BIOGRAPHICAL SKETCH

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	Completion Date	FIELD OF STUDY
University of St. Andrews, Scotland, UK	BSc (Hons)	06/1989	Biology
University of Manchester, England, UK	PhD	12/1992	Neuroscience
University of Oxford, England, UK	Postdoc	11/1995	Neuroscience
University of Oxford, England, UK	Fellowship	11/1998	Neurophysiology
University of Tennessee, Memphis, USA	Fellowship	11/1998	Neurophysiology

A. Personal Statement

My career has focused on the basal ganglia, a group of subcortical brain nuclei critical for the motivation, selection, and execution of action sequences and the primary site of dysfunction in psychomotor disorders including Parkinson's disease (PD), Huntington's disease (HD), Obsessive-Compulsive Disorder, and addiction. My long-term research goals are to define the cellular, synaptic, and circuit mechanisms underlying normal and pathological basal ganglia activity and the linkage of these activity patterns to psychomotor function and dysfunction. I have published 48 papers encompassing the subthalamic nucleus (STN), external and internal segments of the globus pallidus (GPe and GPi), substantia nigra *pars compacta* (SNc) and *reticulata* (SNr), striatum, and pedunculopontine nucleus (PPN), which have been cited ~ 7,800 times (h index: 39). My laboratory has been supported by NIH-NINDS since its inception in 2000 and I was awarded a Javits Neuroscience Investigator Award in 2012. My group is compact, highly skilled, focused, and committed to rigorous, impactful research. I am in the laboratory most days either doing my own experiments or supervising and training my group. All my former trainees remain in science either running their own labs in academia or industry or are involved in scientific administration and communication. I have published expertise in *in vivo* and *ex vivo* electrophysiology, neuroanatomy at the light and electron microscopic levels, optogenetics, chemogenetics, 2-photon microscopy and uncaging, molecular profiling and manipulation, computational modeling, and mouse behavior. My recent research has focused on alterations in basal ganglia neuron properties and associated circuit dysfunction in PD and HD models.

Selected papers:

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.

Atherton JF, McIver EL, Mullen MR, Wokosin DL, Surmeier DJ, Bevan MD (2016) Early dysfunction and progressive degeneration of the subthalamic nucleus in mouse models of Huntington's disease. Elife e21616. PMCID: PMC5199195.

Chu HY, McIver EL, Kovaleski RF, Atherton JF, Bevan MD (2017) Loss of hyperdirect pathway cortico-subthalamic inputs following degeneration of midbrain dopamine neurons. Neuron 95: 1306-1318. PMCID: PMC5679443.

McIver EL, Atherton JF, Chu HY, Cosgrove KE, Kondapalli J, Wokosin D, Surmeier DJ, Bevan MD (2019) Maladaptive downregulation of autonomous subthalamic nucleus activity following the loss of midbrain dopamine neurons. Cell Rep 28: 992-1002. PMCID: PMC6699776.

Lahiri AK, Bevan MD (2020) Dopaminergic transmission rapidly and persistently enhances excitability of D1 receptor-expressing striatal projection neurons. Neuron (in press).

B. Positions and Honors

Positions

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, Physiology, Northwestern University (adjunct 09/09-08/10)
2009-2010	Professor, Biomedical Science, University of Sheffield
2014-	Professor, Physiology, Northwestern University

Other Experience

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-	NIH Study Section (ad hoc): F02B, CNNT, NSD-C, SMI
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
2012-2016	Member, NIH Study Section: NSD-B
2012-	Director, NIH Training grant, General Motor Control Mechanisms and Disease
2014-2017	Editorial Board, Molecular and Cellular Neuroscience
2015	NIH Study Section: Udall Center Review, ZNS SRB-J(09)
2015-	Departmental and Ad Hoc Tenure and Promotion Committees, Northwestern University
2016	Vice Chair, Basal Ganglia Gordon Research Conference
2016	Organizer, The Subthalamic Nucleus: From Bench to Bedside in Parkinson's Disease. Northwestern University
2017	Chair, Cellular and Functional Heterogeneity of the External Globus Pallidus, International Basal Ganglia Society Triennial Meeting
2018	Chair, Basal Ganglia Gordon Research Conference
2019	Appointments, Tenure & Promotion Committee, Northwestern University

