BIOGRAPHICAL SKETCH

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NAME: **David BELIN**

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POSITION TITLE: Professor of Behavioural Neuroscience

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date	FIELD OF STUDY
Lycée François Magendie (Bordeaux, France)	Baccalaureate	06/1997	Natural Sciences
University of Bordeaux (Bordeaux, France)	BA	06/2000	Cellular and Molecular Physiology
University of Bordeaux (Bordeaux, France)	Masters	06/2002	Neuroscience
University of Bordeaux (Bordeaux, France)	PhD	12/2005	Neuropharmacology
University of Cambridge (Cambridge, UK)	Postdoctoral	05/2009	Experimental Psychology
University of Poitiers (Poitiers, France)	HDR (Habilitation to direct research)	07/2011	Behavioural Neuroscience

A. Personal Statement

I am the dad of a 10-year-old girl, Victoire, the husband of a brilliant neuroscientist, Dr Rauscent, and a professor of Behavioural Neuroscience whose other passion, the study of the biobehavioral basis of the individual vulnerability to develop Impulsive/Compulsive Spectrum Disorders, is only second to my thirst to enthuse young behavioural Neuroscientists with the same passion. Balancing a relatively large teaching load (more than 200 hours of direct contact with undergrads each year) with the organization of the only inter-departmental course in the School of Biological Sciences of the University of Cambridge, with a steady research activity, I have hitherto authored 100 publications, including >90 in peer-reviewed journals, which have, as of March 2025, attracted 10760 citations, (H-factor:41; i-factor:66) according to Google Scholar. Of these, I am first/co-first or last/co-last author on 5 and 50 primary papers, respectively.

Since 2002 when I began my PhD, at a time Hyman and Malenka had argued that *"convincing animal models of addiction—compulsive use despite negative consequences — are lacking*[1]", I have endeavored to investigate the pathophysiology and psychopathology of drug (cocaine, heroin and alcohol) addiction using innovative behavioral procedures in rats (Deroche-Gamonet, Belin & Piazza, Science 2004; Belin et al., Science 2008, Marti-Prats et al., Addiction Biology 2021; Fouyssac et al., EJN 2021, Giuliano et al., 2019). These procedures have proven pivotal for the understanding of the behavioral (Belin et al., Science 2008, Belin et al., Biol. Psy., 2009, Belin et al., Neuropsyhopharmacology 2011), environmental and psychoaffective (Fouyssac et al. EJN, 2021, Marti-Prats et al., Mol. Psy. 2024) factors subserving the individual vulnerability, and resilience, to addiction, as well as their neural and cellular basis (Jones et al., Biol. Psy GOS, 2023, Hynes et al., EJN 2024). Building on the seminal work of Koob and colleagues my research currently aims to identify the biobehavioural signature of compulsion bringing together coping behaviours and the underlying negative reinforcement mechanisms and the role conditioned reinforcers have in the development of maladaptive incentive habits into a general framework of compulsion that can be applied to addictions with and without substance as well as some other compulsive disorders such as OCD (Robbins, Bianca & Belin, Nature Rev. Neurosci. 2024). This transdiagnostic approach to the study of compulsion has lead my laboratory to study compulsive manifestations of coping behaviours (hyperdipsic drinking under a schedule-induced polydipsia procedure) alongside seeking behaviour for cocaine, alcohol and opiates, and high fat high sugar content diet.

Since the beginning of my independent career, in 2009, I have constantly obtained funding in different countries, either as PI (28 grants) or co-PI (3 grants), for an overall amount of ~ £8.5 M£. This has enabled me to broaden my scope to the study of the psychological and neural basis of the vulnerability to develop Impulsive/Compulsive Disorders and establish and maintain an international programme of research aiming to delineate the neurobehavioural signature of compulsivity as a transnosological factor, using sophisticated behavioral procedures in rodents in combination with state-of-the-art neuroscience and neuropsychopharmacological approaches.

