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EDITORIAL

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Finnish neuroscience from past to present

1 | INTRODUCTION

Finland is a small Nordic country (population 5.5 million) that enjoys a richness and diversity of research activities including those in the neurosciences. In this article, we will briefly review the history of neuroscience in Finland from its origins such as the studies into the anatomy, pathology and physiology of the nervous system—which were recognized with the award of the Nobel Prize in Physiology or Medicine—to later discoveries in clinical, molecular and translational neurosciences and pharmacology. The innovative original research of Finnish investigators on weak magnetic fields in the human brain has led to the development of advanced imaging techniques. Another area associated with many recent breakthroughs has been human genetics and the identification of the molecular genetic causes and risk factors of a number of nervous system disorders.

2 | THE BEGINNINGS OF NEUROSCIENCE IN FINLAND (CA. 1600–1900)

For more than 600 years, until 1809, Finland was an integral part of the Kingdom of Sweden. The Helsinki-born, Sigfridus Aronus Forsius (ca. 1560–1624), Professor of Astronomy at the University of Uppsala, became Royal Astronomer and was one of the most prominent scholars of the Nordic renaissance. He was the first Finn, and probably the first Nordic researcher, to consider the nervous system at a scientific level. His extensive treatise "Physica" (Forsius, 1952), completed in 1611 and largely based on Johannes Magirus work "Physiologia Peripatetica" (1597), included a detailed account of the structure and function of the central and peripheral nervous systems and sensory organs. Influenced by Paracelsus, he firmly rejected the still-widespread cardiocentric ideas of Aristotle, instead postulating an encephalocentric view.

The formal academic study of medicine began in Finland in 1640 with the establishment of the Royal Academy of Turku. This was transferred to Helsinki in 1828 and is now known as the University of Helsinki. An independent Helsinki University of Technology (the present Aalto University) was established in 1849. Further multidisciplinary universities with faculties of medicine or natural sciences were founded in Turku 1918 and 1920, Tampere 1925, Jyväskylä 1934, Oulu 1958, and Kuopio 1966 (now the University of Eastern Finland).

During its first century of activity, most of the professors of medicine in the Royal Academy of Turku had earned their doctorates at the leading Dutch universities. Although their teachers included such men as Sylvius and Boerhaave, they did not show any particular interest in neuroscience. Even the extensive thesis "De apoplexia" (1771) written by Johan Haartman (1725–1787), a pupil of Linnaeus, was a mere compilation of current knowledge. The papers of Evert J. Bonsdorff (1810–1898) and his disciples on the comparative anatomy of the cranial nerves and the structure of the human sympathetic nervous system represent the first truly original Finnish contributions to neuroscience. One of his students, Otto E. A. Hjelt (1823–1913), who in 1859 was appointed as the first Professor of Pathological Anatomy in the University of Helsinki, also carried out experimental work on the regeneration of peripheral nerves after excision in rabbits. This work was proposed and supervised by his teacher and life-long friend Rudolf Virchow, the founder of cellular pathology and carried out in 1857–1858 partly in Virchow´s laboratory in the Charité in Berlin and partly in Helsinki.

Hjelt's successor as Professor of Pathological Anatomy was E. Alexander Homén (1851–1926) who had spent his "postdoc" time in the 1880s with Virchow´s brilliant student, Julius Cohnheim, a pioneer of experimental pathology, in Leipzig as well as with Louis-Antoine Ranvier and Jean-Martin Charcot in Paris. Inspired by his prominent teachers, Homén (Figure 1) became not only the first Finnish neuropathologist but also the founder of clinical neurology in Finland. Even from an international point of view, Homén can be considered as one of the first experimental neuropathologists. He carried out experimental studies on the secondary degeneration of the canine spinal tracts after hemisection of the cord and also investigated how cutting the nerve affected the nerve cell somas. He later devoted much of his energy to experimental studies on the effects of the newly discovered bacteria

FIGURE 1 E. Alexander Homén (1851–1926), the first Finnish neuropathologist and the founder of clinical neurology in Finland (photo Matti Haltia & Erkki Kivalo)

and their toxins on the nervous system. Following Virchow's model developed in the Charité, Hjelt had a small clinical ward in the university teaching hospital attached to his institute. Homén transformed this clinical ward into the first specialized clinical neurological unit in Finland. Although Homén published many clinicopathological works, his most notable is the series of publications beginning in 1890 which contain the original clinical and pathological descriptions of hepatolenticular degeneration (also known as Wilson's disease). Kinnier Wilson, in his much later report on the same disease in 1912, not only cited Homén extensively but also republished one of Homén´s patient photographs (Haltia & Kivalo, 1992).

3 | DEVELOPMENT OF CLINICAL NEUROLOGY, NEUROSURGERY AND NEUROPATHOLOGY FROM 1900

Christian Sibelius (1869–1922), one of Homén´s students and the younger brother of the composer Jean Sibelius, carried out pioneering studies of the effects of carbon monoxide on the nervous system, and in 1909 was appointed first as a personal professor and in 1921 as the first full professor of neuropsychiatry in the University of Helsinki. Jarl Hagelstam, another member of Homén´s team, served as personal professor of neurology (Haltia & Kivalo, 1992). The first permanent academic chair of clinical neurology in Finland was only established in the University of Helsinki as late as 1963. Its first holder, Erkki Kivalo (1929–2009), was a far-sighted and highly energetic organizer whose work contributed to the establishment of academic departments of neurology in all five Finnish medical schools in Helsinki, Turku, Tampere, Oulu and Kuopio. Aarno Snellman, a student of Herbert Olivecrona, became the first personal professor of neurosurgery in 1947 and Matti Haltia was appointed the first professor of neuropathology in 1990, both in the University of Helsinki. Over the years, Finnish neurologists, neurosurgeons and neuropathologists have been particularly fascinated by the inherited, degenerative and vascular disorders of the nervous system.

