Meeting Report: NeuroFrance 2023 Cassandre Vielle Thesis Report
24-26 May 2023, Lyon, France

As a young graduate researcher with several unpublished papers, it's hard to convince my peers to grant me a postdoc fellowship. It's been now 6 months since my post-doc ended. I'm taking advantage of this career break to write manuscripts for future publication and applications for post-doctoral fellowships. Thanks to the French Neuroscience Society and the Tianqiao & Chrissy Chen Institute, I received a prize for my thesis work, which should give me the professional recognition I need to get a postdoctoral fellowship. What's more, I am delighted and grateful to know that I have the support and recognition of my peers for a piece of work that I am so passionate about. Thank you very much for your support. As an added bonus, I have been invited to the NeuroFrance 2023 meeting, organized by the French Neuroscience Society, which took place at the Lyon Convention Centre, located in the heart of the Cité Internationale in Lyon, on May 24th-May 26th. NeuroFrance meeting, which takes place once every two years, is fairly general, bringing together neuroscientists from all over the world and from all disciplines -clinicians, psychologists as well as molecular researchers – to share their last discoveries and ideas. Outstanding plenary and special sessions, symposia and poster presentations followed one another over the three days. For me, it was an opportunity to find out about the latest work on addiction, neuromodulation techniques and social behaviour, but also to discover other areas of research, like spatial navigation and neurograstronomy.

Following on from my thesis work, my idea is to improve rodent models of addiction (in order to develop new treatments) by making them more ecologically relevant, particularly in terms of social environment. It is increasingly accepted that our current models poorly reflect what happens in real life in humans. But the effects of the social environment on drug use in rats is still far from being understood. The general topic of my thesis was to assess how the social context can contribute to modulate drug consumption and what is the neurobiological substrate of such a modulation.

In a model of recreational cocaine consumption, the presence of a peer decreases the drug consumption. The first part of the thesis work aimed at addressing the question

whether this is still true after a loss of control over cocaine intake. Familiarity with the peer present during drug-use episode seems to be a critical factor in both rats and humans, since a stranger peer induces a larger decrease in cocaine intake than a familiar one. The second part of the thesis aimed thus at assessing how the presence of a peer is responsible for this decrease in cocaine intake. In this context, vocal communication has been shown to play a key role since playback of ultrasonic vocalizations (USV) modulates cocaine self-administration in rats. The influence of the familiarity with the USV's emitter remained to be tested on cocaine consumption.

In order to investigate the neurobiological substrate of these various influences on cocaine consumption, this work has focused on the subthalamic nucleus (STN). Indeed, STN high-frequency deep brain stimulation (HF-DBS) has been proposed as a potential treatment for substance use disorder, mostly because it shows a dualist effect on incentive motivation for food vs substances of abuse. Confirming the role of the STN and the influence of social context on cocaine use, we showed, that 1) the presence of a stranger peer, naïve to the drug, decrease cocaine consumption in rats having previously lost their control of drug use, similar to STN optogenetic high-frequency stimulation and inhibition. 2) USV emitted by a stranger is rewarding since rats can work for their playback, but not for USV emitted by a familiar peer; suggesting that rats can discriminate vocalizations and have therefore a "vocal signature" 3) stranger, but not familiar, playback of positive USV, decreases cocaine self-administration. 4) STN lesion abolishes the rewarding value of the USVs, independently of their emotional valence or the familiarity with their emitter.

To better understand the mechanisms underlying electric STN HF-DBS effects in motivation, I finalized a study assessing the effects of STN optogenetic high-frequency stimulation and inhibition on rats' motivation for sweet food and cocaine. We showed that optogenetic STN inhibition mimics the bidirectional motivational effects of electric HF-DBS, but its effects are delayed and transient.) In contrast, STN optogenetic high-frequency stimulation decreases motivation, independently of the reward type. Finally, since STN manipulation seems to abolish the modulation provided by the familiarity with a peer, in a last study, I investigated the role of STN in social memory. This last experiment indeed showed that both STN lesions and optogenetic inhibition impairs peer recognition with 30-min delay between the first and second encounter. In the same context, STN HF-stimulation specifically blunts social memory encoding.

Altogether these results highlight the critical role of the social context on drug consumption and how the STN manipulation could be beneficial for the treatment of substance use disorder.

