

# The History of Neuroscience in Autobiography
## Volume 14

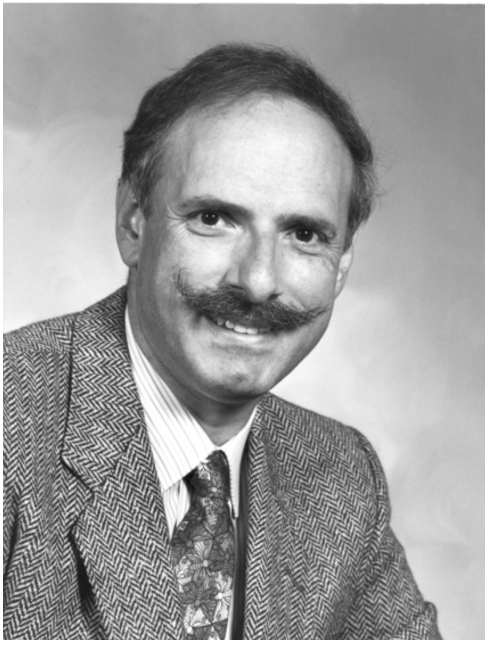
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## Apostolos Georgopoulos

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# Apostolos Georgopoulos (’Απόστολος Π. Γεωργόπουλος)

**Born:**

Patra, Greece
June 16, 1944

**Education:**

National and Kapodistrian University of Athens, Greece, MD, Medicine (1968)
National and Kapodistrian University of Athens, Greece, PhD, Physiology (1969)
Johns Hopkins School of Medicine, Postdoctoral, Neurophysiology (1972–1974)

**Appointments:**

Professor, Department of Neuroscience, Johns Hopkins School of Medicine (1986–1991)
Regents Professor, University of Minnesota (2005–present)
Professor of Neuroscience, University of Minnesota Medical School (1998–present)
American Legion Brain Sciences Chair, University of Minnesota (1991–present)
McKnight Presidential Chair in Cognitive Neuroscience, same, (2004–present)
Director, Brain Sciences Center, Minneapolis VA Medical Center (1991–present)
Director, Center for Cognitive Sciences, University of Minnesota (2004–2014)

**Honors and Awards (Selected):**

King Solomon Prize in Neuroethology (1996)
Fellow, American Association for the Advancement of Science (1997)
Carnegie Centenary Professor, The Carnegie Trust for the Universities of Scotland (2002)
American Academy of Arts and Sciences (2002)
Santiago Grisolia Chair, Valencia, Spain (2003)
National Academy of Medicine (2004)
Academy of Athens, Greece (2006)
Krieg Cortical Discoverer Award, Cajal Club (2006)
Fondation IPSEN Neuronal Plasticity Prize, Paris, France (2009)
Fellow, American Physiological Society (2015)
Bernstein International Prize for Motor Control (2015)
American Legion Distinguished Service Medal (2017)

*Apostolos Georgopoulos discovered the directional tuning of single cell activity in the motor and parietal cortex, a fundamental property linking neural activity to spatial aspects of planned movement. He then used this information to monitor the dynamic neural processes, at the single cell and neuronal ensemble levels, underlying spatial cognitive operations, including memorized movements, memory scanning, mental rotation, mental maze solving, copying geometrical shapes, mental object construction, making spatial categorical judgments, and exploring city maps. He pioneered the use of high (4T) and ultra-high (7T) fMRI to study such processes at the whole brain level in human subjects and the use of magnetoencephalography (MEG) in studying dynamic brain function in health and neuropsychiatric diseases. Currently, using a combination of MEG and biology, he is focusing on identifying blood biomarkers for dementia and evaluating their relation to changes in brain function.*

# Apostolos Georgopoulos

## Prologue

This is a bird's eye view of my scientific career in neuroscience spanning five decades since 1972, when I joined the laboratory of Dr. Vernon B. Mountcastle (see Volume 6) at the Department of Physiology of the Johns Hopkins School of Medicine as a postdoctoral fellow, to the present, still working full time as the director of the Brain Sciences Center at the Minneapolis Veterans Affairs (VA) Medical Center and as Regents Professor of Neuroscience at the University of Minnesota. By necessity, this is a very selective summary stemming from scientific as well as personal considerations, reflecting the excitement at the times of discovery as well as the importance of the discovery. And discovery in my life could be as simple as solving a problem in geometry, solving a problem in chess, finding out how the brain plans a movement, unraveling the neural mechanisms of a cognitive process, getting an insight into the operations of large neural networks, or figuring out brain diseases—to name but a few. During those 50-odd years of my scientific career, I have been blessed with top-notch team members with whom I have shared excitements, joys, disappointments, and never-ending expectations for new discoveries. Thank you!

## The Early Years

I was born in Patra, Greece, in June 1944, a seaport town on the northern shore of Peloponnesus, about 100 kilometers east of Olympia and 160 kilometers west of Mycenae. Patra is the capital of the province of Achaëa, a territory established in northern Peloponnesus circa 1100 BC by the Achaeans, led by Achaeus, son of prince Xuthus. "Achaeans" was practically a synonym for "Greeks" in general in Homer's time. Among others, Achaëa is well known for its white wine and sweet red wine (*Mavrodaphne*). Those early years were very enjoyable, spending the mornings at school (a breeze), playing soccer in the unpaved streets in the afternoons (with plenty of cuts in my knees and a good number of tetanus horse antiserum shots by my mother), and being with family in the evenings. In 1958 we moved to Athens, and things changed drastically: harder time at school (second year of high school, following six years in elementary school), no soccer, and no friends. Nevertheless, human resilience being what it is, I finished at the top of my class which gave me the credentials to transfer the next year to a "select" high school (*Varvakeion Exemplary High School*). This designation of the school derived from the fact that it also served as

postgraduate training ground for high school teachers in general. In fact, most of the times, several postgraduate teachers were in attendance in the back of the classroom, with a class of about 30 students. Then I was struck by my first love: Geometry! During that year, in addition to Greek literature (ancient and modern) and Latin, we were introduced to algebra, geometry, and biology—subjects that were taught all year long. Biology was fine, a lot of new, interesting knowledge; and algebra was straightforward but boring (you just needed to be systematic and careful *but* the correct result was always guaranteed): a very powerful tool indeed but not exciting, just a tool. But geometry!—an apocalyptic revelation: You are given pencil and paper, a ruler (to draw straight lines), a compass (to draw circles/arcs), and a problem to solve using only those two tools. I will never forget the pleasure I had while I was drawing the lines and circles dictated by the problem, and then staring at the drawing as a work of art! I used routinely a sharpened (by a knife, no pencil sharpeners then) Faber No. 2 pencil and white unlined paper, although frequently I drew on thicker black paper using white calligraphy ink with a special pen, really beautiful! And what about the expectation of the new problem to solve. I could hardly wait! The solution was not always easy, and hardly ever trivial to prove using ruler and compass. Many times, the solution was "obvious," in the sense that, for example, you would look at the drawing and "see" that the two angles specified in the problem are indeed equal *but* proving that equality by ruler and compass was not always exactly "obvious." I took special pleasure in the process of solving geometry problems, especially when the solution was not "obvious," however long I would devote to examining the drawing. In such cases, the solution would appear miraculously after, for example, I drew some line: This was the "Aha!" moment, when the solution jumped in front of me in the drawing with the new line! But, of course, the key challenge was to discover which points to connect! I spent many night hours solving geometry "exercises," deeply absorbed and not minding the time passing but then being at ease and peace after I found the solution, which I was frequently dreaming of in the sleep that followed. My favorites were Th. Caronnet's *Exercices de Géometrie; Premier Livre: La ligne droite* (Librairie Vuibert, 1953); and *Deuxieme Livre: La circonférence* (Librairie Vuibert, 1956).

In retrospect, I can trace the excitement I derive in my research (from neuroscience to immunology to medicine) and hobbies (chess, jazz) to the same quality of discovering the solution to a geometry problem by trying, discovering and testing hidden associations, and creating new associations in jazz improvisation. The remaining three years in high school were a breeze. Trigonometry was easy, solid geometry a useful extension of planar geometry, advanced algebra straightforward, and physics and chemistry fundamental in understanding the world and easy to learn. My favorite subject those years was linguistics, more specifically the etymology of

Greek words at various periods following the split of Greek from the Indo-European family ca. 5000 BC. Practically, however, the pressing matter was what to do after high school. In 1962, there were essentially three institutions of higher education, namely two universities (one in Athens, the other in Thessaloniki) and the National Polytechnic School. Entry to any of them was highly competitive and granted after national exams.

The last two years of high school comprised two different tracks to choose from: a "Classics" track with emphasis on Greek literature and history, and a "Practical" track with emphasis on physics, chemistry, and mathematics. The choice of a track depended on the field that a student wanted to pursue (there is no college education in Greece). Typically, students planning to apply to the Polytechnic School chose the Practical track, whereas students planning to pursue other fields (e.g., philology, law, medicine, etc.) typically chose the Classics track. For myself, I knew what I *did not* want to practice in the future (engineering, law, philology, chemistry), so I chose medicine by exclusion. Although medical school was longer (six years) than other disciplines (typically four years), it offered a broad training curriculum for diverse choices covering both clinical and research careers. Both careers were very exciting; in fact, when I graduated from the medical school six years later, I was torn between which one to choose: internal medicine or research in physiology (I loved them both), a decision for which I ultimately relied on the outcome of flipping a coin: It came tails-up, hence I continued in research. However, I never regretted getting a medical education; it provided me with broad knowledge that has helped me many times in my subsequent research career and, practically, a lot of my current research is dedicated to medical research. Hence, my election to the National Academy of Medicine in 2004 was the highest honor I would have wished for—besides my election to the Academy of Athens and the American Academy of Arts and Sciences!

## Medical School (MD) and PhD Dissertation (1962–1969)

I was admitted to the Medical School of the National and Kapodistrian University of Athens in 1962 (came fourth in the national exams, among thousands of applicants for about 150 admissions). The first year of medical school comprised physics, chemistry (inorganic and organic, as separate subjects), biology, and part one of anatomy (bones) and physiology (physiology of the blood). I knew well physics and the two chemistries, and biology, bones, and blood physiology were easy subjects. So, that year I competed playing nonstop chess (which I had learned how to play when I was 16 years old), played 44 consecutive games, won 43, and was placed first in Class III and Class II championships, and shared first place with another player in Class I (the top Class). That same year I won a trophy in a national competition celebrating the October 28th OXI Greek National

Holiday—and stopped any further play! It became obvious that to keep up in competitive chess play, I would have to spend a lot of time in preparing, at the risk of performing poorly in my medical school exams. I loved, and still love, playing chess because it is essentially an incessant discovery process, very similar to solving a problem in geometry but in a dynamic setting—that is, discovering the right sequence of moves to gain an advantage or to solve a chess problem. I also play the alto saxophone, enjoying the improvisation in generating new, unique melodies.

The subjects in the second year were anatomy, physiology, biochemistry, and histology. Anatomy and biochemistry relied on straightforward memorization, and histology was fairly easy for me because I was very good at evaluating images and connecting them to the tissue they came from. Physiology was a revelation! The workings of the various organ systems of the body, their lawful interactions, the resulting homeostastic stability across the lifespan—a true marvel captured so eloquently in Walter B. Cannon's book *The Wisdom of the Body* (1932).

