BIOGRAPHICAL SKETCH

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NAME: Castrén, Eero Hemminki

Orcid ID: 0000-0002-1402-2791 (http://orcid.org/0000-0002-1402-2791)

POSITION TITLE: Academy Professor, Director, Neuroscience Center

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Kuopio, Kuopio, Finland	MD	08/1983	Medicine
University of Kuopio, Kuopio, Finland	PhD	10/1989	Neuropharmacology
National Institute of Health, Bethesda,, MD, USA	Postdoc	1986-89	Neuroscience
Max Planck Institute of Psychiatry, Germany	Postdoc	1990-92	Neurotrophic factors

A. Personal Statement

My research has focused on the effects of neuronal plasticity and neurotrophic factors, particularly the brain-derived neurotrophic factor BDNF, on the adult brain and their role in the mechanism of action of drugs acting on the central nervous system, in particular antidepressant drugs. Our recent findings have revealed that the BDNF receptor TrkB is the site of action for most if not all antidepressants and that experience-dependent neuronal plasticity plays a critical role in the mechanism of antidepressant drug action. Our finding provide a model for the antidepressant drug action from the atomistic interactions all the way to behavior and treatment response. These findings extend beyond the antidepressant action and open a possibility to use pharmacology to reactivate a developmental-like plastic state in adult brain.

B. Positions and Honors

Positions and Employment

2017 – 21 Academy Professor, Neuroscience Center, University of Helsinki.
2013 - 17 Director, Professor, Neuroscience Center, University of Helsinki.
2011 Visiting Professor, Columbia University, New York, US (on leave from the University of Helsinki)
2003 - 12 Sigrid Juselius Professor of Neuroscience, Neuroscience Center, University of Helsinki.
1998 - 2003 Professor of Molecular Pharmacology, A.I. Virtanen Institute, University of Kuopio.
1995 - 98 Research Director, A.I. Virtanen Institute, University of Kuopio.
1992 - 94 Staff Scientist, Max Planck Institute for Psychiatry, Martinsried, Germany.
1990 - 92 Postdoctoral Fellow, Max Planck Institute for Psychiatry, Martinsried, Germany.
1986 - 89 Postdoctoral Fellow, Laboratory of Clinical Science, NIMH, NIH, Bethesda, MD.

Other Experience

2020-22 President, Cajal Advanced Neuroscience Programme
2018-20 Secretary General, Federation of European Neuroscience Associations
2016-18 Secretary General elect, Federation of European Neuroscience Associations
2014-17 Member, Senate of the University of Helsinki.
2011, 2020 Member, Program Committee, European College of Neuropsychopharmacology

2010 Chairman, 10th International Conference on Neurotrophic factors (NGF2010)
June 10-13, Helsinki Finland 1986- Member, Society for Neuroscience
2007- Member, Scientific advisory board, ERA-Net NEURON programme, European Union
2007-09 Member, Scientific Council, University of Helsinki.
2005-10 Member, Scientific Advisory Panel, European College of Neuropsychopharmacology
2003-06 President, Finnish Brain Research Society
2000-03 Director, Kuopio University Neuroscience Center
2002-03 Chairman, Department of Neuroscience, A.I. Virtanen Institute, University of Kuopio.
2002 Organizer and Chairman: International Summer School on Schizophrenia, Kuopio, Finland.
1989-2003 Vice-Dean, A.I. Virtanen Institute, University of Kuopio.
1996 Organizer and Chairman: International symposium on "Neurotrophins in Neuronal Development and Plasticity", August 4-5, 1996, Finland.

Honors

2017 Anna-Monika Prize for outstanding research in the field of depression and antidepressant drugs
2016 Commander of the Order of the Lion of Finland
2014- Full member, The European Dana Alliance for the Brain
2013-17 Advanced Investigator Grant, European Research Council.
2012 Fellow, European College of Neuropsychopharmacology
2011 Schaefer Scholarship, Columbia University, New York.
2004- Member, Finnish Academy of Science and Letters
2003-13 Sigrid Juselius Professorship in Neuroscience, Neuroscience Center, University of Helsinki.
1993 Fellowship, Max Planck Society, Germany.
1990-92 Fellowship, Alexander von Humboldt Foundation, Germany.
1990 Best thesis award, the Finnish Society of Pharmacology
1989-90 Scientific Assistant Fellowship, Academy of Finland.
1986-89 Visiting Fellowship, Fogarty International Center.