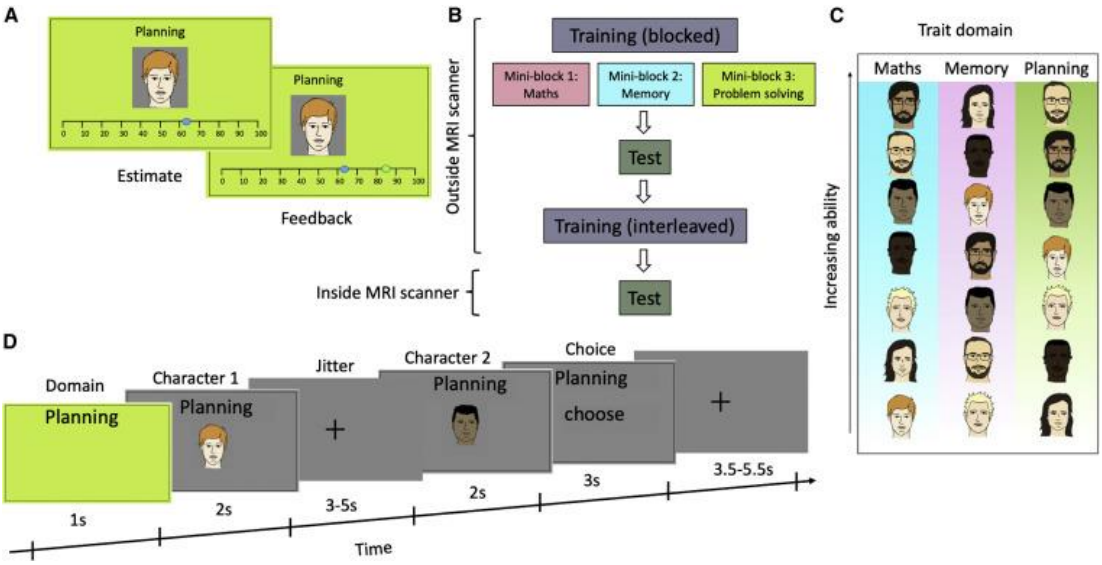
1) What special about the social brain? Dr. Matthew Rushworth

One of the most attractive Special Lecture was from Dr. Matthew Rushworth. Dr. Rushworth is Watts Professor of Experimental Psychology at the University of Oxford where his laboratory is funded by the Wellcome Trust and Medical Research Council. His research focuses on decision-making and social cognition. Notably, he is interested in how the social context influences our choices and how we learn from others. He uses neuroimaging techniques to compare brain circuits involved in decision between humans and non-human primates.

Pic from *https://www.science.org/doi/10.1126/science.1232769*

Dr. Rushworth introduced his presentation with a photography of a group of vervet monkeys, the youngest of which is sitting on a box containing food. He and the others do not seem to be considering the food in this box, but all three are enjoying the food in the box next to it. In this very famous experiment, Van de Waal et al. (2013) showed that individuals learn what to eat (here the pink food) and what to avoid (the blue one) from more experienced individuals within their social group. Not only did young animals learn from observing older animals, but immigrating males switched their food preference to that of their new group. This elegant experiment illustrates the critical value of the social context in everyday learning and decision-making. Through the lecture, Dr. Rushworth reviewed recent work from his team highlighting the involvement of the dorsomedial prefrontal cortex (dmPFC) in the selection and organization of social information. Notably, he showed that when primates use social and non-social (i.e. inanimate objects) cues to take a decision,

they give more credence to the social information (even if this one is irrelevant), and this is correlated with the activity of the dmPFC.



Pic from Mahmoodi et al. (2023) publica9on. *https://doi.org/10.1016/j.neuron.2022.12.030*

Nevertheless, we do not place the same value on all social information. A context-dependent social judgement helps us to identify those with whom it would be best to cooperate. Mahmoodi, Rushworth et al. (2023) developed an experimental framework for studying how the human brain represents information about multi-faceted individuals (i.e., advisors with task-specific abilities) in a flexible context-dependent manner, and how it selects and extracts relevant information and filters out irrelevant information. In this framework, a given advisor will be of great help to the subject in solving a maths problem (giving relevant information in this dimension), but of little help in solving a memory problem (thus giving irrelevant information). Using human fMRI, they identified distinct neural representations in dmPFC and anterior insula (AI) supporting separation and selection of information for context-dependent social judgement. Variables that were relevant and irrelevant for choice were reflected in dmPFC activity. Techniques of non-invasive brain stimulation allowed them to show that dmPFC disruption reduces the ability to select the advisor favored by the relevant trait, by increasing the effect of the irrelevant information. This result suggests that dmPFC activity mediates context-dependent separation of relevant and irrelevant social information. In contrast, AI activity encoded variables that were not relevant for choice (e.g. the identity of the advisor) and AI disruption decreased the impact of the relevant information on choice. Overall, these results suggest that context-dependent social judgment is supported by a neural network in which dmPFC underpins the context-dependent separation of relevant and irrelevant information and in which AI underpins the selection of the relevant information upon which the current choice is based.

