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Guiraud Laetitia

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Altered neuroplasticity processes in the hippocampus of the *Crtc1* knockout mouse model of major depressive disorder

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Faculté de biologie et de médecine
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par

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Prof. Nicole Déglon

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ABSTRACT

Currently, there are more than 163 million people suffering from major depressive disorder (MDD) worldwide, making it the third leading cause of burden of disease, with a lifetime prevalence of 16% (higher in women). MDD is both a genetic and environmental disease, and the alteration of several susceptibility genes results in dysfunctional mood regulation.

Neuroplasticity and cognitive functions are both altered in MDD. Chronic stress can lead to altered neuroplasticity, partly resulting from decreased function of the transcription factor CREB. It has notably been shown that the interaction of CREB-regulated transcription coactivator 1 (CRTC1) and CREB is critical in some neuroplasticity processes, like brain-derived neurotrophic factor (BDNF) expression regulation or maintenance of LTP in the hippocampus.

Our laboratory generated a *Crtc1*$^{-/-}$ mouse line, which exhibited behavioural and molecular features mirroring MDD. The males of this mouse model show aggressiveness, decreased interest in pleasurable activity, decreased social interactions, increased anxiety, and a blunted response to antidepressants. They also show a decreased BDNF expression along with a decrease turnover in dopamine and serotonin.

Using different viral tools and immunolabeling techniques, we show an altered morphology of the granule cells in the dentate gyrus of these mice as well as an abnormal density of dendritic spines. We also show a modification of the densities of cells connecting to these granule cells: the parvalbumine (PV) interneurons and the mossy cells.

Taken together, our data uncover a disruption in the plasticity processes combined with an excitation-inhibition imbalance in the dentate gyrus of the hippocampus that support the depressive-like phenotype of the *Crtc1*$^{-/-}$ mouse model.

RÉSUMÉ

Actuellement, plus de 163 millions de personnes souffrent de dépression majeure dans le monde, ce qui en fait la 3e maladie représentant un fardeau social, avec une prévalence de 16% au cours de la vie. La dépression est une maladie à composantes génétiques et environnementales, et l'altération de certains gènes dits de susceptibilité a pour conséquence une dérégulation de l'humeur.

La neuroplasticité et les fonctions cognitives sont altérées chez les patients dépressifs. Le stress chronique peut provoquer une altération de la plasticité qui aura comme conséquence, parmi d'autres, une diminution de la fonction du facteur de transcription CREB. Il a été montré que l'interaction de CRTC1 et CREB est critique pour certains processus de neuroplasticité, comme la régulation de l'expression de BDNF ou encore le maintien de la potentialisation à long terme dans l'hippocampe.

Notre laboratoire a généré une lignée de souris knock-out pour le gène *Crtc1*, qui présente des caractéristiques comportementales et moléculaires de la dépression. Les souris mâles de ce modèle sont agressives, ont moins d'intérêt pour des activités plaisantes, sont moins intéressées par les interactions sociales, sont plus anxieuses et réagissent inégalement à un traitement aux antidépresseurs. Ces souris montrent également une diminution de l'expression de BDNF avec une diminution du renouvellement de la dopamine et de la sérotonine.

En utilisant différents outils et techniques d'immuno-marquage, nous avons pu montrer une altération de la morphologie des neurones granulaires du gyrus denté avec une densité des épines dendritiques anormale. Nous avons également montré une modification de la densité des cellules connectées aux neurones granulaires : les interneurones à parvalbumine et les neurones « moussus ».

Dans l'ensemble, ces résultats montrent une perturbation des processus de plasticité combinée avec un déséquilibre de la balance excitation-inhibition dans le gyrus denté de l'hippocampe qui soutient le phénotype dépressif de notre modèle de souris *Crtc1*$^{-/-}$.

LIST OF ABBREVIATIONS

5-HT	Serotonin
AAV	Adeno-associated virus
ACTH	Adrenocorticotropic hormone
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AVP	Vasopressin
b-zip	Basic leucine zipper
BDNF	Brain-derived neurotrophic factor
BrdU	5-bromo-2'-deoxyuridine
BSA	Bovine serum albumine
CA1, 2 or 3	Cornu Ammonis 1, 2 or 3
Ca^{2+}	Calcium
CaM	Calmoduline
cAMP	Cyclic adenosine monophosphate
CaMK	Ca^{2+}/CaM-dependent kinase
CBP	CREB binding protein
CMV	Cytomegalovirus
CRE	cAMP response element
CREB	cAMP response element-binding protein
CRH	Adrenocorticotropic hormone-releasing factor
CRS	Chronic restraint stress
CRTC	CREB-regulated transcription coactivator
CSDS	Chronic social defeat stress
DA	Dopamine
DBS	Deep brain stimulation
dCA	Dorsal cornu ammonis
dDG	Dorsal dentate gyrus
DG	Dentate gyrus
DNA	Deoxyribonucleic acid
DSM-V	Diagnostic and Statistical Manual of mental disorders fifth edition
ECT	Electroconvulsive therapy
FGF	Fibroblast growth factor
G-CSF	Granulocyte colony-stimulating factor

GABA	Gamma-aminobutyric acid
GCL	Granular Cell layer
GFP	Green fluorescent protein
GluR2/3	AMPA receptor subunits 2 and 3
GTPases	Guanosine triphosphate hydrolase
GWAS	Genome-wide association studies
HDAC	Histone deacetylase
HPA	Hypothalamic-pituitary-adrenal
HPC	Hippocampus
IPC	Intermediate progenitor cell
IGF-1	Insulin-like growth factor
JNK	c-Jun amino terminal kinase
KO	Knock-out
L-LTP	Late phase long-term potentiation
LTP	Long-term potentiation
MDD	Major depressive disorders
MAO	Monoamine oxidase
MAOIs	Monoamine oxidase inhibitors
MAPK	Mitogen-activated protein kinase
ML1, 2 or 3	Molecular layer 1, 2 or 3
MMLV	Moloney murine leukemia virus
mPFC	medial prefrontal cortex
mRNA	messenger ribonucleic acid
mTOR	Mammalian target of rapamycin
NAc	Nucleus accumbens
NDRI	Norepinephrine-dopamine reuptake inhibitor
NE	Norepinephrine
NF-kB	Nuclear factor kappa B
NGS	Normal goat serum
NIH	Novelty induced hypophagia
NMDA	N-methyl-D-aspartic acid
NMDAR	N-methyl-D-aspartic acid receptor
NPC	Neuronal precursor cells
OSFST	Open-space forced-swim test
p75NTR	p75 neurotrophin receptor

PBS	Phosphate buffer saline
PCR	Polymerase chain reaction
PFC	Prefrontal cortex
PI3K	Phosphatidylinositol 3-kinase
PKA or C	Protein kinase A or C
PLC	Phospholipase C-γ
PS	Presenilin
PV	Parvalbumin
PVN	Paraventricular nucleus
RFP	Red fluorescent protein
RGLs	Type 1 radial glia-like cells
RhoA	Ras homolog gene family member A
SARI	Serotonin receptor antagonist and reuptake inhibitor
SAHA	Suberoylanilide hydroxamic acid
Ser133	Serine 133
SGZ	Subgranular zone
Shh	Sonic hedgehog
SIK	Salt-inducible kinase
SNRI	Serotonin-norepinephrine reuptake inhibitor
SVZ	Subventricular zone
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressant
TMS	Transcranial magnetic stimulation
TPH	Tryptophan hydroxylase
TRD	Treatment resistant depression
TrkB	Tyrosine kinase B
UCMS	Unpredictable chronic mild stress
vCA	Ventral cornu ammonis
vDG	Ventral dentate gyrus
VEGF	Vascular endothelial growth factor
Vmat	Vesicular monoamine transporter
VTA	Ventral tegmental area
WT	Wild type

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INTRODUCTION

I. Major depressive disorder (MDD)

Depression is nowadays a common name, used from describing a transient mood of sadness or discouragement, to a serious condition of inconsolable misery that could interfere with work, social life, or family life, and in the worst scenarios could lead to suicide.

As described in the Diagnostic and Statistical Manual of mental disorders fifth edition ("DSM-5"), depressive disorders include disruptive mood dysregulation disorder, major depressive disorder, persistent depressive disorder (dysthymia), premenstrual dysphoric disorder, substance/medication-induced depressive disorder, and unspecified depressive disorder. The common features for all of these are sadness, emptiness, or irritable mood, in conjugation with somatic and cognitive dysfunctions affecting the life of the individual and its capacities to function. The differences are about duration, timing or presumed etiology.

a) Epidemiology

There are more than 163 million people suffering from MDD in the world (James et al., 2018). According to the World Health Organisation, MDD is the third leading cause of burden of disease in the world and is thought to be ranked first by 2030. The lifetime prevalence of the disease is approximately 16%, with a higher prevalence in women (Depressive Disorder, DSM-5 selections, 2015).

b) Diagnosis

Currently, the diagnosis of MDD is essentially based on subjective criteria, observed by the patient himself, his surroundings, and his psychiatrist. The criterion symptoms are listed in the DSM-5 (Table 1). They should be present most of the day, almost every day, for a period of at least two consecutive weeks. One of them must be one of the first two main symptoms: depressed mood or loss of interest or pleasure in all activities; and the patient must also show at least four of the other symptoms.

1. Depressed mood
2. Diminished interest or pleasure in almost all activities
3. Significant weight loss or gain, or decrease or increase in appetite
4. Insomnia or hypersomnia
5. Psychomotor agitation or retardation
6. Fatigue or loss of energy
7. Feelings of worthlessness or inappropriate or excessive guilt
8. Diminished ability to think or concentrate
9. Recurrent thoughts of a suicidal plan, or a suicide attempt or a specific plan for committing suicide

Table 1. Criteria for diagnosis of major depressive disorder (MDD). Diagnosis of MDD requires five of the symptoms to be present for at least 2 weeks (including either depressed mood or anhedonia, or both), causing difficulty functioning

These symptoms are to be taken in consideration with other medical diseases of the patient, to be attributed to the correct condition and not misdiagnosed. Unfortunately, for now, there is no laboratory test permitting an objective and certain diagnosis of MDD, despite an extensive literature on neuroanatomy and neurophysiology of the disease. Some teams tried to identify genes that could help diagnose: the most important targets are genes that regulate neurotransmitters such as serotonin or dopamine, but also genes of key regulator protein such as brain-derived neurotrophic factor (BDNF; Lohoff, 2010). However, it is complicated to separate the environmental risk factor from the genetic influence; the heritability of MDD is between 31% and 42% (Sullivan et al., 2000), but nobody reached a consensus, and the list of genes identified are mostly risk factors (Bilello, 2016).

c) Risk factors

Depression is influenced by several risk factors such as genetic, epigenetic, endocrine and environmental factors (Duman et al., 2016; Figure 1). Genetic variability is involved in 35-40% of the variance in depression. Genome-wide association studies (GWAS) have not found any recurrent loci for MDD. This could be because of the low number of MDD cases reported in these studies, but it could also be because of the

heterogeneity of the disease. One of the GWAS regrouping data of 60’000 cases were able to connect immunology, neuronal signaling, synaptic density, histone methylation with psychiatric disorders (including MDD), suggesting an association of risk variants for this disease (O’Dushlaine et al., 2015). Basically, depression is complex and heterogeneous, mainly because of the diversity of genetic vulnerability associated with the environmental susceptibility, such as early-life stress or trauma.