New, ongoing and recently completed projects that I would like to highlight include:

1. Rosetrees grant: "*Comfort eating as a gateway to obesity*" (PI), 01/05/2025-30/04/2028. £136k
2. MRC research grant MR/W019647/1 "Striatal astrocytic mechanisms underlying the development of compulsive drug seeking habits" (PI), 01/10/2022-30/09/2025. £822.65k

3. Shionogi grant: therapeutic potential of new dopamine and purinergic receptor antagonists, 01/03/2024-28/02/2028. £1998k
4. MRC programme grant MR/N02530X/1 "Neurobehavioural mechanisms of addiction: vulnerability, circuits and drug memories" (co-applicant, co-PI), 01/10/2016-30/09/2022. £4062k.

Citations:

1. Marti-Prats L, Giuliano C, Domi A, Puaud M, Pena-Oliver Y, Fouyssac M, McKenzie C, Everitt BJ, **Belin D** (2023) *The development of compulsive coping behavior depends on the engagement of dorsolateral striatum dopamine-dependent mechanisms*, Molecular Psychiatry, 28(11) 4666-4678.
2. Fouyssac M, Pena-Oliver Y, Puaud M, Lim N, Giuliano C, Everitt BJ & **Belin D** (2022) *Negative urgency exacerbates relapse to cocaine seeking following abstinence*, Biological Psychiatry 91(12) 1051-1060.
3. Fouyssac M, Puaud M, Ducret E, Marti-Prats L, Vanhille N, Ansquer S, Zhang X, Belin-Rauscent A, Giuliano C, Houeto JL, Everitt BJ, **Belin D** (2021) *Environment-dependent behavioral traits and experiential factors shape addiction vulnerability*. European Journal of Neuroscience, 53(6) 1794-1808.
4. Marti-Prats L, Belin-Rauscent A, Fouyssac M, Puaud M, Cocker P, Everitt BJ, **Belin D** (2021) Baclofen decreases compulsive alcohol drinking in rats characterized by reduced levels of GAT-3 in the central amygdala, Addiction Biology, e13011.
5. Giuliano C, Peña-Oliver Y, Goodlett CR, Cardinal RN, Robbins TW, Bullmore ET, **Belin D*** & Everitt BJ* (2017) *Individual vulnerability for compulsive alcohol seeking in rats: Evidence for a long-lasting compulsive alcohol seeking phenotype in rats*. Neuropsychopharmacology 43(4) 728-738. *: co-last authors

1. Robbins TW, Bianca P & **Belin D** (2024) *From compulsivity to compulsion: the neural basis of compulsive disorders,* Nature Reviews Neuroscience 25(5) 313-333, https://doi.org/10.1038/s41583-024-00807-z
6.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2025-	Treasurer Elect of IBRO
2024-	Adjunct professor, Mount Sinai, NY, USA
2023-present	Professor of Behavioural Neuroscience (grade 12-1st class), Dept of Psychology, Cambridge
2021-23	Professor of Behavioural Neuroscience (grade 11-2nd class), Dept of Psychology, Cambridge
2021-present	Section Editor, European Journal of Neuroscience (Wiley)
2019-present	Associate Editor, Brain Communications (Oxford University Press).
2018- present	Undergraduate Tutor, Homerton College, University of Cambridge
2017- present	Fellow of Homerton College, University of Cambridge
2017-19	International Fellow of the Chinese Academy of Science.
2017-20	Visiting scientist, Intramural Research Programme, NIDA, Baltimore, USA
2016-present	Director of Studies in Psychological and Behavioural Sciences, Homerton College, Cambridge
2015-present	Reviewing Editor for Addiction Biology
2014-present	Advisory Editor of Psychopharmacology
2014-2022	Senior Editor of Brain and Behavior (Wiley)
2013- present	Senior Researcher at INSERM (France)
2019-21	Reader in Behavioural Neuroscience, Department of Psychology, University of Cambridge
2016-19	Lecturer in Behavioural Neuroscience, Department of Psychology, University of Cambridge
2014-2016	Fellow of Emmanuel College, University of Cambridge. 30/09/2016
2013-16	Lecturer in Neuroscience, Department of Pharmacology, University of Cambridge.
2012-2014	Co-Director of an INSERM European laboratory (EAL) Associated with Pr Everitt's lab at the Department of Psychology of Cambridge (UK).
2012-2014	Director of the INSERM team Psychobiology of Compulsive Disorders ranked A+ by the AERES and one of the 3 best research teams in Neuroscience by the INSERM (A+).
2011–present	Reviewer for the MRC (UK), ANR (France)
2009-2013	INSERM AVENIR team leader (ranked 1st in the 2009 recruitment round).
2009-13	INSERM Research Associate CR2 position (ranked 1st), CNRS UMR 6187 & Université de Poitiers, France.

