Brain Exploration, Off the Beaten Path

Model organisms, such as rodents, monkeys, or *Drosophila*, have driven much of recent research in neuroscience. However, studies in other, more unusual systems have broadened the types of questions that are being asked and have revealed the diverse ways in which species tackle common problems. *Cell* editor Mirna Kvajo talked with Nachum Ulanovsky, Gilles Laurent, and Anthony Leonardo about their research and how studying bats, reptiles, and dragonflies informs big questions in neuroscience. An annotated excerpt of the conversation appears below, and the full conversation is available with the article online.

Anthony Leonardo
Janelia Research Campus

Nachum Ulanovsky
Weizmann Institute of Science

Gilles Laurent
MPI for Brain Research

Mirna Kvajo: It seems that a lot if not most of research in neuroscience is being done in a couple of model organisms; we hear about mice, we hear about rats, the *Drosophila*, and then also monkeys. Most of these organisms are used to address a broad spectrum of questions, and something that is happening now is a raised awareness about how many of these questions we can actually ask [in these traditional systems]. And it seems that there's a surge of interest in alternative model organisms.

The three of you are using something that people could call alternative organisms, right? You're working on bats, the dragonfly, reptiles. Just to start off, I wanted to understand what are your reasons for picking these organisms? What kind of questions are you asking, and are some of these questions such that can't be asked in other types of organisms?

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Anthony Leonardo: I'll speak up first. We study prediction in dragonflies and how they anticipate where prey is going and use this to construct a flight path. That process requires internal models of how the body works and how the prey moves. And the reason we've been studying prediction there is largely because the problem the animal solves is very clear when you look at the behavior … In the case of our system, this sort of prey capture is not unlike reaching out your arm to grab something, so it's really a ubiquitous behavior and you could study it in any one of a number of systems. But because of how these animals do the behavior: it's easy to elicit and they do it with a certain amount of complexity, and they have to solve it with certain accuracy, all those things conspire to make the system much easier to understand than in other places. That's been the reason for me: it's not that it's the only place to study it, but we think it's the cleanest, clearest place, and then we can take what we've learned there and apply it to other systems.

Nachum Ulanovsky: Maybe I could continue on that. I think this idea some call Krogh's Principle. The notion that for every problem or every question in biology there are some organisms that are particularly useful to address it. It could be because their behavior is very precise. In our case of the bats, we are studying place cells, grid cells, head-direction cells—the spatial system. The one reason is indeed that, on one hand, the bat is a mammal, so the anatomy of its hippocampal system is very similar to rodents, so we have that constraint. On the other

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(L to R) Mirna Kvajo, Nachum Ulanovsky, Gilles Laurent, and Anthony Leonardo

hand, there are certain questions that are difficult to ask in rodents, but they're more approachable in bats. For example, the representation of 3D space or representation of very large spaces because they fly long distances …

There is another component to that, or another reason to study non-standard animals, and this is the comparative approach. Contrast and compare, so that what we find [in bats] is that a lot of the things are very similar [to rats]; we find place cells, grid cells, head-direction cells. But there are certain things that are very different, so, for example, the theta oscillations are very prominent in the [rat] hippocampal system, and we don't see that in the bat. This means that those theories of grid cells that rely in an obligatory manner on a perfect oscillation, this argues against them. This comparative approach is very powerful and used to be prevalent in neuroscience, and unfortunately it disappeared. But I agree with you, I feel it has a little bit of a comeback recently.

Gilles Laurent: I think that Nachum and Anthony have summarized things really well. Forty, thirty years ago people used what they called model systems, and it was a common thing that you'd go to Neuroscience [Society for Neuroscience meeting] and people would work on Tritonia and crabs and bats and barn owls and so on, and little by little all this has disappeared, and as you guys were saying now, you're trying to force all these things back onto one species and for sometimes good reasons, but not always. I think all of us agree on the danger of this trend, which means that, practically, a population of scientists able to tackle interesting problems on a variety of species, to take into account the diversity of the animal world, of evolution, of comparisons and their value it's going to disappear as a culture, and that's really dangerous.

MK: I'm curious, I'm sure that all of you must have challenges, and you must be envious of people who are using well-standardized and well-understood models which have a lot of tools, and especially now in this age of tool making, you must feel like, "OK, I wish I could do this in my model." How do

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you think about this? Do you think that, for your particular models, or just in general, there's going to be an age of tools, or are you adjusting your questions to what you can ask?