Studies both in rodent models and in human showed that depressive subjects showed epigenetic modifications, including histone and deoxyribonucleic acid (DNA) modifications, which are mainly associated with stress and depressive behaviour (Menke and Binder, 2014; Nestler, 2014). These epigenetic modifications can constitute a novel heritable neuro-adaptative form of response to stress.

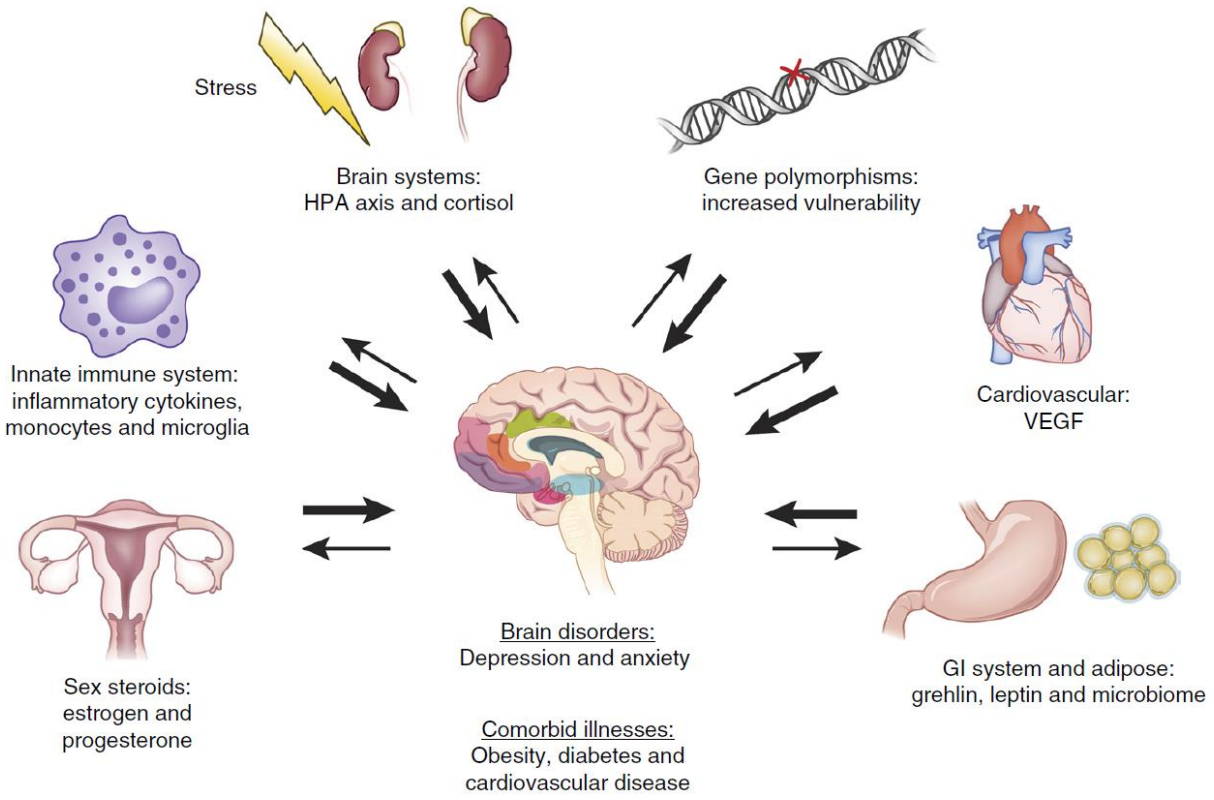


Figure 1. Heterogeneity of depression and influences on susceptibility to depression. Depression is heterogeneous because of the multiple factors that can induce the disease. Among all of them, there is the effect of stress on the HPA axis, the immune system with the inflammatory response, the microbiome, the cardiovascular system, the fluctuation of ovarian steroids and of course the genetic diversity. These factors can participate to the occurrence of the disease as long with comorbid illnesses such as obesity or diabetes. From Duman et al., 2016.

d) Mechanism

1. Monoamine hypothesis

The exact pathophysiology of MDD has not been fully identified yet. Based on different observation from treatments to fundamental research, there have been a few hypotheses trying to explain the premise and development of the pathology.

In the 1950s, the antihypertensive reserpine was found to induce depression in patients. The mechanism of action of this drug was discovered a few years later: reserpine causes prolonged depletion of serotonin, and the time course of serotonin depletion and recovery correlated (Baumeister et al., 2003). But rather than the action on serotonin, another team (Carlsson et al., 1957) showed that reserpine depletes catecholamines. The catecholamines are adrenaline, norepinephrine (NE), and dopamine (DA); these three neurotransmitters are secreted by the adrenal medulla and their blood concentration is increased under a stressful situation. This discovery, associated with the identification of iproniazid's mechanism as a monoamine oxidase inhibitor, led to the monoamine hypothesis for the physiopathology of depression. This hypothesis predicts that the onset of depression is due to a depletion in the levels of serotonin (5-HT), NE and/or DA in the central nervous system.

Serotonin metabolites are reduced in patients diagnosed with MDD and some antidepressants have been shown to increase the levels of serotonin in the brain, such as tricyclic antidepressants (TCA), selective serotonin reuptake inhibitors (SSRI), and serotonin-norepinephrine reuptake inhibitors (SNRI; Dean and Keshavan, 2017). A study in which tryptophan (essential amino-acid, precursor of serotonin) is depleted in patients and in healthy subjects showed that serotonin is essential for the correct functioning of antidepressants, but is also not sufficient to develop depressive symptoms by itself (Bell et al., 2001). Also, two studies have linked genetic abnormalities of serotonin neurotransmission with depressive symptoms: one on the serotonin transporter (SLC6A4) and the other on the 5-HT autoreceptors HTR1A and HTR2A (Caspi et al., 2010; Fabbri et al., 2013).

Norepinephrine is involved in mood regulation. Indeed, medication that inhibit the reuptake of NE are effective as antidepressants: TCA, SNRI, and norepinephrine-dopamine reuptake inhibitors (NDRI; Dean and Keshavan, 2017). As for serotonin, there had been a study to evaluate the importance of NE in the depression neurobiology by depleting the availability of catecholamines. Patients with depression,

before receiving any treatment, were subjected to this depletion, but there were no changes in the severity and in the type of depressive symptoms (Miller et al., 1996). This depletion in healthy control had also no effects (Delgado and Moreno, 2000). These data suggested that there was more than a monoamine depletion to explain the neurobiology of depression.

Dopaminergic neurons from the ventral tegmental area (VTA) and projecting to the nucleus accumbens (NAc) are part of the reward and motivation pathway. An alteration of the dopaminergic transmission could be involved in the pathophysiology of depression. Indeed, some of the neurovegetative symptoms such as anhedonia and reduced motivation are linked to the reward system, and neurological disease targeting the dopaminergic system such as Parkinson's disease can cause depression (Dean and Keshavan, 2017). Also, the antidepressant bupropion increases dopamine level in the brain, adding evidence to the role of dopamine in the pathophysiology of depression.

Moreover, these three neurotransmitters influence each other's concentrations in the brain. Dopamine can decrease the release of NE in the locus coeruleus, NE influences the release of dopamine in the VTA, and DA and NE increase serotonin release in the dorsal raphe nucleus. All of it suggest that they are all interconnected, and if one is dysregulated, it will influence the other two. However, studies suggest that a change in those monoamines' concentrations are not sufficient to provoke depression. There is a delay in the efficacy of the antidepressant (from a few days to a few weeks) involving a more complex mechanism at stake than just elevating the monoamine concentration (Dean and Keshavan, 2017).

2. HPA axis

In the organism, the stress response is mediated principally by the hypothalamic-pituitary-adrenal (HPA) axis. In response to stress, hypophysiotropic neurons from the medial parvocellular subdivision of the paraventricular nucleus (PVN) of the hypothalamus will secrete adrenocorticotrophic hormone-releasing factor (CRH) and vasopressin (AVP), which will activate the secretion of adrenocorticotrophic hormone (ACTH) from the pituitary. The ACTH will activate the secretion of glucocorticoids (cortisol in human and corticosterone in rodents) from the adrenal cortex. The glucocorticoids will then bind to their receptor in multiple tissues, including

the HPA axis in which they are responsible for feedback inhibition on hypothalamus for the release of CRH and AVP, and on pituitary for ACTH. Glucocorticoids are responsible for the regulation of physiological changes such as increased cardiovascular tone, respiratory rate, along with decreased vegetative function such as digestion, growth, reproduction, and immunity (Smith and Vale, 2006).

Stress is often related to depression. Studies show that in vulnerable individuals, stressful events can trigger depression (Kendler et al., 1999) and in children, stressful events such as mistreatment or neglect can induce depression later in life (Pechtel and Pizzagalli, 2011). In the last years, several studies reported abnormalities in the HPA axis and hyperactive response to stress in depressed patients (Dean and Keshavan, 2017). Some studies reported an increased cortisol level in the saliva, plasma and urine of depressed patient, and increased size and activity of pituitary and adrenal glands had also been observed in these patients (Nemeroff and Vale, 2005). There are data supporting the idea that glucocorticoid-mediated feedback inhibition is impaired in depressive patients: the oral administration of a synthetic glucocorticoid called dexamethasone does not suppress the HPA axis in depressed patients; whereas a small dose of dexamethasone is sufficient to induce the feedback inhibition and restore normal cortisol level within 24h in healthy subjects (Pariante and Lightman, 2008). It is a possibility that the lack of positive effect of cortisol in the brain, due to glucocorticoid resistance, could be involved in the pathogenesis of depression (Pariante, 2006).

3. Network hypothesis

The network hypothesis to explain the etiology of depression finds its origins in the evidence of the role of neurogenesis in depression and in the neurogenic effects of antidepressant (Santarelli et al., 2003). The neurogenic effects of the serotonin could explain the delay observed with the use of antidepressant inhibiting the reuptake of serotonin (Vetencourt et al., 2008).

Recent studies have shown that in depressed patients, the volume of both the hippocampus (HPC) and amygdala are decreased, and this decrease is correlated with the length of illness, the duration of treatment and the severity of the disease (Duman et al., 2016; McQueen et al., 2008; Savitz and Drevets, 2009). In post-mortem studies, a decrease in the number of synapses in the prefrontal cortex (PFC) has been

found in depressed patients (Kang et al., 2012; Figure 2). These observations in humans have been corroborated with studies in rodents, in which it was shown that stress has a deleterious effect on neurons and glia in both the PFC and the HPC.