3.1 | Discovery of neurological diseases and their molecular causes

The rather unique population history of Finland with long-term stable regional subpopulations, the excellent population and health registers, and the generally favourable attitude towards medical research are all factors explaining why Finland is such a good country for investigating genetic factors in human diseases. From the 1970s onwards, close collaboration between clinical neurologists, clinical geneticists and neuropathologists has led to the discovery and/or characterization of a number of previously unrecognized or poorly known monogenic disorders of the nervous system and musculature.

3.1.1 | Childhood-onset diseases

Early examples of childhood-onset diseases include the detailed clinical and biochemical characterization of aspartylglycosaminuria by Seppo Autio, Jorma Palo and their collaborators (Palo & Mattsson, 1970). At neuropathological examination, aspartylglycosaminuria showed the features of a generalized lysosomal storage disorder (Haltia, Palo, & Autio, 1975). Another early example is infantile neuronal ceroid lipofuscinosis (CLN1), described jointly by the child neurologist, Pirkko Santavuori and Matti Haltia and their collaborators (Haltia, Rapola, & Santavuori, 1973; Haltia, Rapola, Santavuori, & Keranen, 1973; Santavuori, Haltia, Rapola, & Raitta, 1973). Additional examples of fruitful interactions between paediatric neurologists and neuropathologists, particularly Anders Paetau, are listed in Table 1. It was the identification and careful clinical and pathological characterization of these diseases which laid the foundations for the successful elucidation of the underlying causative genetic defects. The genes and mutations responsible for almost all of these disorders have already been identified, largely by the groups of renowned molecular geneticists at the University of Helsinki, Albert

TABLE 1 Early-onset neurological disorders discovered and/or characterized by Finnish investigators

Disease	References
Aspartylglycosaminuria (AGU)	Palo and Mattsson (1970) and Haltia et al. (1975)
Infantile neuronal ceroid lipofuscinosis (CLN1)	Haltia, Rapola and Santavuori (1973), Haltia, Rapola, Santavuori and Keranen (1973) and Santavuori et al. (1973)
Late infantile neuronal ceroid lipofuscinosis (CLN5)	See Mole and Haltia (2015)
Progressive epilepsy with mental retardation (CLN8)	See Mole and Haltia (2015)
Congenital neuronal ceroid lipofuscinosis (CLN10)	See Mole and Haltia (2015)
Progressive myoclonus epilepsy (EPN1)	Haltia, Kristensson, and Sourander (1969) and Koskiniemi, Donner, Majuri, Haltia, and Norio (1974)
Progressive encephalopathy with oedema, hypsarrhythmia and optic atrophy (PEHO)	Haltia and Somer (1993) and Salonen, Somer, Haltia, Lorentz, and Norio (1991)
Muscle–eye–brain disease (MEB)	Haltia et al. (1997) and Santavuori et al. (1998)
Hydrolethalus syndrome	Paetau et al. (2008)
Infantile onset spinocerebellar ataxia (IOSCA)	Koskinen et al. (1994) and Lonnqvist, Paetau, Nikali, Boguslawski, and Pihko (1998)
Foetal motoneuron disease	Nousiainen et al. (2008)

de la Chapelle, Leena Peltonen, Anna-Elina Lehesjoki and Juha Kere. In the case of aspartylglycosaminuria, a mouse model was developed and it was observed that an adenovirus-mediated gene transfer resulted in decreased lysosomal storage in the brain, and a total correction in the liver (Peltola et al., 1998).

3.1.2 | Adult-onset diseases

New forms of adult-onset monogenic neurological disorders have been identified through collaboration of clinicians, neuropathologists and clinical and molecular geneticists. Early examples include hereditary gelsolin amyloidosis (Meretoja disease), with cranial and peripheral neuropathy (Haltia et al., 1990; Meretoja, 1969) caused by mutations in the gelsolin gene (Levy et al., 1990), and a presenile frontotemporal dementia with bone lesions called polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy (PLOSL or Nasu-Hakola disease; Hakola, 1972; Paloneva et al., 2001). PLOSL is caused by mutations in the TYROBP and TREM2 genes which both code for components of the same membrane signalling complex (Paloneva et al., 2000, 2002). Creutzfeldt-Jakob disease, identified in a Finnish family (Haltia, Kovanen, Crevel, Bots, & Stefanko, 1979), co-segregated with the codon 178^{Asn} PRNP mutation (Goldfarb et al., 1991). Strikingly, this dominantly inherited disease was also shown to be transmissible (Goldfarb et al., 1992). Two Finnish families with phenotypically perplexing forms of presenile Alzheimer´s disease proved to be particularly interesting. Their challenging molecular genetic analysis was performed in collaboration with John Hardy's group. The first family, who displayed prominent myoclonus, turned out to be linked to chromosome 14 (Haltia et al., 1994) and they were shown to carry one of the first mutations to be identified in the presenilin-1 gene (Alzheimer's Disease Collaborative, Group, 1995). In contrast, variant Alzheimer´s disease with spastic paraparesis and "cotton wool plaques" (Crook et al., 1998) was shown to be caused by a deletion of exon 9 of the presenilin 1 gene (Prihar et al., 1999). One of the latest findings is related to familial and sporadic forms of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia. About 50% of the Finnish familial and 20% of the sporadic cases have a hexanucleotide repeat expansion in the *C9ORF72* gene (Laaksovirta et al., 2010; Renton et al., 2011). About 30% of all Finnish ALS patients have a *C9ORF72* or *SOD1*D91A* gene mutation, making Finland well-suited for mutation-based clinical trials. A special type of late onset spinal muscular atrophy (Jokela type; Jokela et al., 2011), with slow progression (sometimes initially diagnosed as ALS), was identified in northern Karelian families and was found to be caused by a *CHCHD10* mutation (Penttila et al., 2015).

Inherited myopathies first discovered by Finnish investigators include X-linked myopathy with excessive autophagy

(Kalimo et al., 1988) and tibial muscular dystrophy (Udd et al., 1998). The latter condition is caused by mutations in the gene encoding the giant skeletal-muscle protein, titin (Hackman et al., 2002).

