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Embrace the uncertainty

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Ever since Werner Heisenberg formulated the uncertainty principle, physics has been grappling with the unsettling realization that the universe does not function like clockwork—a metaphor Newton introduced and which held sway for centuries. In a world where predictability and uncertainty intertwine, interpretations range from die-hard determinists, who reject quantum events despite the mounting evidence, to more esoteric merchants of doubt who exploit the ambiguity.

If Werner Heisenberg brought uncertainty to physics, his son, Martin Heisenberg, sought to introduce uncertainty into neuroscience. Returning from a postdoctoral stint at CalTech with Max Delbrück, the trained geneticist embarked on a neuroscience career in the late 1960s at the Max Planck Institute for Biological Cybernetics in Tübingen. At the time, neuroscience remained deeply deterministic. Two decades earlier, Donald Hebb's *The Organization of Behavior* had framed behavior in terms of stimulus and response—along with what transpires in the "interval between them", as the subtitle explained. When Martin Heisenberg arrived in Tübingen, Skinnerian behaviorism was a dominant force in the U.S., while the Max Planck Institute where he worked operated under a different, yet equally deterministic assumption: that by precisely controlling the input-output relationships of experimental animals, one could decipher the control logic governing behavior. To this day, the institute retains its name, "biological cybernetics."

In a series of experiments, some initiated in Tübingen and continuing through his later years as a professor in Würzburg, Martin Heisenberg challenged these deterministic foundations. In one such experiment with the fruit fly *Drosophila*, he systematically removed all known sensory inputs that had previously been used to map control loops predicting behavioral responses. If flies were merely biological thermostats, reacting with predictable, corrective responses to external perturbations, then a complete absence of input should result in no response at all. But even in this sensory-deprived state, the flies behaved with striking variability—shifting from one action to another without apparent external trigger. Contrary to the expectations of control theory, no stimulus was necessary for the animals to act. They behaved spontaneously. Or, as the Harvard Law of Animal Behavior wryly states: "Under carefully controlled experimental circumstances, an animal will behave as it damn well pleases." Because this spontaneity was independent of sensory input, it was also fundamentally unpredictable—mirroring the quantum uncertainties Werner Heisenberg had uncovered decades earlier. Animal behavior, it turned out, was not strictly deterministic, but probabilistic. Over time, accumulating evidence has only reinforced this insight.

Many of Martin Heisenberg's experiments relied on equipment that had been in use at the Tübingen institute for many years already. At the heart of these setups were torque meters to which flies were tethered for stationary flight. These measurement devices were sensitive enough to detect the minuscule forces a fruit fly generates when attempting to rotate around its vertical body axis (yaw), typically in the range between piconewton-meters to nanonewton-meters ($\sim 10^{-10}$ Nm). This precision allowed researchers to measure the fly's intended rotational force without the animal actually moving. Since both the body and head were fixed, the fly always faced the same direction, isolating the yaw component from other aspects of flight control. Crucially, this setup also eliminated feedback from the fly's two primary motion-sensing organs—its eyes and its halteres, small gyroscopic structures behind each wing. This rigorous isolation of behavioral variables proved essential to Martin Heisenberg's approach, which he termed "microbehavior."

One such microbehavior that had been extensively studied in Tübingen before Martin Heisenberg arrived was optomotor behavior. Like most animals, flies attempt to stabilize their visual field when confronted with moving stimuli. For example, a tethered fly on the torque meter would generate right-turning torque when presented with vertical gratings rotating from left to right (clockwise from above) around the fly. Earlier research had shown that control theory could reasonably predict the dynamics of these optomotor responses, including rise times and amplitudes. The prevailing conclusion was that these control loops were innate steering mechanisms, allowing flies to maintain a straight trajectory. If visual input indicated an unintended drift, the optomotor response would automatically and predictably correct the displacement.

Martin Heisenberg, however, had reason to question this rigid depiction. If optomotor responses were so hardwired and deterministic, how did flies manage to make voluntary turns? Turning in free flight should generate visual feedback that would, according to control theory, force the fly back onto its previous course. In reality, flies execute sharp turns—body saccades—by rapidly twisting their bodies in midair. Instead of banking like an airplane, they pivot abruptly with a burst of torque. In tethered flight, this manifests as a sudden spike in torque output. Heisenberg discovered that during these voluntary torque spikes, flies temporarily suppress their motion vision, effectively preventing optomotor responses from interfering with their intent to turn. The fly's internal decision to change course overrides its deterministic cruise control. This revelation exposed a fundamental flaw in the assumption of a strict input-output relationship governing behavior: flies were not merely reacting to stimuli—they were acting on their own accord. There seemed to be something fundamentally wrong with the assumption that there was some tight connection between sensory input and motor output.