There was an associate professor in the Department of Physiology (Andreas Granitsas) who had initiated lectures by interested second-year medical students at the end of the school year on a topic of their choice. I was thrilled at the opportunity and chose to work on the role of thyroid hormone in maturation. The main emphasis at that time was on the role of thyroid hormone in oxidative metabolism, a topic of less interest to me. What fascinated me, more specifically, was the dramatic effect of thyroid hormone deficiency during pregnancy, resulting in *cretinism*, a syndrome characterized by severe intellectual disability. I thought that this should, somehow, be connected to (i.e., be the result of) a problem in protein biosynthesis, since that is the pathway that underlies maturation. Therefore, I spent a lot of time in libraries (mostly the library at the National Center for Scientific Research "Demokritos") researching the latest discoveries in protein biosynthesis – what an era was the 1960s! RNA, translation of the genetic code, ribosomes, nucleus, mitochondria. My lecture was well received, particularly by my future wife, Lily (my only and true lifelong love), then a medical student too. I wrote the lecture as a review paper (with 174 references) which was published (in Greek) in the Archives of Medical Sciences in the mid-1960s. To my knowledge, it was the first publication in Greek of the breathtaking advances in protein biosynthesis at that time, in addition to the role of thyroid hormone in it. My interest in thyroid hormone and brain maturation has remained active over the years. A key feature of congenital hypothyroidism is a decrease of the total length of the dendritic segments of the apical tuft and the basal arborization of pyramidal cells [1], resulting in an overall reduction of synapses. In theory, this deficit, and associated intellectual disability, could be corrected if synaptogenesis could be induced in adult brains, a seemingly impossible task. Not taking "no" for an answer, and with the faith of the born optimist

I am, I reconsidered this problem with my student Carrie MacNabb in the late 1990s by inducing congenital hypothyroidism in rats by adding methimazole (an antithyroid drug) to the drinking water of pregnant dams from embryonic day E16 to postnatal day P25 [2, 3], since the maturation effect of thyroid hormone in the rat brain is completed by about 25 days postnatal. (In the human it has been completed at birth.) In collaboration with Eugene O'Hare and James Cleary, experimental psychologists at the Geriatric Research and Education Center at the Minneapolis VA Medical Center, we used a choice alternating lever cyclic-ratio (ALCR) schedule to assess a few months after birth the behavior of normal (control) rats, congenitally hypothyroid rats, and four groups of congenitally hypothyroid rats that received thyroxin (T4) replacement at P1, P7, P13, and P19 days. Normal rats and those that had received T4 replacement at P1, P7, and P13 days performed well in the task, in contrast to those rats without replacement and those with replacement at P19 [2]. These results indicated (a) that congenital hypothyroidism impairs learning when a discrimination between correct and incorrect operanda is made available, and (b) that this defect can be prevented by a timely T4 replacement up to P19. With the advent of drugs that increase the formation of new synapses (e.g., fluoxetine), the prospect of successful intervention in intellectual disability due to congenital hypothyroidism may become reality.

Back to the medical school. As a result of my excellent performance in the physiology exams (9/10 grade), I was accepted as a Student Assistant in the Department of Physiology, where I assisted in the physiology demonstrations to medical students but also participated in ongoing research at the department, leading ultimately to my PhD thesis. I also organized weekly seminars in the department where staff (faculty, postdoctoral fellows, students, visitors) presented on various topics, an exciting weekly event. In 1966 I presented in one of those seminars an intriguing article by Wilder Penfield, "Some mechanisms of consciousness discovered during electrical stimulation of the brain" [4], eliciting "flash-backs" of past experiences by electrical stimulation of the temporal lobe. This article was my first encounter with human neuroscience and made a deep impression on me. Little I knew then that 44 years later, in 2010, I would publish a paper on a very similar topic, identifying with magnetoencephalography (MEG) a temporal lobe focus in patients suffering from posttraumatic stress disorder (PTSD) and associated flash-backs! [5]. Toward the end of medical school, I became fascinated with immunology, and in 1968 I presented in a series of seminars eight articles by E. J. Holborow published in *The Lancet* in 1967 (*An ABC of Modern Immunology, April 15–June 3, 1967*). Again, little I knew then that I would return to that topic 48 years later, in 2016, when I published a paper on immunogenetics of Gulf War Illness (GWI) [6] and then spend 10-plus years on immunogenetics of pathogens and human disease, including viruses [7], PTSD [8], neurodegenerative

diseases [9–17], schizophrenia [18], addiction [19], cancer [20–29], and other diseases [30–38] up to now. Another book that took me by storm was Alvan R. Feinstein's *Clinical Judgment* (1967). Most impressive was his rigorous use of mathematics/set theory/Venn diagrams as a guide to clinical diagnosis and decision-making. I found myself torn in choosing between internal medicine and research for my future career. I was fascinated by internal medicine because it was a continuous discovery process in diagnosing, treating, and monitoring illness, with the added weight of being critical for the health of the patient, a huge responsibility. As I mentioned earlier, I flipped a coin, came up tails, and research became my path. I graduated with honors in 1968 (MD) and obtained the PhD degree in physiology the next year with a dissertation in lipid metabolism. In 1968 I married Lily who gave birth to our two lovely daughters Maria Alexandra (Elma) and Areti in 1970 and 1972, respectively, each of whom graced us with two precious grandchildren.

## Greek Army Service (1969–1971)

Next, I served in the Greek Army for two years (1969–1971; a mandatory service) as a reserve medical officer. I worked at the Army Medical Research Center in Athens, running the 401 Army Hospital's blood bank and participating in the manufacture of meningococcal and cholera vaccines for personnel of the armed forces, carrying out microbiological research on salmonella and shigella, and participating in epidemiological research on meningitis and brucellosis. During that period I coauthored several papers on microbiology, some of which were published in the US journal *Public Health Reports*.

## Neuroscience

In 1967 I came across a paper by Vernon B. Mountcastle that shaped my career in neuroscience ("The Problem of Sensing and the Neural Coding of Sensory Events," in *The Neurosciences*, G. C. Quarton, T. Melnechuk, and F. O. Schmitt (eds). New York, NY: Rockefeller University Press, 1967: 393–408). The step-by-step clear exposition of the neurophysiological processes starting with the application of a stimulus and ending with a perceptual construct became a lifelong road map for me in trying to decipher the intervening processes in that fantastic chain of events. I was most impressed by the exquisite quantitative treatment of the data at each step, a methodological "imprinting" in my research career up to this very moment. Indeed, in 1970 I wrote to Dr. Mountcastle inquiring about the possibility of doing a postdoctoral fellowship in his laboratory and—surprise!—he said, "Yes." I was overjoyed. He was taking a bet on me, for I had no experience in electrophysiology or neuroscience. Vernon told me later that he

was impressed by the letters of recommendation by my professors at the university and my microbiology supervisor at the Army Research Center. His bet paid off; about 20 years later I was offered his position as director of the Bard Laboratories of Neurophysiology at Johns Hopkins, an offer I declined and moved to Minnesota, mainly for family reasons.

I was discharged from the Army on April 30, 1971. The next day, Saturday, May 1, Vernon and his wife, Nancy, arrived in Athens from Lebanon, where he had given a series of lectures at the American University of Beirut. The next day, we took a short trip to Cape Sounion where we enjoyed local octopus marinated and grilled, the Greek way (see figure 1). Now, in 1989 Gian Poggio, Ken Johnson, and I organized a meeting to celebrate Vernon's 70th birthday. We designed a poster (see figure 2) and asked Vernon to give us a photo of his for the poster: To my amazement, he gave us the photo I had taken of him during our lunch at Sounion in 1971—and, yes, that picture was placed center stage in the poster (Vernon told me that this was his most favorite picture!)

That evening, we had dinner with my wife and my neurology professor Costas Stefanis at the rooftop restaurant of Hotel Ariston at the Constitution Square overlooking a lighted Parthenon—a memorable evening. Vernon was aware of Costas's work and thought highly of his two papers with Herbert Jasper, reporting on recurrent inhibition in pyramidal tract cells of the motor cortex, investigated using intracellular recordings. These landmark papers were published in the *Journal of Neurophysiology* in 1964 [39, 40], and were read and appreciated by Vernon who was editor in chief of the journal at that time. It was nice to bring these pioneers

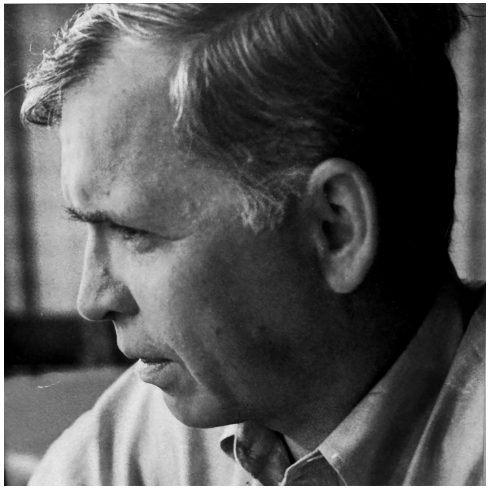


**Fig. 1.** Picture of Dr. Vernon Mountcastle enjoying lunch in Sounion, Greece, on May 2, 1971. (Photo taken by Apostolos Georgopoulos.)

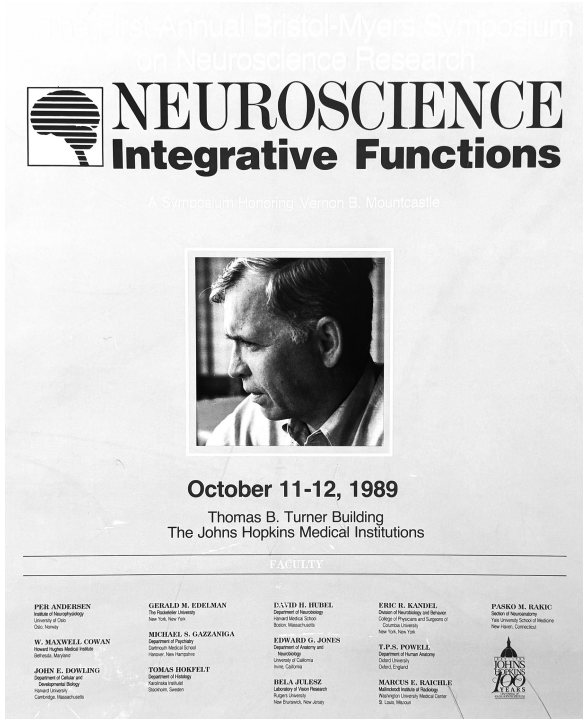



**Fig. 2.** The photo in Fig. 1 was given by Dr. Mountcastle to be the centerpiece of the poster announcing the symposium to honor Dr. Mountcastle's 70th birthday.

together, even for an evening. Both of them referred warmly to that dinner in future conversations with me. Remarkably, 36 years after that dinner, Costas and I wrote a paper where we placed his 1964 studies in the context of my studies on directional tuning, drawing attention to the fundamental role that recurrent inhibition may play in shaping local circuits in the motor cortex [41]. (Nicely, the paper was published in a volume dedicated to the Cajal Club conference in 2006 in Stockholm, celebrating the 100-year anniversary of Ramón y Cajal's Nobel Prize in 1906, a conference I was honored to be invited to and lecture.) In 2010, we followed up with a second paper explicating in more detail our view of the motor cortical circuit [42].

## Johns Hopkins (1972–1974)

### *Parietal Cortex*

In 1971 I applied to the World Health Organization in Geneva for a Research Training Grant, which was funded. My wife (an endocrinologist, also a medical doctor with a PhD degree in physiology) and I were already assistant

professors at the Department of Physiology of the University of Athens and took a two-year educational leave of absence for postdoctoral work at the Department of Physiology of the Johns Hopkins School of Medicine in Baltimore. We arrived at the Friendship International Airport in Baltimore (later renamed Baltimore-Washington International; a regrettable change of a beautiful name) on Sunday, October 22, 1972, with our two daughters in the middle of a beautiful, most colorful Maryland autumn—an unexpected, most pleasant surprise! We stayed for a few days with Vernon and Nancy in their home in the country (in Monkton, Maryland), and then in a furnished apartment at Elkridge Estates in Roland Park for a week, until we moved to a townhouse in Owings Mills, a suburb about 20 miles northwest of Baltimore. I started working in the lab right away; Lily started working in the lab of Giraud Foster, a renowned calcitonin researcher, associate professor at the same Department of Physiology at Hopkins.

In the previous years, the Mountcastle lab was using a LINK computer to control the experiment and collect neural data but at the time of my arrival the lab was being converted to a new behavioral control and data acquisition software based on a Digital Equipment Corporation (DEC) PDP11-20 computer. The design, software, control, and integration was done by Dr. William (Bill) Talbot, a top neurophysiologist with a gift and special interest in computers. This transition took about three months (since my arrival), during which time I typed many hours of protocols of previous experiments dictated by Dr. Mountcastle. This not only improved my understanding of spoken English but, also, subtly and unconsciously, shaped expressing my thoughts in a concise and precise way ("short declarative sentences"), along George Orwell's recommendations [43]. The recordings started successfully using a semicircular track along which a lighted cube/switch was controlled to (a) move at different speeds and (b) dim its light at predetermined locations along its trajectory. The monkey was depressing a ball and reached to hit the dimmed light as soon as possible for a liquid reward. The combinations of speed and locations of dimming were the controlled variables. The team, led by Dr. Mountcastle, consisted of Jim Lynch, Carlos Acuňa, me (postdoctoral fellows), and Hideo Sakata (visiting scientist from the Tokyo Metropolitan Institute). We recorded single cell activity in the superior and inferior parietal cortex (areas 5 and 7, respectively). It was a thrill to listen to brain activity during reaching, grasping, and "winkling." I took the lead in reconstructing penetrations from histological sections and for the statistical analysis of the data. Although I was familiar with basic statistics, the challenge to analyze the data from this experiment was beyond my knowledge at that time. So, Vernon arranged that I consult with Allyn Kimball, professor of biostatistics at the Johns Hopkins School of Public Health. This was another revelation for me, the world of statistics seen through the eyes of a senior, world-renowned, well-seasoned statistician! Essentially, I was his apprentice, meeting in person at his office once or twice a week—I couldn't

wait for the time to pass from one meeting to the next. Indeed, under his guidance, I completed the statistical analyses and earned third authorship in the resulting classic [44].