Selected Honors

2015-19	Founding Fellow of the FENS/Kavli network of Excellence
2010-14	Excellence Award INSERM
2009	Mémain-Pelletier Award from the French Academy Of Science
2009	Young Investigator Award from the EBPS (European Behavioural Pharmacology Society)
2008	AAAS/Science Program for Excellence in Science award
2009	NIH travel award; ISRI conference Washington (USA)

2008 Royal society travel award; SFN conference, Washington (USA)

C. Contributions to Science

1. In search of endophenotypes of vulnerability to develop compulsive drug use/self-administration.

Since my PhD during which I developed a preclinical multisymptomatic model of individual vulnerability to develop addiction to cocaine in rats, I have identified several factors of individual propensity to use drugs that are dissociable from factors, such as impulsivity, that specifically predict the switch from controlled to compulsive cocaine self-administration.

1. Deroche-Gamonet V., Belin D., Piazza PV. (2004) *Evidence for addiction-like behaviour in the rat*. Science 305(5686):1014-7.
2. Belin D., Mar A.C., Dalley J.W., Robbins TW and Everitt B.J. (2008) *High impulsivity predicts the switch to compulsive cocaine taking.* Science, 320(5881): 1352-1355.
3. Belin D., Balado E., Piazza P.V. and Deroche-Gamonet V. (2009) *Pattern of intake and drug craving predict the development of cocaine addiction-like behaviour in rats.* Biological Psychiatry, 65(10):863-868.
4. Belin D., Berson N., Balado, E., Piazza P.V., Deroche-Gamonet V. (2011) *High novelty preference rats are predisposed to compulsive cocaine self- administration,* Neuropsychopharmacolgy*, 36:569-579.*
5. Belin D & Deroche-Gamonet V (2012) *Responses to novelty and vulnerability to cocaine addiction: contribution of a multi-symptomatic animal model.* Cold Spring Harbor perspectives in medicine 2 (11), a011940.
6. Vanhille N., Belin-Rauscent A., Mar A., Ducret E. & Belin D. (2015) *High locomotor reactivity to novelty is associated with an increased* propensity to choose saccharine over cocaine: new insights into the vulnerability to addiction. Neuropsychopharmacology**,** 40 (3), 577-589.

This approach has proven very useful at the time of the COVID-19 related lockdowns and their mental health consequences when it enabled the evidence, using prospective longitudinal studies in large cohorts of rats, that the engagement in drug use in a state of exteroceptive, social and affective deprivation exacerbates the vulnerability to develop compulsive cocaine or alcohol intake.

7. Fouyssac M, Puaud M, Ducret E, Marti-Prats L, Vanhille N, Ansquer S, Zhang X, Belin-Rauscent A, Giuliano C, Houeto JL, Everitt BJ, Belin D (2021) Environment-dependent behavioral traits and experiential factors shape addiction vulnerability. European Journal of Neuroscience, 53(6) 1794-1808.

More recently, we have developed a machine learning-assisted tool to identify whether an individual rat is vulnerable or not to developing addiction-like behaviour, thereby bringing preclinical models of addiction closer to the individual level at which diagnosis occurs in humans.

