BIOGRAPHICAL SKETCH

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NAME: Bevan, Mark David

eRA COMMONS USER NAME: M-BEVAN

POSITION TITLE: Professor, Department of Physiology, Northwestern University, Chicago IL 60611

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of St. Andrews, Scotland, UK	BSc (Hons)	09/85-06/89	Biology
University of Manchester, England, UK	PhD	09/89-06/93	Neuroscience
University of Oxford, England, UK	Postdoctoral	12/92-11/95	Neuroscience
University of Oxford, England, UK	Fellowship	12/95-11/98	Neurophysiology
University of Tennessee, Memphis, USA	Fellowship	12/95-11/98	Neurophysiology

A. Personal Statement

My career has focused on the factors controlling the activity patterns of neurons in the subthalamic nucleus and associated basal ganglia in health and in Parkinson's and Huntington's disease models. My early training was in cellular and systems electrophysiology (mentor Dr CJ Wilson) and neuroanatomy (mentor Dr JP Bolam). I established an independent laboratory 15 years ago and have maintained an active presence at the bench. Through interactions with colleagues at Northwestern University my laboratory has incorporated additional approaches including viral vector-based genetic manipulations (e.g. optogenetics and chemogenetics), 2-photon microscopy and uncaging, computational modeling and molecular profiling. Like most neuroscientists, my objective is to understand the principles governing the normal operation of the nervous system and to apply this knowledge to the study of disease mechanisms.

I have trained and mentored 7 graduate students and 8 postdoctoral fellows. Several have gone on to Faculty positions and run their own groups in academia. Others direct research programs in industry or are involved in scientific administration and communication. I take training and mentorship as seriously as any aspect of my profession. The ultimate goal of my training is to produce outstanding, ethical, independent, creative, organized and technically skilled scientists that will make impactful contributions to biomedical research and related fields. My love for research places me in the laboratory most days, either doing my own experiments or participating in and supervising the work of others. This practice allows me to directly and intensively supervise and train scientists. In addition, I place considerable emphasis on training good laboratory practice and data analysis, interpretation and communication.

Atherton JF, Kitano K, Baufreton J, Fan K, Wokosin D, Tkatch T, Shigemoto R, Surmeier DJ, Bevan MD (2010) Selective participation of somatodendritic HCN channels in inhibitory but not excitatory synaptic integration in neurons of the subthalamic nucleus. J Neurosci 30: 16025-16040. PMCID: PMC3073577.
Fan KY, Baufreton J, Surmeier DJ, Chan CS, Bevan MD (2012) Proliferation of external globus pallidus-subthalamic nucleus synapses following degeneration of midbrain dopamine neurons. J Neurosci 32: 13718-28. PMCID: PMC3475197.
Atherton JF, Menard A, Urbain N, Bevan MD (2013) Short-term depression of external globus pallidus-subthalamic nucleus synaptic transmission and implications for patterning subthalamic activity. J Neurosci. 33: 7130-44. PMCID: PMC3678728.

Chu HY, Atherton JF, Wokosin D, Surmeier DJ, Bevan MD (2015) Heterosynaptic regulation of external globus pallidus inputs to the subthalamic nucleus by the motor cortex. Neuron 85: 364-76. PMCID: PMC4304914.

B. Positions and Honors

Positions and Employment

1992-1995	Wellcome Trust Postdoctoral Scientist, Oxford University
1995-1998	Wellcome Trust Advanced Training Fellow, Oxford University
1998-2000	Research Fellow, MRC Anatomical Neuropharmacology Unit, Oxford University
2000-2003	Assistant Professor, Anatomy & Neurobiology, University of Tennessee
2003-2014	Associate Professor (adjunct 09/09-08/10), Physiology, Northwestern University
2009-2010	Professor, Biomedical Science, University of Sheffield
2014-	Professor, Physiology, Northwestern University

