The remote roots of consciousness in fruit-fly selective attention?

Bruno van Swinderen

Summary

A mechanistic study of consciousness need not be confined to human complexity. Other animals also display key behaviors and responses that have long been intimately tied to the measure of consciousness in humans. Among them are some very well-defined and measurable endpoints: selective attention, sleep and general anesthesia. That these three variables associated with changes in consciousness might exist even in a fruit-fly does not necessarily imply that a fly is ''conscious'', but it does suggest that some of the problems central to the field of consciousness studies could be investigated in a model organism such as *Drosophila melanogaster*. Demonstrating suppression of unattended stimuli, which is central to attention studies in humans, is now possible in *Drosophila* by measuring neural correlates of visual selection. By combining such studies with an eventual understanding of suppression in other arousal states in the fly, such as sleep and general anesthesia, we might be unraveling mechanisms relevant to consciousness as well. *BioEssays* 27:321–330, 2005.
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Introduction

Fly cognition, encased in only about 200,000 neurons, will one day be well understood and predictable. Yet, will our knowledge of the workings of a fly's brain transfer to that stew of perception and experience that we term ''consciousness'' in humans? If consciousness is self-awareness, then flies are very unlikely to be conscious in the sense that we humans appreciate the concept. It might therefore seem impossible to study consciousness in an organism where the phenomenon does not exist. For want of adequate behavioral measures of self-awareness, we often substitute checklists of ''intelligent'' behavior. Many ''simple'' animals display what appears to be intelligent behavior, but that in itself does not qualify as a marker of consciousness. For example, bees display impressive capabilities of navigation,[1] contextual learning,[2] visual binding (of illusory contours)[3] and even forms of abstrac-

The Neurosciences Institute, 10640 John Jay Hopkins Dr, San Diego, CA 92121. E-mail: van@nsi.edu

tion.[4,5] Certain jumping spiders have been shown, by their eye movements, to be capable of planning ahead their complicated approach to a prey.[6] Even fruit flies display evidence of contextual learning,[7] second-order conditioning,[8] and object invariance (the ability to recognize an object as being the same or different regardless of where it impacts the eyes).[9] Yet, it is not by documenting such examples of intelligence that we will ever convince psychologists (for example) that invertebrates such as flies can be used to study mechanisms relevant to consciousness. Providing a checklist of a dozen or more anthropocentric criteria may be the wrong approach here. We could, hypothetically, demonstrate flies burying their dead and we would still be faced with the fact that simple robots could be programmed to do the same without ever touching upon mechanisms of consciousness.

An alternative approach is to be agnostic about an insect's potential subjective experience and instead tackle quantitative variables associated with changes in consciousness. Rather than asking whether a fly has consciousness, which can only be entertained philosophically and is not the point of this essay, we might use ''the fly'' *Drosophila melanogaster* to study key changes in behavioral responsiveness, which can be approached mechanistically. Just as *Drosophila* has proved useful toward understanding phenomena such as nervous system development[10] or circadian rhythms,[11] *Drosophila* may also prove useful toward understanding general anesthesia, sleep and selective attention—three consciousness-related variables accessible to fly research. Unlike some nebulous checklists for consciousness (language, play, abstraction and the like), these variables benefit from very well-defined criteria for their evaluation (quantitative behavioral responsiveness levels) and they consequently seem entirely knowable at a mechanistic level. The reversible loss of arousal can be defined and measured by criteria independent of the conscious reports associated to them by humans, and these measures have been shown to be remarkably similar across animal phyla.[12,13] Animals as divergent as insects and humans require daily sleep[14] and can be reversibly rendered ''inert'' with virtually identical concentrations of anesthetic compounds.[15] Furthermore, studies of fruit flies and other invertebrates show that sleep and general anesthesia do not require the brain structures traditionally associated with

consciousness, such as the cortex and thalamus.[16] This suggests that some fundamental mechanisms supporting arousal emerged prior to the evolution of a cortex. By focusing on the phenomenally complex human brain in the study of consciousness, we may overlook the possibility that all brains, from invertebrates to humans, may have a common way of governing arousal.

Sleep and general anesthesia in *Drosophila melanogaster* are already well-established, albeit by a still relatively small group of researchers. Sleep research in flies was recently reviewed in this journal,[17] and general anesthesia in flies was also recently reviewed.[16] In the current essay, I will focus on the flip-side of arousal in the fly, selective attention—a trickier problem. A discussion on selective attention is tricky because it tends to conjure up the "whacky" problem of consciousness (which can be safely ignored in sleep and anesthesia studies). Rather than ignore this problem, I will reconsider the relationship between attention and consciousness in the light of recent work on selective attention in the fruit fly. I hope to make the case that selective attention can be studied on several levels (behavioral, electrophysiological and genetic) in *Drosophila*, at least on par with the other more sophisticated non-human animals commonly used in cognitive studies (e.g. rats or monkeys). I will outline certain similarities with human attention which are, as for sleep and general anesthesia, striking enough to suggest, again, the possibility of a common mechanism. Since *Drosophila* lends itself very well to investigating biological mechanisms, a genetic approach to relating different states of arousal in the fly is proposed to complement the traditional studies of such states in humans and other mammals.