8. Jadhav K, Jamot B, Deroche-Gamonet V, Belin D* & Boutrel B* (2022) *Addicted or not? A new machine learning-assisted tool for the diagnosis of addiction-like behavior in individual rats.* European Journal of Neuroscience*, 56(11)6069-6083.* PMID: 36215170, *: co-last authors. **: co-last authors.*

I have further demonstrated that ingestive, consummatory responses, such as drinking water, can be instrumental if they are used to achieve a change in internal state that is not related to the homeostatic process these consummatory responses have evolved to support (fluid deficit in the context of drinking), bringing back a drive reduction theory of motivation, originally formulated by Hull, to the fore. This theoretical framework allows a learning theory-based interpretation of polydipsia and its compulsive manifestation, hyperdipsia. While contemporary learning theory does not account for the phenomenon of polydipsia, since any response-US association is rooted in contingencies with external, physical USs, an account of adjunctive drinking as an instrumental response the goal of which is a decrease in an aversive internal state, reconciles all the all the experimental results using schedule-induced polydipsia while fitting extremely well in a negative reinforcement-driven view of compulsion, long supported by Koob and Colleagues. In this context, I have demonstrated that hyperdipsia is associated with the engagement of anterior dorsolateral striatum dopamine-dependent habit system.

9. Marti-Prats L, Giuliano C, Domi A, Puaud M, Pena-Oliver Y, Fouyssac M, McKenzie C, Everitt BJ, **Belin D** (2023) *The development of compulsive coping behavior depends on the engagement of dorsolateral striatum dopamine-dependent mechanisms.* Molecular Psychiatry 28(11) 4666-4678, https://doi.org/10.1038/s41380-023-02256-z.

2. Mechanisms of loss of control over drug self-administration across drug classes

Aware that the vulnerability to develop addition may be different across drug classes, I initiated a research programme aiming to study systematically the factors involved in the loss of control over cocaine or heroin self-administration at a time I chaired a symposium I organized at the Society for Neuroscience meeting in San Diego in 2010 (*522. Differential Neuropsychobiological Substrates of Opioid and Psychostimulant Addiction*) which resulted in the writing of a now seminal review. Thus, work carried out in my laboratory demonstrated that while impulsivity promotes the loss of control over cocaine self-administration, it does not confer such vulnerability to escalate heroin self-administration. Similarly, anxiety predicts the escalation of cocaine, but not heroin self-administration. At the neural systems level we have demonstrated that the anterior insula exerts a different influence on the development and expression of escalated cocaine or heroin self-administration. In addition, we identified that the tyrosine kinase inhibitor masitinb decreases the reinforcing and motivational incentive properties of cocaine, but not that of heroin.

1. McNamara R, Everitt BJ, Robbins, TW, Dalley J and **Belin D** (2010) *Trait-like Impulsivity Does Not Predict Escalation of Heroin Self-Administration in the Rat*. Psychopharmacology 212:453-46.

2. Badiani A, **Belin D**, Epstein D, Calu D & Shaham Y (2011) *Heroin and cocaine addictions: the differences do matter.* Nature Reviews Neuroscience 12:685–700.
3. Dilleen R, Pelloux Y, Mar AC, Molander A, Robbins TW, Everitt BJ, Dalley JW, **Belin D** (2012) *High anxiety is a predisposing endophenotype for loss of control over cocaine, but not heroin, self-administration in rats*. Psychopharmacology (Berl), 222:89-97.
4. Rotgé JY, Cocker P, Daniel ML, Belin-Rauscent A, Everitt BJ, **Belin D** (2017) *Bidirectional regulation over the development and expression of loss of control over cocaine intake by the anterior insula.* Psychopharmacology (234(9-10):1623-1631.
5. Joshi D, Puaud M, Fouyssac M, Belin-Rauscent A, Everitt BJ, **Belin D** (2020) The insular cortex in the rat exerts an inhibitory influence over the loss of control of heroin intake and subsequent propensity to relapse. European Journal of Neuroscience, 52 (9), 4115-4126.
6. Belin-Rauscent A, Lacoste J, Hermine O, Moussy A, Everitt BJ & **Belin D** (2018) *The tyrosine kinase inhibitor Masitinib selectively decreases the reinforcing and motivational properties of cocaine, but not heroin in male Sprague Dawley Rats,* Psychopharmacology 235(5) 1545-56.