C. Contribution to Science

1. Activity-dependent regulation of BDNF expression: Neuronal activity has for a long time been known to regulate synaptic connectivity and strength, but how this happens has been unclear. Brain-derived neurotrophic factor, BDNF, the second member of neurotrophin family after NGF, was cloned in the lab of Hans Thoenen lab just before I joined his lab as a postdoc in 1990. We soon discovered, first inducing activity by epileptic seizures, that BDNF expression in brain was regulated by neuronal activity. My previous experience as a postdoc at the NIH 1986-89 working on receptor autoradiography had taught me that in brain, localization matters, therefore, I developed in situ hybridization to localize the neuronal types where BDNF expression was increased by activity. I also demonstrated not only seizure activity, but also normal physiological activity, such as light in the visual cortex and osmotic challenge in the hypothalamus, regulated BDNF expression. These studies laid the foundation to the critical role of BDNF as a critical mediator between neuronal activity and synaptic connectivity and strength.

   a. Castrén E., Zafra F., Thoenen H. and Lindholm D. Light regulates the expression of brain-derived neurotrophic factor mRNA in rat visual cortex. ***Proc. Natl. Acad. Sci. USA*** 89: 9444-9446, 1992.
   b. Zafra, F., Castrén, E., Thoenen, H., Lindholm, D. Interplay between glutamate and GABA transmitter systems in the physiological regulation of NGF and BDNF synthesis in hippocampal neurons. ***Proc. Natl. Acad. Sci. USA*** 88: 10037-10041, 1991.
   c. Castrén E., Pitkänen M., Sirviö J., Parsadanian A., Lindholm D., Thoenen H. and Riekkinen P.J. The induction of LTP increases BDNF and NGF mRNA but decreases NT-3 mRNA in the dentate gyrus. ***NeuroReport*** 4: 895-898, 1993.
   d. Castrén E., Thoenen H., Lindholm D. Brian-derived neurotrophic factor mRNA is expressed in the septum, hypothalamus and in adrenergic brain stem nuclei of adult rat brain and is increased by osmotic stimulation in the paraventricular nucleus. ***Neuroscience*** 64: 71-80, 1995.

2. Mouse models of BDNF function in adult brain: Mice lacking BDNF or its receptor TrkB die before adulthood, which prevented their use for the understanding of their physiological and pathological role in adult brain. Before the advent of cre-lox technology, my lab that I set up 1995 at the University of Kuopio, Finland, conditionally reduced TrkB signaling in mice by overexpressing a dominant-negative truncated TrkB in adult neurons to investigate the role of TrkB in brain disorders. We also used the same system to overexpress TrkB in neurons and showed that increased expression of TrkB induced beneficial behavioral effects that were largely opposite to those found when BDNF levels were reduced. In a series of papers using these mice we demonstrated the role of TrkB signaling in memory and learning as well as in ischemic stroke, epilepsy and Alzheimer's disease. Subsequent studies, using other models have largely confirmed our original findings that emphasize the critical role of BDNF signaling in normal brain function and in recovery from insults.

   a. Saarelainen T., Lukkarinen J.A., Koponen S., Gröhn O.H.J., Jolkkonen J., Koponen E., Haapasalo A., Alhonen L., Wong G., Jari Koistinaho J., Kauppinen R.A. and **Castrén E**. Transgenic mice overexpressing truncated trkB neurotrophin receptor in neurons show increased susceptibility to cortical injury after focal cerebral ischemia. ***Mol. Cell. Neurosci***. 16: 87-96, 2000
   b. Saarelainen T., Pussinen R., Koponen E., Alhonen L., Wong G., Sirviö J. and **Castrén E**. Transgenic mice overexpressing truncated trkB neurotrophin receptors in neurons have impaired spatial memory but normal hippocampal LTP. ***Synapse*** 38: 102-104, 2000.
   c. Lähteinen S., Pitkänen A., Saarelainen T., Nissinen J., Koponen E. and **Castrén E**. Decreased BDNF signalling in transgenic mice reduces epileptogenesis. ***Eur. J. Neurosci***. 15: 721-734, 2002.
   d. Koponen E., Võikar V., Riekki R., Saarelainen T., Rauramaa T., Rauvala H., Taira T., **Castrén E**. Transgenic mice overexpressingg the full-length neurotrophin receptor trkB exhibit increased activation of trkB/PLCγ pathway, reduced anxiety, and facilitated learning. ***Mol. Cell. Neurosci.*** 26: 166-181, 2004.

