

## Interview with Apostolos P. Georgopoulos

■ APG studied Medicine and Physiology at the University of Athens in Greece where he obtained his M.D. and Ph.D. degrees. He was trained in neurophysiology by Vernon B. Mountcastle at Johns Hopkins and, after a brief return to Athens, he came back to Johns Hopkins. He ascended the faculty ranks and promoted to Professor of Neuroscience in 1986.

He was a member of the Philip Bard Laboratories of Neurophysiology at the Department of Neuroscience until 1991 when he moved to Minnesota as the American Legion Brain Sciences Chair at the Minneapolis Veterans Affairs Medical Center and the University of Minnesota. ■

**JOCN:** Over the years you have chosen to examine the motor system and how it is organized in your effort to elucidate mechanisms of cognition. Why study the motor system? Can you tell us a little about what led you to this approach?

**APG:** There was nothing special about the motor system in itself. Rather, my use of it in cognitive studies was a combination of my early interest in higher brain functions, my fascination with Vernon B. Mountcastle's work in the somatosensory system, and my imprinting-like exposure to the study of parietal mechanisms of reaching in space. Let me amplify on these aspects.

I studied medicine (in Athens, Greece) with the goal of becoming a psychiatrist, an initial hint at my interest in the brain, psychology, and behavior. During the last 4 years of my 6-year medical school studies, I worked as a teaching research assistant in the Physiology Department to acquire a firm background in physiology. Although my work was focused on metabolism, it sparked my long-lasting interest in investigating function, that is, in understanding "how things work." It was during those years of the mid-to-late 1960s that I became fascinated with Vernon's work on the somatosensory system, work that covered the whole waterfront from primary afferents to cortical organization to behavior. His strongly quantitative approach to studying the system at those different levels gave me the conceptual tool by which to study, in years to come, higher brain function. By the end of medical school in 1968 I had given up on becoming a psychiatrist. I had decided to pursue research full time and made a huge change of subject, from metabo-

lism to neurophysiology. I wrote to Vernon in 1969 to explore the possibility of doing a fellowship with him and, indeed, he accepted me—quite incredible to me. I completed my 2-year army service, and in 1972 I came to Johns Hopkins as a postdoctoral fellow in Vernon's lab. What a time! The recordings in areas 5 and 7 were in full swing then, and the big story was the unexpected finding of reaching cells in these areas that, based on anatomical work, were expected to be on the somatosensory side. This exposure marked my long-term interest in the motor system and specifically in the brain mechanisms of movement in space. After a massive work on primary pain afferents [Georgopoulos, A. P. (1976). Functional properties of primary afferent units probably related to pain mechanisms in primate glabrous skin. *Journal of Neurophysiology* 39, 71-83] and a short return to Greece, I embarked on studying the motor system, from 1976 to this moment, in various ways, from simply motor psychophysics to its use as a tool for studying cognitive function. So, you see, my encounter with the motor system was rather accidental, but it evolved to be a very rich, challenging experience, the more so the more I used it as a tool for studying the brain mechanisms of cognitive function. Nevertheless, I could have happily studied cognitive functions associated with sensory or limbic systems instead, and, indeed, I may!

**JOCN:** Fascinating and yet not all that uncommon. When I went to work with Roger Sperry, it was to study nerve regeneration. I became converted to other topics because of the particular activities going on in his lab at

the time. Speaking of Sperry, he used to say, "Perception is the preparation for response." Do you see getting ready to respond a key to understanding perception as well?

**APG:** Not necessarily. How about "getting ready not to respond?" I am sure that several aspects of perception (e.g., sharpness, awareness, vividness, etc., and even the probability of detecting a stimulus) could very well be changed depending on the "motor set," but I see that more as a motor effect on perception than as a tool to understanding perception itself.

**JOCN:** Okay, the motor system. How would you characterize how the systems neuroscientist views motor function? And how has that view changed over the last three decades?

