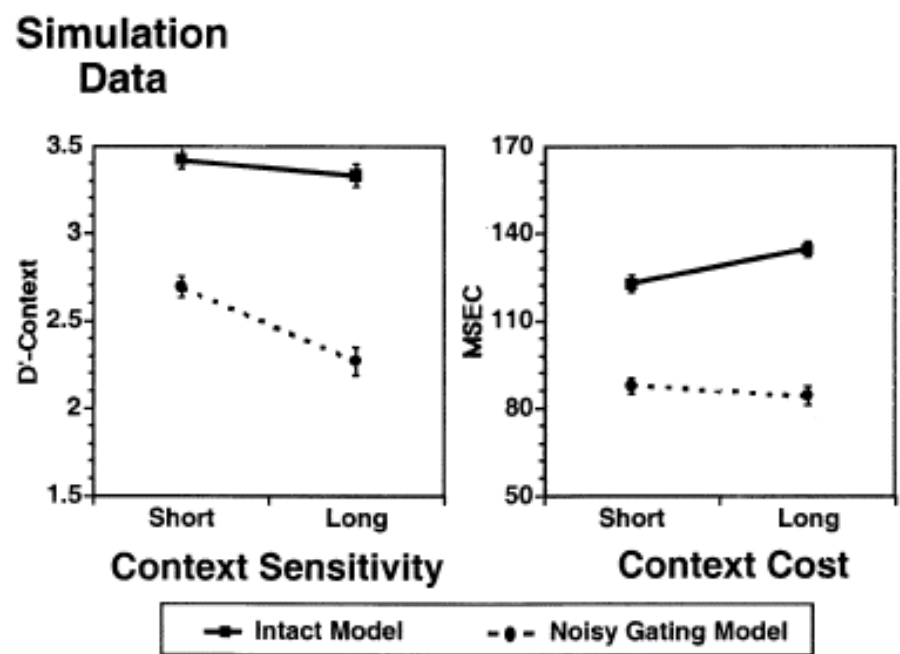
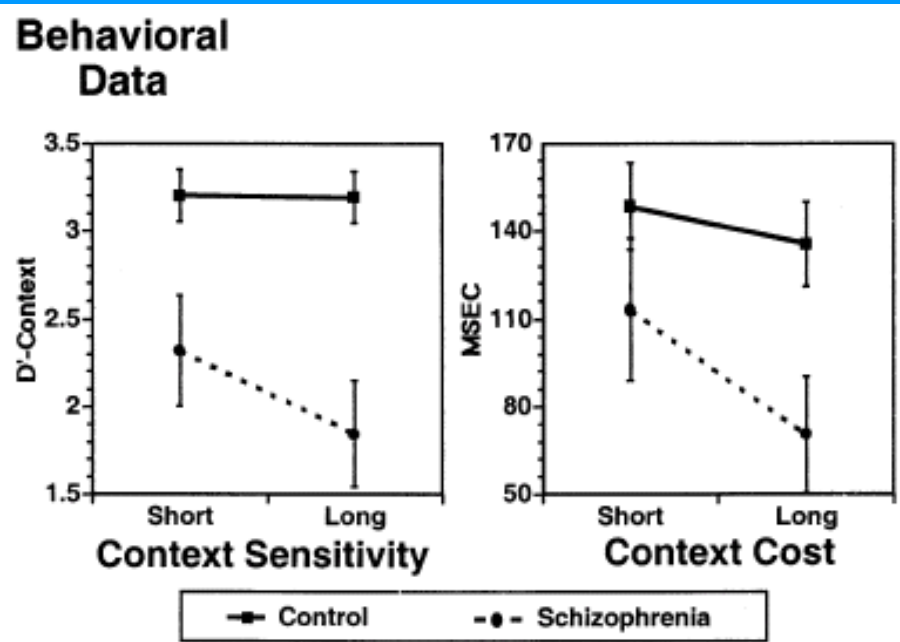
Braver's model of noisy dopamine (DA)



