

BIOGRAPHICAL SKETCH

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NAME: **Alban de Kerchove d'Exaerde**

eRA COMMONS USER NAME (credential, e.g., agency login):

POSITION TITLE: **Research Director**

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 Louvain (UCL), Belgium	B. S.	06/1986	Biology, Chemistry, Physical and Agronomic Sciences
University of Louvain (UCL), Belgium	M.S.	09/1989	Biology, Biochemistry, Chemistry and Engineering
University of Louvain (UCL), Belgium	PhD	02/1996	Molecular Biology, Biochemistry, Cell biology
Pasteur Institute, Paris, France	Postdoctoral	04/2000	Neuroscience (animal models, nAChR)
Université Libre de Bruxelles (ULB), Belgium	Postdoctoral	09/2002	Neuroscience (basal ganglia)

A. Personal Statement

I initially learned molecular biology and biochemistry during my PhD to decipher the role plasma membrane H⁺-ATPase in yeast and plant (P.I. Pr André Goffeau). Next, I learned molecular neurobiology, mouse transgenesis, single cell PCR by working on the physiology of nAChRs in NMJ and in catecholaminergic neurons during my postdoctoral fellowship at Pasteur Institute in Paris (P.I. Pr Jean-Pierre Changeux). For the past 18 years, my main interest is the study of the roles of neuronal populations and genes in pathophysiology of Basal Ganglia (BG), mainly in neuropsychiatric models and in the striatum. Our program is based on our ability to target and manipulate genetically and specifically the two populations of Medium Spiny Neurons (MSN) in the striatum to evaluate their contributions or the contribution of specific genes in MSNs in various behaviors. Our group was the first to demonstrate in vivo that the MSNs of the indirect pathway of BG has an inhibitory effect on locomotion and drug preference and are necessary for drug sensitization and cataleptic effect of antipsychotic by a proper genetic targeting of this population.

1. A. de Kerchove d'Exaerde, P. Supply, J.-P. Dufour, P. Bogaerts, D. Thinès, A. Goffeau, and M. Boutry (1995). Functional complementation of a null mutation of the yeast *Saccharomyces cerevisiae* plasma membrane H⁺-ATPase by a plant H⁺-ATPase gene. *J. Biol. Chem.* **270**, 23828-23837.
2. P. Morsomme, A. de Kerchove d'Exaerde, S. DeMeester, D. Thinès, A. Goffeau, and M. Boutry (1996). Single point mutation in various domains of a plant plasma membrane H⁺-ATPase expressed in *Saccharomyces cerevisiae* increase H⁺-pumping and permit yeast growth at low pH. *EMBO J.* **15**, 5513-5526.
3. L. Schaeffer*, A. de Kerchove d'Exaerde*, and J.-P. Changeux (2001). Targeting transcription at the neuromuscular synapse. *Neuron* **31**, 15-22. * Both authors contributed equally to this work.
4. A. de Kerchove d'Exaerde, J. Cartaud, A. Ravel-Chapuis, T. Seroz, F. Pasteau, L.M. Angus, B.J. Jasmin, J.-P. Changeux, and L. Schaeffer (2002). Expression of mutant Ets protein at the neuromuscular synapse causes alterations in morphology and gene expression, *EMBO Rep.* **3**, 1075-1081.

B. Positions and Honors

Positions and Employment

- 10/2017 Research Director, Fund for Scientific Research, FRS-FNRS, School of Medicine, Lab. Neurophysiology, Université Libre de Bruxelles (ULB), Belgium.
- 2013-17 Senior Research Associate, Fund for Scientific Research, FRS-FNRS, School of Medicine, Lab. Neurophysiology, Université Libre de Bruxelles (ULB), Belgium.
- 2002-13 Research Associate, Fund for Scientific Research, FRS-FNRS, School of Medicine, Lab. Neurophysiology, Université Libre de Bruxelles (ULB), Belgium.
- 2000-02 Post-doctoral Fellow. School of Medicine, Lab. Neurophysiology, Université Libre de Bruxelles (ULB), Belgium.
- 1996-2000 Post-doctoral Fellow. Unit of Molecular Neurobiology. Pasteur Institute, Paris, France.

