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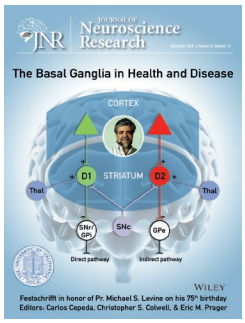
INTRODUCTION



Michael S. Levine: Research pioneer of basal ganglia function and dysfunction. A small tribute on the occasion of his 75th birthday anniversary

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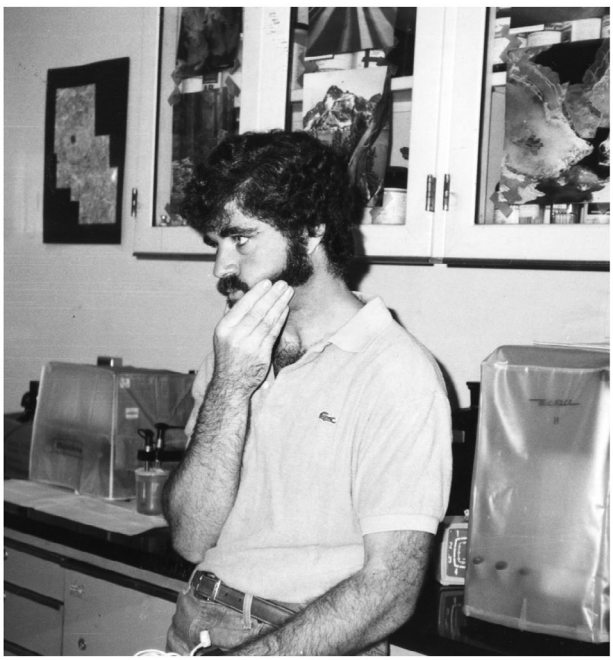

Professor Michael Steven Levine (Mike for friends and family) has touched many lives as a teacher, scientist, mentor, and colleague. For over 50 years, Mike has been sculpting the careers and personalities of hundreds of basic scientists, neurologists, neurosurgeons, teachers, lawyers, and other professionals. Most of his students have developed successful careers and always remember him as a cherished mentor and friend. It is not surprising that former students and colleagues routinely come back to him for advice and guidance. Beloved by his students and respected by his peers, Mike's contributions to science are only eclipsed by his contributions to academic life at the University of California Los Angeles (UCLA). Mike's career as a teacher began in parallel with his research and it is difficult to tell which part of his job he loves more. For 50 years, he has taught a myriad of undergraduate and graduate students. His pedagogic skills are unsurpassed. Former students never forget his graphic demonstrations about how the basal ganglia work to orchestrate movements. We vividly recall one of Mike's talks at a Gordon conference where he clearly explained electrophysiology to a diverse audience with little experience in these techniques. To explain electrophysiology to a layperson or even to a scientist not versed in the field is not an easy task. But Mike could make it simple and understandable, and after his talk everyone felt they were expert electrophysiologists. During the discussion, someone in the audience said, "You chose the wrong profession, you should have been a preacher". Fortunately for us, he became a scientist.

After obtaining his Ph.D. degree in Physiological Psychology (1970) at the University of Rochester in New York, Mike's goal was to learn single-cell electrophysiological recordings to be able to correlate neuronal activity and behavior. At the time, two premier laboratories fulfilled this requirement: Dr. Edward V. Evarts' lab at the National Institute of Mental Health in Bethesda and Dr. Nathaniel Buchwald's at UCLA. A number of fateful circumstances, including the appeal of California weather and lifestyle, led Mike to choose UCLA. How fortunate we have been for this decision. His close collaboration with Dr. Chester Hull—a longtime collaborator of Nat Buchwald—and other postdocs produced a series of landmark papers using *in vivo* intracellular recordings to examine the connectivity of the caudate nucleus with other basal ganglia nuclei, the thalamus, and the cerebral cortex. His work opened new roads that had been unexplored at the time including basal ganglia development and the detrimental changes that occur during aging. Only the few lucky (or unlucky we should say) investigators who have attempted to do intracellular recordings of medium-sized spiny neurons (MSNs) *in vivo* could understand how difficult and time-consuming this is. This work represented a heroic effort, and Mike rose to the challenge. Intracellular recordings were made much simpler when *in vitro* slices became the technique of choice to study striatal neuron properties and synaptic connectivity. Fully aware of the advantages of this technique, Buchwald's lab moved in that direction and Mike

played a very important role. By that time (in the mid-1980s), Mike had become full professor and was the *de facto* leader of the lab. Without being overly demanding, he always managed to get the best out of the postdocs working in the lab. His knowledge of mechanics and electronics allowed him to become a trouble-shooting expert. When postdocs had a problem with electronic noise, Mike was there to fix it. In every aspect, he is a problem solver.