3.1.3 | Mitochondrial disorders

Important research on mitochondrial abnormalities inducing both neurodegenerative and muscle disorders has been carried out by the groups of Anu Suomalainen (Helsinki), Howard Jacobs (Tampere) and Kari Majamaa (Oulu). The neurologist, Maria Rantamäki (Tampere), reported details of a family with autosomal recessive ataxia with thalamic lesions (Rantamaki et al., 2001). Similar families were found in other European countries, which led to the identification of one of the most common inherited ataxia syndromes in the Western world, neurodegenerative disorder MIRAS (mitochondrial autosomal recessive ataxia syndrome), caused by mutations in the POLG1 gene (Hakonen et al., 2005; Van Goethem et al., 2004). Dozens of further genetic defects have been discovered in mitochondrial disorders in Finland and, importantly, some of these conditions have been subjected to animal modelling and translational treatment trials (Nunnari & Suomalainen, 2012; Suomalainen & Battersby, 2017).

3.2 | Identification of genetic risk factors of common neurological diseases

Soon after the discovery of the APOE e4 allele as a major risk factor of Alzheimer's disease (Strittmatter et al., 1993), Polvikoski and co-workers (Polvikoski et al., 1995) conducted the first population-based neuropathological study of its impact. This demonstrated that APOE e4 is associated with increased cortical deposition of amyloid beta protein. In another Finnish population-based study, the magnitude of the genetic effect of APOE e4 was put into perspective. This study investigated a cohort of 980 people aged 69–78 and observed that even in subjects homozygous for APOE e4, about 80% were non-demented (Kuusisto et al., 1994). A convincing link was also found between Alzheimer's disease and insulin metabolism (Kuusisto et al., 1997), and mid-life serum cholesterol levels in two Finnish population-based studies (Kivipelto et al., 2001; Notkola et al., 1998). These and other epidemiological observations led to a randomized controlled trial (the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability, FINGER), which demonstrated that a multidomain intervention on vascular risk factors helps in the maintenance of cognitive functions in elderly people (Ngandu et al., 2015). A more recent population-based study showed that 1 in 200 people in Eastern Finland carry an APP*A673T variant that confers some protection from Alzheimer's disease and that this variant associates with decreased amyloid peptide levels in plasma (Martiskainen et al., 2017).

Some of the genetic studies investigating common migraine were originally initiated in Finland, but these soon expanded to involve large multinational consortia. These have revealed that vascular factors play a predominant role in the mechanisms of migraine (Gormley et al., 2016). Exceptional familial clustering of multiple sclerosis (MS) was discovered in the western Finnish region of Southern Ostrobothnia (Wikstrom, 1975). Genetic studies of families from this region resulted in the first genetic linkages in MS (Kuokkanen et al., 1996; Tienari et al., 1992, 1993). Studies in Parkinson´s disease have shown that rare variants of mitochondrial DNA polymerase gamma (POLG1) are risk factors in Parkinson´s disease in Finland (Eerola et al., 2010; Luoma et al., 2007; Ylonen et al., 2017).

3.3 | Cerebrovascular disorders: Pioneering new treatments

Helsinki University Hospital, along with Heidelberg University Hospital, were the first centres to start thrombolysis treatments in acute ischaemic stroke. Two neurologists, Markku Kaste and Perttu Lindsberg, played an important role not only in setting up these treatments but also in characterizing the molecular events of the thrombotic vascular wall (Lindsberg, Carpen, Paetau, Karjalainen-Lindsberg, & Kaste, 1996).

The Department of Neurosurgery in the Helsinki University Hospital has a long tradition of offering surgical treatment of intracerebral aneurysms and became a world class centre of cerebrovascular surgery under the leadership of Juha Hernesniemi. He and his fellow neurosurgeons, Mika Niemelä (Helsinki), Juhana Frösen and Juha Jääskeläinen (both in Kuopio now), initiated studies on the histochemistry of the ruptured aneurysm wall and established an experimental model of arterial aneurysms (Frosen et al., 2004; Marbacher et al., 2014).

4 | DISCOVERIES IN PSYCHIATRY: FROM PET IMAGING TO GENETICS AND TRANSLATION

Many Finnish psychiatrists and neuroscientists have applied biological approaches to psychiatric problems. Much of the work in this field has been conducted using the positron emission tomography (PET) technique in the national PET centre in Turku (neuroscience studies led by Jarmo Hietala and Juha Rinne). Among these studies, the report of the contribution of the A1 allele on dopamine D_2 receptor availability

has attracted considerable interest (Pohjalainen et al., 1998). Other imaging studies using MRI have revealed that there is a decreased volume of the posterior hippocampus in subjects with psychopathy (Laakso et al., 2001).

Severe impulsivity/aggression leading to suicidal, violent and criminal acts was found to be associated with blunted serotonin neurotransmission by Markku Linnoila (1947–1998), Mika Scheinin, Matti Virkkunen and collaborators (Linnoila et al., 1983), identifying a form of early-onset male alcoholism with a tendency to impulsive and violent behaviour. More recently, it was found that some of the individuals with this type of behaviour have an early stop codon that inactivates 5-HT_{2B} receptors in a Finnish population (Bevilacqua et al., 2010).