Behavioral selection

Attention has often been considered a component of the larger phenomenon of consciousness.[18–20] As a result, any discussion of attention is often burdened with the accumulated paraphernalia of consciousness studies, such as free-will, thalamocortical loops, global workspaces, language and souls. Subjectively, it appears obvious that some attentional processes are under our conscious control: we selectively direct our attention to various targets in a fully conscious and motivated manner, as if attention were a "spotlight" of sorts. In contrast, our attention is often drawn, unconsciously at first, to salient stimuli such as loud noises, bright lights or movements. Attention may thus appear to be evoked sometimes and motivational other times. The traditional view of attention-like processes in animals such as insects is that they are driven by immediate external events, whereby salient stimuli evoke a fixed motor pattern that could be interpreted as a form of selective discrimination. For example, a male fruit fly will court and mate with a female fly once pheromonal, visual and mechanosensory cues coalesce in the right pattern, above a certain threshold.[21]

Yet, insects do not always respond to the same cues in the same way, partially because of the additional dimension of learning and memory. Insects (and most animals) actively probe their environment in an experience-dependent manner, and they react selectively to stimuli according to the behavioral relevance or "salience" of the stimulus, which is modulated by memory.[22] There are several convincing demonstrations of experience-dependent selection (or learning) in flies, which include associative conditioning,[23] incidental learning,[24] and even second-order conditioning.[8] But, whether these demonstrations of learning can be interpreted as involving selective attention-like mechanisms requires more than the measure of behavioral choice. One requires ways of monitoring simultaneously the suppression or uncoupling of other stimuli as the choice is being made; there may never have been any selection at all.

Behavioral suppression

Several studies on selective "attention" in insects have focused on the response to visual stimuli in flies. Initial experiments highlighted the optomotor responses found throughout the animal kingdom: flies (and humans) orient towards the direction of apparent motion, thereby minimizing the sequential activity of photoreceptor groups (retinal slip) and stabilizing their worldview.[25,26] Optomotor studies in flies were given a boost with the development of biofeedback devices, where the angular position of an image rotating around a fly in a flight arena could be controlled by the animal's behavior (Fig. 1). During tethered "closed-loop" flight, flies demonstrate their "perception" of objects by using body torques in order to hold a dynamic object still in part of their visual field.[27,28] Flies are able to control optic flow with precision, but, interestingly, do not always "choose" to do so, sometimes letting images slip by for seconds before "grabbing" them again behaviorally. Although such capricious control resembles changes in "attention", these behaviors were originally viewed as afferent processes based on multistable networks residing primarily in the optic lobes and thorax, bypassing the central brain — in other words, a "reflex".[29]

Most researchers studying behavior in *Drosophila melanogaster* might counter this unsatisfying explanation with rich anecdotes suggesting that some form of selective "attention" over-rides optomotor responses. For example, my colleague Herman Dierick who works on fly aggression describes how, following a fight bout between two males in a cage full of flies, the victorious male will sometimes keep track of (orient itself to) the defeated male, which dive-bombs around amongst a constellation of other flies. Clearly, the retinal slip caused by all the other flies, some which are looming closer, is ignored and an optomotor response is selected for only one memorable individual. Relevant to such casual observations is recent work showing that visual pattern recognition in tethered flies is invariant for retinal position.[9]
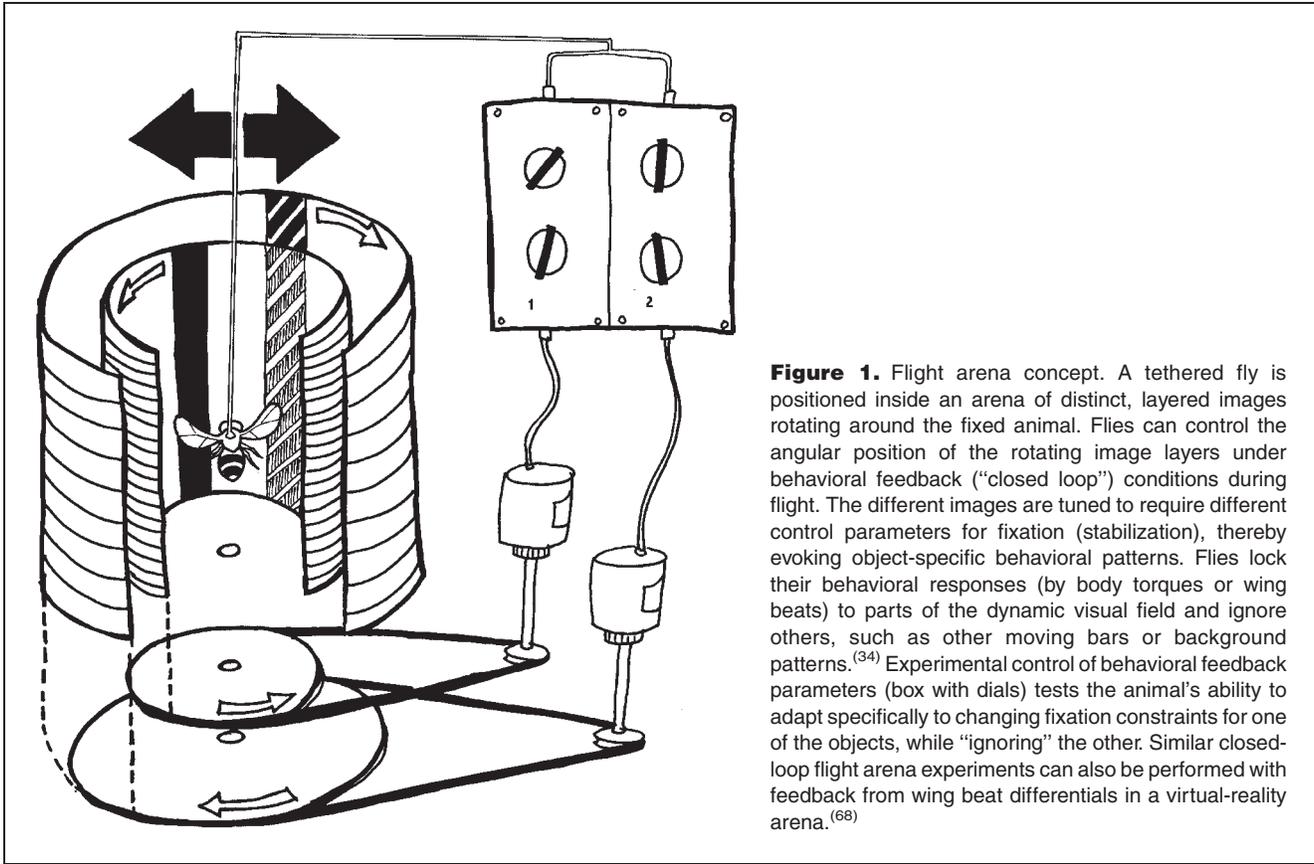
Figure 1. Flight arena concept. A tethered fly is positioned inside an arena of distinct, layered images rotating around the fixed animal. Flies can control the angular position of the rotating image layers under behavioral feedback ("closed loop") conditions during flight. The different images are tuned to require different control parameters for fixation (stabilization), thereby evoking object-specific behavioral patterns. Flies lock their behavioral responses (by body torques or wing beats) to parts of the dynamic visual field and ignore others, such as other moving bars or background patterns.[34] Experimental control of behavioral feedback parameters (box with dials) tests the animal's ability to adapt specifically to changing fixation constraints for one of the objects, while "ignoring" the other. Similar closed-loop flight arena experiments can also be performed with feedback from wing beat differentials in a virtual-reality arena.[68]