### *Primary Skin Nociceptive Afferents*

In the beginning of 1974 Dr. Mountcastle suggested that I learn a technique that I could apply upon my return to Greece at the end of the year. Such a suitable technique at the lab was recording from primary afferents innervating the glabrous skin of the monkey's hand. The previous leader in that lab was Dr. Ian Darian-Smith who had left for Australia before my arrival to hold a faculty position at the Department of Anatomy at the University of Melbourne. There were two bright graduate students finishing up their PhD dissertations, Randall (Randy) Long and Carol LaMotte, who trained me how to dissect single primary afferents from the median and ulnar nerves, and how to study their responses to heat and cold stimuli quantitatively. I am grateful to them for their patience, guidance, and support in enabling me to carry out extensive recordings of large numbers of high-threshold nociceptive afferents (345 Aδ and 191 C fibers) resulting in a major single-authored publication in 1976 [45], followed by another paper reporting the results of quantitative analyses of neuronal responses to noxious stimuli [46]. A pioneer in describing the properties of Aδ fibers was Ainsley Iggo at the University of Edinburgh; it was a special pleasure when I met him 24 years later, in 1997, while I was visiting that university to give the Ninth Annual Distinguished Lecture at their Center for Neuroscience—a vivid flashback!

## Greece Interlude (1974–1976)

We returned to Greece on December 1, 1974, back to our faculty positions at the Department of Physiology of the University of Athens Medical School. Unfortunately, despite all my efforts, there was no possibility of conducting neurophysiological research there. We took the risk and resigned from our university jobs and immigrated to the United States in 1976, following a formal invitation from Johns Hopkins University. All family members (my wife, our two daughters, and myself) got green cards and later became naturalized US citizens in the early 1980s.

## Johns Hopkins (1976–1991)

### *Basal Ganglia*

I arrived at the Dulles International airport in Washington, DC, on April 19, 1976, ahead of the rest of the family who joined me on July 26 that year. I was delighted to get back to the lab! The new team in the primary

afferent lab consisted now of James Campbell, Robert LaMotte, and Richard Meyer, all immersed in research using an infrared carbon dioxide laser designed to deliver to the skin noncontact, radiant heat stimuli at 0.1–25 deg C steps with fast rise times (200–250 ms). So, I returned to the central nervous system joining Mahlon DeLong (and his graduate student Michael Crutcher) on basal ganglia research. For three years (1976–1979) we recorded single cell activity in the globus pallidus (external and internal segments, $GP_e$ and $GP_i$, respectively), substantia nigra (pars compacta and pars reticulata), and the subthalamic nucleus. The most striking finding in those studies was the short latencies of neuronal responses in the subthalamic nucleus (STN). In the traditional scheme of those days, the subthalamic nucleus received input from $GP_e$ and sent its output to $GP_i$. This arrangement would predict that the latencies of response of STN neurons to the movement-triggering visual stimulus would be longer than those of $GP_e$ neurons, which was not the case: STN neurons had shorter response latencies than $GP_e$ or $GP_i$ neurons, as well as a higher percentage of movement-related neurons [47]. This implied a direct input to STN from the motor cortex, the now well-recognized "hyperdirect pathway." Mahlon and I became close lifelong friends.

*Motor Cortex: Directional Tuning*

In 1979 I moved to a new space (my lab), refocusing my work from basal ganglia to cerebral cortex, more specifically on the motor cortex and area 5 of the superior parietal lobule. Since the early parietal recordings [44], I had been intrigued by the strong effect that the direction of movement had on neural activity. In those experiments, we studied cells the activity of which increased with reaching toward the target; yet their activity would decrease as the arm was brought back to its resting position in front of the monkey. This observation was the seed of the new design I implemented from 1979 onward in recordings from the motor cortex and area 5 of the parietal cortex. The key aspect of the design was to vary the direction of movement in a systematic way, such that the whole directional continuum would be covered and neural activity evaluated across the complete directional range. This design was implemented in a device that consisted of a plate and an articulated arm (manipulandum) that could move freely on it [48, 49]. A transparent ring of plexiglass was attached to the distal end of the arm, enabling the monkey to position it on top of a lighted LED. Underneath the plate there were nine LEDs, one at the center and eight around it in a clock-face design, every 45 degrees. The center LED came on, and the monkey grasped the manipulandum distally and moved it to "capture" the lighted LED at the center. Then the center LED was turned off while one of the peripheral LEDs came on, and the monkey was trained to move the handle from the center to

the lighted LED for a liquid reward; this was the genesis of the "center ➔ out" task. Thus, movements were made from the center to eight different directions in a pseudorandom order. The key new aspect of this design was the *emphasis on the spatial aspects of the movement trajectory*, not the muscles that implement it, a drastic change in how the motor cortex was regarded since, for more than a century, it was simply known as an "upper motor neuron."

By 1980, John Kalaska had joined me as a postdoctoral fellow (from Canada), followed by Roberto Caminiti (postdoctoral fellow from Italy) and Joe Massey (senior physicist at the Applied Physics Laboratory in Jessup, Maryland)—a dream team! Our first recordings were in the arm area of the motor cortex, contralateral to the moving arm. Spike trains were plotted in real time on a Tektronix analog screen: As the monkey made movements in different directions, we could see the directional tuning of neural activity jumping second-by-second in front of our eyes! Cell activity was highest with movements in a specific direction (the "preferred" direction) and decreased gradually with movements in directions farther and farther apart from the preferred one. Different cells had different preferred directions that covered the whole directional continuum. The original device had only eight lighted targets (LEDs) but we quickly had a new one where the lighted target was produced by a laser beam, thus enabling for a higher sampling of the directional space and for any arbitrary placement of the target. The statistical analysis of those data presented new challenges, namely (a) the characterization of the directional tuning using a sinusoidal multiple linear regression, and (b) the analysis of the distribution of preferred directions using directional statistics. For the former issue, I reconnected with Professor Allyn Kimball, my old teacher and statistics mentor in the early 1970s, who now enlightened me on the sinusoidal regression, an analysis that allowed a precise estimate of the preferred direction. Next, we generalized the directional tuning for reaching movements to visual targets in 3-D space [50, 51]. The 3-D preferred directions were extensively analyzed in later studies [52, 53] and their mapping in motor cortex presented [54, 55].

At that time, in the early 1980s, Dr. Mountcastle and Dr. Mark Molliver, a professor in the Anatomy Department, organized a neuroscience course (annually) in which Tom Powell, Vernon's old collaborator (since the 1950s) and close friend, came from Oxford to teach neuroanatomy. Tom and I immediately struck a common note and became lifelong friends. He was a true giant in brain neuroanatomy, a wonderful and very warm person, and a precious friend. We kept up our contact over the years and in 1983 my wife (Lily) and I had the good fortune to visit him in Oxford (in the context of a lecture I gave there), enjoy his hospitality, and meet his student John Sloper (see figure 3).



**Fig. 3.** At Tom Powell's office at the University of Oxford, 1983. From left to right: My wife (Lily), myself, Tom Powell, and John Sloper.

*Reaching vs. Finger Movements*

Behaviorally, reaching movements are different from fine finger movements. They always involve coordinated activity of several muscles and they are directed to targets in space, visual or other. Then, it is not surprising that corticospinal axons from the proximal arm area of the motor cortex impinge on interneurons without making monosynaptic connections to motoneurons, a common feature of motor cortical neurons controlling distal finger muscles. Moreover, reaching movements have a target and their goal is to bring the hand to the target. Therefore, *the* essential aspect of reaching movements is that they operate in *extrapersonal space,* moving the hand from its current position to the target. Now, the essential attributes of spatial trajectories are their direction and amplitude and, for a movement, its instantaneous 3-D velocity vector. At the single cell level, these features are well captured by the 2/3-D directional tuning and the orderly relation of single motor cortical cell activity to the instantaneous velocity of the movement [56]; and similarly at the population level, as documented by the overall direction of the 2/3-D population vector [57], its moment-to-moment variation and the derived movement trajectory in 3-D space [58]. In 1989, Sten Grillner (see Volume 9) and I published a perspective in *Science* proposing that reaching movements achieve their goal by engaging the integrated sensorimotor circuitry of the spinal cord [59], which acts as a "smart device" [60]. In a subsequent paper, I formalized this hypothesis more explicitly [61].

*Population Vector*

In 1983, we published a paper where preferred directions, weighted by cell activity in a given movement direction, predicted accurately, as an ensemble ("neuronal population vector"), the direction of that movement [62]. It should be noted that the key discovery that made the computation of a population



**Fig. 4.** Sten Grillner and myself, Karolinska Institutet, Stockholm, 2006. (Courtesy of Tomas Hökfelt.)

vector possible was the *directional tuning*: without it, no preferred direction would exist, and no population vector could be computed. At that time, the computation of the population vector relied on preferred directions estimated from recording at different times. Later, we compared the population vector derived from such analysis with a population vector computed from cells recorded simultaneously, with practically identical results [63]. The population vector turned out to be good predictor of the direction of reaching in 3-D space [50, 58] and was illustrated in our first cover (figure 5). To me, it has been most gratifying to see the application of this measure in various fields and, most importantly, its successful application in neuroprosthetics, pioneered by Andy Schwartz [64]. In March 1987 I presented the 3-D directional tuning and population vector results at the 53rd Stated Meeting of Neuroscience Research Program Associates at the Rockefeller University. The presentation was well received, particularly by Max Cowan, editor-in-chief then of the *Journal of Neuroscience*. It was the first time we met and the beginning of long-term association. Our 3-D reaching papers were published in the *Journal of Neuroscience* in 1988.

The population vector was a key contribution to computational neuroscience but, for me, its exciting attribute was its potential to serve as a window to neural mechanisms underlying cognitive operations happening during the response time. In that respect, the most interesting aspect turned out to be the robustness of the population vector across time. When calculated every 10 ms from stimulus onset onward, it started growing in length and pointing in the direction of the upcoming movement at a latency of ~100 ms, that is, from early on during the reaction time [57]. That meant that we could get a glance at the directional operations unfolding covertly during the reaction time and this method became the seed of using the population vector as a tool/marker of spatial-cognitive operations, including memorized upcoming movement, mental rotation, memory scanning, and mental maze solving.




**Fig. 5.** 3-D population vector. (*Science* cover photograph, 26 September 1986.)

*Force*

In studies of motor cortical activity in relation to exerted static force, previous research had typically limited force exertion by the hand in two opposite directions (e.g., flexion-extension) along one dimension. In our study [65], we extended the force parameter space by training monkeys to exert static forces in 3-D dimensions and of different magnitudes. We found that the activity of the large majority of cells (78.6%) varied significantly only with the direction (but not the magnitude) of force, whereas only 7.1% of cells related to force magnitude alone, and 14.3% to both direction and magnitude. These findings underscore the prominence of directional control signal in the motor cortex and suggest that the direction of force can be controlled independently of its magnitude.

In contrast to static force, which is stable over time, the dynamic force producing a motion is of a different species. We investigated the relation of cell activity in the motor cortex to the direction of 2-D isometric force under dynamic conditions, where three key force variables were distinguished:

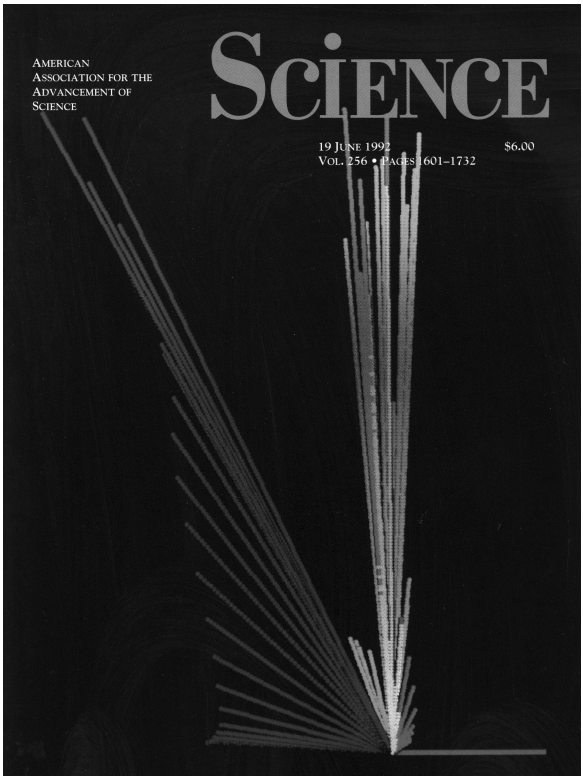



**Fig. 6.** Neural coding of dynamic isometric force. (*Science* cover photograph, 19 June 1992.)

the force exerted by the monkey, the net force, and the change in force [66]. Single cell activity was directionally tuned and, remarkably, this tuning was invariant across different directions of the bias force. Surprisingly, cell activity was not related to the direction of force exerted by the monkey, which changed drastically as the direction of bias force changed. In contrast, the direction of net force, the direction of force change, and the visually instructed direction all remained quite invariant and congruent in a trial, and are good candidates for the directional variables, alone or in combination, to which motor cortical activity might relate. Remarkably, the population vector also pointed in the direction of net force, not the force exerted by the monkey [66]—another *Science* cover (figure 6).

