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Interview

Interview with Jon Kaas

■ Jon Kaas received a Ph.D. in Psychology with Irving Diamond at Duke University and completed a postdoctoral fellowship with Clinton Woolsey in neurophysiology at the University of Wisconsin, where he also collaborated with Ray Guillery. After 4 years as an Assistant Professor in Neurophysiology at Wisconsin, he moved to the Department of Psychology at Vanderbilt University where he is currently Centennial Professor. Awards include the Earl Sutherland Prize, Javits Neuroscience Investigator Award, Krieg Cortical Discoverer Award, and American Psychological Association Distinguished Scientific Contribution Award. ■

JOCN: Over the years, you have been one the founding participants of studying cortical mechanisms from both an anatomical and physiologic point of view. You have extensively studied the sensory and motor cortical maps of dozens of different species. Why have you taken the comparative approach? What does it teach us?

JK: My main reason for using a comparative approach is that I'm interested in the evolution of complex brains, such as the human brain from the much simpler brains of early mammals. Because the fossil record tells us so little about brain evolution, most of our conclusions must come from studies of extant mammals. The consistencies and variations across species provide valuable clues about brain evolution. For example, the evidence that all studied primates have the middle temporal visual area, MT, argues that the area emerged with or before the first primates. But, I've also become interested in the issue of scaling. As a graduate student, I had the good fortune to have a class with the great comparative physiologist, Knut Schmidt-Nielsen, and he wrote a book on why animal size is so important. The consequences of a person and a mouse, for example, falling off a five-story building would be quite different. But Schmidt-Nielson had little to say about brains and how brains must be redesigned when they get bigger or smaller. Currently, we are comparing the organizations of some of the biggest and smallest of mammalian brains. Small brains, of course, have to get along with few neurons, whereas the conduction times of the longer connections of large brains become a problem. We think this means that small brains function best with fewer subdivisions, whereas large brains need to be more modular. Finally, unusual specializations in brains may reveal general principles. The mouse barrel field at first seemed to be a unique feature of the somatosensory cortex for rodents, but now it seems to reflect the general tendency for groups of neurons with different sources of activation to segregate within the brain.

JOCN: Do you mean cells that don't fire alike wind up as barrel fields?

JK: I mean that the mechanisms that lead to the development of the barrel field are general. The barrel field is an isomorph of the whisker pad of the face. Such isomorphs are seen in the somatosensory cortex for the digits of the hand in monkeys, the rays of the nose in star-nosed moles, and in other mammals. They correspond to discontinuities in the receptor surface and thus to disjunctions in neural activity patterns that are relayed from the periphery. Extra whiskers and extra rays on the nose add extra parts to the isomorphs at several levels of processing. These findings indicate that a direct genetic code for the structure of the isomorphs is unlikely. The same developmental factors that lead to isomorphs are likely to be important in forming columns, layers, and modules throughout brains.

JOCN: How do you envision one species becoming another from the perspective of brain change? There seems to be a view out there that one simple genetic change throws up new sets of cortical columns to handle possible new functions. Do you subscribe to that or do you think mutations occur in existing circuits?

JK: The evolution of a new species with a different brain of course involves genetic change, but most genetic changes would effect the brain in only very indirect ways. Small alterations in the timing of developmental events and exposure to the environment could have a major impact in the subsequent design of the brain. For

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example, cats have the light "on" and the light "off" classes of lateral geniculate cells mixed in the same layers, whereas they are segregated in separate layers in mink and ferrets. This could be a consequence of mink and ferrets being born and exposed to light at an earlier developmental stage rather than having a gene for new geniculate layers. Genes that have very specific and localized effects on brain circuits may exist, but the great responsiveness of the developing brain to altered activity patterns suggest that it is common in evolution for genes to have widespread, indirect effects on brain circuits. For example, in Siamese cats, a gene for reduced eye and coat pigment also leads to misdirected retinal projections, which are followed by a series of alterations and adjustments in cortical representations of the retina.

JOCN: That assertion raises so many fascinating issues. Let's start with the classic problem of the development of the visual system. The dominant idea amongst evolutionary biologists is that during the course of evolution events occurred that allowed organisms to have a visual system that had an efficiency of, say, 5%. Gradually, mutations occurred that raised the level of efficiency to 10, then 20, then 50%, up until the exquisite visual system we now enjoy. Are you suggesting each one of the genetic events that fed that process occurred to genes that were primarily having effects on other somatic events? How do you know that, and why couldn't it be the other way around?