The need to over-ride certain optomotor responses is also evident during self-motion. This was studied in detail by Collett and colleagues in the hoverfly *Syritta pipiens*, where the optomotor response was shown to be controlled by shifting portions ("poles") of the fly retina, depending on flight style (sideways, forward) or on whether the animal was tracking an object or not.[30,31] Collett concludes that an animal must in some very broad sense "know" what the consequences of its actions are going to be for it to appropriately select responses across certain retinal patches and ignore others. Subsequent electrophysiological investigations in the larger blowfly identified unique classes of neurons in the optic lobes that respond only to small moving objects on textured backgrounds, and other neurons that respond only to background motion.[32,33] Nevertheless, behaviorally relevant selection of optic output must somehow occur, whether that optic source is confined to patches of retina or ensembles of specialized neurons, while other large swathes of retinal action are "ignored". In a way, the ongoing dynamics between retinal output selection and suppression in relation to experience begin to resemble what we might call attention. A careful study of this phenomenon requires a controlled visual environment presenting multiple image choices, and means by which the fly can "report" its visual selections.

Fly virtual reality

The closed-loop flight arena (Fig. 1) provides an elegant paradigm for studying visual selection in tethered flies, since the interplay between optic flow and behavior can be manipulated. Distinct, rotating objects are tuned to require different control parameters for fixation, thereby evoking object-specific behavioral patterns. Flies lock their behavioral responses (by body torques or wing beats) to parts of the dynamic visual field and ignore others, such as other moving bars or background patterns.[34] Fixation behavior in the arena is of variable latency and vigor, and behavioral responses are rarely stereotypical, except by being generally exploratory in nature.[24,35] The virtual reality environment of this paradigm allows for the design of some interesting experiments testing the limits of optomotor flexibility in non-natural situations. For example, if the closed-loop electronics are reversed such as to counter optomotor responses (e.g, turning with images makes them flow even faster), flies will quickly adapt to this odd situation and still manage to stabilize their object of fixation, violated optomotor reflexes notwithstanding.[28] Such experimental control of closed-loop fixation has convincingly demonstrated that visually driven behavioral responses become extremely flexible when feedback allows the fly to control its visual environment. Further, the capacity for visual

selection to be steered (via conditioning experiments) by other sensory modalities, such as odor or heat, suggests that such selection in the fly is not confined to the optic lobes.[36,37] As in humans, fly visual selection recruits different parts of the brain in associating disparate stimuli or stimulus modalities.

Attention in humans is partitioned serially in time between simultaneous stimuli.[38] Flies have been shown in open-loop (no-feedback) flight arena experiments to respond to simultaneous images in a similar way.[28,34] A stationary object in the fly's visual field will reduce the response to a (second) suddenly moving object by 50%, compared to responses to the suddenly moving object alone. This suggests that the behavioral response is subject to a limited resource partitioned among potential percepts. Similarly, two objects oscillating at the same frequency but in anti-phase on laterally opposite sides of the arena will evoke a response pattern that is very similar to that seen for a single-object oscillation, except with spontaneous switches from one phase to the other. In humans, competing images presented to either eye separately cannot be reconciled, and are therefore perceived in alternation one at a time.[39] Although the human effect involves a completely different neuroanatomy than the effect in flies, a common mechanism is not excluded.