Honors

1993-	Invited Speaker (selected): Universities of Bordeaux, Edinburgh, Leeds, Minnesota, Montreal, Oxford, Sheffield, and Tennessee; Emory, Northwestern, Rosalind Franklin, and Wayne State Universities; UCLA, UCSF Gladstone Institute, UTSA, UTSW; American Neurological Association Annual Meeting, Annual CHDI Therapeutics Conference, Basal Ganglia Gordon Research Conference, British Neuroscience Association Annual Meeting, CHDI Workshop on Basal Ganglia, CHDI Workshop on CNS Circuitry Dysfunction and Molecular Mechanisms in Huntington's Disease, Federation of European Neurosciences Triennial Meeting, International Basal Ganglia Society Triennial Meeting, International Congress of Physiological Sciences, Merck & Co., Neural Control of Movement Annual Meeting, NIAAA, NIH NIDA Workshop on Deep Brain Stimulation, NIH NINDS Workshop on Neural Interfaces, OptoDBS Meeting, Research Update in Neuroscience for Neurosurgeons, Society for Neuroscience Annual Meeting, TEVA Pharmaceuticals, Udall Center Directors Meeting, Winter Conference on Brain Research, 4th World Parkinson Congress

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
2012-2019	Jacob Javits Neuroscience Investigator Award

C. Contributions to Science

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

At the outset of this work, the STN was considered to be a simple relay in the indirect pathway. The fine microcircuitry and synaptic connectivity of the STN was not well understood due to the limitations of tracing techniques that had been applied previously. Using recently developed, more sensitive neuronal tracers in combination with correlated light and electron microscopy, I helped to define the position of the STN in the cortico-basal ganglia-thalamo-cortical circuit 1) movement-suppressing hyperdirect and indirect pathway STN inputs converge with movement-promoting striatal direct pathway inputs onto individual basal ganglia output neurons[1] 2) STN neurons and reciprocally connected, GABAergic GPe neurons innervate common pools of basal ganglia output neurons in the SNr (and GPi)[1] 3) through their extensive dendrites, individual STN neurons integrate inputs from functionally heterogeneous cortico-basal ganglia-thalamo-cortical loops[2] 4) a subset of prototypic 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 PPN[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, 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
3. 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.
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

Although the key role of the STN in cortico-basal ganglia-thalamo-cortical circuit function was widely accepted, the intrinsic physiological and synaptic properties of STN neurons were largely unknown. 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, I discovered membrane properties of STN neurons that underlie their autonomous discharge and dynamic integration of synaptic input 1) the autonomous firing of STN neurons is driven by persistent Na_v channel current[1]. In addition, autonomously generated action potentials activate $Ca_v2.2$ channels, which activates SK_{Ca} channels that underlie an afterhyperpolarization that promotes rhythmic firing[1] 2) $GABA_A$ receptor-mediated inhibition: deactivates postsynaptic STN Na_v channels, resetting the autonomous oscillatory firing cycle[2]; de-inactivates postsynaptic STN Na_v channels, transiently enhancing excitatory synaptic integration; de-inactivates postsynaptic STN Ca_v1 and Ca_v3 channels, promoting rebound burst firing[2,3] 3) somatodendritic STN HCN2/3 channels, which are activated at voltages < -70 mV, oppose hyperpolarization arising from GABAergic inhibition[3] 4) autonomous STN activity is disrupted in PD models through increased conductance of K_{ATP} channels. Chemogenetic restoration of lost autonomous STN activity ameliorates motor dysfunction in PD mice[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. 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.
3. 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.
4. McIver EL, Atherton JF, Chu HY, Cosgrove KE, Kondapalli J, Wokosin D, Surmeier DJ, Bevan MD (2019) Maladaptive downregulation of autonomous subthalamic nucleus activity following the loss of midbrain dopamine neurons. Cell Rep 28: 992-1002. PMCID: PMC6699776.