### *Instructed and Memorized Delay*

In a previous study, we had shown that activity in a subset of movement-related cells in the motor cortex persisted during a delay period in the

absence of overt movement [67]. During that instructed delay period, during which the lighted target was on, the population vector pointed in the direction of the stimulus, the same as the direction of the upcoming movement. Then we extended this study by turning off the target light, such that the monkey had to keep in memory the direction of the movement to be made when a "go" signal appeared. We found that, remarkably, motor cortical cell activity persisted in a subset of cells and that the population vector again pointed in the memorized direction of the upcoming movement [68]. This finding was unexpected because it was then widely assumed (actually, taken for granted) that motor cortex is a kind of "upper motor neuron" of traditional neurology and that neural events during delay/memory periods were the province of the prefrontal cortex. In fact, in the years that followed, several studies by different research groups documented activity in the motor cortex that persisted during periods when certain aspects of the task had to be kept in memory for subsequent performance. Given that motor cortical neurons projecting to the regions of the spinal cord innervating proximal arms terminate on interneurons, it is not surprising that spinal interneurons show modulation of their activity during an instructed delay period [69].

### *Mental Rotation*

I explored this idea during the second half of 1980s using a motor mental rotation paradigm, inspired by the work of Roger Shepard and Lynn Cooper on mental rotation of visual images [70]. In our paradigm, the item expected to be rotated was the direction of an upcoming movement. We first tested this in human subjects performing in the same 2-D apparatus used in neural recordings. Subjects held the manipulandum at the center of the board and then a light appeared at a random spot on the circumference of an imaginary circle. Subjects were instructed to move at an instructed angle from the direction of the stimulus—for example, 90 deg clockwise (CW); the angle and the direction (CW, CCW) differed for different blocks of trials. We found that the reaction time (RT) increased in a linear fashion with the angle [71], similarly to what had been found in the Shepard and Cooper experiments for visual images.

Our hypothesis was that a population vector in the stimulus direction is formed in the brain and that it rotates to the movement direction, according to the instruction. We further assumed that this rotation is a time-consuming process, hence the increase of the RT with the rotation angle. We then implemented this paradigm in monkeys trained to move the handle in the 2-D apparatus at a 90 deg CCW angle from a stimulus direction. During training, the stimulus appeared at random locations on the circumference of an imaginary circle, hence the movement amplitude was kept constant. Surprisingly, monkeys learned the task and we

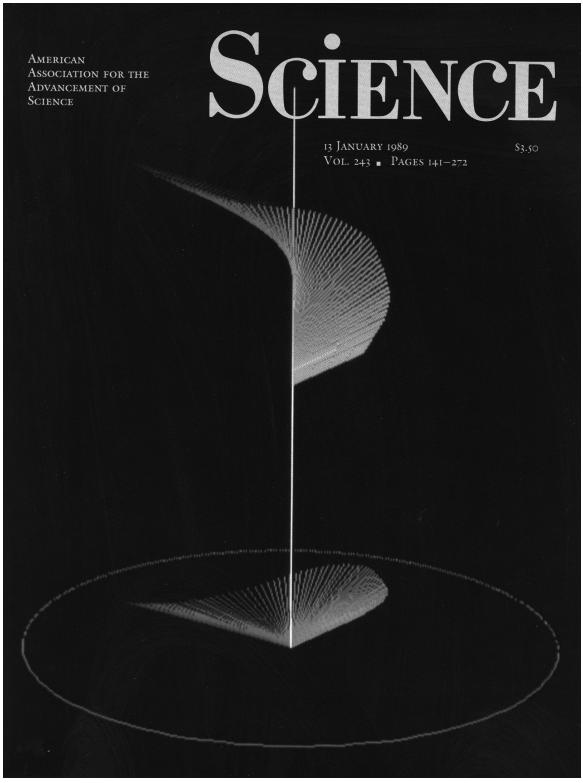



**Fig. 7.** Mental rotation of the neuronal population vector. (*Science* cover photograph, 13 January 1989.)

were able to record cell activity in the motor cortex during the task. We found that, indeed, the population vector rotated CCW from the stimulus direction to the movement direction [72, 73]—another *Science* cover. A comprehensive exposition of the neuronal population story was published in Science in 1993, together with the results of simulations of interactions between directionally tuned cells (figure 8) [74].

*Memory Scanning*

We followed up with a different task (context recall memory scanning), where a movement still had to be made in a different direction from the stimulus direction but in a context where the two directions were dissociated. In this task, visual stimuli were presented successively on a circle (list presentation phase), and then one of them (test stimulus) changed color; the monkey had to make a single motor response toward the stimulus that immediately followed the test stimulus in the list. Neural activity




**Fig. 8.** Directionally tuned artificial neural networks. (*Science* cover photograph, 2 April 1993.)

in the motor cortex changed abruptly from the pattern associated with the stimulus direction to the pattern associated with the movement direction without engaging the activity of cells with preference to other movement directions [75]. Thus, the differential engagement of differential of directionally tuned cells in the mental rotation and memory scanning tasks provided a remarkable insight into the neural mechanisms underlying these two distinct cognitive processes. More detailed analysis of the neural mechanisms of the memory scanning process was published in subsequent papers [76, 77].

*Information-Theoretical Analyses*

From early on, I had been fascinated by the possibility that an information-theoretical framework could serve as a common ground expressing diverse data and their relations in an abstract, unit-free space. I had expressed this intuitive idea in a letter to Dr. Mountcastle in 1970, while discussing

potential ways to quantify "information" contained in central nervous system (CNS) populations. My inspiration was the paper by Werner and Mountcastle on "Neural Activity in Mechanoreceptive Cutaneous Afferents: Stimulus-Response Relations, Weber Functions, and Information Transmission" [78]. I confess that, to this very day, that paper has been one of the most influential in my scientific career. I paid dues to that approach and published several papers on information transmission in dynamic visuomotor coordination [79], population vectors of reaching movements [80], production and visual guidance of dynamic isometric force [81, 82], and information theoretical analysis of spatial decisions in cognitive development [83] with very interesting insights into the processes involved.

## Minnesota (1991–present)

In 1991, we moved to Minnesota. I was offered the American Legion Brain Sciences Chair at the University of Minnesota and the directorship of the Brain Sciences Center at the Minneapolis VA Medical Center (https://brain.umn.edu/), both of which I gladly accepted. We set up a multielectrode single cell recording laboratory and carried out four different experiments: neural coding of dynamic force, memorized delay of straight movements, memorized movement trajectory with a 90 deg turn, and motor memory scanning. In addition, my research branched in two new directions: functional magnetic resonance imaging (fMRI) and artificial neuron network modeling. At the time of my arrival in Minneapolis, the University of Minnesota had one of the three high-field magnets at 4 Tesla in the United States, directed by Kâmil Uğurbil. We connected right away on a snowy November afternoon and began a most pleasant and productive collaboration lasting to this very day. To me it was a dream come true to have a look at the human brain in action using the most advanced noninvasive technology. We hit the ground running with our first paper on motor cortical representation of finger movements published in Science in 1993 [84], followed in the same year by another paper in *Journal of Neurophysiology* with more detailed results [85]. As an aside, in 1992 we applied for a NIH grant to become a National BioTechnology Research Center. We had a site visit by a NIH review committee, and we were happy with our presentations. The next day, Kâmil received a call from the chairman of the committee to let him know that the committee was impressed but also that they wanted one important item cleared up before making their recommendations to the funding agency. This important question was: "Can a Turk (Kâmil) and a Greek (me) really work together?!" Of course, Kâmil and I were best friends, and Kâmil explained to them that, actually, we are both Aegean (!), and reassured them that our fruitful collaboration is to be taken for granted—it is indeed still thriving! So, our application was funded and Kâmil's Center for Magnetic Resonance Research became a National Biotechnology Research Center.

In the mid-1990s, we used the 4T fMRI facility at the Center for Magnetic Resonance Research of the university to investigate the relations between BOLD activation and mental rotation in the human cerebral cortex. We used the standard Shepard and Metzler [86] 3-D mental rotation task. Twenty-four participants viewed two 3-D images and were asked to indicate whether they were the same or mirror images [87]. Using a hierarchical tree clustering analysis, we found that the rate of mental rotation and speed of performance were co-localized in the same branch with the right precentral cortical activation. This reinforced our original visualization of the population vector rotating in the motor cortex during performance of a 2-D motor mental rotation task. In a subsequent paper, we took advantage of the long reaction times in the Metzler and Shepard task to perform a time-resolved fMRI study and found that the width of the BOLD hemodynamic function was correlated with the reaction time, trial by trial [88]. Finally, in a motor mental rotation fMRI study [89] we analyzed voxel-by-voxel data and regressed BOLD activation against motor mental rotation angle. We found significant linear, positive associations in various areas, with overall slopes 2.4x higher in men than in women (both groups performing equally well). These findings documented the dependence of single voxel BOLD activity on mental rotation angle and pointed to a more efficient processing in women than in men, in keeping with a similar difference found in mental object construction task [90].

*Visuomotor Coordination*

In the early 1980s, in parallel with our research on directional tuning, we investigated dynamic eye-hand coordination by changing the location of the visual target at various times during the reaction time. In a set of trials, the target was in the opposite direction from that of the initial target. In those trials, the hand moved initially toward the first target, then abruptly changed direction and moved to the second target. Thus, the extent of the first movement was a linear function of the time for which the first light stayed on. Single cell activity in the motor cortex faithfully changed shortly after the change of target to initiate the second movement [91]. These findings documenting a continuous, online visuomotor control were in contrast with the prevailing view at that time that fast, reaching movements are ballistic in nature, emitted as a whole, and had to complete before another movement was initiated. In contrast, our findings pointed to a fluid, flexible, millisecond-by-millisecond visuomotor control.

These dynamic interactions were fascinating but I did not intend to pursue them further. However, a new encounter sowed the seed for future studies in that field. In 1984 I gave an invited lecture at an international conference on "generation and modulation of action patterns," held in

Bielefeld, West Germany. There I met two other speakers, namely David Lee, from the University of Edinburgh, Scotland, and Claes von Hoftsten, from Uppsala University, Sweden. Dave had brought with him a bottle of Lagavulin single malt Scotch whisky and invited Claes and me to share it in his hotel room amid discussion of motor control issues. Indeed, we nursed the bottle overnight and shared our ideas about visual control of movement, each bringing our own perspective to the table. I was excited to hear from Claes first-hand about the capacity of 15-week infants to reach and grasp an object moving at 15 cm/s, and of 18-week-olds to reach and grasp objects moving at 30 cm/s, at which speed the object moved twice the length of the infant's arm [92]. Even more amazing was the predictive nature of these reaches to moving targets at that early age [93]. These findings further cemented my view that dynamic visuomotor coordination is hardwired in a fluid, seamless interaction between visual areas and the motor cortex. A different angle in visuomotor coordination was provided by Dave's tau [$\tau$] [94], namely the time to hit the target, given a distance $d$ from the target and an instantaneous speed $s$: $\tau = \frac{d}{s}$. This measure has proved to be of critical importance in initiating action toward a target. By sunrise, our friendship had been established and a future research program for me was laid out. Indeed, in the mid-1990s, we carried out plenty of research into the neurophysiological mechanisms underlying the interception of moving targets [94–102], and in 2009 Dave and I coauthored a paper, first-authored by our co-advisee May Tan, on neural mechanisms of $\tau$ in the human brain as revealed by magnetoencephalography [103], research performed in my laboratory. Dave and I became lifelong friends, with several cross visits to Edinburgh and Minneapolis, which were always a perfect combination of pleasure, science, and collaboration.