- Attractor networks
- Trained to perform AX-CPT

- DA changes strength of intrinsic connections within PFC
- Alters the ease with which context is updated/maintained
- DA unit is noisy – elevated tonic, decreased phasic levels

Braver's model of noisy dopamine (DA)



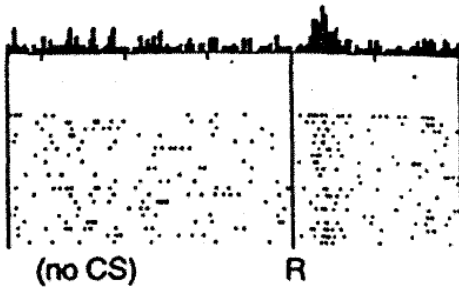
- Patients are less affected by context
- Model does a fairly good job
- Network context behaviour
 - Lower phasic level: update process frequently failed
 - Higher tonic level: noise interfered during the delay, causing rapid decay

Common themes

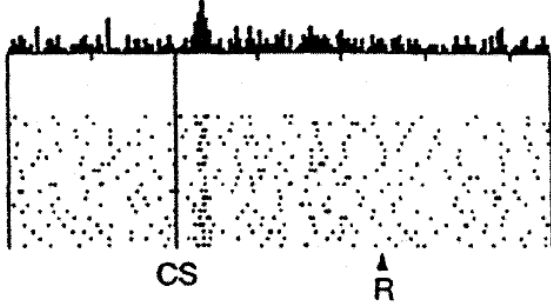
- Both consider altered connectivity
- Braver proposes:
 - A biological means of modulation
 - A functional consequence: context instability
- What is DA doing here? Currently 2 views:
 - Prediction error for temporal difference learning
 - Highlights the consequences of your actions

Temporal difference learning

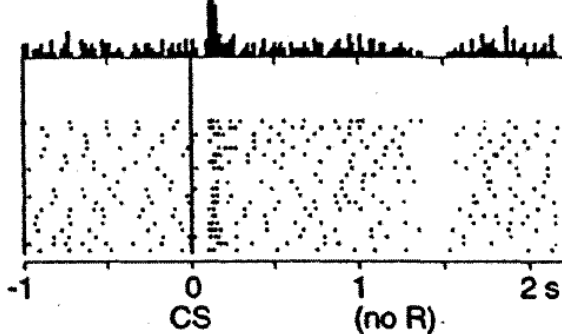
No prediction
Reward occurs



Reward predicted
Reward occurs



Reward predicted
No reward occurs



- Reinforcement learning
 - Learn the values associated with state-action pairs
 - Implement this to select the most valuable action for a given state

$$\delta(t) = (r(t) + \gamma V(t+1)) - V(t)$$

$$V(t) = V(t) + \alpha \delta(t)$$

- Smith et al., 2007

Latent inhibition and conditioned avoidance

Pre-exposure



Wow, what was that?



Boring...

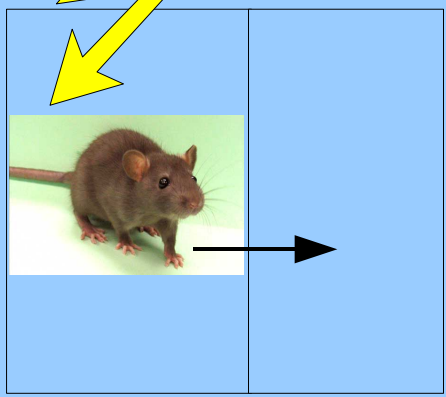
Conditioned avoidance



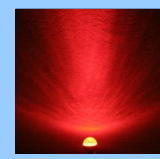
CS



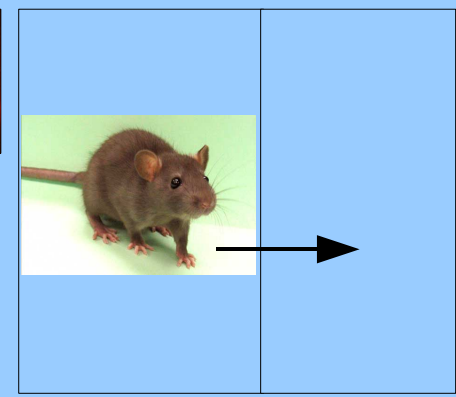
...