**APG:** Ah, the motor system! For better or worse, there is no coherent view of motor function by systems neuroscientists. Instead, there exists a healthy diversity. You still have the muscle diehards who believe that the CNS is a glorified muscle (or muscle spindle), obvious or hidden, and who, therefore, contend that all neural activity in motor structures, from the cerebellum to cortex, has somehow to be explained, by default, with reference to that one, real or virtual, muscle. Of course, it doesn't make any sense. CNS motor areas are embedded within brain networks that relate to the task conditions leading to the initiation of movement, and natural movements rarely, if ever, involve just one muscle. Thus neuronal activity in these areas potentially could relate to a whole range of variables reflecting those factors, and several experiments during the past three decades have addressed this problem and identified subsets of cells involved in different aspects of the initiation and control of movement.

Now, I believe that a major change in our outlook of the motor function over the past three decades has been in accepting, using, and understanding the complexity of the issues involved and in actively investigating the neural mechanisms of complex motor functions. For example, people now tend to think of the reaching movement as a unit, the parameters of which (e.g., direction and amplitude) could be specified and controlled by the CNS, in contrast to earlier views that laid all emphasis on single joint movements as the unit of organization. The extent of this conceptual shift and its practical consequences can be appreciated by the fact that many current studies routinely use reaching movements in all kinds of experiments instead of single joint movements; also, "directional tuning" has almost become jargon. In addition, the neural mechanisms of more general aspects of motor function are being investigated more frequently, regarding, for example, such exotic themes as frames of reference, task-specific conditions, and cognitive operations, including motor learning and memory, and spatial transformations. Finally, the advent of func-

tional brain imaging and transcranial magnetic stimulation have opened new avenues for studying these problems, and, as these techniques become more refined and more powerful, I expect a real blooming of the field. So, a lot of things have changed, for the better.

**JOCN:** A perhaps disproportionate amount of research in systems neuroscience has been conducted in sensory systems. Can you comment on what advantages the motor systems neuroscientist has over the sensory systems neuroscientist? Is the motor community, with its greater understanding of the "output" of the nervous system, better situated to answer the questions of how information is represented and how the information in neural representations is actually put to use?

**APG:** After all, there are more sensory systems than the motor system, so the effort on the former may seem to, but actually may not, be disproportionate. I think the edge is still with the sensory systems, for several reasons. First, a traditional advantage has been that the input to the nervous system can be precisely controlled. Second, the neural representations at intermediate levels of processing can be analyzed precisely, as the beautiful work of Vernon Mountcastle and his colleagues in the somatosensory system has exemplified over the years, tracing the series of events from primary skin afferents to the thalamus to the somatosensory cortex, while characterizing the behavior in parallel and comparing the psychophysical capacities with the neural representations. Now, another advantage of the sensory systems research, in my opinion, lies in the fact that, almost by definition, the ultimate goal of that research is to elucidate the CNS mechanisms of perception, a practically open-ended goal that strikes at the root of most fascinating questions and problems. Compared to that, CNS research in motor systems is almost impoverished: There is a disproportionate concern with muscle control. For example, the CNS events that lead to the initiation of a motor output are so transparent that they are usually either ignored or taken for granted, and their study is commonly regarded as lying outside the legitimate realm of motor physiology. So, in sensory physiology the horizon is broad, and is allowed to be broad, but in motor physiology the horizon is also broad but is only allowed to be very narrow. No wonder then that sensory physiologists are encroaching more and more into what I would consider to be a prime motor field, namely, decision making and movement initiation.