2) Clinical and preclinical expertise to tackle addictive behaviors in our modern societies

This very exciting symposium, chaired by Drs. Katia Befort and Dominique Massotte, reviewed recent and original work on various addictive behaviours which are increasingly common in modern societies.

The first talk 'The choice to eat junk food, and how this affects the brain's control on feeding' was given by Dr. Susanne La Fleur (UMC Amsterdam University). To model the problems of obesity and diabetes caused by junk food, Dr. La Fleur and her team use a rodent model in which, in addition to their kibble, animals are given food containing a lot of fat (high-fat diet; HF) and/or food containing a lot of sugar (high-sugar diet; HS). Using this model, they showed that animals subjected to the HF+HS diet consume more food than HF-only and control animals. Moreover, they consume more frequently food than animals subjected to a HF+HS forced diet, mimicking humans' snacking. Dr. La Fleur and her team further showed that HS diet increases fat intake by altering the endocannabinoid system in the amygdala and the nucleus accumbens. She also presented some key findings on the way the sucralose modifies feeding behavior. Sucralose is a sweetener that is much used by people who want to go on a diet. Nevertheless, it does neither activate the reward system, nor a calorie-detection system in the lateral hypothalamus. As a result, consumption of sucralose increases feeding behavior.

The second talk 'Preclinical models of binge eating behaviour: focus on the interaction between cannabinoid and opioid system genes' was given by Dr. Claudio D'Addario (Università degli Studi di Teramo). Dr. D'Addario's work focuses on the influence of genetic, environmental and epigenetic factors on the risk to develop eating disorders, notably binge eating. He presented the classical rodent model used to study binge eating behaviour. In this model, rats are subjected to cycles of food restriction and frustration (i.e., the animal sees but cannot reach food). The use of this model allowed Dr. D'Addario and his team to reveal an alteration of the endocannabinoid system in the nucleus accumbens. Binge eating behaviors also decreased the level of DAT (dopamine-transporter) in the nucleus accumbens and in the prefrontal cortex, whereas the level of dopamine D2 receptor was shown to increase in the ventral tegmental area. Overall, these results, in accordance with the work of Dr. La Fleur, reveal the dramatic impact of binge eating on the reward circuitry. Then, Dr. D'Addario introduced new models to study binge eating behavior and its molecular consequences. To study the effects of the environment and the epigenetic on such behavior, he and his team decided to use C. elegans instead of rats. What a surprise to learn that we can model binge eating behavior on C. elegans! And indeed, they replicated their results obtained from rodents. Finally, they took sample of saliva in control humans and in individuals suffering from eating disorders. Their results revealed that binge eating decreases dopamine transporter (DAT) methylation in human saliva, whereas it increases dopamine D2

receptor methylation. Interestingly, saliva samples also revealed important differences in the microbiota compared to that of the control population. Future studies would explore the involvement of the oral microbiota in epigenetics phenomenon in the reward circuit.

The third talk 'Gambling disorder: future prevention and treatment strategies' was given by Dr. Amandine Luquiens (psychiatrist at the Nîmes University Hospital(CHU)). For a neuroscientist working on addiction, gambling disorder does not look like other addictive behaviors. Indeed, in this context, environmental factors increasing the risk of addiction are specific. For instance, while the consumption of substance of abuse (cocaine, alcohol, food, etc) is more escalated when the substances are not always available, the risk to 'escalate' gambling is increased when it is always available. As a result, online gambling is a real issue. Another particularity is that the population suffering from gambling disorder avoids professional intervention, rendering research and treatment more difficult. Dr. Luquiens presented the situation of gambling disorder in France, in which gambling has been only recently authorized. The prevalence of the disease has increased 5-fold in 5 years! Dr. Luquiens and her team work at different levels of the addiction cycle. They showed for instance that the presence of pictograms on games decreases the risk to develop gambling disorder. Cognitive training, on the other hand, is efficient in helping people to regain the control. Finally, increasing the latency before receiving betting advertising again diminishes the risk of relapse. Overall, her presentation highlighted the importance of public health policies in the management of gambling disorder.

The fourth talk 'New tools to probe addiction related circuits: highlighting an habenular network implicated in stress-induced reinstatement' was given by Dr. Victor Mathis (Strasbourg University). Dr. Mathis work highlighted the involvement of a glutamatergic projection from the medial prefrontal cortex (mPFC) to the lateral habenula (lHb) in the stress-induced relapse in a mouse model of cocaine consumption. He then presented a new tool that allowed him to identify the whole circuit which is involved in such stress-induced relapse; neurons of the lHb receiving projections from the mPFC project in return on the Locus Coeruleus (LC) and the ventral tegmental area (VTA). They then used the crelox-flipase tool with DREAAD to modulate the activity of specific pathways. Dr. Mathis and his team used such systems to reveal that only the mPFC-lHb-LC, but not the mPFC-lHb-VTA, pathway was involved in stress-induced relapse. Overall, these results suggest that specific subcircuits are anatomically linked but specialized in some behaviors.