US



CS



Latent inhibition and conditioned avoidance

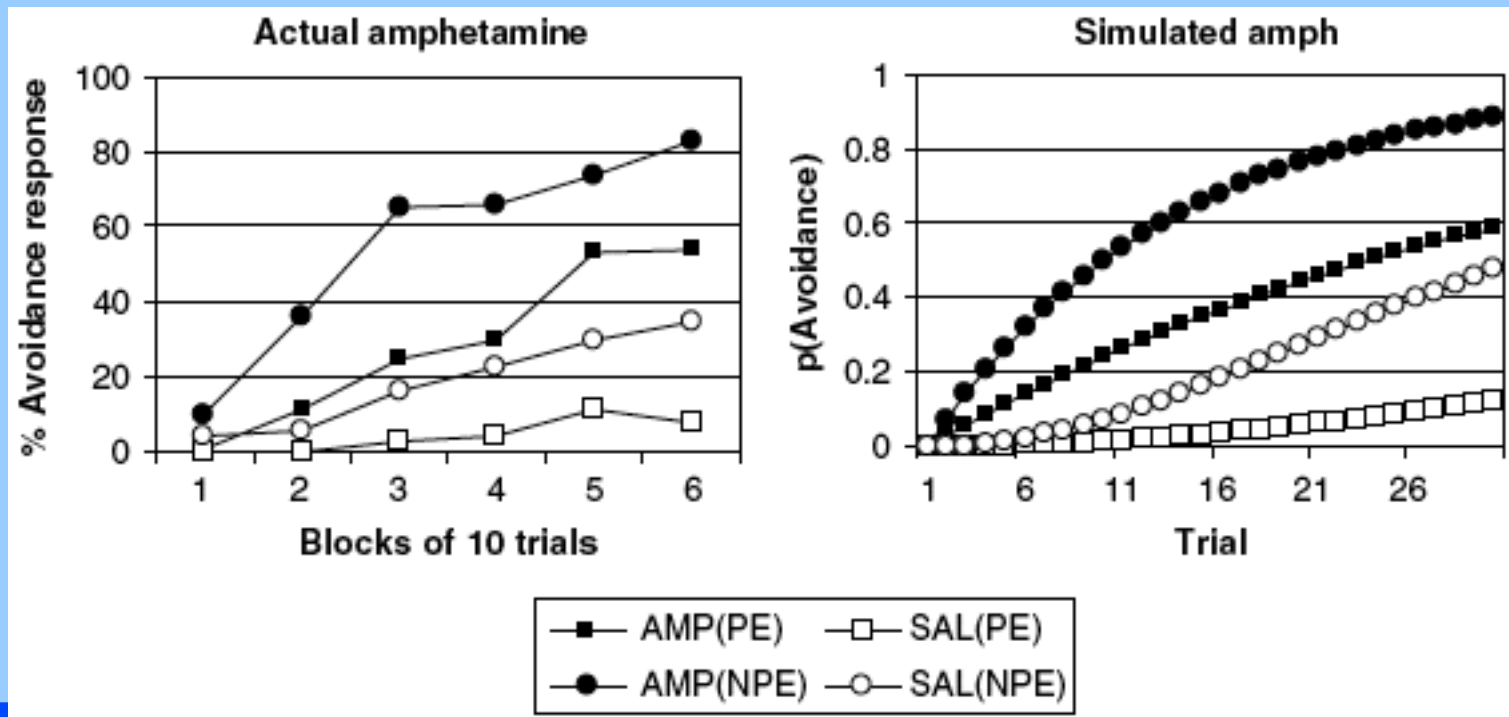
- Both conditioned avoidance and latent inhibition are dysfunctional in patients with schizophrenia
- Also if you're under the influence of amphetamine...
- ...so its seen as a valid animal model to test pharmaceuticals
- D2-blocking antipsychotics return behaviour to normal

