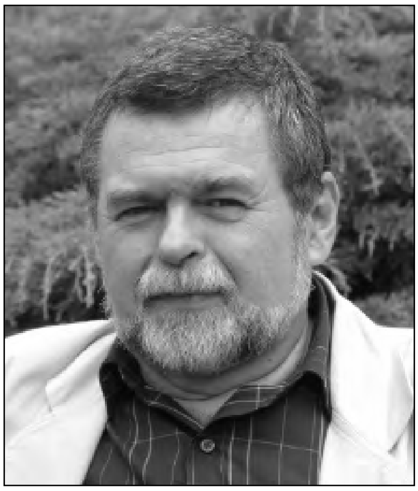
OBITUARY

Acta Neurobiol Exp 2024, 84: i–v



PROFESSOR STEFAN KASICKI (1947–2024)

AND HIS CONTRIBUTION TO UNDERSTANDING THE NEURAL NETWORKS MEDIATING LOCOMOTION

Stefan Kasicki, born in Łódź in 1947, graduated with a master's degree from the Faculty of Physics at the University of Warsaw in 1972. He began his scientific career at the Nencki Institute while still a student, conducting his master's research under Zofia Afelt's supervision in the Laboratory of the Limbic System, headed at the time by Elżbieta Fonberg. Under Afelt's supervision, he also carried out his PhD research entitled "Coordination of Limb Movements during Symmetric Type of Locomotion in a Cat" (defended in 1979). From the very beginning, he was fascinated by muscle activity during locomotor behavior, which set the stage for his development of methods to record muscle activity and later research on how the brain organizes itself into neural motor systems controlling the circuity of spinal cord central pattern generators (CPGs) for locomotion.

Development and application of EMG methodology

In the early 1980s, Stefan, together with Zofia Afelt and a group of colleagues from Pavel Hnik's laboratory at the Institute of Physiology of the Czechoslovak Academy of Sciences (since 1992 the Czech Academy of Sciences), helped develop a method for recording the electrical activity of muscles (electromyography, EMG) in freely moving rats (Hnik et al., 1978; 1985). This innovation enabled chronic EMG recording in freely moving rats while also allowing detailed investigation of interlimb and intermuscular coordination, as well as the mechanisms of modulation of locomotor patterns, such as ensuring a smooth transition from slow locomotion to running. This method is still used at the Nencki Institute to determine the effectiveness of repair strategies after spinal cord injuries in experimental rodents.

Mastering the method of chronic rat EMG recordings facilitated Stefan's studies on the role of afferent inputs in locomotor control (Hnik et al., 1981; 1982). EMGs provide objective information about muscle use, locomotor patterns, and reflex activity in freely moving animals. Stefan's first study with Hnik and Vejsada investigated the role of afferentation in hindlimb muscle activity during rat locomotion. They examined changes in the EMG of extensor and flexor muscles after unilateral deafferentation (Hnik et al., 1981). They found that a relatively normal EMG pattern of locomotion developed within 2-6 days after injury, along with the appearance of spontaneous activity in deafferented extensor muscles. A follow-up study was carried out using bilateral deafferentation to test whether the preserved activity could be due, at least in part, to sensory inflow from the contralateral hindlimb (Hnik et al., 1982). Despite impaired locomotion, the basic EMG features were preserved even after bilateral deafferentation, confirming the presence of locomotor CPGs in the rat spinal cord. However, as expected, the locomotor EMG pattern was especially pronounced when the rats were allowed to move freely in a large space. The locomotor patterns after bilateral deafferentation easily shifted to a synchronous "gallop" motion, i.e., both forelimbs and both hindlimbs moved forward in parallel, not in alternating manner as during normal locomotion. This rarely happens in intact rats and only during very fast locomotion. Based on these results, Stefan and his colleagues concluded that bilateral deafferentation leads to impaired fine adjustment of movement due to the elimination of sensory feedback, while the appearance of spontaneous activity in deafferented extensor muscles is due to suprasegmental influences. These studies would not have been possible without the use of the chronic EMG recording methods developed by Stefan and his colleagues.

Stefan applied his pioneering EMG methods to investigate the development of muscle activity in neonatal rats. In one of his studies carried out with Urszula Sławińska at the Nencki Institute, he demonstrated that the EMG patterns of the extensor soleus muscle, when transferred from its original location to the antagonistic flexor muscle site in neonatal rats could be modified according to new physiological demands (Sławińska & Kasicki 2002). Although muscle innervation was preserved, the EMG pattern was not altered when the muscle transformation was carried out in adults. They concluded that the readjustment of spinal networks to new functional demands depended on two crucial factors: the immaturity of the nervous system at the time of surgery and the preserved afferent innervation of the transposed muscle.