It is difficult to single out which contributions from Mike's lab have had the most impact. Besides unraveling the functional connectivity of the striatum with other structures and opening new roads to study development and aging in the striatum, a number of discoveries will always be associated with his name. One of them was helping disentangle the complex and diverse ways by which dopamine (DA) modulates MSN excitability and glutamatergic neurotransmission. Another one was providing a solid basis to examine altered synaptic transmission along the corticostriatal pathway in Huntington's disease (HD) and other neurodegenerative diseases. In the late 1980s and early 1990s, the effects of DA on striatal neuron intrinsic and synaptic excitability remained unclear and controversial. A series of landmark papers from Mike's lab demonstrated that the effects of DA were dependent on the type of glutamate and DA receptor activated. Thus, activation of DA D1 receptors increased excitability whereas activation of DA D2 receptors decreased excitability. This differential modulation provided insights for a better understanding of striatal function in physiological and pathological conditions. Mike also has been a pioneer in HD research. Soon after Gillian Bates generated the first transgenic mouse model of HD in 1996, Mike's lab jumped at the opportunity to unravel MSNs' intrinsic and synaptic alterations. Contrary to the prevailing belief that glutamate transmission along the corticostriatal pathway should be increased in HD, his lab found that there is a disconnection between the cortex and the striatum with disease progression, which renders MSNs susceptible to degeneration. However, the changes were shown to be biphasic—early increases in glutamate transmission when overt symptoms start followed by late decreases at the fully symptomatic stage. Cognizant of the importance of using novel techniques to survive in a very competitive field of study, Mike's lab has always strived to implement state-of-the-art techniques to advance knowledge. The application of optogenetic and calcium imaging techniques was instrumental to a better understanding of altered excitability and connectivity of cortical and striatal neurons in mouse models of HD. Scientific rigor and originality have been the key ingredients that allowed Mike to be funded by a number of agencies throughout his successful career. Likewise, the more than 250 articles published in peer-reviewed journals attest to his devotion for science.

Research and education are already demanding and full-time jobs but somehow Mike has found time to perform a large number of administrative duties. As his career progressed, he served as Associate Director of the Intellectual and Developmental Disabilities Research Center, Chair of the Undergraduate and Graduate Interdepartmental Programs in Neuroscience, Special Assistant to the Vice Chancellor for Academic Affairs at UCLA, and now Vice Chancellor of Academic Personnel for the entire UCLA campus. He also served as member of a study section at the NIH, Chair of the Gordon Conference on CAG Triplet Repeat Disorders, and Chair of the Winter Conference on Brain Research. Parenthetically, Mike also served as Associate Editor of the *Journal of Neuroscience Research*, the *Journal of Neuroscience*, and other journals.

One may wonder if Mike has time to do other things besides science, which requires full-time commitment and focus. Somehow he does, possibly because he knows the rules of economic decisions (as Wolfram Schultz would say) and ways to maximize time usage. His favorite hobbies include jogging, hiking, skiing, and kayaking. In company with his longtime friend Scott Chandler, ocean kayaking occupied Mike's weekends for about 10 years. However, his real passion is traveling to remote regions of the world to take pictures of endangered animal species. His love for nature has taken him to the farthest corners of the earth, from Antarctica to Mount Everest, from Alaska to Tanzania, from Yosemite to Sumatra. A friend of panda bears, elephants, white tigers, orangutans, gorillas, and so on, themed pictures adorn the walls of his office and are included in his book collection of travel pictures. Mike has a remarkable memory; listening to his travel adventures is fascinating. He can recite for hours all the places he has visited, how he got there, and what he saw. As longtime friend Dave Sibley said in his commentary, “Mike has a remarkable hippocampus.” We would also add that he has the memory of an elephant and his frontal cortex is equally remarkable.

We can say that Mike Levine is a scientist's scientist. If you look at labs investigating the inner workings of the basal ganglia in the United States and around the world, almost invariably you will find a connection to Mike. He has taught hundreds of basal ganglia scientists how research should be conducted. As Casey Cromwell writes in his tribute to Mike, “Primary investigators leading research teams should mirror Mike Levine's efforts in climbing the mountain of scientific inquiry by performing analyses at different levels.” If just a few words had to be used to describe Mike, we would say scientific and personal integrity. However, we believe that most valued by students and friends is Mike's fairness and generosity. Almost as admirable is the fact that even after reaching the pinnacle of his career, he has always remained humble in his achievements. People frequently ask when Mike is going to retire. We can say not any time soon. He is still very much involved in every aspect of scientific inquiry going on in his lab and is always on top of the literature.