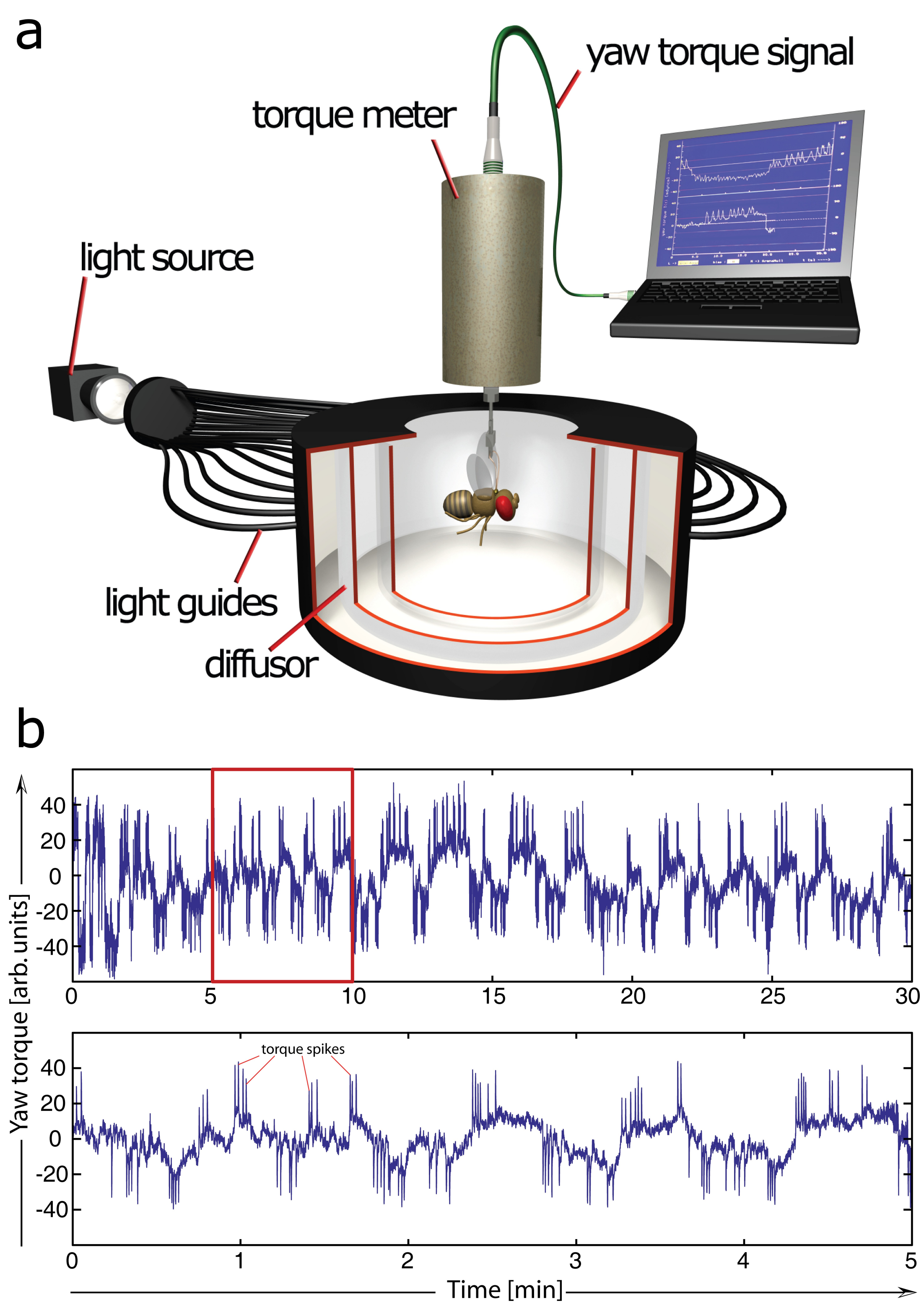

Fig. 1: Torque meter setup and yaw torque traces

Today, we know that analogous processes occur in human eye saccades, enabling us to shift our gaze seamlessly. In flies, recent research has identified octopaminergic centrifugal neurons as the agents responsible for suppressing motion vision during voluntary movements. The recently completed connectome of *Drosophila* reveals nearly a thousand such centrifugal neurons projecting from the brain to the optic lobes. Some serve to briefly shut down motion vision, while others fine-tune the sensitivity of motion-detecting neurons based on the fly's behavioral state. When at rest, the fly's motion sensitivity is low, increasing when it starts to walk and peaking in flight. The precise function of most of the centrifugal neurons remains unknown for now, but what is already clear is that a fly perceives the world differently depending on whether it is sitting still or in motion. This is just one example of what modern neuroscience now describes as “active sensing,” where an animal’s behavior actively shapes its sensory input rather than passively receiving information from the environment.