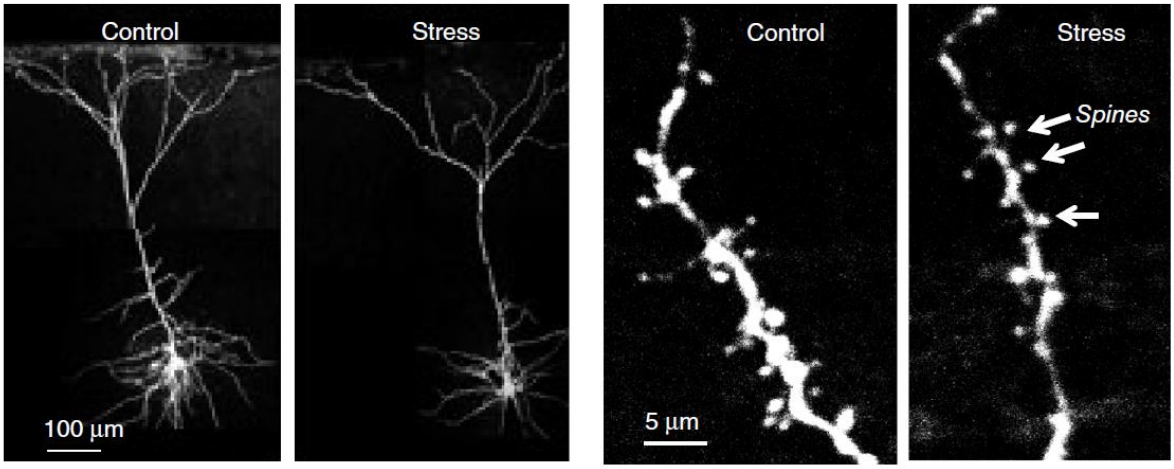


Figure 2. Chronic stress causes atrophy of neuronal process and decreased synapse number. Visualisation of pyramidal neurons from mPFC section, filled with neurobiotin and using two-photon laser-scanning microscopy. Rats have been submitted to a repeated restraint stress. The two pictures on the left depict the reduced complexity of the dendritic tree of the stressed neurons. On the right, the images show magnified dendrites: repeated stress decreased the number of spines. From Duman et al., 2016.

The brain has great plasticity capacities, of reorganisation, growth, and elimination of unnecessary elements with the objective of efficient and precise circuitry. One of the most studied actors of these neuroplasticity processes is brain-derived neurotrophic factor (BDNF). BDNF is a neurotrophin involved in, among other functions, the survival of existing neurons, and promotes the differentiation of new neurons and synapses (Acheson et al., 1995). In patients diagnosed with MDD, the level of BDNF in the serum is decreased (Monteleone et al., 2008) and when BDNF is knocked-out in the dorsal dentate gyrus of rats, they develop depressive behaviour (Taliaz et al., 2010). Fluoxetine can increase BDNF messenger ribonucleic acid (mRNA) level in the dentate gyrus of rats (Molteni et al., 2006).

All this suggesting that there could be a neuroplasticity component in the etiology of MDD, and that BDNF could be an important player in these processes.

e) Treatments

The treatment for depression can be a combination of antidepressant and psychotherapy. It exists numerous drugs with a variety of biological effects.

The firsts historically used are the TCA and the monoamine oxidase inhibitors (MAOIs). The firstly used MAOI antidepressant was iproniazid, which was initially developed for the treatment of tuberculosis. Iproniazid had a psychoenergizing effect in tuberculosis patients, which suggested that this compound could be an antidepressant. The monoamine oxidase (MAO) catalyses the oxidative deamination of some monoamines, such has 5-HT, histamine, DA, NE and adrenaline. The MAOIs will inhibit these reactions, resulting in an increased concentration of these compounds in the brain. There are two forms of MAO: MAOA and MAOB. They are both able to deaminate DA, NE and adrenaline, but with different specificity. Inhibitors of both isoenzymes exist and can be reversible or not. They are mainly used as antidepressant, but they can also be of use in Parkinson's disease or Alzheimer's disease (Youdim et al., 2006). Even though the MAOIs are still used as antidepressant, they provoke a range of side effects. MAOA interact with tyramine in the small intestine. The inhibition of MAOA allows tyramine to enter the blood circulation, tyramine is then internalised by adrenergic neurons in the ventrolateral medulla, increasing the quantity of NE released in the synaptic cleft. This increase will lead to stimulation of the cardiovascular sympathetic system, provoking hypertension that could be lethal for some patients (Feighner, 1999; Youdim et al., 2006). MAOIs can also interact with other antidepressant such as other MAOIs, TCAs or SSRIs. Side effects of MAOIs also include hypotension, weight gain, sexual dysfunction, liver toxicity and haemorrhage. Despite all these drawbacks, there are still patients responding better to the MAOIs than to any other antidepressants.

The first TCA described as an antidepressant was imipramine, by the Swiss Roland Kuhn in 1957 (Owens, 2014). Used first as a sedative, this molecule induced mania in patients, making it a candidate for depression treatment. TCAs block the reuptake of 5-HT and NE in the presynaptic terminal, increasing their concentration in the synaptic cleft. This increase is thought to be at the origin of the antidepressant effect. TCAs also act as competitive antagonists for post-synaptic cholinergic, muscarinic and histaminergic receptors (Hillhouse and Porter, 2015; Moraczewski and Aedma, 2021). The differential affinities for all these receptors are responsible for diverse adverse effects. The most commons are constipation, dizziness, and xerostomia (dry mouth; Trindade et al., 1998). The blockade of cholinergic receptors can lead to blurred vision, constipation, xerostomia, confusion, urinary retention, and tachycardia (Güloglu et al., 2011). The blockade of adrenergic receptors can lead to

orthostatic hypotension and dizziness (Güloglu et al., 2011; Trindade et al., 1998). The blockade of histaminergic receptors can lead to sedation, increased appetite, weight gain and confusion (David and Gourion, 2016). TCA overdose in patients can provoke seizures, but it can also be lethal by complete heart block. Tetracyclic antidepressants have been developed in the 1960s, to obtain new antidepressants, but there was no clinical importance for these (Fangmann et al., 2008).

Serotonin, in the 1960s, was already thought to have a role in MDD; a post-mortem study showed decreased level of serotonin in depressive patients (Hillhouse and Porter, 2015; Shaw et al., 1967). In 1974, fluoxetine was the first selective serotonin reuptake inhibitor (SSRI) described and suggested as an antidepressant drug (Wong et al., 1974). Fluoxetine has been launched to the US market in 1988 and followed by many SSRIs. SSRIs are 20-1500 fold more selective for serotonin transporters over NE, and have very little specificity with postsynaptic receptors such as adrenergic, histaminergic, muscarinic and dopaminergic receptors (Owens et al., 1997). SSRIs do not act on the presynaptic release of serotonin, neither on the postsynaptic receptor, but rather on the reuptake of serotonin, provoking an increased concentration of serotonin in the synaptic cleft. Despite this targeted specificity, SSRIs still have side effects such as nausea, insomnia, and sexual dysfunction (Papakostas, 2008).

Another form of antidepressant is the SNRI: the first on the market was Venlafaxine, in 1993 (Hillhouse and Porter, 2015). The SNRIs act as the TCAs, they block serotonin and norepinephrine reuptake, increasing their concentration in the synaptic cleft. However, they have little to no affinity with adrenergic, histaminergic, muscarinic, or postsynaptic serotonin receptors. Side effects are similar to other antidepressants (nausea, sexual dysfunction, hypertension) and depend on the molecule.

On top of all these compounds, there are antidepressants classed as “atypical” such as bupropion, mirtazapine, mianserin, trazodone and nefazodone. Bupropion is classed as atypical because its affinity is directed toward dopamine and norepinephrine transporters (Hillhouse and Porter, 2015). The affinity with dopamine transporter is higher than with norepinephrine transporter, and it has no affinity to serotonin transporters or receptors. Bupropion is as effective as other antidepressants, with side effects including dry mouth, nausea and insomnia (Feighner et al., 1986; Moreira, 2011) and has the lowest risk of sexual dysfunction compared to other

antidepressants (Clayton, 2002). Mirtazapine acts on serotonin and norepinephrine, but not through reuptake as SSRIs do. Mirtazapine blocks serotonin receptors 2A, 2C and 3, resulting in an increased noradrenergic activity and serotoninergic specific activity (Feighner, 1999). This specific activity minimizes the usual side effects of TCAs or SSRIs. However, mirtazapine has a little antihistaminic effect, provoking sedation, increased appetite, and weight gain. Mianserin is a tetracyclic antidepressant, but with a structure and chemical effects close to mirtazapine. Trazodone and nefazodone act as serotonin receptor antagonist and reuptake inhibitor (SARI). Nefazodone has been withdrawn from the market because of reported cases of liver toxicity and death.

Despite the variety of choice for the antidepressant treatment, some patients do not respond to these treatments and can have a treatment-resistant depression (TRD). A recent publication based on the US population showed that among the 8.9 million people medically treated for MDD, 2.8 million had TRD (30% ; Zhdanava et al., 2021). For these patients, the disease can be more severe, and they are at a higher risk of suicide. The strategies for these patients are to switch antidepressant, to combine antidepressants, or to combine the antidepressant treatment with another non-antidepressant medication (Ruberto et al., 2020). Among the non-antidepressant medications, the ones that have been shown to have some effects are lithium, anti-psychotics (second generation), thyroid hormone (triiodothyronine (T3)), Lamotrigine (anti-convulsant). These combinations have similar efficacy response, but they each have their own benefits and drawbacks, regarding tolerability and response time.

More recently, research is focusing mainly on glutamate and its receptors N-methyl-D-aspartate (NMDA). Esketamine, the S-enantiomer of ketamine, has recently been approved (25.02.2020 in Switzerland) as a fast-acting antidepressant (nasal spray – Spravato^{TM}). Ketamine is a non-competitive NMDA antagonist, used firstly for anaesthesia and analgesia, and administrated intravenously. S-ketamine has a higher affinity for NMDA receptor and has less undesirable effect than ketamine (psychotomimetic effects, drowsiness, lethargy, and cognitive impairment ; Canuso et al., 2018). Ketamine's action on NMDA is thought to increase the activation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, activating the downstream cascade that will reduce the phosphorylation of eukaryotic elongation factor 2 kinase (eEF2k) and eukaryotic elongation factor 2 (eEF2), that will, in the end,

increase BDNF production (Autry et al., 2011). It is also thought to act on the modulation of the mammalian target of rapamycin (mTOR) pathway that will increase BDNF production, as well. This will result in increased brain plasticity and improved synaptic transmission (Ignácio et al., 2016; Shinohara et al., 2021).

Psychotherapy can also be used as a treatment for depression. In a review of 34 studies, it has been shown that 75% of mental disorder patients prefer psychotherapy rather than pharmacological treatment (McHugh et al., 2013). Indeed, pharmacological treatment implies some safety concerns and side effects, whereas psychotherapy doesn't. Psychotherapy alone is recommended as an initial treatment for mild to moderate depressed patients but can also be combined with an antidepressant prescription. Cuijpers and colleagues, in a recently published study, analysed 58 studies with more than 9000 patients to compare the response, remission and acceptance of psychotherapy and pharmacotherapy (Cuijpers et al., 2021). They found no difference between psychotherapy and pharmacotherapy, but they did find a greater difference between combined strategy and psychotherapy alone. The methods of psychotherapy are: cognitive behavioral therapy (based on behavioral activation and cognitive intervention and reconstruction; (Beck, 1993)), interpersonal psychotherapy therapy (based on interpersonal relationship theory; (Klerman and Weissman, 1993)), psychodynamic psychotherapy (from early psychoanalysis, with object relation theory, self-psychology, and attachment theory; (Shedler, 2010)), problem solving therapy (Slife and Weaver, 1992), mindfulness-based intervention (Morgan, 2003), or also music therapy (short-term; (Aalbers et al., 2017; Bruscia, 1991)) or reminiscence therapy (Woods et al., 2018). These therapies are used by psychiatrist and psychotherapists, but thanks to the internet growth, some of them can be delivered online, such as the cognitive behavioral therapy and the interpersonal psychotherapy (Fang, 2019).