3. Corticostriatal mechanisms subserving the development of incentive habits.

In spite of the fact that individuals with an addiction spend most of their time engaged in activities aiming to procure the substance, and do so regularly, if not daily, little research has focused on this drug foraging, or drug seeking, behavior. Still, it is during this drug seeking behavior, which in humans is often maintained by the contingent presentation of drug paired cues (conditioned reinforcers, like money) that individuals manifest the compulsive nature of their behavior. I have thus, since 2008, sought to understand the psychological and neural mechanisms of cue-controlled drug seeking behavior. I first developed a theory that reconciles the pavlovian (incentive sensitization), affective (hedonic allostasis) and instrumental components of addition (actions and habits), so called the incentive habit hypothesis, to provide a framework within which to test specific predictions about the psychological and neural basis of compulsive drug seeking. Thus, I demonstrated that functional shifts occur within the striatum, from a network involving the nucleus accumbens and the posterior dorsomedial striatum to a network involving dopaminergic innervation of the dorsolateral striatum and its control by the nucleus accumbens core when cocaine seeking becomes habitual. I then investigated the neural mechanisms influencing the recruitment, and the long-term maintenance, of dorsolateral striatum-dependent cocaine seeking habits and demonstrated that the basolateral amygdala triggers intrastriatal shifts, but subsequently disengages, so that it is the central nucleus of the amygdala that maintains dorsolateral-striatum-dependent maladaptive habits over protracted periods of time. I further showed that this engagement of dorsolateral striatal dopamine-dependent mechanisms over the course of drug seeking occurred for heroin and alcohol and that it was paralleled, in the case of the latter by the development of alcohol seeking habits. I further showed that an inability to relinquish these dorsolateral striatum dopamine-dependent drug seeking habits in the face of adverse consequences contributed to the emergence of compulsion, a tendency predicted by structural and functional alterations in a dual fronto-striatal system. In trying to link the previous evidence that impulsivity is a behavioral trait of vulnerability to develop compulsion, I then established that impulsivity results in a retarded functional transition to dorsolateral striatum control over cocaine seeking, demonstrating that the speed of does not predict vulnerability to addiction, but instead by the nature of the cellular mechanisms subserving, this transition.

1. **Belin D** and Everitt BJ (2008) *Cocaine-Seeking Habits Depend upon Dopamine-Dependent Serial Connectivity Linking the Ventral with the Dorsal Striatum*. Neuron 57, 432-44.
2. **Belin D**, Jonkman S, Dickinson A, Robbins TW and Everitt BJ (2009) *Parallel and integrative processes within the striatum: relevance for the neurobiology of addiction*. Behavioural Brain Research 199 (1), 89-102.
3. Murray J, **Belin D**, Everitt BJ. (2012) *Double dissociation of the dorsomedial and dorsolateral striatum control over the acquisition and performance of cocaine seeking*. Neuropsychopharmacology 37 (11), 2456-2466.
4. Murray J, Everitt BJ, **Belin D** (2012) *N-Acetylcysteine reduces early and late-stage cocaine seeking without affecting cocaine taking in rats,* Addiction Biology 17, 437-440.
5. **Belin D**, Belin-Rauscent A, Murray JE, Everitt BJ (2013) *Drug addiction: a failure in regulation maladaptive incentive habits.* Current Opinion in Neurobiology 23 (4), 564-572.
6. Murray J., Dilleen R., Pelloux Y., Economidou D., Jordan ER., Dalley JW., **Belin D*** & Everitt BJ* (2014) *Increased impulsivity retards the transition to dorsolateral striatal dopamine control of cocaine seeking.* Biological Psychiatry 76 (1):15–22 *: co-last authors
7. Murray JE, Belin-Rauscent A, Simon M, Giuliano C, Benoît-Marand M, Everitt BJ* & **Belin D*** (2015) Basolateral and central amygdala differentially recruit and maintain dorsolateral striatum-dependent cocaine-seeking. Nature Communications 6, 1-9. *: co last authors
8. Giuliano C, Peña-Oliver Y, Goodlett CR, Cardinal RN, Robbins TW, Bullmore ET, **Belin D*** & Everitt BJ* (2017) *Individual vulnerability for compulsive alcohol seeking in rats: Evidence for a long-lasting compulsive alcohol seeking phenotype in rats.* Neuropsychopharmacology 43(4), 728-738. *: co-last authors
9. Hodebourg R, Murray J, Fouyssac M, Puaud M, Everitt BJ & **Belin D** (2018) *Heroin seeking becomes dependent on dorsal striatal dopaminergic mechanisms and can be decreased by N-acetylcysteine,* European Journal of Neuroscience 50 (3), 2036-2044.