Latent inhibition and conditioned avoidance

- Modelled effects of LI and medication as modifiers of learning rate

$$V(t) = V(t) + \alpha\phi\delta_{\text{rec}}(t)$$

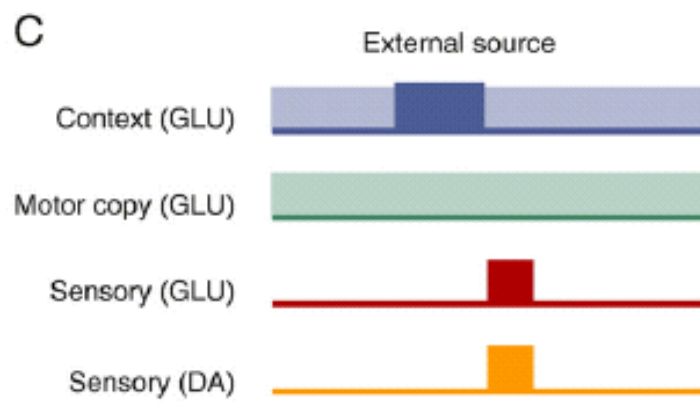
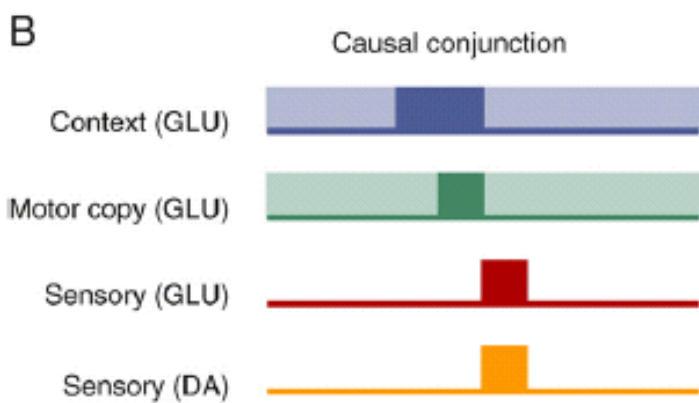
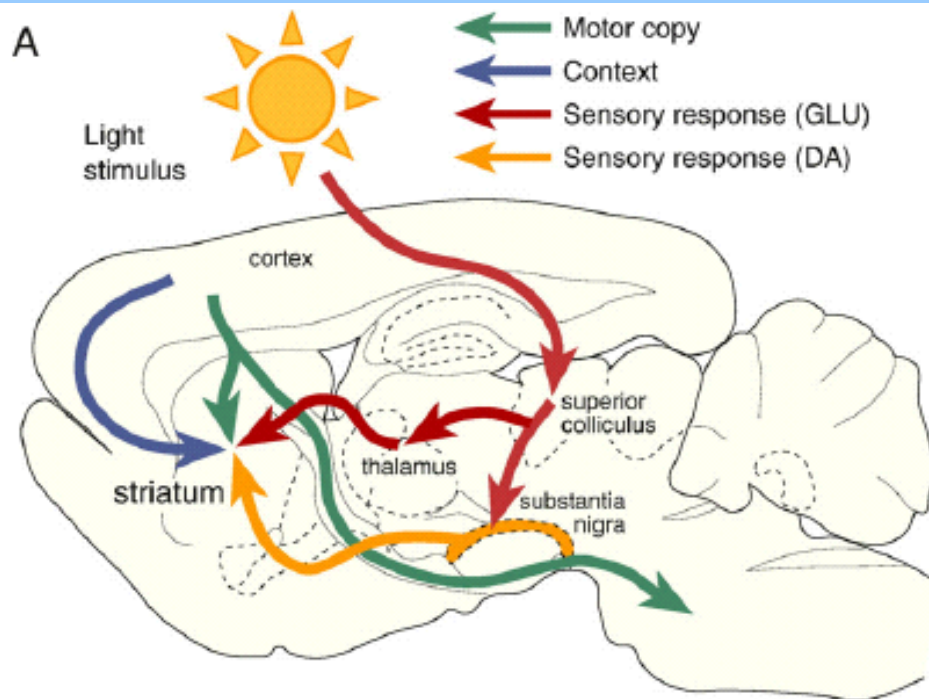
- Added a constant to the prediction error to simulate amphetamine



