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ON THE ROLE OF PARVALBUMIN INTERNEURONS IN NEURONAL NETWORK ACTIVITY IN THE PREFRONTAL CORTEX

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On the role of parvalbumin interneurons in neuronal network activity in the prefrontal cortex

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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Minha alma é uma orquestra oculta; não sei que instrumentos tange e range,
cordas e harpas, tímbales e tambores, dentro de mim. Só me conheço como sinfonia.

– "Livro do Desassossego, por Bernardo Soares," Fernando Pessoa

POPULAR SCIENCE SUMMARY OF THE THESIS

The brain is a complex, enigmatic organ composed of a multitude of neurons. These neurons are interconnected, composing a networked web of connections that in the human brain goes up to the trillions. The overall activity of these intermingled networks of neurons leads to the body being able to react to its environment. One of the ways that neurons use their network of connections to communicate with each other is by releasing chemicals called neurotransmitters. For example, when a recipient neuron receives the excitatory neurotransmitter glutamate via receptors placed on its surface, the neuron responds by eliciting an electrical signal called action potential. We say that the neuron "fired". If, on the other hand, the recipient neuron receives the inhibitory neurotransmitter GABA, it will be less likely to fire. These cycles in excitation and inhibition create voltage fluctuations outside the neurons that we call "brain oscillations".

These oscillations are heavily studied because they tell us information about what the brain is doing. For instance, they can help us infer how brain activity is organized temporally, how the brain responds to sensory input, or how it elicits a movement. Brain oscillations do not look to be very informative at first sight. However, after being decomposed into smaller components, based on the frequency of their fluctuation, one can find that different frequencies will have a bigger or smaller amplitude depending on the behavior of the individual being recorded. Moreover, these various classes of oscillations look different if a person is awake or asleep, giving us an insight into how the brain is operating during these specific states. The difference in amplitude for specific oscillations usually depends on how the neurons are activated or inhibited and the timing of that cycle — the faster they are activated/inhibited, the higher the frequency — but also whether they fire in synchrony or more randomly.

Oscillations are rhythmic and reflect the synchronization of the neurons' activity. This could be compared to the noise made by people clapping at a concert at the end of a song. It starts by being uncoordinated, but when the clapping becomes synchronized — because people are clapping at the same time/frequency — the sound gets louder at that specific beat or frequency. When recording the brain oscillations with electrodes, we can therefore infer the activity of neurons by the impact of specific frequencies. For example, some sensory stimuli are known to specifically increase signals that oscillate at 30-80 cycles per second (30-80 hertz, or Hz).

These oscillations are called gamma oscillations and are strongly correlated to cognitive processes like attention, working memory and visual processing. Indeed, their amplitude specifically and narrowly increases when a human or an animal performs a cognitive task. Significantly, these evoked gamma oscillations are weaker during the performance of similar tasks in patients with schizophrenia. However, when we observe the brain activity of these same patients between two tasks or when at rest, a constant, wide-ranging and increased noise in the gamma range is detected. These aberrant gamma oscillations have been replicated in animal models of schizophrenia, in which neurons that release the inhibitory neurotransmitter GABA are dysfunctional. But very little is currently known about how the inhibitory neurons generate proper narrow gamma oscillation during a task and, at the same time, are paradoxically associated, when dysfunctional, with increased broad noise in the gamma range during rest.

In Paper I, we tried to solve this issue by testing the suggestion that the broadband increase in amplitude spanning the entire gamma-band might not always be a rhythm but could result from

asynchronous and noisy communication between neurons. For this, we recorded the brain activity of transgenic mice that lacked a receptor essential for the proper activity of inhibitory neurons. Since this receptor had been removed only in the inhibitory neurons, it allowed us to precisely observe the effect of impairing the activity of these neurons. We found that the activity recorded during rest was increased and associated with the neurons' asynchronous activity.

It is as if these specific neurons were not able anymore to hear that other cells around them were clapping on cue after the song was finished, making it difficult for them to follow the rhythm of collective synchronization. This led to the inhibitory neurons in our concert room clapping at random and making noise during the song as well. Importantly, we replicated this noisy activity by applying ketamine locally to the brain of normal mice, which might explain how ketamine mimics the symptoms of schizophrenia in humans. Surprisingly, similar ketamine application in transgenic mice did not cause any such changes. We explain this by suggesting that ketamine needs the inhibitory neuron receptor removed in the transgenic mice to have an effect on the brain.

In Paper II, we expressed a modified receptor in the same inhibitory neurons as in Paper I, this time with the help of a virus injected in a specific area of the brain called the prefrontal cortex. The virus we generated induces the expression of a modified receptor that is usually critical for how brain connections are maintained. The modified receptor was injected in adult transgenic mice and competed with the normal receptor, making it less effective. Thus, this approach allowed us to target the neurons we wanted to study in the specific brain area important for social behavior, and avoid interference with other brain areas as well as with developmental processes. This precision was necessary, as alterations specific to this receptor in inhibitory neurons of the prefrontal cortex have been found in postmortem examination of patients with neuropsychiatric disorders such as schizophrenia.

We found that the modified receptor altered the inhibitory neurons in which it was expressed both morphologically and functionally. When recording the brain activity of transgenic mice while socially interacting with other mice, we found an increased number of excitatory neurons and abnormal gamma oscillations within the prefrontal cortex, which was correlated with unusually aggressive behavior. These results suggest that the modified receptor in inhibitory neurons reduced their inhibitory connection with excitatory neurons, allowing them to be activated imprecisely.

In conclusion, abnormal gamma oscillations were observed in both studies. Changes in gamma are widely reported in both animal models and human studies, but at the same time, the heterogeneity of gamma-band abnormalities so far recorded has limited the translation of these findings into clinical settings. A better understanding of how to interpret gamma oscillation results may thus be a helpful guide in developing approaches where we can use gamma oscillations to track changes due to disorders but also changes elicited by drugs. Moreover, the results in this thesis contribute to our understanding of the biological mechanisms behind neuronal and circuit modifications due to dysfunctional receptors implicated in neuropsychiatry disorders, especially schizophrenia. This information can be used to develop targeted diagnoses, as well as interventions aimed at more specifically treating cognitive impairments seen in neuropsychiatry disorders.

Résumé grand public de la thèse

Le cerveau est un organe complexe composé d'une multitude de neurones. Ces neurones sont amplement interconnectés, constituant un réseau de connexions qui, dans le cerveau humain, peut atteindre les billions. L'activité de ces réseaux entremêlés de neurones guide le corps dans son interaction avec son milieu. L'un des procédés que les neurones utilisent pour communiquer entre eux consiste à libérer des composés chimiques appelés neurotransmetteurs. Par exemple, lorsqu'un neurone reçoit du glutamate, un neurotransmetteur excitateur, via des récepteurs placés à sa surface, cela provoque un signal électrique appelé potentiel d'action. Nous disons que le neurone a « déchargé ». Si, en revanche, le neurone reçoit le neurotransmetteur inhibiteur GABA, il sera moins susceptible de produire un potentiel d'action. Ces cycles d'excitation et d'inhibition génèrent des fluctuations du signal électrique en dehors des neurones appelées « oscillations cérébrales ».

Ces oscillations sont très étudiées car elles fournissent des informations sur ce que fait le cerveau. Par exemple, elles peuvent nous aider à déduire comment l'activité cérébrale est organisée temporellement, mais aussi comment le cerveau répond à des influx sensoriels ou déclenche un mouvement. Les oscillations cérébrales ne paraissent pas très informatives à première vue. Cependant, après avoir été découpées en composantes plus petites, en fonction de la fréquence de leur fluctuation, on peut constater que différentes fréquences auront une amplitude plus ou moins grande en fonction du comportement du sujet. De plus, ces distinctes classes d'oscillations semblent différentes si un individu est éveillé ou endormi, ce qui nous donne un aperçu du fonctionnement du cerveau pendant ces états spécifiques. La différence d'amplitude pour des oscillations spécifiques dépend généralement de la façon dont les neurones sont activés ou inhibés et de la durée de ce cycle - plus le cycle activation / inhibition est rapide, plus la fréquence est élevée - mais aussi s'ils se déchargent de manière synchronisée ou de manière plus aléatoire.

Les oscillations sont généralement rythmiques et reflètent la synchronisation de l'activité des neurones. Cela pourrait être comparé au bruit fait par des gens applaudissant lors d'un concert à la fin d'un morceau de musique. Cela commence par être désorganisé, mais lorsque les applaudissements s'harmonisent - parce que les gens applaudissent en même temps / à la même fréquence - le son devient plus intense à cette fréquence spécifique. Lors de l'enregistrement des oscillations avec des électrodes, on peut donc déduire l'activité des neurones par l'intensité des différentes fréquences. Par exemple, certains stimuli sensoriels sont connus pour augmenter spécifiquement les signaux qui oscillent à 30-80 cycles par seconde (30-80 hertz ou Hz).

Ces oscillations sont appelées oscillations gamma et sont fortement corrélées à des processus cognitifs tels que l'attention, la mémoire de travail et le traitement visuel. En effet, leur amplitude augmente spécifiquement et étroitement lorsqu'un humain ou un animal effectue une tâche cognitive. De manière significative, ces oscillations gamma évoquées sont plus faibles lors de l'exécution de tâches similaires chez les patients atteints de schizophrénie. Cependant, lorsque nous observons l'activité cérébrale de ces mêmes patients entre deux tâches ou au repos, on peut détecter une activité bruyante constante et élevée correspondant plus ou moins aux ondes gamma. Ces oscillations gamma aberrantes ont été répliquées dans des modèles animaux de schizophrénie, dans lesquels les neurones qui libèrent le neurotransmetteur inhibiteur GABA sont dysfonctionnels. Malgré cela on sait actuellement très peu de choses sur la façon

dont les neurones inhibiteurs génèrent les ondes cérébrales gamma pendant une tâche et en même temps sont paradoxalement associés, lorsqu'ils sont dysfonctionnels, à une augmentation d'un rythme gamma associé à du bruit de fond au repos.

Dans l'étude I, nous avons essayé de résoudre ce problème en testant l'hypothèse selon laquelle l'augmentation de la fréquence élevée couvrant toute la bande gamma pourrait ne pas toujours être un rythme mais pourrait être le résultat d'une communication asynchrone et bruyante entre les neurones. Pour cela, nous avons enregistré l'activité cérébrale de souris transgéniques dépourvues d'un récepteur important pour l'activité des neurones inhibiteurs. Ce récepteur, n'ayant été éliminé que dans les neurones inhibiteurs, nous a permis d'observer spécifiquement l'effet de modifier l'activité de ces neurones. Nous avons constaté que l'activité enregistrée au repos était augmentée et associée à une activité asynchrone des neurones.

En somme, ce serait comme si ces neurones spécifiques n'étaient plus capables d'entendre que d'autres cellules autour d'eux applaudissaient après la fin de la musique, ce qui les empêche de suivre la cadence collective. Cela conduit les neurones inhibiteurs de notre salle de concert à applaudir au hasard et à faire du bruit pendant que les musiciens jouent. Nous avons notamment reproduit cette activité bruyante en appliquant de la kétamine localement sur le cerveau de souris normales, ce qui pourrait expliquer comment la kétamine imite les symptômes de la schizophrénie chez l'homme. De manière surprenante, une application similaire de kétamine chez des souris transgéniques n'a pas provoqué de tels changements. Nous expliquons cela en suggérant que la kétamine a besoin du récepteur neuronal inhibiteur éliminé chez les souris transgéniques pour avoir un effet sur le cerveau.

Dans l'étude II, nous avons exprimé un récepteur modifié dans les mêmes types de neurones inhibiteurs que dans l'article I, mais cette fois à l'aide d'un virus qui a été injecté dans une zone spécifique du cerveau appelée cortex préfrontal. Le virus que nous avons généré induit l'expression d'un récepteur modifié qui est généralement crucial pour la façon dont les connexions cérébrales sont maintenues. Le récepteur modifié a été injecté à des souris transgéniques adultes et est entré en compétition avec le récepteur normal, le rendant moins efficace. Ainsi, cette approche nous a permis de cibler les neurones que nous voulions étudier dans une zone spécifique du cerveau connue pour être importante pour le comportement social, et d'éviter les interférences avec d'autres zones cérébrales ainsi qu'avec les processus de développement. Il était important d'être précis, car des altérations spécifiques de ce récepteur dans les neurones inhibiteurs du cortex préfrontal ont été retrouvées lors de l'examen post-mortem de patients souffrant de troubles neuropsychiatriques tels que la schizophrénie.

Nous avons donc constaté que le récepteur modifié changeait les neurones inhibiteurs dans lesquels il était exprimé à la fois morphologiquement et fonctionnellement. Lors de l'enregistrement de l'activité cérébrale des souris transgéniques alors qu'elles interagissent socialement avec d'autres souris, nous avons trouvé un nombre accru de neurones excitateurs et des oscillations gamma anormales dans le cortex préfrontal, le tout corrélé à un comportement inhabituellement agressif. Ces résultats suggèrent que le récepteur modifié dans les neurones inhibiteurs a réduit leur connexion inhibitrice avec les neurones excitateurs, leur permettant d'être activés de manière imprécise.

En conclusion, des oscillations gamma anormales ont été observées dans les deux études. Les altérations des ondes cérébrales gamma sont largement rapportées dans les modèles animaux et dans les études humaines, mais cependant l'hétérogénéité des anomalies correspondant aux oscillations gamma observées jusqu'à présent a limité le potentiel translationnel de ces résultats dans des contextes cliniques. Une meilleure conception des différentes manières d'interpréter les résultats des oscillations gamma peut donc être utile dans le développement d'approches où nous pouvons utiliser ces oscillations afin de suivre les changements dus aux troubles mais aussi les changements induits par la médication. De plus, les résultats de cette thèse ont pour but de contribuer à une plus grande compréhension des mécanismes biologiques à l'origine des modifications neuronales et des circuits, dues à des récepteurs dysfonctionnels impliqués dans les troubles neuropsychiatriques, dont la schizophrénie. Nous espérons que ces résultats pourront être utilisés dans le développement de diagnostics plus ciblés, ainsi que d’interventions visant à traiter plus spécifiquement les déficiences cognitives observées dans les troubles neuropsychiatriques.

ABSTRACT

The prefrontal cortex (PFC) is an area important for executive functions, the initiation and temporal organization of goal-directed behavior, as well as social behaviors. Inhibitory interneurons expressing parvalbumin (PV) have a vital role in modulating PFC circuit plasticity and output, as inhibition by PV interneurons on excitatory pyramidal neurons regulates the excitability of the network. Thus, dysfunctions of prefrontal PV interneurons are implicated in the pathophysiology of a range of PFC-dependent neuropsychiatric disorders characterized by excitation and inhibition (E/I) imbalance and impaired gamma oscillations.

In particular, the hypofunction of receptors important for neurotransmission and regulating cellular functions, such as the N-methyl-D-aspartate receptors (NMDARs) and the tyrosine receptor kinase B (trkB), has been implicated in PV dysfunction. Notably, this hypofunction is known to impair the normal development of PV interneurons. However, it can also affect adult brain activity. The effects of altered receptors on PV interneurons are multiple, from impaired morphological connectivity to disruption of intrinsic activity, but have not yet been fully characterized. Moreover, the effects of deficits of PV neuron-mediated inhibition on neuronal network activity are complex, involved with compensatory mechanisms, and not fully understood either. For instance, the E/I imbalance due to PV inhibition has been suggested to functionally disrupt the cortex, which can be observed through an abnormal increase in broadband gamma activity. But as the synchronous activity of cortical PV interneurons is necessary for the generation of cortical gamma oscillations, it is paradoxical that deficient PV inhibition is associated with increased broadband gamma power.

This thesis aims to examine the role of PV interneurons in shaping neuronal network activity in the mouse PFC by investigating the microscopic to macroscopic functional effects of disrupting receptors necessary for the proper activity of PV interneurons.

In paper I, we observed that the increase of broadband gamma power due to NMDAR hypofunction in PV neurons is associated with asynchronies of network activity, confirming that dysfunction of neuronal inhibition can cause desynchronization at multiple time scales (affecting entrainment of spikes by the LFP, as well as cross-frequency coupling and brain states fragmentation). In Paper II, we prompted and analyzed the rippling effect of PV dysfunction in the adult PFC by expressing a dominant-negative trkB receptor specifically in PV interneurons. Despite avoiding interfering with the development of the brain, we found pronounced morphological and functional alterations in the targeted PV interneurons. These changes were associated with unusual aggressive behavior coupled with gamma-band alterations and a decreased modulation of prefrontal excitatory neuronal populations by PV interneurons.

Thus, the work presented in this thesis furthers our understanding of the role of PV function in PFC circuitry, particularly of two receptors that are central to the role of PV interneurons in coordinating local circuit activity. A better understanding of the potential mechanisms that could explain the neuronal changes seen in individuals with neuropsychiatric dysfunctions could lead to using gamma oscillations or BDNF-trkB levels as biomarkers in psychiatric disorders. It also presents possibilities for potential treatments designed around reestablishing E/I balance by modifying receptor levels in particular cell types.

LIST OF SCIENTIFIC PAPERS

I. Network asynchrony underlying increased broadband gamma power.
The Journal of Neuroscience. 2021 Mar 31;41(13):2944-2963.
Nicolas Guyon, Leonardo Rakauskas Zacharias, Eliezyer Fermino de Oliveira, Hoseok Kim, João Pereira Leite, Cleiton Lopes-Aguiar, Marie Carlén

II. Adult trkB signaling in parvalbumin interneurons is essential to prefrontal network dynamics.
The Journal of Neuroscience. 2021 Apr 7;41(14):3120-3141.
Nicolas Guyon, Leonardo Rakauskas Zacharias, Josina Anna van Lunteren, Jana Immenschuh, Janos Fuzik, Antje Märtin, Yang Xuan, Misha Zilberter, Hoseok Kim, Konstantinos Meletis, Cleiton Lopes-Aguiar, Marie Carlén,

CONTENTS

LIST OF ABBREVIATIONS

AAV	Adeno-associated virus
ACA	Anterior cingulate area
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
BDNF	Brain-derived neurotrophic factor
CFC	Cross-frequency coupling
DIO	Double-floxed inverted open-reading-frame
EEG	Electroencephalograms
E/I	Excitatory/inhibitory
EPSC	Excitatory postsynaptic current
eYFP	Enhanced yellow fluorescent protein
FACS	Fluorescence-activated cell sorting
GABA	Gamma-Aminobutyric acid
GAD	Glutamic acid decarboxylase
GAT-1	GABA transporter-1
HFB	High-frequency band
HFOs	High-frequency oscillations
ILA	Infralimbic area
IPSC	Inhibitory postsynaptic current
LFP	Local field potential
MK-801	Dizocilpine
mPFC	Medial prefrontal cortex
NMDAR	N-methyl-D-aspartate receptor
NR1	NMDA receptor subunit 1
NREM	Non-rapid eye movement
ORB	Orbital area
p75NTR	p75 neurotrophin receptor
PCA	Principal component analysis
PCP	Phenylcyclohexyl piperidine or Phencyclidine
PFC	Prefrontal cortex
PL	Prelimbic cortex
PSD	Power spectral density
PV	Parvalbumin
REM	Rapid eye movement
snRNAseq	Single nuclei RNA sequencing
trkB	Tyrosine receptor kinase B
trkB.DN	Dominant-negative trkB
trkB.FL	Full-length trkB
trkB.T	Truncated trkB
VIP	Vaso-intestinal peptide
VTA	Ventral tegmental area

1 INTRODUCTION

1.1 THE PREFRONTAL CORTEX

Located in the forefront of the brain, the prefrontal cortex (PFC) is a distinctive region involved in various brain functions and processes linked to cognition and goal-oriented actions. The PFC has been labeled a major evolutionary specialization, as its relative size peaks in primates – up to 30% of the cortical domain is occupied by the PFC in humans (Carlén, 2017; Smaers et al., 2017).

The work in this thesis has been performed in mice (*Mus musculus*) to, among other things, make use of techniques allowing the spatially and timely restricted manipulation and recording of cell-type-specific activity. I will therefore focus on the role of the PFC in this model organism. However, a debate continues about the use of mice for studying the PFC, notably whether one can translate the concept of prefrontal cortex between species, even though a growing body of research has revealed functional homologies in rodents and primates (Carlén, 2017; Laubach et al., 2018). For example, hallmark functions of the PFC, like working memory, attention, and behavioral flexibility, have been conceived based on findings in primates and successfully replicated in rodents (Kamigaki and Dan, 2017; Kim et al., 2016b; Liu et al., 2014). It is thus conceptually feasible to use the rodent PFC to shed light on the functional properties of the primate brain, including the human brain (Carlén, 2017; Le Merre et al., 2021). Besides, the mouse PFC is involved in sensory processing, the preparation of motor functions, attention (Kim et al., 2016b), working memory (Kim et al., 2016a), and social behavior (Felix-Ortiz et al., 2016; Levy et al., 2019; Yizhar and Levy, 2021; Yizhar et al., 2011), among other cognitive behaviors (Le Merre et al., 2021).

Functionally, the PFC integrates internal and external information regarding the present state in order to represent future goals and predict future actions. This capacity allows the temporal organization of behavior in mammals as well as the initiation of goal-directed behaviors (Fuster, 2015). Specifically, it is thought that sensory information flows from the periphery via the thalamus and sensory cortical regions right up to the PFC, in a “bottom-up” fashion. In the PFC, sensory information is then assimilated with information about the state and the goal, as well as previous experience (Fuster, 2015). From the PFC, the information is then sent back to other cortical regions, like the motor cortex, and to subcortical regions that are implicated in the selection and execution of movement. This “top-down” or “executive” signal is thus thought to be essential for guiding, biasing and modulating activity in downstream regions for the appropriate action in response to a situation. For instance, pharmacological perturbation of PFC activity causes disruptions of cortex-wide activity necessary for correctly performing a task (Allen et al., 2017; Makino et al., 2017).

The pattern of connections to and from the medial prefrontal cortex reflects this functional capacity to work as a highly integrative network. The primary inputs to the mouse PFC are originated locally. However, the PFC is also densely interconnected with the rest of the cortex and with numerous subcortical brain regions, receiving and projecting to a vast number of regions in a reciprocal manner, making it the area with the highest proportion of feedback projections (Ährlund-Richter et al., 2019; Harris et al., 2019; Le Merre et al., 2021). Common connections to and from the PFC arise from the motor and sensory cortical regions but also

regions involved in arousal, memory, emotional and social responses, like the basal forebrain, thalamus, amygdala, hippocampus dorsal raphe nucleus and locus coeruleus (Ährlund-Richter et al., 2019; Collins et al., 2018; Hoover and Vertes, 2007).

Being an essential part of the integrative network underlying cognition, dysfunctions of the prefrontal cortex have been causally implicated in a multitude of neuropsychiatric disorders. Patients with prefrontal damage usually show signs of deficits in decision making, disrupted selective attention for relevant inputs, and increased distractibility by irrelevant stimuli, as well as impaired working memory (Lewis et al., 2005). For instance, epilepsy, autism spectrum disorder, and schizophrenia have been related to malfunctions in the PFC neuronal circuitry, particularly involving the disorganized firing of subsets of neurons, affecting its local and long-range connectivity (Cho et al., 2015; Homayoun and Moghaddam, 2007; Lewis et al., 2005; Schmitt et al., 2017; Yizhar et al., 2011). Research on the several mechanisms that could produce pathological changes in the PFC circuitry is essential to link these PFC dysfunctions to cognitive impairments in neuropsychiatric disorders (Gordon, 2016; Marín, 2012; Tang et al., 2021).

1.1.1 General organization of the mPFC

The PFC can be said to be an "umbrella term" for cortical regions located in the forefront of the brain (Le Merre et al., 2021). The PFC has thus been historically divided into several sub-regions - divisions based mainly on anatomical and histological examinations of the brain. Mice possess fewer prefrontal regions than primates, and all regions in the prefrontal cortex of mice lack the layer IV (e.g. the regions are agranular). In rodents, the cortical regions thus identified as shaping the prefrontal cortex are the prelimbic area (PL), the infralimbic area (ILA), the anterior cingulate areas (ACA) and the orbital areas (ORB). Both the papers presented in this thesis use the term medial prefrontal cortex (mPFC) to depict the more medial regions of the mice PFC (ventral ACA, PL, ILA and medial ORB) (**Figs. 1a, b**). However, several ways of classifying the PFC still prevail today, primarily based on cytoarchitecture or connectivity (Ährlund-Richter et al., 2019), but no clear function has yet been given to each specific area – in humans, as in their homologous regions in rodents (Euston et al., 2012). More research is thus needed in order to define the functions of each sub-region of the PFC (Carlén, 2017).