## *Copying Geometrical Shapes*

### Development

Copying shapes and figures is a complex process that, depending on the experimental conditions, engages the visual and motor systems in a sequential, coordinated way under direct visual guidance when the shape is presented (e.g., on a screen or a sheet of paper) or under memory-driven guidance when the shape is drawn from memory on command. However, a completed shape can be constructed by adding together nonadjacent parts, as has been reported in a patient with brain damage [104]. A different issue concerns the "goodness" of the copied shape—that is, how much a drawn shape resembles the presented template. Interestingly, in Williams syndrome the copying of even simple geometrical shapes is disturbed. This could be due to abnormal brain maturation or to a developmental arrest,

in which case the imperfectly drawn shapes would resemble the drawings by young children. We tested the latter hypothesis in a collaborative study [105] with Barbara Landau, who provided us with drawings of simple geometrical shapes by older participants with Williams syndrome (6–14 years old) and drawings of the same shapes by young children (3–6 years old). We then showed pairs of the same shapes drawn by children in the two groups to human raters whom we asked to indicate in an analog scale (moving a cursor along a line) the degree of similarity between the shapes in a pair. We found that the shapes drawn by the Williams syndrome participants resembled closely those drawn by young children, indicating a developmental arrest in accurate drawing rather than a novel, qualitative abnormality [105].

### Neurophysiology: Karl Lashley

Be that as it may, shapes are typically drawn as consecutive linear, piecemeal segments. We studied the neurophysiological mechanisms of drawing simple geometrical shapes by training monkeys to copy four geometrical shapes (triangle, trapezoid, square, inverted triangle); a shape was traced on the side of a screen, and the monkey would copy it on the right side. Amazingly, monkeys traced those shapes nicely! We then recorded the activity of individual neurons simultaneously in small ensembles in the prefrontal cortex while monkeys copied those geometrical shapes, drawing them as sequences of movement segments (sides of the shapes). These segments, being of different directions, were associated with distinct patterns of neuronal ensemble activity [106]. Remarkably, these patterns were present during the time preceding the actual drawing, providing direct evidence for Karl Lashley's hypothesis according to which, prior to emitting an action consisting of serial component parts, those parts are represented in the brain in the same sequence. In addition, an analysis of errors in copying and their neural correlates lent further support to this hypothesis: When monkeys drew a shape incorrectly by transposing component sides of the shape, that order was also present in the neural representation of the sequence prior to drawing the shape, as predicted by Lashley's explanation of transpositional errors; typical examples include emitting a sentence (series of words) and typing (hitting typewriter keys serially), where transposition errors in typing letters would be explained as the outcome of a mix-up of their serial order in the postulated neural representation of the whole word preceding its typing. We further analyzed the relations between copying and neural activity in the prefrontal [107, 108] and parietal cortex [109, 110], and extended these studies to humans using fMRI [111, 112] and MEG [113–115].

*Cognitive Operations Unrelated to Hand Movement*

Starting in the late 1990s, we embarked on studying cognitive processes that were not tied to arm movements. In addition to behavioral evaluation (B), using methods of experimental psychology, we investigated underlying brain mechanisms using multielectrode neurophysiological recordings (N) in monkeys, and fMRI (at 4 and 7 Tesla) and magnetoencephalography (MEG) in humans. These studies covered a wide variety of cognitive processes, including mental object construction (B [116], fMRI [90], N [117]]), mental maze solving (B [118, 119], fMRI [120, 121]), categorical high-low judgments (B [122], N [123, 124]), exploring city maps (B [125, 126] MEG [127]) in collaboration with John Peponis, professor of architecture at the Georgia Institute of Technology, cognitive entropy (B [83]), spatial relations (MEG [128]), tactile illusions (MEG [129]), visual illusions (MEG [130]), optical flow (N [131, 132]), decision-making (MEG [133]), and language processing (MEG [134, 135]). Details can be found in the papers listed above; here I highlight some of the findings.

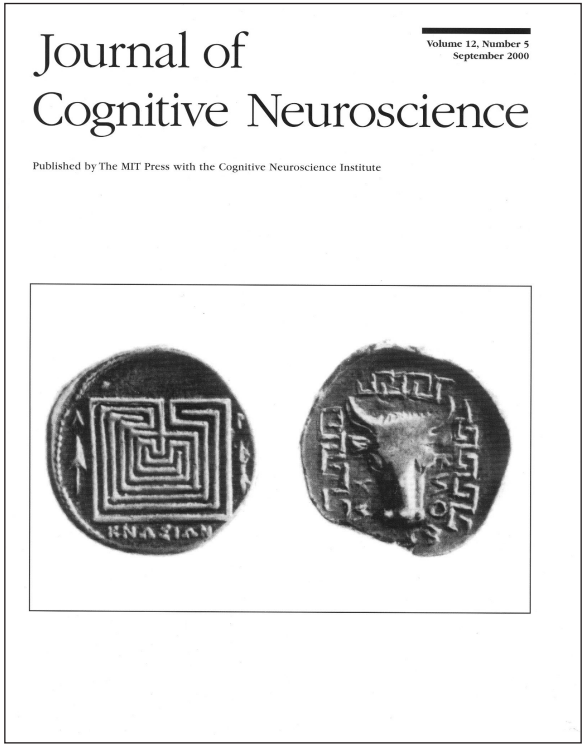



**Fig. 9.** The Labyrinth and the Minotaur. (Cover photograph, *Journal of Cognitive Neuroscience*, September 2000.)

*Mental Maze Solving*

Performance

Following our first study in human subjects [118], we compared spatial attention and visual processing capabilities of humans and rhesus macaques by developing a visual maze task that both could perform [119], as follows. Maze stimuli were randomly generated and were constructed of orthogonal line segments displayed on a monitor. Each was octagonal in outline and contained a central square (the "start box"). A single ("main") path, containing a random number of turns, extended outward from the start box, and either reached an exit in the maze's perimeter or a blind ending within the maze. Subjects maintained ocular fixation within the start box and indicated their judgment whether the path reached an exit or not by depressing one of two keys (humans) or foot pedals (monkeys). Successful maze solution by human subjects required a minimum viewing time. Replacing the maze with a masking stimulus after a variable interval revealed that the percent correct performance increased systematically with greater viewing time, reaching a plateau of approximately 85% correct if mazes were visible for 500 ms or more. A multiple linear regression analysis determined that the response time of both species depended upon several parameters of the main path, including the number of turns, total length, and exit status. Human and nonhuman primates required comparable time to process each turn in the path, whereas monkeys were faster than humans in processing each unit of path length [119]. The data suggested that a covert analysis of the maze proceeds from the center outward along the main path in the absence of saccadic eye movements, and that both monkeys and humans undertake such an analysis during the solution of visual mazes.

*Neural Recordings*

We recorded neural activity in parietal area 7a during a visual maze task while monkeys mentally followed a path without moving their eyes or hand. Remarkably, recordings of single cell activity revealed very similar neural mechanisms underlying the solution of mazes in area 7a of the parietal cortex [136, 137] and the arm area of the motor cortex [137] in the absence of eye or hand/arm movements, since the motor response required was foot movement. The basic finding was the directional tuning to the path emanating from the center of the maze, irrespective of whether the path exited the maze or not ("exit status"). Figures 10 and 11 show the time course of population activity in the two areas, remarkably similar and with practically identical onset times. These findings suggest a distributed processing of maze solution. Finally, the population vector's time course pointed in the direction of the main path, when the path was straight,




**Fig. 10.** Directional tuning of mental maze tracing. (Cover photograph, *Cerebral Cortex*, January 2004.)

but it turned when the path had a turn [138]. In summary, altogether, the direction and time course of the population vector during a memorized delay, motor mental rotation, motor memory scanning, and during maze solving all supported and fulfilled my original hypothesis and expectation that the population vector could serve as a "window" into the fine-grain brain mechanisms of dynamically evolving cognitive processes, another dream come true for me.

The neurophysiological studies above were complemented by two studies of mental maze solving by human subjects using fMRI of the superior parietal lobule (SPL) at high (4T) [120] and ultra-high (7T) magnetic field strengths [121]. In the 4T and 7T acquisitions, 42.4% and 51.5% of the

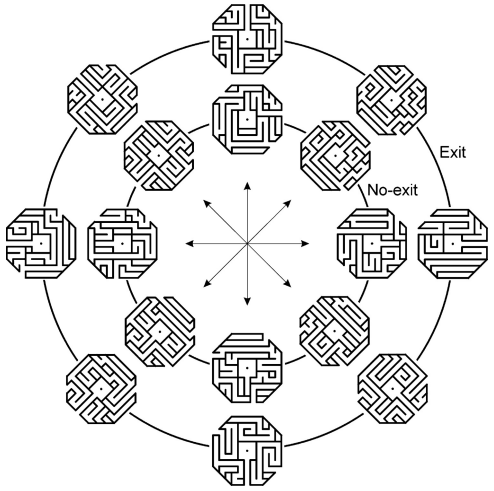



**Fig. 11.** Design of maze solving experiment [137].

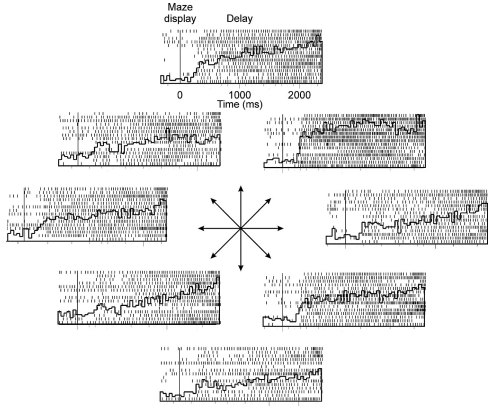



**Fig. 12.** Directional maze tuning of the activity of a cell recorded in primary motor cortex [137].

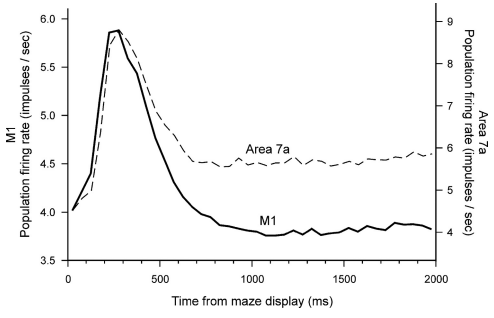



**Fig. 13.** Time-course of population activity in primary motor cortex (solid line) and area 7a (dashed line) during the delay period of the maze task [137].

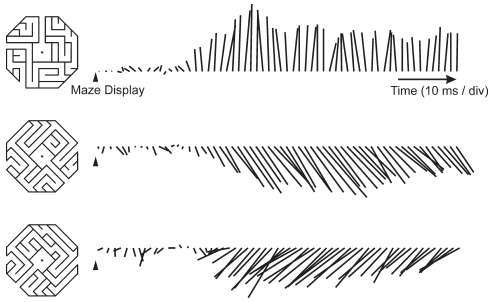



**Fig. 14.** The neuronal population vector tracing the maze exit path [138].

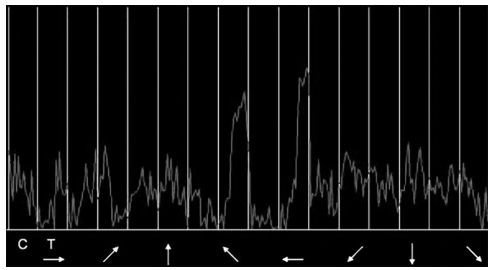



**Fig. 15.** Maze directional tuning of the BOLD (blood oxygenation level dependent) signal of a single voxel in the superior parietal lobule of a human participant recorded at 4T [120].

voxels were directionally tuned (an example from a single voxel is shown in figure 14), respectively, indicating a coherent tuning of local neuronal populations contributing to the change of the single-voxel BOLD signal. Preferred directions ranged throughout the directional continuum of 360°, and the population vector pointed very accurately in the direction of the maze path [120]. The ultra-high field (7T) study provided new, precise insights into the spatial representation of maze path directional tuning in human SPL. More specifically, we found that voxels tuned in similar preferred directions clustered in discrete ensembles in a honeycomb manner (see figure 15).

### *Neural Networks*

In 1991 Alex Lukashin, a brilliant artificial neural network modeler, joined my team for an original and productive research project on modeling motor cortical operations using massively interconnected neural networks. We used massively, nonsymmetrically, interconnected networks and simulated annealing to model dynamic directional operations [139–141], trajectory

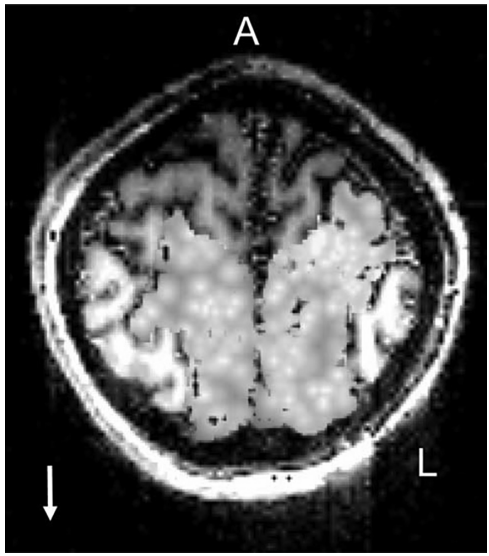



**Fig. 16.** Mapping of the downward (±22.5°) preferred direction (reference direction; white arrow) in a single slice of the superior parietal lobule of a participant, recorded at 7T [121].

formation (one-at-a-time [142] and in parallel [143]), exertion of force [144], and a potential neuroprosthetic controller [145].