You ask whether "the motor community, with its greater understanding of the 'output' of the nervous system, [is] better situated to answer the questions of how information is represented and how the information in neural representations is actually put to use." But you assume all of this, and it is hardly true. The hard-core motor community does not have any better understanding of the output of the brain, and I believe that,

with a few exceptions, this community may not be really interested in the question of how information is represented and how the information in neural representations is actually put to use. Interestingly, these questions have been taken up and studied thoroughly at the circuit level, as exemplified by the impressive work of Sten Grillner and his colleagues on the lamprey spinal cord. Unfortunately, CNS motor physiology in the monkey is still dominated by all kinds of questions revolving around the muscle, and although these questions are very important, they leave a lot to be desired when the part is taken for the whole—that is, when the broad question about central representations of the CNS output are taken to be “nothing but” questions about muscle control. There is more work now being done on visuo-motor coordination, but this is concerned more with sensorimotor interactions than with the neural mechanisms of representation of motor information in the brain and how that information is put to use. I am sorry if I sound pessimistic, but the sensory field has proved to be much more open minded than the motor field.

**JOCN:** Let's look at where motor control theory has an impact on cognitive issues. Many people think that to explain motor learning we need to invoke the formation of internal models.

**APG:** I think a good test of that idea would be to see what happens in the brain during motor learning. This can provide the crucial information needed to test this hypothesis. For example, the recent recording experiments of Emilio Bizzi and his colleagues in behaving monkeys during learning of a force field are in this direction. But the crucial question is how you visualize an internal model. Of course, there are many different classes of models, and there are probably different ways to visualize them. I have been concerned with a specific class, namely, the internal representation of spatial-motor models, such as motor trajectories.

**JOCN:** Well, let me be specific. When golfers finally master a golf shot, they have stored in their brain the dynamics of the arm, those of the club, plus the trajectories that are necessary to implement the “perfect shot.” However, a skill like golf is based on a number of shots. Does each shot have an internal model?

**APG:** It may or may not, depending on the specific task and environmental circumstances. Again, neural evidence could prove crucial in deciding this issue. However, I doubt that each individual shot will have a separate internal model. I would rather envision the learning (or practicing) process as a shot-by-shot updating of a general variance-covariance matrix (or a set of such matrices) of the relevant variables. Now, the next shot could be the result of a selection process (try a shot out of several possible ones), an instruction process (explicitly plan the

shot), or both. Whatever this process, the “practice” matrix will be updated accordingly. Actually, we discussed some of these issues back in 1981 when we tried to explain how monkeys learned to move a handle in 2-D space [Georgopoulos, A. P., Kalaska, J. E., & Massey, J. T. (1981). Spatial trajectories and reaction times of aimed movements: Effects of practice, uncertainty and change in target location. *Journal of Neurophysiology* 46, 725–743].

Let me amplify a bit on the visualization of an internal model of a motor trajectory. As I mentioned in my previous answer, part of my work has been on the issue of representation of spatial hand trajectories as they evolve in time, a line of research that Andy Schwartz has pursued nicely more recently [Schwartz, A. B. (1994). Direct cortical representation of drawing. *Science*, 265, 540–542]. The way we tried to solve this problem was to record single-cell activity during the trajectory and then recover (i.e., reconstruct) the trajectory from the neural events. The first and crucial aspect of this endeavor was to relate the neural activity to the trajectory itself (instead of to the muscles, for example). This revealed immediately that single-cell activity is broadly tuned to the direction of movement, a finding that pushed the question to the level of the neuronal ensemble rather than that of an individual cell. The next step involved the extraction from the population of a unique signal that could get us back to the trajectory. Ken Johnson suggested that we try a weighted vector sum of directional contributions of single cells, and it worked: the direction of this signal (the “population vector”) was a good predictor of the direction of movement. Three aspects of this analysis are remarkable, namely, its simplicity, its robustness, and its spatial outcome. With respect to simplicity, it is noteworthy that the ongoing calculation of the population vector is a simple procedure, for it (1) assumes the directional selectivity of single cells, which is apparent, (2) involves weighting of vectorial contributions by single cells on the basis of the change in cell activity, which is reasonable, and (3) relies on the vectorial summation of these contributions, which is practically the simplest procedure to obtain a unique outcome. With respect to robustness, the population vector is a robust measure, for it can still convey a good directional signal even with relatively few (~100) cells and also when calculated for small (i.e., 10 to 20 msec) time bins. Finally, it is noteworthy that the population vector is a spatial measure, isomorphic in direction with the direction of arm movement in space: This population analysis transforms aggregates of purely temporal spike trains into a spatio-temporal population vector. It is this property that makes the population vector especially useful, for, through it, the directional tendency of the neuronal ensemble can be monitored in the absence of overt behavior and therefore an insight can be gained into the brain correlates of spatial cognitive processes as they evolve in time. Indeed, by calculating the population