The cellular organization of the PFC is considered to be canonically organized by layers and by columns. Organization conserved not only between species, but also similar to other cortical areas (except for the lack of layer 4). However, although a general organization pattern is observed (**Figs. 1b, c**), a definite circuit has not yet been defined for the PFC (Douglas and Martin, 2007; Harris and Shepherd, 2015). Importantly, the syntax allowing the translation of this structural organization into function is still not entirely known. It has nevertheless been shown that cortical neurons within prefrontal columns are inter-connected, and receive thalamic inputs, across all layers (Constantinople and Bruno, 2013), while larger excitatory pyramidal neurons of the lower layers generate most of the output from the PFC to the thalamus and other subcortical parts of the brain. Placed among the pyramidal neurons, gamma-Aminobutyric acid (GABA)-ergic inhibitory interneurons are mostly found in layers 2 to 6, locally restricting where they spread both their axonal and dendritic arbors (Tremblay et al., 2016). Although highly interconnected locally, they still receive inputs from other cortical and subcortical regions (Ährlund-Richter et al., 2019). Furthermore, there are distinct recruitment

patterns of GABAergic interneurons by local excitatory networks, forming feedforward and feedback inhibitory loops, as well as disinhibitory paths due to the significant interconnections between inhibitory interneurons. The mechanistic underpinnings of how these various inhibitory circuits are formed and how the neuronal circuits process different inputs and shape reliable output patterns are not fully understood. Studies considering the morphology and connection patterns of specific cell-types while investigating their function are necessary to pinpoint their possible implications for proper mPFC function.

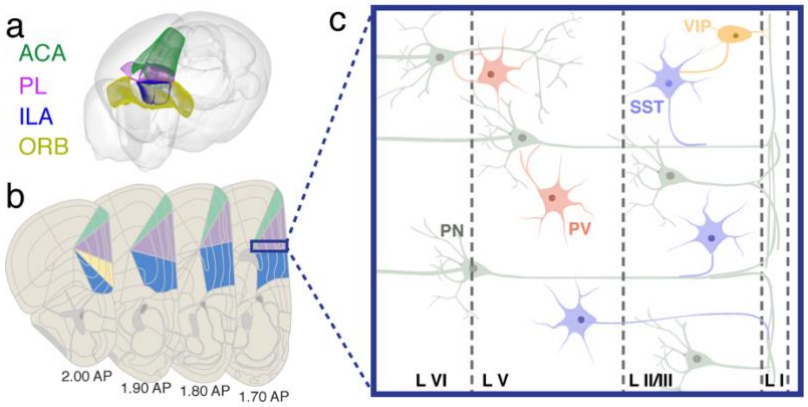

Figure 1 - Organization of the mPFC. (a) 3D representation of the organization of the different sub-regions composing the mouse PFC. **(b)** Coronal section depicting the mPFC sub-regions from +1.70 to +2.00 antero-posterior relative to Bregma. Colors represent the same regions as in (a). **(c)** Schematic illustration representing the cellular organization and distinct layer profile of the mPFC of the mouse. PN: pyramidal neurons. 3D mouse brain made with SBA Composer. Pyramidal neuron (doi.org/10.5281/zenodo.3925905) by Federico Claudi, as well as the interneuron (doi.org/10.5281/zenodo.3925929) were adapted from scidraw.io.

1.1.2 Prefrontal cell-types

At the cellular level, the mouse prefrontal local circuitry consists of 44% of glia cells and 55% of neurons (Erö et al., 2018). The neurons can furthermore be separated into two main populations depending on if they release either the excitatory (glutamate) or inhibitory (GABA) neurotransmitters. The presence of a small percentage (around 1%) of dopaminergic, serotonergic, or cholinergic neuromodulatory neurons is also suggested to be present in the PFC, but is out of the scope of this thesis (Erö et al., 2018).

The glutamatergic principal excitatory neurons referred throughout this thesis as pyramidal neurons constitute around 82% of the neurons in the PFC. They are thus the primary component of the PFC, performing local computation and being the primary communicators between different cortical areas, as well as with other regions of the brain.

Intertwined among the pyramidal neurons, inhibitory GABAergic interneurons are smaller in number, representing 14% of the neurons in the PFC, but more diverse regarding morphology, connectivity and physiology, as well as molecularly (Marín, 2012). Interneurons contribute mostly to the local network, but some are known to send projections to subcortical regions (Lee et al., 2014). The use of molecular markers, morphology, intrinsic firing patterns, but also of the localization of synaptic targeting on pyramidal neurons compartments, allows the further classification of interneurons into more precise cell-types, sharing common molecular, morphological and circuitry traits (Fishell and Kepecs, 2020).

As such, recent single-cell transcriptomics data showed that GABAergic interneurons could be divided into six main sub-classes, further separated into 61 types (Tasic et al., 2018).

The most common class of GABAergic interneurons in the PFC are the parvalbumin (PV), somatostatin, and vaso-intestinal peptide (VIP) neurons (**Fig. 1c**) (Tremblay et al., 2016). PV interneurons make synaptic contact onto the soma or the initial segment of the axon of the pyramidal neurons, while somatostatin neurons target the dendrites of pyramidal neurons (Fishell and Kepecs, 2020). VIP expressing neurons send their inhibitory synapses onto other GABAergic interneurons, having a disinhibitory effect on the circuit. Of note, the PFC has a higher density of somatostatin neurons and a lower density of PV interneurons, unlike other cortical regions (Kim et al., 2017). However, the functional ramifications of such a difference are not known.

All in all, interneurons provide inhibitory input important for feedback inhibition, information gating and other regulatory aspects of the microcircuit, making them vital to the control of excitability and oscillatory rhythms in the PFC. It is, therefore, necessary to characterize *in vivo* the activity of these different elementary neuronal components to improve our understanding of the local computations performed by cortical circuits.

1.2 PARVALBUMIN INTERNEURONS

Among the several cell-types pertaining to the group of GABAergic inhibitory interneurons, the ones expressing the calcium-binding protein parvalbumin have been considerably studied due to their central role in several sets of PFC-dependent behaviors (Hu et al., 2014; Tremblay et al., 2016). This magnified interest was made possible by their relatively easy identification via their fast-spiking phenotype or the labeling with antibodies of the specific PV marker. Furthermore, the specific targeting of the promoter for the PV gene via the use of genetic and viral methods allows them to be labeled with fluorescent proteins or manipulated with optogenetics methods (e.g. light-manipulation of neurons that have been genetically modified to express light-sensitive receptors or channels) (Hu et al., 2014). The term “PV neuron” is used here to refer to all PV-positive neurons found in the brain, including subcortical areas, as these are not defined as interneurons. Whereas the term “PV interneurons” is used to refer specifically to PV-positive neurons found in the cortex, including the PFC.

Therefore, quite a lot has been learned about the function of PV interneurons, notably in the cortex (Bartos et al., 2007; Cardin et al., 2009; Hu et al., 2014; Lewis et al., 2005). PV activity is crucial during development but also during the maintenance of cortical activity in the adult brain. Some attention has been focused on the proper function of PV interneurons in the PFC circuitry, as this has extensive implication in understanding normal cortical computation but also in understanding impaired circuit dynamics underlying neuropsychiatric disorders (Kim et al., 2016b; Lewis et al., 2005; Pafundo et al., 2018; Sohal et al., 2009).

PV interneurons are categorized by their fast firing rates and their narrow-spiking shape. Their complex dendritic and axonal arborization allows them to integrate multiple layers inputs and, at the same time, modulate the activity of several pyramidal neurons. PV interneurons are densely interconnected through gap junctions and exert potent inhibition onto pyramidal neurons. These two features are assumed to help the PV interneurons to generate an innate firing range in the gamma range (30–80 Hz; Buzsáki and Draguhn 2004). They are therefore

known as potent regulators of local network activities (Hu et al., 2014), and synchronous activation of PV interneurons is sufficient for the generation of gamma oscillations (Cardin et al., 2009; Sohal et al., 2009). Furthermore, PV interneurons have been shown to mediate the excitation–inhibition balance and regulate the timing of pyramidal neurons (Ferguson and Gao, 2018a; Hu et al., 2014; Moore et al., 2010; Yizhar et al., 2011).

More specifically, PV interneurons are characterized at the morphological level by their notable axonal targeting near the soma of adjacent pyramidal neurons. This particularity allows them to tightly control the output of pyramidal neurons, as they innervate them at the location where action potentials are initiated (Hu et al., 2014). Furthermore, two sub-classes of PV interneurons can be separated based on the axonal innervation area. The basket neurons have their main direct inhibitory output onto the cell-body of the pyramidal neurons, their axons forming a basket-like structure around the soma and proximal dendrites. In comparison, chandelier neurons target the initial segment of the pyramidal neuron's axon (Karube et al., 2004).

Furthermore, PV interneuron axonal connections have been shown to be dense and nonspecific (Karube et al., 2004; Packer and Yuste, 2011), allowing the PV interneuron to control local circuits activity. For instance, PV's axons show widespread arborization and have a high number of boutons placed all along their extension, allowing them to make connections with a large number of neurons. Thus, by balancing excitation within the area covered by their axons, they form what is called a "blanket of inhibition" stretched over local pyramidal neurons (Karnani et al., 2014). However, it has been demonstrated that PV interneurons adapt their morphology and their synapses, depending on the local circuit activity (Dehorter et al., 2015; Ferguson and Gao, 2018a), suggesting that despite making broad connections with a multitude of neurons, they might be more specifically controlling the function of certain neuron types or ensembles (Agetsuma et al., 2018; Fishell and Kepecs, 2020; Kim et al., 2016b; Kvitsiani et al., 2013).

On the other end, cortical PV interneurons complex and long dendritic arborization allow them to sample their inputs from local neurons. They receive numerous excitatory inputs from a large population of local pyramidal neurons, as well as inhibitory inputs from other interneurons. Moreover, helped by the fact that their dendritic arbor span across several cortical layers, PV interneurons also receive inputs from diverse feedback and feedforward pathways originating from numerous cortical and subcortical regions (Ährlund-Richter et al., 2019; Tremblay et al., 2016).

Prefrontal PV activity is correlated with several cognitive behaviors, as PV firing activity can be positively or negatively modulated during specific phases of a behavioral task (Lagler et al., 2016), including during attention (Kim et al., 2016b), foraging (Kvitsiani et al., 2013) or social behavior (Selimbeyoglu et al., 2017; Yizhar et al., 2011). The modulation of the activity of PV interneurons is associated with the inhibition of certain pyramidal neurons and the increased activity of other local pyramidal neurons (Kim et al., 2016b), suggesting that this specific modulation of groups of neurons is essential for the proper delineation of neuronal ensembles relevant for optimal performance during behavior. PV interneurons are thus proposed to participate in neuronal ensembles formation by controlling the ensemble size through inhibition of less efficiently recruited neurons (Holtmaat and Caroni, 2016).

1.3 PREFRONTAL CIRCUIT ACTIVITY

1.3.1 Excitatory/inhibitory balance

Homeostasis is a process that allows a system or living organism to adjust its internal environment to resist and adapt to external forces of change through feedback control, acting comparably in the same way as thermostats or autopilots.

There is a growing body of literature that recognizes the importance of homeostasis in local circuits of the brain via the balanced interaction between excitatory and inhibitory neurons to generate proper local operations and long-range neuronal communication (Hoftman et al., 2017; Pozo and Goda, 2010; Rich and Wenner, 2007; Turrigiano, 2011). The role of this close pairing between excitation and inhibition is not entirely clear, but it is thought to be necessary for how fast and accurate neurons can respond, as it could work as a fine-tuning mechanism at the network level (Okun and Lampl, 2008). Specifically, the excitatory output of neurons can be modulated by excitatory and inhibitory feedback from adjacent neurons, offering a more controlled local network response (Hennequin et al., 2017; Turrigiano and Nelson, 2004).

Therefore, the E/I balance seems essential for how brain networks respond to stimuli by regulating the excitatory inputs, and how it communicates by controlling the neuronal output (Froemke, 2015; Turrigiano, 2011). Indeed, balanced inhibition is known to be important in shaping the tuning of neurons to specific sensory cues (Atallah et al., 2012; Tao et al., 2014). It is also central to information transmission by allowing activity to propagate through the network without losing or enhancing too much of the activity in the system. In the same fashion, E/I balance is known to be essential for brain plasticity and the capacity of the brain to change at the cellular and network level. For example, there is an over-excitation of the brain during its early development. But subsequently, the maturation of neurons that release inhibitory neurotransmitters leads to an increased inhibition that balances the E/I level. This stabilization of the neuronal networks continues and is shaped by environmental experiences during the critical period (Reh et al., 2020; Takesian and Hensch, 2013). Concomitantly, brain states, like sleep or wake, are known to gate the homeostatic processes that help in stabilizing neuronal circuits. This stability is maintained by controlling firing rates within a normal set-point range, but only during some brain states, for example, during sleep (Hengen et al., 2016; Tononi and Cirelli, 2014).

The mechanisms underlying the maintenance of an accurate E/I balance are diverse and intricate. Previous research suggests that homeostatic regulation of neuronal firing could be achieved by two different mechanisms – either by synaptic changes that adjust the balance between excitatory and inhibitory inputs, or by intrinsic modification of the balance of inward and outward voltage-dependent currents (Turrigiano, 2011). The change in synaptic strength, also called synaptic scaling, is thus believed to be accompanied by changes in the accumulation of receptors like NMDA, AMPA, or trkB, at synaptic sites (Rich and Wenner, 2007; Turrigiano and Nelson, 2004), or by adjustment in neurotransmitters or neurotrophins content of synaptic vesicles (Pozo and Goda, 2010).

Consequently, abnormalities in the neuron structure, dendritic arborization, deficits at the synapses including changes in the formation and placement of receptors, altered neurotransmitters synthesis and transport, or alterations in long-range communication between

brain structures, are known to be involved in the E/I imbalances that can result in various malfunctions at the cellular and network level. This imbalance has been observed in multiple psychiatric and neurological conditions such as autism, schizophrenia, and epilepsy, among others (Hoftman et al., 2017; Lee et al., 2017a). For example, when inhibition is blocked pharmacologically, improper inhibition leads to generalized neuronal firing, aberrant neuronal oscillatory activity, cognitive deficits and several psychiatric comorbidities found in epilepsy (Marín, 2012; Valero et al., 2017).

1.3.2 Neuronal ensembles

While there is no commonly accepted proper definition of neuronal ensemble, it can be defined as a stable group of co-active neurons dynamically involved in particular neuronal computations (Carrillo-Reid and Yuste, 2020a). Neurons belonging to a neuronal ensemble fire together in a time window that allows the consolidation of the connections between them. A sensory stimulus would be therefore denoted by the overall change of activity of a population of neurons, instead of individual neurons, and different sensory stimuli could be represented in the activation of different neuronal ensembles. Manipulation of neuronal ensembles with stimulation of selected patterns of neurons with holographic optogenetics has been shown to be sufficient to control behavior in a Go/No-Go task (Carrillo-Reid and Yuste, 2020b).

As neuronal ensembles are constituted of recurrent connections between excitatory neurons and inhibitory interneurons, the activity of inhibitory interneurons can strengthen the connectivity of most engaged neurons, while weakening less engaged neurons, leading to a spatial definition of the ensemble. They can also help define the temporal aspect of the activation of neuronal ensemble, or orchestrate the transitions between neuronal ensembles, by firing at a different phase of oscillations or brain states (Buzsáki, 2010). In other words, interneurons could orchestrate which and when neuronal ensembles play (Agetsuma et al., 2018), and thus modifying interneurons function can alter neuronal ensembles (Agetsuma et al., 2018; Hamm et al., 2017). Therefore, proper functioning of interneurons and balanced excitatory/inhibitory activity might be critical for the temporal and spatial manutention of neuronal ensemble dynamics (Agetsuma et al., 2018).

As referred previously, prefrontal cortical activity seems to follow the cellular organization of the mPFC, going through layers and within columns. However, how prefrontal neurons are recruited and maintained among different ensembles during behavior remains unclear. Several lines of evidence suggest that active maintenance of a specific neuronal representation, or ensemble, in the mPFC is necessary for the performance of behaviors. Previous works have thus recorded sustained increase or decrease of the firing rate of a population of neurons during a variety of behavioral tasks, notably during attentional processing (Fujisawa et al., 2008; Kim et al., 2016b) or working memory (Kamigaki and Dan, 2017; Liu et al., 2014). Furthermore, manipulating specifically the behaviorally responsive neuronal population, notably by stimulating neighboring PV interneurons, is enough to disrupt the behavioral outcome (Kim et al., 2016b). Of note, although the activity of distinct neuronal ensembles can be collectively reflected in neuronal oscillations, these are temporally defined and lack spatial resolution, thus representing a powerful but indirect way to measure neuronal ensemble activity (Buzsáki, 2010).

Lastly, aberrant neuronal ensemble size, ensemble hyperactivity, as well as non-physiological synchronization or temporal variability of ensembles, have been suggested to be illustrations of neuronal ensemble dysfunction underlying various disorders such as epilepsy (Wenzel et al., 2019a) or neuropsychiatric disorders (Hamm et al., 2017, 2020). Moreover, isoflurane anesthesia disrupts population activity patterns by causing the fragmentation of the neuronal ensembles into separate individual neuronal activity. Interestingly, this reversible process is suggested to be a required effect for the loss of consciousness induced by drugs (Wenzel et al., 2019b). Together, these studies indicate that local neuronal ensembles could provide a circuit substrate for the brain's formation and selection of cognitive processes, which are key for behaviors and deficient in many neuropsychiatric disorders.

1.4 SYNCHRONY IN THE BRAIN

The synchronous activity of local neuronal populations or neuronal ensembles, but also between multiple regionally distributed neuronal ensembles, can be observed through synchronized oscillations in LFP recordings. This synchronization of activity is largely thought to depend on the alternation of excitation and inhibition that paces ensembles of neurons and thus on the activity of PV interneurons. Synchronization of activity is thus supported by the important networks of local feedforward and feedback connections between neurons and long-range connections between regions (Mathalon and Sohal, 2015).

The coordinated organization of neuronal activities, and coordinated interaction between neuronal oscillations, are important to understand the temporal and spatial functional organization of neurons and are suggested to be a fundamental organizing principle of the brain (Buzsáki and Watson, 2012; Wilson et al., 2018).

1.4.1 Oscillatory activity

The rhythmic activity of neurons creates what is called neuronal oscillations. More specifically, they are the result of membrane currents, movements of ions like sodium and potassium across the cell membrane of neurons (Buzsáki et al., 2012). Oscillations are measured as electroencephalograms (EEGs), on the scalp of a subject, or local field potentials (LFPs), when recorded intracranially, and represent highly coordinated neuronal activity that occurs rhythmically over a variety of frequency bands (<1Hz to up to 500 Hz) in the intact mammalian brain. It is thus suggested that neuronal oscillations reflect the recurrent variations in neuronal excitability of brain circuits. The different oscillatory frequency bands are proposed to echo the various hierarchies of brain processing (Cannon et al., 2014).

Therefore, oscillations would reflect the fluctuating synchronous activity of a local circuit of neurons at different time scales, alternations between brain states, or faster fluctuation between depolarized and hyperpolarized states. These variations are suggested to create a temporal organization of activity, with inputs having a higher or smaller chance to activate certain neuronal populations depending on the state of the circuit. Neuronal oscillations are also proposed to help separate information from noise by entraining neuronal spiking and thus causally maintaining neuronal ensembles, e.g. arranging populations of neurons into groups whose synchrony exceeds the overall recurring noise (Wilson et al., 2018). Here noise denotes brain activity not directly related to the measured event but that may be critical in other situations. Therefore, when the coordinated output from a neuronal ensemble reaches the same

target neuron at the same time, the impact on that postsynaptic neuron will be more significant (Buzsáki, 2006). Thus, the synchronous firing of neurons with reciprocal interaction improves the output of the neuronal population to a downstream target. Concurringly, LFP synchronicity between two separate brain areas are interpreted as improving their connectivity and making their communication more selective and effective, a concept called "communication through coherence" (Fries, 2015; Harris and Gordon, 2015).

Theoretical framework and empirical evidence have implicated neuronal dysfunction in the generation and coordination of brain oscillations in the pathophysiology of neuropsychiatric disorders (Buzsáki and Wang, 2012; Buzsáki and Watson, 2012; Gonzalez-Burgos et al., 2015; Mathalon and Sohal, 2015). These dysfunctions have been detected in different levels of neuronal organizations, from LFP and brain states readouts to single-neuron activity. It is, therefore, essential to understand the biological causes underlying these oscillatory changes and to pinpoint the neuronal circuitry responsible for the concomitant symptoms.

1.4.1.1 Oscillatory activities of the PFC

The mouse PFC can be considered a rich oscillatory hub, as prefrontal oscillations are found to be strongly coupled to distinct behavioral and cognitive states (Sohal, 2016). The work in this thesis focuses on the main oscillations found in the mouse PFC, particularly the delta (0.5-4 Hz), the gamma (30-80 Hz) and the high-frequency oscillations (HFOs; 100-150 Hz). Of note, LFP frequency bands have been conventionally and artificially defined by frequency range criteria rather than mechanisms (Belluscio et al., 2012), which can conceal the links between physiological and circuit mechanisms and behavioral effect.

The delta oscillation (0.5-4 Hz) is a slow oscillation prominent in slow-wave sleep or when mice are quiet (restful wake). This slow oscillation is thought to be critical in grouping other brain rhythms, notably modulating the amplitude of gamma and HFOs, and organizing neuronal synchrony by allowing periods of depolarization and periods of hyperpolarization (Steriade, 2006). The cortically generated delta oscillation is thought to depend on thalamocortical inputs, but a part of delta oscillation still exists in the cortex after removing the thalamus (Steriade, 2006). This persistent delta could be due to an often-overlooked oscillation around 4 Hz caused by breathing activity that has been demonstrated to overlap with delta oscillations in the mouse PFC. This breathing-entrained oscillation can modulate the amplitude of HFOs (Tort et al., 2018). Thus, delta oscillations should be carefully analyzed to detect the presence of breathing signals to avoid potential confounds (Jung and Carlén, 2021).

The gamma oscillation is defined as a synchronized rhythmic high-frequency activity (Buzsáki and Wang, 2012) and is thus usually easily identified as a narrow peak in the gamma band (30-80 Hz). Gamma oscillation is believed to play a causal role in many cognitive behaviors, including those dependent on the mPFC (Kim et al., 2016b; Sohal, 2016; Steriade, 2006; Uhlhaas and Singer, 2010). The timescale of the gamma cycle, approximately 10-30 milliseconds, is hypothesized to be ideal for synchronizing the activity of PFC neuronal ensembles, enabling them to efficiently transmit and receive information (de Almeida et al., 2013; Buzsáki and Watson, 2012; Fujisawa et al., 2008). This rapid cycle is thought to be primarily generated locally by the synchronized inhibition of pyramidal neurons by PV

interneurons, resulting in synchronous entrainment of excitatory firing within local cortical circuits (Cardin et al., 2009; Sohal et al., 2009).

Reduced task-evoked narrow-gamma power has been observed in both clinical studies as well as in mouse models of neuropsychiatric disorders (Gonzalez-Burgos et al., 2015; Senkowski and Gallinat, 2015), and optogenetic restoration of local narrow gamma activity has been found to rescue impairments in cognitive flexibility in a model of autism spectrum disorder (Cho et al., 2015). However, impairments in prefrontal circuits also increase the power of LFP in a broadband manner, including the gamma-band (Billingslea et al., 2014; Carlén et al., 2012; Cho et al., 2015; del Pino et al., 2013), making it difficult to pinpoint the mechanisms behind typical and pathological gamma activity (Cardin, 2016; Sohal, 2016). We refer to "broadband" as a term describing the LFP activities spanning across several frequency bands, in contrast to "narrow" which is defined by a peak centered in a specific frequency.

HFOs are LFPs that are found around 100-150 Hz, and although there are often called "epsilon" or as "high" or "fast" gamma oscillations (Jung and Carlén, 2021), it is assumed that the generation of gamma (30-80 Hz) and HFOs oscillations are mechanistically distinct (Buzsáki and Wang, 2012; Ray and Maunsell, 2011). They are thought to play several key roles in brain functions such as sleeping and waking cycles, cognitive processing, and memory consolidation. However, studies have suggested that HFOs may reflect action potentials from synchronous neuronal firing (Buzsáki et al., 2012). It is further thought that increased spike frequency and synchrony increases spectral power over a broad range, particularly in frequencies higher than 100 Hz, thus making HFOs an index of spiking synchrony (Belluscio et al., 2012; Manning et al., 2009). However, Scheffer-Teixeira and colleagues argue against the idea that all high-frequency LFP activity stems from spike contamination and that HFOs can also contain genuine oscillatory activity (Scheffer-Teixeira et al., 2013). Despite the importance of HFOs, there remains a paucity of evidence on its mechanisms.

1.4.2 Cortical deactivated and activated states

The brain is constantly active and shows spontaneous patterns of activity even when not receiving any sensory input. Thus, brain activity is influenced by the interaction of external stimuli together with spontaneous patterns, called brain states, that are produced endogenously (Harris and Thiele, 2011). This spontaneous electrical activity shift between states, largely between several stages of sleep, restful and aroused waking. Because neuronal spiking dynamics can be contingent as much on the brain state as on sensory inputs, it is necessary to always consider the brain state to understand how information is processed by a population of neurons. Because the work presented in this thesis is based on cortical activity, we will use the term cortical states to define these dynamics of network activity. Furthermore, it is important to consider that cortical states are not binomial but are defined along a continuum of network dynamics.