Alternating selection

The preceding examples of fly selection and suppression demonstrate a critical aspect of fixation common to many animals: it is rarely sustained for one target percept for very long, but rather, it shifts or alternates among targets. Any investigation of behavioral selection must consider this phenomenon, as it confounds the motive in selection. Alternating selection has been examined extensively in behavioral choice experiments in flies (closed loop flight or walking assays) where it has been referred to as "sustained spontaneous alternation".[35,40,41] Flies will persistently walk (or fly) back and forth between two salient visual targets, "attending" to each for a while until the other somehow wrenches it away. It is not clear whether such sudden alternations in behavior are at all goal-directed in flies. The timing of alternations is not strictly periodic and often seems random, yet it might appear maladaptive for flies if their behavior were released without a good reason and only as an accident of a random-number generator in their brains. Sudden shifts in behavior have been studied in flies on shorter time scales as well, where they appear as flight saccades, occurring in the context of object fixation in closed-loop flight.[28] The saccades do not occur in response to anything detectable (the visual stimuli are not saccading), yet they seem to be employed in a meaningful way. They reveal possibly novel visual stimuli outside the center of fixation, and they probe parts of the visual field that might be associated experimentally with other sensory modalities such as odors or heat. Martin Heisenberg and colleagues have suggested that behavioral saccades, or sudden spontaneous

alternations, may act on behavior in the same way as mutations act on evolution: chance events that produce changes that will be selected according to their advantage to the organism.[28] Such alternating behavior resembles ancient mechanisms such as the tumbling versus swimming behavior of certain bacteria.[42] As with genetic mutations, there is no "goal" involved here per se, but just naturally selected outcomes of such spontaneous behavior within a specific environment. In animals with learning and memory capabilities, spontaneous alternations might dwell on those stimuli that prove to be more salient (relevant) to the animal for its survival. Motivation is, in this sense, history. Sudden spontaneous alternations in flies might thus support the consolidation of salience which, in turn, sustains "attention". The serial nature of human attention seems just as necessary in flies for salience to be efficiently established; connections must be drawn between single causes and effects, and spontaneous saccades may force all animals into making those connections, or perish.

Salience and memory

Salience is intertwined with memory, especially short-term or "working" memory. Salient stimuli draw attention, often via change from a previous state, and working memory provides a mechanism for an animal to detect change. Yet, the mechanisms subserving selective attention and memory must be related or intertwined because each seems causal to the other: memory steers attention, yet attention results in memory formation. Although this mutually causal relationship may seem to create a problem of "infinite regress" in understanding its genesis (the chicken or the egg?), the relationship instead suggests that a form of neural evolution occurred within the lifetime of an animal.[43] Likewise, if human consciousness emerges—even in part—from perceptual processes intertwined with memory, this makes it difficult to study as a final product in the adult without considering its evolution from more basic constituents (e.g. saccades and neuronal group selection[43]) throughout the early life of a person. As in phylogenetic analysis (deducing evolutionary relationships between species), this problem calls for techniques that allow us to study the sequence of changes throughout the development of an attentive brain. One would be in a good position to study mechanisms of attention in an animal offering an array of tools with which to track its neural development and plasticity alongside behavior.

Mushroom bodies

The *Drosophila melanogaster* nervous system can be systematically manipulated throughout its life by various genetic tools, which facilitates our ability to investigate the mechanisms supporting the phenomena displayed by the animal in behavioral assays.[22] For instance, mutations affecting a variety of signaling, structural and transcription genes modulate learn-

ing behavior.[44] Although attention-like mechanisms would appear to be a pre-requisite for learning, these genetic resources have rarely been examined in discrimination paradigms (instead of association). Classical conditioning experiments in *Drosophila* mutants have shown that synaptic output from brain structures called "mushroom bodies" is crucial for the retrieval of associations between specific olfactory stimuli and electric shocks.[45] These bilateral structures (see Fig. 2A) are involved in memory formation and retrieval in most insects studied for learning assays.[46–49] The mushroom bodies have also been associated with visual

selection by examining, in visual fixation paradigms, some of the same *Drosophila* learning mutants gleaned from odor conditioning screens.[41,50,51] This argues for a certain overlap between association and discrimination, as might be expected. When tested in visual selection paradigms, learning and memory mutants in *Drosophila* are either unable to fixate on visual stimuli or fail to seek novelty, depending on whether they are flying or walking, respectively.[41,50,51] Comparative studies of discrimination and association with such mutants offer insights into the connections between perception and learning in flies, thereby outlining the framework for a speculative attention mechanism (Fig. 2B).