10. Giuliano C, **Belin D***, Everitt BJE* (2019) *Compulsive alcohol seeking results from a failure to disengage dorsolateral striatal control over behavior.* Journal of Neuroscience 39 (9), 1744-1754. *: co-last authors
11. Giuliano C, Puaud M, Cardinal R.N, **Belin D***, Everitt BJ* (2021) *Individual differences in the engagement of habitual control over alcohol seeking predicts the development of compulsive alcohol seeking and drinking,* Addiction Biology, e13041. Doi: https://doi.org/10.1111/adb.13041. *: co-last authors
12. Puaud M, Higuera-Matas A, Brunault P, Everitt BJ, **Belin D** (2021) *The Basolateral amygdala ➔ Nucleus Accumbens core circuit mediates the conditioned reinforcing effects of cocaine-paired cues on cocaine seeking,* Biological Psychiatry, 89 (4) 356-365.
13. Jones JA, Belin-Rauscent A, Jupp B, Fouyssac M, Sawiak SJ, Zhukovsky P, Hebdon L, Velazquez Sanchez C, Robbins TW, Everitt BJ, **Belin D***, Dalley JW* (2023), *Neurobehavioral precursors of compulsive cocaine-seeking in dual fronto-striatal circuits*. Biological Psychiatry GOS, 4(1) 194-202, *: co-last authors

More recently, our research has demonstrated the contribution of incentive habits (or habitual cue-controlled drug seeking habits) to the high tendency to relapse that individuals display following abstinence, and established that these aberrant learning processes results in the engagement of goal-directed behaviors at relapse, the goal being to engage in the drug seeking habit, but not the drug. This work provides the first experimental evidence to the incentive habit theory of addiction that I developed in 2008, which intends to bring together the elements of learning, incentive motivation and affective states involved in SUD, in particular, the maladaptive habit theory and the seminal hedonic allostasis theory of addiction, and its extension, namely the hyperkatifeia's framework of SUD proposed by Koob.

14. Fouyssac M, Pena-Oliver Y, Puaud M, Lim N, Giuliano C, Everitt BJ & **Belin D** (2022) *Negative urgency exacerbates relapse to cocaine seeking following abstinence,* Biological 91(12) 1051-1060, doi: 10.1016/j.biopsych.2021.10.009

We have also tested the hypothesis in humans that conditioned reinforcers, which are response produced, and hence experienced mode often from a first-person visual perspective) and conditioned stimuli do not similarly capture attentional resources and response readiness in individuals with a smoking habit. As predicted, using EEG recordings while participants engaged in a tailored Go/noGo task using a new battery of images presented either as a first- or third-person visual perspective, the former had a greater ability to disrupt EEG signals related to attention and motivation than the latter, while also facilitating habitual response tendencies. Thereby this study demonstrated the first neurophysiological signature of incentive habits in humans.