vector as a time-varying signal, we were able to visualize not only movement trajectories but also cognitive processes such as mental rotation [Georgopoulos, A. P., Lurito, J. T., Petrides, M., Schwartz, A. B., & Massey, J. T. (1989). Mental rotation of the neuronal population vector. *Science* 243, 234–236] and context-recall memory scanning [Pellizzer, G., Sargent, P., & Georgopoulos, A. P. (1995). Motor cortical activity in a context-recall task. *Science*, 269, 702–705]. It very possible that such a population approach can provide the tools for visualizing, and monitoring changes in internal models during motor learning and practice.

**JOCN:** So, aspects of the various shots must be in common. Does this mean some sharing of elements of the internal models, or are all the internal models that we have learned from birth sitting in the cortex like monads in perfect isolation?

**APG:** I believe there must be sharing, and, again, neurophysiological evidence may prove crucial. We were faced head-on with this problem in our recent work of modeling motor trajectories using a biologically inspired neural network model [Lukashin, A. V. & Georgopoulos, A. P. (1994). A neural network for coding of trajectories by time series of neuronal population vectors. *Neural Computation*, 6, 19–28]. We then proposed a scheme of partial overlap of neural networks involved in performance of motor trajectories [Lukashin, A. V., Wilcox, G. L., & Georgopoulos, A. P. (1994). Overlapping neural networks for multiple motor engrams. *Proceedings of the National Academy of Sciences U.S.A.* 91, 8651–8654], and I speculated on the selectionist ideas in my *TINS* article [Georgopoulos, A. P. (1995). Current issues in directional motor control. *Trends in Neuroscience*, 18, 506–510]. Still, I think the exciting idea is that the internal model(s) hypothesis can be tested by using brain-related information, stemming either from neurophysiological or functional neuroimaging (and related) experiments.

**JOCN:** The execution of what we have learned (i.e., the internal model) needs to be adjusted to the variable circumstances of life. How is this adjustment implemented?

**APG:** I don't know. Apparently, it has to be a trial-and-error process, but this is too general a formulation to do justice to the problem.

**JOCN:** Generalization of what we have learned is also an unsolved problem. How do you think about that problem?

**APG:** I'm afraid I don't have much to suggest for this problem either.

**JOCN:** There are hints that the motor system may pro-

duce movements by combining smaller units. What do you think?

**APG:** I believe that this is probably the case at the initial stages of learning a complex motor skill. However, I also believe that when that skill is well learned, it is produced (and represented in the brain) as a new, whole unit rather than as an aggregate of simpler units. Take the reaching movement as an example. In some sense, you can think of it as a rather complex, multijoint motor skill acquired during infancy by stringing together simple, single-joint movements. [I amplified on this idea in my article, Georgopoulos, A. P. (1986). On reaching, *Annual Review of Neuroscience*, 9, 147–170]. In my opinion, when reaching is mastered, it is produced as a unit and represented in the brain as such. This idea, of course, lies at the bottom of my experimental approach in the study of the brain mechanisms of reaching during the past 18 years. The paper by Mountcastle and his colleagues in 1975 [Mountcastle, V. B., Lynch, J. C., Georgopoulos, A. P., Sakata, H., & Acuna, C. (1986). Posterior parietal association cortex of the monkey: Command functions for operations within extrapersonal space. *Journal of Neurophysiology* 38, 871–908], put forth the hypothesis, for the first time in cortical physiology, that reaching may be specified and controlled as a single unit. In a way, you can see my subsequent work as an elaboration of these cortical mechanisms of “wholistic” reaching in the space and, lately, the time, domains. By now, there is evidence from various labs that movements of the whole limb may indeed be represented as units and not as strings of simpler components. [I discussed these recent results in my article: Georgopoulos, A. P. (1994). New concepts in generation of movement. *Neuron*, 13, 257–268.]