While a variety of terminologies are used to define cortical states, this thesis will use the terms "activated" state instead of "asynchronized" or "desynchronized" state to name wakefulness and rapid eye movement (REM) sleep, and "deactivated" states in place of "synchronized" or "inactivated" state to designate slow-wave sleep (also known as nonrapid eye movement (NREM) sleep) or restful wake. Historically, the activated state had been defined as a state

associated with a global cortical desynchronization concomitant with the occurrence of low-voltage, high-frequency (> 20 Hz) oscillations. In contrast, the deactivated state was compared to a state of global cortical synchronization marked by high-voltage, low-frequency (< 10Hz) activities (Sanchez-Vives and McCormick, 2000). However, wakefulness was found not to be necessarily desynchronized, as several high-frequency oscillations are found to be synchronized between cortical regions, and slow-wave sleep, not completely synchronized either, activated and deactivated states were preferred as to avoid unwarranted confusion (Harris and Thiele, 2011; Steriade, 2000).

Several oscillatory activity patterns can be thus identified within cortical states, usually well separated between deactivated states, which are primarily marked by slow oscillation (0.5–1 Hz), delta (1–4 Hz), and spindles (7–15 Hz), and activated states that are associated with beta (20–30 Hz) and gamma (30–80 Hz) oscillations, as well as HFOs (> 100 Hz) (Harris and Thiele, 2011; McKenna et al., 2017; Steriade, 2006). They can thus be used to separate the different spontaneous activity into states. However, fast oscillations (> 30 Hz) also appear, with lower incidence, during deactivated states (Compte et al., 2008), while low-frequency oscillations have been recorded during activated states (Poulet and Crochet, 2019). These low-frequency oscillations recorded during activated states in the mPFC could be, as previously stated, due to breathing-associated signal conductance.

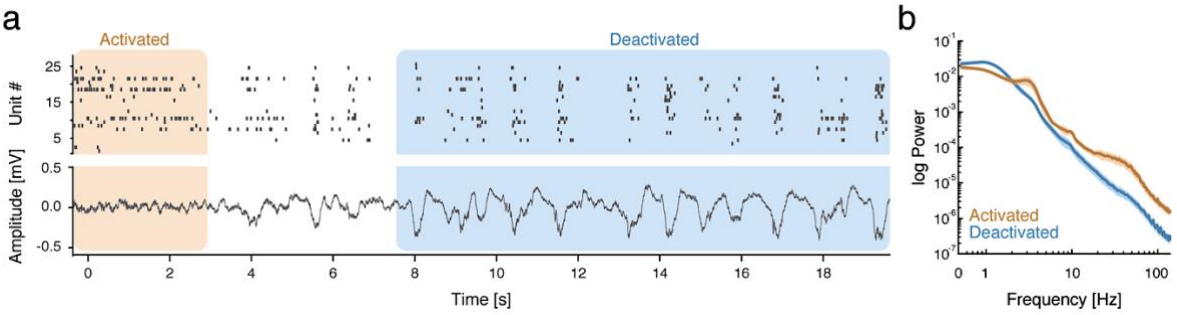

Figure 2 - Cortical states recorded under anesthesia (a) Example of single-unit activity (spikes; up) and oscillatory activity (LFP, bottom) during a typical transition between activated and deactivated states produced by urethane. **(b)** Power spectral density analyses unveil that deactivated states are mainly marked by slow oscillations (<2 Hz), while activated states are associated with the increased activity in higher frequencies (> 20 Hz).

Cortical states can also be recorded under anesthesia. For example, urethane-anesthetized mice display spontaneous cyclic state alternation between deactivated states that resemble slow-wave sleep oscillations and activated states resembling REM sleep oscillations (Clement et al., 2008). This opens up the possibility of using urethane to better study how neuronal activity is associated with states and possibly network synchronization while avoiding the noise due to motor activity seen in freely moving recordings **(Fig. 2)**.

Overall, the mechanisms behind the apparition of local cortical states are not clear, as states are shown to influence neuronal activity but may also emerge from the interactions between populations of neurons (Goldman et al., 2019; Harris and Thiele, 2011). Pharmacological perturbation of neuronal activity has been found to lead to a switch of state. For example, acute administration of the NMDAR antagonist ketamine alters the cyclic alternations between

deactivated and activated states in urethane anesthetized rats (Lopes-Aguiar et al., 2020). Furthermore, ascending projection from reticular formation or the basal forebrain to the cortex regulates the transition between states recorded in the mPFC (Kim et al., 2015; McKenna et al., 2017). Still, several studies looking at cortical states have demonstrated that the different patterns of activity underlying cortical states influence the synchrony of local neuron activity as well as the processing of sensory input during different behaviors and levels of arousal (Poulet and Crochet, 2019). For example, in the barrel cortex of behaving mice, it has been shown that fast-spiking GABAergic interneurons (putative PV interneurons) fire synchronously at a high frequency during restful wake and are largely driven by the synchronous slow oscillations. Therefore, they inhibit non-fast-spiking interneurons as well as pyramidal neurons, who fire sparsely and uncorrelated during brief but large and cell-specific depolarizations. Whereas during active wakefulness, the increased ascending glutamatergic or neuromodulatory inputs lead to a more active phase with the slow large-amplitude oscillations being suppressed and the membrane potential synchrony being reduced as well, causing the fast-spiking GABAergic interneurons to decrease their firing rates, possibly due to enhanced inhibition by non-fast-spiking interneurons, while pyramidal neurons are less restricted to fire (Gentet et al., 2010). An implication of this is the possibility that the cortical states are controlling local neuronal activity by principally modulating fast-spiking GABAergic interneurons firing patterns. However, if and how PV interneurons and other interneurons influence cortical states alternations is not clear yet. Therefore, it would be interesting to investigate if E/I imbalance due to dysfunctional PV interneurons might affect back cortical states by desynchronizing these patterns of hyperpolarization and depolarization.

1.4.3 UP and DOWN states

As indicated above, the deactivated state is also known as the synchronized state, as it fluctuates strongly and synchronously in a timescale of 100 milliseconds or slower. This slow fluctuation is constituted by cyclic alternations between DOWN and UP states (**Fig. 3**). During DOWN states, a marked period of populational inhibition can be observed, while during UP states, cortical neurons are more actively firing (Haider et al., 2006; Harris and Thiele, 2011; Steriade et al., 1993). Additionally, gamma oscillations are found to be nested to the delta oscillations (they are principally found at the peak of delta wave, and thus are modulated by the delta oscillation phase), possibly linked to the higher activity of PV interneurons during the UP states (McKenna et al., 2017; Puig et al., 2008; Steriade, 2006).

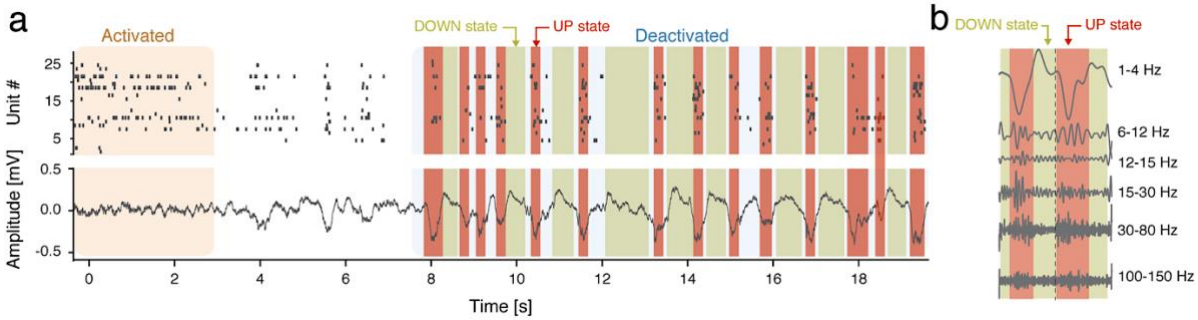

Figure 3 - Cyclic alternations between DOWN and UP states. (a) The deactivated states can be further divided between DOWN states, defined by hyperpolarization and low single-unit activity, and UP states, defined by depolarization, units firing and **(b)** nested high-frequency activities. Adapted with permission from Guyon et al. 2021 (Paper I).

Thus, the slow oscillation has been tightly correlated with the activity of both cortical pyramidal neurons and inhibitory interneurons and is made up of a prolonged depolarizing UP-state, when pyramidal cells fire, followed by a long-lasting hyperpolarizing DOWN-state, with no pyramidal spiking activity due to the inhibitory action of the interneurons (Steriade, 2006). The mechanisms responsible for generating slow oscillations are not entirely understood, but ascending thalamocortical excitatory and neuromodulatory inputs and a balanced excitation and inhibition seems to be a major prerequisite for the persistent activity during the UP-state (Jercog et al., 2017).

Interestingly, previous results indicate that synaptic inhibition by PV interneurons has a significant role in the termination of the UP-state, as well as in synchronizing the onsets of DOWN-states (Zucca et al., 2017). Thus, it should be possible that the dysfunction of the PV interneuron diminishes the synchronous alternation between UP and DOWN, for instance, through E/I imbalance and/or hypoactivation by neuromodulators, and underlie some of the clinical sleep disturbance found in animal models of schizophrenia (Phillips et al., 2012). Furthermore, the transition between UP and DOWN states allows to precisely observe the firing patterns of the different cell types (Massi et al., 2012), and therefore how well the E/I balance is maintained by the interneuron's control over pyramidal cell activity. This close link between neuronal activity and UP and DOWN states suggests that the synchronous activity during this state transition is an identifiable marker of E/I imbalance in the dysfunctional brain activity.

1.4.4 Cross frequency coupling

It has also been shown that neuronal oscillations of different frequency bands can interact in a synchronous manner (Hyafil et al., 2015; Jensen and Colgin, 2007; Lisman and Buzsáki, 2008). This interaction, called cross-frequency coupling (CFC), has been described not only at the local circuitry but also between regions across the brain (Canolty and Knight, 2010; Harris and Gordon, 2015). Locally, it is suggested that the interactions between oscillatory frequency bands could be controlling baseline excitability and stimulus-related responses in a neuronal circuit by structuring the temporal activity pattern of the neuronal population to better process the periodic inputs it receives from external sensory input or other brain areas (Lakatos et al., 2005; Lisman, 2012; Wilson et al., 2018). Globally, synchrony between active regions would allow for effective exchange of information across these regions (Buzsáki, 2006).

Among the described interactions, "phase-amplitude coupling" looks precisely at how the amplitude of high-frequency oscillations is modulated by the phase of low-frequency oscillations (Tort et al., 2010). The gamma power modulation by theta or alpha oscillations has been extensively studied, since it is thought that nested gamma cycles may serve as mechanisms for sustaining working memory activity or perceptual functions (Fujisawa et al., 2008; Steriade, 2006).

It is suggested that nonspecific increased oscillatory power over a large range of frequencies, as well as increased synchrony or cross-frequency coupling, could all be correlated with an aberrant state of hyperexcitability and altered information flow, causing cognitive dysfunctions and psychotic symptoms seen in schizophrenia-like disorders (Caixeta et al., 2013). For instance, studies blocking the NMDA receptors with low doses of ketamine show not only an

increase in the power of gamma and delta oscillations, but also that ketamine produced an increase in phase-amplitude coupling between these two bands. However, a higher dose of ketamine disrupts the coupling between these two oscillations (Caixeta et al., 2013; Lopes-Aguiar et al., 2020). Caixeta and colleagues thus suggested that NMDAR hypofunction could lead to functionally hyper-connected, and synchronized, structures concomitant with an over-processing of information, as seen in epilepsy. However, the neuronal mechanisms behind these cross-frequency coupling alterations and their functional consequences are still not entirely clear (Hyafil et al., 2015).

1.5 N-METHYL-D-ASPARTATE RECEPTOR

The NMDA receptors are glutamate-gated ion channels that form, with the AMPA receptors, the predominant types of receptors found in neurons. NMDARs are encountered throughout cortical and subcortical areas. Importantly, they are present in the mPFC, including in PV interneurons (Paoletti et al., 2013).

NMDARs are composed of tetrameric complexes, consisting of fourteen different subunit types, incorporated into three subfamilies, NR1, NR2 and NR3 (Also known as GluN1, GluN2 and GluN3). These subunits combine in a semi-flexible way, resulting in a myriad of receptor subtypes, typically associating two obligatory NR1 with a mix of NR2 or NR3 subunits (Paoletti et al., 2013). NR1 and NR3 subunits bind to glycine, while the NR2 subunits bind to glutamate and control the electrophysiological properties of the NMDAR.

This diversity in subunit composition and expression leads to varied permeation, gating and trafficking properties. NMDARs are involved in several important circuits and cognitive processes that involve plasticity, learning, and memory (Paoletti et al., 2013). Previous research has established that the alterations of NMDAR signaling properties are linked to neurological and neuropsychiatric disorders (Cohen et al., 2015; Lau and Zukin, 2007; Moghaddam and Javitt, 2012; Paoletti et al., 2013). For instance, evidence from the expression of NMDARs in postmortem tissue of individuals who had schizophrenia show a reduction in the NR1 subunits in the PFC (Catts et al., 2016). Furthermore, NMDAR hyperactivity is known to contribute to neuronal death by allowing excessive Ca2+ influx into the cell. However, NMDAR hypofunction is also detrimental (Mohn et al., 1999), as reduced NMDAR presence or decreased NMDAR activity in GABAergic neurons leads to an imbalance between excitation and inhibition in the neuronal network (Billingslea et al., 2014; Cohen et al., 2015; Homayoun and Moghaddam, 2007; Pafundo et al., 2018).

Besides, the disruption of the E/I balance by acute treatment with non-competitive NMDAR antagonists, e.g., dizocilpine (MK-801), ketamine, and phencyclidine (PCP), is considered a useful pharmacological model of schizophrenia (Krystal et al., 1994; Lisman et al., 2008). Administration of this class of drugs reproduces both positive and negative, as well as cognitive, symptoms displayed in the disorder, e.g., stereotyped behaviors, working memory deficits, sensory-motor gating disruption, as well as emotional and social impairments (Moghaddam and Javitt, 2012). It has been suggested that NMDAR antagonists more effectively target GABAergic inhibitory neurons than the pyramidal excitatory neurons. In accordance with this idea, it has been demonstrated that systemic injection of MK-801 impacts the activity in the mPFC by enhancing the firing rate of pyramidal neurons due to decreasing

activity of putative PV interneurons (Homayoun and Moghaddam, 2007). These results support the assumption that PV interneurons control the activity of neuronal networks through NMDAR-dependent disinhibition of local pyramidal neurons. In a like manner, NMDAR antagonists are also known to trigger aberrant gamma oscillations associated with stereotypy and hyper-locomotion, depending on the dose. Furthermore, long-term dysfunctions induced by NMDAR antagonists (hours to days after treatment) on sensory-motor gating disruption, social interaction, emotional memory, and working memory have been correlated with the disruption of gamma oscillations (Moghaddam and Javitt, 2012).

1.5.1.1 NMDARs in PV interneuron and gamma oscillations

NMDA receptors in PV interneurons have been implicated in the emergence of gamma oscillations (Gonzalez-Burgos and Lewis, 2012; Lisman et al., 2008), as NMDAR antagonists were early associated with increased power in fast-frequency oscillations, including the gamma range (30-80 Hz).

As such, ketamine is associated with an increase in gamma oscillations power in cortical and subcortical regions in human EEG studies (Rivolta et al., 2015), as well as in pre-clinical recordings (Caixeta et al., 2013; Hakami et al., 2009; Lopes-Aguiar et al., 2020; Picard et al., 2019). The gamma oscillation abnormalities caused by NMDAR antagonists included not only deficits in evoked oscillations but also an abnormal increase in baseline power (Gonzalez-Burgos and Lewis, 2012; Lazarewicz et al., 2010). This effect was seen in both gamma (30−80 Hz) and high-frequency- band (> 80 Hz). However, questions have been raised whether the effects observed on gamma oscillations are specifically caused by NMDAR hypofunction (Gonzalez-Burgos and Lewis, 2012). NMDAR antagonists, such as Ketamine, PCP, and MK-801, have been shown to bind to other receptors types apart from NMDARs and impact the effectiveness of other neurotransmitters or signaling pathways.

The use of mutant mice lacking NMDAR globally or in specific cell-types allowed to isolate potential mechanisms of altered gamma oscillations, and directly test the hypothesis that NMDAR dysfunction in PV interneurons is critical for the manifestation of pathological gamma abnormalities. Thus, previous works addressed this question by studying mice lacking NMDAR selectively in PV neurons (Carlén et al., 2012; Korotkova et al., 2010). In short, these animals displayed enhanced baseline cortical (**Fig. 4a**) and hippocampal gamma oscillations. They also showed decreased induction of gamma by the optogenetic stimulation of PV interneurons (**Fig. 4b**). NMDAR hypofunction affected not only gamma oscillatory activities but also cross-frequency coupling between the phase of theta oscillation and amplitude of gamma oscillation (Korotkova et al., 2010). At the behavioral level, the mice exhibited compromised social, spatial and working memory (Billingslea et al., 2014; Carlén et al., 2012; Korotkova et al., 2010). Importantly, the use of mutant mice showed that lack of NMDARs in PV neurons blunts the gamma surge in response to NMDAR antagonist (**Fig. 4c**), proposing that cortical PV interneurons are a central target of NMDAR antagonists (Carlén et al., 2012; Hudson et al., 2020; Picard et al., 2019). The gamma increase after NMDAR antagonist could therefore be due to desynchrony generated by disinhibition of pyramidal activity. However, it is unclear if the increase in baseline gamma oscillations (>30 Hz) by NMDAR antagonist are distinct from the increased spontaneous broadband gamma oscillations (>30 Hz also) observed in genetic models of deficient NMDAR activity in PV interneurons.

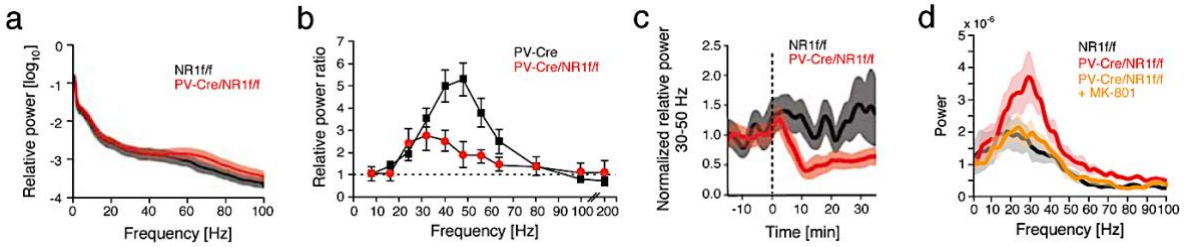

Figure 4 - Gamma oscillation impairments in mice lacking NMDAR selectively in PV neurons. (a) LFP power recorded from awake NR1f/f control mice and mice lacking NMDAR in PV neurons (PV-Cre/NR1f/f mice). Baseline broadband oscillations (60-100 Hz) power are increased in PV-Cre/NR1f/f mice, including part of the gamma-band (30-80 Hz). **(b)** Mean power ratio in different LFP frequency bands in response to light-stimulation of PV neurons expressing channelrhodopsin-2 (ChR2) at frequencies from 8 Hz to 200 Hz. Gamma oscillations (30–80 Hz) generation is decreased in PV-Cre/NR1f/f mice compared to control mice. **(c)** Average relative power in the 30–50 Hz gamma-band 15 min before to 35min after administration of MK-801 (dashed line). Administration of MK-801 increases significantly in relative gamma power in control mice but reduces in a significant way the relative gamma power in PV-Cre/NR1f/f mice. **(d)** Computational model of the effect on the LFP power of reducing excitability of PV neurons caused by genetic or drug-induced NMDAR hypofunction in PV neurons. Mean ± SEM. Adapted with permission from Carlén et al. 2012.

Another much-debated question is whether the increase in spontaneous broadband gamma power is generated in the same way as the narrow gamma-band. Sohal and Rubenstein argued that the increased baseline gamma oscillations activity measured via a broadband increase in power across a wide range of frequencies might reflect an increase in neuronal activity composed of arrhythmic and not well-synchronized neuronal firing in local circuits - a neuronal "noise" possibly coming from E/I imbalance (Sohal and Rubenstein, 2019). Computational modeling has supposed that the absence of slow excitatory NMDA currents decreases the excitability of PV interneurons, leading to a reduced sensitivity to asynchronous activation (noisy excitatory drive) and thus only allowing neuronal firing when getting more synchronous excitatory inputs (Carlén et al., 2012; Jadi et al., 2016). This "suppression boundary" mechanism (Börgers and Kopell, 2005) would lead to an increase in broadband gamma activity (**Fig. 4d**). Besides, this model further explained the decreased gamma power evoked by administration of NMDAR antagonists by showing that MK-801 reduced even more the synchronous excitation onto the PV interneurons of the mutant mice lacking NMDAR activity in PV neurons, already less sensitive to activation, and resulted in a decrease in gamma power. However, a study by Yizhar and colleagues showed that elevation of excitation of the mPFC produced a broadband increase in spontaneous gamma power (Yizhar et al., 2011). It is still unclear whether this broadband gamma is the result of hyper-synchronization or simply increased background noise due to increased cortical activity, thus causing asynchronization of the network.

1.5.1.2 NMDAR hypofunction and single unit activity

Additionally, there has been little quantitative analysis on how NMDAR hypofunction affects single-unit activity and LFP-spike coupling. Many of the studies investigating the NMDAR hypofunction model of schizophrenia have focused mainly on LFP oscillations. As such, little is known about the effect of NMDAR antagonists such as ketamine on the single-unit firing of different cell-types. Systemic administration of the NMDAR antagonist MK-801 has been shown to evoke an increased firing in the mPFC of rats (Molina et al., 2014). Notably, the

synchronization of single-unit firing was found to be decreased, and the spike trains disorganized. This adds to both modeling and experimental findings showing that genetic knockout of NMDARs in PV neurons results in increased variability of cortical excitatory activity **(Fig. 5)** (Carlén et al., 2012; Jadi et al., 2016). Together, these studies indicate that NMDAR hypofunction could lead to desynchronization of neuronal activity concomitant with increased baseline broadband oscillation power.

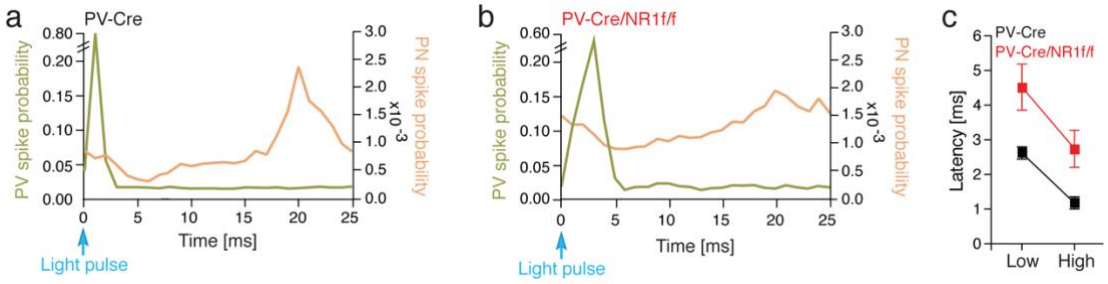

Figure 5 - Impaired inhibition of single-unit PN activity after light activation of PV units in PV-Cre/NR1f/f mice. (a) Overlaid pyramidal neuron (PN; n = 17 neurons) and PV (n = 9 neurons) population averages from the PV-Cre control mice, with 0 set as the time of the light flash on each cycle. PV population average shows a light evoked peak in firing at 1-2 ms. The PN population average shows a decrease in spike probability around 4-10 ms after the light flash and an increase in spike probability around 20 ms. **(b)** Overlaid PN (n = 4) and PV (n = 6) population averages from the PV-Cre/NR1f/f mice. PV population average shows a larger light evoked peak in firing at 1-5 ms, while PN population average shows a slightly elevated spontaneous firing rate, a smaller decrease in spike probability around 4-10 ms after the light flash, and a modest increase in spike probability around 20 ms. **(c)** Mean light-evoked spike latency for PV interneurons in control mice was 2.62 ± 1.2 ms at low power (31 mW/mm2) and 1.18 ± 1.2 ms at high power (68 mW/mm2). Mean light-evoked spike latency for PV interneurons in PV-Cre/NR1f/f mice was significantly longer (4.52 ± 2.2 ms at low power and 2.74 ± 2.2 ms at high power; Mann-Whitney test; $P < 0.05$ in both cases). In addition, the variance of the spike latencies was significantly higher across cells in PV-Cre/NR1f/f mice than in control mice (F test; $P < 0.05$). Adapted with permission from Carlén et al. 2012.

1.6 BDNF-TRKB SIGNALING

The brain-derived neurotrophic factor (BDNF) is a member of the family of growth factors called neurotrophins that influence the proliferation, differentiation, survival, and death of neurons and glia. BDNF is secreted in most parts of the central nervous system, with the highest levels detected in the cortex and the hippocampus (Armanini et al., 1995). Although BDNF was first characterized as instrumental in the development of the brain (Huang et al., 1999), it is now clear that BDNF has multiple roles in the adult nervous system, such as regulating synaptic structure and connections, the release of neurotransmitter, and synaptic plasticity (Kowiański et al., 2018; Nagappan and Lu, 2005; Park and Poo, 2013), Thus, BDNF signaling is thought to be critical for the maintenance and refinement of neuronal circuits as one of its main roles is to regulate neuronal morphology.