Teaching

- Professor of Neuroscience, "*Normal and Pathological neurotransmission*", MA1 in Biomedical Sciences, Faculty of Medicine, Université Libre de Bruxelles (ULB) (2007-)
- Professor of Molecular and Cellular Biology, "*Animal Models*", MA1 in Biomedical Sciences, Faculty of Medicine, ULB (2007-).
- Professor of Neurobiology "*Neurobiology*", MA1 Biochemistry and Cellular and Molecular Biology, Faculty of Sciences, ULB (2008-).
- Professor of "*Research Techniques in Neuroscience*", MA-1 in Biomedical Sciences, Faculty of Medicine, University of Mons (2018-).
- Promoter of Ph.D. thesis (15) and Master thesis (25) in Faculties of Sciences, Biomedical and Medical Sciences.

Committee

- President of Belgian Society of Neuroscience (BSN), Belgium
- Member of Governing Council of Federation of European Neuroscience Societies (FENS)
- Member of the scientific board of Fondation de France Psychiatric Disease Committee
- Member of the scientific board of Institut de Recherche en Santé Publique (IReSP), Addiction Committee (France)
- Member of HCERES (France)
- Vice-president of « Permanent Research Commission of Faculty of Medicine » (ULB)
- Expert Reviewer Medical Research Council (MRC) (UK)
- Expert Reviewer Wellcome Trust (UK)
- Expert Reviewer Agence Nationale de la Recherche (ANR) (France)
- Expert Reviewer Fondation pour la Recherche Médicale (FMR) (France)
- Expert Reviewer Fondation pour la Recherche sur le Cerveau (FRC) (France)
- Expert Reviewer Agence National de Sécurité Sanitaire de l'alimentation, de l'Environnement et du Travail (ANSES) (France) et Institut National du Cancer (INCa) (France)
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- Expert Reviewer Paris Sciences et Lettres (PSL) Research University (France)
- Expert Reviewer Institut Pasteur, Paris (France)
- Expert Reviewer Agreenskill (EU)
- Expert Reviewer Federation for Brain Research (France)

Editorial Activity

- Review Editor: Frontiers in Cellular Neuroscience
- Referee for scientific journals: Behavioural Brain Research, Biological Psychiatry, BioTechniques, BMC Psychiatry, Cerebral Cortex, Current Biology, eLife, EMBO Journal, European Journal of Neuroscience, European Journal of Biochemistry, Frontiers in Computational Neuroscience, Frontiers in Neural Circuits, Frontiers in Neurology, Gene &

Development, Journal of Neurochemistry, Journal of Neuroscience, Molecular Neurobiology, Molecular Psychiatry, Neuroscience, Neuroscience Bulletin, PloS One, Translational Psychiatry..

Honors

- 2018 Triennial Prize of the Foundation Simone and Pierre Clerdent
- 1999-2000 Training and Mobility Research Grant, EEC.
- 1996-1999 Marie Curie Research Training Grants, Category 30, EEC.
- 1990-96 PhD Students, Unit of Physiological Biochemistry, Université Catholique de Louvain (UCL), Belgium.
- 1993-95 PhD Fellowship FDS, UCL, Belgium
- 1990-93 PhD Fellowship IRSIA, Belgium.

Professional Memberships

- Society for Neuroscience
- Federation of European Neuroscience Societies
- International Basal Ganglia Society
- Belgian Society of Neuroscience

C. Contributions to Science

1. nAChRs subtypes in dopaminergic and noradrenergic neurons.