As early as the 1960s, the excellent "Finnish person file registers" have been used in designing epidemiological cohort studies as well as twin and adoption studies, with the aim of clarifying the contributions of genetic and environmental factors in the development of schizophrenia (Isohanni et al., 2001; Tienari et al., 2004). The successful family studies initiated by Leena Peltonen and Jouko Lönnqvist (Ekelund et al., 2001) have expanded and are now large international genome-wide association studies; this was necessary in order to include sufficient schizophrenic subjects to allow the identification of common and rare genetic variants with small joint effects on susceptibility (Schizophrenia Working Group of the Psychiatric Genomics, 2014). The eventual success in psychiatric genetics has stimulated the ongoing SUPER study, which will enrol more than ten thousand psychotic patients with the goal of analysing genetic risk factors as a part of the international Stanley Global Neuropsychiatric Genomics Initiative (https://www.fimm.fi/en/research/grand-challenge-programmes/finnish-genomes-empowering-personalised-and-predictive-health/super). One exciting recent development in population-wide psychiatric genomics is the large FinnGen project (https://www.finngen.fi), led by Aarno Palotie, which intends to determine how genes affect ~~our~~ diseases and drug responses, including nervous system diseases, by combining clinical characteristics with genome-wide polymorphisms among different disease categories, using the valuable biobank collections from Finnish hospitals and research institutions.

Other important topics in psychiatry have included the characterization of suicide victims and the methods to reduce suicides and attempted suicides in studies led by Jouko Lönnqvist (Henriksson et al., 1993). The increased research interest and public attention being devoted to depression and attempted suicides have been associated with an approximately 50% reduction in suicides in Finland from 1990 to 2015.

Several neuroscientists in Finland have started translational studies in psychiatry. The group of Eero Castrén has increased our understanding of how antidepressants modify brain plasticity (Castren & Kojima, 2017; Sairanen, Lucas, Ernfors, Castren, & Castren, 2005). There has also been a major focus on gene polymorphisms identified in both animal models and human patients, one example being research on anxiety disorders and the mouse models devised by Iiris Hovatta and her group (Hovatta et al., 2005). Heikki Rauvala's group has cloned and conducted pioneering work on the AMIGO-Kv2.1 potassium channel complex (Kuja-Panula, Kiiltomaki, Yamashiro, Rouhiainen, & Rauvala, 2003). They found schizophrenia-like behavioural and pharmacological abnormalities in AMIGO knock-out mice. Based on these findings and in collaboration with the psychiatrist, Tiina Paunio, AMIGO loss-of-function variants were discovered as risk factors of schizophrenia (Peltola et al., 2016).

5 | ADVANCES IN TRANSLATIONAL NEUROLOGY

Neurotrophic factors are important regulators of neural development and differentiation acting via specific membrane-bound receptors which influence gene expression. These molecules have also raised high hopes that it may be possible to develop effective therapies for various neurodegenerative diseases. One family of neurotrophic factors, the neurotrophins, has been the focus of interest of Finnish scientists working on nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF; Castren, Zafra, Thoenen, & Lindholm, 1992; Lindholm, Heumann, Meyer, & Thoenen, 1987; Zafra, Castren, Thoenen, & Lindholm, 1991) in the laboratory of Hans Thoenen in the Max Planck Institute for Psychiatry in Munich. The work on BDNF in neuronal plasticity has continued in Helsinki in the group of Eero Castrén (Karpova et al., 2011; Maya Vetencourt et al., 2008), whilst Dan Lindholm has studied neuronal apoptosis (Hyrskyluoto et al., 2013) and novel functions for NGF and its precursor, pro-NGF in lipid signalling (Pham et al., 2019). Glial cell-derived neurotrophic factor (GDNF) is another trophic factor that promotes the survival of cultured mesencephalic dopaminergic neurons which are known to degenerate in Parkinson's disease. In another laboratory in Helsinki, Mart Saarma has studied the function of GDNF and its receptors in the brain and other tissues (Airaksinen & Saarma, 2002). In addition, the Saarma group (University of Helsinki) has cloned a newly discovered trophic factor, named "cerebral dopamine neurotrophic factor" (CDNF), an endoplasmic reticulum-associated molecule which possesses neuroprotective and neurorestorative properties in rodent and primate models of Parkinson's disease (Garea-Rodriguez et al., 2016; Lindahl, Saarma, & Lindholm, 2017; Lindholm et al., 2007). The first clinical trials with CDNF in Parkinson's disease patients are currently ongoing, launched by the Finnish Company, Herantis Pharma.

Along with trophic factors, different stem cells may have been shown to have some potential in the treatment of Parkinson's disease and other neurodegenerative disorders. The technology of induced pluripotent stem cells (iPSCs) in neuroscience has been advocated in Finland by Jari Koistinaho and some other investigators (Holmqvist et al., 2016; Oksanen et al., 2017).

Epileptic seizures with rewiring of neuronal connections can be a consequence of ischaemic and traumatic brain injuries. In Kuopio, Asla Pitkänen has delved into the molecular mechanisms and gene alterations in post-ischaemic brain in order to understand the process of epileptogenesis (Pitkanen, Ekolle Ndode-Ekane, Lapinlampi, & Puhakka, 2018). Epilepsy is also associated with mutations in specific genes controlling neuronal development and excitation, altering the balance between the excitatory glutamate and the inhibitory GABAergic systems. Several genes linked to epilepsy and encephalopathy have been described by the group of Anna-Elina Lehesjoki (Anttonen et al., 2017; Virtaneva et al., 1997).

6 | SIGNIFICANT DISCOVERIES IN NEUROPHYSIOLOGY

Homén´s colleague, Robert Tigerstedt (1853–1923), Professor of Physiology in the University of Helsinki (1900–1919) and a world authority in circulatory physiology, also initiated a tradition of neurophysiology in Helsinki.