Much research on the role of BDNF has focused on plasticity processes. BDNF-trkB signaling (**Fig. 6**), elicited through the binding of BDNF to trkB, causes intracellular signaling cascades that contribute to the transcription of genes central for synaptic plasticity and processes like long-term potentiation (Minichiello, 2009). But these diverse intracellular signaling cascades are also known to regulate widely diverse functions, such as cell migration, survival and death,

as well as the outgrowth and pruning of neurites, formation of synapses, neuronal communication and synaptic plasticity (Chao, 2003; Kowiański et al., 2018; Lu et al., 2005, 2014), making it difficult to categorize the full function of BDNF-trkB signaling. Moreover, impaired BDNF-trkB signaling has been extensively associated with the pathophysiology of many neurodegenerative disorders, depression, anxiety and other psychiatric disorders (Autry and Monteggia, 2012; Castrén, 2014; Mitre et al., 2016; Woo and Lu, 2006). However, little is known about the role of BDNF-trkB signaling at the network level, particularly in the precise mechanisms underlying trkB dysfunction in the mature brain.

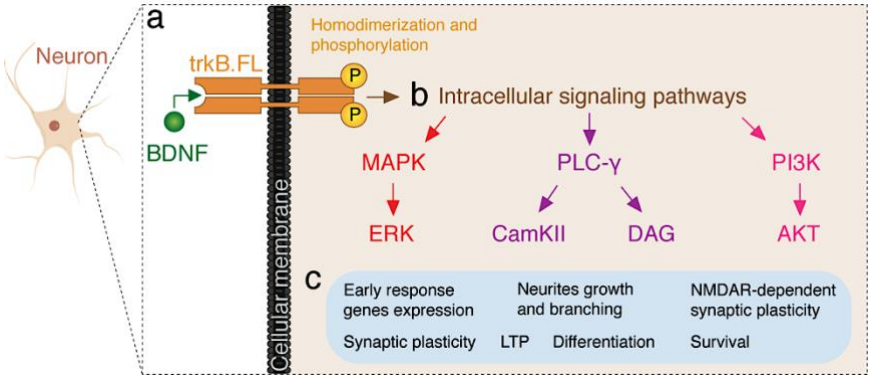

Figure 6 – Overview of the BDNF-trkB signaling pathways. Binding of BDNF to the full-length trkB **(a)** triggers the homodimerization and phosphorylation of trkBs, which elicits three main intracellular signaling pathways **(b)**, through the activation of: Ras–mitogen-activated protein kinase (MAPK) which promotes extracellular signal-regulated kinase (ERK) signaling; phospholipase Cγ (PLC-γ), which promotes the generation of diacylglycerol (DAG) and Ca2+/calmodulin-dependent protein kinase II (CaMKII); phosphatidylinositol 3-kinase (PI3K)-Akt cascade. The activation of these pathways leads to numerous physiological processes, of which some are shown in **(c)**. Image of neuron was adapted from scidraw.io (doi.org/10.5281/zenodo.3925929).

1.6.1 trkB receptors

The trkB gene *NTRK2* is able to transcribe several splice variants, including the full-length trkB (trkB.FL), but also truncated variants (trkB.T), i.e., receptors lacking the catalytic kinase domain (Klein et al., 1990; Stoilov et al., 2002). TrkB.FL is composed of an extracellular ligand-binding domain, a transmembrane domain, and an intracellular domain that includes the highly conserved catalytic kinase domain (Benito-Gutiérrez et al., 2006; Klein et al., 1990). The C-terminal truncated trkB receptors (of which the trkB.T1 is the most studied) hold the same extracellular and transmembrane domains, but their intracellular part consists of a unique short sequence of amino acid residues (Fenner, 2012; Ohira and Hayashi, 2009).

For this reason, overexpressing truncated versions of trkB might offer the possibility to impair BDNF-trkB signalization. Indeed, the truncated receptors were found to function as inhibitory modulators of neurotrophins responsiveness (Eide et al., 1996; Ohira and Hayashi, 2009; Stoilov et al., 2002). Truncated trkBs behave as dominant-negative isoforms by competing for BDNF and forming nonfunctional heterodimers with the full-length version of the receptor (Haapasalo et al., 2002). For example, overexpressing trkB.T1 has been shown to reduce trkB phosphorylation (Saarelainen et al., 2003), adding to the findings indicating that truncated

trkBs negatively regulate the full-length trkB signaling (Carim-Todd et al., 2009). However, trkB.T1 also holds BDNF independent functions and its involvement in regulating neuronal and glial mechanisms is not yet completely understood (Fenner, 2012).

1.6.2 BDNF-trkB signaling in prefrontal PV interneuron activity

It has previously been suggested that a potential role for BDNF is to control the neuronal activity in the PFC (Galloway et al., 2008). Galloway and colleagues further hypothesize that this control of prefrontal neural activity is dependent on BDNF-trkB signaling in PV interneurons. In the same vein, it has been suggested that BDNF-trkB signaling in the cortex could serve as a way to stabilize the inhibitory drive of PV interneurons (Marty et al., 1997) and thus mediate the excitatory/inhibitory balance of the local network (Woo and Lu, 2006).

However, while trkB is expressed in pyramidal neurons and in inhibitory GABAergic neurons - PV neurons express trkB abundantly - BDNF is essentially secreted by pyramidal neurons (Gorba and Wahle, 1999; Hashimoto et al., 2005; Marty et al., 1997). As *in situ* expression of BDNF confirmed that cortical GABAergic interneurons, including PV interneurons, do not synthesize BDNF themselves, it has been proposed that BDNF act in a paracrine manner, modulating the presynaptic inhibitory activity, the GABA expression levels, as well as the morphology, of cortical PV interneurons. This has been shown to occur via the release of BDNF from postsynaptic pyramidal neurons (Huang et al., 1999; Jiao et al., 2011).

Functional evidence of this interaction between BDNF-trkB signaling and PV interneurons have been observed in neuropsychiatric patients. For instance, changes in the expression of trkB in PV interneurons have been associated with the pathophysiology of schizophrenia. Most postmortem studies indicate that both BDNF and trkB proteins are downregulated in the brain tissue of individuals who had schizophrenia (**Fig. 7a**) (Hashimoto et al., 2005; Ray et al., 2014; Takahashi et al., 2000; Weickert et al., 2003, 2005), although a recent study report that trkB mRNA levels in the PFC did not differ between postmortem tissue of people with schizophrenia and healthy comparison subjects (Reinhart et al., 2015). Furthermore, the expression of truncated trkB isoforms was found to be increased in the prefrontal cortex (Wong et al., 2013). Both the decrease in trkB.FL and the increase in truncated trkBs are correlated with decreased GABA markers in PFC tissue of schizophrenic patients (Wong et al., 2013). Taken overall, these changes have been suggested to lead to the hypofunction of the prefrontal cortex (Hashimoto et al., 2005; Lewis et al., 2005)

The results from postmortem studies of neuropsychiatric patients are corroborated by animal studies showing a reduction in GABA markers when trkB function is inhibited for 20 days in the adult brain, suggesting that the maintenance of GABA levels involves BDNF-trkB signaling (Chen et al., 2011; Porcher et al., 2018). Furthermore, findings obtained by knockout of trkB (knockout affecting all isoforms) specifically in PV neurons (Xenos et al., 2018; Zheng et al., 2011) and cortical GABAergic interneurons (Tan et al., 2018) reported several morphological as well as functional alterations, including neuronal desynchronizations affecting the LFP gamma-band and E/I imbalance. The absence of trkB in PV interneurons during the development also led to a significant loss of inhibitory synapses onto prefrontal pyramidal neurons, indicating an essential role of BDNF-trkB signaling in the clustering of GABAergic synapses (Xenos et al., 2018). Additionally, Zheng and colleagues found in the

hippocampus of mice lacking trkB in PV neurons a reduced inhibitory drive onto pyramidal neurons, as well as disrupted gamma oscillations (**Fig. 7b**). They further observed impaired spiking entrainment to the gamma LFP in PV interneurons (**Fig. 7c**) (Zheng et al., 2011). Reduced induced gamma oscillations were also found in *in vivo* recordings of the sensory cortex of transgenic mice, along with the increased firing of pyramidal neurons (Xenos et al., 2018). Collectively, these studies outline a critical role for BDNF-trkB signaling in PV interneurons for proper GABAergic control of the local circuit, reducing the reliability of pyramidal firing and leading to E/I imbalance. However, these physiological changes might be caused by global and developmental adaptations caused by the genetic deletion of trkB in PV neurons.

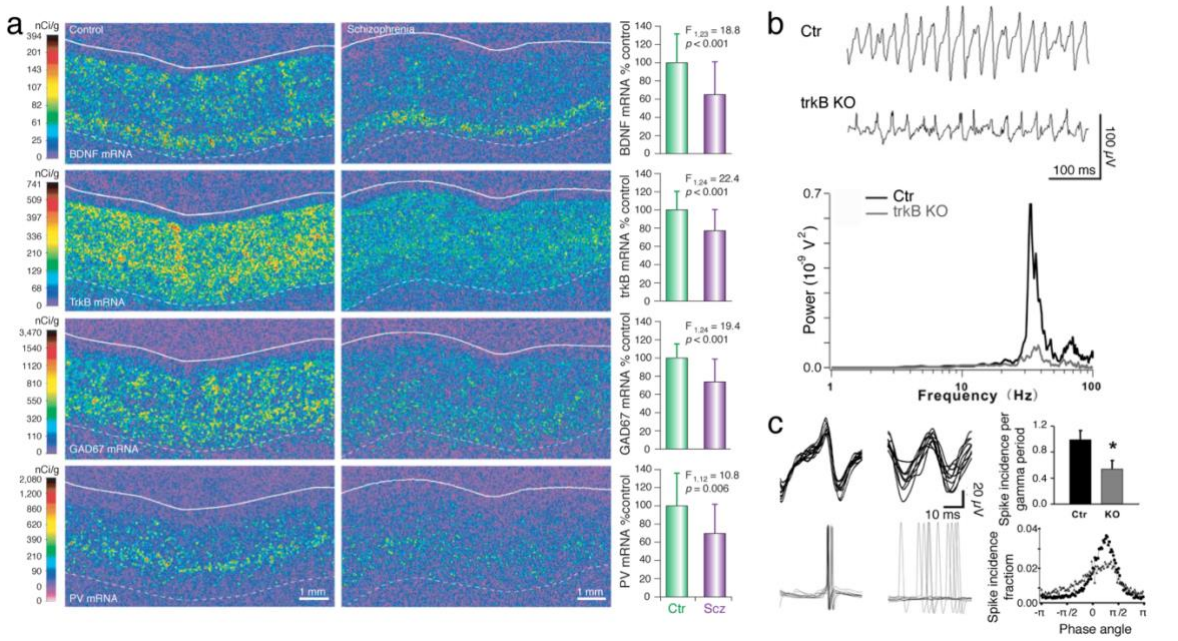

Figure 7 - BDNF-trkB signaling and PV interneurons. (a) Reduced BDNF, trkB and GAD67 and PV mRNA expression in the dorsolateral PFC of an individual with schizophrenia compared to a healthy control. Solid lines: pial surface. Broken lines: border between the grey and white matter. Right: Expression of each transcript in individuals with schizophrenia (Scz) and matched control subjects (Ctr). Mean ± SD. F: Fisher's F distribution. nCi/g: nanoCuries/gram. **(b)** Representative traces (up) of oscillations induced by carbachol. PSD (bottom) indicating a significant reduction in the peak amplitude at a frequency corresponding to the gamma-band (~40 Hz) in trkB knockout mice compared to control mice. **(c)** (left) Impaired firing phase distribution in PV interneurons in trkB knockout mice. (right) The average spike incidence per gamma cycle in trkB knockout mice was significantly reduced compared with control mice. *$p < 0.05$. The spike recorded in fast-spiking interneurons was wider in trkB knockout mice than in control mice. (a) was adapted with permission from Lewis et al. 2005 and (b, c) from Zheng et al. 2011, PNAS.

In terms of behavior, despite the extensive links with several brain disorders (Andero et al., 2014; Ninan, 2014; Qi et al., 2015), the role of trkB signaling in mPFC behavioral correlates are still poorly understood. For instance, unspecific deletion of trkB in corticolimbic GABAergic interneurons (affecting the cortex and hippocampus, but not the cerebellum) has been correlated with PV dysfunctions in the mPFC and social dominance abnormalities and aggressive behavior (Tan et al., 2018), but as these alterations are not cell and region-specific, they cannot pinpoint precisely the mechanisms behind the behavioral alterations.

Therefore, despite what we know of the role of BDNF-trkB signaling in neuronal development and synaptic function, the question of how trkB in PV interneurons might modulate and control pyramidal neurons excitatory and oscillatory activity has so far not been answered. Further studies are thus needed to determine how BDNF-trkB signaling impairments lead to functional changes in PV interneurons and disrupt excitation/inhibition balance that could lie at the core of both network and behavioral disorders.

1.7 REGULATION OF SOCIAL PROCESSING BY THE PREFRONTAL PV INTERNEURONS

Social behavior is a fundamental process across species that requires the integration of a wide variety of behaviors, including attention, reward-seeking, motivation, awareness of self and others, social hierarchy, agonistic behavior, and flexibility in adapting one's behavior to others in a group (Bicks et al., 2015; Yizhar and Levy, 2021). Changes in social behaviors, along with defects in decision making and the processing of emotion, were observed after the railroad worker Phineas Gage's skull was penetrated by a metal rod in 1849 (Damasio et al., 1994). Four decades later, Ferrier and Yeo found by surgically removing the prefrontal part of the brain of a baboon that he lost interest in other baboons and that his interactions with other baboons were changed (Ferrier and Yeo, 1884).

Since then, several brain regions like the hypothalamus or the ventral tegmental area (VTA), or neuropeptides like oxytocin, have been found to have a fundamental role in social interactions (Dölen et al., 2013), but the PFC remains one of the critical regions for social processing (Bicks et al., 2015; Wang et al., 2011; Yizhar and Levy, 2021). Indeed, it has been shown that the optogenetic manipulation of projection pathways linking regions like the amygdala or nucleus accumbens to the mPFC can modulate social behaviors (Felix-Ortiz et al., 2016; Murugan et al., 2017), highlighting the integrative and functional importance of the mPFC in these behaviors. However, manipulation of the projection from VTA to the nucleus accumbens was shown to sufficient to promote prosocial interactions, while optogenetic activation of the projection from VTA to mPFC had no effect on social interaction but was associated with anxiety-like effects (Gunaydin et al., 2014). Therefore, although the mPFC has been implicated in social behavior, understanding which neurons or pathways are relevant or how they contribute has been challenging, in part due to the complexity of the underlying circuitry.

At the local circuit level, synchronous oscillatory activity and correct E/I balance are thought to be a crucial mechanism for the role of mPFC in social behaviors (Cao et al., 2018; Liu et al., 2020; Selimbeyoglu et al., 2017; Wang et al., 2011; Yizhar et al., 2011). For example, potentiating or depressing AMPA receptor activity, leading to higher excitability, primarily in pyramidal neurons in the mPFC, was sufficient to modulate dominance behavior and hierarchy in a group of mice (Wang et al., 2011). The increase of E/I ratio in the rat mPFC was also linked with reduced social preference after the impairment of inputs from the mediodorsal thalamus to mPFC GABAergic neurons. However, the preference for social cues was recovered after pharmacogenetically increasing the activity of PV neurons, suggesting that proper PV interneurons activity in the rat PFC is required for social behavior (Ferguson and Gao, 2018b). Similarly, Bicks and colleagues found that juvenile social isolation caused alteration of mice prefrontal PV interneurons. They also observed that prefrontal PV interneurons were active

during social interaction and that manipulating their activity modulated social approach (Bicks et al., 2020). However, it is still not known whether the role of prefrontal PV interneurons in social behaviors is specific to the social domain or is due to their involvement in a range of cognitive processes dependent on the PFC, like attention, that are used during social behaviors. Besides, it is still unclear which functional or compensatory factors could induce PV dysfunction, circuit impairments and deficiencies in social processing. While some research has been carried out on how manipulating PV interneurons might impact mPFC activity, the mechanism by which it affects neuronal ensembles, coordinating communications with other cortical and subcortical regions involved in regulating different social functions, has not been established.

This section has attempted to provide a summary of the literature relating to the role of prefrontal PV interneurons in the formation and maintenance of local circuit activity, with an emphasis on the role played by NMDAR and trkB receptors. However, several questions remain, which both works in this thesis have tried to address. For example, research to date has not yet determined if and how increases in broadband gamma are fundamentally different from narrow-band increases in gamma power caused by rhythmic feedback inhibition by PV interneurons (e.g. in response to sensory stimulus). Also, the mechanism by which asynchronous neuronal activity caused by deficient PV inhibition could manifest as an increased power over a broad range of LFP frequencies (that includes the gamma-band), or affects cortical states, has not been established. Additionally, much regarding the role of BDNF-trkB signaling in the adult brain is unclear. Moreover, it has not been possible to conclusively pinpoint functional or behavioral alterations to cell and region-specific changes in BDNF-trkB signaling, notably in the PV interneurons of the mPFC.

2 RESEARCH AIMS

The general aim of this thesis is to understand the role of parvalbumin interneurons in shaping the neuronal network activity in the mouse prefrontal cortex. We are particularly interested in how receptors important for proper activity of parvalbumin interneurons lead to deficiency affecting various aspects, from molecular, circuit to behavior. More specifically, the aims are:

I - To understand if and how increased prefrontal broadband gamma power could be associated with neuronal activity with decreased synchronicity. For this reason, we aim to evaluate how the NMDAR hypofunction in PV neurons in the PFC leads to altered neuronal and oscillatory activity, notably affecting faster oscillations that include the gamma-band. Additionally, we aim to evaluate if the electrophysiological changes observed following the administration of NMDAR antagonists (such as ketamine) are consistent with oscillatory alterations observed in genetic models of NMDAR deficiency (PAPER I).

II - To understand how alterations in mature PV interneurons specifically in the PFC lead to circuit and behavior alterations. For this, we aim to investigate how the dysfunction of BDNF-trkB signaling affects PV interneuron activity and its role in the PFC circuitry in the adult brain (PAPER II).

3 MATERIALS AND METHODS

This section will briefly present and discuss the main techniques applied in both papers, as well as possible alternatives and novel approaches that are becoming more viable with further development. The research presented in Paper I used mainly electrophysiology recordings, while Paper II used cellular, physiological, and behavioral readouts for the functional dissection of the role of PV in the PFC. Please refer to the already well-described methods sections in both papers for further details. Lastly, I will succinctly discuss ethical considerations emanating from the use of animals, neuroscience tools, and publication practices.

3.1 SPECIFIC TARGETING AND MANIPULATION OF PV NEURONS

As it became possible to characterize populations of neurons that express specific molecular markers, such as PV protein, it became feasible to target specific classes of neurons genetically. This ability to experimentally be able to target PV neurons in a precise manner allowed a better understanding of the morphology and function of PV neurons (Cardin et al., 2009; Hu et al., 2014; Sohal et al., 2009).

3.1.1 Cre-lox system and transgenic animals

One of the main technologies used to perform selective genetic targeting of a defined neuronal population is the Cre-lox system. Cre recombinase is an enzyme that executes the recombination between two DNA recognition sites (called loxP sites). DNA sequences found between two loxP sites are said to be "floxed". Thus, placing loxP sites correctly around a specific gene allows its activation, deletion, or replacement with other genes. The Cre-lox system allows switching the orientation of DNA sequences as two loxP sites in opposite orientation to each other invert the intervening piece of DNA. It can also remove the DNA sequence as two loxP sites in direct orientation dictate excision of the intervening DNA between the sites leaving one loxP site behind. The fact that the activity of the Cre enzyme can be controlled so that it is expressed in a particular cell type allowed us to delete the NR1 subunit of the NMDAR or express the truncated version of trkB specifically in PV neurons. Targeted DNA changes are extremely useful to perform modifications that affect only specific cell types, as some knockout, such as NR1 or trkB, are lethal if expressed globally (Forrest et al., 1994; Luikart et al., 2003).

3.1.2 NR1 floxed transgenic line

In Paper I, we studied the role of NMDAR in PV neurons using a transgenic mouse line initially created and characterized in our research group (Carlén et al., 2012). PV-Cre/NR1f/f mice were obtained by crossing mice with Cre recombinase expression in PV neurons (PV-Cre mice) with mice carrying floxed alleles of the NR1 subunit (NR1f/f mice). This mouse line lacked the NMDAR subunit NR1 specifically in PV-expressing neurons. Since NR1 is the essential subunit for NMDAR, NR1 deletion results in loss of functional NMDARs (Forrest et al., 1994). Unlike mouse models of NMDAR hypofunction in all neurons, no severe developmental, anatomical (**Figs. 8a, b**) or behavioral abnormalities, except for selective cognitive impairments, were found in PV-Cre/NR1f/f mice. Nevertheless, loss of NMDAR currents in cortical PV interneurons was previously confirmed by ex-vivo recordings in PV-Cre/NR1f/f mice (**Fig. 8c**), leading to functional impairments at the circuit level (Carlén et al., 2012).

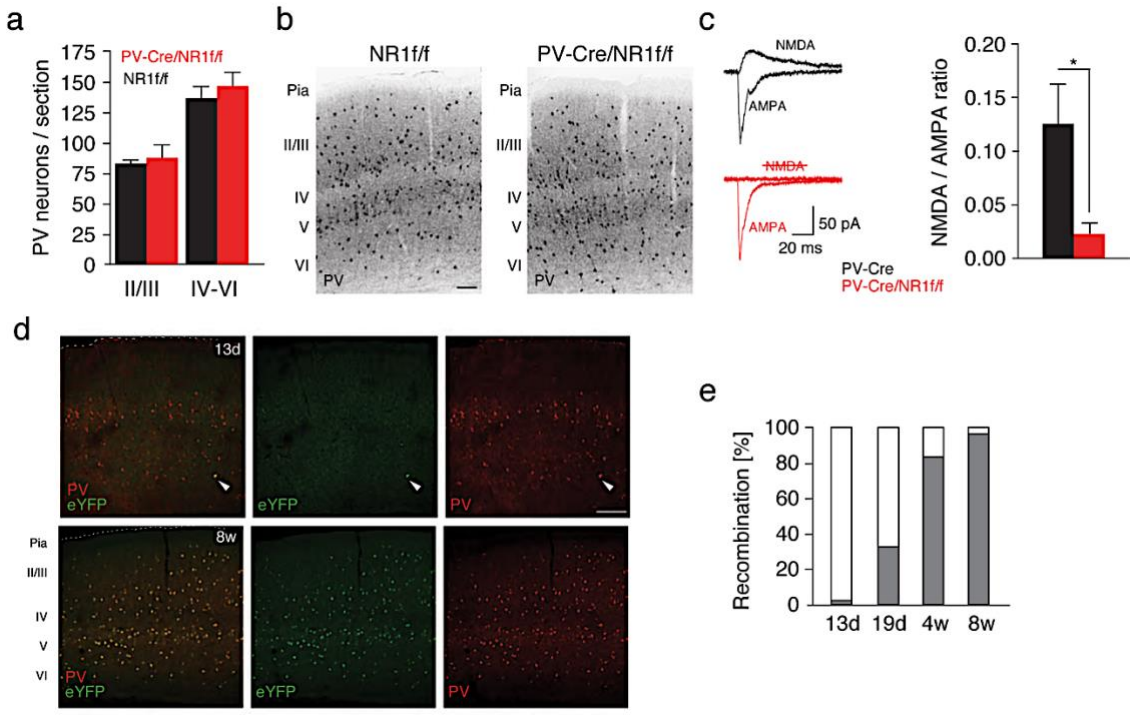

Figure 8 - Genetic ablation of NMDAR specifically in PV neurons. (a) Layer distribution of PV neurons in NR1f/f control and PV-Cre/NR1f/f mice at 11 weeks. **(b)** Immunohistochemistry for PV neurons in the somatosensory cortex shows similar distribution of PV neurons in an adult NR1f/f and PV-Cre/NR1f/f mouse. **(c)** Functional loss of NMDAR currents in PV neurons in PV-Cre/NR1f/f mice while the AMPA currents are preserved. (left) Sample EPSC traces mediated by the AMPAR (downward) and NMDAR (upward) from a control PV-Cre mouse and a PV-Cre/NR1f/f mouse. (right) NMDAR EPSC/AMPAR EPSC ratio in control PV-Cre and PV-Cre/NR1f/f mice. **(d)** Recombination in PV-Cre mice. At 13d, only scattered PV interneurons have recombined in somatosensory cortex (up; example pointed by white arrowhead), while near-complete recombination was observed at 8w (bottom). **(e)** Quantification of recombination from the PV locus in somatosensory cortex at different time points. * $p < 0.05$; error bars, mean ± S.E.M. Scale bars: (b,d) 200 µm. Adapted with permission from Carlén et al. 2012.

The PV-Cre-driven recombination was previously quantified and validated in PV-Cre mice crossed to the R26R-EYFP Cre reporter mouse line by counting PV neurons co-labeled with eYFP (Carlén et al., 2012). This showed that Cre-recombination happened postnatally and increased during development, attaining almost complete recombination at week 8 postnatal in the somatosensory cortex (**Figs. 8d, e**). From this, we can assume that PV-Cre-driven recombination of NR1 followed the same time course and that the circuit impairments seen in Paper I could have been due to increased NMDAR hypofunction during development. Furthermore, as we briefly discuss in Paper I, NMDAR hypofunction in PV-Cre/NR1f/f affects all PV neurons throughout the brain. The global knockout of NMDAR in PV neurons, therefore, affects PV neurons in several brain areas with significant anatomical and functional connections to the PFC, such as the basal forebrain, hippocampus or thalamus (Cohen et al., 2015; Kim et al., 2015) and thus could be behind the impairment seen in the PFC. Therefore, the chronic and global effect of the NMDAR hypofunction might make it challenging to pinpoint precisely when or in which area of the brain PV neuron dysfunction causes the impairments we observed in the PFC.