Visual selection experiments in the closed-loop flight arena have shown that the mushroom bodies not only guide the dynamics of tracking behavior, but also provide the ability for the animal to extract salience from "messy" compound stimuli. This includes contextual generalization and selecting (discriminating) among contradictory cues in classical conditioning experiments.[7,52] A fly's selective behavior is not a linear function of stimulus parameters but, as in humans, will "jump to conclusions" about the salience of a stimulus. This can be demonstrated by conditioning flies to avoid a stimulus with two parameters (shape and color) that can then be mixed and matched and quantitatively changed in subsequent choice tests. Wild-type (normal) flies assign salience reliably to one parameter (e.g. color) even as it changes, but beyond a certain level of change, salience (evidenced by the fly's behavioral selection) suddenly flips entirely to the other parameter (e.g. shape). However, with genetically controlled defects in the memory-forming mushroom bodies, flies instead respond to changing choice parameters in a more linear and, presumably, maladaptive fashion.[52] In such mutants, the likelihood of flies switching parameters is a simple function of the parameters' quantitative characteristics. In a normal fly, switching is not a
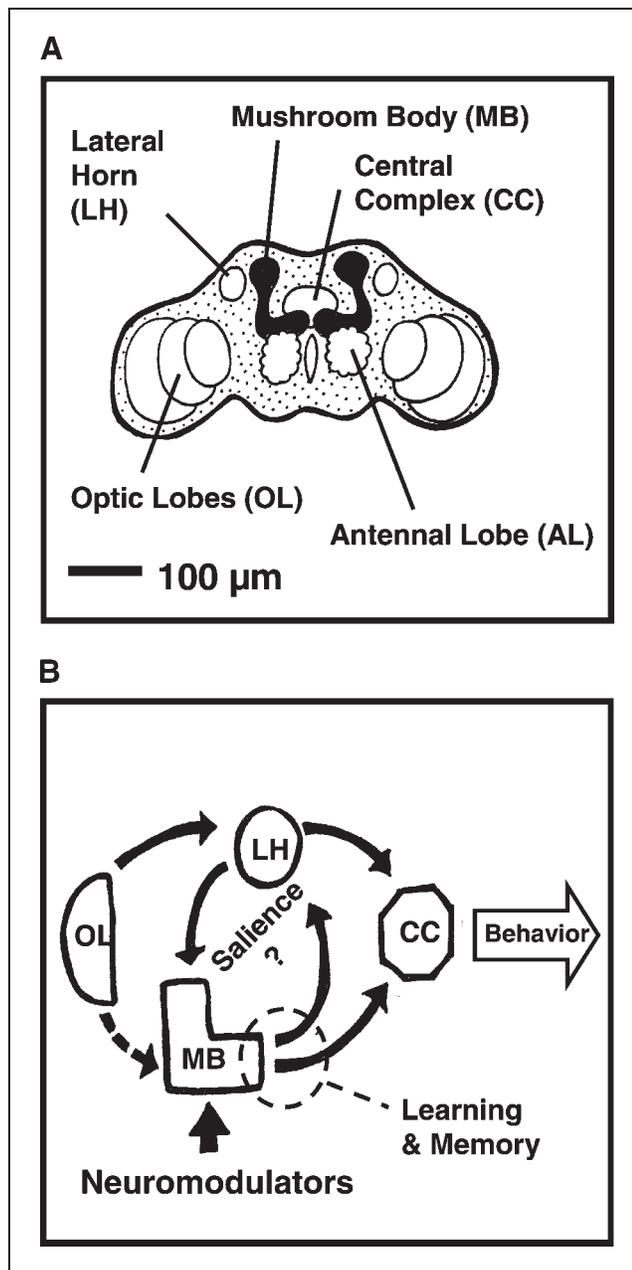

Figure 2. *Drosophila* neuroanatomy. **A:** Schematic of the brain of *Drosophila melanogaster*, with select structures indicated. The two bilaterally symmetrical mushroom bodies (MB) are shown darkened. The medial protocerebrum is roughly in the area bracketed by both mushroom bodies, including the central complex (CC). Below the brain is a 100 μm scale. **B:** A speculative model relating memory/learning mechanisms with salience/discrimination in the *Drosophila* brain. Visual input to the optic lobes (OL) reaches the lateral horn (LH) and mushroom bodies (MB) by direct and indirect pathways,[49] respectively. Some forms of learning and memory are mediated by neuromodulators and cAMP signaling pathways, which modify synaptic output from the MB.[44] Output from the MB and LH converge in the central complex (CC) to control motor behavior.[69] Connections between the LH and MB[70] could gate the level of salience of a visual stimulus via an oscillatory mechanism similar to that found in the neuroanatomy of the locust, albeit for smell.[66]

graded response to quantitative aspects of stimuli, but rather "pops out" at a dynamic threshold, somewhat like our own sudden awareness of an object or a memory (like the classic hidden Dalmatian picture in psychology textbooks). It is conceivable that such "pop out" salience effects in the fly are not unique to conditioning experiments in the laboratory, but rather are serially ongoing with respect to the animal's interaction with its dynamic environment. The challenge is to begin reconstructing the molecular and neural machineries that allow insects to discriminate and assign salience in such an experience-dependent manner. For a number of reasons, the power of genetics has not been well applied to this problem, even though the memory-forming mushroom bodies and the array of learning mutants[44] seem to be promising starting points in this endeavor.

The missing piece

Although attention-like mechanisms may accomplish similar functions in insects and mammals, the obvious association of attention with consciousness in humans complicates and perhaps even hinders the investigation of attention analogs in animals. Thus, the phenomenon is called "selective attention" in mammals, but "selective discrimination" in flies. The problem is more than just a semantic one: by relegating fly behavioral selection to the dubious "reflex" category of selective discrimination, we presuppose that there must exist a fundamental difference between mechanisms of behavioral selection in insects and higher animals, a difference that must closely parallel an imaginary consciousness divide, and which hence must be tied to mammalian neuroanatomy. Yet, even monkeys are in the same bag as flies with respect to demonstrations of selection: neither can report to us verbally what they were attending to in the past. We rely on their behavior to infer their "attentional" state.