On the occasion of his 75th birthday and 50 years as a scientist and teacher, a small sample of pupils and friends joined forces to dedicate this special issue (SI) to Mike's accomplishments. This is a collection of original papers, reviews, commentaries, and reminiscences. Original papers and reviews are loosely organized into three large themes, basal ganglia connectivity and normal function, DA–glutamate interactions, and alterations in neurodegenerative disorders. The first paper, by **Maxime Assous** and **Jim Tepper** (Rutgers University, Newark, NJ), presents original data on two types of newly discovered striatal GABAergic interneurons, tyrosine hydroxylase-expressing interneurons and spontaneously active bursty interneurons. Using optogenetic stimulation, the authors examine interneuron-specific cortical and thalamic inputs and how

these excitatory inputs interact with intrinsic striatal microcircuits to sculpt inhibitory effects on MSNs. **Eric Prager** and **Josh Plotkin** (Stony Brook University, New York) provide an updated overview of the differences between the striatal striosome and surrounding matrix compartments in terms of gene expression, circuitry, electrophysiology, and how each region is affected by neuromodulators. **Edgar Garcia-Rill** (University of Arkansas for Medical Sciences, Little Rock), in his review, considers the role of brainstem structures, in particular the pedunculopontine nucleus (PPN, an area richly innervated by the basal ganglia), in the generation of gamma oscillations. Gamma activity is a pattern of neural oscillation in humans with a frequency around 40 Hz that can be measured using EEG recordings. The gamma band oscillation is commonly viewed as a marker of arousal and alterations in gamma activity have been proposed as a biomarker for a variety of diseases of the nervous system. Notably, stimulation of the PPN can be used to treat symptoms of Parkinson's disease (PD). A review by **Steve Siviy** (Gettysburg College, Pennsylvania) discusses the role of the basal ganglia in social play of juvenile rats, emphasizes the differences found depending on rat strains, and examines the role of DA in social play and behavioral flexibility.

Midway between normal and dysfunctional striatum, **Howard Casey Cromwell** (Bowling Green State University, Ohio) provides a comprehensive review highlighting the necessity for integrating diverse levels of analysis to understand striatal function. Convergent evidence from *in vitro* and *in vivo* models should be able to coalesce and improve our understanding of the basal ganglia. Cromwell discusses in detail the role of DA–glutamate interactions to explain inhibitory gating, self-injurious behavior, and reward valuation. **Cynthia Crawford** and her team (California State University, San Bernardino) have been exploring these interrelationships. In their study, Dr. Crawford reports her latest work exploring D2 receptor internalization in cocaine-induced locomotor activity at different ages.

One of the important areas of basal ganglia research has been understanding the role of the reward circuit, in particular, the nucleus accumbens (NAc), in addiction. Continuing along the line of striatal plasticity and DA–glutamate interactions, **Nigel Bamford** and **Wengang Wang** (Yale University, New Haven, CT), in an original research article, demonstrate that repeated amphetamine administration in mice induces a long-lasting depression of cortico-accumbal activity during withdrawal, but this depression is reversed and converted into synaptic potentiation by subsequent amphetamine challenge. This paradoxical excitation could underlie habit formation and dependence. **Mary Kay Lobo** (University of Maryland, Baltimore) and collaborators, **Ramesh Chandra** and **Cali Calarco**, examine the possibility that mitochondrial morphology varies between the neurons in the NAc D1-MSN and D2-MSN populations. They demonstrate differential mitochondrial size and identify a potential molecular mediator of these mitochondrial differences in NAc MSN subtypes.