It is thus desirable to control both spatial and temporal aspects of transgene expression. This precision can be reached by using region-specific molecular markers for spatial specificity (Tan et al., 2018) or using techniques that regulate temporal expression of Cre recombinase, such as the activation of Cre recombinase fused to the estrogen receptor by the addition of tamoxifen. One of the approaches we decided to use to control the spatial and temporal aspects of our manipulation was to utilize a viral delivery method.

3.1.3 Viral delivery

The viral delivery of genetic material to the brain has been made possible by replacing part of viruses with an expression cassette containing the genes of interest. Placing the gene of interest between loxP sites and injecting the virus in transgenic animals with Cre recombinase expression in specific cell-types allows the precise expression of the gene of interest in a local and temporal manner (Heldt and Ressler, 2009). This has allowed the significant development of Cre-dependent viruses carrying modified receptors, opsins, and fluorescent markers. We used the Cre/loxP dependent viral vector strategy, via adeno-associated viruses (AAV), in both papers presented in this thesis. It is worth noticing that AAVs are known to have a low level of pathogenicity, having no association with diseases, but are still able to reach an effective level of transgene expression (Urban and Rossier, 2012). More specifically, our vectors had the sequence of interest flanked by two sets of incompatible lox sites, called double-floxed inverted open-reading-frame (DIO). In the presence of Cre recombinase, the open-reading-frame is inverted and can be expressed under the promoter present in the AAV, for instance, the elongation factor 1-alpha (EF1α) promoter.

In Paper I, we used an AAV vector with Cre-dependent expression of channelrhodopsin-2 (ChR2) fused to mCherry (AAV-DIO-ChR2-mCherry) to identify PV interneurons via light-activation (opto-tagging). The use of an AAV vector in Paper II allowed us to bypass the developmental and more long-term changes due to trkB signaling and offered us a chance to induce local manipulations in an adult brain. In both papers, we used the AAV-DIO-eYFP virus as control by simply expressing the fluorophore eYFP in PV interneurons.

3.1.4 Viral expression of trkB.DN-mCherry

We decided to express a truncated version of the trkB specifically in PV interneurons. This truncated receptor can compete with the normal receptor for BDNF, thus reducing BDNF-trkB signaling in these neurons. For this, we used a trkB.T1 plasmid in which the small intracellular part of the truncated receptor was replaced by the monomeric red fluorescent protein mCherry. This allowed the easy detection of neurons expressing this trkB construct. As such, our engineered receptor retains the capacity of sequestering BDNF as the standard trkB.T1, but its complete lack of intracellular part does not elicit the still relatively unknown trkB.T1 intracellular signaling cascades (Fenner, 2012). We chose to call our engineered receptor trkB.DN-mCherry, “DN” standing for dominant-negative, as a dominant-negative receptor is a receptor that is able to disrupt the activity of the wild-type receptor when overexpressed.

To deliver trkB.DN-mCherry in a temporally, spatially, and cell-type-specific controlled manner, we generated an AAV vector with Cre-dependent expression of trkB.DN-mCherry, AAV-DIO-trkB.DN-mCherry (full name AAV5-Ef1a-DIO-TrkB.DN-TM570-mCherry) (**Fig. 9**). By bilateral injection of 0.5 µl of AAV-DIO-trkB.DN-mCherry into the PFC of 2-month-

old mice, the conditional transduction of PV interneurons was spatially restricted to the PFC and allowed us to manipulate the BDNF-trkB signaling after normal development, and thus provide a more accurate assessment for its role in the mature brain.

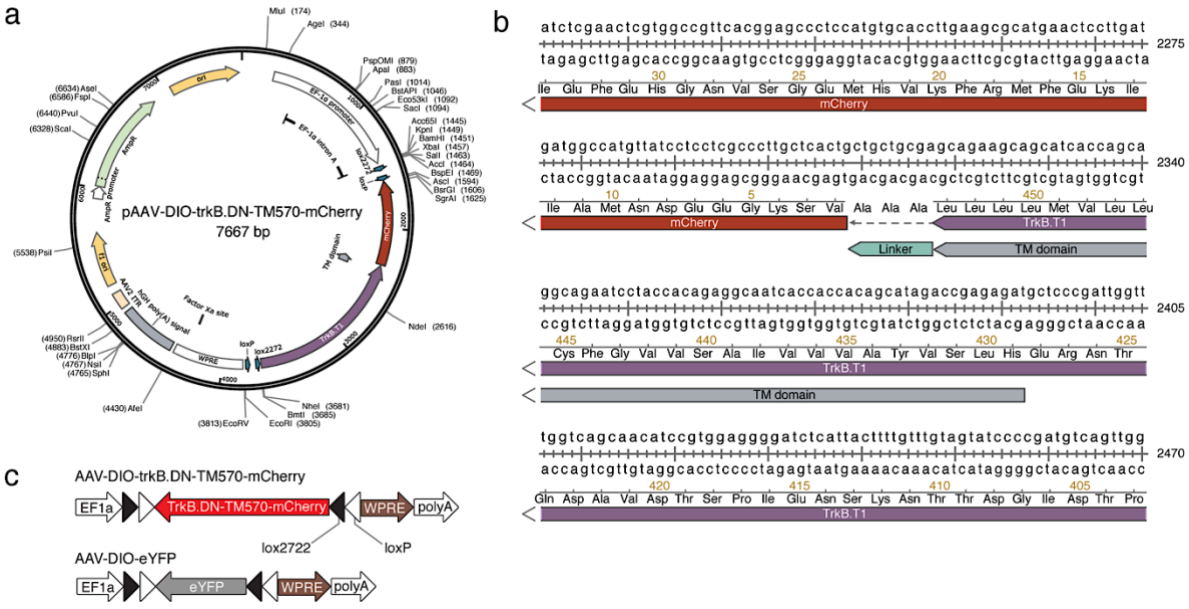

Figure 9 – Information about AAV-DIO-trkB.DN-mCherry and AAV-DIO-eYFP viruses (a) Full sequence map of the vector pAAV-DIO-trkB.DN-TM570-mCherry for Cre-inducible expression of trkB.DN-mCherry (Image created with SnapGene). **(b)** Highlight of the sequence part around the link of mCherry and the transmembrane domain (TM domain) of trkB.T1, forming the vector AAV-DIO-trkB.DN-mCherry. **(c)** The viral vectors used in Paper II. AAV-DIO-trkB.DN-TM570-mCherry: AAV vector with Cre-dependent expression of a truncated version of the trkB receptor fused to mCherry, AAV-DIO-eYFP (full name AAV5-Ef1a-DIO-eYFP): AAV vector with Cre-dependent expression of eYFP. L-ITR and R-ITR: Left and Right Inverted Terminal Repeat (ITR) sequences; EF1a: elongation factor 1a promoter; WPRE: Woodchuck hepatitis virus Posttranscriptional Regulatory Element.

Altogether, we successfully managed to manipulate two kinds of receptors expressed in PV neurons and study their aftermath on the function of those neurons. In the meantime, new methods have emerged and will make this kind of manipulation cheaper, less time-consuming, and able to deal with longer sequences of genes than AAVs. The development of viral (but also non-viral) delivery methods for technologies like the CRISPR-Cas9 system that can be intracranially injected and safely edit genes in any cell type in the brains of adult animals offers new possibilities to manipulate NMDAR or trkB in a spatial and time selective manner. For example, the focal knockout of mGluR5, a metabotropic NMDA receptor, in adult mice has been successful, reversing the behavioral phenotype in a fragile X mental retardation 1 KO mice (Sandoval et al., 2020).

3.2 MOLECULAR AND CELLULAR READOUTS

Genetic manipulation studies are widely used to grasp the mechanisms underlying complex behaviors and model molecular, cellular, and circuit alterations resulting from aberrant gene expression. Previous work suggests that increased expression of truncated trkB results in

decreased levels of trkB.FL (Haapasalo et al., 2002). Most previous works used Western blot to compare neurotrophic protein levels in transgenic mice versus control mice brain tissue. However, since transduced PV interneurons represented only 56% of PFC PV interneurons, we decided to examine if the expression of trkB.DN-mCherry altered the levels of endogenous trkB by using two immunohistochemistry steps instead. As trkB.DN-mCherry has an extracellular domain that is 100% homologous to the extracellular domain of trkB.FL (Fenner, 2012), but lacks the intracellular trkB domain, we used antibodies targeting the extracellular domain and intracellular domain of trkB receptors to compare their amounts in the soma of trkB.DN-mCherry or eYFP virus-transduced PV interneurons. This allowed us to obtain the corrected total cell fluorescence (Mean fluorescence of the area of interest minus mean fluorescence of the background), measured with the widely used open-source FIJI software (Schindelin et al., 2012), and calculate an intracellular/ extracellular ratio.

We further used immunostaining to examine if the expression of trkB.DN-mCherry led to changes in GABAergic proteins, as trkB is known to control the gene transcription of GABA-related proteins, as well as parvalbumin protein level, in cortical interneurons (Lewis et al., 2005; Sánchez-Huertas and Rico, 2011; Woo and Lu, 2006). Although we managed to get an overview of the alterations at the level of proteins, further quantification is needed to understand molecular changes better. The use of fluorescence-activated cell sorting (FACS) to sort PV interneurons based on the mCherry/eYFP fluorescence could be a viable alternative to compare protein levels with an enzyme-linked immunosorbent assay (known as ELISA) or quantify alterations at the mRNA level with snRNA-seq.

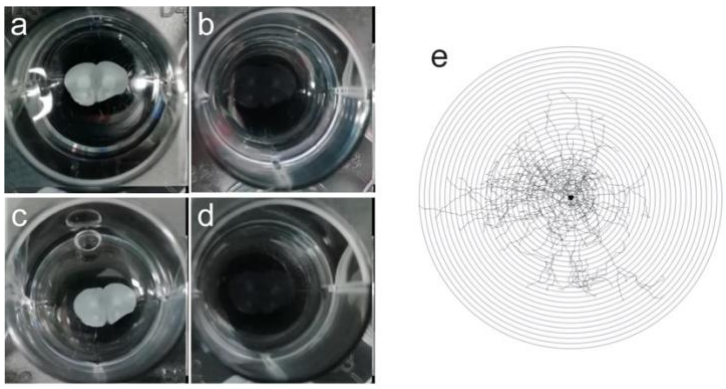

Figure 10 - Cubic and Sholl analysis. (a-d) Clearing of the brain slices. **(a)** coronal brain slice (40 µm thick) before clearing; **(b)** after incubation with CUBIC reagent 1 overnight; **(c)** after washing of brain slice before blocking; **(d)** after incubation with CUBIC reagent 2 overnight. Imaging is done with CUBIC reagent 2. **(e)** Sholl analysis. Digitally applied concentric rings spaced 10 µm apart are centered on the soma center, and the number of intersections between the neuronal process and ring at a given radius is counted. Estimates for morphological attributes of the neuron are then analyzed.

Additionally, we checked for potential morphological alteration in transduced PV interneurons in the mPFC, including dendritic and axonal arborization and the number of axonal inhibitory terminals. After filling patched PV interneurons with biocytin, we cleared 200 µm tick mPFC slices with CUBIC (**Figs. 10a-d**), an easy 2-steps histology tissue clearing method (Ariel, 2017; Susaki et al., 2014), and stained them for PV, mCherry or eYFP, and gephyrin, a marker specific to postsynaptic inhibitory synapses, before imaging them with a confocal microscope. This allowed us to perform Sholl analysis (counting of the number of neurite intersections that occur at fixed distances from the soma in concentric circles, see **Fig. 10e**) and quantify the number of axonal boutons (see method section of the Paper II, for a full description).

3.3 SOCIAL INTERACTION

In paper II, we submitted trkB.DN and control eYFP mice to a series of behavioral tests to evaluate any deficits in social interaction and anxiety behavior (**Fig.11**). For the latter, we subjected the mice to the open field test and the elevated plus-maze 70 days after viral injections. Mice used in behavioral experiments were single-housed prior to the social interaction essay. Another reason for single-housing mice was that the animals used for electrophysiology recording (n=10) were implanted with drives. It was thus necessary to compare the anxiety levels between trkB.DN and eYFP control mice.

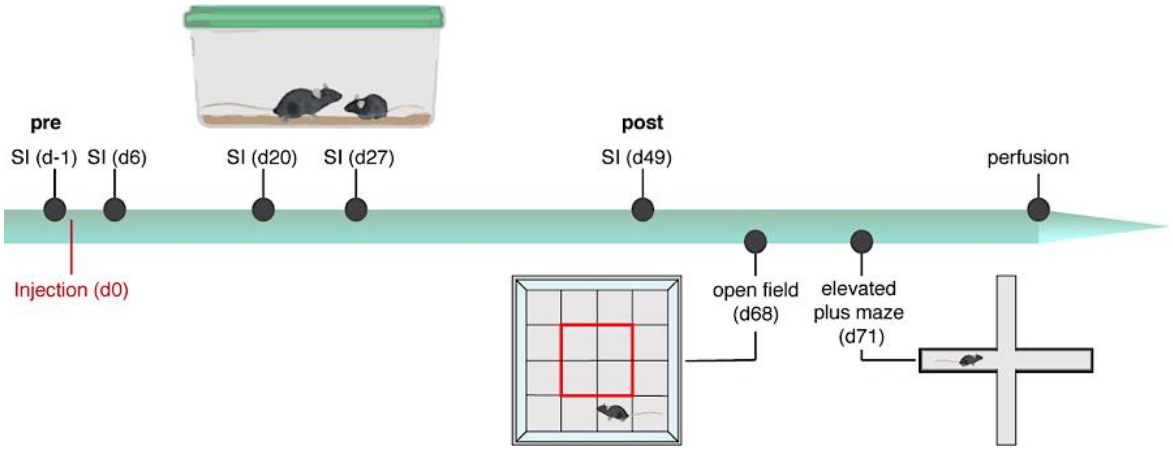

Figure 11 - Timeline of behavioral experiments. d: day; SI: Social interaction; pre and post: refer to the day before and the 49th day after the injection of eYFP or trkB-mCherry virus into the mPFC.

To test the social ability of trkB.DN mice, we decided to use a resident-intruder task, a well-validated test (Winslow, 2003) in which an intruder mouse is introduced into the home-cage of the tested mouse. To limit the aggressive behaviors, we used juvenile intruder mice, as they are not seen as threatening as adult mice (Winslow, 2003), and we selected only non-aggressive male mice by testing them one day before injecting the trkB.DN-mCherry or eYFP viruses. Further social tests like the dominance tube test are needed in the future to probe the causes of the higher aggression levels seen in trkB.DN mice. This will be useful to compare to cases of enhanced dominance levels seen in PV-trkB knockout mice (Tan et al., 2018). Moreover, the social recognition test that examines social short-term memory deficits, for example, could be used to understand if the aggressive phenotype is due to a recognition deficit (Winslow, 2003).

To measure in detail the behavior during the resident-intruder task, we used DeepLabCut (Mathis et al., 2018), an open-source software package for animal pose tracking that allowed us to follow our resident mouse around the cage and get its trajectory, as well as its mean velocity. DeepLabCut uses convolutional deep learning to track over time several points initially selected by the user on the animals. However, it does not automatically interpret the behavior associated with the location of the points. For this, we subsequently used a custom-made Matlab script that helped an experimenter blind to the treatment (eYFP or trkB.DN-mCherry) to manually score several social and non-social behaviors that happen during the resident-intruder task (**Fig. 12a**). Based on previous literature and the behavior observed during

the experiment, we chose to focus on exploration, digging, grooming, tail rattling, sniffing, and aggressive (attack, fighting as kicking, biting, and wrestling) behaviors (**Fig. 12b**). We used these categories to score the amount and percentage of time spent in each social and non-social behavior, as reported in Figure 5 of Paper II). This manual scoring was sufficient to allow behavioral comparisons between groups. However, the temporal resolution of manual annotation of behavior does not allow for optimum synchronization to recorded neural data from in vivo electrophysiological recording.

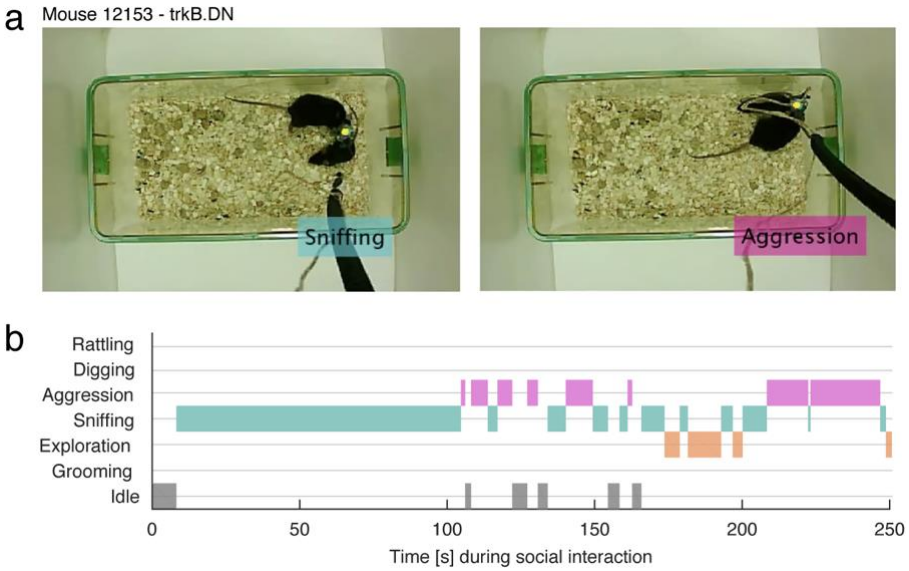

Figure 12 - Example of movement tracking and behavioral classification. **(a)** The trkB.DN mouse movement was tracked (yellow dots in videos) during the resident-intruder protocol while interacting with a C57 juvenile mouse. (**b)** Manual classification of behaviors over time.

Several new open-source tools are attempting to close the gap between tracking and behavior classification by inferring what actions animals perform by analyzing the output of an automated tracker. Besides, different new strategies are allowing the simultaneous tracking of multiple animals, using radio frequency identification (RFID) tags or multi-camera 3D systems (de Chaumont et al., 2019). The development and increased usage of these open-source software will hopefully allow growing a library of pose estimation and behavioral predictive classifiers for the easy categorizations of social behaviors in groups of several animals (Nilsson et al., 2020). These new tools will also allow us to monitor and describe the complex repertoire parts of behaviors in a more detailed way and hopefully be able to match them with neuronal activity (Datta et al., 2019).

3.4 RECORDING THE ACTIVITY OF THE PFC

3.4.1 *Ex vivo* electrophysiology

In paper II, we used whole-cell patch-clamp electrophysiology to investigate the electrophysiological effect of trkB-mCherry expression in PV interneurons. These experiments were done (by colleagues) on *ex vivo* brain tissue. Current-clamp electrophysiology allowed the recording of the activity of PV interneurons present in the mPFC at a highly temporal, electrical, and spatial resolution, giving us knowledge about the intrinsic properties of the PV interneurons and their firing patterns. We used voltage-clamp to record pyramidal neurons to

probe the level of excitatory and inhibitory activity in the local circuit. Furthermore, we performed paired-recording of connected PV and pyramidal neurons to examine if any synaptic connectivity alteration was caused by the expression of trkB.DN-mCherry.

3.4.2 *In vivo* electrophysiology

In Paper I, we recorded LFP and single-unit activity in the PFC (**Fig. 13a**) of urethane anesthetized mice. As we wanted to probe the relation between local PV interneurons and oscillatory activity, the use of urethane anesthesia was significant in two ways. First, the anesthesia setup allowed us to reduce any movement aspect of the neuronal activity, as movement-related activity can profoundly affect cortical states (Poulet and Crochet, 2019), while NMDAR antagonist induced locomotion has been found to affect gamma power (Hakami et al., 2009). Second, since urethane displays spontaneous fluctuations between a deactivated state, characterized by slow oscillations and an activated state, characterized by faster oscillations (>3Hz)(Clement et al., 2008), we used these transitions in cortical activity to probe the variation in PV neuron activity. Finally, we recorded neuronal activity for around two hours with a four-shank silicon probe with two tetrodes each (total eight tetrodes per probe; (**Fig. 13b**), harvesting around 30 well-defined units per mice after spike-clustering.

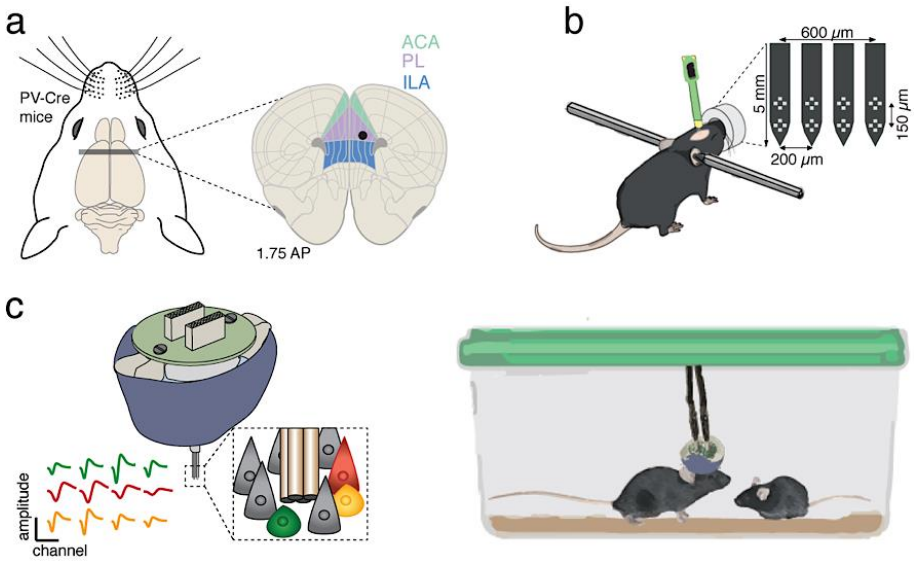

Figure 13 – *In vivo* electrophysiology setups. (a) Adult PV-Cre, trkB.DN, and PV-Cre/NR1f/f mice (>2 months old) were recorded with silicon probe or microdrive into the mPFC (dot: coordinates from Bregma: +1.75 mm antero-posterior, mediolateral: +0.30 mm, dorsoventral: -2.00 mm) **(b)** Sketch of the anesthetized recording setup with a four-shanks silicon probe with eight tetrodes (see magnified detail). **(c)** Illustration of the implanted microdrive (left) used to record the neuronal activity of the mPFC during social interaction (right). Each microdrive had seven tetrodes and one electromyography electrode to record movement. The bundling together of four small electrodes helps to assign extracellular action potentials into a probable cell, as the amplitude of the signal varies across the four channels due to the spatial distribution of the individual channels. Mouse head by Emmet Thompson (https://doi.org/10.5281/zenodo.3925943) in (a) and mouse (https://doi.org/10.5281/zenodo.3926027) by Ethan Tyler and Lex Kravitz in (b) were adapted from scidraw.io.

In Paper II, we recorded LFP and single-unit activity during behavior and under urethane anesthesia. For the freely moving recordings, we used a handmade drive with seven tetrodes and one electromyography recording electrode (**Fig. 13c**) based on the open-source FlexDrive (Voigts et al., 2013). For the urethane recordings, we used the same four-shank silicon probes as for Paper I (**Fig. 13b**). Both methods provided us with an adequate number of units recorded per animal (~10 units per mice during the social interaction and ~35 units per mice during the urethane recording), with a lower yield during the social interaction caused by the restricted time of the recording. PV interneurons usually represent a small fraction of recorded units (< 10%), and the number of putative PV units we recorded was not sufficient for proper comparison between animals or groups. We, therefore, focused analysis on pyramidal neurons. I will discuss alternative methods for recording neuronal activity in the perspectives chapter of this thesis.

Moreover, to elicit a change in neuronal activity within the mPFC circuitry and follow the response of the pyramidal neurons, we utilized the tail pinch protocol, which is a classic method using a short 7s pinch to the tail of the mouse to produce an arousal signal traveling from the reticular system to the cortex, including the mPFC (Carceller et al., 2020; Mantz et al., 1988; Massi et al., 2012).

3.4.3 Electrophysiology data analysis

In Paper I, we focused heavily on electrophysiology data analysis, and as such, we tried to describe the reasons for each analysis as much as possible. I will, therefore, only briefly present here some of the analyses we performed.