Unsurprisingly, as a geneticist, Martin Heisenberg played a key role in the emergence of neurogenetics, which uses genetic tools to probe the workings of the nervous system. His lab conducted large-scale mutagenesis screens to identify genes essential for motion vision or for brain structure. Among the mutants he studied was *rol/sol* (*reduced optic lobes, small optic lobes*), a double mutant with drastically diminished optic lobes. These flies were not blind—they could still orient toward a light source (phototaxis)—but they entirely lacked optomotor responses. According to prevailing wisdom at the time, this should have made straight flight impossible. To test this assumption, Heisenberg placed *rol/sol* flies in a *Drosophila* flight simulator, where a single vertical stripe moved around the fly in response to the fly’s yaw torque, mimicking visual feedback from turning. Wild-type flies in this setup fixated on the stripe, keeping it centered in their frontal visual field by adjusting their yaw torque. Biological cybernetics suggested that without optomotor responses, *rol/sol* flies should fail catastrophically. Instead, while their fixation ability was noticeably impaired, they still managed to fly straight toward the stripe. This unexpected result demonstrated that optomotor responses, though helpful, were not essential for stable flight. They acted as an enhancement rather than a prerequisite, supplementing an independent flight control system. But if optomotor reflexes weren’t necessary, what underlying mechanism allowed these mutant flies to stay on course?

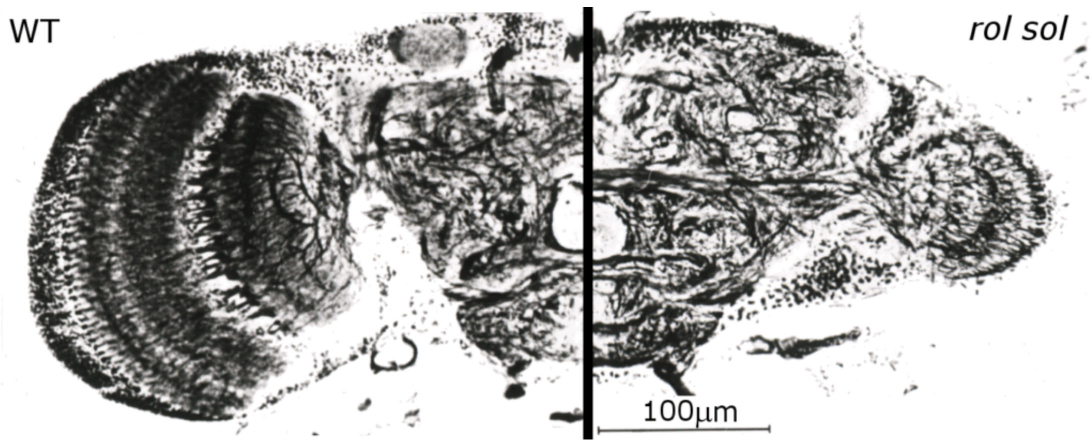

Fig. 2: The brain structure of rol/sol mutant flies

If anything, a second experiment with these *rol/sol* flies dealt an even greater blow to the deterministic view of flight control. In a standard flight simulation, steering to the right induces leftward motion, and vice versa. However, in this experiment, Martin Heisenberg reversed the coupling—so that the more the fly attempted to turn right, the more the stripe moved to the right, and the same for leftward turns. Remarkably, the behavior of *rol/sol* double mutants remained unchanged between these conditions. This not only reinforced the conclusion that *rol/sol* flies were incapable of perceiving motion, but it also revealed the only possible way they could keep the stripe fixated: by correlating their own actions with the stripe’s position and adjusting their behavior accordingly. Deprived of motion vision, the flies had no choice but to explore and discover through trial and error what actions would keep them on course. Just like the sensory-deprived flies from Heisenberg's earlier experiments, the genetic loss of motion perception exposed an underlying spontaneity in behavior—an exploratory drive independent of deterministic input-output loops. Freed from inborn reflexes that would have caused incorrect turns, *rol/sol* mutants flew straight just as effectively whether the coupling was normal or inverted.