One problem with behavioral studies of attention, especially in invertebrates (which lack the neuroanatomical crutches available in monkey research), is precisely that they often involve behavior alone. Demonstrations of attentional suppression by behavioral methods alone are never entirely convincing for a number of reasons. First, an animal by definition cannot be in two places at once. By observing a fly's choice behavior, we have little way of knowing whether the alternative choice was even on its radar (except perhaps in some of the elaborate flight arena experiments discussed earlier). Yet, evidence of suppression is just as important as evidence of selection in order to study "attention" in an animal. Another problem with purely behavioral studies of attention is that we know that attention in humans can be dissociated from a motor output; we do not have to be orienting or moving toward a stimulus in order to attend to it. Perhaps we have been reluctant to call selective fly behavior "attention" precisely because it is a motor behavior, while our (adult) attention is so clearly independent of what our muscles are doing. Further-

more, it is often difficult to distinguish an animal's ability to assign salience to a stimulus from its ability to perform the motor task at hand: a fly must walk or fly adequately, for example. A thorough genetic dissection of the *Drosophila* brain might produce animals fully able to assign salience but unable to *show us* that they have, thus sabotaging any adequate investigation of the phenomenon. This is probably the main reason why some of the sophisticated behavioral selection phenotypes, discussed earlier, have not been further investigated genetically. Finally, any selective behavior, regardless of how non-linear and "intelligent" it is, can always be described as a very elaborate motor program. The missing piece here is evidence of attention occurring within the brain of an insect, independent of motor behavior.

Selective attention in the fly brain

A recent study of visual selection in *Drosophila* showed that several properties of selective attention are represented by 20−30 Hz local-field-potential (LFP) activity in the fly brain.[53] LFP recordings were made in the medial protocerebrum (mpc), a region of the fly brain bracketed by the mushroom bodies (see Fig. 2A), during a similar behavioral feedback paradigm as shown in Fig. 1, but with brain recordings performed alongside the behavioral selection. Object fixation evoked transiently increased 20−30 Hz activity in closed-loop flight, suggesting that this brain activity was associated with the onset of selection. Critically, transient changes in fly 20−30 Hz brain activity were also found to be associated with selection in animals that were not flying or overtly tracking objects behaviorally: Brain activity was correlated selectively to "tagged", distinct images made salient by conditioning (with heat or odor), at the expense of other simultaneous images, without any observable correlated behavior such as twitches or flight dynamics (a schematic explaining how such selection in fly brain activity can be identified is shown in Fig. 3). Such brain potentials bring to mind gamma (30−80 Hz) activity in the human EEG, which is also transient and modulated by salience,[54] as well as neural correlates of attention in the primate visual cortex.[55] A neural correlate of salience in the fly brain provides an answer to the confounding behavioral issues raised earlier, and encourages a genetic strategy towards understanding how choices are made in the fly. Not too unexpectedly, considering previous work outlined above, the first fly mutants analyzed for this phenotype indicate that synaptic output from the mushroom bodies is critical for the normal attentive brain response.[53] Recent experiments also show that neuromodulators such as dopamine appear to be crucial as well in governing visual selective attention in the fly. Attenuating synaptic output from dopaminergic neurons impairs behavioral fixation[56] as well as the 20−30 Hz brain response to visual salience (R. Andretic, B. van Swinderen and R.J. Greenspan, unpublished data) The parallels with human deficiencies are intriguing: without being able to retrieve
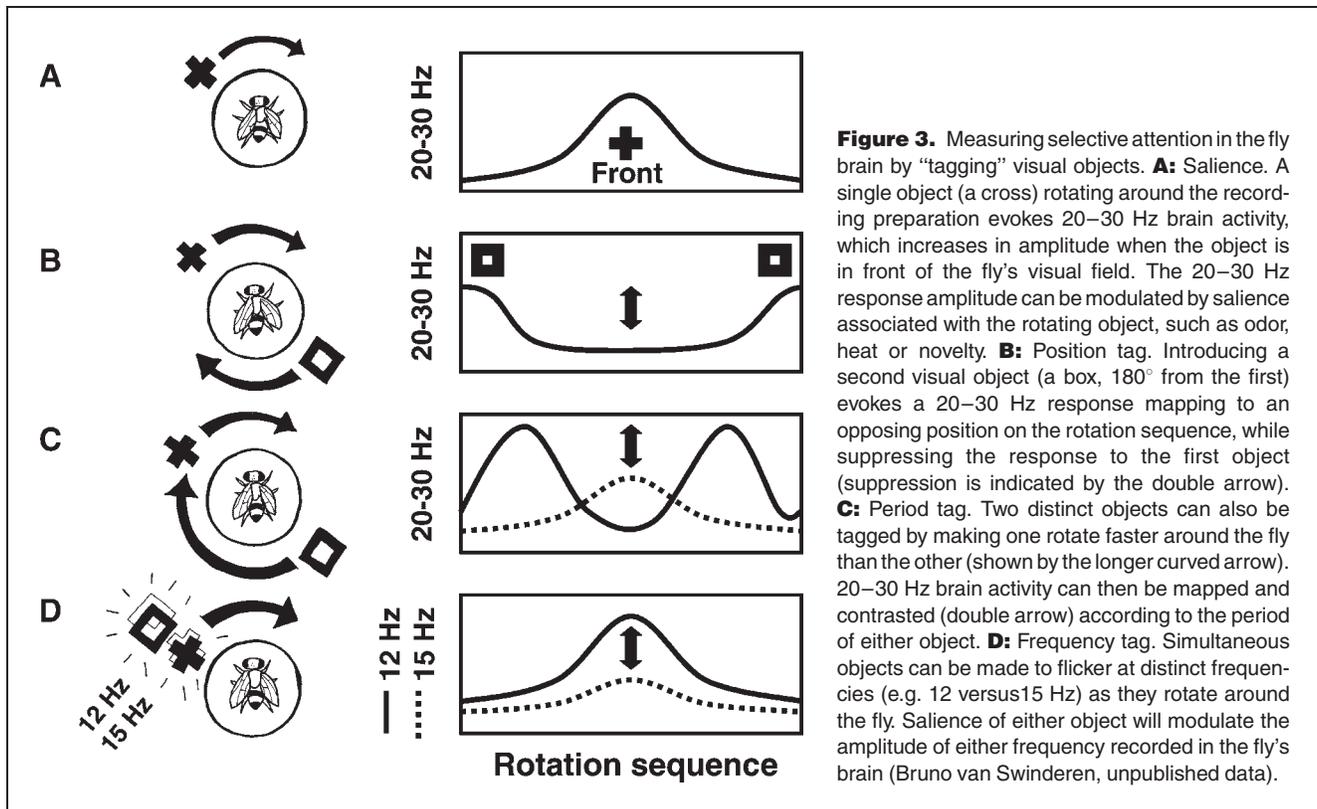
Figure 3. Measuring selective attention in the fly brain by "tagging" visual objects. **A:** Salience. A single object (a cross) rotating around the recording preparation evokes 20–30 Hz brain activity, which increases in amplitude when the object is in front of the fly's visual field. The 20–30 Hz response amplitude can be modulated by salience associated with the rotating object, such as odor, heat or novelty. **B:** Position tag. Introducing a second visual object (a box, 180° from the first) evokes a 20–30 Hz response mapping to an opposing position on the rotation sequence, while suppressing the response to the first object (suppression is indicated by the double arrow). **C:** Period tag. Two distinct objects can also be tagged by making one rotate faster around the fly than the other (shown by the longer curved arrow). 20–30 Hz brain activity can then be mapped and contrasted (double arrow) according to the period of either object. **D:** Frequency tag. Simultaneous objects can be made to flicker at distinct frequencies (e.g. 12 versus15 Hz) as they rotate around the fly. Salience of either object will modulate the amplitude of either frequency recorded in the fly's brain (Bruno van Swinderen, unpublished data).