Neural network models of CPG

Alongside the early *in vivo* studies described above, Stefan began collaborating with Wojciech Zmysłowski from the Institute of Biocybernetics and Biomedical Engineering at the Polish Academy of Sciences (currently the Nałęcz Institute of Biocybernetics and Biomedical Engineering, PAS). This collaboration resulted in four significant papers, most notably a neural network model of locomotion. Their model was constructed using electronic analog units simulating the fundamental properties of neurons, and they posited that the muscle control system operates hierarchically at two levels: supraspinal and spinal. They suggested that even at the spinal level, it is possible to distinguish three sublevels – the CPGs (limbs of the fore- and hind-girdles) and propriospinal interneurons connecting these CPGs as well as motoneurons. Their first modeling study focused on processes responsible for coordinating limb movements during locomotion to simulate *in vivo* conditions. This model could mimic a cat walking on a treadmill, forcing both hindlimbs to generate limb stepping at different frequencies, demonstrating the influence of various afferent inflows on spinal cord generators (Zmysłowski & Kasicki 1980; 1982). In a later model, they proposed a neuronal network composed of motoneurons, Ia interneurons, and Renshaw cells corresponding to the spinal cord circuitry driving the muscles of one joint. This model was used to investigate the generation of signals driving individual muscles during locomotor movements (Zmysłowski & Kasicki 1986). At that time, it was undoubtedly pioneering research. In the pre-miniaturization era, the electronic analog model they developed, occupied an entire wall of the laboratory at the Institute of Biocybernetics! This pioneering research helped spark interest in the emerging field of neuroinformatics in Poland.

Neurophysiological mechanisms of motor coordination

Stefan was acutely aware of the importance of afferent inputs in locomotion from personal experience, having lost both lower limbs in an accident. Despite this, most people did not notice his disability, as he moved easily with the help of a crutch. In scientific conversations, he often drew on his personal experiences, surprising colleagues by explaining that the lack of sensory information made it completely impossible for him to walk in the darkness or climb a single step unaided.

In his quest to understand the cellular mechanisms of locomotion at the spinal cord circuitry level, Stefan initiated collaborative projects with several eminent international experts. Notably, he worked with Sten Grillner at the Nobel Institute for Neurophysiology in Stockholm, Sweden, and James T. Buchanan at Marquette University in Milwaukee, USA. Both researchers were investigating the neural mechanisms of central pattern generators underlying locomotion in the spinal cord of a lamprey. These collaborations resulted in several important papers.

In Grillner's lab, Stefan focused on the descending control systems originating from reticular neurons. These systems are represented throughout the vertebrate kingdom and appear early in phylogeny. The lamprey central nervous system shares many basic features with higher vertebrates, including mammals, but contains fewer neurons. The large neurons named Müller cells or Mauthner cells attracted Stefan's attention. The intracellular activity of all examined reticulospinal neurons showed strong coupling with other types of spinal motor activity during fictive locomotion, in phase with the ipsilateral motoneurons (Kasicki et al., 1986; 1989; Brodin et al., 1988). These results demonstrated that the excitation of spinal networks originates from the brainstem, as in higher vertebrates. Stefan's research indicated that the lamprey nervous system can serve as a useful model for investigating the role of supraspinal structures in the control of motor behavior.

When Stefan joined Buchanan's lab, the simple network for segmental locomotor CPGs in the lamprey spinal cord had already been proposed. This network was based on the synaptic connectivity of identified neuron classes. The locomotor rhythm of the spinal cord with increasing concentrations of excitatory amino acid in the bath had already been demonstrated. Stefan built on these studies to identify the neurotransmitter released by inhibitory interneurons in the lamprey spinal cord (McPearson et al., 1994; Buchanan & Kasicki, 1995; 1999). These investigations, although not addressing the anatomic and physiological bases of coupling strength, provided an overall measure of the functional lengths of intersegmental inhibitory signals from CPG units crucial for controlling motoneuron activity patterns during fictive swimming in lampreys. These signals appear to be relatively short distances, typically the nearest-neighbor in length.