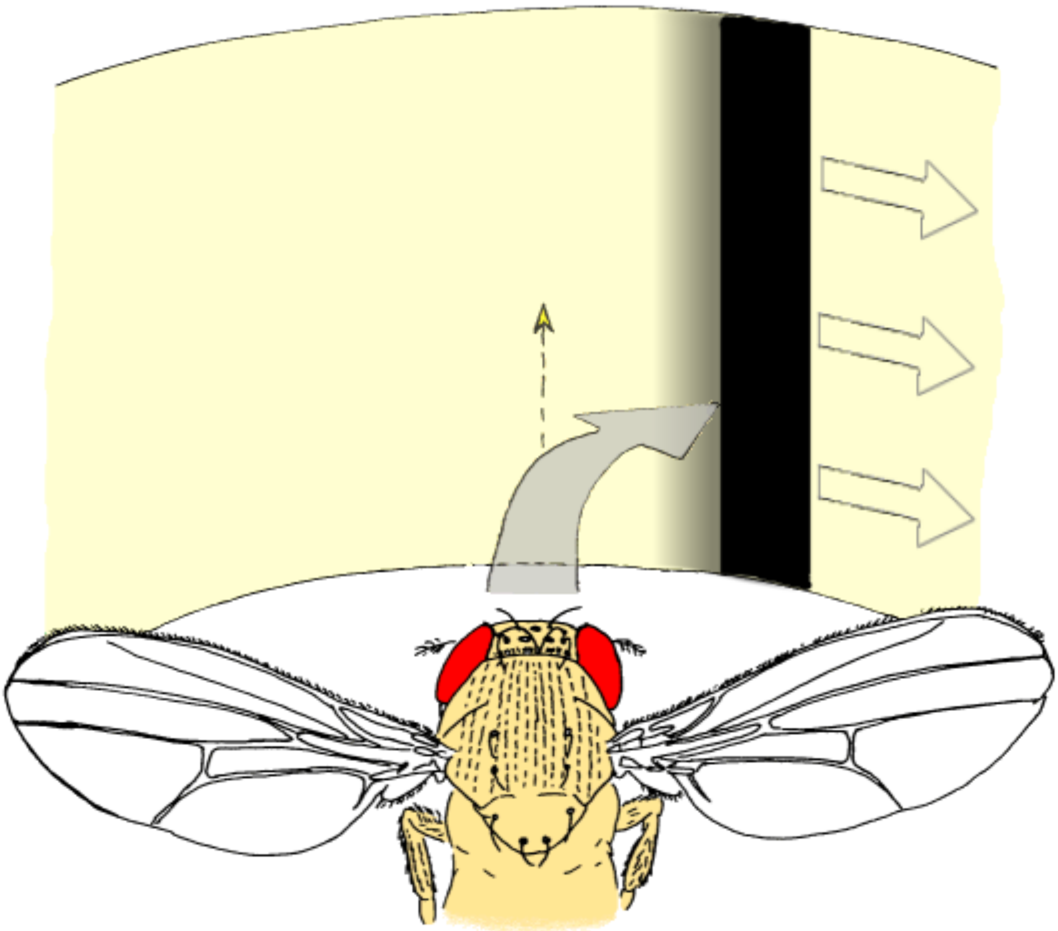

Fig. 3: Schematic depiction of "inversion googles" experiments: when the fly attempts to turn towards a stripe, the stripe moves in the opposite direction than it would in free flight.

When Martin Heisenberg subjected wild-type flies to the same "inversion goggles" experiment, they struggled far more with the altered coupling, unable to stabilize the movement of the vertical stripe. Their optomotor responses, typically crucial for flight control, instead became a hindrance. However, as time passed, an intriguing behavioral pattern emerged. Initially, the flies flailed, sending the stripe spinning wildly. But gradually, they adapted, first learning to keep the stripe behind them, where their abdomen blocked it from view. With continued exposure, they began to bring the stripe forward in fits and starts, interspersed with rapid rotations. After 40 to 50 minutes, they had learned to fixate on the stripe almost as effectively as the *rol/sol* flies. Since this task required overriding their innate optomotor reflexes, the flies could not have relied on any hardwired strategy. Instead, they had to suppress their automatic responses and actively discover which movements brought the stripe into position. These findings not only challenged the idea that optomotor reflexes are fixed and essential for flight—they revealed that, under the right conditions, they could be *unlearned*. Rather than behaving as rigid input-output machines, these experiments suggested that animals operate in the opposite direction: they generate behavior first, then evaluate the sensory consequences to guide their actions.