3.4.3.1 Power spectral density of LFP

As the LFP is an electric signal, a majority of tools applied for its analysis come from the field of signal-processing and electronic communication. One of the main tools is the use of Fourier transform to convert a signal from its original domain, like time, to a representation in the frequency domain. In our case, the LFP can be thus decomposed into several discrete temporal frequency components in hertz (gamma, delta, theta, etc.). The LFP is commonly visualized with power spectral density (PSD) plots. In short, we can use a power spectrum to describe the distribution of power of the LFP into its frequency components. This helps identify which frequency of the signal is the most dominant. For example, we can observe with a PSD which frequency of the LFP is increased by a task, like the typical narrow peak around 40 Hz when the power in the gamma oscillation is increased during cognitive tasks. There are several ways to estimate the PSD of a signal. Here we mostly use Welch's method. This approach, averaging the Fourier transform with some overlapping, reduces the noise in the estimated power spectra in exchange for reducing the frequency resolution. As we are primarily interested in frequencies from 0.5 to 150 Hz, Welch's method is thus an adequate method for comparing the LFP.

There has been a discussion over the interpretation of PSD, as diverse events can be displayed in a similar fashion on a PSD. For example, the increase of power in a particular frequency band of the PSD could result from the increased number of oscillations in that frequency but could also be due to a higher firing rate of local neurons (Manning et al., 2009). To understand the origin of the increased power in the PV-Cre/NR1f/f mice, we decided to use, along with the PSD, other analyses of the synchronous nature of the oscillation.

3.4.3.2 Cross-frequency coupling analyses

One of such analyses is the CFC analysis. In a nutshell, analysis of CFC focuses on the synchronous relationships between the amplitude, phase, and frequency of two rhythms from different frequency bands. There are several ways to measure different types of cross-frequency coupling. In the LFP, the amplitude of fast oscillations, typically 30–100 Hz, are routinely coupled to the phase of oscillatory activity at slower frequencies, most commonly at the theta or delta frequency. To see if the lack of NMDAR in PV neurons altered this coupling, we first used phase-amplitude comodulation maps (comodulograms), which allowed us to identify at which phase of the slower frequencies we could find the strongest high-frequency amplitude modulation by scanning multiple frequency pairs searching for cross-frequency coupling (Tort et al., 2010). For this, we calculated a modulation index, which is a measure of the intensity of the coupling. Therefore, if the mean amplitude of fast oscillation is uniformly distributed over the phases of slower oscillation (meaning lack of phase-amplitude coupling), we have MI = 0. On the other hand, an MI value of 1 would denote an oscillation that just exists in a single-phase bin and disappears at the other phases of the slower oscillation (Tort et al., 2010). Therefore, the low-frequency band (0.5-2 Hz) used for the MI analyses was identified by building phase-amplitude comodulation maps aimed to identify the strongest phase modulation of the broadband gamma and high-frequency band (HFB) amplitudes. The comodulation maps were constructed based on the calculation of the MI at phase frequencies from 0.5 Hz to 6 Hz (in steps of 1 Hz) and amplitude frequencies from 30 Hz to 150 Hz (in steps of 5 Hz). There are several discussions on the potential limitations of the different methodological toolbox that exist to analyze cross-frequency coupling (Aru et al., 2015). For example, as most only focus on one type of cross-frequency coupling (Phase-amplitude here, but also phase-phase or amplitude-amplitude), it has been argued that the choice of method restricts the type of cross-frequency coupling detectable in data (Nadalin et al., 2019; Tort et al., 2010). In our case, we found the MI to be suitable to show that synchrony was modified in PV-Cre/NR1f/f or after ketamine application in PV-Cre controls.

3.4.3.3 Spectral entropy and high-frequency index

We used two measures to quantify and qualify the level of frequency dispersion (and consequently the level of synchronization in the neuronal activity) in the PSD. First, we performed an analysis of the spectral entropy (based on Shannon entropy) of the LFP (30-150Hz), where a narrower power distribution results in lower entropy values, while a large power distribution, as in the case of broadband activity, results in higher entropy values. Secondly, we calculated a high-frequency index (the power ratio between the 200-300 Hz and the 30-150 Hz band - the latter including the aberrant bands in PV-Cre/NR1f/f mice) to quantify the contribution of spectral leakage caused by increased spiking activity to the LFP power in the 30-150 Hz frequency band. We focused on 200-300 Hz to avoid the typical multi-unit activity frequency band (>300 Hz) and to as far as possible exclude frequencies possibly reflecting true oscillations (<200 Hz) (Menendez de la Prida et al., 2015). The 200-300 Hz band is considered to reflect noisy activity typical of spectral leakage (Ray and Maunsell, 2011; Scheffer-Teixeira et al., 2013), and we, therefore, focused on this band. These measures were adapted from methods previously used to define events with epileptic signals from control LFP (Valero et al., 2017) and allowed us to separate events with asynchronous signals from more synchronous events.

3.4.3.4 Single-unit activity analyses

For single-unit activity, after spike sorting and cell classification (well described in both papers), we predominantly focused our analysis on the mean firing rate (in spike/s or z-scored against its baseline activity) of individual neurons and of populations of neurons. This allowed us to straightforwardly quantify changes in activity during UP and DOWN states in Paper I or after social interaction or tail pinch stimuli in Paper II. However, the relatively low single-unit yield did not allow us to analyze single-unit data for the PV neuron population in Paper II, which might in the future warrant the use of recently developed probes that can record up to 400 units (see perspectives).

Moreover, the mean firing rate is only one of the many factors defining the activity pattern of a neuronal population. With this in mind, in Paper II, we used neural trajectories to analyze the activity dynamics of wide spiking neurons recorded during social interaction as well as during the tail pinch experiment. In general, to understand the dynamics of a neuronal population, it is important to measure how the pattern of many different neuronal activity variables evolves over time. However, this neuronal activity data is high-dimensional, can be variable with patterns evolving along time, and can be organized at multiple temporal and spatial scales, making it difficult to be visualized. To better picture the neuronal population dynamics, we thus reduced its complexity by using a principal component analysis (PCA). This dimensionality reduction allowed us to take the single-unit activity dataset, which is assumed to be made of many variables and collapses its highly complex number of variables into a lower-dimensional space where these are more easily visualized. Given a set of data about single-unit activity features, the PCA can distinguish an ordered set of principal components (PCs), each of which forms a different "axis" representing progressively less variance present in the data (Datta et al., 2019; Pang et al., 2016). Therefore, this trimmed version of the dataset can serve as a useful lower-dimensional approximation of the original data and allows the analysis of the dynamic of complex datasets by following fewer variables. In our case, we chose to restrict to the two principal components, PC1 and PC2, which explained the variability of the dataset the most. Furthermore, to consider the evolution of the neuronal dynamic alongside the social interaction or the tail pinch, we plotted the evolution of the PC1 and PC2 along time. These neuronal trajectories allowed us to visualize the change in the dynamics of the neuronal activity along the experimental timeline (Pessoa, 2019).

3.4.3.5 Considerations on neurophysiology data analyses

Finally, I will end this section on electrophysiology data by shortly considering some opportunities to improve data sharing. In our two projects, we mainly relied on homemade scripts to analyze our data. This is beneficial, as we tailored our analysis to the format of our data and did not have to rely on expensive and somewhat limited software. However, it is difficult and time-consuming, and added efforts are needed to make the scripts available for anyone to use. Furthermore, the lack of a standardized system to collect and share the vast amount of produced data among researchers, as well as the lack of a standard data format, makes comparison across laboratories and replication of experiments difficult. As the electrophysiology data collected becomes larger and more complex, its analysis relies more and more on heavy computational methods. There is, therefore, a necessity for an improvement in data analysis standards to not only allow collaborations around easily shareable datasets, but

also to allow the development of open-source hardware and analysis software for neurophysiology data. Several open-source and collaborative projects have been set up, and we used several in our analysis, but further efforts seem to be needed. One example is the development of a common data standard for neurophysiology called Neurodata Without Borders. It is designed to store neurophysiology data from diverse sources, including data from *ex vivo* and *in vivo* electrophysiology experiments, data from optical physiology experiments, as well as movement or eye tracking and stimulus data. As more labs join this movement to share data, the easier it will be to find ways to do so, but till then, it is still time-consuming and requires somewhat advanced coding skills, which adds quite a lot of strain on top of routine data analysis. Efforts should be made to incentivize such procedures by contributing special funding specifically for such initiatives, for example. Research institutes should also emphasize this, making sure they develop structures for data storage that allow such data to be uploaded, curated and shared, as well as employ software developers to help with such measures.

3.5 ETHICAL CONSIDERATIONS

For the purpose of the research carried out for this thesis, we used many techniques based on invasive approaches, recording both *in vitro* and *in vivo* neuronal activity in transgenic animals after modifying their brain activity with genetic engineering, optogenetics, and viral injection techniques. Our main aim is to understand the primary function of the prefrontal cortex in the integration and coordination of information being internally generated with that received from the external world. Consequently, we aim to identify potential cellular and molecular targets for novel therapies for neuropsychiatric disorders by studying how cellular changes lead to altered neuronal communication and distorted brain activity. We hope this will lead future research to identify better cellular and network targets for medical interventions in neuropsychiatric disorders. While there are serious ethical questions to consider regarding the use of animals to help answer these questions, we believe the benefits of such research outweigh the ethical issues that emerge when we use invasive techniques in animals. However, for this to hold good, we should ensure that the scientific research question and methods are as fitting as possible. This is not only important for the ethical management of animals but also for the proper scientific quality of results.

One of the ways we aimed to do so, in this case, was to apply the 3 R Principle (Reduction, Replacement, Refinement) by aiming to use the minimal number of animals possible to reach a conclusion; with adequate care before, during, and after any operation; and by analyzing the results obtained during the study as effectively as possible. Animal research at Karolinska Institutet is strictly regulated and comes under both Swedish and EU legislation on animal welfare. Additionally, taking courses on laboratory animals is necessary to be able to carry out animal experiments at Karolinska Institutet. Therefore, any experiment included in this thesis has been weighed against their impact on the animals and performed as thoughtfully as possible.

Another way to reduce the number of animal experiments is to avoid the unnecessary repetition of studies (while still keeping in mind that replication is fundamental) by sharing negative data, and by making material, methods, and data as transparent as possible via open-source and open-access initiatives. This open science aspect has been key to the elaboration of our two articles, as it was important to be able to share tools, data, and software between collaborators.

3.5.1 On the need to open sources

Money should not be a determining factor of the prospects of a project being published in a high-impact factor journal. But the development and use of new technologies do cost money, and therefore funding agencies and research institutes should make sure to finance the open-source sharing of such resources. Ensuring that technologies are cheap and easily usable anywhere in the world is one of the main steps for higher equity and diversity in science. Further, this allows one to be more transparent about the work and analysis, helping in the replication of the data harvested and thus contributing to cumulative science (Gleeson et al., 2017).

Examples of open-source tools not yet cited that we used in our projects include open-access repositories like Zenodo, where we uploaded supplementary data as well as code for data analysis. We used the Allen Mouse Brain Atlas to check their gene expression maps and register the location of our electrophysiology probes. We used several open-source tools for neuroscience experiments available at Open Ephys, like the FlexDrive, and now have started using the Neuropixel recording probes developed by the International Brain Laboratory. These initiatives promote open-source data acquisition, analysis, management, and sharing, allowing the implementation of cheaper experiments, easier replication of experiments and analysis across labs. Please refer to https://open-neuroscience.com/ for more open source projects related to neuroscience.

3.5.2 On the need to open access

The research in this thesis has been primarily funded by Swedish, Brazilian and European grants, of which most are originally financed by taxpayers. Moreover, Ph.D. students in Sweden have the status of state employee. This gave me enhanced responsibility to share and make available the results of our work to the public. To make results available to the greatest number of people, publishing in open-access is fundamental. Open-access allows any researcher or layman to read the results without having to pay a fee, thus not having to pay twice for the research they helped to fund. Our choice to publish with The Journal of Neuroscience meets these values, as it is a journal owned and published by the Society of Neuroscience and not a traditional for-profit publisher. Also, as a delayed open-access journal, The Journal of Neuroscience allows publication under “gold open access” for a fee, thereby allowing the choice to make an article freely available from its publication date. More importantly, all papers are made freely available after six months. Furthermore, the Journal of Neuroscience has adopted the Creative Commons Attribution 4.0 International (CC BY) license, responding positively to an initiative by a group of neuroscientists (of which I was part) (McKiernan et al., 2014), meaning that the copyrights are kept with the authors and that anybody can use the data for scientific purposes, provided that the original article is credited. This allows researchers to upload several versions (including an accepted, peer-reviewed version) of their manuscripts to a preprint repository like bioRxiv.

In addition, research funders like European Research Council (ERC) and Karolinska Institutet demand open access publishing. Researchers have to make their peer-reviewed publications openly and freely available by either publishing their article open access or by self-archiving their manuscript in an open archive within six months of publication. We thus followed

Karolinska Institutet's open-access mandate by self-archiving both articles presented in this thesis on the KI Open Archive (http://openarchive.ki.se/).

Finally, as science comes from shared resources and should be returned to society at large, we made efforts to disseminate our methods and results to the lay public by contributing to popular science articles with the help of science journalists. This should also lead to the sharing of ideas and hypotheses with scientists in other fields and help foster cross-disciplinary collaborations.

4 RESULTS AND DISCUSSION

This thesis set out to investigate the role of PV interneurons in the neuronal activity of the mPFC. Here I summarize the main results obtained in both papers and offer additional possible explanations of findings not included in the articles.

4.1 NMDAR ACTIVITY IN PV NEURONS AND ASYNCHRONOUS MPFC NEURONAL ACTIVITY

The goal of this study was to investigate if and how increased prefrontal broadband gamma power caused by PV dysfunction could be associated with asynchronous neuronal activity. For this, we used not only male and female mice lacking NMDAR activity specifically in PV neurons, but also local application of the NMDAR antagonist ketamine to model deficient PV inhibition. These approaches allowed us to understand better the impact of PV dysfunction due to NMDAR hypofunction on the PFC's neuronal circuit function and its link with brain oscillations, notably in the gamma-band and HFB.

Our postulate was based on previous works in which it was demonstrated that light stimulating PV interneurons specifically could generate narrow gamma oscillations at 40Hz (Cardin et al., 2009) and that lack of NMDAR activity in PV neurons led to altered gamma oscillations and cognitive deficits (Carlén et al., 2012). More specifically, these changes in the LFP included decreased narrow gamma power induced by optogenetic stimulation but also a baseline power increase in a broad range of frequencies that included the gamma-band.

We performed *in vivo* acute recordings of the mPFC of mice lacking the NMDAR subunit NR1 in PV neurons (PV-Cre/NR1f/f) and in control animals with intact NMDARs (PV-Cre) to examine how the lack of NMDARs in PV neurons affects the synchrony of the neuronal activity, from the cortical states to the relationship between LFPs and spikes. The mice were anesthetized with urethane and fixed in a stereotaxic frame to allow positioning in the mPFC of an optical fiber and a silicon probe. We recorded basal LFP and single-unit activity in the mPFC. We used the fact that, like during natural sleep, urethane-anesthetized oscillatory activity fluctuates between two main cortical states to investigate how PV dysfunction affects the different states of activity in the cortex and possible changes in the natural transition between low and high neuronal activity.

4.1.1 Altered cortical states

We found that the lack of NMDAR activity in PV neurons affected the dynamics of the cortical states. The differences between PV-Cre/NR1f/f mice and PV-Cre mice were specifically found in the deactivated states, with increased state frequency and shorter state duration in mice lacking NMDAR in PV neurons. As deactivated states can be further divided into DOWN and UP states, we found that the duration of the states was also affected, with more variable DOWN states and shorter UP state duration. As noted previously, the deactivated state is also known as the synchronized state (Harris and Thiele, 2011), as its UP and DOWN activity follows precise slow fluctuation patterns of around 100 milliseconds or more. Thus, it is interesting that the alterations we observed were primarily seen in this synchronous state, while we did not observe any changes in the asynchronous/activated state. We thus decided to look further into the deactivated state to investigate the causes of this loss of synchronous activity.

4.1.2 Asynchronous neuronal activity

We first confirmed that long-term deficiency of PV inhibition is a contributor to the abnormal broadband increase, as mice lacking NMDAR activity in PV neurons displayed increased power across a broad frequency band, including the broadband gamma-band (30-60Hz) and the HFB (100-150Hz), in the deactivated state compared to the PV-Cre mice. In PV-Cre/NR1f/f mice, this abnormal increased high-frequency power was apparent during DOWN states, usually defined by low high-frequency power. This result hinted that the LFP activity was not fluctuating in a standard periodic manner in these animals.

We next found that this increased broadband gamma was associated with reduced coupling between the phase of slow oscillation and the amplitude of fast oscillations (>30Hz). It was important to avoid the main confounds when analyzing phase-amplitude CFC (Aru et al., 2015). For this, we first checked the presence of oscillations by making sure that the PSD showed a clear peak in the frequency band defining the phase. We also verified that the power in the low-frequency band used for the phase (0.5-2 Hz) was not different between PV-Cre and PV-Cre/NR1f/f, as changes in power in the bandwidth used for the phase can affect measures of phase-amplitude CFC (Nadalin et al., 2019). Finally, it was also essential to select the bandwidth of both the phase and the amplitude by analyzing the comodulogram based on our data (here, we based it on the prominent bands in the PV-Cre mice comodulogram) and not by canonically fixing them based on the literature. This lower coordination between faster and slower oscillations of the LFP of PV-Cre/NR1f/f confirms that the neuronal activity is less synchronized, as per the continuous presence of increased gamma and HFB power during both UP and DOWN states.

We then decided to quantify and qualify the level of synchronization in the neuronal activity in the UP and DOWN events by analyzing the spectral entropy and the level of spectral leakage by spiking activity. We observed that the lack of NMDAR in PV neurons increased the presence of events with high spectral entropy/high HF index with increased 30-150 Hz power. These events were also positively correlated with higher firing rate and increased power in the gamma-band (30-60Hz) and the HFB. This finding suggests that events of lower synchrony are caused by a shift in spectral leakage due to a higher firing rate, as seen in Manning 2009, Ray & Maunsell 2011, and Scheffer-Teixeira et al., 2013. However, as discussed in Paper I, work in other species indicates that broadband high-frequency activity can also reflect increased voltage fluctuations subthreshold to neural firing (Leszczyński et al., 2020), so still consistent with an increased E/I ratio.

4.1.3 Disorganization of single-unit activity

As we observed asynchronous activity correlated with a higher firing rate, we next decided to investigate the single-unit activity during the transition between the UP and DOWN states. We found that the lack of NMDAR activity in PV neurons is accompanied by increased firing rates of pyramidal neurons during DOWN states, as well as significantly increased variability in the spike-timing of pyramidal neurons and significantly increased spike latency of PV interneurons. This disorganization of single-unit activity in PV-Cre/NR1f/f mice was further observed in the LFP-spike entrainment, as spiking activity was more broadly entrained, in particular by frequencies < 40 Hz, while control and previous results show that neuronal spiking is usually coupled with higher LFP frequencies (50-180Hz).

The observed increased PV spike latency and the increase in pyramidal neurons' firing rate during DOWN states are consistent with previous findings (**Fig. 5**; Carlén et al., 2012). It also supports the idea that the increased E/I ratio is related to the increased spontaneous broadband gamma power (Sohal and Rubenstein, 2019; Yizhar et al., 2011). Different mechanisms of NMDAR hypofunction in PV neurons have been proposed to be implicated in this increase in excitatory activity (Jadi et al., 2016). Both the decrease of postsynaptic NMDAR activity in PV neurons, resulting in a reduced PV excitability (Carlén et al., 2012), and the decrease in presynaptic NMDAR activity of PV neurons, reducing the inhibitory postsynaptic currents (IPSCs) and the strength of synaptic inhibition of PV to pyramidal neuron (Pafundo et al., 2018), could explain the increased spiking asynchrony associated with a decrease of power in low-frequency LFP oscillations and abnormal increase in high-frequency LFP oscillations.

4.1.4 Diverse asynchronies caused by ketamine application or by the removal of NMDAR from PV neurons

The second set of results showed that disparate mechanisms underlie the increased power of broadband gamma caused by genetic alteration of PV neurons and ketamine application. In mice with intact NMDAR activity in PV neurons, local ketamine application resulted in a desynchronized state, characterized by lower amplitude and higher frequencies of LFP oscillations, and reduced modulation of gamma amplitude by the 0.5- 2Hz phase. These results were similar to those obtained when recording PV-Cre/NR1f/f mice (without ketamine). But surprisingly, local application of ketamine failed to induce a state of increased broadband gamma power and to induce the increase of neuronal activity in PV-Cre/NR1f/f mice. Furthermore, ketamine application completely disorganized the CFC between the amplitude of the gamma-band and the phase of slow-oscillations in mice with intact NMDAR in PV neurons while not changing the CFC in PV-Cre/NR1f/f mice.

As previously mentioned in the literature review, many electrophysiological studies with NMDAR antagonists report alterations in LFP oscillations, but the effects on single-unit activity are still discussed (Fitzgerald and Watson, 2019). Several studies looking at NMDAR antagonists in the mPFC reported disparate effects on single-unit activity, with some studies reporting increased and more irregular firing (Homayoun and Moghaddam, 2007; Molina et al., 2014; Wood et al., 2012), while some did not report any increase in firing activity (Kiss et al., 2011). Here, we show that the single-unit firing activity of both putative pyramidal and PV interneurons in mice with intact NMDAR activity in PV neurons is modified by local application of ketamine. Ketamine prompted a desynchronized state, diminishing the presence of UP and DOWN activity and thus eliciting the single-unit firing to be more persistent **(Fig. 14)**. This was reflected in the observed increased firing rate of both putative pyramidal and PV neurons of the PV-Cre mice.

Additionally, while analysis of the entrainment of spikes to the LFP showed that ketamine application was able to shift the spiking entrainment to higher frequencies (>200Hz) in mice with intact NMDAR activity in PV neurons, no changes in the spike entrainment were observed after ketamine in mice lacking NMDAR activity in PV neurons. These results confirmed that NMDAR in PV interneurons are primordial for ketamine potentiation of single-unit activity, increasing their firing rate and potentially disconnecting the spike-discharge from ongoing oscillations. It also supports the view that the increased asynchronous activity elicited by

ketamine application might seem similar to the baseline asynchrony found in mice lacking NMDAR activity in PV neurons but relies on separate circuit mechanisms depending on PV neurons.

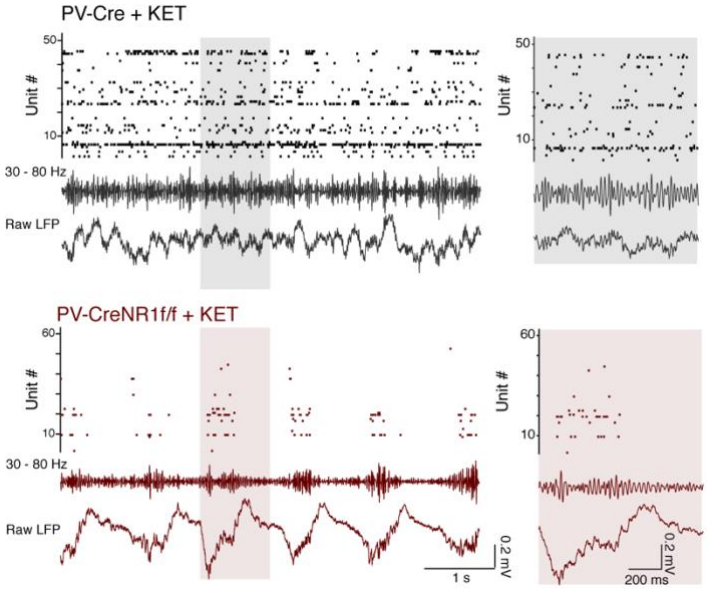

Figure 14 - Prefrontal single-unit activity after local application of ketamine. Representative (6 seconds) single-unit activity, filtered LFP in the 30-80 Hz band, and raw LFP traces for a PV-Cre (Up) and a PV-Cre/NR1f/f mouse (Bottom) after ketamine application. Right panel shows 1 second close-up of the activity highlighted on the left panel. Adapted with permission from Paper I – Guyon et al. 2021a

Furthermore, these LFP and single-unit changes were observed after we applied ketamine locally on the PFC. Kiss and colleagues reported that no changes in LFP were seen after local microinjection in the mPFC of the NMDAR antagonist MK-801, suggesting that the cortex is not the primary site of action of systemically administered NMDAR antagonists (Kiss et al., 2011). We cannot exonerate that the ketamine application affected other brain regions, mainly through their afferents in the mPFC, for example, inputs from the mediodorsal thalamus, hippocampus or nucleus accumbens (Jodo, 2013; Kulikova et al., 2012; Lee et al., 2017b). However, our results clearly show that local disruption of NMDAR by ketamine affects the PFC circuits.

The increased broadband gamma power seen in both cases (chronic NMDAR knockout and acute ketamine) are dependent on the proper activity of NMDAR in PV neurons, but in the case of the PV-Cre/NR1f/f, NMDAR activity has been chronically deficient, including during the development phase of the brain. This chronic effect must induce proper structural changes, not only on PV interneurons morphology and activity, but also on other local cells that need proper PV activity to develop. NMDAR levels have been shown to be influenced by activity and/or experience (Lee and Zhou, 2019). Thus, it will be interesting to manipulate NMDAR at different time points to separate the long-term and short-term NMDAR deficits effects on the mPFC circuit.

Together, the result from Paper I provide important insights into how PV dysfunction by modulating NMDAR affected the mPFC dynamics at different timescales, notably adding to the literature on the role of NMDAR hypofunction in PV neurons in neuronal activity (Nakazawa et al., 2017) the presence of impaired spike-LFP coupling and LFP phase-amplitude coupling.