Even though medication and psychotherapy stay the most popular treatment for MDD, there are other solutions, old and new, that can be considered. A technique still in use despite attacks from medical and non-medical world is electroconvulsive therapy (ECT), which consists in the administration of brief electrical stimulation of the brain (McDonald and Fochtmann, 2019; Pandarakalam, 2018; Figure 3). This technique is usually used for TRD patients, but it is not well tolerated by patients

because of the side effects of temporary memory impairment-retrograde and anterograde amnesia (Pandarakalam, 2018). A more recent technique using electromagnetic energy to alter brain processes is transcranial magnetic stimulation (TMS). TMS machine produce electromagnetic pulse, which can modify specific neural activities. Unlike ECT, TMS does not impair cognitive functions and can then be used as a complement therapy (Pandarakalam, 2018). However, a meta-study conducted by Chen and his colleagues in 2016 showed that even though TMS is better tolerated by patients, ECT is more efficient to treat MDD (Chen et al., 2017).

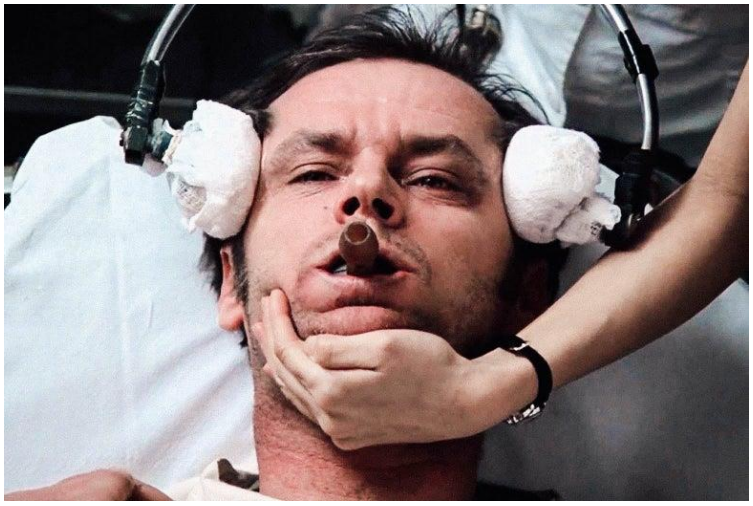


Figure 3. Jack Nicholson in One Flew Over The Cuckoo's Nest (Palus, 2019). The story of this movie is about people in a psychiatric hospital. Here, the main character interpreted by Jack Nicholson is depicted receiving electroconvulsive therapy.

Another technique used is vagal nerve stimulation. A generator is placed in the chest of the patient and connected to the left vagus nerve, sending every 3 to 5 min a 30 second stimulation. Hypotheses are that this stimulation could change NE, 5-HT, DA and gamma-aminobutyric acid (GABA) concentrations; it may induce neural network activation. However, this treatment seems to work better in the long run, and could not be adapted to an acute treatment for TRD (Pandarakalam, 2018).

The heaviest and the "last hope treatment" is the psychosurgery, which is considered for patients resisting to every treatment possible, with a severe and disabling form of depression. The procedures are anterior cingulotomy and subcaudate tractotomy, which will cut the connexion between the prefrontal cortex and the centre for emotions of the limbic system (Pandarakalam, 2018). The cingulotomy will interrupt the connexion from the dorsal anterior cingular cortex to the orbitofrontal

cortex, amygdala and hippocampus via the cingulum bundle (Figure 4A, B and C). This operation has a response rate of 30 to 40% in MDD patients, depending if they do only the cingulotomy or not (Lapidus et al., 2013). The subcaudate tractotomy will interrupt the connexion from the cortex to the thalamus via the striatum (Figure 4D). The response rate is 55% in depressed patients (Lapidus et al., 2013).

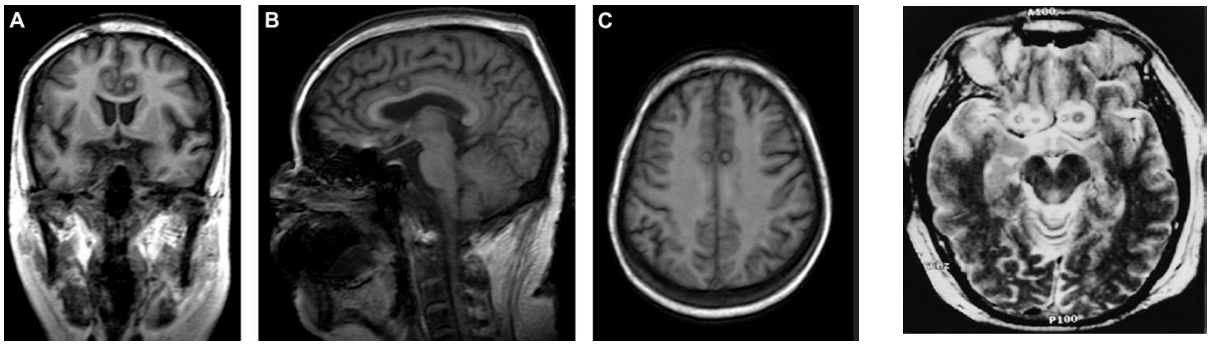


Figure 4. MRI images from patients that received surgical intervention to treat their depression. Anterior cingulotomy with coronal (A) sagittal (B) and axial (C) T1-weighted MRI images, 1 week after cingulotomy (Yen et al., 2009). (D) Subcaudate tractotomy, axial T2-weighted MRI image (Gaviria and Ade, 2009).

With the same strategy of modifying the activity of specific brain region to treat depression, deep brain stimulation (DBS) can be used. The subcallosal cingulate is a target widely studied for this technique, and showed response rate between 41 and 66% in patients (Riva-Posse et al., 2013).

f) Prevention

Due to the poor remission outcomes of MDD patients, attention has been growing toward prevention of the disease. A meta-study observing prevention outcomes on a non-depressed population showed that with a preventive intervention (Cognitive behavioural therapy, interpersonal psychotherapy or problem solving therapy), the incidence of depression was lowered by 21% compared to control group (van Zoonen et al., 2014).

Ongoing explorations of the human body show growing evidence for a link between the microbiome of the gut and the brain. Researchers are finding out that the microbiome could influence the neuropsychiatric symptoms, and that it could be a target to prevent or treat those symptoms (Evrensel and Ceylan, 2015). A meta-analysis published in 2016 highlighted the effects of probiotics on depression (Huang

et al., 2016). Four studies examining non-depressed patients showed that probiotics could participate in reducing the incidence of depression (Huang et al., 2016).

A meta-study by Huang and his colleagues highlights the deleterious effect of mentally passive behaviours, such as watching television, on the risk of developing depression (Huang et al., 2020). Furthermore, a study conducted on 24,000 participants with a 13-year follow-up concluded that substituting mentally passive sedentary behaviour with mentally active sedentary behaviour, light physical activity or moderate-to-vigorous activity could reduce the risk of depression symptoms by 5%, 13% and 19% respectively (Hallgren et al., 2020).

g) Animal models

Depression is a complex disease, very heterogenous among patients and is often present with other illnesses, making it quite complicated to study. The availability of samples from patients (blood) are not enough to study the disease, and the study of post-mortem tissues have also its limitations. For all these reasons, animal models provide great insights for the neurobiological processes and cellular pathways involved in depression. The animal models are very different from the human disease, but still allow a better apprehension by covering different aspects of the disease.

The use of animal model can happen through different constructs (Nestler and Hyman, 2010). Firstly, the phenotype can be similar to sick humans, this is called face validity. Secondly, the process that leads the humans to sickness can be reproduced in the animal, this is called construct validity. Thirdly, the animal model can be sensible to pharmacological or non-pharmacological interventions, which proved their efficacy in humans, and this is called predictive validity. Based on the etiology of depression, animal models have been developed regarding stress exposure, gene-environment interaction, administration of glucocorticoids, and gene manipulation (Wang et al., 2017).

To provoke depression-like symptoms in rodents, several paradigms exist:

- Learned helplessness. Theorised in 1972 by Seligman with dogs. The animal is placed in a cage with no escape and is submitted to electric shock. When tested in the same context with an escape, a significant part of the animals will not try to escape (Seligman, 1972). Seligman proposed that it was a depression model because it creates a situation where the animal has no hope, no control and cannot escape, which

leads to a depressive reaction. It is the inability to control traumatic event that provoke the helpless phenotype. Symptoms developed in rodents after this paradigm are: decreased mobility, decreased eating and drinking, weight loss, decreased grooming, decreased competitive behaviour, sleep disturbances (Wang et al., 2017). An ensemble of symptoms that can be precautiously compared with the human's ones, making this an interesting model for depression.

- Unpredictable chronic mild stress (UCMS). The rodents receive different stressors randomly during several weeks. Stressors include food or water deprivation, cage tilt, soiled bedding, overnight illumination, etc. The rodents will develop a depressive phenotype due to the unpredictable stress stimuli, they get a decreased reward sensitivity and develop anhedonia (Katz et al., 1981; Willner, 1991).

- Early life stress model. This model is based on the principle that early life stressor can increase the risk of developing depression later in life (Kendler et al., 2002). One of the most common paradigms for this is the maternal separation, in which the pups are separated from their mother during the postnatal period from a few hours to a few days, depending on the protocols. The interruption of the mother-pup interaction alters the HPA axis response.

- Olfactory bulbectomy. Surgical removing of the olfactory bulbs induces many biological and behavioural modifications that are similar to the ones observed in MDD patients (Kelly et al., 1997; Song and Leonard, 2005), and antidepressant can reverse the depressive behaviour in this model (Jarosik et al., 2007).

- Social defeat model. The social defeat stress model is based on the emotional and psychological stress provoked by a confrontation to social conflict (Agid et al., 2000). The tested rodent is introduced in the cage of a bigger, older, aggressive, and dominant male rodent, and is attacked and defeated by the resident. This is repeated several times, and after the paradigm is complete, the intruder mouse shows anhedonia, decreased sexual behaviour, increased defensive behaviour, increased anxiety, decreased locomotor and exploratory activity, changes in circadian rhythm, alteration in feeding and body weight, sleep disturbance and impaired immune function (Bohus et al., 1993; Koolhaas et al., 1997; Martinez et al., 1998; Meerlo et al., 1996).

- Chronic restraint stress model. Rodents are restraint during two hours a day for 14 to 21 days, and develop damaged CA3 pyramidal cells, increased corticosteroid levels, increased aggressive behaviour, depressed behaviour and cell death (Conrad et al., 1999; Wood et al., 2003; Zhang et al., 2014).

- Glucocorticoid/corticosterone model. The level of corticosterone in individuals can be used as a diagnostic, but it can also be manipulated to induce a depressive state (Gregus et al., 2005).