**JOCN:** Finally, and looking a little into the future, the study of the plasticity of the motor system seems to be important for the development of the field. Do you think there is a good potential for the technique of chronic multiple cell recording in behaving animals to help elucidate how neurons change with experience? Indeed, can genetic and molecular biology help to investigate these problems, that is, to study the development of cells that change when an animal learns a new task?

**APG:** All of the above. Obviously chronic multiple cell recording is an essential tool for monitoring changes in cell activity longitudinally during learning of a new task. It is important that several areas be monitored simultaneously because there is evidence from gross electrode recordings that different areas (e.g., motor cortex, premotor cortex, cerebellum) may be involved at various stages of motor learning [see, for example, Gamba, H. & Sasaki, K. (1984). Studies on cortical field potentials recorded during learning processes of visually initiated hand movements in monkeys. *Experimental Brain Research* 55, 26–32]. The challenge will be to analyze the

changes in neuronal activity so that they can be interpreted within the context of motor learning.

Cellular/molecular events should be also a fascinating part of the story. I believe that approaches and techniques employed in other situations [e.g., sleep/wakefulness, see Cirelli, C., Pompeiano, M., & Tononi, G. (1996). Neuronal gene expression in the waking state: A role for the locus coeruleus. *Science*, 274, 1211-1215], can be very useful in tracing molecular biological events in motor learning. The challenge again will be to distinguish general-purpose changes from changes specific to the particular learning case. Now, we know that the latter involves selective, time-dependent engagement of various areas, and, therefore, it would be crucial to identify and monitor changes in, for example, gene expression, in these different areas. I think such studies are feasible and very exciting.

Finally, you mention genetics. I believe that this is another very fertile ground for research in motor learning, as it has proved to be for other problems [e.g., the biological clock, see Takahashi, J. S. (1996). The biological clock: It's all in the genes. *Progressive Brain Research* 111, 5-9]. We may have to stick to the mouse, but that is fine—mice can learn too. Actually, there are some interesting facts about mice; for example, they have strong handedness—even pure strains are either left- or right-handed: how about trying to change a mouse's handedness? Also, there might exist (or be produced) strains of mice that are impaired in learning specific motor tasks. A combination of behavioral, electrophysiological, molecular biological, genetic, and genomic approaches could produce some very interesting insights into the brain mechanisms of motor learning at these different levels. I have myself embarked recently on such

a multifaceted endeavor in studying congenitally hypothyroid rats (and, I hope, mice), and it is very exciting. The ultimate truth may always be elusive, but the search for it will not be dull. It's like in Cavafy's poem "Ithaka" [excerpts from "Ithaka," in *C. P. Cavafy Collected Poems*, translated from Greek by E. Keeley and P. Sherrard, edited by G. Savidis, Princeton University Press, Princeton, NJ, 1975, pp. 66-69]:

"As you set out for Ithaka  
hope your road is a long one,  
full of adventure, full of discovery

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Keep Ithaka always in your mind.  
Arriving there is what you're destined for.  
But don't hurry the journey at all.  
Better if it lasts for years,  
so you're old by the time you reach the island,  
wealthy with all you've gained on the way,  
not expecting Ithaka to make you rich.  
Ithaka gave you the journey.  
Without her you wouldn't have set out.  
She has nothing to give you now.

And if you find her poor, Ithaka won't have fooled  
you.  
Wise as you will have become, so full of  
experience,  
You'll have understood by then what these  
Ithakas mean.

JOCN: Thank you.