*Magnetoencephalography*

The new millennium rushed in with a new tool that enabled us to monitor dynamic activity in the human brain millisecond-by-millisecond in a totally noninvasive way, namely MEG. The short history of acquisition of a MEG instrument in our center is as follows. In the late 1990s, US Senator Pete Domenici expressed a strong interest in a congressional appropriation to fund research in mental health using the latest tools for evaluating brain function. He and his wife, Nancy, were very active in activities and initiatives supporting mental health. Naturally, he consulted about it with Steve Hyman, director of the National Institute for Mental Health (NIMH) regarding the status of high-end instrumentation in brain research in humans. In the MRI field, the name of the game was imaging at high magnetic field strength. At that time, there were precious few high-field 4T magnets in the country, so the purchase of a next generation, ultra-high field magnet at 7T was an obvious choice. Now, fMRI at any field strength lacks the requisite temporal resolution at which the brain works. For example, a typical simple reaction time is of the order of 200 ms: The traffic light turns red, you break ASAP, the whole stimulus-response takes

less than 1 s. By contrast, a typical time interval between two successive image acquisition in fMRI (repetition time) is about 2 s, and even the currently fastest repetition time of 700 ms (in the Human Connectome data) is just too long to provide useful data for processes completed within a 200 ms reaction time. MEG is the only way to obtain noninvasively dynamic brain data on a millisecond-by-millisecond basis by measuring magnetic fields generated by the motion of ions across dentritic membranes. Gaining access to the workings of the human brain was an early dream of mine. I did my first experiments with MEG in the mid-1980s at the Applied Physics Laboratory (APL) in Jessup, Maryland, where I obtained permission for the recordings through the academic affiliation of APL with Johns Hopkins University (JHU) and a JHU-APL Program Project Biomedical Engineering grant from NIH in which I was a coinvestigator. It was a thrill to record ongoing activity from my own motor cortex, with all supporting equipment made of wood to minimize magnetic interference—a strange setup! MEG recordings from the motor cortex even with few, or even single, channels are possible because the human motor cortex is primarily located in the anterior bank of the central sulcus and the MEG signal is high when the MEG sensor is oriented perpendicularly to the dendrites of the neurons, an almost perfect arrangement. It was a very rewarding proof of principle but we could not complete a study due to limited availability of the MEG instrument. The possibility of using MEG came up again in 1990, when I was offered a position at the Center of Neural Sciences of New York University, where there existed a whole-head MEG facility directed by the pioneers in that field, Loyd Kaufman and Sam Williamson.

Then, in 1994 I was being recruited by Dr. Gerald Fischbach at Harvard, to join his Department of Neurobiology as a tenured professor. During my visits there I had long discussions with Dr. Fischbach and Dr. Hyman (who was the acting director of Harvard's Mind Brain Behavior [MBB] Interfaculty Initiative) regarding a state-of-the art instrumentation for studying brain function in humans in health and disease. The point was that my main research using multielectrode recordings in primates would be fully accommodated at the department, but my role and contribution to the MBB initiative would best be served by establishing and carrying out noninvasive research in human subjects. There was a 3T magnet at Beth Israel Hospital and a 4T magnet at Mass General, but we needed a MEG to add monitoring of dynamic brain processing. Dr. Fischbach and Dr. Hyman were both persuaded and enthusiastic about the breadth and depth of this plan. I still have the blueprints of my proposed lab space in the Department of Neurobiology (actually next to Dr. Linda Buck's lab). A potential space for placement of the MEG instrument was identified and an exceptionally attractive offer was made. For various reasons, my wife and I decided to stay in Minnesota but the MEG seed was sown.

By 1998, when Senator Domenici expressed interest in supporting high-end brain research for mental illness, the landscape had changed drastically: Both of the people who were recruiting me to Harvard were now at the helm of the two major neuroscience institutes at the NIH; Steve Hyman was the director of NIMH and Gerald Fischbach was the director of the National Institute of Neurological Disorders and Stroke (NINDS). Dr. Hyman was Senator Domenici's main consultant, and I want to believe that my deliberations with him and Dr. Fischbach in the previous years contributed to the final decision that funds that the senator procured through a congressional appropriation be allocated to the purchase of ultra-high field magnets (7T) and MEG instruments. Three sites were identified to receive those instruments, namely Massachusetts General Hospital at Harvard (7T magnet + MEG; Dr. Bruce Rosen, PI), Center for Magnetic Resonance Research of the University of Minnesota (7T magnet, Dr. Uğurbil, PI and MEG, myself, PI), and University of New Mexico Medical School (4T magnet and MEG). The MEG instrument was placed in a special suite at the Brain Sciences of the Minneapolis VA Medical Center (the Domenici Research Center for Mental Illness) and the dedication ceremony was held on August 6, 2001.

Based on the advice of Dr. Ed Flynn, a top expert in MEG, we purchased a state-of-the-art MEG instrument consisting of 248 axial gradiometers covering the whole head. We also recruited Dr. Art Leuthold, a MEG physicist, to manage the facility that, thanks to him, is still working like a charm 25 years later. So, my dream finally came true and with it a gradual change in my scientific directions. Although I continued pursuing basic



**Fig. 17.** The MEG instrument at the Brain Sciences Center, Minneapolis VA Medical Center.

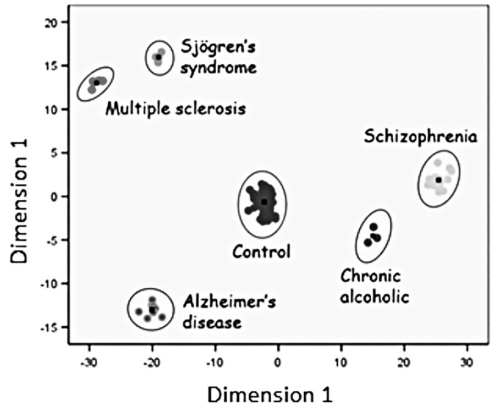



**Fig. 18.** 100% correct classification of the MEG pattern of six diseases, as indicated (unpublished).

research using MEG, as a physician by training, I always had an almost vocational interest in human disease. In parallel with basic research, I extended my focus on diseases affecting the brain. MEG measures magnetic fields down to $10^{-15}$ Tesla, about 1 billionth of the strength of the earth's magnetic field. It is enclosed in a heavily shielded room and has been working like a charm since 2000 until this very day. We have acquired close to 4,000 MEG scans in various projects, and we are currently acquiring several scans weekly.

Obviously, the brain functions as a massively interconnected network, so the first analysis we did was to get a picture of all interactions. For that purpose, we computed all pairwise zero-lag cross-correlations (N = 30,628, given 248 sensors) and plotted them in a MEG-sensor map, with intensity scaled by their strength and keeping their sign (green for positive, red for negative). A key methodological point is that MEG time series, being acquired at 1.017 kH sampling rate (i.e., every 0.083 ms), are highly autocorrelated, in addition to the presence of trends and propagation of noise. This means that the MEG time series cannot be cross-correlated as raw data because all their internal features and time-varying dependencies will show up spuriously in the cross- correlation function (CCF). This is a well-known issue in time series analysis that was dealt with decisively in the 1970s by Box and Jenkins [146], Granger and Newbold [147], Priestley [148], and other giants in that field. The main application of time series analysis in those times was in econometrics, where, for example, relying on the wrong analysis of time series of shares in the stock market would lead to wrong decisions and potentially substantial losses.

The solution is to convert the time series to white noise ("prewhitening") by removing autocorrelations, trends, and noise propagation, a procedure implemented by fitting an Auto Regressive Integrated Moving

Average (ARIMA) model [146] and taking the residuals ("innovations") for CCF analysis. This ensures that the CCF results reflect true associations between the two series. Alternatively, a linear regression approach can be used where the autoregressive, trend, and noise propagation factors can be specified as independent variables and, again, using the residuals for CCF analyses. By the way, these considerations hold for any kind of time series. In neuroscience, extensive work has been published on cross-correlations of fMRI time series, in the vast majority of cases without prewhitening, an unfortunate cause of potentially spurious results. In 2011, we published the correct processing and analysis of fMRI time series in a very explicit way [149] and illustrated the contrast between correct and spurious CCF, when data were not prewhitened. In a specific application, we used fMRI CCFs to discriminate brain patterns of patients with posttraumatic stress disorder (PTSD) from brain patterns of healthy subjects [150]. Applying the discriminant analysis to zero-lag correlations of prewhitened fMRI time series data ("noise correlations") yielded a very high, correct discrimination outcome (93.3% sensitivity, 95.1% specificity), whereas applying the same analysis to zero-lag correlations of raw fMRI time series yielded only chance outcomes.

Back to MEG, in 2005 we described and applied the ARIMA model to prewhiten (i.e., convert to white noise) 248-sensor time series (N = 45,000 time samples each) and compute, using their residuals ("innovations") 30,628 CCFs during performance of three visuomotor, shape-copying tasks [113]. Then, an intriguing observation opened the door for extensive research into brain diseases: At rest, the patterns of these 30,628 zero-lag cross-correlations were very similar across healthy subjects [151]. This close similarity of MEG brain patterns across healthy individuals provided a "normative" background to detect deviations in brain disease. This led to our most significant paper in that topic, namely the capability of MEG zero-lag cross-correlations to successfully discriminate disease affecting the brain [152]. Using a genetic algorithm, we were able to identify small subsets of these correlations (< 20) which discriminated 100% correctly (with most correct classification probabilities > 0.95) 142 brain patterns of six groups (healthy controls, Alzheimer's disease, schizophrenia, chronic alcoholism, Sjogren's syndrome, multiple sclerosis).

### *Human Diseases*

From 2005 onward, we started parallel research on brain health and disease, from development to old age. In addition to fMRI and MEG as brain-directed methods and methods of experimental/cognitive psychology, we added immunogenetics (see details below), and, more recently, blood biomarkers for dementia and neurodegeneration. These approaches were complemented by recordings in neural cultures by microelectrode

arrays [153, 154] and determining the effects of various factors on spreading and apoptosis in neural cultures.

### Post Traumatic Stress Disorder

The impetus for disease-related studies came in 2008, when I was provided with seed funds to investigate (using MEG) the brain mechanisms in PTSD, a disease of major concern to veterans. PTSD is the only mental health disorder with a known origin, namely the exposure to a traumatic event. Brian Engdahl, a clinical psychologist at the Minneapolis VA hospital and a long-time expert on PTSD, spearheaded the work. We identified a focus of significant difference in cross-correlations from healthy controls in the superior temporal gyrus of the right hemisphere [5], broadly corresponding to the area implicated in reenactment of old experiences in Penfield's study [4]. We followed up with research on PTSD using both MEG and fMRI to develop methods for PTSD diagnosis and staging [150]. In one of our PTSD studies using MEG, we identified brain network changes underlying post-traumatic growth [155], a topic of perennial interest.

In subsequent studies using fMRI, we found that PTSD is characterized by increased overall cross-correlations compared with controls [156], which actually increase in strength progressively between areas further along in the sensory processing chain delineated by Jones and Powell [157]. Since only a fraction of people exposed to serious traumatic events develop PTSD, it is still an open question as to what makes some people more vulnerable than others. Predisposing experiences (e.g., abuse during childhood, previous exposures to traumatic events, etc.) certainly play a role but cannot inform the biological basis of developing PTSD. Conversely, what makes a person resilient to trauma? We identified decorrelation of the interactions of the right temporal area with other brain areas [158] as a neural mechanism of resilience to trauma. With respect to biological factors, we produced evidence that the apolipoprotein E allele *Apoε2* may confer resilience [159], whereas certain immune-related alleles may confer resilience or susceptibility [8]. In 2018 we proposed a two-hit model for the biological origin of PTSD, namely a traumatic event occurring on the background of increased glutamatergic neurotransmission due to ongoing neuroinflammation [160] as a result of various possible viral and bacterial insults; the adverse effects of such insults would be reduced or neutralized by the presence of certain immune-related alleles, such as those identified in our study [8].