15. Dampuré J, Agudelo-Orjuela P, Van Der Meij M, **Belin D*** & Barber H* (2023), *Electrophysiological signature of the interplay between habits and inhibition in response to smoking-related cues in individuals with a smoking habit: an ERP* study. European Journal of Neuroscience 57(8) 1335-1352, doi:https://doi.org/10.1111/ejn.15942, *: co-last authors.

Over the past three years, we have revealed that striatal astrocytes actually undergo drug-induced adaptations in the level of expression of the dopamine transporter across functional domains of the striatum, including the aDLS dopamine-dependent habit system, long before the development of incentive heroin or cocaine-seeking habits.

16. Hynes T, Fouyssac M, Puaud M, Chernoff C, Stiebahl S, **Belin D** (2024) *Pan-striatal reduction in the expression of the astrocytic dopamine transporter precedes the development of dorsolateral striatum dopamine-dependent incentive heroin seeking habits,* European Journal of Neuroscience 59(10) 2502-2521
17. Fouyssac M, Hynes T, Belin-Rauscent A, Joshi D & **Belin D** (2024) I*ncentive cocaine-seeking habits and their compulsive manifestation emerge after a downregulation of the dopamine transporter in striatal astrocytes. (re-submitted to EJN, preprint available at:* **doi:** https://doi.org/10.1101/2024.11.19.624285)

Further investigations of the transcriptomic profile of striatal astrocytes in male and female rats revealed differences in the basal level of expression of the DAT, as well as that of connexins and oestrogen receptors. These differences are suggestive of a sex-dependent divergent role of the striatal astrocytic syncytium in the control of the development of aDLS dopamine-dependent incentive drug-seeking habits. This was causally investigated using viral-mediated astrocyte-specific expression of either a calcium extruder, which prevents syncytium engagement, or a Gq DREADD, the activation of which results in the promotion of calcium waves throughout the syncytium. Activation of NAcC astrocytes prevented the devolvement of control of drug-seeking to the aDLS in males while it expedited it in females. In contrast, inhibition of NAcC astrocytic syncytium caused a more rapid devolvement of control to aDLS-dopamine-dependent mechanisms in males, while having no effect in females. These findings present compelling evidence that NAcC astrocytes gate the neural systems adaptations involved in the development of aDLS dopamine-dependent drug-seeking habits in a sex-dependent manner. A manuscript reporting these findings is currently being prepared for publication.

Finally, our research has established that N-acetylcysteine, which promotes voluntary abstinence in the face of punishment in rats having escalated their cocaine self-administration, but does not influence cocaine or heroin taking, profoundly decreases habitual, dorsolateral striatum dopamine dependent cocaine and heroin seeking.

1. Ducret E, Puaud M, Lacoste J, Belin-Rauscent A, Fouyssac M., Dugast E, Murray JE, Everitt BJ, Houeto JL & **Belin D** (2015) *N-Acetylcysteine Facilitates Self-Imposed Abstinence After Escalation of Cocaine Intake,* Biological Psychiatry 80 (3), 226-34.

Role of the insula in impulse control, addiction and the switch from impulsivity to compulsion

While investigating the psychological and neural basis of the vulnerability to develop compulsivity, it became apparent that interoceptive mechanisms, and the underlying insula, should play a pivotal role in both impulsivity and compulsivity, not only in addiction, but also in conditions such as obsessive compulsive disorder and impulse control deficits in Parkinson's Disease. Thus, research in my laboratory and in collaboration with several colleagues in France and in the UK, first

established that there is, in the context of non-drug related compulsive disorders, such as the compulsive adjunctive behavior observed in a Schedule-Induced Polydipsia procedure, or impulse control deficits in Parkinson's disease, a pre-existing heightened impulsivity trait that predicts an increased propensity to develop these impulsive/compulsive behaviors. We then determined structural and functional correlates of impulsivity in the insular cortex, and causally demonstrated that the insula, necessary for performing well in the rat version of the Iowa Gambling task contributes to impulsivity and the transition to compulsive behaviors.