I first became interested in the neuroscience of neuropsychiatric disease during my postdoc. I have characterised by a combination of single cell PCR and patch clamp recordings on nicotinic acetylcholine receptor (nAChR) subunit knock-out mice ($\beta 2^{-/-}$, $\alpha 4^{-/-}$ (Marubio et al., 1999)) and $\alpha 7^{-/-}$ mice) two principal nAChR subtypes with distinct pharmacology expressed by DA neurons of the SN and VTA (Klink et al., 2001). The same approach has been applied to the Locus coeruleus and we identified two classes of neurons (Léna et al. 1999). Neurons in the catecholamine nuclei thus exhibit a diversity of nAChRs that might differentially modulate reinforcement and motor behavior in nicotine addiction. On the other hand, epidemiological evidence indicates that nicotine and cocaine addiction are positively correlated. We have demonstrated that the inhibition of both $\alpha 7$ and $\beta 2$ containing nAChRs is necessary to prevent development of sensitization of cocaine-elicited increases in extracellular dopamine levels in the NAc (Zanetti et al., 2006).

1. L. M. Marubio, M. Arroyo-Jimenez, M. Cordero-Euresquin, C. Léna, N. Le Novère, A. de Kerchove d'Exaerde, M. Huchet, M. I. Damaj and J.-P. Changeux (1999). Reduced nicotine-elicited antinociception in mice lacking the neural alpha-4 nicotinic receptor subunit. *Nature* **398**, 805-810.
2. R. Klink*, A. de Kerchove d'Exaerde*, M. Zoli, and J.-P. Changeux (2001). Molecular and physiological diversity of nicotinic acetylcholine receptors in the midbrain dopaminergic nuclei. *J. Neurosci.* **21**, 1452-1483. * Both authors contributed equally to this work.
3. C. Léna*, A. de Kerchove d'Exaerde*, M. Cordero-Erausquin, N. Le Novère, M. Arroyo-Jimenez and J.-P. Changeux (1999). Diversity and distribution of nicotinic acetylcholine receptors in the *locus ceruleus* neurons. *Proc. Natl. Acad. Sci. USA* **96**, 12126-12131. * Both authors contributed equally to this work.
4. L. Zanetti, A. de Kerchove d'Exaerde, A. Zanardi, J.-P. Changeux, M.R. Picciotto, and M. Zoli (2006). Inhibition of both alpha7* and beta2* nicotinic acetylcholine receptors is necessary to prevent development of sensitization to cocaine-elicited increases in extracellular dopamine levels in the ventral striatum. *Psychopharmacology* **187**, 181-188.

2. Distribution of iMSNs and dMSNs in striatal subregions and their role in motor and reward functions.

Two intermingled striatal projection systems, called d and i pathways and composed of dMSNs and iMSNs express dopamine D_1 receptors (D1R) whereas iMSNs specifically express dopamine D_2 receptors (D2R) and adenosine A_{2A} receptors ($A_{2A}R$). We have generated the first genetic model allowing selective ablation of i-MSNs mediated by Cre recombinase expression thanks to our A_{2A} -Cre mouse. Thanks to this transgenic we provided the first in vivo demonstration of the motor inhibitory role of iMSNs and an unexpected involvement in limiting the drug-reinforcement process (Durieux et al., 2009). Next, we characterized the role of iMSNs and dMSNs in DMS, DLS in locomotion, reactivity to novelty, motor learning, cataleptic effect of haloperidol, locomotor sensitization, and reward effect by selective ablation of iMSNs or dMSNs in these striatal subregions (Durieux et al., 2012). We also unravelled the respective contribution of iMSN and dMSN in DMS, DLS and NAc in male sexual behavior showing a prominent role of the dMSNs of the different subregions (Detraux et al., 2021). By using a reversal serial sequence using a two-presses serial order operant

task, we showed that optogenetic ChR2 activation of dMSNs and iMSNs of the DLS did not change the learning rate of the sequence, but activation of dMSNs facilitated the acquisition of a reversal serial order task and iMSNs activation induced a deficit in the acquisition of the task (Laurent et al., 2017).