4.2 BDNF-TRKB SIGNALING IN PV INTERNEURONS IN THE ADULT MPFC

Our second study aimed to further our understanding of the role of BDNF-trkB signaling in PV interneurons on the PFC circuitry dynamics, in the adult brain precisely. We focused on the role of trkB receptors in PV interneurons as trkB knockout, specifically in PV interneurons, leads to morphology, oscillatory and behavioral alterations. Specifically, we examined the effect of expressing a dominant-negative version of trkB, a truncated form of the trkB receptor that binds BDNF but does not trigger any intracellular signaling pathways, specifically in prefrontal PV interneurons. The hypothesis was that the expression of the DN receptor in the mPFC PV interneurons of mice would compete with full-length trkB receptors and impact the normal cellular functions of the PV interneurons. We postulated that the sustained expression of the DN receptor would change the inhibitory output of transduced PV interneurons, possibly leading to a change in the architecture and E/I balance of the local neuronal network, affecting how the PFC would process a different kind of inputs.

We first used single nuclei RNA sequencing (snRNAseq) to confirm that PV interneurons expressed trkB and did not express any BDNF, as reported by previous immunohistochemistry experiments (Gorba and Wahle, 1999; Huang et al., 1999). This result was important to choose how to manipulate BDNF-trkB signaling in PV interneurons precisely. Based on the snRNAseq and the several approaches previously reported to impair BDNF-trkB signaling in PV interneurons, we decided to target trkB activity by expressing a truncated version of trkB that would compete for the endogenous BDNF released by neighbor cells, including pyramidal neurons (Jiao et al., 2011). A reduction of the trkB.FL/trkB.T ratio has been shown to lead to circuits and functional alterations (Carim-Todd et al., 2009; Eide et al., 1996; Fenner, 2012; Heimel et al., 2010).

To alter BDNF-trkB signaling, we thus generated a virus that triggers the expression of trkB.DN. By injecting the AAV-DIO-trkB.DN-mCherry in adult mice (~2 months old), we avoided interfering with the BDNF-trkB signaling necessary for normal development of the brain, and could therefore study the effects of altered BDNF-trkB signaling specifically in PV interneurons in the adult PFC. The viral injections were specifically aimed at the PFC, targeting the PL and IL sub-areas, transducing 57% of PV interneurons in these areas. Furthermore, 96% of trkB.DN-mCherry neurons were positive for PV immunohistochemistry staining, showing that the expression of our virus is restricted to PV interneurons.

4.2.1 Molecular and morphological alterations

We first confirmed with immunohistochemistry that trkB.DN competed with the full-length trkB receptors in the transduced PV interneurons, as we found reduced expression of trkB.FL on their surface. We also checked how it affected proteins necessary for regular inhibitory activity of PV interneurons and found lower fluorescence intensity of GABA while levels of PV protein in the transduced neurons remained similar to the control neurons. The fact that PV levels were not lower contrasted with previous PV-trkB knockout studies (Xenos et al., 2018; Zheng et al., 2011), possibly because in our case, PV interneuron development was not impaired.

A possible explanation for the reduced levels of GABA in PV interneurons expressing trkB.DN-mCherry is the reduced transcription of the glutamic acid decarboxylase (GAD)

enzymes or GABA transporter-1 (GAT-1) that triggers a lower production or reuptake of GABA, respectively. Previous works indicate that BDNF-trkB signaling regulates the expression of GAD65, GAD67, and GAT1, via the trkB-dependent ERK-MAPK pathway (Lee et al., 2019; Porcher et al., 2018; Sánchez-Huertas and Rico, 2011). As GAD67 is responsible for more than 90% of the basal level of GABA production (Lee et al., 2019), the decreased transcription of GAD67 would be enough to cause reduced GABA levels. Furthermore, GATs are responsible for the reuptake of GABA, and the expression of GAT-1 on the cellular surface of interneurons is upregulated by the activation of trkB through ERK-MAPK (Lee et al., 2019; Porcher et al., 2018). Decreased BDNF-trkB signaling might thus hinder the replenishment of pools of GABA in interneurons. Our study was limited by the fact that we could not precisely quantify protein levels since the transduction efficiency of the virus was around 56.8% of PV interneurons. Using Western blot as an alternative to quantify protein levels would need to be associated with techniques like FACS to isolate only PV interneurons transduced with the AAV. Therefore, future quantification of these two proteins in trkB.DN-mCherry expressing PV interneurons will be needed to apprehend the mechanism behind the decreased GABA presence fully.

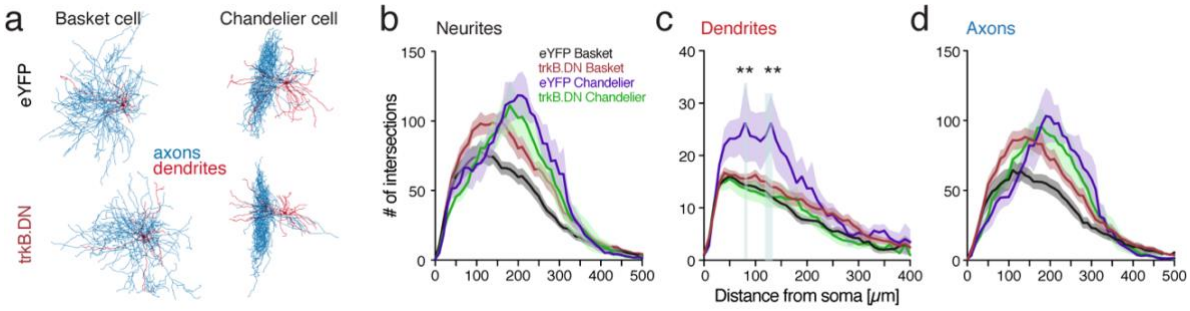

Figure 15 - Morphological difference between PV basket and chandelier neurons. (a) Representative reconstructions of biocytin-filled mPFC PV basket neurons and chandelier neurons, respectively, in eYFP mice (top) and trkB.DN mice (bottom) showing distinctive morphological features. Blue: axons, red: dendrites. **(b-d)** Sholl profile of basket (eYFP: n=14 neurons, 8 mice; trkB.DN: n = 13 neurons, 6 mice) and chandelier (eYFP: n= 7 neurons, 5 mice; trkB.DN: n= 4 neurons, 4 mice) PV interneurons. **(b)** All neurites, **(c)** dendrites and **(d)** axonal arbors. Dendrites from trkB.DN mice were significantly less complex than the dendrites from eYFP mice. Blue shading outlines the distances from the soma in which the mean number of intersections differs between trkB.DN-mCherry positive PV chandelier neurons and their eYFP control (gray). For distance bin 80 µm: t = 3.705, p = 0.015; For bins 120-130 µm: t = 4.211; p = 0.002. Significance was tested with multiple t-tests with the Holm-Sidak method.

We then found that reduced BDNF-trkB signaling in mPFC PV interneurons led to pronounced morphological alterations. The notable difference in morphology between the two main types of PV interneuron, basket neurons and chandelier neurons **(Fig. 15)**, made us focus solely on basket neurons, as the number of chandelier neurons patched was too low for proper comparison between trkB.DN and eYFP mice. Remarkably, using a Sholl analysis, we found that trkB.DN-mCherry expression in mPFC PV interneurons promoted increased neuronal morphological complexity, affecting both dendrites and axons length. The axonal complexity

was more pronounced in distances from the soma (100–200 mm). A distance where basket neurons are known to densely innervate local pyramidal neurons (Tremblay et al., 2016). The longer length of axons observed in trkB.DN mice affected the density of synaptic inhibitory boutons. The boutons were less dense in trkB.DN mice, but the total number of synaptic boutons per entire axon did not finally differ between the trkB.DN and eYFP mice. PV boutons were colocalized with the postsynaptic marker gephyrin, thus suggesting that they kept their ability to make proper connections with postsynaptic structures.

The longer axons and dendrites could be due to adaptations aiming to compensate for the decreased responsiveness in the PV interneurons. The total dendritic length of a PV interneuron can range from 4 to 9 mm, while the axons can measure up to 50 mm (usually around 24 mm in the PFC; see review by Hu, Gan, and Jonas 2014). Here, we observed that the mean length of dendrites (5.3 mm) and axons (34.3 mm) measured in trkB.DN were significantly higher than the controls (3.9 mm and 24.9 mm, respectively). However, the observed lengths in trkB.DN are situated within the upper limit of the standard length range, suggesting that these changes are not morphologically abnormal and still being homeostatically controlled (Samsonovich and Ascoli, 2006).

The morphology changes could also be due to the alteration of the trkB.FL/trkB.T ratio. BDNF-trkB signaling is engaged in regulating the neuron morphology, and the truncated receptor trkB.T1 concurs in the refinement of the growth or decrease of dendrites, axons, and synaptic structures (Ohira and Hayashi, 2009). The overlapping expression of multiple neurotrophic receptors and their ligands has been implicated in the growth and disintegration of axons (Deinhardt and Chao, 2014; Park and Poo, 2013) and in the participation of the formation and remodeling of cellular connectivity, a process that continues to be present in the adult brain (Bellon et al., 2011). For example, the mechanisms that BDNF uses to alternatively promote growth or pruning of axons depend on the various levels of trkB or p75 neurotrophin receptor (p75NTR) activation. BDNF engages p75NTR in the absence of trkB to facilitate axon pruning (Singh et al., 2008). The truncated receptor trkB.T1 is also involved, acting in this process by not letting BDNF activate neither trkB nor p75NTR (Baho et al., 2019; Michaelsen et al., 2010). Future studies looking at how the expression of trkB.DN affects the function of other proteins, like p75NTR, in PV interneurons would be necessary to understand further the mechanisms by which neurotrophins modulate axonal arborization in the adult brain.

Furthermore, modifying the trkB.FL-trkB.T ratio could be a way for the neurons to regulate from where they get their information. The increase in dendritic arbor length and complexity we observed fits with the role of the truncated trkBs regarding the extension of dendrites, as trkB signaling is known to enhance the growth and branching of dendrites (Deinhardt and Chao, 2014). In particular, previous research proposed that trkB.FL promotes the addition of short branches in dendrites proximal to the soma, whereas trkB.T1 induces the extension of dendrites in regions more distal to the soma (Yacoubian and Lo, 2000). As the trkB isoforms appear to act in a mutually inhibitory manner, this data suggests that expression of the correct set of trkB isoforms is needed for the normal development of dendrites (Bellon et al., 2011). Expressing trkB.DN-mCherry in PV interneurons might have blocked the normal signaling pathways necessary for the dendrites to adapt to their inputs. As a proper connectivity pattern is acquired by adjusting already existing connections based on inputs (Bellon et al., 2011), the incapacity to modify the neuronal structure in response to activity-dependent mechanisms by

fine-tuning the neurotrophic response could lead to aberrant network oscillatory activity and abnormal generalized response of the mPFC circuit to external cues.

4.2.2 Reduced sensitivity and firing activity of PV interneurons

As our long-term expression of trkB.DN-mCherry in mPFC PV interneurons led to molecular and morphological changes, we continued to investigate how these changes could affect the intrinsic properties of transduced PV interneurons and the local circuitry activity. Principally, we found reduced sensitivity of PV interneurons to excitatory inputs due to the significantly increased membrane time constant and increased firing rate adaptation. The reduced responsiveness of PV interneurons to fast frequency inputs, along with dendritic arbor morphology alterations, can conceivably affect local network oscillatory activities (Jadi et al., 2016; Otte et al., 2010; Wang, 2010).

The altered membrane properties of PV interneurons were concomitant with increased firing adaptation and reduced spontaneous firing of PV interneurons, indicating a deficient inhibitory activity of PV interneurons in the local network, as observed in the trending reduction in IPSC frequency in pyramidal neurons. However, altered basal synaptic transmission was not evident, as no effects of reduced BDNF-trkB signaling on the short-term synaptic plasticity between PV interneurons and connected pyramidal neurons were observed in the paired whole-cell recordings. Conversely, the removal of presynaptic trkB in neurons of the hippocampus has been shown to result in an increased paired-pulse ratio, indicating a reduced presynaptic release probability (Lin et al., 2018). Presynaptic and postsynaptic BDNF-trkB signaling in PV interneurons might thus be affected differently by the expression of trkB.DN-mCherry. Moreover, expression of trkB.DN-mCherry might trigger adaptations that preserve synaptic strength (Lin et al., 2018).

4.2.3 Social behavior dysfunctions

We found these functional and circuit changes to be associated with increased aggression and anxiety in behaving mice. TrkB.DN mice exhibited heightened aggression when tested in a resident-intruder test with juvenile mice compared to control mice. It has been proposed that impaired BDNF-trkB signaling in the prefrontal cortex plays an important role in aggression. Particularly, several works report that aggressive behavior is correlated with reduced trkB.FL/trkB.T ratio. For example, in the frontal cortex of aggressive rats, the level of the trkB.FL receptor protein was decreased, while trkB.T protein levels were increased, suggesting that a reduced trkB.FL/trkB.T ratio is prevalent in highly aggressive rats (Ilchibaeva et al., 2018). Furthermore, restoring proper BDNF-trkB signaling in BDNF knockout mice by decreasing the levels of trkB.T1 reduced aggressive behavior in the resident-intruder test (Carim-Todd et al., 2009). Another study showed that abnormal aggression in a Post-Weaning Social Isolation-Induced Aggression model is linked with lower BDNF, higher levels of trkB.T, and a decreased trkB.FL/trkB.T ratio. Treatment with the drug fluoxetine, an antidepressant of the selective serotonin reuptake inhibitor (SSRI) class, reduced trkB.T1 levels, restoring the trkB.FL/trkB.T ratio and diminishing aggression (Mikics et al., 2018). Moreover, a study using a conditional knockout mouse in which trkB (all isoforms) was ablated from a majority of corticolimbic GABAergic interneurons postnatally shows that mutant mice did not display enhanced aggression in the resident-intruder test. However, mutant mice were more dominant

and showed more aggression in another agonistic behavior test in which they analyzed the behavior of group-housed mice after switching to a novel context, concurrent with the idea that BDNF-trkB signaling impairment in inhibitory interneurons is linked with aggressive and dominant behaviors (Tan et al., 2018).

TrkB.DN mice displayed normal locomotion (no hyperactivity). However, we observed higher anxiety-related behaviors in trkB.DN mice, when compared to eYFP controls, relative to the number of entry and head-dips in the open arms of the elevated plus-maze test, and to time spent in the center in the first 3min of the open field test. As mice which were used in behavioral experiments were single-housed prior to the social interaction essay, this could have affected their anxiety levels and thus their BDNF-trkB activity, as prefrontal BDNF-trkB activity is stress-modulated (Barfield and Gourley, 2018; Gray et al., 2013), and the lower level of BDNF has been implicated in anxiety phenotype (Notaras and van den Buuse, 2020). Moreover, the mPFC is part of circuits that are known to be involved in social interaction and anxiety-related behaviors, as in the case of the reciprocal projections between the amygdala and the mPFC (Allsop et al., 2014; Felix-Ortiz et al., 2016). Further research should be undertaken to disentangle more specifically which components of these circuits influence both (or either) social and anxiety-related aspects of behavior, and therefore develop a complete picture of the links between affective and social cognition.

4.2.4 Altered prefrontal excitatory dynamics

To assess how the circuit impairments seen in *ex vivo* and *in vivo* acute recordings are linked to behavioral changes, we recorded LFP and single-unit activity in the mPFC in freely moving animals. We performed recordings during a nine-minute baseline period followed by four-minute of social interaction with a juvenile intruder. After the removal of the intruder mouse, we kept recording for ten more minutes. We focused on analyzing mPFC responses and circuit dynamics in relation to the start of social interaction. We found that reduced trkB signaling in mPFC PV interneurons affected the local oscillatory network activity. More specifically, mice with the expression of trkB.DN in mPFC PV interneurons showed a broadband increase of baseline LFP power and a reduced modulation of mPFC oscillations triggered by social interaction, compared to eYFP mice. This deficient induction of synchronous activities over a broad frequency band we observed in response to social stimuli is similar to the reduction in local network gamma oscillatory induced by a drug or visual stimuli reported in mouse models with genetic deletion of trkB in PV neurons (Xenos et al., 2018; Zheng et al., 2011). However, Xenos and colleagues also reported that the ablation of trkB in PV neurons during adolescence decreased spontaneous broadband power in a frequency range between 20 to 100 Hz, contrasting with our observation during baseline. This disparity might be due to distinct morphologic changes between the postnatal knock-out models and the sustained expression of trkB.DN in the adult.

Furthermore, the reduction of trkB signaling directly affected prefrontal population dynamics, with a significantly larger proportion of pyramidal neurons being positively modulated by social interaction in trkB.DN mice than in eYFP mice. Specifically, we found that the mean population firing rate of the mPFC pyramidal neurons was higher in trkB.DN than in eYFP mice during social interaction. We divided the pyramidal population into three subpopulations based on their firing during social interaction (yielding positively, negatively, and not

modulated neurons, respectively). The mean firing rates of the three subpopulations were not significantly different between trkB.DN and eYFP mice. However, the proportion of positively modulated pyramidal neurons was higher in trkB.DN mice than in eYFP mice. Thus, the increased mean firing rate of the (whole) pyramidal population in trkB.DN mice was not a result of increased spiking in individual pyramidal neurons but a result of more pyramidal neurons being recruited by social interaction in trkB.DN mice. The positively modulated pyramidal neurons were responsible for the higher variability in the population response to social interaction in trkB.DN mice, compared to the eYFP mice, as analyzed with neuronal trajectory plots.

Generalized neuronal ensemble activity, detected in the abnormal proportion of positively modulated pyramidal neurons, might be underlying social impairments. Indeed, the oscillatory and single-unit results are consistent with those of Liu and colleagues, who recently observed that social interaction increased the firing of prefrontal PV interneurons as well as increased LFP gamma (20 - 50 Hz) power. They also found that optogenetic synchronization of PV interneurons, specifically at gamma frequency, improved sociability. Besides, specific inhibition of mPFC PV interneurons with chemogenetics reduced gamma activity and impaired sociability. Equally important, they found that most pyramidal neurons did not respond (60%), while a small population showed increased (26%) or decreased (14%) firing rates during social interaction (Liu et al., 2020).

Additionally, to ensure that the observed differences in the Euclidean distance between trkB.DN and eYFP mice were not a mere result of their differences in the proportion of positively modulated neurons, we performed a bootstrapped version of the population trajectory analysis, where neurons from each of the three pyramidal subpopulations were randomly selected and analyzed in every 10000 repetitions. This analysis identified that the increased variability of the pyramidal population in trkB.DN mice was driven by altered dynamics in the positively modulated subpopulation specifically. As the increased firing of individual pyramidal neurons is not likely to underlie the increased Euclidean distance in trkB.DN mice, other patterns of activity detected by principal components are responsible for the variability in population dynamics.

Finally, we checked if the altered population-level dynamics observed in trkB.DN mice during social interaction were limited to this behavior or could be generalized to other functional states known to engage separate mPFC circuitry. For this, while recording in anesthetized mice, we used a tail pinch stimulation and found that the change in PFC activity patterns caused by a tail pinch induced similar abnormal modulation of pyramidal neurons and altered dynamics as seen during social interaction.

Surprisingly, similar pyramidal population dynamics were observed in both social interaction and tail pinch. A possible explanation for these results is that the sustained effect of trkB.DN-mCherry expression in PV interneurons may lead to changes in the organization of pre-established neuronal ensembles, usually differently activated by diverse stimuli. Thus, it can be suggested that this disorganization of neuronal activity reflects the recruitment of typically unresponsive neurons in the mPFC. For instance, morphological or functional adaptations leading to E/I imbalance might explain this disorganization (Sohal and Rubenstein, 2019; Turrigiano, 2011) by possibly reducing the inhibitory inputs of a portion of pyramidal neurons.

Moreover, the reduced firing rate of PV interneurons could increase the excitatory activity of pyramidal neurons to which they are still connected (Dehorter et al., 2017; Fujisawa et al., 2008; Hamm et al., 2017; Tremblay et al., 2016). Therefore, the association of these two occurrences could provide the pyramidal neurons with the possibility to increase the range of their excitation, and gather new neurons to previously assembled circuits through different long-term potentiation processes. The disorganization of neuronal activity in trkB.DN mice during the social interaction could thus lead to a behavioral response based on the misinterpretation of stimuli or the unspecific activation of aggression-related networks (Aleyasin et al., 2018).

Our PCA analyses revealed abnormalities in the population-level dynamics of the mPFC pyramidal neurons in trkB.DN mice. Curiously, the first two principal components explained only 23.4% and 14.0% of the variance seen in the eYFP mice during the social interaction experiment. This is a low percentage compared, for example, to the 75% for the first two PCs in Levy et al. 2019. This result could be explained by the heterogeneity of behaviors within the social interaction or inter-mouse variability within the same group. If we could have investigated the firing patterns separately during each behavior (Levy and colleagues used six discrete odors), we might have found a better percentage of variance explained by the principal components for the different behaviors. In contrast, in trkB.DN mice, the first two principal components explain more of the variance (42.8% and 11.3% of variance, respectively). That is, regardless of behavioral variability, the dynamics of these units seem to be more "uniform" (generalized to the different behaviors). If we had analyzed the behaviors individually, we might have observed that the recorded units in the eYFP mice describe one of the behaviors very well while not explaining others as well. However, in trkB.DN mice, the activity recorded during each behavior could be expected to have a similar percentage of explanation by the principal components. Further recordings during discrete social and non-social behaviors, as discussed briefly in the method section of this thesis, would be necessary to check this hypothesis.

However, in contrast with the complexity inherent to the social behavior, the tail pinch is (a priori) a unique variable, but the first two principal components in the eYFP mice still only explained a small percentage of the variance seen in the neuronal activity (25.2% and 19.2%, respectively), while PC1 and PC2 in the trkB.DN mice explained 68.4% and 8.6% of variance. One hypothesis is that, as PV interneurons activity is altered in trkB.DN mice, allowing the pyramidal neurons to become disorderly responsive to the tail pinch, the pyramidal activity goes on to explain more of the increased variability found in the neuronal patterns. On the other hand, the tail pinch has been shown to increase the firing rate of inhibitory interneurons but not the firing of pyramidal neurons in the mPFC (Massi et al., 2012). It can thus be suggested that if we had been able to observe the dynamics of PV interneurons in PV-Cre mice during the tail pinch, they would have been more tuned to the tail pinch than local pyramidal neurons. It will be required to analyze the dynamics of PV interneurons (see perspective) to evaluate their level of impairment and understand how they can organize local circuit activity in response to the tail pinch.

4.2.5 On potential sexual dimorphic differences

Additionally, BDNF-trkB signaling in PV interneurons might be influenced by sex-steroid hormones, exposing the existence of differences caused by sexual dimorphism (Lucas et al., 2014; Notaras and van den Buuse, 2020). Our study does not directly address this factor while using both females and males in most experiments. We nevertheless verified that sex was not a variable that could explain the differences between PV-Cre controls and trkB.DN mice in our morphological (**Fig. 16**), molecular and *ex vivo* electrophysiology recordings. As only males were used in behavioral and *in vivo* electrophysiological recordings experiments, further work would be necessary to precisely check the role of sex differences in the altered BDNF-trkB signaling effects in PV interneurons.

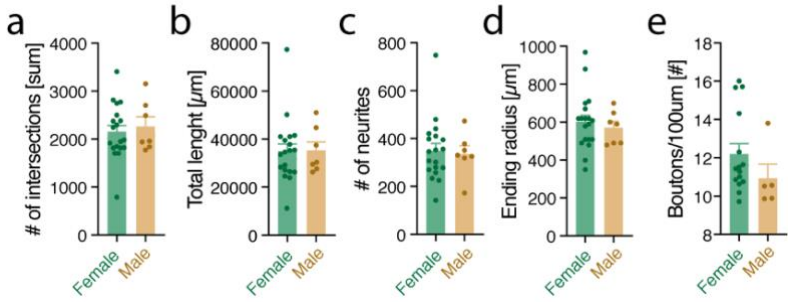

Figure 16 - Morphological comparison between female and male eYFP and trkB.DN mice. (a-d) Data based on Sholl analysis of the biocytin-filled mPFC PV basket neurons (Female mice: n = 19; male mice: n = 7). **(a)** No differences were detected in the total number of intersections of neurites of PV basket neurons from female mice and male mice. Female: 2155 ± 130.2; Male: 2268 ± 198.5; $U = 60$, $p = 0.7347$. **(b)** No differences were detected in the total neurite's length of PV basket neurons from female mice and male mice. Female: 35024 ± 3085; Male: 35381 ± 3582 µm; $U = 61$, $p = 0.7777$. **(c)** No differences were detected in the number of neurites of PV basket neurons from female mice and male mice. Female: 350.4 ± 29.51; Male: 336.3 ± 33.85; $U = 66$, $p = 0.9999$. **(d)** No differences were detected in the ending radius of the neurites of PV basket neurons from female mice and male mice. Female: 602.1 ± 34.10 µm; Male: 571.4 ± 32.91 µm; $U = 56.50$, $p = 0.5812$. **(e)** No differences were detected in the number of axonal boutons/100 µm in biocytin-filled mPFC PV basket neurons (Female mice: n = 15; Male mice: n = 5 neurons). Female: 12.21 ± 0.55; Male: 10.94 ± 0.73; $U = 17$, $p = 0.0806$. The Wilcoxon rank-sum test was used to assess significance.