Other Experience and Professional Memberships

1994-	Member, Society for Neuroscience
1995	Organizer, British Neuroscience Association Symposium, Movement Disorders
1998-	Graduate Student Mentor/Committee Member: Oxford University, University of Tennessee, Sheffield University, Northwestern University
2002-	Reviewer, Wellcome Trust
2003-	Faculty, Northwestern Interdepartmental Neuroscience Program (NUIN)
2003	Organizer, Society for Neuroscience Symposium, 'Rhythmicity and Synchrony in the STN-GPe network'
2005-	Editorial Board, Neuroscience
2005-	Preceptor, NIH Training grants: General Motor Control Mechanisms and Disease; Mechanisms of Aging and Dementia; Neurobiology of Information Storage
2005-present	NIH Study Section: Fo2B, CNNT, NSD-C, SMI (ad hoc)
2006-2008	Chair, NUIN Student Advisory Committee
2007-	Reviewer, European Commission
2008-2012	Member, NIH Study Section: SMI
2009-	Reviewing Editor, Frontiers in Neuropharmacology, Cellular Neuroscience
2011	Guest Editor, Neuroscience: Special Edition, Function and Dysfunction of the Basal Ganglia
2011-2013	Member, NUIN Advisory Board and NUIN Advisory and Progress to PhD Committee
2012-	Member, NIH Study Section: NSD-B
2012-	Associate Director, NIH Training grant, General Motor Control Mechanisms and Disease
2014-	Basal Ganglia Gordon Research Conference (vice-president elect, 2016)
2014	Editorial Board, Molecular and Cellular Neuroscience
2015	NIH Study Section: Udall Center Review, ZNS SRB-J(09)

Honors and Awards

1993-	Invited Speaker (selected): Bordeaux, Edinburgh, Emory, Leeds, Montreal, Northwestern, Oxford, Rosalind Franklin, Sheffield, Tennessee, UCLA, UTSA, UTSW, Wayne State; Annual CHDI Therapeutics Conference, Basal Ganglia Gordon Research Conference, British Neuroscience Association Annual Meeting, CHDI Workshop on Basal Ganglia, Federation of European Neurosciences Triennial Meeting, International Basal Ganglia Society Triennial Meeting, International Congress of Physiological Sciences, NIH NIDA Workshop on Deep Brain Stimulation, NIH NINDS Workshop on Neural Interfaces, Research Update in Neuroscience for Neurosurgeons, Society for Neuroscience Annual Meeting, TEVA pharmaceuticals.
1995-1998	Advanced Training Fellow, Wellcome Trust
1995-2003	Sponsored Presentations, British Neuroscience Association, Federation of European Neurosciences, Society for Neuroscience, USA.
2006	National Parkinson Foundation Mega Grant
2007-	Tenure, Northwestern University
2012-	Jacob Javits Neuroscience Investigator Award

C. Contribution to Science

1. The glutamatergic subthalamic nucleus (STN) is a key node in the cortico-basal ganglia-thalamo-cortical circuit

Using multiple neuronal tracers in combination with correlated light and electron microscopy, we helped to define the key position of the subthalamic nucleus (STN) in the cortico-basal ganglia-thalamo-cortical circuit. A) Movement-suppressing hyperdirect and indirect pathway STN inputs converge with movement-promoting striatal direct pathway inputs onto individual basal ganglia output neurons[1]. B) STN neurons and reciprocally connected, GABAergic external globus pallidus (GPe) neurons converge onto and thus powerfully control common basal ganglia output neurons in the substantia nigra *pars reticulata* (SNr) (and internal segment of the globus pallidus (GPi))[1]. C) Through their extensive dendrites, individual STN neurons integrate inputs from functionally heterogeneous cortico-basal ganglia-thalamo-cortical loops. D) A subset of GPe neurons that are reciprocally connected with the STN also innervate the striatum, where they selectively target GABAergic PV-expressing fast spiking interneurons and GABAergic nitric oxide synthase-expressing low threshold spiking interneurons[3]. 5) The STN receives neurochemically and functionally distinct inputs from cholinergic, glutamatergic and GABAergic neurons of the pedunculopontine nucleus[4].

1. Bevan MD, Bolam JP, Crossman AR (1994) Convergent synaptic input from the neostriatum and the subthalamus onto identified nigrothalamic neurons in the rat. Eur J Neurosci 6: 320-34. PMID: 8019671

2. Bevan MD, Booth PAC, Eaton SA, Bolam JP (1998) Selective innervation of neostriatal interneurons by a subclass of neuron in the globus pallidus of the rat. J Neurosci 18: 9438-52. PMID: 9801382.

3. Bevan MD, Clarke NP, Bolam JP (1997) Synaptic integration of functionally diverse pallidal information in the entopeduncular nucleus and the subthalamic nucleus of the rat. J Neurosci 17: 308-324. PMID: 8987757.