### Gulf War Illness: A Brain + Disease

Gulf War Illness (GWI; now called Chronic Multisymptom Illness [CMI]) is a debilitating disease that has affected about one-third of the approximately 600,000 veterans enlisted during the first Persian (Gulf) War of 1990–1991. It is characterized by chronic fatigue, pain, neurocognitive/mood symptoms,

and also by symptoms affecting other organ systems, including respiratory, bowel, and skin. It has afflicted deployed and nondeployed veterans, many of whom present with overall declining health over the years. In 2000 I was asked by Dr. Paul Hoffman, medical director of the Veterans Affairs Central Office, to form a committee to investigate brain-related issues of veterans suffering from GWI using a comprehensive approach. I was honored to be chosen to lead this investigation, at the center of veterans' health, and I gladly accepted. It was an intriguing issue to investigate but also, as a VA employee, I had both a real and a moral obligation to lead this investigation. Indeed, I put together an impressive US-wide committee with multimodal expertise, including neuropsychology, MRI, positron emission tomography (PET) (for assessing brain monoamines), and MEG. The study was ready to start in 2001 but the new VA chief of research (Dr. Nelda Wray) abruptly terminated the study before it had a chance to even start; no explanation was given, a very puzzling decision until today.

Now, as fate had it, in 2013, I was asked again by the chief of the VA Research Office (Dr. Tim O'Leary) to investigate veterans' health with GWI in general, and their brain function in particular, using MEG and MRI. Indeed, we identified neural network abnormalities in GWI using MEG [161] and, in subsequent studies, we further documented abnormalities in GWI brains using structural and functional MRI, including the presence of atrophy [162]. We identified six immune-related HLA alleles that were protective against GWI but which the veterans with GWI lacked. One of them (HLA DRB1*13:02) was particularly effective in preventing this brain atrophy [35]. Interestingly, that same allele also prevented brain atrophy in healthy women veterans across the lifespan [163]. These findings pointed to the persistence of harmful antigens against which DRB1*13:02 would be effective. We investigated this hypothesis of "persistent antigens" by assessing the effects of blood serum from GWI patients on function and morphology of brain cultures in vitro, including cultures of embryonic mouse brain and neuroblastoma N2A line [164]. Blood serum from GWI and healthy GW veterans was added, alone and in combination, to the culture and its effects on the function and morphology of the culture assessed. Neural network function was assessed using electrophysiological recordings from multielectrode arrays in mouse brain cultures, whereas morphological assessments (neural growth and cell apoptosis) were done in neuroblastoma cultures. In contrast to healthy serum, the addition of GWI serum disrupted neural network communication and caused reduced cell growth and increased apoptosis. All of these detrimental effects were prevented or ameliorated by the concomitant addition of serum from healthy GW veterans. These findings indicated that GWI serum contains neuropathogenic factors that can be neutralized by healthy serum and provided evidence for the presence of persistent antigens circulating in GWI blood that could be neutralized, possibly by specific antibodies present in the healthy serum.

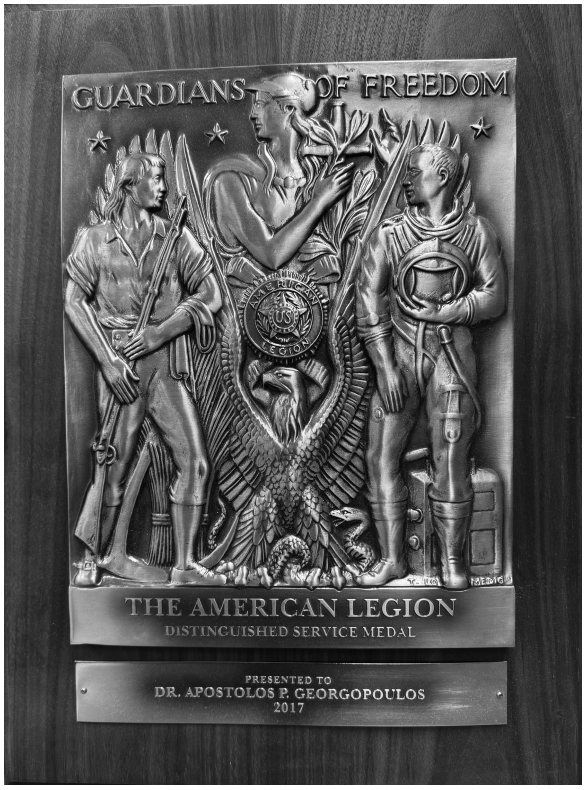



**Fig. 19.** The American Legion Distinguished Service Medal awarded to Dr. Georgopoulos in 2017.

Since all enlisted veterans received many vaccines, we hypothesized that such harmful factors in the blood could include persistent vaccine antigens that could be harmful by themselves but which would be eliminated by the *successful mounting of antibodies against them*. Indeed, adding to the serum antibodies specific for vaccine antigens that the veterans received ameliorated the adverse effects of the GWI on spreading and apoptosis in cultures. The antigen contained in the anthrax vaccine administered to the veterans has been the focus of our current research in that field [165]. In recognition of this work on GWI, I was awarded in 2017 the American Legion Distinguished Service Medal (figure 19).

The case of GWI is interesting because its symptomatology is very similar to that observed in other chronic disorders, including Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) and Long COVID [31, 166]. All three are chronic diseases and all have brain involvement, which is also present in another chronic illness—Post-Treatment Lyme Disease Syndrome (PTLDS) [167]. Any insight into the mechanisms

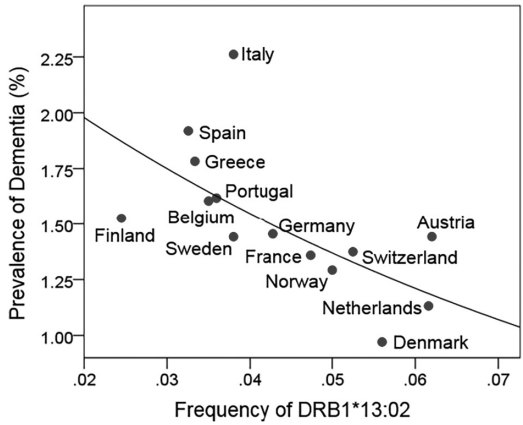



**Fig. 20.** Dementia prevalence decreases with increasing frequency of Human Leukocyte Antigen (HLA) allele DRB1*13:02 in 14 continental western European countries [10]. See figure 1 in [10] for flags in color.

involved in brain abnormalities would have major implications in a wide range of chronic conditions affecting the brain.

### Other Brain Diseases

Since 2005 I have extended my research to the study of traditional brain diseases [10–33], including Alzheimer's disease and other dementias, Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis, and brain cancer [10–33]. With my long-term collaborator, Dr. Lisa James, we have been pursuing during the past 15-odd years three main avenues of research, namely epidemiology, immunogenetics, and viruses. The basic rationale rests on the hypothesis that viruses are a "hit" that can trigger those diseases when other factors are present (e.g., environmental). Viral infections are handled by the immune system, with a prominent role of the adaptive immunity involving immune genes of HLA Class I (HLA-I) and HLA-II alleles. This is the most highly polymorphic system in the human chromosome, located in chromosome 6, comprising thousands of HLA molecules that code for cell surface glycoproteins that bind to viral (and other) antigens leading to elimination of the virus (HLA-I system) and initiate the production of antibodies against it (HLA-II system). Although the very high polymorphism of the HLA system ensures the success of the population in surviving viral insults, an individual carries only 12 alleles (6 from Class I and 6 from Class II), which leads to substantial uncertainty about the success of a specific individual – the outcome would depend on the specific alleles and the specific virus. Now, there is epidemiological information concerning the prevalence of a disease in a particular country, where there is also information about the prevalence (i.e., frequency) of

HLA alleles in the same country as well. Lastly, there is information about how effectively a given HLA molecule can bind to a viral antigen to predict, with a degree of confidence, a successful defense against the virus. Given a disease of interest, we would like to know (a) the prevalence of the disease in a set of countries, and (b) the frequency (prevalence) of HLA alleles in the same countries (the more alleles the better). Then, we can test for associations between the two prevalences and gain an insight into the possible connection of specific alleles to the disease. Given the identification of such alleles, we can then (c) estimate *in silico* their predicted binding affinity to a number of candidate viruses (e.g., human herpes viruses) to generate hypotheses about the virus(es) that could be "hits" for the disease.

In the first series of our studies, we focused on 14 Continental Western European (CWE) countries, where life expectancy was practically identical, and obtained data on (a) the prevalence of dementia of the Alzheimer's type and (b) the frequency of 127 HLA alleles (69 HLA-I and 58 HLA-II) [10]. We then computed, for each HLA allele, the correlation between the disease prevalence and the allele frequency across counties to generate an "immunogenetic profile" for the disease, where the rows are the HLA alleles and the values are the correlation of the allele to the disease; negative values would indicate a protective role of the allele, where positive values would indicate a predisposing role. In our first publication we focused on HLA DRB1*13:02 allele that we had found to be protective against brain atrophy in GWI [35] and healthy aging [163], and protective against increased neural network variability in healthy aging (see below). Dementia prevalence decreased exponentially with increasing DRB1*13:02 frequency (see figures 20 and 21). The Spearman rank correlation between dementia prevalence and DRB1*13:02 frequency in CWE countries was –0.750 (P = 0.002), indicating a robust, strong protective role of that allele against dementia of the Alzheimer's type.

Remarkably, this association was independent of apolipoprotein E4 (apoE4) prevalence, a known risk factor for Alzheimer's disease (partial correlation of dementia vs DRB1*13:02 prevalence, controlling for apoE4 prevalence = –0.782, P = 0.002). Doubling of the DRB1*13:02 frequency was associated with 31% reduction in the prevalence of dementia. Two more alleles with a strong protective effect were identified later (DRB1*01:01 and DRB1*15:01). Finally, we determined *in silico* the predicted binding affinities of these alleles to all nine types of human herpes viruses (HHV), with the highest one being for HHV6 and HHV7 [16], thus closing the dementia-HLA-virus loop. In the following years we published on the association between viruses, multiple sclerosis, and brain cancer, and the sharing of HLA immunogenetic profiles between Alzheimer's disease and Parkinson's disease [12], and between multiple sclerosis and brain cancer [26].

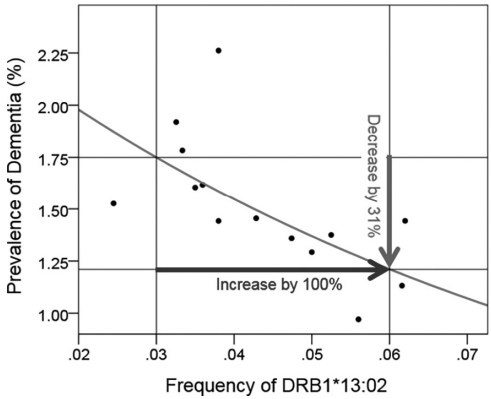



**Fig. 21.** Quantitative assessment of the data in Fig. 20 [10].

*The Healthy Brain Aging Project*

In 2010 we initiated a longitudinal project focused on evaluating brain health in adult women US veterans using cognitive assessment, MEG and MRI acquisitions, lifestyle (including detailed nutrition information), immunogenetic profile, apoE genotype, and blood draw for current and future tests [168]. Several published papers provide an overview of the scope of the project. In the first paper [169], we reported on the systematic effect of the apoE genotype on synchronous neural interactions (SNI) assessed by MEG, where the SNI distribution in brains with the ApoE2/2 genotype have the lowest variance and coefficient of variation, as opposed to those with the ApoE4/4 genotype which have the highest variance and coefficient of variation. From a brain function viewpoint, the variation in the neural interactions seem to be a sensitive measure of the "goodness" of brain functional status, a supposition supported by a subsequent paper from our group [170], which documented an increased variation in the SNI distribution during aging. This increased variation was prevented in carriers of HLA alleles DRB1*13:01/02 [171]. Similarly, the brain atrophy observed during healthy brain aging was absent in women carrying those alleles, predominantly the DRB1*13:02 allele [163]. With respect to blood-related measurements, we found that addition of serum to neuroblastoma cultures increased with age (independently of apoE genotype) and was significantly associated with seropositivity only to human herpes virus 5 (HHV5, cytomegalic virus), among the six HHV viruses the seroprevalence of which could be tested (HHv1-HHV6) [172]. Currently, we are measuring blood biomarkers for dementia ($A\beta_{1\text{-}40}$, $A\beta_{1\text{-}42}$, $A\beta_{1\text{-}42}$ /$A\beta_{1\text{-}40}$ ratio, neurofilament light chain, total Tau, phosphorylated Tau181, and phosphorylated Tau217). In a recent paper [173] we reported the increase of these biomarkers with age, which was steeper in the presence of HHV seropositivity.