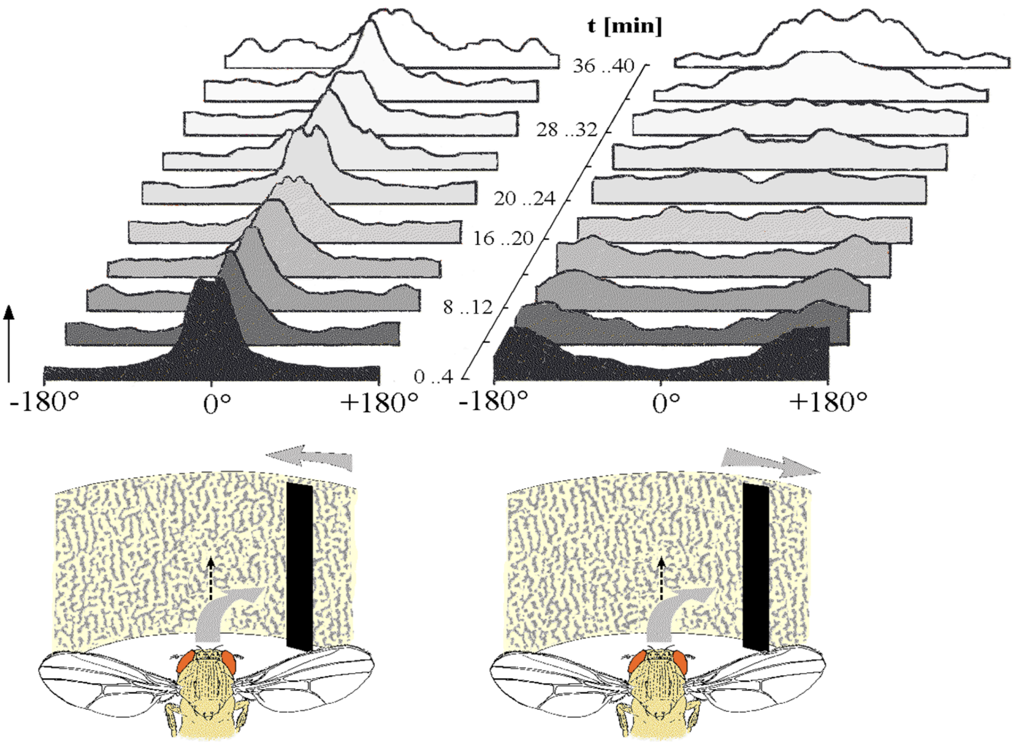

Fig. 4: Wild type flies at the torque meter with realistic coupling between torque and rotation of a single, vertical stripe (left) and with inverted coupling (right).

Beyond reinforcing the idea that fly behavior is *active* rather than merely *reactive*, these findings also provided strong evidence for operant learning in insects. Operant (or instrumental) learning occurs when an action is consistently followed by a consequence, allowing an animal to adjust its behavior to maximize future outcomes. In these experiments, both wild-type and *rol/sol* flies generated spontaneous movements and then modified their actions based on sensory feedback. Over the years, Martin Heisenberg conducted a long series of experiments testing whether flies could learn to associate arbitrary motor outputs with meaningful sensory inputs. These included connections between torque and banana odor, leg posture and stripe rotation, torque and heat, and many others.

While these experiments were deliberately artificial, one in particular—the operant coupling of heat to the fly's yaw torque—hinted at potential real-world, ethological relevance. In this setup, flies were tethered in the sensory deprivation chamber, but this time, an invisible infrared heat beam was triggered whenever they generated, say, right-turning yaw torque. The flies had no prior knowledge of this rule; they had to experiment with different movements until they discovered how to keep the heat off. Remarkably, within minutes, they learned to avoid the punished torque domain, and after just eight minutes of training, they continued avoiding it even when the heat was permanently switched off. Their spontaneous actions had shifted—

fewer punished movements, more rewarded ones. While their behavior remained probabilistic, operant conditioning had subtly reshaped the likelihood of certain actions over others.

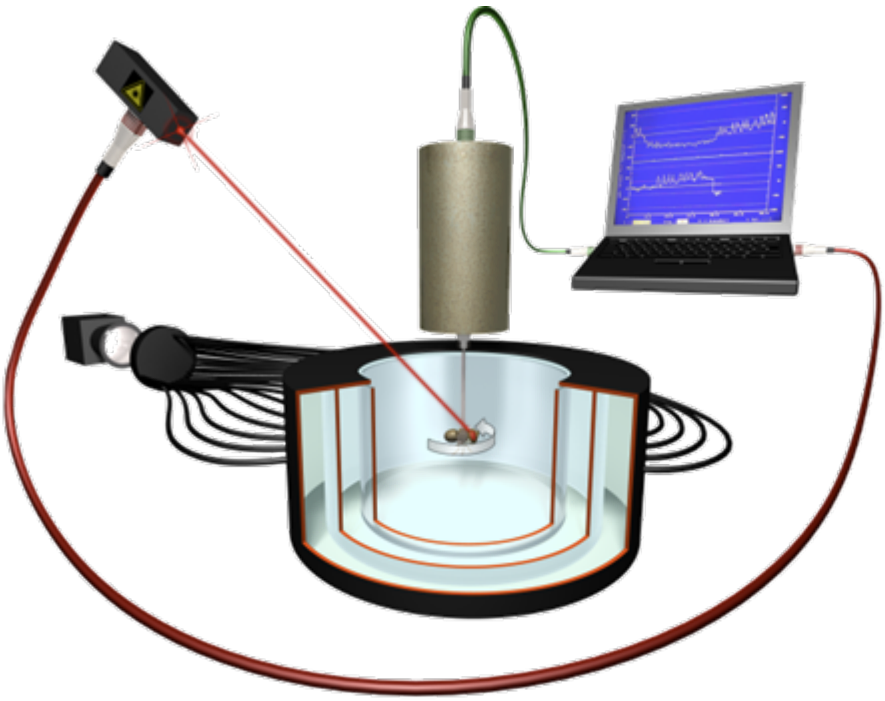

Fig. 5: Torque learning setup. No other stimulus is contingent on the fly's behavior, only the heat. In this example, left turning attempts are punished while right turning attempts are rewarded.

This experimental setup was, of course, an artificial construct—no natural scenario would require a fly to avoid heat by constantly turning in one direction. However, one could imagine situations in which flies must consistently generate torque in a particular way. A prime example is a fly with asymmetrical wings due to injury. If such a fly attempted to fly straight by beating both wings equally, it would rotate uncontrollably toward the damaged side. To compensate, the damaged wing would need to generate more force, or the healthy wing would need to reduce its output—or both adjustments would need to occur simultaneously.