Ragnar Granit (1900–1991, Figure 2), a postdoctoral student of Charles Scott Sherrington and Professor of Physiology in the University of Helsinki in 1935–1940, carried this research tradition further by investigating the physiology of vision. He received the Nobel Prize in Physiology or Medicine in 1967 together with Keffer Hartline and George Wald for their discoveries concerning the primary physiological and chemical visual processes in the eye, identifying different types of cones in the retina representing three characteristic spectral sensitivities. Granit started his medical studies in the University of Helsinki in 1919, and while he was interested in the art of painting, he became familiar with the psychologist and philosopher, Eino Kaila, and the discipline of experimental psychology. After revealing the dependence of colour perception on lighting and context in his doctoral thesis, Granit became convinced that any progress in understanding colour vision would need neurophysiological analyses based on electrophysiology. Following the pioneering neuroanatomical studies of Santiago Ramón y Cajal, the retina seemed to represent a particularly interesting research target, especially in the first stages of vision. During his postdoctoral period in Oxford in 1928 and 1932–1933, he perfected the measurement of the electroretinogram (ERG). His major achievement was to analyse the vertebrate ERG response as a sum of three separable components. Thereafter in Helsinki,

FIGURE 2 Ragnar Granit (1900–1991) in his Stockholm study in May 1990 (photo Andreo Larsen)

he founded the ERG laboratory in the Department of Physiology and published important basic information on the functions of the retina. He appreciated there was a need to obtain more detailed data of the action potentials of individual neurons. In the same department, Alwar Wilska (1911–1987) was developing the production of sharp glass–metal electrodes for single neuron recordings, work in which Granit's student, Gunnar Svaetichin, participated and made further refinements. In 1939, Granit and Svaetichin used the microelectrodes to record the activity peaks of frog retinal ganglion cells following stimulation with light at specific wavelengths, especially the responses to blue, green and red light. Their article published in 1939 "Principles and technique of the electrophysiological analysis of colour perception with the aid of microelectrodes" (Granit & Svaetichin, 1939) formed the foundation for a large research programme that was realized in the early 1940s in the Karolinska Institute, Stockholm, to which Granit had been invited after the Winter War between Finland and the Soviet Union. His results on multiple species led Granit to formulate his so-called modulator–dominator theory of colour vision, which, however, has not stood up to the test of time. Nonetheless, Granit was the first scientist to demonstrate experimentally that colour information could be extracted from population responses of neuron types with different spectral sensitivities. The characteristics of rods and cones were then unknown, but Granit stressed the fact that the brain receives the information only via the coded responses from the retinal ganglion neurons. Granit's book, "Sensory Mechanisms of the Retina" (Granit, 1947), became well-known around the world. His work has had lasting effects on Finnish neuroscience.

Kai Otto Donner (1922–1995) undertook his doctoral studies in Granit's laboratory and brought visual neuroscience back to Helsinki. Active representatives of this line of research include Veijo Virsu (1941–2018), Tom Reuter and Kristian Donner and their students (Aho, Donner, Hyden, Larsen, & Reuter, 1988; Govardovskii, Fyhrquist, Reuter, Kuzmin, & Donner, 2000; Koskelainen, Ala-Laurila, Fyhrquist, & Donner, 2000; Rovamo & Virsu, 1979; Virsu & Rovamo, 1979). Another Finnish PhD student of Granit, Christina Enroth-Cugell (1919–2016) took these ideas to the USA.

Towards the end of 1940s, Granit shifted his scientific interest to the regulation of muscular movements. This second significant research programme of Granit has been considered to have equal standing to his work on the retina, but it has not stimulated the same kind of research tradition in Finland as his vision research.

Juhani Hyvärinen (1937–1983, Figure 3) was a Finnish neurophysiologist who received his postdoctoral training in the laboratory of Vernon B. Mountcastle at Johns Hopkins University, where he learned to study single neurons in conscious primates, a method that made it possible to explore neuronal mechanisms of higher cortical functions, such as cognition, learning and memory. Supported by funding from the USA, Hyvärinen was one of the first European neuroscientists to exploit this valuable technique. In his primate laboratory in Helsinki, Hyvärinen made several pioneering findings such as describing the function of neurons in the parietal association cortex (Hyvarinen & Poranen, 1974). He demonstrated that attention modulates the responses of neurons in the primary somatosensory cortex (Hyvarinen, Poranen, & Jokinen, 1980), and showed that early visual deprivation triggers cortical plasticity, as a result of which somatosensory inputs to the visual associative cortex become enhanced (Hyvarinen, Carlson & Hyvarinen, 1981).

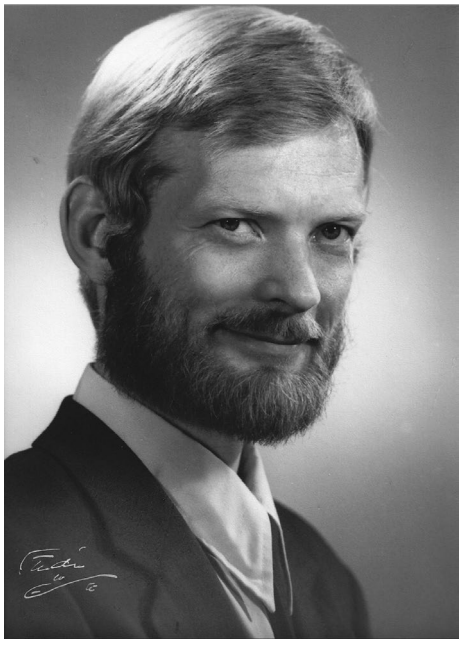

FIGURE 3 Juhani Hyvärinen (1937–1983; photo Lea Hyvärinen)

