Model checking of 5th hypotheses

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1 The experiment

Fig. 1A shows the experiment we are going to use which falls in the category having patience to receive a reward: a rat needs to learn to approach a gap in a wall and then wait at that gap until the food becomes visible.

In Fig. 1A the path of the animal towards the food is shown as a dotted line. At 1) the animal sees the gap in the wall as a visual cue. Then at 2) the animal stops and waits. Then the food appears (visually) and the animal approaches 3).

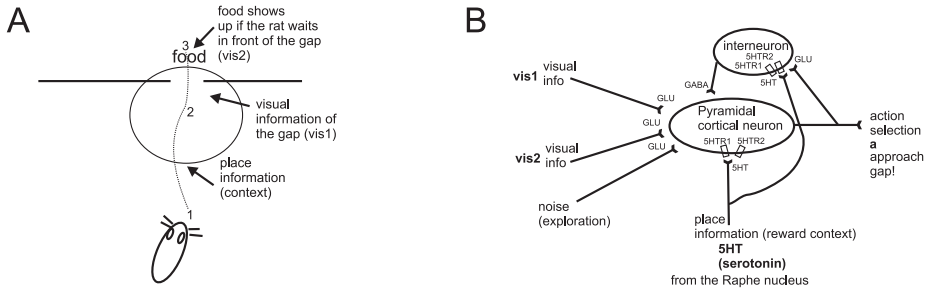

Figure 1: The microcircuit. *vis*1: active when the gap can be seen. *vis*2 active when the food can be seen. GLU=glutamate, GABA=gaba, 5HT=serotonin, 5HTR1=5HT receptor type 1, 5HTR2=5HT receptor type 2. a = action trigger.

2 The microcircuit

Fig. 1B shows a cortical pyramidal neuron and an inhibitory neuron which performs feedback inhibition creating a negative feedback.

The pyramidal receives excitatory glutamatergic (GLU) from sensory areass. Here we just focus on visual input which we call "vis1" and "vis2". It also receives some other inputs which we just call "noise". In this simple model GLU

acts via standard AMPA receptors and excites (=depolarises) the pyramidal neuron. If a certain threshold has been reached it fires and generates an output.

In addition to this the pyramidal neuron receives serotonin (5HT) from the raphe nucleus. This is released at both the pyramidal neuron and the interneuron. In contrast to GLU we have now *two* receptors: 5HTR1 and 5HTR2:

- *5HTR1* is an inhibitory receptor. It decreases the membrane potential towards the resting potential of the neuron. Thus is makes it harder for the neuron to fire.
- *5HTR2* is an excitatory receptor. This increases the membrane potential in a similar way such as GLU does so it helps the pyramidal neuron to fire.

The interneuron has the role of stabilising activity and is not of importance for now!