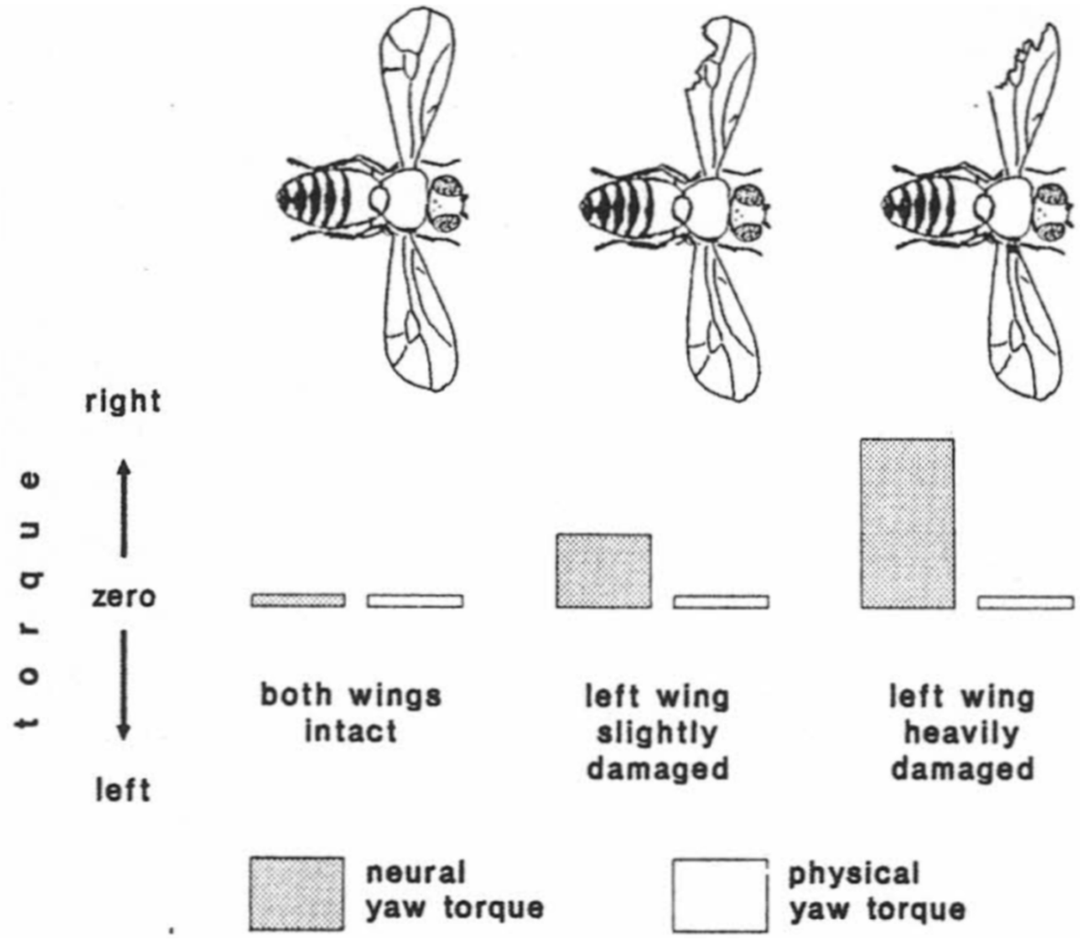

Fig. 6: When the wings are asymmetric, straight flight requires the nervous system to generate torque towards one side to compensate for the less effective wing.

Traditionally, optomotor reflexes were thought to handle such corrections, stabilizing flight by counteracting unintended rotations. But what happens when the fly *intends* to turn and, hence, the optomotor response was switched off? If optomotor reflexes alone couldn't account for these adjustments, how did the fly's nervous system compensate for such asymmetry? The heat-based yaw torque learning experiment offered a potential answer: flies can learn to reset their torque balance. If this operant experiment really had such ethological relevance, it could provide an evolutionary rationale for why animals are not rigid, deterministic machines but instead operate with an intrinsic level of unpredictability: it is an adaptive trait shaped by natural selection to manage unpredictable circumstances – even flying in sensory deprivation chambers where experimenters can turn on life-threatening heat.

Today, genetic data on operant torque learning suggests this process traces back roughly 550 million years, to the last common ancestor of vertebrates and invertebrates. A well-known gene involved in this learning mechanism is the fly ortholog of the human *FOXP2* gene, which is crucial for speech acquisition. Decades ago, B.F. Skinner likened language learning to the operant conditioning he described in pigeons and rats, only to be famously rebuked by Noam Chomsky, whose critique helped launch the Cognitive Revolution against behaviorism. Yet modern neuroscience has vindicated at least part of Skinner's intuition—at least for the speech aspects of language. Acquiring language as an infant and learning to shift torque preferences in a fly share the operant organization and the evolutionary ancestry of the underlying mechanism.