1. P.F. Durieux, B. Bearzatto, S. Guiducci, T. Buch, A. Waisman, M. Zoli, S.N. Schiffmann and A. de Kerchove d'Exaerde (2009). D2R-Striatopallidal neurons inhibit locomotor and drug reward processes. *Nat. Neurosci.* **12**, 393-395.
2. P.F. Durieux, S.N. Schiffmann and A. de Kerchove d'Exaerde (2012). Cell-type-specific loss in the striatum reveals differential regulation of motor control and response to dopaminergic drugs by D1R- and D2R-neurons in distinct dorsal striatum subregions. *EMBO J.* **31**, 640-53.
3. M. Laurent, J.-F. De Backer, D. Rial, S. N. Schiffmann and A. de Kerchove d'Exaerde (2017). Bidirectional control of reversal in a dual action task by direct and indirect pathway activation in the dorsolateral striatum in mice. *Front. Behav. Neurosci.* **11**, 256.
4. B. Detraux, A. Vilella, A De Groote, S.N. Schiffmann, M. Zoli and A. de Kerchove d'Exaerde (2021). Dorsal and ventral striatal neuronal subpopulations differentially disrupt male mouse copulatory behavior. *European Neuropsychopharmacol.* In press.

3. Identification of specific genes for signal transduction and behaviours in MSNs by specific gene inactivation.

We set up a reliable method applied on adult brain to identify and generate specific i- and d-MSN gene profiles. Our approach led to the identification of new i- and d-MSN-specific genes and demonstrated that ecto-5'-nucleotidase (NT5e), producing adenosine, is specifically expressed in iMSNs and implicated of NT5e in motor learning (Ena et al., 2013). We also discovered that G-protein-regulated inducer of neurite outgrowth 3 (GPRIN3) is mainly expressed in iMSN and mediates D2R functions in the striatum by acting on neuronal arborization, electrophysiological properties, motivation and cocaine-induced locomotion (Karadurmus et al. 2019). The major afferents to the striatum come from glutamatergic neurons and the role of glutamate NMDA receptors (NMDA-Rs) in the striatum was characterized in dMSNs but not in iMSNs. We generated a conditional i-MSN NMDA KO mouse model to address its functions in i-MSNs. At the cellular level, deletion of GluN1 in iMSNs reduces the number and strength of the excitatory cortico-iMSNs synapses. The decrease of input integration leads to dysfunction in BG output, which is seen as reduced habituation, delay in goal-directed learning, lack of associative behaviour, and impairment in action selection or skill learning (Lambot et al., 2016).

Dopamine modulates striatal plasticity and we unraveled that striatal spike-timing-dependent long-term potentiation (tLTP) mediated by endocannabinoids is impaired in Parkinson's disease model and controlled by D2R located presynaptically in cortical terminal afferences (Xu et al., 2018).

1. S.L. Ena, J.F. De Backer, S.N. Schiffmann and A. de Kerchove d'Exaerde (2013). FACS-array profiling identifies Ecto-5' nucleotidase as a striatopallidal neuron-specific gene involved in striatal-dependent learning. *J. Neurosci.* **33**, 8794-8809.
2. D. Karadurmus, D. Rial, J. F. De Backer, D. Communi, A. de Kerchove d'Exaerde* and S. N. Schiffmann* (2019). GPRIN3 Controls Neuronal Excitability, Morphology, and Striatal-Dependent Behaviors in the Indirect Pathway of the Striatum. *J. Neurosci.* **39**, 7513-7528.
3. L. Lambot, E. Chaves Rodriguez, D. Houtteman, Y. Li, S.N. Schiffmann, D. Gall and A. de Kerchove d'Exaerde (2016). Striatopallidal Neuron NMDA receptors control synaptic connectivity, locomotor, and goal-directed behaviors. *J. Neurosci.* **36**, 4976-4992.
4. .H Xu, S. Perez, A. Cornil, B. Detraux, I. Prokin, Y. Cui, B. Degos, H. Berry, A. de Kerchove d'Exaerde and L. Venance (2018). Dopamine-endocannabinoid interactionmediate spike-timing-dependent potentiation in the striatum. *Nat. Comm.* **9**, 4118.

4. Identification of specific genes and circuits involved in psychiatric diseases

We discovered that *Maged1* (*Melanoma antigen genes d1*) has a mandatory role in behaviours related to drug addiction in BG. Mice lacking *Maged1* are insensitive to the behavioural effects of cocaine. Electrophysiological experiments in brain slices and conditional KO mice demonstrated that *Maged1* is critical for cortico-accumbal neurotransmission.