Altogether, these studies from this longitudinal project interweave with, and complement, our main approach that ties age, cognitive assessment, brain measures, and immunogenetics to blood biomarkers of the status of brain biology.

*John C. Eccles*

In the early 1980s I met John "Jack" Eccles at a dinner in Dr. Mountcastle's home. Dr. Eccles was visiting Baltimore and was Vernon's houseguest. We were immediately engaged in philosophy (!) - I was a keen logical positivist then and an admirer of Karl Popper. As it happened, he had with him the yet unpublished notes of his *Dialogues with Popper* and he graciously shared them with me! Their book was published in 1984 (Karl Popper and John C. Eccles: *The Self and Its Brain. An Argument for Interactionism*. Routledge, London, UK), a remarkable contribution to neurophilosophy. That evening, he asked me a favor: to support the journal *Experimental Brain Research* by submitting my papers there. He felt very strongly about the journal – after all, he was a member of its inaugural editorial board (in good company with P. Dell, D. M. MacKay, D. Ploog, J. Szentágothai, H. Waelsch, and Otto D. Creutzfeldt as editor in chief) and had published the first two papers in the inaugural issue of it in 1966! [174, 175]. Indeed I promised. I published my first cortex paper on directional tuning in the motor cortex in the new *Journal of Neuroscience* [176] as a contribution to our Society for Neuroscience and a tribute to Max Cowan, the editor in chief of the journal. However, most of my papers in subsequent years were published in *Experimental Brain Research*, keeping my commitment to Eccles.

We kept frequent contact over the years. We spent a good time discussing cortical neurophysiology and other matters in 1983, at the Schloss Ringberg (Bavaria) Conference on *The Cerebral Events in Voluntary Movement: The Supplementary Motor and Premotor Areas*, organized by J. C. Eccles, O. D. Creutzfeldt, and M. Wiesendanger. In 1987, while directing the neuroscience course for the medical students at Hopkins, I learned that Dr. Eccles was visiting at the Neuroscience Research Program at the Rockefeller University in New York. Now, in my course, I had arranged that the last lecture be given by a prominent neuroscientist (Walle Nauta being a frequent lecturer), so that the students get a flavor of great research. So, I grasped at the opportunity and invited Dr. Eccles to come and give that lecture – he gladly accepted! Indeed, on March 11, 1987, he delivered a vibrant, exciting lecture on "The History of Ideas Concerning the Development of Synaptic Transmission." I had the good idea to tape it, and I routinely show it to my colleagues. In 2013 I mentioned this lecture to Gordon Shepherd during the meeting of International Neuroinformatics Coordinating Facility (INCF) in Stockholm, and he asked me to send him a copy

of the tape to be deposited in some archive of the Society for Neuroscience – it may still be there. The last time I met Dr. Eccles was in 1990 in Stockholm at the meeting of the European Neuroscience Association, where I delivered a plenary lecture. At that time, I was trying to decide whether to accept the offer from Minneapolis or stay at Hopkins. I discussed this with Dr. Eccles and asked for his advice. He strongly advised me to move to Minnesota, a decision we made on Thanksgiving in 1990. His advice weighed heavily in my decision.

*Gerald M. Edelman*

Before ending, I want to pay tribute and dedicate this scientific autobiography to Gerry Edelman who had been my most ardent intellectual supporter since the early 1980s. I first met Gerry in 1982, at the first Neuroscience Research Program (NRP) meeting at the Rockefeller University. Gerry was very excited about the work of Nikolai Bernstein, which I also admired. Gerry complimented me on my presentation, which was published in 1984 in a volume of that meeting [57]. Our ideas about how the brain works at the systems/neural network levels were very similar, and we discussed and refined them over the years. In 1992 I was elected a NRP associate and tremendously enjoyed our regular meetings, exemplars of free thinking among diverse neuroscientists, with Gerry an incessant facilitator with razor-sharp intellect, judgment, and vision. One of those meetings was dedicated to "Prewhitening," the basic statistical method for assessing the relations between time series, as I have discussed in a previous section. Gerry thought this was a truly fundamental tool, hence the meeting which was chaired by Tom Albright. Gerry was a keen musician, concert-level violinist, and very proud of the concert-grade, award-winning auditorium at the Neuroscience Institute in La Jolla. So, he was intrigued by my paper linking prewhitening and music [177], which further reinforced his appreciation of prewhitening as a necessary and powerful tool to discover hidden relations between time series (in any field) and, as importantly, to avoid spurious, misleading correlations. Figure 22 depicts the placement of instruments in a 2-D multidimensional scaling space, derived by correlating residuals of prewhitened time series of orchestral scores of various instruments in L. V. Beethoven's *Symphony No. 7*, Movement No. 2 [177].

In 1993, by Gerry's invitation, I delivered the Sherrington Lecture at the Department of Neurobiology of the Scripps Research Institute, one of my highest honors. The latest grand event was the celebration of the 50th anniversary of the Neuroscience Research Program, actually a celebration of Gerry's lifelong contributions to neuroscience. The last time I saw Gerry and Einar Gall was at a meeting on the Future of Brain Research, organized by Gerry and Einar in La Jolla in March 2013, almost a year before his untimely death. He was as sharp as ever!

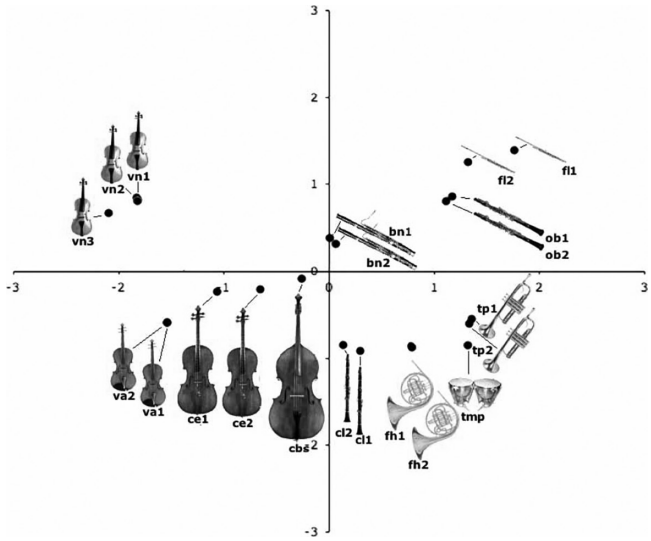



**Fig. 22.** Recovery of orchestral arrangements of instruments derived by correlating residuals of prewhitened time series of respective musical scores of those instruments in L. V. Beethoven's *Symphony No. 7*, Movement No. 2 [177]. See text for details.

I frequently peruse Gerry's books – all hand-dedicated to me with his black ink pen and calligraphic writing, rediscovering his insights and perspectives. But what I miss most is his calling me, all of a sudden, to discuss and exchange ideas, always an exciting wake-up call to my daily routine. Their memory still does.

*American Academy of Arts and Sciences*

Of all the honors I have received, my election as fellow to the American Academy of Arts and Sciences in 2002 was extra special because it gave me the opportunity to nominate to this oldest academy in the country people from other fields of Arts and Sciences, outside my professional field of neuroscience. This was in keeping with the vision of the Academy's founders John Adams, James Bowdoin, John Hancock, and 59 other scholar-patriots who founded the academy in 1780 during the American Revolution as a way for the new republic to honor accomplished individuals and engage them in advancing the public good through the cultivation of "every art and science." So, I am proud that I nominated, over the past twenty-odd years, diverse and top-rank persons who have made history in their fields and who were actually elected in the first round! They include jazz legends Sonny Rollins (2010) and David Brubeck (2011); legal feminist Catharine McKinnon; Elizabeth A. Long, professor of law at the University of Michigan Law School (2004); Clive Cookson, technology editor, *Financial*

*Times* (2015); William Kling, president, American Public Media Group (2014); and Joan Gabel, chancellor, University of Pittsburgh (2024).

## Epilogue

It has been a long, exciting journey that, luckily, still goes on. I am pleased that, essentially, I could pursue research projects with intrinsic value, implications for medicine and health, and wider applicability to other species [178–180]. I have been asked frequently what I would do if I won the lottery and became an instant billionaire: "I would do exactly the same as I have been doing!" I cannot overemphasize the foundational, *sine qua non*, role my research teams have had all those years. I am proud to see my team members and collaborators thriving in several institutions, carrying the torch of scientific discovery and transmitting their knowledge to their own collaborators. All said and done, I couldn't have wished for anything else! The original inspiration of geometry miraculously materialized in every thread of my research during the past 50-odd years of my research

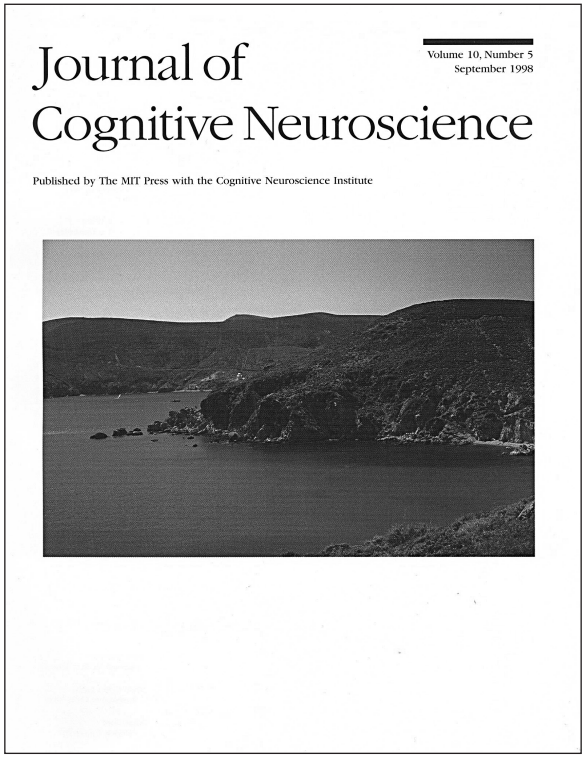



**Fig. 23.** Ithaki, a Greek island in the Ionian sea, home of Ὀδυσσεύς (Odysseus; Ulysses), King of Ithaki. My picture, 1984. (Cover photograph, *Journal of Cognitive Neuroscience*, September 1998) [181].

and filled my life with revelations I would not have dreamt of in my youth, and yet I am living them now in my old age, as we speak, thanks to my wonderful team: Dr. Lisa James leads the Healthy Brain Aging Project and, together with Dr. Brian Engdahl, are the key investigators in PTSD research; Dr. Peka Christova leads research and analyses of MRI data of the Human Connectome Project; Dr. Art Leuthold still holds ably the MEG fort; Dr. George Stratigopoulos leads the biochemical and cell biological research on blood biomarkers for early detection of dementia; and Stacy Dolan (research nurse), Laura Kalipe (senior laboratory technician), and Matt Sanders (computer scientist) provide invaluable support.

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## The Journey to Ithaka

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 I cited in my interview with Mike Gazzaniga [182]:

Ιθάκη (Κωνσταντίνος Καβάφης, 1911)

| | |
|---|---|
| Σα βγεις στον πηγαιμό για την Ιθάκη, | As you set out for Ithaka |
| να εύχεσαι νάναι μακρύς ο δρόμος, | hope your road is a long one, |
| γεμάτος περιπέτειες, γεμάτος γνώσεις | full of adventure, full of discovery … |

| | |
|---|---|
| Πάντα στον νου σου νάχεις την Ιθάκη. | Keep Ithaka always in your mind. |
| Το φθάσιμον εκεί είν' ο προορισμός σου. | Arriving there is what you're destined for. |
| Αλλά μη βιάζεις το ταξείδι διόλου. | But don't hurry the journey at all. |
| Καλλίτερα χρόνια πολλά να διαρκέσει· | Better if it lasts for years, |
| και γέρος πια ν' αράξεις στο νησί, | so you're old by the time you reach the island, |
| πλούσιος με όσα κέρδισες στον δρόμο, | wealthy with all you've gained on the way, |
| μη προσδοκώντας πλούτη να σε δώσει η Ιθάκη. | not expecting Ithaka to make you rich. |
| Η Ιθάκη σ' έδωσε τ' ωραίο ταξείδι. | Ithaka gave you the journey. |
| Χωρίς αυτήν δεν θάβγαινες στον δρόμο. | Without her you wouldn't have set out. |
| Άλλα δεν έχει να σε δώσει πια. | She has nothing to give you now. |
| Κι αν πτωχική την βρεις, η Ιθάκη δεν σε γέλασε. | And if you find her poor, Ithaka won't have fooled you. |
| Έτσι σοφός που έγινες, με τόση πείρα, | Wise as you will have become, so full of experience, |
| ήδη θα το κατάλαβες η Ιθάκες τι σημαίνουν. | You'll have understood by then what these Ithakas mean. |

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