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Heisenberg's Roadmap Guides our Journey to the Small Cognitive World of *Drosophila*

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Abstract: Professor Martin Heisenberg is one of the pioneers in the exploration of neuroethology. With his inspiration and earnest help, we employed the fruitfly as a model system to investigate the underlying neural mechanism of cognitive behaviors. Here, we recalled the help from Martin in the early years and introduced some findings from our lab about visual cognition behaviors in *Drosophila*, such as decision making, selective attention, and experience-dependent visual pattern recognition. From the results so far, the circuit composed of mushroom bodies, central complex, and dopaminergic neurons may play an essential role in these behaviors.

Keywords: visual cognition behavior, decision making, selective attention, pattern recognition

INTRODUCTION

My scientific career has been very closely linked together with Martin Heisenberg for the past 15 years. In 1992, when the 19th International Congress of Entomology was held in Beijing, both Dr. Karl Georg Götz from the Max Planck Institue for Biological Cybernetics in Tuebingen, and I were invited to organize a special session on visual information processing in insects. At this meeting, Dr. Reinhard Wolf, a colleague of Professor Martin Heisenberg, had given a very nice talk on visual learning and memory of *Drosophila*, utilizing a visual flight simulator. This talk provoked my keen interest to study learning and memory in flies. I, at once, asked Dr. Reinhard Wolf to pass on my earnest request to Dr. M. Heisenberg to collaborate on similar study. After receiving a positive and friendly response from M. Heisenberg at the end of 1992, I left for Würzburg University for 3 months and then went to the Max Planck Institute for Biological Cybernetics for another 3 months to learn how to study visual learning in fruit flies by using a flight simulator. Finally, I built the first laboratory for visual learning and memory of *Drosophila* in China in 1994 with the valuable help of Professors K. Goetz and M. Heisenberg. Their kindly help always keeps deeply in my heart. There is an old Chinese idiom saying: ''One who drinks water should cherish the headwaters.''

Visual cognition and related neural correlates

As Dobzhansky pointed out: ''Nothing in biology makes sense except in the light of evolution.'' As for neuroscience, we agree with a modified version, that ''Nothing makes sense in neuroscience except in the light of behavior,'' brains control behaviors, and behavior needs to be explained by the physiological and anatomical properties of the underlying neural substrate. To understand how the brain works as a whole, we need to establish the rules on how the brain brings out a reasonable behavior. When we are facing a huge complexity of human brain, the organization of the neural circuits and the interaction among molecular nets in the nervous system is elaborate, even puzzling and fascinating. Due to its sophisticated genetic methodology, relatively simple anatomy, rich behaviors, and remarkable conservation of molecular mechanisms, as compared to mammals, *Drosophila* has become the ''Jack of all trades'' in life sciences. With the efforts of Martin Heisenberg and his colleagues, our knowledge about the fly brain has been updated frequently in multiple areas, such as visual and olfactory processing (Heisenberg et al., 1985), motor control (Strauss & Heisenberg 1993), cognitive behavior, including visual pattern recognition and memory traces localization (Liu et al., 1999, 2006), visual classic and operant conditioning, and some higher

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level cognition (Tang et al., 2004). Heisenberg's concept guides us to study visual cognition in *Drosophila*.

In recent years, our lab has been engaged in the study on visual learning and memory, decision making, and beyond. Our aim is to explore the ''cognitive behavior atoms'' in the fly brain, to precisely identify the underlying neural circuits (Brand & Perrimon, 1993), to shed light on our understanding of the genes-brain-behavior relationship, and to seek the answers to ''mind questions.'' It seems likely to us that such efforts are in their infancy, but we have already made some progress in studying visual cognition in *Drosophila*.

Our first attempt was to explore the decision-making process when facing conflict based on visual cues in *Drosophila*. Human and nonhuman primates can make a choice to get an advantageous response among available options based on economic value evaluation (Kahneman & Tversky, 1984; Schultz, 2000; Sugrue et al., 2005; Padoa-Schioppa & Assad 2006; Schultz, 2007; Niv et al., 2007). This type of decision-making process is commonly considered a higher level complex cognitive function. It raises three challenging questions to neuroscientists: 1) Where does the decision actually occur?, 2) How do prior knowledge and expectations combine with current sensory data during ongoing decision processing?, and 3) What processes select the appropriate information among competing alternatives in a particular context (Platt, 2002)? We asked whether decision making is a patent only for high-level animals or human beings. Do *Drosophila* make value-based decisions? To answer these questions, we have designed a ''shape/color'' dilemma in which individual flies were conditioned to choose a flight direction in accordance with the color and shape cues in the flight simulator. Following the training, the flies' decisions were tested with the color and shape cues reversed. We revealed that flies in the ''paradoxical'' situation resolved the ''shape/color'' or ''color/position'' dilemma by taking into account the reliability of the current information during retrieval. Wild-type flies could make firm, stable choices on the basis of small differences in the relative salience of competitive cues. The decision curve of wild types (*WTB* and *CS*) exhibited a sharp, complete transition as a function of the relative salience (shape vs. color), and it could be fit by a sigmoid function. It indicated that conditioned flies interpreted the cue saliency as a representation of punishment probability and altered their choice strategy accordingly. Thus, the value-based decision making is not the patent of high-level animals and human beings; even *Drosophila* can make a clear-cut, salience-based decision among competing alternatives (Tang & Guo, 2001; Zhang et al., 2007). Thus, life is an endless series of decisions, regardless of whether it be in fruitflies or human beings.