Altogether, the mechanistic relationship between all the observed changes in PV interneuron physiology and alterations of network activity following PV-specific expression of a trkB dominant-negative receptor remains hard to explain. It will be essential to be able to reverse the effects of the trkB.DN on PV interneurons. The use of new tools like light-activated trkB receptors or pharmacogenetics targeting specifically trkB in PV interneurons will allow such spatially and cell-type restricted approach in reversing the abnormal phenotype (Kramer et al., 2013; Mondoloni et al., 2019; Winkel et al., 2020).

5 CONCLUSION AND PERSPECTIVES

This thesis examined the role of PV interneurons in the mPFC, with a focus on two receptors that are central for PV interneurons' connectivity, activity, and role in coordinating local circuit activity. The main goal was to investigate the causal links between molecular processes, circuit function, and behavior, and understand how these different levels are coordinated towards the proper functioning of the PFC. Thus, we used genetic and viral methods allowing for cell-type selective knockout of NMDARs, or cell- and time-specific expression of a truncated version of trkB, in order to disrupt PV function. We monitored the changes at the molecular, cellular, circuit and behavioral levels, and our experiments confirmed that deleting NMDAR, or manipulating the BDNF-trkB signaling pathway, specifically in PV neurons, is sufficient to trigger significant abnormalities in mPFC circuit function, as well as behavioral alterations. We also used this opportunity to understand better the physiological mechanisms by which mesoscopic signals like gamma-band (30-80 Hz) and HFB (100-150 Hz) are generated at the cellular level. Overall, the two studies presented in this thesis strengthen the idea that PV interneurons are critical for regulating and delimiting prefrontal responses to different classes of inputs.

5.1 PV DYSFUNCTION AND ASYNCHRONOUS ACTIVITY

One of the more significant findings to emerge from this thesis is that PV dysfunction contributes to asynchronous activity underlying enhanced broadband gamma power. The term "increased basal gamma oscillations" used in literature to define an increased broadband power in the gamma range (30-80Hz) is thus not the most appropriate way to describe this aberrant activity. Additionally, our results suggest that the aberrant increase in broadband power can originate from different sources, as distinct mechanisms are behind the altered inhibitory activity. The increase in baseline broadband power was observed in both models of PV dysfunction in a wide range of frequencies (30-150Hz in Paper I and > 6 Hz in Paper II), including the gamma-band (30-80Hz).

Thus, it will be important to dissect the origin of gamma alterations and asynchronous activities when observed in animal models or patients of neuropsychiatric disorders, as the circuit modifications leading to these changes might differ depending on their source. A limitation of the study presented in Paper II is that the NMDAR knockout might lead to developmental alterations that are not fully assessed. Therefore, we do not fully understand which specific alterations in PV interneurons lead to asynchronous activities. Particularly, it would be essential to figure out the link between modified intrinsic properties and genetic factors, receptors expression or morphological alterations, as well as dissect the potential compensatory mechanisms due to developmental alterations initiated by the genetic knockout of NMDAR. For instance, further research should be undertaken to explore how NMDAR hypofunction in PV neurons affects both the inputs and outputs of PV interneurons by quantifying the strength of their connections with target neurons, with paired patch-clamp recordings. Conversely, a future study could assess the effects of the sustained expression of trkB.DN in PV interneurons on the mPFC dynamics at different timescales, replicating the analysis used in Paper I to examine if these changes lead to similar asynchronous activity.

Additionally, our results show that NMDAR in PV interneurons are critical for the desynchronizing effect of ketamine in the mPFC, a region that is highly involved in psychiatric disorders such as schizophrenia and autism. However, the mechanisms between the two kinds of NMDAR hypofunction, caused by NMDAR antagonists or caused by genetic ablation of NMDAR, seemed to differ. This was highlighted by the lack of response to ketamine in PV-Cre/NR1f/f mice, as well as the difference in the entrainment of spikes to the LFP between the two approaches. These findings have significant implications for the understanding of the NMDAR hypofunction hypothesis of schizophrenia, as this hypothesis is based on observations that NMDAR antagonists induce, in normal human subjects, symptoms similar to those with schizophrenia (Krystal et al., 1994). Our results add more complexity to the heated debate around NMDAR dysregulation and the phenomenology of schizophrenia (Bianciardi and Uhlhaas, 2021; Gonzalez-Burgos and Lewis, 2012; Lee and Zhou, 2019; Lisman, 2012; Pafundo et al., 2018). It will thus be important to investigate the mechanisms that differ between the two kinds of NMDAR hypofunction so that we can pinpoint how the ensuing neuronal circuit dysfunction relates to the phenomenology of the disease.

Importantly, we demonstrated that multiple synchronous and asynchronous activities could co-exist within the neuronal activity, and thus, LFP or EEG activity in the gamma-band should not be read uniformly. This asynchronous neuronal activity can appear and mask true rhythms in the analysis of the power of specific oscillatory bands, for example, when the gamma-band is defined canonically. Thus, it is important to verify from the start the presence of synchronous oscillations and asynchronous activity (Donoghue et al., 2020). This can be done by detecting if the signal in a PSD plot presents meaningful peaks, as genuine oscillations are usually noticeable as narrowband power peaks above the aperiodic component of the signal.

It is also sensible to not idiosyncratically define specific bands prior to the analysis in order to calculate and compare the power of these specific bands. It is recommended to detect potential differences on the full spectrum of frequencies spanning from 1–200 Hz and then specify at which range of frequencies (in hertz) these differences correspond. Consequently, reporting differences this way would also allow better comparison between studies, as many use different frequency ranges to define the gamma-band, for example.

Moreover, recorded neural oscillations can show variations in their peak frequencies, depending on the brain region or brain state. It is important to consider such variations as many studies also limit their analysis to predefined bands and miss reporting potential changes that can happen just outside or across these bands. Description of the brain state in which one is analyzing LFP signal is thus essential, as brain states might modulate not only the peak frequency but also the overall signal-to-noise ratio. For example, inactive and possibly tired subjects may show very different modulation in LFP compared to subjects engaged in active tasks (Donoghue et al., 2020; Fitzgerald and Watson, 2018).

Our research has also shown that both NMDAR and trkB are critical for PV interneurons role in proper synchronous activity, confirming previous results linking PV interneurons firing and synchronous activity in the gamma range (30-80 Hz; Cardin et al. 2009; Sohal et al. 2009; Zheng et al. 2011; Carlén et al. 2012). Abnormal PV activity due to dysfunction of trkB led to impaired gamma rhythm induction after a social challenge, while specific dysfunction of NMDAR in PV neurons blocked the effects of ketamine on faster oscillations, including the

gamma-band. This supports the notion that dysfunction of PV interneurons is enough to generate neuronal activity changes, such as the reduced sensory-evoked gamma power observed in individuals with schizophrenia (White and Siegel, 2016). Further work is needed to fully understand the interactions of PV neurons with other cell types in the production of synchrony in the local circuit, as well as between areas.

Synchronous activities, principally at higher frequencies, are important for local PFC circuitry, but they are also involved in the coupling of cross-regional or cross-hemispheric activity (Adhikari et al., 2011; Cho et al., 2020; Fernandez et al., 2017). As such, the role of mPFC cannot be separated from the several cortical and subcortical regions from which it receives and to which it sends projections. It will be interesting to look at cross-frequency coupling between regions, including the PFC, thalamus, hippocampus and others, to see if synchronous activities between highly connected regions are modified in both PV-Cre/NR1f/f mice or trkB.DN mice.

Also, as locally recorded brain activity can reflect activity not only from the local circuit but also from more distant sources that overlap both spatially as well as temporally (Donoghue et al., 2021), it will be important to understand if the observed asynchrony, due to oscillatory activity alterations, is restricted to the mPFC. This could give us an insight into how local synchrony is. As discussed in Paper I, the ablation of NMDAR in PV neurons is global in PV-Cre/NR1f/f mice, and as such, the abnormal oscillatory activity we recorded in the mPFC might also be caused by PV neuron dysfunction in other regions like the thalamic reticular nucleus or the basal forebrain. Further research should be carried out to record activity in these regions simultaneously to pinpoint if asynchronous activities are purely instigated by local circuit alterations or more global ones.

5.2 PV DYSFUNCTION AND CORTICAL STATES IMPAIRMENTS

NMDAR hypofunction in PV neurons led to impaired coordination of cortical states, with notably more fragmented deactivated states. These results were obtained in urethane anesthesia, a useful model of sleep-like brain oscillations (Clement et al., 2008; Hauer et al., 2019). As such, the fragmentation of the deactivated state in Paper I parallels findings of fragmentation specific to NREM sleep, in mouse models of schizophrenia involving PV interneuron dysfunction (Phillips et al., 2012). The mPFC is one of the principal cortical regions that receives projections from the subcortical ascending system (including the reticular formation and basal forebrain) that promotes wakefulness (McKenna et al., 2017). Therefore, cortical state impairments in the PFC are proposed to indicate impairment of sleep regulation by the brain. Recording the activity of PV neurons in different regions involved in sleep/wake transitions, including the mPFC, during sleep will be of importance. Non-only to understand more closely the mechanisms linking PV interneurons with cortical state coordination, but also to understand the pathological mechanisms affecting sleep architecture, as sleep and circadian rhythm dysfunctions are comorbidities of neuropsychiatric disorders like schizophrenia (Chouinard et al., 2004). Additionally, these recordings during sleep should be done not only in PV-Cre/NR1f/f mice but also in trkB.DN mice as BDNF-trkB signaling has also been implicated in sleep dysfunctions (Garner et al., 2018; Watson et al., 2015).

5.3 PV DYSFUNCTION AND CIRCUIT ALTERATIONS

Many more questions that we could answer experimentally appeared during the elaboration of the work presented in Paper II. For instance, we observed significant morphological alterations in PV interneurons after the expression of trkB.DN-mCherry in these neurons. Notably, the dendritic branches were not only more complex but their radius was increased, thus covering a bigger receptive field. This is functionally important since the dendrite arbor determines what signals a neuron receives and how these signals are integrated. The local and distal connectivity disruption caused by either hypoconnected or hyperconnected neurons has been suggested to underlie neuropsychiatric disorders (Forrest et al., 2018). It is possible that the longer and more complex dendritic trees we observed increased the number of unspecific synaptic contacts and thus sampled excessive circuit inputs, leading to higher sensitivity to neuronal "noise". However, we did not evaluate further if dendritic alterations led to changes in dendritic spines in the PV interneurons. A further study with more focus on the dendritic arborization of PV interneurons is therefore suggested to gather the extent of dendritic modifications and investigate the possible link with impaired circuit activity in mPFC recorded via LFP after trkB.DN-mCherry expression.

Additionally, the extent of the possible alterations on other neurons due to PV dysfunction is still unknown. Further investigation is needed to pinpoint how alterations found in models of PV dysfunction lead to functional, and maybe morphological, changes in different cell types in the circuit. Remarkably, a recent work utilizing mice with NR1 subunit knockout in cortical and hippocampal GABAergic neurons showed reduced dendritic lengths in adult, but not juvenile, local pyramidal neurons in the mPFC (Pafundo et al., 2021). Pafundo and colleagues further propose that this impact on adult pyramidal neurons is observable only when the mPFC receives increased activity, e.g., when recruited for more cognitively demanding tasks. They further claim that this might be causing the altered computations underlying the behavioral deficits observed in animals with NMDAR hypofunction. Interestingly, these findings parallel our single-unit observation in Paper II, where the alterations in pyramidal neurons' single-unit and population dynamics in trkB.DN mice were surprisingly restricted to when inputs (from the social interaction or the tail pinch) supposedly arrived at the mPFC. No differences in firing rate were observed during the baseline between the trkB.DN and control mice. Therefore, future work should not only consider how specific changes in PV interneurons alter their function but also consider the effect on other pyramidal and GABAergic interneurons in the vicinity.

Another question raised by the results in Paper II is how local the changes are due to spatially restricted trkB.DN-mCherry expression in adult PV interneurons. Recording neuronal activity within the area transduced by the AAV virus and compare it with the activity outside this area might permit us to see if trkB.DN-mCherry expression in PV interneurons affects just the local circuit or also disrupts adjacent cortical circuits and regions receiving afferent input from mPFC. One suggestion would be to simultaneously record the several mPFC subdivisions using the Neuropixel 2.0 probe with four shanks (Jun et al., 2017; Steinmetz et al., 2021). The possibility to record from 384 sites distributed over four shanks could enable the recording of around 500 or more well-isolated units and LFP activity simultaneously over several areas and layers of the mPFC. This would allow us to compare alterations from recording sites inside the

virally transduced area versus areas outside by analyzing LFP traces patterns and spectral power distribution along probe track, or by possibly constructing current source density maps, as already done to explore differences between cortical layers (Senzai et al., 2019).

Furthermore, it will be essential to understand how the impairment of BDNF-trkB signaling specific to PV interneurons alters PV single-unit activity. This could be done by checking whether the PV interneurons actually have a decreased activity during a stimulus, or are temporally or spatially disorganized. The use of probes with a higher yield in units recorded would allow having enough neurons recorded to focus single-unit analysis on PV interneurons. The study published in Paper II was limited by the absence of single-unit activity analysis on PV interneurons due to the low number of recorded neurons of this cell-type. Consequently, we focused on the much more numerous pyramidal neurons. We thus observed the results of our manipulation in PV interneurons indirectly, following only the pyramidal neurons activity in response to social interaction or tail pinch. Therefore, to pinpoint how dysfunction of PV interneuron affect the architecture of neuronal ensembles, recording of enough PV interneurons would be necessary not only to perform firing rate and population dynamics analysis as we did with pyramidal neurons, but also analysis of cross-correlation between PV interneurons and neighboring neurons (Agetsuma et al., 2018; Senzai et al., 2019).

Moreover, the precise mechanism of how selective impairment of PV function in the mPFC alters behavior remains to be elucidated. We observed that the increase in pyramidal neurons firing activity in trkB.DN mice is generalized to several stimuli. It will be important to investigate how this generalization occurs. The use of fluorescence imaging to record *in vivo* calcium activity from neurons in the mPFC will permit us to observe spatially if the pyramidal neurons are activated nonspecifically over several stimuli (Agetsuma et al., 2018; Hamm et al., 2017). Fluorescence imaging allows precise spatial mapping of activity and the rapid improvement of genetically encoded calcium indicators like GCamp, voltage indicators (Knöpfel and Song, 2019), or neurotransmitter and neuromodulator sensors (Sabatini and Tian, 2020), offers a plethora of tools to reveal spatiotemporal dynamics that were till now difficult to record. For example, fluorescence microscope (miniscope) recordings while mice freely explored social targets showed that mPFC pyramidal neurons formed two non-overlapping populations with opposing neuronal activities (Liang et al., 2018). These distinct neuronal populations were tuned to different social targets, and the systemic administration of the NMDAR antagonist PCP disordered these mPFC neural ensembles. Recording with miniscope during the resident-intruder test and further post-hoc confirmation of which PV interneurons were trkB.DN-mCherry-positive would thus allow us to observe how neighboring cells are affected by altered PV activity and follow the activity of these neuronal ensembles during the diverse behaviors.

Additionally, there has been more attention on studying social behavior as synchronous cognitive processes between interacting individual subjects (Dumas et al., 2010; Kingsbury and Hong, 2020). Social interactions markedly influence individual neuronal activity and behaviors (Liang et al., 2018). Recently, correlated neuronal activity has been observed between the brains of socially interacting humans, but also mice or bats (Kingsbury et al., 2019; Zhang and Yartsev, 2019), with particular emphasis on synchronous oscillatory activities, including gamma oscillations (Kingsbury and Hong, 2020). Moreover, most results have been

focused on social dynamics between two mice, but there has been recent effort to study how the interaction between individuals affects large groups. Research questions that could be asked include if altered neuronal activity in one mouse can change the interactions between individuals, including within a group (Torquet et al., 2018). For instance, it would be interesting to understand how the observed altered oscillatory activities in the mPFC of trkB.DN mice might be reducing synchronization of neural processes across subjects, affecting both the resident as well as the intruder. New tracking and wireless recording technologies are allowing researchers to record the neuronal activity of two or more mice simultaneously and possibly manipulate the activity of one of them, as their interactions are tracked (de Chaumont et al., 2019; Kingsbury and Hong, 2020; Torquet et al., 2018), opening the door to exciting future research. Finally, these approaches could be applied to studies of NMDAR hypofunction — as NMDAR are also found to be implicated in social behavior (Gao and Mack, 2021) — or other mouse models of schizophrenia and autism spectrum disorders, paving the way for future investigations into the neuronal mechanisms underlying social behavior deficits.

5.4 MANIPULATION OF RECEPTORS TO STUDY PV FUNCTION

An issue that was not addressed in this study was whether it is possible to restore proper BDNF-trkB signaling in these neurons and see if we can rescue the morphological, functional and behavioral impairments. Future work should thus use pharmacological or genetic approaches, like the re-expression of NMDAR in NR1 knockout mice or light-control of photo-switchable trkB receptors (Lee and Zhou, 2019; Leopold et al., 2019; Mielnik et al., 2020; Winkel et al., 2020), to identify the mechanisms behind the abnormal phenotype observed after expression of trkB.DN-mCherry or hypofunction of NMDAR in PV interneurons.

Finally, another key point for future research will be to check how several receptors are linked and act together. We investigated in this thesis the function of only one receptor expressed by PV interneurons at a time. However, PV interneuron activity is modulated by several co-active receptors at the same time, including AMPA, p75, serotonergic, dopaminergic, or acetylcholine receptors, among others. Notably, crosstalk between BDNF-trkB signaling and NMDAR activity has been investigated (Björkholm and Monteggia, 2016; Minichiello, 2009; Ninan, 2014; Otis et al., 2014), and both receptors have been found to be the binding targets of drugs like ketamine. In recent work, activation of trkB was shown to be necessary for the antidepressant-related slow effect of ketamine (Casarotto et al., 2021), while NMDARs have been implicated in the rapid antidepressant effect of ketamine (Abdallah et al., 2015). Further research needs to examine the interactions between several co-receptors more closely by following and manipulating the function of these receptors simultaneously.

5.5 POTENCIAL CLINICAL RELEVANCE

The findings included in this thesis pertain to the basic neuroscience field but have several important implications for future practice. For instance, it is interesting to note that functional aspects of circuitry such as neuronal types and brain oscillations are evolutionary conserved. Despite changes in brain volume, the oscillatory patterns in the cortex, or synchronous activity recorded between different brain regions, are tightly preserved among mammals (Buzsáki and Watson, 2012; Buzsáki et al., 2013). Additionally, parvalbumin-like interneuron-types are conserved in reptiles and mammals (Hodge et al., 2019; Tosches et al., 2018), while trkB is

highly conserved among vertebrates (Benito-Gutiérrez et al., 2006). So, understanding the function of neuronal types and the circuitry in mice has the potential to be translated into other species and further help understand human brain function. As such, the knowledge of the mechanisms behind altered brain dynamics might provide promising ways to characterize neuropsychiatric disorders from the perspective of brain activity.

Furthermore, a better understanding of how to interpret the power of particular oscillations, as well as the synchronization of neuronal activity and the cross-frequency relationships between the various frequency ranges, may be a useful guide in developing approaches where we can use oscillations as biomarkers. It has also suggested that gamma power measurements can be used to track changes due to disorders but also changes elicited by drugs.

For instance, increased baseline broadband gamma has been observed in animal models and individuals with schizophrenia and autism spectrum disorders, and as such, may underlie some of the common features among these two neuropsychiatric disorders. The increased baseline LFP power might conceal different functional abnormalities seen in schizophrenia and autism spectrum disorders depending on which stage of development it emerges. As such, increased baseline broadband power emerging specifically in adults (post-adolescent) may lead to hallucinations or delusions as observed in subjects with schizophrenia by interfering with previously developed neuronal ensembles found in sensory and higher-order cognitive processing areas (White and Siegel, 2016). However, it has been suggested that changes in baseline broadband power happening postnatally would not interfere with already formed ensembles of neurons. Instead, it would lead to neuronal circuit compensations that might possibly evolve into functional impairments present in autism spectrum disorders. Therefore, manipulating the function of PV interneurons at different development stages will help understand the impaired mechanisms behind the increased baseline broadband activity.

This information can be used to develop targeted therapeutic interventions aimed at reversing the increase in baseline broadband power or elevate the reduced evoked/induced gamma power. Using neuropharmacological or noninvasive brain stimulation interventions like transcranial magnetic stimulation to manipulate specific circuits remotely might improve perceptual and cognitive processing (Nimpf and Keays, 2017).

Research on cell-specific, circuit-specific mechanisms will be crucial to advance the neuropsychiatry field and enhance our understanding of how disorders develop (Ford and Young, 2021). Studies using tools to directly or indirectly downregulate receptors functions or signaling pathways in a temporal and spatial controlled manner may help reveal how genetic and environmental factors lead to the dysfunction of specific neurons. Furthermore, spatially manipulating neurons will give important insight on where and when alterations in circuit activity occur during development, and how those changes lead to behavioral deficits. These findings will hopefully move psychiatry beyond nonspecific diagnoses, as well as adopt more targeted treatments **(Fig. 17)**, as unspecified brain-wide pharmacological drugs produce unwanted side effects on patients.

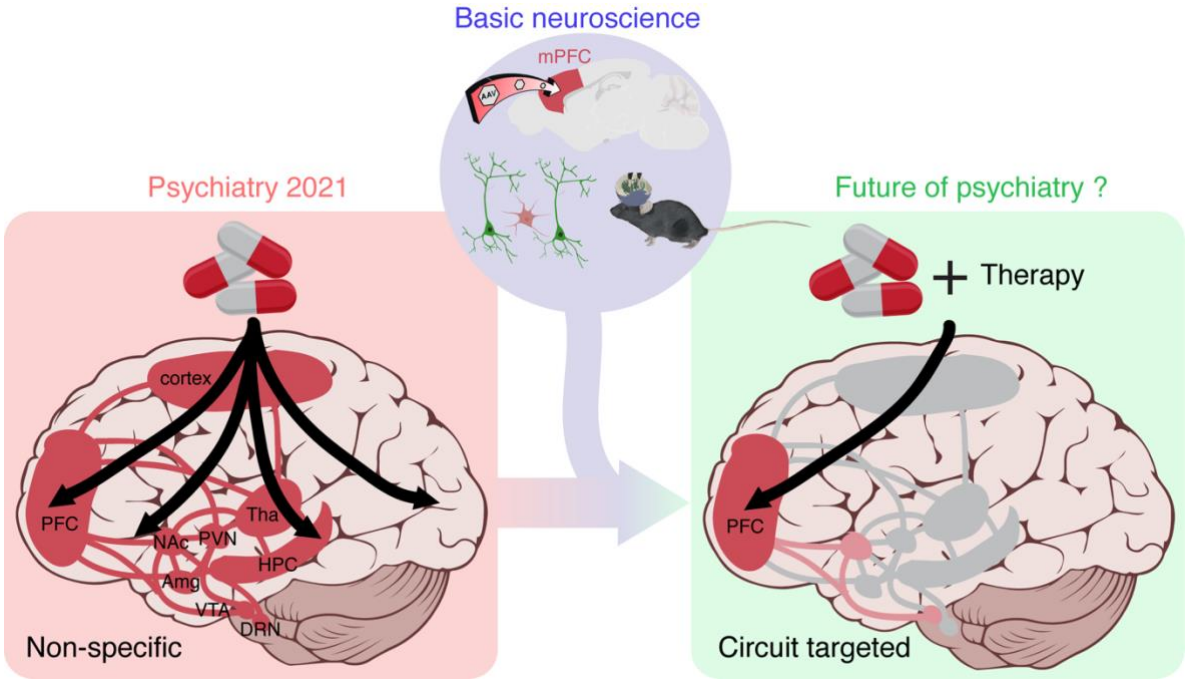

Figure 17 - Translational potential to apply circuit-level approaches into the diagnosis and treatment of neuropsychiatric disorders. Non-specific pharmacological drugs affect indiscriminately all brain regions, including pathways involved in social cognition: including the mPFC, rest of the cortex, amygdala (AMG), paraventricular nucleus of the hypothalamus (PVN), thalamus (Tha), nucleus accumbens (NAc), hippocampus (HPC), ventral tegmental area (VTA) and dorsal raphe nuclei (DRN). Applying knowledge from basic neuroscience has the potential to improve diagnosis, use biomarkers to uncover and monitor pathological alterations, and reduce side-effects by using cell and/or circuit-specific pharmacological drugs. Adapted with permission from Ford and Young, 2021. Human brains (doi.org/10.5281/zenodo.3925925) by Macauley Smith Breault, sagittal view of the mouse brain (doi.org/10.5281/zenodo.3925911) and pyramidal neuron (doi.org/10.5281/zenodo.3925905) by Federico Claudi, pill (doi.org/10.5281/zenodo.3926307) by Daniel Clough, as well as the interneuron (doi.org/10.5281/zenodo.3925929) were adapted from scidraw.io.

Finally, I am hopeful that our understanding of the biological processes that underlie brain functions will reduce stigma about brain disorders. This increased knowledge about why certain behaviors occur will lead not only to more evolved treatments, but also better societal adaptations and acceptance.

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