The results described above showed that while locomotion is a natural motor behavior, it is only seemingly an automatic activity. To the outside observer, it seemed smooth and seamless; however, this coordination is complex and involves afferent feedback from joints, skin, and muscle receptors, which allows movement to be adjusted to the intended goal. Achieving this requires neuronal networks of the spinal cord (CPGs, interneurons, and motoneurons) and appropriate supraspinal structures, i.e., networks that initiate and modulate motor behavior.

Complementing his research on the mechanisms of locomotion, Stefan also studied the coordination between locomotor activity and respiration. Much of this work was carried out in collaboration with Jaroslaw R. Romaniuk from the Medical Research Center of the Polish Academy of Sciences (currently the Mossakowski Medical Research Institute, PAS) and a group of Russian researchers, Viktor A. Selionov and Oleg V. Kazennikov, alumni of the school established by Grigori N. Orlovsky and Mark L. Shik. This Russian team was the first to show that electrical stimulation of specific brain structures could induce different forms of motor behavior in cats: locomotion (subthalamic locomotor region), escape (mesencephalic locomotor region), or defense behaviors (posterior hypothalamus). The investigations, conducted in Poland, demonstrated that while respiratory changes could be induced alongside electrically-induced locomotion (subthalamic/mesencephalic locomotor region stimulation), the associated increase in lung ventilation dissipated more rapidly than the respiratory changes following stimulation of the "defense" structure. These results confirmed that the integration of the systems controlling respiratory and locomotor responses is influenced by the behavioral context (Kasicki et al., 1991; Romaniuk et al., 1986; 1994).

Affective state, oscillations, and movement

Stefan was fascinated by the fluidity and coordination of locomotion mechanisms, particularly how these features are influenced by connectivity between motor and limbic structures of the brain and the spinal cord, which can vary with emotional state. His interest in the role of emotions in controlling locomotor activity led him to secure a permanent position in the Laboratory of the Limbic System, at the time headed by Elżbieta Fonberg. Stefan's expertise in the chronic electrophysiological recordings of deep brain structures enabled him to investigate the flow of information between the motor and limbic structures studied in Fonberg's laboratory. He continued to advance these studies with Katarzyna Blinowska from the Faculty of Physics, University of Warsaw, and Jolanta Zagrodzka, who developed the lines of research initiated by Elżbieta Fonberg. His pioneering electrophysiological techniques significantly broadened the scope of studies on the activity of limbic structures, including the hippocampus. He studied the control mechanisms of core movements, and how they depend on the emotional state, such as novel environmental stimuli, as well as in models of post-traumatic stress. In one of the early studies investigating the limbic system in freely moving rats, he demonstrated that the frequency of the hippocampal rhythm depends on the speed of locomotion, which, in turn, was related to emotional state (Sławińska & Kasicki 1995; 1998). To compare the strength of limbic-motor interactions in selected behavioral situations, Stefan introduced multichannel recordings of field potentials from various limbic system structures in freely moving rats during locomotor tasks with different types of reinforcement. Advanced computational analyses not only confirmed the existence of functional connections between specific limbic structures but also revealed the dynamics of these connections in relation to the motivational-emotional context of the task (Korzeniewska et al., 1997a,b).

The collaboration with Mark J. Hunt, who joined Stefan's laboratory in 2006, expanded the scope of research carried out under the guidance of Stefan Kasicki. This partnership extended the laboratory's electrophysiological studies to the area of neuropsychopharmacology. This theme focused on understanding how psychoactive compounds, in particular ketamine, impact the fundamental frequencies of the rat brain, with an emphasis on frequencies above the gamma range, known as high-frequency oscillations (for review see Hunt & Kasicki 2013). Much of the pioneering research on this activity was carried out in Stefan's laboratory and resulted in twelve original research papers and one review. Notable highlights include studies demonstrating that antipsychotic compounds used to treat schizophrenia can slow down this fast rhythm (Olszewski et al., 2013a; Hunt et al., 2015). Additionally, Kasicki and Hunt's research into the neuroanatomical localization primarily focused on the nucleus accumbens (Hunt et al., 2011; Goda et al., 2013); however, they also showed that the brain regions where this fast activity can be recorded are not necessarily the generators (Olszewski et al., 2013b). The source(s) of this fast rhythm, remain debated by researchers to this day. Alongside overseeing *in vivo* experiments, Stefan actively developed scripts to streamline data analysis, the fundamentals of some of his scripts remain in use today. Even after retiring at the end of 2017, Stefan never stopped his interest in understanding the neurophysiological part of these experiments. He continued to visit the Nencki Institute to check on ongoing projects and engage in discussions until the COVID-19 pandemic disrupted these activities.