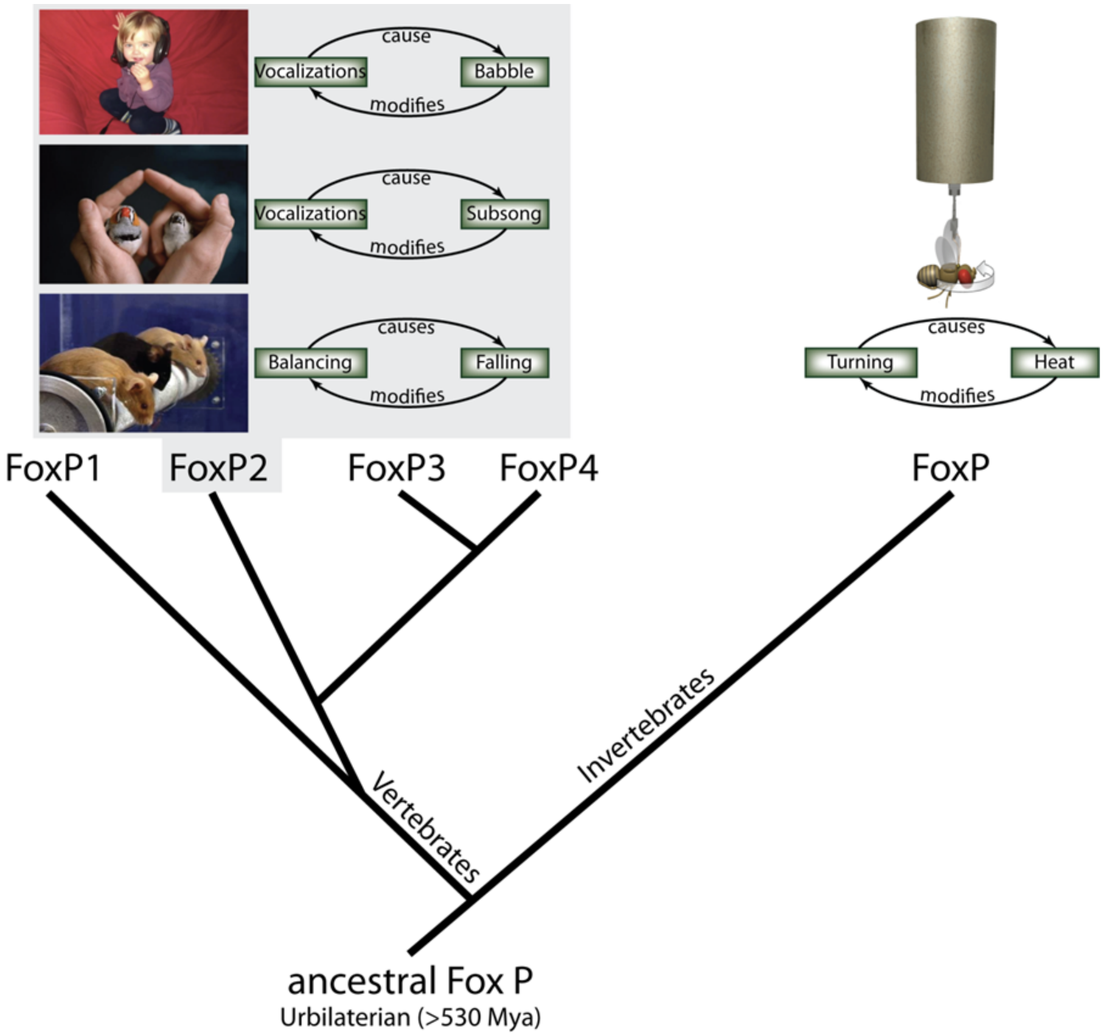

Fig. 7: FoxP phylogeny

There were no torque meters 550 million years ago, so why would this mechanism have evolved? Emerging evidence about the neurons in which these genes manifest plasticity may provide a plausible answer. Researchers using a combination of gene expression analysis and optomotor experiments, identified a distinct set of motor neurons in the ventral nerve cord. These neurons expressed two known operant learning genes, from which it had been known that selectively knocking out either one in just these motor neurons eliminated learning. A key breakthrough came from an optomotor test conducted after operant training. Echoing Martin Heisenberg's findings from decades earlier, researchers observed that optomotor responses were not fixed but instead modified by learning. Notably, the magnitude of optomotor reflexes decreased specifically in the torque domain associated with heat punishment, while remaining unchanged for unpunished domains. Since the brain sends optomotor commands directly to precisely those flight steering motor neurons, these findings suggest that the steering neurons themselves serve as sites of plasticity—reshaped by experience, fine-tuned by operant learning. It seems plausible that early bilaterian animals around 550 million years ago were all facing similar problems when learning how to move their newly evolved bodies and their appendages in space. The genetic data suggest that in the end an operant learning process won out in the struggle for survival: the animals which tried out the large array of new movements they had just evolved and then were able to store the successful ones in their motor control systems, became the ancestors of all extant vertebrate and invertebrate animals today.