- Genetic models. Some genetic lines of rat can be used as a depression model. The flinders sensitive line shows hypoactivity in the forced swim test and in the open field; under stress it shows a decrease preference for saccharin, and they have low 5-HT synthesis in the brain (Overstreet and Russell, 1982; Pucilowski and Overstreet, 1993). The Holtzman albino strain is a very good line for the learned helplessness model of depression, since they escape less than other strains (Padilla et al., 2009). A line has been created with the rats that were showing the most depressive symptoms after an inescapable shock paradigm: the congenital learned helplessness (Willner and Belzung, 2015). Finally, the Wistar-Kyoto strain shows psychomotor retardation, behavioural inhibition, learned helplessness, social withdrawal, and physiological dysfunction (Nam et al., 2014).

- Transgenic models. One model is based on the tryptophan hydroxylase (TPH) which is an enzyme involved in 5-HT synthesis. The double knockout for both isoforms, TPH1 and TPH2, shows decreased 5-HT levels, increased marble burying, and increased immobility in the tail suspension test (Walther et al., 2003). Another model is based on the vesicular monoamine transporter (Vmat), which is composed of two proteins Vmat1 and Vmat2. The Vmat2+/- mice show increased immobility in the forced swim test and tail suspension test, anhedonia and higher sensitivity to learned helplessness paradigm (Fukui et al., 2007).

Concerning the face validity construct, a clear difficulty is to transpose human depression symptoms in rodents, and how to assess them. In terms of cognition and emotion, some studies show that rodents with depressive phenotype, in a fear conditioning paradigm, would freeze longer period of time and would have a greater incidence of anticipatory freezing (Brandão et al., 2008; Dibbets et al., 2015). Another symptom for depression in rodents would be behavioural despair. Porsolt, in 1977, created a paradigm called the forced swim test in which a mouse is introduced in a cylinder tank filled with water (Porsolt et al., 1977). Behavioural despair is then measured from the time the mouse is immobile, based on a basic suggestion that the mouse would firstly try to escape. The validity of this test has been debated recently. It has been suggested that the immobility of the mouse could be more like a coping

mechanism (switch from active to passive behaviour) in order for it to keep its energy for when it could actually escape (Molendijk and de Kloet, 2015). The tail suspension test is also based on the observation of immobility time in mice, considered as behavioural despair (Steru et al., 1985). This test is often performed to assess the efficacy of antidepressants.

Depressed rodents can show a certain acceptance to an unpleasant or even painful situation: this is called helplessness. Helplessness can be measured with a paradigm of shock avoidance, in which the animal is submitted to electrical foot shock (Seligman, 1972). A control animal will move to escape the chock, but a depressed animal can just stay in the electrical shock spot until it goes off (Maier and Seligman, 1976). Anxiety, closely related to depression, can be measured in rodents with the elevated plus maze, which is a maze with four arms, two with walls (closed arms) and two without (open arms). Anxiety is measured as time spent in the type of arms. An anxious animals will spend more time in the closed arms (Pellow et al., 1985). Anxiety, together with locomotor activity, can also be measured in an open field. A depressed rodent will run less in the open field, and will run closer to the periphery than to the centre of the field, the centre being defined as anxiogenic due to its exposition (Denenberg, 1969). Anhedonia is considered also as a tool to measure depression in rodents. Anhedonia is defined as the loss of interest for something that was once pleasurable. Anhedonia is often measured through a sucrose preference test. Two bottles are presented to the rodent, one with water, the other with water and added sucrose. Depressed animal will show a decreased preference for the sucrose bottle compared to control animals.

Despite the numerous ways of inducing depressive-like behaviour and measuring this behaviour and its response to antidepressants, there is still no perfect way of investigating depression in mice. Since even depression in human is a very complex and diverse process, it is very difficult to study. These methods can only help in the global comprehension of the neurobiology behind this disease, and there is still a long way to go before reaching a more complete understanding of this psychiatric disorder.

II. Neurogenesis

a) What is neurogenesis?

Neurogenesis is the process by which new neurons are added and connected to the brain circuitry. There are two type of neurogenesis, the one that occurs during the embryonic development of the organism and the one that occurs during adulthood. During the development, the central nervous system is derived from the neural tube, the neurons will form from neural stem cells contained in this neural tube. The neurons newly formed do not directly integrate a circuit but must migrate long distances, mature and then grow axon and dendrites to be integrated into the neural circuit. The number and type of neurons are regulated by molecular and genetic factors, notably the Notch signaling pathway (Kageyama et al., 2008).

Adult neurogenesis is also a transformation of neural stem cells into neurons, happening in specific neurogenic brain regions. The two regions involved in this process are the subgranular zone (SGZ), in the dentate gyrus of the hippocampus and the subventricular zone (SVZ) of the lateral ventricles. The neurons formed from the SGZ will form granular neurons in the hippocampus, whereas the neurons from the SVZ will migrate to the olfactory bulb to become interneurons and participate to the sense of smell (Gage, 2000). Adult neurogenesis is a very complex, finely tuned and dynamic process and can be modulated by pharmacological, physiological and pathological stimuli.

In the hippocampus, the adult neural stem cells, called type 1 radial glia-like cells (RGLs), can be found between the granular cell layer and the hilus: the sub-granular zone. These stem cells have two main capacities : the possibility to self-renew through cell division and the possibility to generate specialized cell types through differentiation (Gage, 2000). The RGLs can generate both intermediate progenitor cells (IPC) and astroglia progenitors. Astroglia progenitors do not proliferate much compared to IPCs and differentiate into mature astrocytes. IPCs proliferate and progressively differentiate through multiple steps before becoming neurons (Bonaguidi et al., 2012; Figure 5). These processes are highly regulated by internal and external factors.

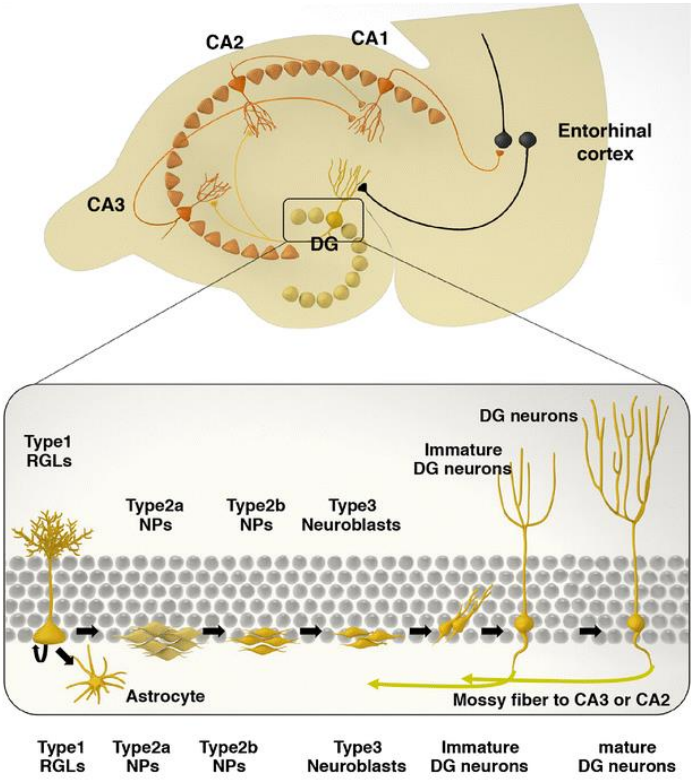


Figure 5. Schematic neurocircuitry of the hippocampus (upper panel). Neurogenesis progression from type1 RGLs (stem cells) to matured integrated granular neurons (lower panel). Adapted from Toda and Gage, 2018.

b) Neurogenesis regulations

Adult neurogenesis is regulated by epigenetic modifications, through DNA methylation, histone acetylation and chromatin remodelling (Figure 6, upper panel). DNA methylation is a process by which the pluripotency genes are silenced (Mohn et al., 2008). Also, proteins such as DNA-damage inducible protein 45β (GADD45β) can alleviate DNA methylation on elementary neuronal genes such as *bdnf* or *fgf1* (Ma et al., 2009), making DNA methylation a critical process for neurogenesis. Histone deacetylase 1 and 2 (HDAC 1 and 2) are involved in the maturation of progenitors into mature neurons and in the survival of the neurons, and HDAC 3 and 5 are highly expressed neuronal stem cells and progenitors and regulate their proliferation and differentiation (Niklison-Chirou et al., 2020).

Adult neurogenesis is also highly regulated by transcription factors (Figure 6, lower panel). Sox 2 is one of the most studied and is involved in the self-renewal of the stem cells (Wegner, 2011). Sox2 regulates the expression of sonic hedgehog (Shh) pathway and represses NeuroD1, which promotes the differentiation of the progenitor into a neuron. The last steps of the adult neurogenesis, which are

maturation and integration into the network are under the control of the cyclic adenosine monophosphate (cAMP) response element binding protein (CREB; Lonze and Ginty, 2002), and CREB is also involved in the survival of the newborn neurons.

Adult neurogenesis is also under the regulation of metabolic processes. Mitochondria, glycolysis and some key actors of the oxidative phosphorylation influence the growth of axons and dendrites and the synaptic activity (Khacho and Slack, 2017; Raefsky and Mattson, 2017; Zheng et al., 2016).

Not all the cells generated from these successive divisions will survive and integrate the hippocampus circuitry. If the neuron generated is not able to make proper connections, it will trigger the intracellular cell death mechanisms (Kuhn, 2015). However, some external signals such as hormones or neurotrophic factors (fibroblast growth factor (FGF)-2, BDNF, granulocyte colony-stimulating factor (G-CSF), vascular endothelial growth factor (VEGF)) can stimulate the anti-apoptosis pathway and prevent the cell death (Kuhn, 2015).

From the very early stages, neural progenitors receive neurotransmitter inputs. First GABA will trigger the pathways regulating proliferation, survival, and growth. GABA inputs are excitatory at the beginning, and following the glutamatergic inputs, they become inhibitory (C. V. Dieni et al., 2012). Glutamatergic inputs come from the dentate granule cells, but also from the entorhinal cortex (layer II) to the middle and outer molecular layer and contralateral hilar mossy cells to the inner molecular layer (Berg et al., 2013; Kumamoto et al., 2012; Witter, 2007). The effect of glutamate inputs seems to vary depending on the receptor activated, so the neurotransmitter, instead of having a crucial role, acts more like a modulator (Berg et al., 2013). The dentate gyrus (DG) also receives inputs of dopamine from the midbrain (Gasbarri et al., 1994), of acetylcholine from the medial septum (Dougherty and Milner, 1999), of serotonin from the raphe nucleus and of adrenaline from the locus coeruleus (Mongeau et al., 1997). All these neurotransmitter have an effect on proliferation (Brezun and Daszuta, 1999; Jang et al., 2002; Kippin et al., 2005; Malberg et al., 2000).