6.1 | Intracellular electrophysiology

There was no work carried out in Finland on intracellular electrophysiology until the mid-1970s. All the outstanding experiments done by Granit and others described above were based on extracellular recordings of unit spikes or on local field potentials generated by neuronal populations. This situation changed in 1974, when Kai Kaila (University of Helsinki), working as an autodidact undergraduate student with no funding in the Department of Zoology, re-invented the method of optimizing sharp microelectrodes, and constructed "Field Effect Transistor"-based differential amplifiers to record resting membrane potentials as well as action potentials in crayfish giant axons. Later, the pioneering work by Kaila and co-workers on the biophysical and ionic basis of GABAergic transmission led to a substantial revision and elaboration of the concept of classical postsynaptic inhibition proposed by Sir John C. Eccles, who subsequently received the Nobel Prize in 1963. In a seminal article (Kaila & Voipio, 1987), Kaila and Voipio showed that, in addition to Cl^-, bicarbonate ions (HCO_3^-) were responsible for a major depolarizing component of the current mediated by $GABA_A$ receptors. This finding resolved what had seemed "paradoxical" observations of depolarizing GABA actions in mature cortical neurons, which are now considered to play a role in seizures and epilepsy. Later, Kaila and co-workers published another important article (Rivera et al., 1999), where they identified the K^+-Cl^- cotransporter KCC2 as the major ion pump that is not only essential for hyperpolarizing "Eccles-type" inhibitory currents, but also underlies the presently well-known developmental shift from the depolarizing to hyperpolarizing actions of GABA which occur during neuronal maturation. Apart from the ontogeny of GABAergic signalling, KCC2 and related transporters are now also recognized as key molecules in the field of neuronal plasticity and trauma, as well as in psychiatric disorders, epilepsy, chronic pain and many other CNS diseases (Kaila, Price, Payne, Puskarjov, & Voipio, 2014).

7 | LOW TEMPERATURE PHYSICS, WEAK MAGNETIC FIELDS AND MAGNETOENCEPHALOGRAPHY

The physicist, Olli V. Lounasmaa (1930–2002), founded the Low Temperature Laboratory in 1965 at the Helsinki University of Technology in Otaniemi, Espoo, the present Aalto University. His laboratory became world famous in

achieving records in low temperatures, based on their research into superfluid helium-3 and nuclear magnetism. Research on brain mechanisms was started in 1980 using innovative superconducting quantum interference devices capable of detecting the weak magnetic fields produced by the human brain (Hari & Lounasmaa, 1989). These innovations were patented, and in 1989, five researchers from the laboratory founded a company to promote the commercialization and further development of the magnetoencephalograph (MEG). This new technology has continued to generate innovative research as well as expanding the researcher community. Lounasmaa's long-term collaborator, clinical neurophysiologist Riitta Hari, created and has led the brain research unit of the laboratory since 1982 onwards. She undertook the first single-channel MEG recordings of auditory cortex activity as early as 1978 with Prof. Toivo E. Katila's research team working in a small wooden sauna in the forest near the Otaniemi campus. Hari's solid background in both basic and clinical neurophysiology helped her research team to apply MEG to crucial questions, including the neural sources of different sensory-evoked responses and brain oscillations, cortical motor control, multisensory perception, cognition and social interactions (Hari, 2017).

This line of research is still very active. Risto Ilmoniemi founded the company Nexstim to commercialize transcranial magnetic stimulation technology. In 2018, they were awarded the first Finnish-led European Research Council Synergy grant for the ConnectToBrain project to develop a clinical application of a novel technique, called multi-locus transcranial magnetic stimulation.

7.1 | Neural computation

In the field of neural computation, the mathematician Teuvo Kohonen, who worked in the Helsinki University of Technology (the present Aalto University), has pioneered fundamental theories of associative memory and mapping, and developed concepts of self-organized neural maps and neural networks ("Kohonen maps"; Kohonen, 1982, 1990).

8 | COGNITIVE BRAIN RESEARCH AND MISMATCH NEGATIVITY

The brain is able to differentiate deviant stimuli when these are present in a series of repeated stimuli; this is thought to be a correlate of how the brain processes memories. Two Finnish psychologists, Risto Näätänen and Sirkka Mäntysalo, undertook seminal interpretations of the EEG recordings performed by Mäntysalo in the Institute for Perception TNO (National Defence Organisation), the Netherlands. They identified a negative component of sound-related potentials (Naatanen, Gaillard, & Mantysalo, 1978), which they termed mismatch negativity (MMN). MMN was elicited by presenting deviant-pitch tones among repetitive standard-pitch tones both when the subject listened actively to the tone stream and when it was ignored that is asking the listeners to focus on another tone stream. Therefore, MMN was regarded as reflecting automatic (pre-attentive) sensory processing, unlike for example, P300 (or P3b), another widely studied event-related potential. This interpretation has been supported by numerous subsequent studies (for a review, see Naatanen, Paavilainen, Rinne, & Alho, 2007). The MMN response has proved to be an important tool in perception and attention research and in many cognition-related experiments and studies of brain diseases and states. MMN is currently being studied as a biomarker in many brain disorders, including developmental linguistic disorders, psychoses, and alcohol and substance use disorders (Naatanen et al., 2011). MMN is evoked by almost any kind of change in a repetitive sound and higher-order irregularities and is therefore postulated to indicate automatic auditory intelligence (Naatanen, Astikainen, Ruusuvirta, & Huotilainen, 2010) and predictive coding in auditory perception (Denham & Winkler, 2017).

9 | PIONEERING ADVANCES IN CHEMICAL NEUROANATOMY: IMAGING CATECHOLAMINES

Olavi Eränkö (1924–1984, Figure 4) studied medicine in the University of Helsinki, and was particularly interested in physiology, the discipline of his first publication in 1940s. His fundamental studies on the fluorescence of formaldehyde-fixed adrenal gland led to the discovery of formaldehyde-induced fluorescence of catecholamines (Eranko, 1957). His

FIGURE 4 Olavi Eränkö (1924–1984) in his laboratory (photo Department of Anatomy, University of Helsinki)

further development of the method, involving freeze-drying of tissues (Eranko, 1954) and the treatment with formaldehyde vapour, paved the way to detailed analyses of the aminergic neuron systems in the brain (Eranko, 1967), subsequently perfected by several Swedish scientists in the groups of Nils-Åke Hillarp and Bengt Falck (Carlsson, Falck, Hillarp, Thieme, & Torp, 1961; Falck, Thieme, Hillarp, & Torp, 1962).