3. Role of BDNF/TrkB in the antidepressant drug effects. Very little was known about the possible role of neurotrophic factors as mediators of effects of drugs used for the treatment of brain disorders. By exploiting the mouse models my lab had developed, we were the first to show that BDNF signaling through TrkB was critical for the behavioral effects of antidepressant drugs and that antidepressants activate TrkB receptor signaling and in rodents. We have then shown that essentially all antidepressant drugs directly bind to TrkB and thereby allosterically potentiate BDNF signaling, revealing a completely novel mechanism of antidepressant drug action. We have found that volatile anesthetics such as isoflurane activate TrkB signaling and show antidepressant-like behavioral effects in rodents, which is consistent with clinical studies showing antidepressant effects of isoflurane. These findings are the foundation for the now widely acknowledged role for BDNF in mood disorders and antidepressant effects and made me one of the first representatives of the emerging field of developmental neuropharmacology.

   a. Casarotto P.C., Girych M., Fred S.M., Kovaleva, V., Moliner R., Enkavi G., Biojone C., Cannarozzo C., Sahu, M.P., Kaurinkoski, K., Brunello C.A., Steinzeig A., Winkel F., Patil S., Vestring S., Serchov T., Diniz C.R.A.F., Laukkanen L., Cardon I., Antila H., Rog T., Piepponen, T.P., Bramham C.R., Normann C., Lauri S.E., Saarma M., Vattulainen I., **Castrén E.** Antidepressant drugs act by directly binding to TRKB neurotrophin receptors. ***Cell*** 184, 1299–1313, https://doi.org/10.1016/j.cell.2021.01.034, 2021.
   b. Saarelainen T., Hendolin P., Koponen E., Lucas G., MacDonald E., Agerman K., Haapasalo A., Nawa H., Ernfors P., Aloyz R. and **Castrén E.** Activation of the trkB neurotrophin receptor is induced by antidepressant drugs and is required for antidepressant-induced behavioral effects. ***J. Neurosci***. 23: 349-357, 2003.
   c. Antila H., Ryazantseva M, Popova D., Sipilä P., Guirado R., Kohtala S., Yalcin I., Lindholm J., Vesa L., Sato V., Cordeira J., Autio H., Kislin M., Rios M., Joca S., Casarotto, P., Khiroug L,. Lauri S., Taira T., **Castrén E**.* and Rantamäki T.* Isoflurane produces antidepressant effects and induces TrkB signaling in rodents. *Corresponding authors. ***Sci. Reports*** 10;7: 7811. doi: 10.1038/s41598-017-08166-9, 2017.
   d. Rantamäki T., Hendolin P., Kankaanpää A., Mijatovic J., Piepponen P., Domenici E., Chao M.V., Männistö P.T. and Castrén E. Pharmacologically diverse antidepressants rapidly activate Brain-derived neurotrophic factor (BDNF) receptor trkB and induce phospholipase-Cγ signaling pathways in mouse brain. ***Neuropsychopharmacology***, 32: 2152–2162, 2007.