certain forms of memory, and without a "balanced" neuromodulatory system assigning value[57] to stimuli, selective attention is probably impaired in flies as well as humans.

Arousal in the fly brain

Fruit flies sleep, as was demonstrated recently by behavioral criteria such as increased arousal thresholds during prolonged immobility at night, or sleep rebound following mechanical sleep deprivation.[58,59] However, as was the case for selective attention, an independent measure of arousal (sleep versus wake) in the fly brain seems necessary to convince us that such a state in flies is more than just a correlate of motor behavior. Human studies have such independent measures in the EEG.[54] Immobile, unresponsive humans sitting on a couch watching TV do not display the delta waves characteristic of mammalian sleep; motor behavior and arousal state can be uncoupled in the short term. Brain activity recordings from the *Drosophila* medial protocerebrum (mpc) showed that this is true for flies as well.[60] Although sleep in flies is characterized by decreased brain activity (1–100 Hz), the increased brain activity recorded during wakefulness can be independent of movement. Thus, wakefulness, like visual selection, has a neural correlate in fly brain activity independent of the motor behaviors usually utilized to identify that state.

Arousal state in an animal is nevertheless primarily defined by behavioral responsiveness. Thus, sleep and general anesthesia are characterized by increased arousal thresholds (decreased behavioral responsiveness to irritating stimuli). However, selective attention is also characterized by increased arousal thresholds, namely, for all the simultaneous stimuli that are being ignored. It appears that during wakefulness in general, the brain is suppressing the perception of stimuli almost as much as during sleep, with the exception of that one dynamic, yet narrow window of selection. Recent work on arousal states in *Drosophila* showed that behavioral responsiveness to mechanical stimuli can be as low in a moving (i.e., awake) fly as during sleep.[61] One cannot conclude that all such heightened arousal thresholds indicate sleep since, in many cases, flies are moving as much on average as they ordinarily do while awake and responsive. Similarly, our own arousal thresholds to someone calling our name, for example, may be as high while we concentrate on an exam as when we sleep. In humans, sleep and wake states are very different conscious states,[54] so we often assume that these must involve very different brain mechanisms, rather than a continuum of suppression or uncoupling. We assume that the consciousness of our waking (or dreaming) states must therefore stem from something entirely different and unique that is absent during deep sleep. Such neo-dualism stemming

from categorizing our own sleep/wake dichotomies may be misleading insofar as understanding these states, and perhaps deters us from investigating mechanistic continuity with simpler animals. Yet, in both flies and humans, brains appear to be disabling perception of most stimuli at any given time, just more so during sleep. Understanding what governs the dynamics of suppression in fly brain activity may be more relevant to consciousness studies than searching for signs of (human) intelligence in other animals.

