Neural circuit for relief learning in Drosophila
Förderprogramm der Schram-Stiftung 2014

Dr. Ayse Yarali
Group leader
Leibniz Institute forNeurobiology
Brenneckestr. 6
39118 Magdeburg, GERMANY
p: +49-391-6263-9-221-1
f: +49-391-6263-9-225-9

Memories of punishment and relief in a mini-brain

*Animals act based both on present circumstances and on predictions into the future. The predictive aspect of action-choice is possible owing to "associative learning", e.g., stimuli that **precede** a painful event are later on **avoided** as they signal upcoming **pain**. In such learning, relative timing of events is critical: Stimuli that **follow** a painful event are subsequently **approached** as they predict **relief**. What is a minimal neuronal circuit-solution for supporting such opposite kinds of learning? We will use the fruit fly to tackle this question, with the hope of revealing evolutionarily conserved principles that apply to a variety of organisms and can be implemented in robotic device.*

Flies, when trained with an odour that **precedes** electric shock, later on **avoid** this odour as a signal for the "painful" **punishment**. When the timing of odour and shock are reversed, such that the odour **follows** shock, this odour is subsequently **approached** as it signals a "feeling of **relief"**. Thus, an experience with shock leaves the flies with two opposite memories, about stimuli that precede *versus* those that follow (Figure 1A). The same is true for rodents and man; thus the effect of relative event timing seems to be a fundamental property of associative learning. How do brains implement this property? Fruit fly indeed is a suitable model for posing this question. The fly brain has only about 100 000-times as many neurons as the human brain. Using transgenic methods, any chosen individual neuron can be monitored, blocked or artificially activated in the brain of an awake, behaving fly! The relative simplicity and experimental accessibility of its brain makes the fly unbeatable in terms of the level of detail at which we can study neuronal circuits underlying behaviours.

A beautifully detailed circuit account of fly punishment learning has indeed emerged in the last 10 years (Figure 1B). During odour-shock training, the odour activates a set of "sensory neurons" that pass on the signal to "projection neurons", which carry it both to a brain area critical for the innate olfactory behaviour and to the so called "mushroom bodies" (MB). Amongst the MB neurons, only a small subset responds to a given odour. Shock on the other hand, in addition to likely activating an innate nociceptive behaviour pathway, induces a dopaminergic "punishment signal" delivered onto all MB neurons. Thus, in that handful of MB neurons responsive to the used odour, the odour- and the punishment signals converge, triggering molecular events

that lead to a modification of synaptic output. This modification constitutes a trace for the punishment memory regarding the particular odour.

Upon encountering this odour again, this memory trace is “read out” by output neurons that are post-synaptic to the MB, leading to learned avoidance. Recently, individual dopaminergic neuron-, MB neuron- and output neuron-types have been identified for carrying the punishment signal as well as for harbouring and reading out punishment memories, respectively. It is however unknown how the effect of event timing is implemented within this minimal circuit.

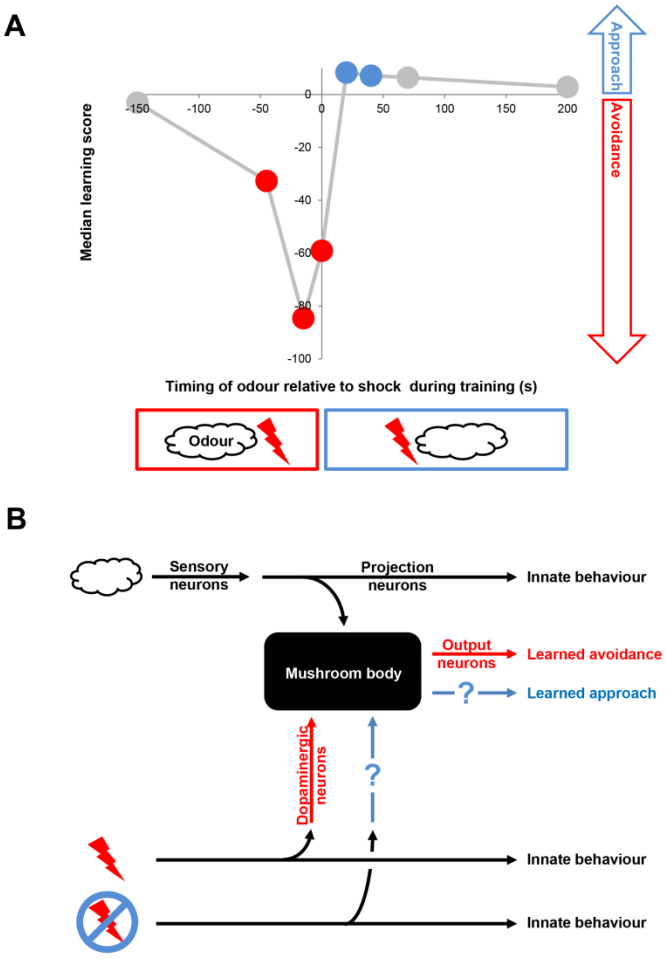

Figure 1
(A) **Punishment** *versus* **relief** learning in the fruit fly. (B) A minimal mushroom body-centred circuit for **punishment** learning in the fruit fly along with the questions posed with respect to **relief** learning. Please see the main text for details.

Relief learning, just as punishment learning, relies on MB-function, prompting us to ask (Figure 1B): Which neurons signal relief to the MB? Which MB neurons harbour relief memories? And, which neurons read out relief memories from the MB leading to learned approach? We will tackle these questions using a novel transgenic method that enables targeting individual chosen neurons in the behaving fly. In line with the questions above, we will block, in each case one at a time, the activity of all dopaminergic neuron-types pre-synaptic to the MB; all MB neuron-types; and all output neuron-types post-synaptic to the MB, assaying for effects on relief learning. Combining our findings with those on punishment learning will reveal how a minimal MB-centred circuit supports the formation, storage and retrieval of these opposite memories. In the future, we wish to implement this circuit in a quantitative model for robotic applications. Furthermore, we hope that the principles we discover in the fly may guide research on the brain mechanisms of event timing-dependent opposite memories in rodents and man.