****

Stefan Kasicki dedicated his entire scientific career to the Limbic System Laboratory at the Nencki Institute. He joined the Institute immediately after his graduation in 1973 and remained a valued member throughout his professional life. His roles included trainee (1973-1974), PhD student (1974-1976), senior assistant (1976-1979), assistant professor (1979-1997), associate professor (1997-2011), and full professor (from 2011). In 1994, he became the Head of the Laboratory of the Limbic System, a position he held until his retirement in 2017. Stefan was also a dedicated member of the Institute's Scientific Council since 1995. From the establishment of the Nencki Foundation for the Support of Biological Sciences in 2012, he actively contributed and was elected the first President of the Foundation's Management Board (2012-2017).

Stefan was extensively involved in the ethics of animal experimentation, introducing regular staff training that extended to other Polish scientific centers. He played a crucial role in the preparation of the Animal Protection Act and served as a parliamentary expert for the Polish Academy of Sciences during its creation. Stefan was a member of the National Ethical Committee for Animal Experiments at the Ministry of Science and Higher Education and actively participated in the Directorate-General for the Environment of the European Commission, contributing to the Technical Working Group of Experts amending the Directive on the protection and use of animals in scientific experiments.

As described in detail above, Stefan played a major role in introducing new electrophysiological recording techniques and analyses, which greatly enhanced the reputation of the Nencki Institute. Despite his disability, Stefan embraced research and general love of life with great enthusiasm, inspiring many who knew or worked with him. Although Stefan is no longer with us, his scientific research continues to influence the next generation of scientists who build on his original findings.

Stefan Kasicki sadly passed away in Warsaw on May 28, 2024, at the age of 76.

Urszula Sławińska, Mark Jeremy Hunt, Andrzej Wróbel

REFERENCES

Brodin L, Grillner S, Dubuc R, Ohta Y, Kasicki S, Hökfelt T. (1988) Reticulospinal neurons in lamprey: transmitters, synaptic interactions and their role during locomotion. *Arch Ital Biol.* 126(4): 317–345.

Buchanan JT, Kasicki S. (1995) Activities of spinal neurons during brain stem-dependent fictive swimming in lamprey. *J Neurophysiol.* 73(1): 80–87. doi: 10.1152/jn.1995.73.1.80.

Buchanan JT, Kasicki S.J. (1999) Segmental distribution of common synaptic inputs to spinal motoneurons during fictive swimming in the lamprey. *Neurophysiol.* Sep;82(3): 1156–1163. doi: 10.1152/jn.1999.82.3.1156.

Goda SA, Piasecka J, Olszewski M, Kasicki S, Hunt MJ. (2013) Serotonergic hallucinogens differentially modify gamma and high frequency oscillations in the rat nucleus accumbens. *Psychopharmacology (Berl).* 228(2): 271–282. doi: 10.1007/s00213-013-3057-1.

Hník P, Kasicki S, Afelt Z, Vejsada R, Krekule I. (1978) Chronic polyelectromyography in awake, unrestrained animals. *Physiol Bohemoslov,* 27(5): 485–492.

Hník P, Vejsada R, Kasicki S. (1981) Reflex and locomotor changes following unilateral deafferentation of rat hind limb assessed by chronic electromyography. *Neuroscience*, 6(2): 195–203. doi: 10.1016/0306--4522(81)90055-5.

Hník P, Vejsada R, Kasicki S. (1982) EMG changes in rat hind limb muscles following bilateral deafferentation. *Pflugers Arch.* 395(3): 182–185. doi: 10.1007/BF00584806.

Hník P, Vejsada R, Kasicki S, Afelt Z. (1985) The use of chronic polyelectromyography in neurophysiological and behavioural experiments. *Physiol Bohemoslov.* 34 Suppl: 53–56.

Hunt MJ, Olszewski M, Piasecka J, Whittington MA, Kasicki S. (2015) Effects of NMDA receptor antagonists and antipsychotics on high frequency oscillations recorded in the nucleus accumbens of freely moving mice. *Psychopharmacology (Berl).* 232(24): 4525–4535. doi: 10.1007/s00213-015-4073-0.

Hunt MJ, Kasicki S. (2013) A systematic review of the effects of NMDA receptor antagonists on oscillatory activity recorded in vivo. *J Psychopharmacol.* 27(11): 972–986. doi: 10.1177/0269881113495117.