JK: I have no problem with the proposal that there are genes that have a very specific effect on one part of the visual system or another. Yet, genes often have many effects, some good and some bad, and the ways the effects are mediated are often poorly understood, and they may be very indirect. I gave an example of a gene in Siamese cats that "improved" coat color and at the same time impaired vision. There might be another gene that improves the optical quality of the lens of the eye but causes some problem in the skin. But, let's consider the issue of improving a visual system by 5% steps over many generations. A mutation that improved the image quality of the eye by 5% would still relate to a system designed for poorer image. How would we upgrade the rest of the system? You couldn't do it mutation by mutation so that each level would be subsequently upgraded by 5% because each mutation must immediately improve the performance of the complete system and visual behavior for it to be retained by selection pressure. Thus, it seems likely that the many parts of a complex system are highly interactive and that changes at one level cascade through the system. We already have considerable evidence for this from developmental studies. What I'm suggesting is that an improvement in the quality of the optical image would alter processing in the retina. This in turn would alter the development of all subsequent stations in the visual system in ways that would create smaller receptive fields, more precise representations, more detailed vision, and more adaptive visual behavior because the system is already designed to respond to image quality. More broadly, each processing station in all systems is developmentally responsive to the modes, quality, and quantity of activating inputs.

JOCN: Do you have an idea about how that might work?

JK: The most likely way for neurons to influence the development of other neurons and alter the design of anatomical circuits is through the activity patterns that emerge early and become increasingly complex. Neurons are also good at transporting molecules they make or acquire from the extracellular environment, and this is another but less likely source of information. In addition the products of activity-dependent genes could be transported from neuron to neuron, thus integrating the two types of communication.

JOCN: Before moving on to the issue of plasticity, could you reflect on the issue of cerebral specialization? Specifically, neuropsychological data clearly suggest there are specific cortical regions dedicated to particular functions. Thus, the fusiform gyrus seems active during facial recognition tasks. Broca's area is involved in language. What is it that makes these areas do different kinds of processing? Is the same cortical computational unit, the cortical column, computing differently or are there real structural differences in the areas that drives the different kind of processing that must exist at these sites?

JK: The cortex has a very flexible organization that can be modified for specific functions through use-dependent competition for synaptic space. The outcomes of competition depend on the types, density, timing, and activity of inputs to a field. Of course, outputs are modified in the same way. I'm not sure what factors are important in guiding inputs to different cortical regions. Because certain patterns are retained across individuals and species, some chemical prespecification must be involved, but many or most fields may emerge out of the dynamics of the competition once a general framework has been achieved. Most but probably not all of the structural differences between areas and cortical modules develop as general-purpose circuits that are modified by activity-dependent competition.

In small-brained mammals, much of the cortex is dominated by inputs reflecting simple transformations of patterns relayed from the receptor sheets, and each area is broadly involved in sensory functions. In more complex brains, narrowly specialized fields may form in regions of the cortex dominated by highly processed inputs. Nevertheless, abilities such as facial recognition undoubtedly involve much of a processing system, although performance may critically depend on some subdivisions.

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JOCN: Looking through the microscope, can you tell the difference between one region of the human association cortex and another? Can you tell the difference between the fusiform cortex in a human as opposed to a chimpanzee?

JK: I'm not sure. We have illustrated distinctions between subdivisions of the visual cortex in the temporal lobe of monkeys, but anyone familiar with the history of architectonic studies should realize the need for great caution. Investigators have differed greatly in where they placed architectonic boundaries over much of the cortex, leading one to wonder what these proposed boundaries mean, and the use of architectonic features to identify homologous areas across the mammalian taxa clearly can be a dangerous enterprise. Brodmann, for example, misidentified the less differentiated medial part of area 17 of squirrels as area 18, and this error still persists in current portrayals of a medial "area 18" in the visual cortex of rats. Yet, the study of cortical architecture has been very useful. Such studies should be even more informative in the future as we use electrophysiological recordings and functional imaging to evaluate the meanings of architectonic patterns. Early investigators could only evaluate cyto- and myelo-architectonic features of the cortex, whereas we now have a range of new chemical and immunochemical procedures that can be made with these methods, but it is best to start out with the better understood sensory and motor areas. With Todd Preuss, we are now comparing the architecture of such areas in humans, chimpanzees, and monkeys.