Further, expression of *Maged1* in the prefrontal cortex (PFC) and amygdala, but not in dopaminergic or striatal neurons, is required for cocaine-induced extracellular DA release in the NAc as well as cocaine-mediated behavioural sensitization and acute cocaine effect respectively. This work identifies *Maged1* as a critical molecule involved in cellular processes in BG and behavioural models of addiction (De Backer et al, 2018).

mTOR (mammalian target of rapamycin) is a protein kinase associated, as the striatum, with neurodevelopmental and psychiatric disorders such as autism spectrum disorder and schizophrenia. We identified mTOR signaling in d-MSNs as an important regulator electrophysiological properties and spines density of spontaneous locomotion affecting social

interaction and repetitive behavior through an intricate mechanism involving RhoA and culminating in Kv1.1 overfunction (Rial et al., 2020).

1. J. F. De Backer, S. Monlezun, B. Detraux, A. Gazan, L. Vanopdenbosch, J. Cheron, G. Cannazza, S. Valverde, L. Cantacorps, M. Nassar M, L. Venance, O. Valverde, P. Faure, M. Zoli, O. De Backer, D. Gall, S. N. Schiffmann and A. de Kerchove d'Exaerde (2018). Deletion of *Maged1* in mice abolishes locomotor and reinforcing effects of cocaine. *EMBO Rep.* **19**, e45089.

2. D. Rial, E. Puighermanal, M. Chazalon, E. Valjent, S.N. Schiffmann and A. de Kerchove d'Exaerde (2020). Mammalian Target of Rapamycin-RhoA Signaling Impairments in Direct Striatal Projection Neurons Induce Altered Behaviors and Striatal Physiology in Mice. *Biol. Psy.* **88**, 945-954.

<https://www.ncbi.nlm.nih.gov/sites/myncbi/1jaYhfULTuwQpC/bibliography/57396240/public/?sort=date&direction=ascending>
<http://orcid.org/0000-0002-0682-5877>

D. Additional Information: Research Support and/or Scholastic Performance

Research Support

Ongoing:

Triennial Prize Foundation Simone et Pierre Clerdent (de Kerchove d'Exaerde-PI)	10/1/18 - 12/30/21
Genetic Identification of the neural circuits involved in Attention deficit/Hyperactivity disorder (ADHD).	
Research Project FRS-FNRS 33659288 (PDR) (de Kerchove d'Exaerde-PI)	1/1/19 - 12/31/22
Identification of striatal correlates of procedural memory formation and Flexibility	
Equipment Project FRS-FNRS 33659296 (EQP)	1/1/19 - 12/31/22
Identification of striatal correlates of procedural memory formation and Flexibility	

Completed last five year

WELBIO - ADVANCED GRANT 25085495 [AGR]. (de Kerchove d'Exaerde-PI)	10/1/15 - 9/30/19
Genetic Identification of the neural circuits involved in Attentiondeficit/Hyperactivity disorder (ADHD).	
Research Project FRS-FNRS T0005.15 (PDR) (de Kerchove d'Exaerde-PI)	10/1/15 - 9/30/19
Genetic identification of thalamic and monoaminergic circuitries involved in striatal-dependent behaviors.	
Post-doc fellowship Marie Curie Skłodowska actions from the EU Framework Program for Research and Innovation (de Kerchove d'Exaerde- PI)	10/1/16 - 9/30/18
Genetic Identification of the neural circuits involved in Attentiondeficit/Hyperactivity disorder (ADHD).	
Great Equipment project FNRS GEQ U.G023.15. (de Kerchove d'Exaerde- Co PI)	1/1/15 - 12/31/16
Support and development of new technologies in the ULB Transgenic Mouse facility.	
Research Project F.R.S.M 3.4501.11 (de Kerchove d'Exaerde- PI)	1/1/11 - 12/31/14
Striatal neuronal populations and genes involved in drug addiction, motor control and instrumental learning: a transgenic approach	
Research Project ARC OTP 4.110.G.000015(de Kerchove d'Exaerde- Co PI)	10/1/10 - 9/30/15
Pathophysiology of brain plasticity processes in memory consolidation.	