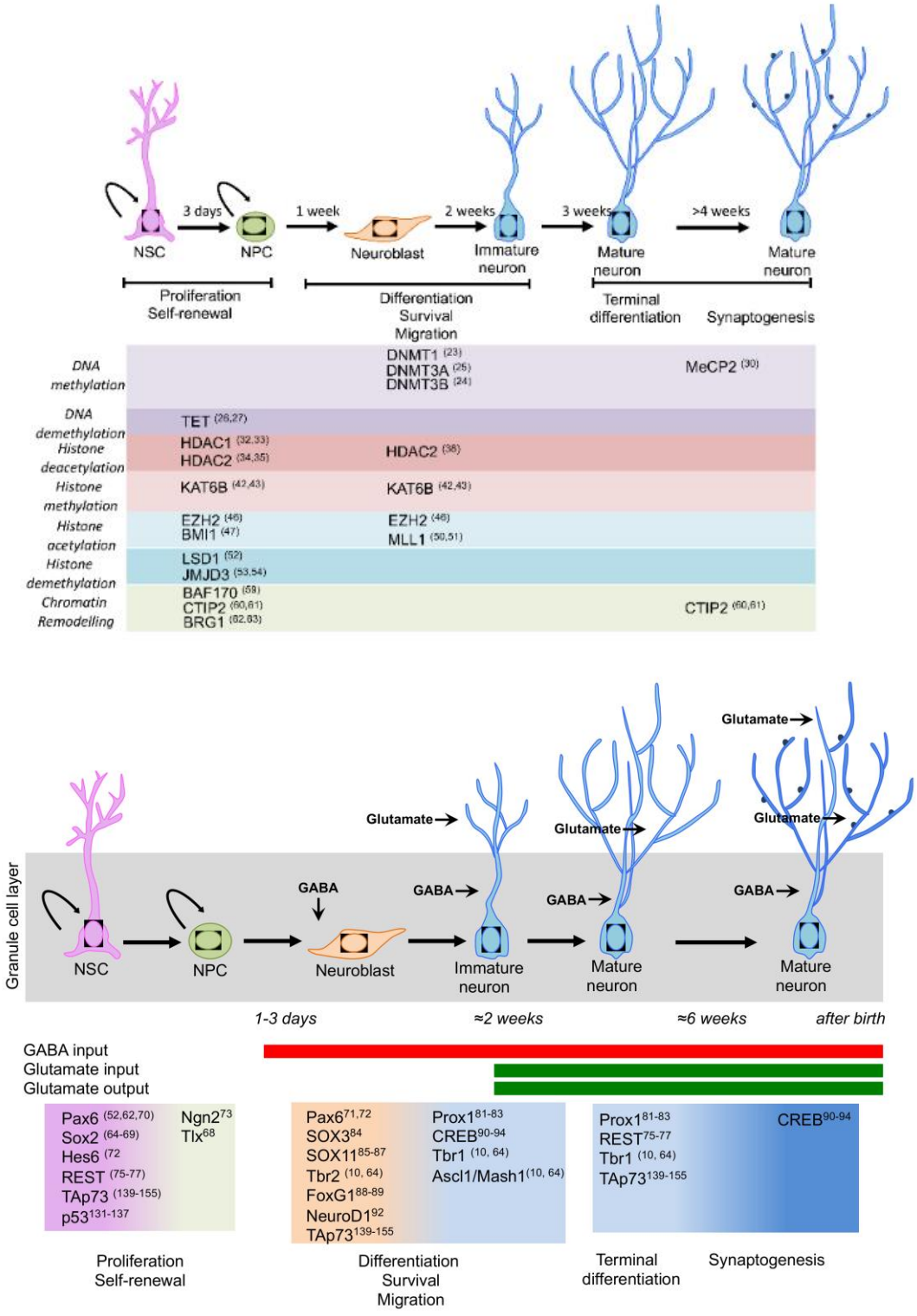


Figure 6. Representation of the main stages of neurogenesis. Representation with the epigenetic machinery involved in each of these steps (upper panel). Representation of the main stages of neurogenesis with the transcription factors involved in the processes (lower panel). From Niklison-Chirou et al., 2020.

Neurogenesis is under the influence of environmental/external factors. Physical exercice has been showed to increase neurogenesis, and this increase seems to be directly related to the increase of neurotrophic factors such as BDNF and VEGF (Shohayeb et al., 2018). Diet can also have an impact on neurogenesis processes: diet restriction can increase proliferation and neuronal differentiation, and seems to be also mediated by BDNF (Shohayeb et al., 2018). Antidepressant can also have an influence on proliferation, differentiation and survival (Micheli et al., 2018).

c) Spine development

The complete and detailed study of dendritic spines allows to evaluate the maturity and integrity of the newborn neurons (from 3 to 8 weeks ; Toni et al., 2008). This evaluation can be done through the observation of the density and the shape of these spines (Espósito et al., 2005). The newborn neurons begin to form spines from their 16th day, and the density increases between their 3rd and 8th week (Zhao et al., 2006). Those spines can be classified in four categories depending on their morphology: stubby, filopodia, thin and mushroom (Nimchinsky et al., 2002; Richetin et al., 2015; Figure 7). Thin and mushroom spines are the most represented in mature neurons.

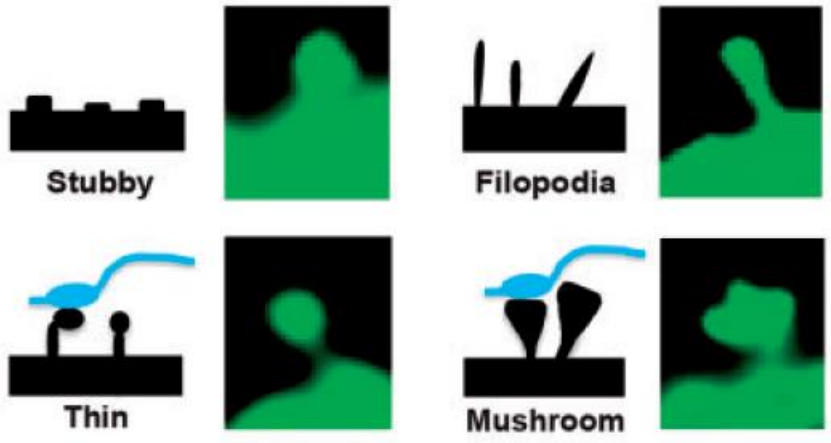


Figure 7. Illustration depicting different spines subtypes based on their morphology. The stubby spines are recognisable because they look like bump on the dendrite. Filopodia are thin protrusion without a defined neck or head, they are uniform. The thin spines have a short and thin neck, usually not visible, and a little round head. The mushroom spines have a big neck and a big uneven head. From Richetin et al., 2015.

d) Adult neurogenesis and depression

Quickly after the discovery of neurogenesis in the adult mammal brain, Kempermann theorized that this process may be involved in the pathology of psychiatric diseases, and notably in major depressive disorder (Kempermann, 2002). He based this theory on the decreased hippocampal volume of depressed patient, and the increased neurogenesis observed after antidepressant treatment (Kempermann, 2002; Kempermann and Kronenberg, 2003). The number of granule cells and the granule cell layer volume in the dentate gyrus of depressed patients are decreased, whereas the hippocampal volume and the granule cell layer volume of depressed patients that received antidepressant treatment are increased (Boldrini et al., 2013, 2012, 2009). In addition, the delay required for the antidepressant to actually have an effect on patient corresponds to the time needed for the new-born neurons to be included and functional in the hippocampal circuitry (Ge et al., 2007; Jacobs et al., 2000). Many studies showed that antidepressant treatment increases adult neurogenesis in rodents, non-human primates and humans (Mahar et al., 2014). However, Sahay et al. showed that a forced increase in adult neurogenesis is not sufficient to induce antidepressant effects, meaning that the only increase in neurogenesis is not enough to develop the antidepressant effect, but that these effects need the actual monoaminergic modulation from the drugs (Sahay et al., 2011). And another study showed that the effects of antidepressants rely more on the neurons formed during development (Samuels et al., 2015). A recent paper underline the necessary distinction between proper neurogenesis and the activity of the newborn neurons: they showed that suppressing the activity of newborn neurons abolishes the antidepressant effects of fluoxetine, and that activating these newborn neurons reverses the depressive symptoms resulting from a stress procedure (Tunc-Ozcan et al., 2019). Overall adult neurogenesis seems to promote a resilience effect against stress, either by preventing these effects or by rescuing these effects (Abrous et al., 2021).

Adult neurogenesis is affected by stress and depression, and is also essential for the antidepressant to work properly. Neurogenesis and depression are tightly linked.

III. BDNF, CREB, CRTC1

a) BDNF

First isolated from pig brain in 1982 by Yves-Alain Barde and Hans Thoenen (Barde et al., 1982), brain derived neurotrophic factor is a protein, member of the neurotrophin family with nerve growth factor, neurotrophin 3 and neurotrophin 4 (Leal et al., 2017). BDNF is expressed in nearly all the brain regions (Hofer et al., 1990), but have different effects depending on the type of cells that express it. BDNF has been widely studied over the past 40 years, and researchers have found that it can be involved in development, regulation of gliogenesis, neurogenesis and synaptogenesis, neuroprotection, but also short- and long-term synaptic interactions (Kowiański et al., 2018).

In human, BDNF is encoded by the *BDNF* gene, and both its expression and release are mediated by neuronal activity (Leal et al., 2017). BDNF is first produced as a pre-pro-protein in the endoplasmic reticulum (Lu, 2003), the protein is then translocated into the Golgi apparatus and the pre-domain is cleaved. Pro-BDNF is then cleaved again to separate the pro-domain from the mature BDNF in intracellular vesicles (Foltran and Diaz, 2016). Both the mature form of BDNF and the pro-BDNF are released in the extracellular space; in neurons, it happens following a membrane depolarisation (S. Dieni et al., 2012). Pro-BDNF can bind to the p75 neurotrophin receptor (p75NTR) and with the sortilin receptor; this complex can activate three pathways. First, it can activate the Ras homolog gene family member A (RhoA)-dependent signaling pathway, leading to the development and motility of the neural growth cone (Reichardt, 2006). Second, it can activate the nuclear factor kappa B (NF-kB), promoting the neuronal survival and the regulation of the number of neurons during development (Reichardt, 2006). Finally, it can activate the c-Jun amino terminal kinase (JNK)-related pathway, leading to apoptosis processes (Teng et al., 2005). On the other side, mature BDNF binds to tyrosine kinase B (TrkB) receptor. The dimerization of the TrkB receptor with the autophosphorylation of its tyrosine residues results in the formation of the phosphorylated-TrkB receptor (Kaplan and Miller, 2000). The phosphorylated-TrkB receptor can activate different kinases, triggering diverse signaling cascades: phosphatidylinositol 3-kinase (PI3K), mitogen-activated protein kinase (MAPK), phospholipase C-γ (PLC-γ) and guanosine triphosphate hydrolase (GTP-ases) of the Ras homolog (Rho) gene family (Kowiański et al., 2018). All these

pathways will trigger different mechanisms: anti-apoptosis, synaptic plasticity, dendritic growth and branching through protein synthesis and cytoskeleton development (Gonzalez et al., 2016; Jaworski et al., 2005; Kumar et al., 2005; Minichiello, 2009; Park and Poo, 2013). MAPK signaling is required to trigger the phosphorylation of CREB (Xing et al., 1998). At the pre-synaptic site, BDNF modulates the release of glutamate by inducing the phosphorylation of proteins that regulate the availability of vesicles and by recruiting motor complexes that move the vesicles on the cytoskeleton (Jovanovic et al., 2000; Yano et al., 2006). At the post-synaptic site, BDNF can modulate the trafficking and synaptic delivery of AMPA receptor, as long with the trafficking, phosphorylation and open probability of NMDA receptor, which will regulate the synaptic transmission (Caldeira et al., 2007; Levine et al., 1998). BDNF is also involved in the long-term potentiation (LTP) process in the hippocampus. LTP in the CA1 upregulates BDNF mRNA levels; LTP is impaired in BDNF knock-out models, and BDNF reexpression restores this impairment (Korte et al., 1996, 1995; Patterson et al., 1996, 1992). The binding of BDNF with its receptor TrkB is required for LTP induction in the CA1 (Chen et al., 1999). Neuronal activity will adjust the morphology and the number of spines. BDNF has been shown to develop neurite branching and growth, but also spine density and morphology (Ji et al., 2010; Zagrebelsky and Korte, 2014). External BDNF application can increase the number of spines, and, through the activation of one Rho-GTPase cascade, BDNF can trigger the spine head enlargement (Alonso et al., 2004; Lai et al., 2012). BDNF is also necessary for the LTP-induced spine head enlargement and can also activate the synthesis of cytoskeleton proteins in the spine head (Bosch et al., 2014; Briz et al., 2015).