JOCN: Within the field of cognitive neuroscience we are always hearing how modular this or that function seems to be. We hear of the idea of domain specificity, the idea that specific adaptations have been built up through natural selection to carry out specific functions. We assume there are distinct circuits in the brain that enable these specific functions, with humans having more of these specific circuits than chimps and chimps more than monkeys. And yet you tell us, at this point it is hard to see differences and also a dangerous game to play. What could be more fundamental than to search for these differences? Put differently, why isn't more attention paid to comparative anatomy, including the human?

JK: Part of the reason researchers devote so little attention to comparative anatomy is that the approach is difficult and time consuming. In addition, brain circuits and modules may be very different in function across species and yet look very similar. Thus, after much research effort, you might have little to say that seems important. Success, I think, will be greater when patterns of connections, neuron response properties, architectonics, and behavior are all studied at once. Of course this is difficult in chimpanzees and humans. Finally, it is easier to demonstrate and talk about similarities than differences. It is now obvious, for example, that all primates have the extrastriate visual area, MT. Yet, we also know that macaque monkeys have a much larger region of the posterior parietal cortex that is devoted to vision than the prosimian galagos do; unfortunately, it is not yet clear what macaques have in terms of modules and cortical areas in the posterior parietal cortex that galagos do not. However, some differences in the cortex have been found. There is evidence that the second somatosensory area, S2, of monkeys depends on inputs from the primary somatosensory cortex for activation, whereas S2 in prosimians and most mammals is activated in parallel from the ventroposterior nucleus in the thalamus. Thus, S2 in anthropoid primates is more devoted to the further processing of cortically processed information. I find this basic difference in circuits that occurs so early in the cortical hierarchy to be intriguing.

JOCN: Your early work with Michael Merzenich and others set the stage for what has been a huge explosion of interest in the concept of cortical plasticity. To hear some tell the story, the cortex is almost infinitely modifiable by experience, and yet others say it can be modified only along preexisting lines that are latently present. What is your view and indeed, how do you think about the problem of brain plasticity?

JK: We are still trying to find out how much the functional circuitry of the mature brain can be modified. Mike and I started by trying to see if the systematic representation of the body surface in the primary somatosensory cortex of monkeys can be changed. There was evidence for alterations in subcortical representations from the work of Pat Wall and others, but subcortical maps are small, and this makes them difficult to investigate. Thus, we started with the large, two-dimensional map of the hand in S-1 of monkeys and found that if you deactivate about half of this map by sectioning the median nerve to the hand, the deprived cortex becomes responsive to the remaining afferents from the hand over several weeks of recovery. The results were convincing, and the long recovery time indicated that the reactivation involved more than a simple rebalancing of a dynamic network. We now know that reorganizations of sensory representations can be mediated by changes in how systems are activated during training and experience, and factors such as attention and release of neuromodulators such as acetylcholine can be important. Over months to years of recovery, cortical reactivations can be massive, and they sometimes involve the growth of new connections at both cortical and subcortical levels. Although some of these massive reorganizations may lead to unfortunate outcomes, such as phantom limb pain, I feel that processing systems, especially at cortical levels, are designed to be plastic. The extent of most of the demonstrated changes are compat-

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ible with the view that connections are locally strengthened and weakened within a preexisting framework that allows structures to be multipotential. Thus, we commonly modify processing circuits with experience and practice so that they better mediate the relevant behaviors that vary from individual to individual and from time to time. A fixed brain would not be nearly as useful.

JOCN: No one seriously argues against plasticity, if by that you mean the capacity to adapt to changing environmental conditions and through learning. the issue centers on the mechanisms of this change. Correct? Are you saying most studies to date are consistent with the view that the changes are occurring within a preexisting neural framework? It is not that new circuits are self-organizing is it?