4. Bevan MD, Bolam JP (1995) Cholinergic, GABAergic and glutamate-enriched inputs from the mesopontine tegmentum to the subthalamic nucleus in the rat. J Neurosci 15: 7105-20. PMID: 7472465.

2. STN neurons possess intrinsic membrane properties that underlie their autonomous discharge and dictate their mode of synaptic integration

Using patch clamp recording of neurons in *ex vivo* brain slices in conjunction with 2-photon imaging and glutamate uncaging, single cell molecular profiling, computational modeling and correlated light and electron microscopy, we showed that STN neurons possess intrinsic membrane properties that underlie their autonomous discharge and active, dynamic integration of synaptic inputs. A) The autonomous firing of STN neurons is driven by persistent Na_v channel current[1]. B) Autonomously generated action potentials activate $Ca_v2.2$ channels, which leads to the activation of SK_{Ca} channels, which generate an afterhyperpolarization that promotes rhythmic firing[2]. C) $GABA_A$ receptor-mediated inhibition: deactivates postsynaptic STN Na_v channels and thus resets autonomous firing[3]; de-inactivates postsynaptic STN Na_v channels and thus transiently enhances excitatory synaptic integration post-inhibition[3]; de-inactivates postsynaptic STN Ca_v1 and Ca_v3 channels and thus triggers rebound burst firing post-inhibition[2,4]. D) Somatodendritic STN HCN2/3 channels, which are activated at voltages < -70 mV, actively oppose hyperpolarization due to GABAergic inhibition[4].

1. Bevan MD, Wilson CJ (1999) Mechanisms underlying spontaneous oscillation and rhythmic firing in rat subthalamic neurons. J Neurosci 19: 7617-28. PMID: 10460267.

2. Hallworth NE, Wilson CJ, Bevan MD (2003) Apamin-sensitive small-conductance calcium-activated potassium channels, through their selective coupling to voltage-gated calcium channels, are critical determinants of the precision, pace and pattern of action potential generation in rat subthalamic nucleus neurons *in vitro*. J Neurosci 23: 7525-42. PMID: 12930791.

3. Baufreton J, Atherton JF, Surmeier DJ, Bevan MD (2005) Enhancement of excitatory synaptic integration by GABAergic inhibition in the subthalamic nucleus. J Neurosci 25: 8505-17. PMID: 16162932.

4. Atherton JF, Kitano K, Baufreton J, Fan K, Wokosin D, Tkatch T, Shigemoto R, Surmeier DJ, Bevan MD (2010) Selective participation of somatodendritic HCN channels in inhibitory but not excitatory synaptic integration in neurons of the subthalamic nucleus. J Neurosci 30: 16025-16040. PMCID: PMC3073577.

3. Unitary properties and plasticity of GPe-STN connections

Using patch clamp recording of neurons in *ex vivo* brain slices in combination with 2-photon imaging and GABA uncaging, molecular profiling, computational modeling and correlated light and electron microscopy, we described the morphological and physiological properties of GPe-STN synaptic connections and showed that chronic loss of dopamine triggers heterosynaptic plastic changes in these properties. A) Each GPe-STN axon forms a sparse, spatially distributed terminal field that synapses on small number of widely dispersed STN

neurons. Individual GPe-STN axons form multiple synaptic connections with an individual postsynaptic neuron and thus generate powerful $GABA_A$ receptor-mediated GPe-STN unitary conductances (~5-15 nS)[1,2]. B) However, the potency of unitary GPe-STN synaptic connections is limited by profound short-term synaptic depression (due to depletion of release-ready vesicles), which reduces the reliability and amplitude of unitary transmission. C) Following degeneration of SN dopamine neurons, the strength of GPe-STN connections increases profoundly through proliferation of functional synaptic connections per axon terminal[3]. D) The strengthening of GPe-STN connections that follows the loss of dopaminergic neuromodulation is triggered by excessive activation of NMDA receptors at motor cortex-STN synapses[4].