Conclusions

General anesthesia, sleep and selective attention represent different states of arousal that have been associated with changes in consciousness in humans. Nevertheless, these states are well-defined by behavioral responsiveness criteria that can be identified and measured in *Drosophila*, suggesting that via genetic analysis their mechanisms may be understood. On a broader level, genetic analysis allows different behavioral phenomena such as these to be drawn together in correlation. Genetic studies never assume that a single change in a gene "explains" a phenomenon such as attention or sleep. Rather, changes in distinct phenomena such as attention or sleep can be related precisely because all is held constant in the organism except for one "lesion" at a time affecting a specific network of cells. Thus, it is possible that a suite of molecularly related changes will affect anesthetic sensitivity, sleep, attention, learning and memory "all at once" (i.e, within the same isogenic mutant strains). Or, some changes might increase sleep need without compromising anesthetic sensitivity. In any case, genetic approaches to behavioral responsiveness in *Drosophila* should organize these phenomena to produce a model of arousal that could be compared to electrophysiological and pharmacological data from the same or other species.

One model might describe different forms of arousal as a continuum defined by suppression or uncoupling dynamics in the brain. As discussed, even states of heightened arousal such as attention may be characterized by the suppression of stimuli evident during low arousal, so an ancient mechanism involving suppression of stimuli may be fundamental here. The differential patterns of suppression resulting in anesthesia, sleep, wakefulness, selective attention and even learning could occur via related global mechanisms recruiting (or targeting) most of the brain. Data from researchers currently working on every possible behavioral state in *Drosophila* will surely address whether arousal is essentially one mechanism or many different phenomena in the fly. It would appear, however, that the dynamic suppression mechanisms in the brain that may control arousal state would be operant in just about any *Drosophila* behavior. It may therefore be informative to document the degree of overlap in mutations or microarray data among different behavioral studies where, in effect, an arousal difference may have been evident alongside the

particulars of a specific behavioral difference. Alternatively, comparative genetic studies can be designed to identify common pathways modulating responsiveness to stimuli under different behavioral arousal paradigms.

One form of arousal in *Drosophila*—visual selection—displays key properties associated with attention, suggesting that the quotation marks traditionally guarding this "human" term may some day be discarded. The implications are of course provocative: attention may be widespread among animals. We might even go further and entertain the possibility that our consciousness stems from insect-like attention mechanisms. Instead of only coordinating the consecutive salience of immediate external stimuli, such attention mechanisms may have evolved to encompass as well the neural substrates of memories peculiar to different animals. Those peculiar to humans will always be different to a fly's or a monkey's, even though similar suppression mechanisms may be operant. Thus, human consciousness may come out of attention, rather than the other way around. With this reversed and admittedly simplified view, our issues with consciousness do not stand in the way of our studying aspects of it in model organisms: we can study selective attention. The latter is at least accessible to science, unlike the so-called "hard" questions pertaining to "qualia" (e.g. the inevitable redness of red). A student of consciousness recently reminded us that another "hard" question, "Why is there something instead of nothing", has not prevented us from studying the physical universe.[62]

A strong argument can be made for directing our efforts into fully understanding the *Drosophila melanogaster* brain. Only the size of the period at the end of this sentence, it is the smallest brain shown to display arousal variables similar to our own. Sleep, selective attention and responses to drugs such as general anesthetics or psychostimulants closely parallel human responses.[16,63] The varied array of genetic tools available to the large *Drosophila* community makes every functional network of neurons in the fly potentially accessible to manipulation, and a brain screen for the neuroanatomy controlling selective attention in the fly is currently underway by, at least, this author. One may ask, then, why not go even simpler, like with *Caenorhabditis elegans* and its 302 neurons? *C. elegans* behavioral responsiveness is also targeted (reversibly) by general anesthetics at the same concentrations that abolish consciousness in humans.[64] The worm, however, has not been shown (yet) to require sleep and rigorous demonstrations of selective attention in nematodes are difficult to imagine, let alone neural correlates thereof. Perhaps relevant is the fact that *C. elegans* lacks the complexity of a central, differentiated, brain-like network. In contrast, animals with more complex brains, such as monkeys or rats, are "closer" to humans than flies are. Furthermore, brain research on mammalian models is already very advanced and more sophisticated in many respects than *Drosophila* brain

research. The argument for closeness to humans, however, may be true neuroanatomically speaking, but does not necessarily hold for the function of sleep, the reversible mechanism of general anesthesia and suppression phenomena in general. Fly arousal, including perception, now seems just as accessible to study as in any animal below verbal humans, with both behavioral and neural correlates. Although brain electrophysiology is in its infancy in *Drosophila*, much ground can be gained from extensive experimental and computational studies on blowfly vision,[33] honeybee learning[65] and locust olfaction,[66] for example. Combined with recent developments in recording from single neurons in the intact *Drosophila* brain,[67] we can potentially understand thoroughly how a small brain works to govern arousal. We may even be surprised to discover that selective attention is supported by similar mechanisms in humans and flies. Rather than indicating consciousness in flies, such similarities would suggest that the roots of our consciousness are indeed remote.

Acknowledgments

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