Problems with TD learning

- Doesn't account for the influence of pre-exposure
 - Neutral stimulus, no associated predictions
- Opposing view: responds to novel stimuli
 - Not to indicate potential reward...
 - ...but to highlight if you had something to do with bringing that reward about

Highlighting useful actions



Time →

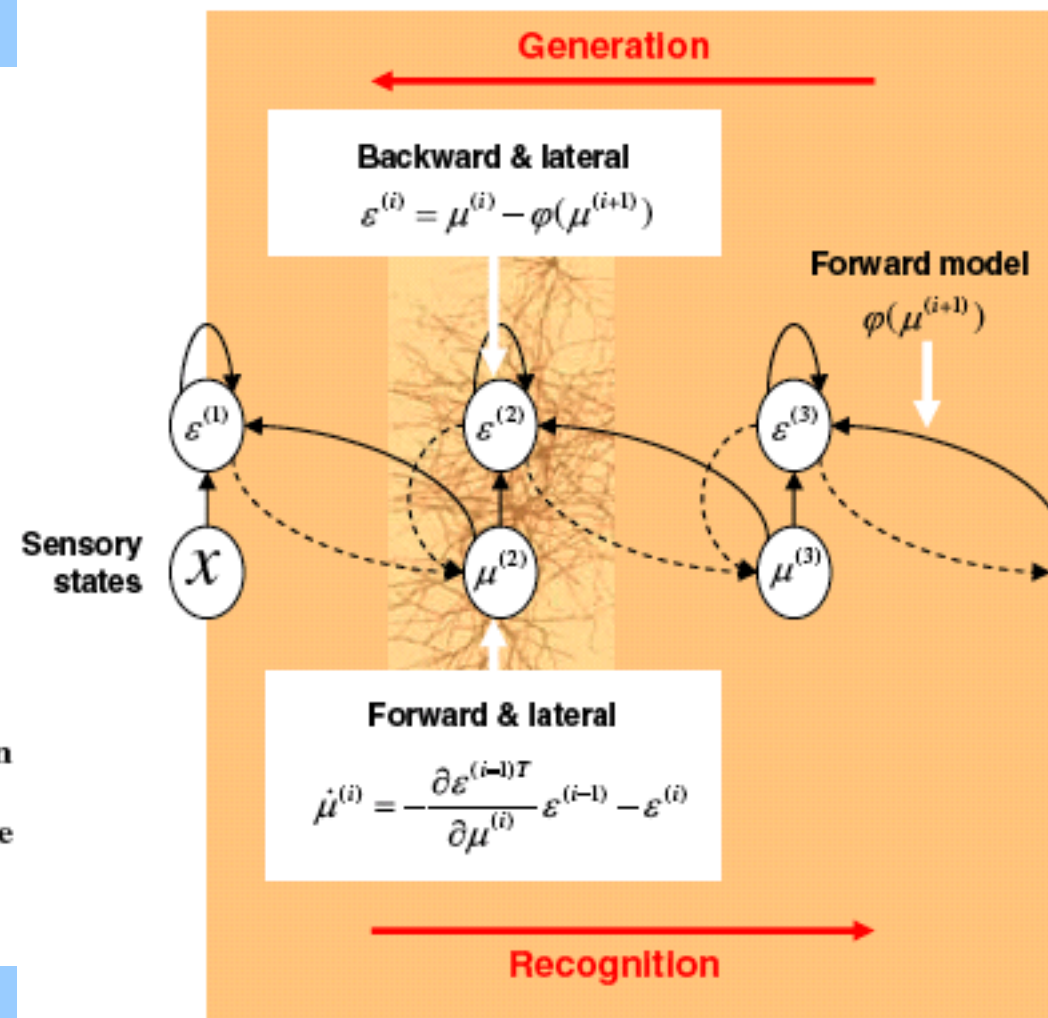
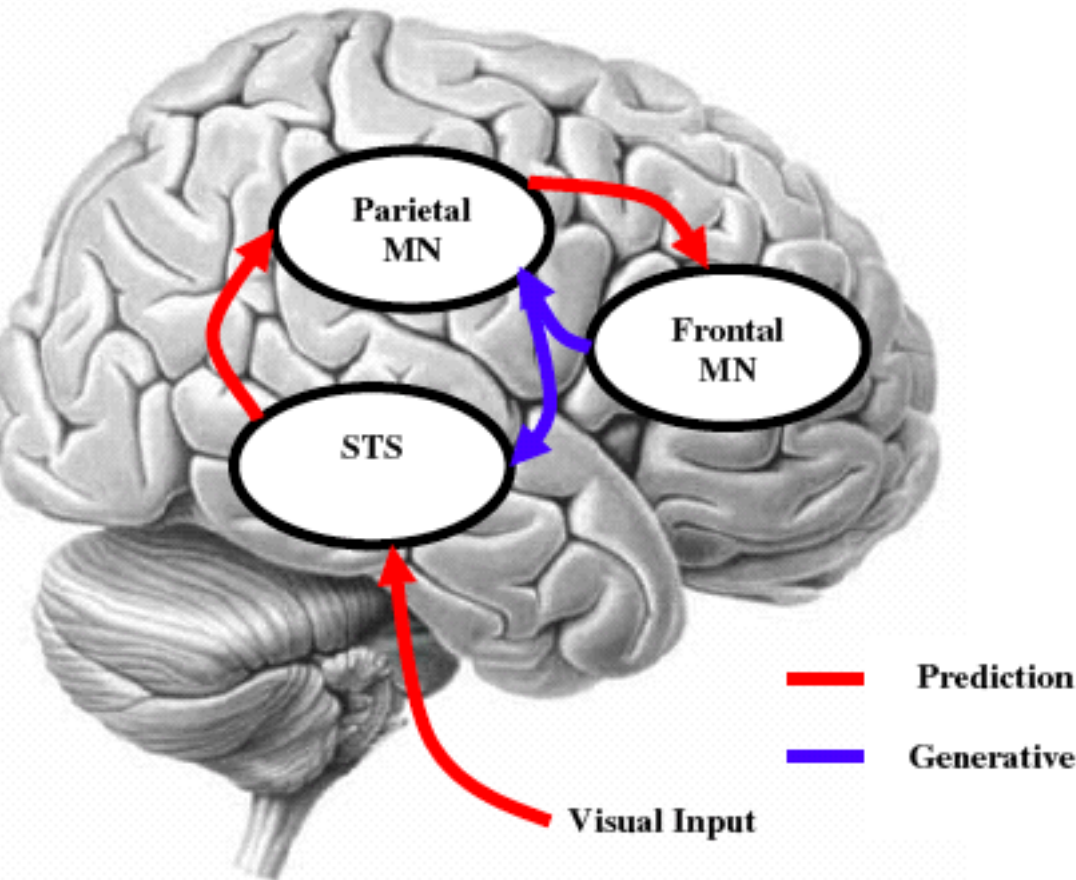
- Redgrave 2007
- Conjunction
- Other studies, novelty=reward
- Actions worth repeating
- If not, DA dips
- Active ignorance

A disturbed sense of self

- Seen in this light, we are converging...
 - DA highlights your influence on what you experience
- Consequences for “context”:
 - Failure to report mismatches...
 - ...which normally prompts appropriate updates
- What is “context”?

A disturbed sense of self

- Forward models of intentions



Chicken and egg

- Is DA dysfunction causing cortical problems?
- Did cortical problems push the DA system too far?
- Computational modelling could make a valuable contribution here
- A grand unified theory of schizophrenia would be very helpful