Further, we found that MBs (mushroom bodies, which are bilaterally symmetric multilobed brain structures in the fly's protocerebrum) are crucial for decision making in flies. Flies lacking MBs seem to have difficulty in resolving ''conflicting'' situations, so no sharp transition could be observed, and the decision making curve became a linear process.

Selective attention is a brain process that restricts perception to more salient stimuli and simultaneously suppresses the perception of competing, less relevant stimuli. Do the flies also use an attention-like mechanism to guide their behavior in the changing environment? We found that MBs mediate the salience-based orientation behavior in object fixation-tracking paradigms in the flight simulator. The fixation-tracking ability of flies without MBs was significantly impaired not only at certain low contrast levels, but also in certain different noise backgrounds (Xi et al., 2008). In a visual orientation paradigm with a noisy background, MB-deficient flies cannot get the normal discrimination as well as wild type with moderate background noise due to the lower signal-noise ratio. Among multiple objects, wild-type flies discriminated the strong stimulus, while MB-deficient flies did not. Our findings suggest that MBs might be the brain center implementing a gating mechanism that passes and amplifies the salient signals and filters out background noise or unrelated signals.

''Generalization means to deduce some 'general (abstract)' information from a certain set of stimuli and to make use of this information in further decision between new and unexpected sets of stimuli'' (Wehner, 1981). Do the flies generalize? Are flies able to abstract and to form some concepts for visual pattern recognition? We found that, following conditioning with a visual feature of objects among combinatorial shape-color features, wild-type flies exhibited a decreased ability to extract the correct visual feature. However, the visual feature extraction ability was greatly enhanced in the flies previously conditioned with that visual feature alone. Moreover, we demonstrated that flies might possess some ability to extract the abstract category of ''shape'', but not restricted to a particular shape. Here we found, again, that MBs are required for this experience-dependent visual pattern recognition (Peng et al., 2007).

All of these findings suggest that the gating function of MBs in visual cognition. A reasonable potential explanation is to consider MB as a ''noise filter'', leaving the strong signal free and restricting the others in the same path. It has been reported more recently that the GABA-ergic system may be a noise filter needed by the MBs for optimal learning (Liu et al., 2007).

As pointed out by Martin Heisenberg (personal communication), the amplification of small salience differences between two conflicting visual cues is an important aspect that enables decisions to transition from linear to sigmoid performance. Dopamine (DA), which is widely distributed in the brains from insects to primates, is broadly employed as both a neural transmitter and synaptic modulator and can be one of the potential components that regulate the gain function. Reinforcement learning theory has been greatly advanced, since the physiological characteristics of DA neurons in the mammalian midbrain were identified. Briefly, DA neurons can be excited into two modes. In reinforcement learning tasks, when the positive reinforcement signals occur, DA will give a sharp cluster of bursts, which is described as the phasic firing mode and is considered to code the prediction error (Schultz, 2002). The other mode is tonic firing, which reflects the animal's expectation to be rewarded before the reinforcement signals emerge. Phasic firing can be the teaching signal in the nervous system that can promote the learning performance, while the tonic activities may increase the DA level in the synaptic cleft for a long while (even up to minutes), which may change the efficiency of synaptic transmission, and the effect can be reflected in higher cognitive behaviors, such as decision making. It has been proposed that dopaminergic signals from the mammalian VTA (ventral tegmental area) implement the gating mechanism by controlling the ''filter'' of afferent information into PFC (prefrontal cortex) (Montague et al., 2004). DA function is partially conserved in insects with that in mammals, since it is only assigned to the aversive conditioning, as demonstrated on behavior and physiology, that is, DA neurons can be excited by the repulsive unconditioning stimuli (US), and the conditioning stimuli (CS) after conditioning. We revealed that the decision making in *Drosophila* consists of two phases: an early phase that requiring DA and MB activities and a late phase independent of these activities. Immunohistological studies have shown that MBs are densely innervated by the axons of dopaminergic neurons (Zhang et al., 2007). Thus, we suggest that the DA-MB circuit regulates salience-based decision making in *Drosophila* by both inhibition gating and gain-control mechanisms. Because of the strong expression of D1-like DA receptors, DAMB/DopR99B and dDA1/DmDOP1, on the MB, DA may affect the MB by selectively regulating its presynaptic properties and changing its transmission efficiency. But the exoneration of MB and DA in simple perceptual choices indicates the existence of a fast pathway that can bring out the behavior and detour the MB-DA circuit. Besides MB, the essential parts of the central complex (CC), including the ellipsoid body (EB), fan-shaped body (FB), and noduli (NO), all have dense dopaminergic staining, indicating a large amount of D1 receptors distributed on these neural structures. Whether the dopaminergic fibers innervating in CC play the same role as in MB is still an open question. So, the function of the three neural substrates in cognitive behavior and how they cooperate interactively is largely uncertain. At present, we know that CC is comprised of the EB, the fan-shaped body (FB), the superior arch (SAR), the protocerebral bridge (PB), and the NO. Most memory-related proteins enriched in MBs are also expressed in the CC, such as *rut*, *dnc,* FAS II, DC0, and so on, indicating that the CC may also play an influential role in cognition like the MB does (Wu et al., 2007). In addition, as discussed above, DA neurons regulate both the CC and the MB. Thus, we suggest that MB, CC, and dopaminergic neurons could be integrated together to mediate high-level cognition. We believe that the fly's brain might throw light on the basic operating principles of the high-level brain.

Finally, with this thought in mind, let us close on a quote from Charles Darwin: ''From so simple a beginning endless forms most beautiful and most wonderful have been, and are being, evolved'' (*On the Origin of Species*, p 490).

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