1. Baufreton J, Kirkham E, Atherton JF, Menard A, Magill PJ, Bolam JP, Bevan MD (2009) Sparse but selective and potent synaptic transmission from the globus pallidus to the subthalamic nucleus. J Neurophysiol 102:532-45.
2. Atherton JF, Menard A, Urbain N, Bevan MD (2013) Short-term depression of external globus pallidus-subthalamic nucleus synaptic transmission and implications for patterning subthalamic activity. J Neurosci 33: 7130-44. PMCID: PMC3678728.
3. Fan KY, Baufreton J, Surmeier DJ, Chan CS, Bevan MD (2012) Proliferation of external globus pallidus-subthalamic nucleus synapses following degeneration of midbrain dopamine neurons. J Neurosci 32: 13718-28. PMCID: PMC3475197.
4. Chu HY, Atherton JF, Wokosin D, Surmeier DJ, Bevan MD (2015) Heterosynaptic regulation of external globus pallidus inputs to the subthalamic nucleus by the motor cortex. Neuron 85: 364-76. PMCID: PMC4304914.

4. Cortical patterning of the STN-GPe network *in vivo* is enhanced following loss of dopamine

Using concurrent *in vivo* electrophysiological recording of the cortex, STN and GPe in urethane-anesthetized rats, we demonstrated that chronic dopamine depletion profoundly increased the sensitivity of the STN-GPe network to rhythmic cortical activity[1,2]. This finding has since been confirmed in awake animals and in Parkinson's disease patients. Abnormally persistent and widespread coherence between the cortex and basal ganglia is thought to be a major pathophysiological consequence of degeneration of substantia nigra dopamine neurons.

1. Magill PJ, Bolam JP, Bevan MD (2000) Relationship of activity in the subthalamic nucleus – globus pallidus network to cortical electroencephalogram. J Neurosci 20: 820-33. PMID: 10632612.
2. Magill PJ, Bolam JP, Bevan MD (2001) Dopamine regulates the impact of the cerebral cortex on the subthalamic nucleus-globus pallidus network. Neuroscience 106: 313-30. PMID: 11566503.

5. Mechanisms underlying burst firing in SNc DA neurons

Using somatic and dendritic patch clamp recording in *ex vivo* brain slices together with 2-photon imaging, we demonstrated that glutamatergic synaptic inputs acting at AMPA and NMDA receptors generated burst firing in SN dopamine neurons[1,2]. Furthermore, action potentials were initiated in the axon and were not reliant on dendritic Ca^{2+} oscillations involving $Ca_v1.3$ and SK_{Ca} channels. These data demonstrated that A) SN dopamine neurons integrate their excitatory inputs in a more conventional manner than was previously suggested B) neuroprotection of SN dopamine neurons with $Ca_v1.3$ channel inhibitors should not impair burst firing of substantia nigra dopamine neurons and therefore their role in associative learning.

1. Blythe SN, Atherton JF, Bevan MD (2007) Synaptic activation of dendritic AMPA and NMDA receptors generates transient high-frequency firing in substantia nigra dopamine neurons *in vitro*. J Neurophysiol 97: 2837-50. PMID: 17251363.
2. Blythe SN, Wokosin D, Atherton JF, Bevan MD (2009) Cellular mechanisms underlying burst firing in substantia nigra dopamine neurons. J Neurosci 29: 15531-41. PMCID: PMC2834564.

A complete bibliography is available at:

http://www.ncbi.nlm.nih.gov/sites/myncbi/mark.bevan.1/bibliography/41149593/public/?sort=date&direction=ascending

D. Research Support

1. 2R37NS041280 Bevan (PI) 04.01.2001 - 05.31.2019
NIH/NINDS
Synaptic Transmission, Plasticity and Integration in the Subthalamic Nucleus
The objectives are to determine the underlying mechanisms and impact of external globus pallidus-subthalamic nucleus synaptic proliferation following loss of dopamine.
Role: PI

2. P50NS047085 Surmeier (Dir) Bevan (PI) 09.30.2003 - 07.31.2018
NIH/NINDS
Rhythmicity and Synchrony in the Basal Ganglia
The objectives are to determine how dopamine and chronic loss of dopamine regulate the patterning of the subthalamic nucleus by motor cortical inputs.
Role: PI (Project 3)

3. A-5071 Surmeier (Dir) Bevan (PI) 04/01/2010 -
CHDI
Project 6. Adaptations in the STN in mouse models of HD
The objective is to determine the effects of mutant huntingtin expression on the subthalamic nucleus.
Role: PI (Project 6)