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The Brain Prize 2011

From Microcircuit Organization to Constellations of Brain Rhythms

Ivan Soltesz

Anatomy & Neurobiology, University of California, Irvine, Irvine, CA, 92697-1280, USA

The Grete Lundbeck European Brain Research Foundation awarded the inaugural Brain Prize 2011 to Péter Somogyi, Tamás Freund and György Buzsáki 'for their wide-ranging, technically and conceptually brilliant research on the functional organization of neuronal circuits in the cerebral cortex, especially in the hippocampus, a region that is crucial for certain forms of memory'. The present article highlights key findings and major conceptual contributions by these three scientists that were recognized by the award.

The Brain Prize 2011 was conferred to Péter Somogyi (Oxford University, UK), Tamás Freund (Institute of Experimental Medicine, Budapest, Hungary) and György Buzsáki (Rutgers University, New Jersey, USA) at a ceremony on May 2, 2011 (Figure 1) in Copenhagen, Denmark, followed by the Prize Lectures the next day. The Grete Lundbeck Foundation is a charitable, non-profit organization that awards the Brain Prize (€1 million, or about $1.4 million) to scientists who have distinguished themselves by an outstanding contribution to European neuroscience (for further information, see www.thebrainprize.org).

Somogyi, Freund and Buzsáki were all born and educated in Hungary, which was, especially under communist times, a truly 'far-from-equilibrium' state that demanded a great deal of 'self-organization' (to borrow terms from system theory that greatly influenced Buzsáki's work) from individuals for success. But, of course, these three scientists did not start their scientific careers in a vacuum. On the contrary, their research into the functional organization of complex brain circuits has been inspired by the remarkable traditions of Hungarian neuroscience, represented by the likes of Károly Schaffer (of 'Schaffer collaterals'), Mihály Lenhossék (who introduced the term 'astrocyte'), János Szentágothai (whose numerous contributions include the recognition of the basis of lateral inhibition in the cerebellar cortex) and others. Indeed, Freund started his scientific endeavors in Somogyi's laboratory, investigating the specificity of interlaminar GABAergic connections using layer-specific microinjections of [^{3}H]GABA in the visual cortex [1] at the Anatomy Institute in Budapest. And it was in the same building at that venerable institute where Somogyi had previously worked with Szentágothai, who, in turn, had been a student of Lenhossék. Buzsáki studied under Endre Grastyán, who, working in the beautiful town of Pécs in southern Hungary, argued that it is the brain outputs (such as motion and consciousness) that control its inputs, and not the other way around. Grastyán's experiments, inspired by his inside-out view of the brain on changes in hippocampal circuitry during dynamic shifts in behavior, deeply resonated with his students, setting Buzsáki on a scientific journey dedicated to the understanding of the characteristic, behavior- and region-dependent constellations of distinct neuronal oscillations, such as theta, gamma and sharp waves, in various parts of the entorhino-hippocampal circuits and beyond [2].

Through their independent careers, punctuated by frequent personal contacts and collaborations, the three scientists have focused their work on structure-function questions fundamentally important to understanding information processing in neuronal circuits, particularly in the hippocampus. Their discoveries, made with sometimes outright virtuosic methods they developed themselves, had what one would describe - using contemporary NIH grant review parlance - as exceptionally 'sustained and wide impact' throughout neurobiology. The still-expanding compendium of fundamental discoveries (for reviews, with references to the original papers, see [2–7]) by the three scientists include the recognition that the synaptic targets of the candlestick-like rows of presynaptic terminals of chandelier cells are the axon initial segments, and not, as previously thought, the apical dendrites of principal cells (Somogyi); the identification of interneuronal subtypes that exclusively control other inhibitory neurons (Freund); the demonstration that interneurons express certain neuropeptides in a highly subtype-dependent manner (Somogyi); the finding of transient modification of hippocampal circuits by neocortex-mediated information processing during learning, followed by reactivation of memory traces during sharp waves (Buzsáki); the identification of the cell type- and brain state-dependent, phase-specific firing of GABAergic interneurons during network oscillations (Somogyi, Buzsáki); the discovery of interneuronal species that project across traditional hippocampal areal boundaries over long distances (Freund, Buzsáki); and the determination of the detailed, high-resolution, cell type- and pathway-dependent localization of various GABA, glutamate and cannabinoid receptors (Somogyi, Freund).

Although their individual and collective research foci have been primarily on basic mechanisms, their work, as emphasized by the Brain Prize committee, also had major impacts on how we think about the mechanistic bases of

Corresponding author: Soltesz, I. (isoltesz@uci.edu).

