Model checking of 5th hypotheses

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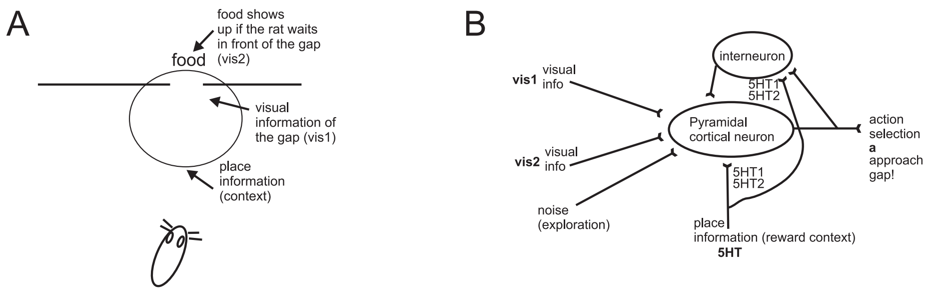

Figure 1: The microcircuit

1 The experiment

Fig. 1A shows the experiment we are going to use which falls in the category of "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 available and thus visible.

What we expect is that the rat will indeed wait. If 5HT is knocked out the rat won't wait and wander off and won't retrive its reward.

2 The microcircuit

Fig. 1B shows a cortical pyramidal neuron and an inhibitory neuron which performs feedback inhibition creating a negative feedback. All synapses are usually plastic and would learn the association between the visual stimulus and the action. We assume that this has already happend. If the output of a goes over a certain threshold the rat will approach the hole with the food.

3 How it works

a is the action which makes the rat go towards the gap where to food is. Also 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 carrot shows up ($vis2 > 0$) this adds to the already strong activity a and that then makes the rat approach the food.

Now the crucial part is the 5HT input. 5HT increases in anticipation of a reward. This is driven by *place* information shown as a circular area around the gap. When the rat enters this circular area 5HT is increased. This drives the two major 5HT receptors in the pyramidal neuron: 5HT1 and 5HT2 whereas 5HT1 is inhibitory and 5HT2 is excitatory. However, the excitatory action can be seen as additive to the value of the neuron whereas the inhibitory one rather as a division operation. So that leads us to a mathematical formulation of it. An action is executed if a is above a certain threshold Θ:

$$a = \Theta\left(\frac{\beta + (\mathrm{vis1} + \mathrm{vis2})\, \mathrm{5HT_{2A}}}{1 + \mathrm{5HT_{1A}}}\right) \tag{1}$$

where $\beta = 0.1$ is a small positive shift which might be even modulated by a random number $\beta = 0.1 + \mathrm{random}$ so that the neuron generates spontaneous actions. If $\mathrm{5HT_{1A}}$ is activated that means that β will be divided by $\mathrm{5HT_{1A}}$ and thus becomes smaller. This means that the baseline moves downwards making it harder for the neuron to trigger an action.

The visual inputs are multiplied by $\mathrm{5HT_{2A}}$ so that this receptor acts as a *gain*.

Let's go through that step by step:

1. The rat sees the gap from the distance: $vis1 > 0$, vis2=0, $5ht = 0$. It approaches the hole in the wall because $a > 0$.

2. The rat is in front of the hole in the wall: $vis1 > 0$, vis2=0, $5ht > 0$. In addition the 5HT signal increases because the rat is expecting a reward. This *decreases* the value of a so that the rat waits. = no action.

3. The food shows up: $vis1 > 0$, vis2¿0, $5ht > 0$ which is indicated by $vis2 > 0$. This leads to again a getting larger even with the strong inhibition and the rat targets the food.

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 5HT1 receptors but also 5HT2 which are excitatory. Their combination makes it harder and harder to generate outputs (see Eq. refpyrcalc). This also means that even in the absence of any sensory input random noise from other brain areas will be suppressed. 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). So animals would lose out if not being patient (= less rewards).

4.2 The Nutt model

Here it is argued that the cortex mainly contains 5HT2 receptors but little 5HT1 receptors. So in Eq 1 the denominator does not exist with $5HT_{1A} = 0$ so we have just a sum of all inputs from both visual inputs and 5HT. This means that when 5HT rises that the pyramidal neuron becomes more sensitive or even generates random actions. This is not observed. However, Nutt argues that using LSD (which only stimulates 5HT2) that with that the pyramidal neurons are getting excited and exploration happens. There is certainly a case for doing exploration but that this would happen then irrespective if it makes sense or not.

For example, if the rat gets LSD then it won't wait in front of the gap and wanders off meaning no reward. 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.

4.3 What could be tested?

The Nutt model completely ignores the 5HT1 receptor whereas the standard model takes into account both receptors 5HT1 and 5HT2. So model checking can compare models with and without 5HT1 receptors.