4. Neuronal plasticity mediates antidepressant drug effects. It has been widely considered that the effects of antidepressant drugs were largely chemical, influencing the levels of monoamines or intracellular signaling

molecules. Based on our discovery of the role of neurotrophins in the antidepressant effects, we hypothesized that the antidepressants promote activity-dependent plasticity of neuronal networks. We first showed that BDNF signaling was critical in the antidepressant-induced increase in adult neurogenesis. Then, using the effects of monocular deprivation in the visual cortex, a classical model of plasticity, we not only demonstrated that antidepressants indeed promoted plasticity, but unexpectedly found that these drugs fully reactivate a developmental critical period-like state of plasticity in rodent visual cortex. To study whether reactivation of developmental plasticity also takes place in a mood-relevant circuit, we used another classical model, Pavlovian fear conditioning, to show that fluoxetine activates plasticity in fear conditioning circuitry, and promotes long-term effects of fear extinction. The fact that antidepressant-induced plasticity does not work on its own but requires activity to guide plastic networks (monocular deprivation and fear extinction in the visual cortex and fear circuit, respectively) provides a neurobiological explanation for the observation that combination of antidepressants and psychotherapy work better than either treatment alone. We have recently shown that TrkB receptor in parvalbumin-containing interneurons is the key mediator of plasticity-promoting effects of antidepressants and orchestrates cortical plasticity. These findings and my very influential review and opinion papers have paved a way to a new framework of depression and antidepressant effect recently endorsed by optogenetic studies and made me an influential opinion leader in the field of mood disorder treatment.

a. Sairanen M., Lucas G., Ernfors P., Castrén M, and **Castrén E**. BDNF and antidepressant drugs have different but coordinated effects on neuronal turnover, proliferation and survival in the adult dentate gyrus. ***J. Neurosci.*** 25: 1089-1094, 2005.
b. Maya Vetencourt JF, Sale A, Viegi A, Baroncelli L., De Pasquale R, O'Leary OF, **Castrén E**. and Maffei L. The antidepressant fluoxetine restores plasticity in the adult visual cortex. ***Science***, 320, 385-388, 2008.
c. Karpova N.N., Pickenhagen A., Lindholm J., Tiraboschi E., Kulesskaya N., Ágústsdóttir A., Antila H., Popova D., Akamine Y., Bahi A., Sullivan R., Hen R., Drew L.J. and **Castrén E**. Fear Erasure in Mouse Requres Synergy Between Antidepressant Drug Treatment and Exposure Therapy. ***Science*** 334:1731-1734, 2011.
d. Winkel F., Ryazantseva M., Voigt M.B., Giuliano Didio G., Lilja A., Llach Pou M., Steinzeig A., Harkki J., Englund J., Khirug S., Rivera C., Palva S., Taira T., Lauri S.E., Umemori J. and **Castrén E.** T Pharmacological and optical activation of TrkB in Parvalbumin interneurons regulates intrinsic states to orchestrate cortical plasticity. ***Mol. Psychiatry***, doi: 10.1038/s41380-021-01211-0. 2021.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/1XW15x2Pv9wQh/bibliography/42892071/public/?sort=date&direction=descending

- **Total number of publications: 212**
- **Total number of citations: 15,100 (WoS), 22,450 (Google Scholar)**
- **h-index: 61 (WoS), 74 (Google Scholar)**
- **Invited lectures or seminars, total 138 international lectures (+ 112 in Finland, total 250)**

D. Research Support

Ongoing Research Support

Academy of Finland, Research Grant: "Neurotrophin signaling in neuronal plasticity and brain disorders". 2020-2021, € 440,000.
Academy of Finland, Research Grant: "Reversal of extracellular matrix inhibition of brain plasticity from inhibition to activation – mechanisms and applications". 2016-2020, € 270,000.
Academy of Finland, Research grant: "Prevention of coronavirus entry by drugs interacting with the COV2 glycoprotein CRAC domain". 2020-2021, 197,042 €
Jane & Aatos Erkko Foundation: "Promotion of neuronal plasticity in the antidepressant drug action", 2019-2024, € 1 000 000
Sigrid Juselius Foundation: "Neuronal plasticity, neurotrophic factors and the antidepressant action". 2020-2022, 270,000 €.
HiLIFE Fellowship: "Pharmacological regulation of neuronal network plasticity", 2018-2020, 180,000 €.

Research Support Completed in the last 5 years

European Research Council, Advanced Investigator Award. "Induction of juvenile-like plasticity in adult brain". 2013-2018, € 2,500,000

Sigrid Juselius Foundation: "Neurotrophins and antidepressant drugs in the adult brain plasticity", 2013-2019 € 1,250,000.