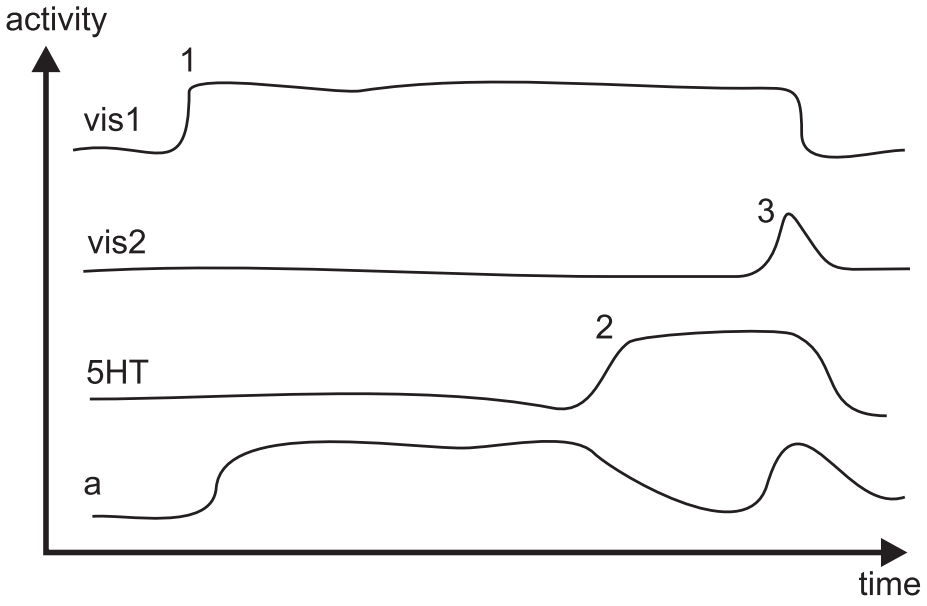

Figure 2: The signal timings. Labels the same as defined in the previous figure.

3 How it works

Let's assume the rat has learned that a) the gap provides potentially food which means that there is a strong pathway from "vis1" to the pyramidal neuron and b) that whenever the food shows up ("vis2") this adds to the already strong

activity a and that then makes the rat approach the food. The feedback pathway via the interneuron stabilises this with its inhibitory feedback.

Let now go through it step by step by linking the behaviour to the activity. Figure 1A shows the three relevant behavioural steps 1,2 and 3 and these are again in Fig. 2 which shows the different activities during these stages:

1. The animal sees the gap $vis1$ and the pyramidal neuron increases its activity which triggers approach behaviour.

2. The animal enters the circular area which triggers the release of 5HT. This inhibits the action a which makes the animal wait.

3. The food becomes now visible ($vis2$) which drives the activity a up again and the animal goes for the food.

The crucial time is between 2 and 3 where the animal needs to wait for the reward. 5HT increases in anticipation of a reward. This is driven by place information shown as the circle around the gap. When the rat enters the circular area 5HT is increased. This drives the two major 5HT receptors in the pyramidal neuron. 5HT1 is inhibitory and 5HT2 is excitatory. That leads us to a mathematical formulation of it:

$$a = \frac{\text{vis1} + \text{vis2} + 5\text{HT}_{2\text{A}}}{1 + 5\text{HT}_{1\text{A}}} \tag{1}$$

This means that when the rat approaches the gap that a high value of 5HT will make a more and more constant and with that the influence of external stimuli will be diminished.

4 Hypothesis

4.1 The standard model

In the standard model high serotonin is associated with focus and sticking to a plan. In order to make this work the overall influence of 5HT needs to be at least inhibitory. However, we not only have 5HTR1 receptors but also 5HTR2 which are excitatory. However, their combination makes it harder and harder to generate outputs. This also means that even in the absence of any sensory input random noise from other brain areas will be suppressed. However, this makes sense because remember the 5HT signal codes the expectation of a reward.

This ties also into the cannabis model where depression is associated with a lack of 5HT (caused by strong inhibition of 5HT by the lateral habenula).

4.2 The Nutt model

Here it is argued that the cortex mainly contains 5HTR2 receptors but little 5HTR1 receptors. So in Eq 1 the denominator does not exist with $5\text{HT}_{1\text{A}} = 0$. This means that when 5HT rises that the pyramidal neuron becomes more

sensitive and causes actions perhaps even if there is a bit of random noise. However, this is not observed. However, Nutt argues that using LSD (which only stimulates 5HTR2) that with that the pyramidal neurons are getting excited and exploration happens. However, this might be good in one case but certainly not here: if the rat gets LSD then it won't wait in front of the gap and wanders off. On the other hand if the gap is no longer providing food and the rat needs to do exploration then it makes sense to force it with perhaps some LSD to make it explore again. This means that other action selection neurons getting excited by 5HT2 as well and attract the rat to another hole.

4.3 What could be tested?

The Nutt model completely ignores the 5HT1 receptor whereas the standard model takes into account both receptors 5HTR1 and 5HTR2. So model checking can look which model provides the most rewards for the rat.