JK: Of course we want to know about mechanisms of plasticity, but we also want to know what parts of the brain can change, how much they can change, how fast they change, and what factors influence the outcome. Is attention, practice, or even neural activity important? Because we learn, no one doubts the existence of plasticity, but plasticity could be restricted to specialized parts of the brain as organs for learning. My guess is that all parts of the brain are mutable but not equally so or in identical ways. Differences in response to stimulation or deprivation will depend in part on the anatomical framework that has already been constructed. For example, cortical areas have widespread lateral connections than can be used for change, whereas the thalamic nuclei do not. Differences will also depend on the intrinsic properties of neurons, especially in how they respond to coactivation. The functions of local circuits can be altered in a number of ways, including the potentiation or weakening of existing synapses, the formation or loss of synapses, the growth of axons and dendrites, the expression of more or less of many different membrane receptors, neural transmitters, or neuromodulators, and so on. The plastic changes in any structure are likely to involve a number of mechanisms, some additive, some permissive, and some fundamental. Most, but not all, of the reorganizations that have been described could be accomplished through local adjustments in preexisting circuits, but this does not rule out local growth and rearrangements within axon arbors and dendritic trees. The reorganization of the somatosensory cortex after section of the median nerve appears to involve the dynamic rebalancing of circuits, the growth of new connections, the modulation of activity by acetylcholine, the potentiation of receptors via the actions of NMDA receptors, and the down regulation of GABA. You can see that determining the precise roles of all the factors involved will be difficult, and they probably will differ according to the type of injury or training, the system and the level in the system. Finally, although it is popular to describe brain circuits as self-organizing, this does not explain very much. We need to know why certain outcomes occur, the factors important in these outcomes, and the other possible outcomes. Treatments and procedures for promoting recoveries from brain damage or effective learning have largely been empirically derived, but we may be able to do better with a sound theoretical approach based on maximizing beneficial changes in the brain.

JOCN: All of those complex cellular events are in the service of something important going on at another level. I assume you would agree that the purpose of the brain is to make decisions. It is a vast network committed to that function. Does that fact commit neuroscience to keep focused at the physiologic level for an explanation on how the brain works. Determining the minute biochemical and molecular mechanisms of synaptic activity is surely interesting, but it will not provide an answer to how the brain works to make decisions. Right?

JK: To some extent, I agree with you. But how does one address the question of how the brain makes decisions? For me, the first step would be to subdivide and restrict the question so that it's not so overwhelming. Because brains vary across individuals, life span, and species, and we don't have time to study all brains, some choices are needed. Some might feel that we can make more progress by studying simple brains, developing brains, or impaired brains. One can also take the point of view that systems in brains make decisions, and these decisions are based on the computations of subsystems and modules within systems. I would start with an effort to determine the parts of the system, what the parts do, and how they interact. Given how little we know about the organization of the neocortex, determining even the parts that belong to a system is a major task. Determining what the parts do and how they interact is harder. Fortunately, we now have the technology to simultaneously sample the responses of hundreds of single neurons within structures and across structures, and this opens the door for major new advances. I am impressed with how much is known about the many biochemical and molecular events that contribute to the functional complexities of individual neurons, and how little this information is used by those making computational models of neural systems. This suggests that the great emphasis on cellular and molecular mechanisms is misplaced if the goal is to see how brains work. Nevertheless, it is undoubtedly useful to make progress at several levels of analysis at once, with the expectation that understandings at each level will ultimately contribute to understandings at other levels. It's hard to predict what advances will be important across levels. Much of the research at any level is descriptive, so the major conclusion at the end of many reports is that we need to know more of the same. The hope is that the descriptions will accumulate and sometimes lead to new insights.

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JOCN: Well, as they say, the wonderful thing about a new idea is that we don't know about it yet. But sometimes a field can be too generous with its colleagues. Again, molecular neurobiology is a fine business, and they have the technologies to produce vast amounts of data. However, if they are barking up a different tree from those interested in how the brain actually enables mind, shouldn't we say so? After all, science is limited by resources, and if we truly want to study how the brain works, we may need to argue for a reallocation of resources.

JK: I would like to see more funds directed toward systems and cognitive neuroscience, and we should work toward that goal by convincing our colleagues that such research can be extremely valuable and informative. The new information that is coming out of functional imaging studies of the human brain is impressive and will help. In addition, these studies draw attention to questions that are best answered with other approaches. I do sense a growing appreciation of cognitive neuroscience, even by molecular neuroscientists. However, all of our neuroscience funds shouldn't be directed toward discovering how the brain enables the mind or makes decisions. The brain controls body weight, for example, and this control is largely beyond the mind. Some research should be directed toward the practical goals of repairing damaged brains and making sure they develop optimally, but we don't necessarily need to know how they work to do this. And I find many of the issues of neuroethology to be extremely interesting and deserving of support, especially in a time of a planned space station, and the question of the minds of remotely related species is a tricky one. Finally, I'm not sure if many of us thought Pinker's book, *How the Mind Works,* would tell us how, but if it did, would we close up shop?

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