The most parsimonious conclusion from this research spanning more than five decades is that flies continuously inject spontaneous actions into their behavioral stream and then evaluate how the world reacts. In the case of flight steering, flies initiate maneuvers, and in natural settings, motion cues from the eyes and halteres inform them about the effectiveness of these movements. While the fly nervous system has evolved to prioritize feedback from these senses —manifesting in mechanisms like optomotor responses—experiments show they can adapt to almost any arbitrary feedback. Importantly, this feedback shapes future behavior by modifying the motor system itself, while seemingly leaving intact the brain circuits that generate spontaneity in the first place (Martin Heisenberg called this faculty "initiating activity"). Inborn behaviors such as optomotor responses may assist the fly on an instantaneous, moment-to-moment basis, while goal-directed adjustments happen via spontaneous actions and the longer term modifications of the motor system after evaluating the outcomes of these actions. This emerging picture raises an intriguing possibility: the ability to initiate spontaneous behavior may be so fundamental that operant learning shapes the fine-tuning of the "envelope", so to say, of individual behaviors rather than altering the core circuits that drive them.

For Martin Heisenberg's experiments to yield reliable results, it was crucial to isolate a single behavioral variable ('microbehavior') from most or all sensory feedback. This allowed him to assign arbitrary sensory feedback to each microbehavior and demonstrate that the fly's nervous system, through trial and error, could determine which behavior controlled which stimulus. The ability to finely dissect the intricate relationships between actions and feedback enabled the identification of steering motor neurons as the site of plasticity in yaw torque learning. This approach will remain crucial as the fly connectome, combined with increasingly precise methods to manipulate individual neurons and circuits, allows for ever finer dissection of the *Drosophila* nervous system. As we gain the ability to manipulate ever smaller sets of neurons with greater precision, our reliance on studying well-defined behaviors that involve approximately the same number of neurons as those being manipulated will become even more important. Behaviors requiring broad neural activity may show little change if only a subset of neurons is altered. Martin Heisenberg, with only hardware, electronics, and early computers at his disposal, pioneered the dissection of microbehavior using physical isolation by experimental design. In the era of machine learning and artificial intelligence, it may become possible to perform this crucial dissection in freely moving animals.

While flight course control in a highly evolved insect species may seem like an esoteric study subject, the evolutionary conservation of these mechanisms suggests that the active, operant organization of fly course control can be generalized to many animal behaviors, including human behavior. This emerging perspective places behavioral uncertainty at the core of nervous system function—not just in operant learning, but as a fundamental principle governing how animals interact with the world. A growing body of evidence across biological disciplines now supports the idea that uncertainty is not a flaw or a limitation but an essential feature of how nervous systems evolved to organize behavior.

While a fly in a sensory deprivation chamber may seem artificial at first, countless natural situations similarly lack clear sensory cues—though perhaps to a lesser degree. Animals frequently make decisions without explicit guidance from their environment. These range from the mundane (e.g., choosing which leg to step forward with) to the complex (e.g., selecting a route around an unknown obstacle). From an ecological and ethological perspective, we now recognize that the ability to choose between options, even in the absence of external cues, is critical for survival. Nervous systems resolve such ambiguities effortlessly, many times a day. A few examples illustrate the broader significance of spontaneous decisions—beyond operant learning—to domains such as survival, self-other distinction, and problem-solving.

Much of the evidence for the evolutionary importance of spontaneous decisions comes from studies of behavioral variability. Acting in an unpredictable manner, even under identical conditions, has been shown to be advantageous in many contexts. In competitive scenarios, for instance, behaving the same way in every instance makes an organism predictable to competitors, prey, or predators—an evolutionary liability. Another key function of spontaneity lies in distinguishing between ex-afferent and re-afferent sensory stimuli. This differentiation is only possible when behavior arises independently of external stimuli. Without it, an organism's nervous system could not determine whether a motion stimulus is caused by an object moving in the environment ("ex-afferent") or by the organism's own movement ("re-afferent"). Operant learning also contributes to problem-solving: most organisms lack complete information about obstacles or resource locations. Exploring different strategies without prior knowledge of which will be beneficial is fundamental to survival and reproduction across species.

While some branches of neuroscience continue to grapple with the fundamental uncertainty Martin Heisenberg introduced to the field—just as parts of physics still struggle with the implications of the uncertainty principle his father formulated—evolutionary biology has largely embraced it. When it became clear that unpredictable behavior could be more evolutionarily stable than deterministic behavior, biologists had little trouble accepting this idea. One reason may be that evolution itself is a fusion of chance and necessity, much like the quantum world Werner Heisenberg described. Unlike physicists, evolutionary biologists have had since Darwin's time to consider the interplay of determinism and randomness in shaping life. The debate between these extremes settled long ago into an understanding that uncertainty is not an obstacle to evolution but an essential, well-harnessed component of it. Eventually, neuroscience may similarly recognize that nervous systems evolved to leverage the problem-solving and life-preserving power of uncertainty, while mitigating its downsides. Perhaps, in time, physics too will fully embrace uncertainty—not as an inconvenience to be minimized, but as a fundamental force that shaped the universe, allowing for the emergence of galaxies, stars, and life itself. Rather than "turtles all the way down", our universe may be better described by "uncertainty all the way up".