The last talk of this session 'Nicotine Reinforcement Is Triggered By Interplay Between Reward And Aversion Circuits' was given by Dr. Joachim Jehl (Sorbonne University). Dr. Jehl work focused on the neural basis of the rewarding and aversive effects of the nicotine, known to modulate tobacco consumption. He showed that while the ventral tegmental area (VTA) controls the rewarding effects of the nicotine, the interpeduncular nucleus (IPN) is responsible for its aversive effects (with a dose-

dependent effect). The IPN reaction to the nicotine is underlined by distinct populations of nAChR. Finally, the IPN projects on the VTA, modulating the rewarding effects of nicotine, through activation of β4 nAChR subunits.

3) NeuroGastronomy: how multisensory context impacts tasting experience?

What a better place than Lyon (world capital of gastronomy) to talk about neurograstronomy? Many of us wanted to attend this special session, chaired by Sylvia Wirth, despite the imminence of lunchtime and the many grumbling stomachs. Dr. Adriana Galinanes Plaza (Institute Paul Bocuse) introduced the session with a talk on 'The role of atmospherics on food experience: how contextual cues influence food perception and behaviour'. Dr. Galinanes Plaza stated that craving for a specific food item is induced by environmental cues (for instance, the appetite for a Christmas food item is driven by a Christmas atmosphere, such as a cold weather, Christmas songs, a family meeting, etc, but not by some summer vacancies in northern countries). She also invited us to think about the concept of a meal (what characteristics do matter?). In line with Meiselman (1912), she thus considers that studying the perception of food requires a specific environment. She modified her lab to transform it into a 'palace of culinary experience'. Indeed, in her lab subjects are invited in a 'classic' restaurant or in an experimental room composed of giant screen, different light, fragrance diffusers, etc. People are also invited to come with their relatives and to judge their expectations before the meal. She presented various studies revealing the effect of the environment on the food experience. For example, the shape of a glass containing an alcoholic cocktail was shown to modulate the rate of consumption, the feeling of thirst and the general appreciation of the cocktail. Another study showed that people appreciate more their food in a restaurant than anywhere else. More surprisingly, being in a café increases the ability to discriminate between different teas. Finally, the light in a room influences wine perception.

Dr. Anne-Lise Saive (Institute Paul Bocuse) continues the session with her talk on 'Cross-modal interactions in food: the effects of color, shape and sound in tasting', focusing on the multisensorial basis of tasting. Illustrating her talk with nice experiments, she detailed us some cross-modal correspondences between sounds, shapes and tastes. For instance, in most people, sweet taste correlates with round shapes, whereas the most disliked tastes correlate with angular shapes. Besides, an increasing number of studies show that a bad wine can be re-equilibrated with music. In opposite, the experience of coffee drinking can be ruined by a white noise.

Dr. Gabriel Lepousez (Institute Pasteur) finally gave a presentation entitled 'Food beyond the mouth: how the brain integration of internal states influences food experience'. Through his talk, Dr. Lepousez revealed how microbiota influences tasting and feeding behaviours. Microbiota send messages to the brain through a communication with intestinal cells (sending themselves serotoninergic projections

to the basal ganglia network), bacteria also release proteins which reach brain receptors (in the hypothalamus) via the bloodstream, and finally, bacterial and viral molecules can spread to the brain during infections. He presented us an experiment in which mice learn to lick a sent to receive an injection of glucose or sucralose in their stomach. In this experiment, mice preferred the sent associated with the injection of glucose and only this one activating the reward system. This preference was blunted by a disruption of the vagus nerve, revealing the key role played by the microbiota in this preference and the activation of the reward circuit.

Sadly, I was not able to attend the last presentation, made by Dr. Shirley Xue Li Lim, entitled 'How odor transcends taste: sensory and neurophysiological approaches of taste-odor interactions'.

Finally, the whole meeting brings me profound inspiration for my future. I am looking forward to NeuroFrance 2025, that should be held in Montpellier.

Thank you again to the French Neuroscience Society and the Tianqiao & Chrissy Chen Institute for this great experience!

Cassandre Vielle is a Graduate Researcher at Aix-Marseille Université. She wrote this meeting report as part of the Tianqiao and Chrissy Chen Institute Science Writers Fellowship which aims to extend the conversation beyond the meeting with the hopes of sparking new ideas and collaborations.