3. Unitary properties and plasticity of GPe-STN connections

The GPe-STN pathway is implicated in pathological cortico-basal ganglia-thalamo-cortical circuit dysfunction in PD but little was known about its anatomical, physiological, and pathophysiological properties. Using patch clamp recording of STN neurons in *ex vivo* brain slices in combination with 2-photon imaging and GABA uncaging, molecular profiling, knockdown of NMDA receptors, computational modeling, and correlated light and electron microscopy, we described the normal morphological and physiological properties of GPe-STN synaptic connections and showed that heterosynaptic plasticity alters these properties following the loss of dopamine 1) each GPe-STN axon forms a sparse, spatially distributed terminal field that synapses on a 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] 2) 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 strength of unitary transmission[2] 3) following degeneration of SN dopaminergic neurons, the strength of GPe-STN connections increases profoundly through proliferation of synaptic connections per axon terminal[3] 4) following the loss of dopaminergic neuromodulation, strengthening of GPe-STN connections is triggered by excessive activation of STN NMDA receptors[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 is profoundly altered 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 altered the sensitivity of the STN-GPe network to cortical slow-wave activity and activation[1,2]. Abnormally persistent and widespread correlated activity in the cortex and basal ganglia is thought to be a pathologically significant consequence of SN dopamine neuron degeneration. Until recently it was thought that aberrant STN patterning and associated motor dysfunction in PD were due to an increase in the strength of hyperdirect pathway cortico-STN transmission. However, we discovered using electrophysiological, optogenetic, chemogenetic, anatomical, and behavioral approaches that cortico-STN transmission is in fact strongly downregulated in parkinsonism and that GPe-STN transmission actively promotes motor dysfunction[3]. Furthermore, we recently completed a major study, which suggests that abnormal cortical patterning of prototypic GPe neurons and STN neurons is largely due to excessive D2-SPN to prototypic GPe neuron transmission and maladaptive circuit plasticity[4].

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.

3. Chu HY, McIver EL, Kovaleski RF, Atherton JF, Bevan MD (2017) Loss of hyperdirect pathway cortico-subthalamic inputs following degeneration of midbrain dopamine neurons. Neuron 95: 1306-1318. PMCID: PMC5679443.

4. Kovaleski RF, Callahan JW, Chazalon M, Baufreton J, Bevan MD (2019). Dysregulation of external globus pallidus-subthalamic nucleus network dynamics in Parkinsonian mice. bioRxiv 774091. [Preprint]. Available from: https://doi.org/10.1101/774091 (under second review at J Physiol).

5. Mechanisms underlying SN dopaminergic neuron activity and transmission

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 trigger burst firing in SN dopaminergic neurons[1,2]. Furthermore, action potential bursts are initiated in the axon and are not dependent on dendritic Ca^{2+} oscillations involving $Ca_v1.3$ and SK_{Ca} channels, as suggested previously. Recently, we used

optogenetic stimulation of dopaminergic axons and perforated patch clamp recording of D1 receptor expressing striatal projection neurons (D1-SPNs) in *ex vivo* brain slices to examine for the first time the impact of native dopaminergic transmission on D1-SPN excitability[3]. We found that dopaminergic transmission rapidly and persistently elevates D1-SPN excitability whether neurons are in the down or up state[3]. Furthermore, excitability increases were consistent with negative modulation of D1-SPN K_v1 and SK channels[3].

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.
3. Lahiri AK, Bevan MD (2020) Dopaminergic transmission rapidly and persistently enhances excitability of D1 receptor-expressing striatal projection neurons. Neuron (in press).

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

Active

1. 2R37NS041280 Bevan (PI) 04.01.2001-05.31.2019 (NCE)
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 transmission changes following the loss of dopamine.
Role: PI

2. A-5071 Surmeier (Dir) Bevan (PI) 04.01.2012-
CHDI
Project 6 – Adaptations in the STN in mouse models of HD - mitochondrial oxidant stress, autonomous firing downregulation, and neurodegeneration; Project 9 – Optogenetic interrogation of STN-GPe network activity in HD mice; Project 10 – Adaptations in the STN in mouse models of HD – afferent and efferent synaptic transmission properties.
The objectives are to determine the cellular, molecular, and circuit mechanisms underlying the dysfunction and degeneration of the STN in mouse models of Huntington's disease.
Role: PI (Projects 6, 9, 10)

3. 2T32NS041234 Bevan & Surmeier (Multi-PI) 07.01.2002-06.30.2023
NIH/NINDS
General Motor Control Mechanisms and Disease Training Program
The objectives are to provide conceptual, technical, quantitative, ethical, and professional training to pre- and post-doctoral scientists conducting research on motor control and motor system disease.
Role: PI

4. Bevan (PI) 01.01.2019-12.31.2023
Northwestern Medicine
Institutional Support Package
The objective is to support the integration and development of state-of-the-art brain circuit interrogation approaches.
Role: PI

Completed

P50NS047085 Surmeier (Dir) Bevan (PI) 09.30.2003-08.31.2019
NIH/NINDS
Rhythmicity and Synchrony in the Basal Ganglia
The objectives are to determine how dopamine and loss of dopamine regulate the patterning of the subthalamic nucleus by the motor cortex
Role: PI (Project 3)