BDNF activity is highly intricated with CREB. The binding of TrkB and BDNF is the main regulator of BDNF transcription, but CREB is the second most important regulator. CREB is directly involved in the BDNF level of expression since it can directly bind to the promoter IV of the *bdnf* gene, which counts several cAMP response element (CRE) sites, be phosphorylated upon activation by TrkB/BDNF and recruit CREB binding protein (CBP)/P300 to activate the transcription of *bdnf* (Esvald et al., 2020). Phosphorylated CREB will not only modulate BDNF transcription, but also the BDNF- induced gene expression (Finkbeiner et al., 1997).

b) CREB

CREB was identified in 1987; the protein is 43kDa, binds to CRE on DNA and is part of the basic leucine zipper domain (b-zip domain) family, which is a family of transcription factor (Montminy and Bilezikjian, 1987; Sakamoto et al., 2011). Upon neuronal activation, the Serine 133 (Ser 133) of CREB can be phosphorylated by various kinases, such as calcium (Ca^{2+})/Calmoduline-dependent kinase (CaMK) II and IV, protein kinase A and C (PKA and PKC) and others (Sakamoto et al., 2011). Phosphorylated CREB can then bind to CBP and P300, and activate transcription (Parker et al., 1996). CREB binding has been found for thousands of loci (Impey et al., 2004), for genes coding for neurotransmitters, transcription factors, growth factors, signal transduction factors, and metabolic enzymes, all of which being involved in neuronal development, plasticity and protection (Sakamoto et al., 2011). At the cognitive level, CREB has been shown to be involved in several kind of memories, such as fear memory, spatial memory, olfactory memory, and object and social recognition memory (Sakamoto et al., 2011). Furthermore, an experiment involving a constitutively active form of CREB showed a lower threshold for the induction of late phase long term potentiation (L-LTP) in the Schaffer collateral and enhanced memory (Viosca et al., 2009). On the other hand, a dephosphorylation of CREB Ser 133 is associated with long-term depression (Thiels et al., 1998). CREB is also critical for neuronal development: a CREB null mice model is non-viable (Lonze et al., 2002; Rudolph et al., 1998), but in a hypomorphic CREB mutant model, CREM seems to follow compensatory mechanism (Hummler et al., 1994). In mature neurons, if CREB is blocked, apoptosis and neurodegeneration are increased (Ao et al., 2006). The regulation of neuronal survival by CREB seems to be mediated through the transcription of different proteins such as BDNF, but also insulin-like growth factor (IGF-1) and leptin (Sakamoto et al., 2011).

c) CRTC1 physiology

CREB can also be activated independently of its phosphorylation on Ser133 and the binding to CBP/P300 (Briand et al., 2015): this activation is happening through the recruitment of the CREB-regulated transcription coactivators (CRTCs). The CRTC family comprises 3 forms: CRTC2 and CRTC3 expressed in all tissues, and CRTC1,

which is mainly expressed in the brain (Kovács et al., 2007; Li et al., 2009, p. 1; Watts et al., 2011). CRTCs have a N-terminal coil-coil domain that allow them to bind to CREB's b-zip domain, triggering its dimerization and binding to the DNA (Saura and Cardinaux, 2017).

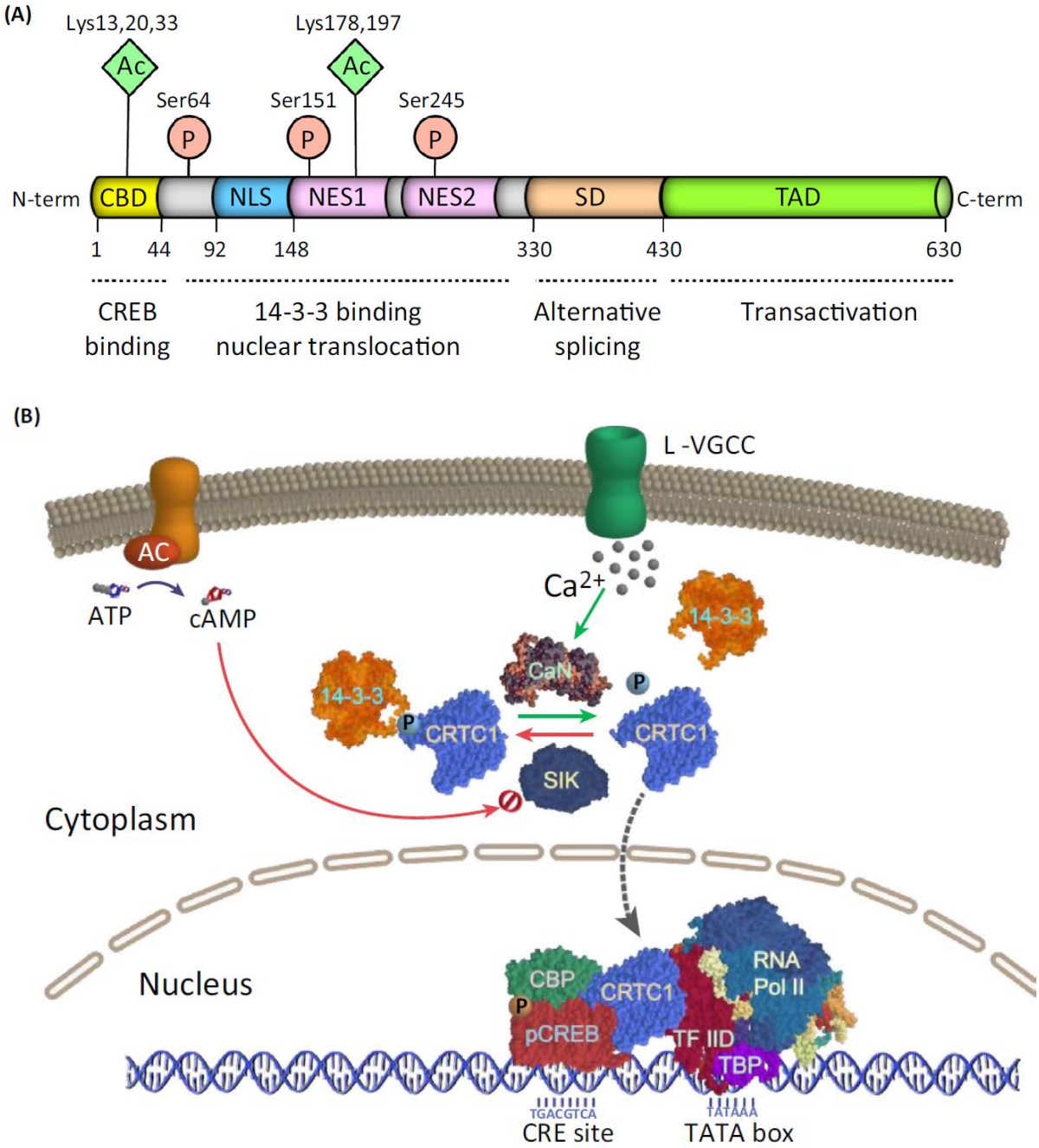


Figure 8. Structure and Regulation of CRTC1. (A) From its N-terminal side, CRTC1 has a CBD site to bind to CREB, then a Nuclear localization sequence (NLS), 2 nuclear export sequences (NES1 and NES2), a splicing domain (SD) and a transactivation domain (TAD). The Serine 64, 151 and 245 phosphorylation promotes association with 14-3-3 protein and the sequestration of CRTC1 in the cytoplasm. (B) Regulation of CRTC1 activity by calcium and cAMP influx into the cytoplasm. From Saura and Cardinaux, 2017.

In basal condition, CRTCs are phosphorylated and sequestered in the cytoplasm by a protein called 14-3-3 (Saura and Cardinaux, 2017). Their activation and translocation are possible upon calcium and cAMP influx into the cytoplasm: the calcium will activate the dephosphorylation of CRTC1 by calcineurin and the cAMP will inhibit the salt-inducible kinases (SIK). Once dephosphorylated, CRTCs can be dissociated from 14-3-3 and translocated into the nucleus to activate CREB-mediated transcription.

In neurons, evidence is growing that CRTC1 is an important actor in plasticity processes. CRTC1 is involved in the maintenance of the hippocampal L-LTP (Kovács et al., 2007; Uchida et al., 2017; Zhou et al., 2006). CRTC1 is localised in the dendritic spines, and upon activation, is transported to the nucleus through the mechanisms involving microtubule and motor transportation dynein (Ch'ng et al., 2015, 2012; Herbst and Martin, 2017). Once in the nucleus, it regulates some essential CREB-regulated genes involved in plasticity : *Bdnf*, *c-fos*, *Zif268/Egr1* and *Arc*, the orphan nuclear receptors *Nr4a1* and *Nr4a2*, and a brain specific growth factor *Fgf1* (Breuillaud et al., 2012; Fukuchi et al., 2015; Nonaka et al., 2014; Parra-Damas et al., 2017, 2014). CRTC1 translocation after glutamate binding to NMDAR is also required for the BDNF-induced dendritic growth in cortical neurons (Briand et al., 2015; Finsterwald et al., 2010; Kovács et al., 2007; Li et al., 2009). Together, all these studies show that CRTC1 is activated and translocated to the nucleus upon synaptic activation, and it will participate in expressing neuroplasticity genes through its binding to CREB.

d) Effects of stress on BDNF and CREB

Chronic stress is associated with decreased BDNF, with different effects depending on the brain region, stressor and stress duration (Choy et al., 2008; Grønli et al., 2006; Miao et al., 2020; Murakami et al., 2005; Xu et al., 2006). A model used as a stress model, corticosterone injection, showed decreased BDNF expression (Smith et al., 1995), meaning that BDNF is under regulation of the level of corticosterone in the brain. BDNF levels have been shown to be decreased in MDD patients, both in plasma and in post-mortem patient's brain, and these levels are increased after antidepressant treatment (Dwivedi, 2009; Lee et al., 2007; Mosiołek et al., 2021). Like BDNF, CREB is downregulated after stress and is upregulated after antidepressant treatment (Alfonso et al., 2006; Dowlatshahi et al., 1998; Nibuya et al.,