EU Joint Programme – Neurodegenerative diseases: "Synaptic circuit protection in Alzheimer's and Huntington's disease". 2016-2019, € 411,685.

Academy of Finland, Research Grant: "Pharmacologically Induced Plasticity in Adult Brain: Role of Interneurons and Activation in the Limbic Cortex". 2012-2016, € 450,000.

E. Other scientific achievements:

Supervised Graduate students and Postdocs

- 24 supervised postdocs: Garry Wong (USA), Sandrine Bichet (France), Simon Beggs (UK), Panu Hendolin (Finland), Arthur Semenov (Russia), Kaisa Kurkinen (Finland), Anton Shmelev (Russia), Ira Milosevich (Croatia), Xuefei Wu (China), Olivia O'Leary (Ireland), Heidi Anthoni (Finland), Tomi Rantamäki (Finland), Nina Karpova (Russia), Antonio Di Lieto (Italy), Ettore Tiraboschi (Italy), Vanina Dahlström-Heuser (Brazil), Henri Autio (Finland), Nobuyaki Matsui (Japan), Liang Zhou (China), Ramon Guirado (Spain), Hanna Antila (Finland), Juan Lima-Ojeda (Mexico/Germany), Madhusmita Sahu (India), Cassiano Diniz (Brazil).
- 4 Postdocs currently in lab: Caroline Biojone (Brazil), Cecilia Brunello (Italy), Plinio Casarotto (Brazil), Juzoh Umemori (Japan).
- 23 graduated PhD students (* joint supervision): Anni-Maija Lindén, Tommi Saarelainen, Outi Kontkanen, Annakaisa Haapasalo, Marketa Marvanova*, Sari Lähteinen, Markus Storvik*, Petri Törönen, Eija Koponen, Jussi Väisänen, Tomi Rantamäki, Mikko Sairanen, Topi Tervonen*, Rimante Minkeviciene*, Tobias Gyarfas (German MD), Henri Autio, Jesse Lindholm, Dmitry Molotkov*, Janne Koskimäki*, Dina Popova*, Hanna Antila*, Anna Steinzeig (Russia, 2019), Fredrike Winkel (Germany, 2019).
- 6 graduate students currently under supervision (expected year of graduation):, Raz Balin (Israel, 2021) Cecilia Cannarozzo (Italy, 2022), Giuliano Didio (Italy, 2021), Merve Fred (Turkey, 2020), Angelina Lesnikova (Russia, 2020), Rafael Moliner (Spain, 2021).

Memberships in scientific advisory boards:

- Scientific advisory panel, European College of Neuropsychopharmacology, member 05-12
- Member, Scientific advisory board, ERA-NEURON programme, EU, 2007-14

Editorial Board Member:

- Associate Editor: Neuronal Signaling.
- Editorial board member: Neuropharmacology, Cellular and Molecular Neurobiology, Neurogenesis, Psychiatry Journal

Organizer of international scientific meetings and symposia:

- Chairman: "Neurotrophins in Neuronal Development and Plasticity", August 4-5, 1996, Rautalampi, Finland.
- Chairman:Interdisciplinary Summer School on Schizophrenia: 29.6.-2.7.2002, Kuopio, Finland.
- Chairman: "Neurogenesis". Targeted expert meeting of the European College of Neuropsychopharmacology, Vienna, Austria, September 2007.
- Co-chairman: "Translational research for psychiatric disorders: from mice to man". Targeted expert meeting of the European Neuropsychopharmacology, Istanbul, Turkey, September 11-12 2009.
- Chairman: "Neurotrophins in Health and Disease. 10th Biannual International Conference on NGF and realted trophic factors" June 10-14, Helsinki, Finland.
- Chairman: "Treatment of developmental disorders in adulthood". Symposium in the Annual Meeting of the Society of Neuroscience, New Orleans, LA, USA, 15.10.2012.

Other activities

- Co-founder: Hermo Pharma Ltd (now, Herantis Pharma, IPO 2014), 2008.

- Medical Officer, Phase 2 clinical trial on the Treatment of Amblyopia in Adulthood (sponsored by Hermo Pharma)
- Co-founder, Finncovery Ltd (drug discovery company, merged to Medikalla Ltd, 10.2.2004)