Hunt MJ, Falinska M, Łeski S, Wójcik DK, Kasicki S. (2011) Differential effects produced by ketamine on oscillatory activity recorded in the rat hippocampus, dorsal striatum and nucleus accumbens. *J Psychopharmacol.* 25(6): 808–821. doi: 10.1177/0269881110362126.

Kasicki S, Grillner S. (1986) Müller cells and other reticulospinal neurones are phasically active during fictive locomotion in the isolated nervous system of the lamprey. *Neurosci Lett.* 69(3): 239–243. doi: 10.1016/0304-3940(86)90486-6.

Kasicki S, Grillner S, Ohta Y, Dubuc R, Brodin L. (1989) Phasic modulation of reticulospinal neurones during fictive locomotion and other types of spinal motor activity in lamprey. *Brain Res.* 484(1–2): 203–216. doi: 10.1016/0006-8993(89)90363-6.

Kasicki S, Korczyński R, Romaniuk JR, Sławińska U. (1991) Two locomotor strips in the diencephalon of thalamic cats. *Acta Neurobiol Exp (Wars).* 51(5–6): 137–143.

Korzeniewska A, Kasicki S, Zagrodzka J. (1997) Electrophysiological correlates of the limbic-motor interactions in various behavioral states in rats. *Behav Brain Res*. 87(1): 69–83. doi: 10.1016/s0166-4328(96)02258-9.

Korzeniewska A, Kasicki S, Kamiński M, Blinowska KJ. (1997) Information flow between hippocampus and related structures during various types of rat's behavior. *J Neurosci Methods.* 73(1): 49–60. doi: 10.1016/s0165-0270(96)02212-1.

McPherson DR, Buchanan JT, Kasicki S. (1994) Effects of strychnine on fictive swimming in the lamprey: evidence for glycinergic inhibition, discrepancies with model predictions, and novel modulatory rhythms. *J Comp Physiol A.* 175(3): 311–321. doi: 10.1007/BF00192990.PMID: 7932300

Olszewski M, Piasecka J, Goda SA, Kasicki S, Hunt MJ. (2013a) Antipsychotic compounds differentially modulate high-frequency oscillations in the rat nucleus accumbens: a comparison of first- and second-generation drugs. *Int J Neuropsychopharmacol.* 16(5): 1009–1020. doi: 10.1017/S1461145712001034.

Olszewski M, Dolowa W, Matulewicz P, Kasicki S, Hunt MJ. (2013b) NMDA receptor antagonist-enhanced high frequency oscillations: are they generated broadly or regionally specific? *Eur Neuropsychopharmacol.* 23(12): 1795–1805. doi: 10.1016/j.euroneuro.2013.01.012.

Romaniuk JR, Kasicki S, Borecka U. (1986) The Breuer-Hering reflex at rest and during electrically induced locomotion in decerebrate cat. *Acta Neurobiol Exp (Wars).* 46(2–3): 141–151.

Romaniuk JR, Kasicki S, Kazennikov OV, Selionov VA. (1994) Respiratory responses to stimulation of spinal or medullary locomotor structures in decerebrate cats. *Acta Neurobiol Exp (Wars).* 54(1): 11–17.

Sławińska U, Kasicki S. (1998) The frequency of rat's hippocampal theta rhythm is related to the speed of locomotion. *Brain Res.* 796(1–2): 3273–3231. doi: 10.1016/s0006-8993(98)00390-4.

Sławińska U, Kasicki S. (1995) Theta-like rhythm in depth EEG activity of hypothalamic areas during spontaneous or electrically induced locomotion in the rat. *Brain Res*. 678(1–2): 117–126. doi: 10.1016/0006-8993(95)00174-o.

Sławińska U, Kasicki S. (2002) Altered electromyographic activity pattern of rat soleus muscle transposed into the bed of antagonist muscle. *J Neurosci.* 22(14): 5808–5812. doi: 10.1523/JNEUROSCI.22-14-05808.2002.

Zmysłowski W, Kasicki S. (1986) Modelling study of spinal generators structure; the role of alpha motoneurons, Renshaw cells and Ia interneurons in locomotion. *Acta Neurobiol Exp (Wars).* 46(1): 57–72.

Zmysłowski W, Kasicki S. (1982) Generation of signals controlling the temporal organization of motoneurons' activity during locomotor movements: modelling study. *Acta Neurobiol Exp (Wars).* 42(2): 183–193.

Zmysłowski W, Kasicki S. (1980) Tuning of the spinal generators: modelling study. *Acta Neurobiol Exp (Wars).* 40(5): 895–909.