Eränkö immediately recognized the importance of the catecholamine fluorescence of adrenal chromaffin cells (Eranko, 1955b), and joined the groups of Marthe Vogt and Sir John Gaddum in Edinburgh to apply his analytical methods to identifying catecholamines. His most widely cited papers include one demonstrating the localization of adrenaline and noradrenaline in the adrenal medulla, published in 1955 in Nature (Eranko, 1955a), and another describing the existence of small intensely fluorescent (SIF) cells in the sympathetic ganglia in 1965 (Eranko & Harkonen, 1965). The latter cells became one of the main targets of Eränkö's research for the rest of his life. All his research was characterized by high scientific rigour. He was a master of methods and method development, including quantitation and statistics. In addition to scientific papers, in 1955 he published a popular handbook "Quantitative methods in histology and microscopic histochemistry." His deep and broad knowledge was always available to all of the young scientists in his department, while serving as the professor and chairman of the Department of Anatomy of the University of Helsinki 1956–1984. In 1984, he was the President of the VII International Congress of Histochemistry and Cytochemistry held in Helsinki. He passed away only a few months after the congress.

10 | ACHIEVEMENTS IN NEUROCHEMISTRY AND NEUROPSYCHOPHARMACOLOGY

Neurochemistry was one of the neuroscience disciplines to expand in Finland in the 1960s. Sakari Piha and Simo S. Oja developed analyzers for amino acids and studied the dynamics of these compounds during brain development. Oja also later focused on the roles of brain-enriched sulphur-amino acids cysteine and glutathione and especially taurine (Saransaari & Oja, 2000).

Several highlights of Finnish brain research have emerged from neuropsychopharmacological laboratories. One very interesting line of study was established by Matti K. Paasonen and Jouko Tuomisto; they examined the effects of psychotropic drugs on brain synapses and on serotonin in a model exploiting blood platelets (Paasonen, 1968; Paasonen & Vogt, 1956; Tuomisto & Tukiainen, 1976).

Many rather unique experimental studies on the biological basis of alcohol addiction were started in the 1950s by Olof Forsander and Kalervo Eriksson in the laboratories of Alko Inc., the Finnish State Alcohol Company. Their experiments were based on selective breeding of rat lines with genetic differences in alcohol preference and alcohol avoidance, (Eriksson, 1968), reviewed in Sommer, Hyytia, and Kiianmaa (2006) as well as for high and low alcohol sensitivity, (Eriksson & Rusi, 1981), reviewed in Korpi et al. (2015). The roles of brain biogenic amines on alcohol-related behaviours were later studied by Liisa Ahtee and Kalervo Kiianmaa, among others. Alcohol preference was associated with a clear predilection for opioid-containing solutions and with strong hyperactivity after opioid administration. Furthermore, administration of opioid antagonists was able to reduce alcohol drinking in these rats, in a manner resembling extinction (Sinclair, 2001). This observation paved the way to the current clinical use of two opioid receptor antagonists, naltrexone and nalmefene, in the treatment of alcohol abuse disorders (Mann, Bladstrom, Torup, Gual, & Brink, 2013). Alcohol-sensitive rats were also highly sensitive to benzodiazepine agonists, such as diazepam. This trait could be traced to a single point mutation of the cerebellum-enriched $GABA_A$ receptor subunit, making the receptor abnormally sensitive to benzodiazepines (Hellevuo, Kiianmaa, & Korpi, 1989; Korpi, Kleingoor, Kettenmann, & Seeburg, 1993; Uusi-Oukari & Korpi, 1990). Unfortunately, clear clinical benefits have still to emerge from this discovery.

Pertti Panula has pioneered in elucidating the histaminergic system in the brains of rats, zebrafish and humans (Panula, Airaksinen, Pirvola, & Kotilainen, 1990; Panula, Pirvola, Auvinen, & Airaksinen, 1989; Panula, Yang, & Costa, 1984; Sundvik & Panula, 2012). His group and collaborators have shown the significance of histamine receptors in various brain diseases, such as Parkinson's disease and alcohol-related behaviours (Haas & Panula, 2003).

Parkinson's disease has been an important topic for Finnish neuroscientists and a successful indication for the largest Finnish pharmaceutical company, Orion Pharma. It successfully developed a peripheral catechol-O-methyltransferase (COMT) inhibitor, entacapone, that is used in combination with levodopa and the peripheral decarboxylase inhibitor carbidopa to enhance the levels of levodopa reaching the brain (Mannisto & Kaakkola, 1999). The company scientists, led by Ismo Ulmanen, were able to clone the COMT gene (Salminen et al., 1990). The whole project was led by the neuropharmacologist, Pekka T. Männistö and the scientific director of Orion, Ariel Gordin. Important contributions to the success of this work can be traced to the neurologists Heikki Teräväinen and Seppo Kaakkola (Helsinki University Hospital) and Urpo Rinne (Turku University Hospital), who undertook treatment trials with patients. Subsequently, Urpo Rinne and Reijo Marttila (University of Turku) have been active in imaging, epidemiology and clinical trials of Parkinson's disease.

Another successful drug development project was started by the Finnish pharmaceutical company, Farmos Inc., and continued by Orion Pharma. This was focused on α-adrenoceptor-acting sedatives and analgesics, detomidine, medetomidine and dexmedetomidine. These drugs are now used as veterinary sedatives. Since these drugs selectively activate α_2-adrenoceptors (Virtanen, Savola, Saano, & Nyman, 1988), their effects can be rapidly reversed by injection of the α_2-antagonist, atipamezole (Haapalinna et al., 1997). More recently, dexmedetomidine has entered intensive care units since it has the ability to evoke light-to-moderate sedation without causing respiratory depression (Kallio et al., 1989). Its mild effect on consciousness has been used to trace the brain regions activated during the return of consciousness. The results have revealed the important roles of activation of the brainstem, thalamus, anterior cingulate cortical arousal networks as well as restored functional connectivity within the frontoparietal network for the restoration of consciousness (Langsjo et al., 2012).