Figure 1. The award ceremony for The Brain Prize 2011. From left: Tamás Freund, György Buzsáki and Péter Somogyi. Reproduced with permission from the Grete Lundbeck Foundation.

neurological and psychiatric diseases. For example, without knowing the unique target selectivity of axo-axonic cells (the modern term introduced by Somogyi for chandelier cells), it would be impossible to understand how pathological alterations in these neurons contribute to the diseased state in schizophrenia and epilepsy [8]. Freund's pioneering work on the functional neuroanatomy of the various, distinctly localized synthesizing and breakdown enzymes involved in endocannabinoid signaling is key to deciphering how breakdown in the control of neurotransmitter release contributes to neurological disorders such as epilepsy [9]. Similarly, Buzsáki's insights into brain rhythms are inherently relevant for research aimed at understanding why virtually every psychiatric disorder is associated with altered neuronal oscillations [10].

Beyond discovering important, novel facts about the brain, the work of Somogyi, Freund and Buzsáki was selected for the award for having fundamentally contributed to the creation of the conceptual framework inspired by 'Cajal's rational psychology' (see [5]). In the words of Colin Blakemore, Chairman of the Selection Committee for The Brain Prize,

> 'In order to know how the brain processes information we need a complete description of the structure of nerve cells and the dynamic characteristics of the connections between them. The work of Péter Somogyi, Tamás Freund and György Buzsáki has provided much of this essential knowledge for the cerebral cortex. Without such painstaking research there will never be full understanding of the brain.'

Somogyi's work in the last decade led to the recognition of the fundamental unity of time and space in the brain, highlighted with the new term 'chronocircuitry' [7]. Freund's work was fundamental in recognizing the novel functional roles that GABA to GABA connections play in the regulation of rhythmic network activity, as is the case for the septo-hippocampal GABAergic projections in the generation of the hippocampal theta rhythm [3]. Buzsáki's research has been instrumental in defining the 'neural syntax' [11], representing a conceptually new approach aimed at understanding the neuronal communication and the role of network oscillations in the brain, and he also greatly contributed to the implementation of graph theory-based approaches to understanding neuronal circuits [2,5]. The overarching, key notion that threads through all of their work is the centrality of the precisely identified cellular subtype, i.e., the deeply held conviction that a major, key pathway to understanding the functional organization of the brain is through the determination of the cell type-dependent, highly characteristic, distinct axonal and dendritic morphology, input-output relationships, expression of neurotransmitter and neuromodulatory receptors, and functional behavior of each of the individual neuronal subtypes that comprise a given neuronal circuitry. Their work has helped us appreciate the fact that it matters greatly whether, for example, a given basket cell is expressing parvalbumin or cholecystokinin (as these two types play distinct roles in the circuit; [6]), or whether a cell identified as 'fast-spiking' based on firing properties alone is a perisomatically projecting axo-axonic cell or a basket cell or a dendritically projecting bistratified cell. Indeed, fast-spiking, parvalbumin-positive basket- and bistratified cells possess significant functional differences in their plasticity processes and responses to neuromodulators (see [12], and the references therein), and it is currently debated whether axo-axonic cells and basket cells exert differential depolarizing versus hyperpolarizing effects on their postsynaptic targets (for a review and original references, see [13]). The power of cell type- and microcircuit-based functional anatomical thinking is especially nicely demonstrated by the initial prediction, then subsequent identification, of the existence of a dendritically targeting cholecystokinin-expressing cell type in the hippocampus (the Schaffer-collateral associated interneurons), which proved to be a homologue of the isocortical double bouquet cell [5,14].

As the French molecular biologist Francois Jacob put it,

> 'One of the deepest, one of the most general functions of living organisms is to look ahead, to produce future' (for reference, see [2]).

Indeed, in a fundamental sense, predicting and producing the future is what neuronal oscillations and chronocircuits are all about. In addition, Somogyi, Freund and Buzsáki significantly contributed to the 'production' of the future in a different way. Namely, through their rigorous training of new generations of neuroscientists in their laboratories over the years, they ensured that their particular, intricately interwoven branches of the NeuroTree (http://neurotree.org) continue to grow and flourish. As a testament to the comprehensive influence of their work in educating the aspiring F1 generation and beyond, graduate students all over the world still can and often do start their introduction to microcircuitry research by browsing what is commonly referred to as the interneuronal 'bible' [3], more than a decade and a half after its publication. The bar is certainly set implausibly high by the awarded trio, so let new generations of neuroscientists find encouragement and inspiration in the classical, beautifully crafted words of the clairvoyant Hungarian poet Attila József [15]:

'You know this well: the poet never lies,
The real is not enough; through its disguise
Tell us the truth which fills the mind with light'

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