1. Ansquer S, Belin-Rauscent A, Dugast E, Duran T, Benatru I, Mar AC, Houeto JL, **Belin D** (2014) *Atomoxetine decreases the vulnerability to develop compulsivity in high impulsive rats* Biological Psychiatry 75 (10), 825-832.
2. Englen M, Ansquer A, Dugast E, Bezard E, **Belin D*** & Fernagut PO* (2016) *Multi-facetted impulsivity following nigral degeneration and dopamine replacement therapy*. Neuropharmacology 109:69-77. *: co last authors
3. Belin-Rauscent A, Daniel ML, Puaud M, Jupp B, Sawiak SJ, Howett D, McKenzie C, Caprioli D, Besson M, Robbins TW, Everitt BJ, Dalley JW & **Belin D** (2016) *From impulses to maladaptive actions: the insula is a neurobiological gate for the development of compulsive disorders.* Molecular Psychiatry 21 (4), 491-9.
4. Daniel ML, Cocker PJ, Lacoste J, Mar AC, Houeto JL, Belin-Rauscent A & **Belin D** (2017) *The anterior insula bidirectionally modulates cost-benefit decision making on a rodent gambling* task, European Journal of Neuroscience 46 (10), 2620-2628.

Noradrenergic mechanisms of compulsion

Since the demonstration that the clinically effective selective noradrenaline reuptake inhibitory Atomoxetine prevents the development of hyperdipsia in highly impulsive vulnerable rats, I have investigated the noradrenergic mechanisms of the development of compulsion. Using a home-made data analysis pipeline for RNAscope in thin sections, we recently identified a neuronal ensemble of TH+, Zif268- and Arc+ cells in the Locus Coeruleus, that emerges in parallel with the development of hyperdipsia in vulnerable rats exposed to a schedule-induced polydipsia procedure. Interestingly, atomoxetine administered to vulnerable individuals having developed hyperdipsia exacerbates compulsion, and this is associated with a change in the noradrenergic transcriptomic landscape of the nucleus accumbens Shell. We are now causally interrogating the function of the LC-NacS pathway in impulsivity, the acquisition of adjunctive responses and the transition to compulsion in vulnerable individuals.

1. Ansquer S*, Belin-Rauscent A*, Dugast E, Duran T, Benatru I, Mar AC, Houeto JL, **Belin D** (2014) *Atomoxetine decreases the vulnerability to develop compulsivity in high impulsive rats.* Biological Psychiatry 75(10), 825-832. doi:10.1016/j.biopsych.2013.09.031. PMID: 24252357.
2. Velazquez-Sanchez C, Muresan L, Marti-Prats L, **Belin D** (2023), *The development of compulsive coping behaviours is associated with a downregulation of Arc in a Locus Coeruleus neuronal ensemble,* Neuropsychopharmacology 8 *653-663,* doi: https://doi.org/10.1038/s41386-022-01522-y
3. Chernoff CS, Belin-Rauscent A, Puaud M, Torrisi SA, Fouyssac M, Németh B., Yu C, Higuera-Matas A, Jones S.* & **Belin D*** (2024) Atomoxetine exacerbates compulsive coping behaviour, which goal-tracker rats do not develop. *bioRxiv*, 2024.2010.2008.617254.

Towards social psychology: tackling the stigma around AUD and SUD

In collaboration with clinicians in the UK I have started investing a substantial amount of time in research aiming to help designing policies and strategies/interventions to tackle and reduce stigma around SUD and AUD.

1. Hytner S., Josselin D., **Belin D*** & Bowden-Jones H* (2024) *Myths and Facts about Alcohol Use Disorder: A Delphi Consensus Study*. Brain Communications, In Press. DOI: 10.1093/braincomms/fcaf035 *: co-last authors
2. Hytner S, Josselin D., **Belin D*** & Bowden Jones O.* (2024) *Challenging the public stigma of alcohol use disorder in the UK using video 'education' and 'contact' interventions: a pilot study.,* Internal Journal of Mental health and Addiction, In Press, doi: 10.1007/s11469-024-01393-y. *: co-last authors

A complete list of my publications can be found at: David Belin GS