Repurposing of drugs already in clinical use is an approach that is presently used for many indications which have remained without satisfactory treatment. One good example is based on the findings of Jari Koistinaho and his group in the University of Eastern Finland, who found that an old, lipid-soluble broad-spectrum antibiotic, minocycline, was not only neuroprotective but also able to inhibit microglial activation (Tikka, Fiebich, Goldsteins, Keinanen, & Koistinaho, 2001). These effects are independent of its anti-microbial properties. This drug is now being widely tested in trials for various neurological and neuropsychiatric diseases.

One interesting observation emerging from the field of sleep research is that there is an increase in the basal forebrain adenosine content during wakefulness which rapidly declines during recovery sleep (Porkka-Heiskanen et al., 1997). This finding fits well with the fact that Finns hold the world record for consuming the highest amount of coffee per capita, and of course, coffee contains large amounts of the adenosine receptor antagonist, caffeine (https://www.telegraph.co.uk/travel/maps-and-graphics/countries-that-drink-the-most-coffee/). Another important finding was the discovery of the connection between the appearance of childhood narcolepsy with cataplexy after vaccination with adjuvant-containing H1N1-influenza vaccine during 2010–11 (Nohynek et al., 2012). This finding reinforced the concept that narcolepsy–cataplexy is an autoimmune disease (Partinen et al., 2014).

11 | BRAIN RESEARCH SOCIETY OF FINLAND, NORDIC MEETINGS AND FINNISH NEUROSCIENCE GRADUATE SCHOOLS

The Brain Research Society of Finland (BRSF, https://www.brsf.org) was founded in 1973 by Olavi Eränkö, and the society promptly joined the International Brain Research Organization (IBRO). The first meeting of BRSF in the same year was devoted to "Memory." BRSF joined the Federation of European Neuroscience Societies (FENS) in 1998 following the first Forum in Berlin, when FENS was established as a successor to the former European Neuroscience Association (ENA). BRSF board members include basic scientists and clinicians, ensuring that the expanding fields of neuroscience are widely represented. Currently, BRSF has over 280 members and it organizes meetings including the Neuroscience Finland meeting, Brain Awareness Week public symposia, and joint meetings with other scientific societies. BRSF promotes neuroscience in Finland also by awarding the "distinguished neuroscientist of the year" and the "best PhD thesis in neuroscience" prizes. Representatives of BRSF have actively taken part in scientific activities of FENS, in different committees and in the FENS-Kavli Network of Excellence, as well as in training schools, and in the work of FENS Governing Council.

Brain Research Society of Finland is actively engaged in promoting neuroscience especially in the Nordic countries. The Finnish neurochemist, Simo S. Oja, organized the first Nordic Neurochemistry meeting in 1976 in Tampere; this was followed by a series of meetings in most Nordic countries. Importantly, these Nordic meetings were recently revived with the first Nordic Neuroscience meeting held in Trondheim, Norway, in 2015, the second in Stockholm, Sweden, 2017, with the third in Helsinki in 2019 (https://www.helsinki.fi/en/conferences/3rd-nordic-neuroscience-meeting-2019).

11.1 | History of doctoral training in neuroscience in Finland

The Finnish Graduate School (GS) system was launched by the Ministry of Education in 1995, largely in response to the lack of structure and cross-compatibility in the different universities and the insufficient amount of teaching (lectures, courses) at the post-graduate level. This GS system resulted in the founding of a large number of professional and well-coordinated doctoral training programmes. The GSs were funded by the Ministry of Education and Culture, the Academy of Finland and the respective universities until 2012, when the reform of national doctoral training ended the earmarked funding for doctoral programmes, and the universities devised their individual doctoral training systems.

The first Finnish doctoral programme in neuroscience was founded by Kai Kaila (University of Helsinki) together with Riitta Hari (Helsinki University of Technology/Aalto University) in 1995. In 1998, the Helsinki Graduate School of Neurobiology was expanded to the nationwide level as the Finnish Graduate School of Neuroscience (FGSN). The FGSN was a joint programme involving the Universities of Helsinki, Aalto (Helsinki University of Technology until 2009), Eastern Finland (University of Kuopio until 2009),

Oulu, Turku, and Åbo Akademi. Research groups in these universities worked in collaboration to develop doctoral training at a national level in neuroscience. Unfortunately, the national collaboration in doctoral education was again reorganized, and the successor of the FGSN, Doctoral Program Brain & Mind (B&M) started in January 2012 as a joint doctoral programme only involving the University of Helsinki and the Aalto University.

These and further developments have led to formalized doctoral training that is equally accessible to all students. After graduation, they have been employed by academic institutes, biotechnology and pharmaceutical companies, hospitals and various government offices, and many of them now constitute the next generation of principal investigators in Finnish neuroscience.

12 | EFFORTS AIMING TO PROMOTE THE INTERACTION OF BASIC AND CLINICAL NEUROSCIENCES

In 2017, the government of Finland decided to allocate funding to establish the "Neurocenter Finland"-network as a part of the national health strategy (https://neurocenterfinland.fi/en/). Its goal is to establish a coordinating unit to facilitate interactions between all sectors of neuroscience (universities, hospitals, industry, patient organizations, government). The network is coordinated by the University of Eastern Finland.

13 | CONCLUSION

The first scientific description by a Finnish scholar of the structure and function of the central and peripheral nervous systems as well as the sensory organs dates back to 1611 AD. However, active original research in neuroanatomy and neuropathology began in Finland first by the middle of the 19th century by Finnish students of Anders Retzius, Rudolf Virchow, Louis-Antoine Ranvier and Jean-Martin Charcot. During the first half of the 20th century, Finnish research in neurophysiology reached a high level and was recognized with the award of the Nobel Prize in Physiology or Medicine. More recently, Finnish neuroscience has rapidly advanced in multiple areas. This has partly reflected the expansion of the Finnish university system, although the Helsinki metropolitan area still remains the hub of research activity. Apart from pure scientific curiosity, the key to success and the main driving force of Finnish neuroscientists has been the development of new innovative methods of investigation. They have also been able to profit from the particular genetic constitution of the Finnish population and the excellent population and health registers.

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The authors declare no conflicts of interest.

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