NU: I think there will be an age of tools for sure. I think that, often, people driven to these exotic or unusual systems are inherently tool builders to some extent. When you pick one of these unusual organisms, you're picking it because it's a question-driven enterprise and that leads very naturally to saying, "What is the tool that I need to answer this question, and can I develop it here?" And certainly in our work, we are very inspired by our colleagues in genetic systems and we'd like to try to develop versions of those tools that we can apply even for our very localized problems, so they're not of ubiquitous use but they solve our problems. So, I think that will come as it's needed; there's no fundamental impediments. It's a question of time, effort, and funding, but it can certainly be done.

GL: I was going to say that the three of us don't work in the purely grant-driven American system. I think that the funding issue is a fundamental one now. Those, the few of us who work on unusual systems, tend to work in systems that allow the funding and provide the funding to do that, and it's becoming less and less possible. And when you talk to your colleagues, they say, "Well the funding situation doesn't allow it." The problem in the funding situation is us; it's driven by us, and this has reached a point that to me is quite dramatic. We don't even have the confidence in pushing for that diversity.

NU: On one hand I agree, and on the other hand I also have colleagues in the U.S. who study unusual animals. And those of them who ask good questions, it's clear that they can get funding. I don't think it's as tough … It's tough maybe, but it's possible, for sure. But, to address your question about tools, so yeah, when you study an unusual animal, you have to develop tools almost by definition because nobody will do it for you. Sometimes this is an unusual tool—like in our case for the bats, we want to study them freely flying, so we have to develop methods to record wirelessly from single neurons in flight, etc. So, these are the kinds of tools we have to develop that don't exist elsewhere in the world. But often times when we're talking about tools in neuroscience nowadays, it's molecular tools, and we need genomes and all these things. I think … with the advent of genome editing, it might become a bit less of an issue.

AL: I started working on an unusual non-genetic system in an era right when genetic systems were really exploding, and it was clear that it was tactically not the wisest decision in terms of certain aspects. And the thing that always sort of struck me is that the genetic access to these sorts of weirdo systems is only going to get easier over time, whereas the computations the animals do and the behaviors they do are fixed. So it's not that mice and flies are going to evolve new behaviors suddenly that you're going to be able to study in them. So there is a real reason and a utility in saying, "OK, this organism is solving this computation, and this is a good place to study it, and we're going to work on it at the level of tools we have now, and gradually more tools will become available and we'll gain deeper levels of understanding it." As opposed to forcing that problem into a genetic system where it's very hard to study and you make progress very slowly, even with the elegance of the tools there.

GL: You could also turn this around by saying that many of the tools that we use now actually come from the study of unusual systems like bioluminescence in jellyfish—you get GFP and the channelrhodopsins and CRISPR/Cas9. That doesn't come from directed research at the beginning; it's really curiosity driven. If we lose this, we lose a lot of these advantages.

AL: Yeah, I think on that same token, it is interesting to notice that a lot of the problems being studied at a deep mechanistic level in our genetic systems are problems that were described at the level of algorithms and principles in other systems—things that we used to study in Hoverflies and locusts and all these sort of exotic creatures that are being tapped. They provided essentially the foundation on which these more mechanistic studies can be built in other systems. And that really arises from the ubiquity of evolution and the fact that these principles do transcend the system, and almost by definition you should be able to look at these things in different places, and the breadth and depth can combine effectively.

I want to add yet another component, another advantage of maintaining this diversity and studying non-standard species: the natural behaviors. I mean, you cannot study a laboratory rat or laboratory mouse in the wild. You can study a wild rat or wild mice, which in some of their behaviors are quite different than the ones in the laboratory. Whereas these non-standard organisms, they are literally wild animals—literally, we capture them from the wild. You can study them also outdoors, so we've been studying the bats, GPS tracking them outdoors, looking at their navigation, etc. I think this really opens your thinking to asking different questions. You see a behavior outdoors and start asking, "How is that implemented?" And you can eventually bring it to a laboratory setting and do a controlled experiment, but even being able to study the animal out in the wild is something that you typically cannot do. Or even if you can, it's not done by most people on standard laboratory animals.