The next group of papers examine mechanisms of HD pathology. In a collaborative work from **Gill Bates** (University College London) and **Marie-Françoise Chesselet** (UCLA) labs, **Nick Franich** describes how incomplete splicing of the mutant Huntingtin (mHTT) protein affects development and phenotype in two models of HD, the Q140 and the HdhQ150. Specifically, the levels of incomplete splicing of the mutant exon 1 HTT protein are greater in the Q140 mice, which could explain the earlier occurrence of the HD phenotype in this model. Thus, lowering the levels of exon 1 *HTT* transcript could be used as a therapeutic strategy. Sleep disturbances are a common feature of neurodegenerative disorders. Work in the **Colwell** laboratory (UCLA) has been exploring mouse models of HD to evaluate the role of the circadian timing system as a cause of these sleep disorders. In their study, **Benjamin Smarr** and colleagues summarize evidence that several of the phenotypes of the Q175 line vary with a diurnal and circadian phase dependence. A network analysis found evidence for disrupted phase coherence between activity, core body temperature, and cardiovascular measures even in young Q175 mutants. This result suggests that loss of phase coherence is a variable that should be considered as a possible biomarker for HD and other neurodegenerative disorders. Striatal development has always been close to Mike's heart. In a review article, **Carlos Cepeda** and collaborators (UCLA) discuss and provide new evidence for aberrant cortical development in HD. Although HD is commonly thought of as a disease that strikes during the middle or old age, HD can occur at almost any period in life. In juvenile HD, they examine the hypothesis that cortical maldevelopment, similar to cortical dysplasia in humans, underlies cortical hyperexcitability observed in HD. **Ellen Koch** and **Lynn Raymond** (University of British Columbia, Canada) provide an extensive review on the role of dysfunctional DA signaling in HD. Their review also highlights Mike's lab contributions to our understanding of DA signaling in the healthy and diseased striatum. A nice complement to the literature on animal models of HD is the study by **Veronica Ghiglieri** and **Paolo Calabresi** (Università di Perugia, Italy) demonstrating that, in the R6/1 mouse model, corticostriatal LTD is lost and confirm the role of aberrant DA–glutamate interactions in the alterations associated with HD symptoms. **Elizabeth Hernández-Echeagaray** (UNAM, Mexico) and her team have been exploring the role of trophic factors—brain-derived neurotrophic factor and neurotrophin-4/5—as modulators of corticostriatal synaptic transmission. In their study, they provide evidence that the modulatory effects of exposure to these neurotrophins depend upon the order that the treatments are administered. These neurotrophins elicit an antagonistic or synergistic effect that depends on the activation of the truncated isoform or the stimulation of the full-length isoform of the tropomyosin receptor kinase B.

The striatum plays a role in numerous disorders, including PD, but we are still a long way from understanding how dysfunctional striatal activity differs from normal *in vivo* activity. **Kwang Lee** and **Sotiris Masmanidis** (UCLA) summarize key results from studies that have examined *in vivo* striatal activity in models of PD. **Joe Watson**, **Ted Sarafian** (UCLA), and collaborators are interested in the mechanisms through which oligomeric forms of α-synuclein cause neurotoxicity in neurodegenerative diseases by inducing mitochondrial injury. Here, they report on small molecules that appear to protect

against oligomerized α-synuclein disruption of mitochondrial function. **Charlie Meshul** (Oregon Health & Science University, Portland) and his collaborators report how sleep deprivation (SD) may interact with the pathology underlying PD. Surprisingly, they found that SD prior to the administration of the neurotoxin, MPTP, does not result in additional loss of the DA marker, tyrosine hydroxylase, within either the striatum or the midbrain/substantia nigra. Overall, the data suggest that prior sleep disruption seen so commonly in PD patients may not accelerate disease progression.

Changes in striatal synaptic plasticity also occur during aging. **John Walsh** (Leonard Davis School of Gerontology, USC, Los Angeles, CA) offers a historical perspective of Mike's contributions to the field, and also an insightful view of the ravaging effects of aging on corticostriatal plasticity. Aging affects the striatum; MSNs reduce in size, lose spines, synaptic plasticity decays. Nonetheless, some people defy aging and Mike is one of those rare cases. Although we all agree that aging is detrimental for learning and memory, in Mike's case we can say that, for some mysterious reason, his synapses are intact and perhaps even strengthened. Jim Surmeier talked about the coexistence of "smart" and "dumb" synapses in the striatum. But in Mike's case, we can agree that all his synapses are really smart. Closely related to the aging process, Alzheimer's disease affects millions worldwide. A little-known fact is that the basal ganglia play a role in dementia. **Damian Cummings, Karina Vitanova** (University College London), and collaborators highlight the fact that the basal ganglia participate in functions beyond motor control. This Special Issue (SI) closes with a number of commentaries and reminiscences from collaborators and close friends of Mike, including **Scott Chandler** (UCLA), **Dave Sibley** (NIH, Bethesda), **Ed Stern** (Bar-Ilan University, Ramat Gan, Israel), **Leslie Thompson** (UC Irvine) and others. We hope these contributions satisfy the high standards that Mike always expected.

Finally, we would like to acknowledge **Eric Prager**, Chief Editor of JNR, for continuous support and for making possible the publication of this SI in honor of Mike Levine. We also thank the reviewers who provided critical comments and suggestions to improve each manuscript, as well as the efforts of the editorial staff at JNR.

Happy 75th Birthday Mike, and many more!

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