1996; Ren et al., 2014; Yamada et al., 2003). Moreover, overexpression of CREB in the dentate gyrus is associated with antidepressant effects (Chen et al., 2001, 2006).

e) CRTC1 in mood disorders

Since CRTC1 plays a role in CREB signaling and *Bdnf* transcription, it was also shown to have a role in the stress response and mood disorders etiopathogenesis. Jean-René Cardinaux' team generated a CRTC1 knock-out mouse line, which presented depression-like behaviour (Breuillaud et al., 2012). These mice present deficit in social interaction, a deficit in the attraction for the opposite sex and they are very aggressive. These mice also show an anxiety for novelty and an emotional response enhanced after footshock stress. At the molecular level, they show a decreased turnover in dopamine and serotonin, combined with a decreased mRNA level of *Bdnf* exon IV ensuing a decrease in BDNF expression level and its receptor TrkB, and a decrease in the CREB regulated genes *c-fos*, *FosB*, *Crem-Icer*, *Somatostatin*, *Cartpt* and *Pgc-1α*, both in the prefrontal cortex and in the hippocampus. Finally, when chronically treated with an antidepressant (fluoxetine, 18mg/kg/day), these mice show a blunted response to the treatment. The treated KO mice showed the same immobility levels in a forced swim paradigm and in the tail suspension test as the non-treated KO mice. However the treatment had a positive effect on the aggressiveness and the anxiety of the KO mice. This mouse model is a very good approach to explore the neurobiology of a depression-like behavior. Later, the same group showed that a treatment with the HDAC inhibitor suberoylanilide hydroxamic acid (SAHA) could improve the depressive behaviour and restore *Bdnf* expression in these mice, suggesting a role of CRTC1 in treatment-resistant depression and that targeting HDACs could be an interesting strategy to treat this kind of depression (Meylan et al., 2016). By investigating the difference in gene expression, they found out that agmatinase was upregulated (Meylan et al., 2016). Agmatinase is an enzyme that degrades agmatine, and the whole agmatinergic system has already been shown to be involved in mood disorders, notably in depressed patients where agmatinase levels are high (Laube and Bernstein, 2017; Neis et al., 2017). An agmatine treatment in the CRTC1 KO mice improved the depressive-like phenotype, indicating an involvement of the agmatinergic system in this mouse model of depression, mirroring this involvement in human depression.

Recently two groups dug deeper into the role of the CRTC1/CREB pathway in the etiopathogenesis of depression, and focused their studies on SIK2, the enzyme responsible for the phosphorylation (inactivation) of CRTC1. Bo Jiang and his colleagues first showed that chronic sodial defeat stress (CSDS) and CUMS models of depression could increase the level of SIK2, which decreases the translocation of CRTC1 into the nucleus and the binding of CRTC1 to CREB (Jiang et al., 2019). They found that overexpressing viraly SIK2 in the hippocampus was enough to induce chronic stress and depressive-like phenotype with a decrease in BDNF expression and neurogenesis. On the contrary, when they knocked down or knocked out SIK2, they saw the opposite effects. They also showed that SIK2-CRTC1 was necessary for antidepressant effects. Later, Yue Liu and her colleagues used an inhibitor of SIK2 on CSDS and CUMS model of depression (Liu et al., 2020). They showed that by repeated administration of this inhibitor, they could induce a protective antidepressant effect in both models, and that this effect is dependent on the CRTC1/CREB/BDNF pathway. This administration also rescued the level of BDNF and neurogenesis in the hippocampus.

All these studies combined showed that CRTC1 plays an essential role in the establishment of depression. However, a study published in 2016 found no direct correlation between CRTC1 polymorphisms and major depressive disorder (Quteineh et al., 2016). Nonetheless, considering the known co-morbidity of obesity and depression, it was shown that CRTC1 polymorphisms play a role with obesity markers (such as fat mass) in individuals with MDD rather than non-depressive individuals. So, even if CRTC1 is not directly associated with the development of depression in individuals, its genetic variants could still have a role in mood disorders or other psychiatric disorders.

The involvement of CRTC1 in the etiopathogenesis of major depressive disorder has been shown by different method in mice but remains elusive in human. This protein needs a lot more investigation, especially at the cellular level, where its role in plasticity and the link with the consequent depressive behaviour is still unclear.

The aim of this thesis is thus to dig deeper into the role of CRTC1 into the plasticity mechanisms. We first managed to show that CRTC1 protein level are decreased upon a chronic stress. Then we tried a viral re-expression of CRTC1 to restore the protein level in our *Crtc1* KO mouse model and explore the effects on its depressive-like behaviour. In term of plasticity we explored both proliferation and survival in males and in females *Crtc1* KO mice, as long with synaptogenesis and we studied granule neuron morphology and spines density in mature neurons. We then studied the memory capacities in these mouse without finding any alteration and finally we explored the vell population in the surroundings of the granule cells. Overall we explored several plasticity processes in our mouse model to try and connect its alteration to the depressive-like behaviour that has been previously described in the model.

MATERIALS AND METHODS

I. Mice

Crtc1$^{-/-}$ mice were generated as previously described (Breuillaud et al., 2012). Mice were housed and bred in the Centre of Psychiatric Neuroscience's animal facility under a 12-hour light-dark cycle, with ad libitum access to tap water and standard rodent chow diet. The *Crtc1*$^{-/-}$ and *Crtc1*$^{+/+}$ animals used in the experiments were generated from breeding cages composed of one *Crtc1*$^{+/-}$ male and two *Crtc1*$^{+/-}$ females, which were backcrossed for at least ten generations with C57BL/6N mice (Charles River Laboratories, Saint-Germain-sur-l'Arbresle, France). After 3 weeks, they were weaned, and group housed (from two to five per cage). All animal experiments were conducted in accordance with the Swiss Federal Veterinary Office's guidelines and were approved by the Cantonal Veterinary Service.

II. Genotyping

Shortly after weaning, a biopsy was performed in the mice ears, also serving for identifying the mice in the cage. The DNA was extracted from the biopsy with a first solution composed of NaOH (25mM) and EDTA (0.2mM), incubated for 25 min at 95°C. The samples were then rapidly brought to room temperature and a second solution was added, composed of Tris HCl pH 5.0 (40mM).

Alleles from all three genotypes were amplified by Polymerase Chain Reaction. The following primers were used:

(a) forward 5'-GGCAGTACATAGCTTCTCTGGTGA-3'

(b) reverse 5'-GCAGGGCAGAGTCAGAGTTGGT-3'

(c) reverse 5'-GACAGTATCGGCCTCAGGAAGAT CG-3'

Crtc1$^{+/+}$ allele was amplified using primers (a) and (b), and *Crtc1*$^{-/-}$ allele using primers (a) and (c) (Figure 9). The following PCR program was used: 3min at 94°C, 35 cycles of 15s at 94°C, 45s at 58°C, 90s at 72°C, and finally 7min at 72°C. Amplified DNA fragments were resolved in a 1% agarose gel.

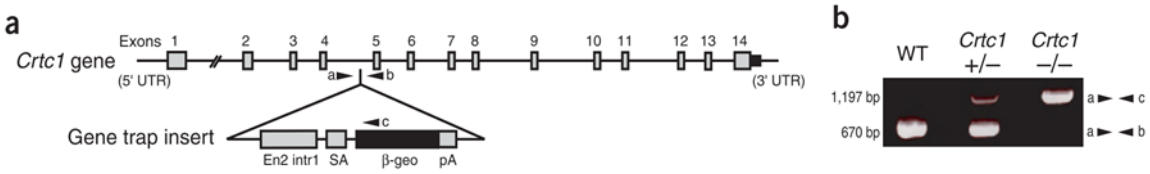


Figure 9. *Crtc1*$^{-/-}$ mice genotyping. (A) Schematic representation of the construction of the gene trap on the *Crtc1* gene with the different locations of the primers a, b and c serving for the genotyping of the mice. (B) Final image of the genotyping procedure with the different profiles of wild type, knock-out and heterozygous mice (taken from Breuillaud et al., 2009).

III. Adeno-Associated Virus Injection

Adeno-associated viruses were purchased from the Viral Vector Production Unit of the Universitat Autònoma de Barcelona and were created as previously described (Parra-Damas et al., 2014). The viruses contained the AAV2 genome with the AAV10 packing vector. The control virus expressed only GFP whereas the CRTC1 virus expressed CRTC1 with a C-terminal myc-tag and GFP; they were both under the regulation of a CMV promoter, which is unspecific. The viruses were either diluted in PBS to reach a final concentration of 3.4E+12 gc/mL and injected bilaterally (0.5 µL) in medial prefrontal cortex (AP +1.7 mm; ML ±0.4 mm; DV -1.4 mm), or undiluted (1.01E+13 gc/mL) and injected bilaterally (0.5 µL) in the ventral hippocampus (AP -3 mm; ML ±3 mm; DV -3.6 mm). The AAV viruses were injected in 6 weeks-old mice.

IV. Moloney Murine Leukemia Virus injection

Moloney Murine Leukemia Viruses (MMLV) were kindly given to us by the group of Nicolas Toni, from their own production. These viruses expressed the red fluorescent protein (RFP) under a CAG promoter. The virus was diluted in PBS with 0.1% of BSA and injected bilaterally in the DG (AP -2 mm; ML ±1.5 mm; DV -2.4 mm). When the cannula was inserted into the brain, it was moved to -2.5 mm, let there for ~5 seconds, and moved back to -2.4 mm to create a tiny hole to ease the virus diffusion. These mice were 10 weeks old when they were injected, and they were sacrificed 21 days after the viral injection.

V. Intracranial surgery

Mice were weighed and injected with buprenorphine (0.1 mg/kg) before being anesthetized with a mix of isoflurane and O_2 (1.5L/min of dioxygen with 2.5% of isoflurane). The mice were then placed in a stereotaxic frame. The head was disinfected with a 70% ethanol solution, hair was cut short with scissors and skin was then disinfected with betadine. Skin was cut from between the eyes until the back of the head and maintained open with clamps. The injection locations (antero-posterior

and medio-lateral) were marked using the stereotaxic coordinates and the skull was pierced with a specific drill. The injection zones were quickly cleaned with a 0.9% saline solution.

The syringe (Hamilton, 5 µL) was placed on a pump and connected to the cannula (30 Gauge) with a tubule. The tubule was filled with water and an air bubble was created before filling the cannula with the viral solution. The cannula was approached to the surface of the brain and slowly inserted (0.2 mm / 5 seconds) until it reached the targeted coordinates. The cannula was let there for 5 minutes and then, the pump injected 0.5 µL of the viral solution at a rate of 0.1 µL per minute. After 5 more minutes, the cannula was slowly removed from the brain and directed toward the other injection location. After the bilateral injection, the skull was rehydrated with a 0.9% saline solution, and the skin was sutured with stitches (4 to 5 depending on the size of the opening).

The concentration of isoflurane in the mask was slowly reduced to zero and the still sleeping mice were injected with 0.9% saline solution (100 µL / 10 g) to rehydrate them before being placed under a heating lamp until they woke up. For three days, the mice were kept with their cagemates in a ventilated closet and injected with buprenorphine (0.1 mg/kg) every 12h.

VI. 5-Bromo-2′-deoxyuridine (BrdU) injection

BrdU (Sigma-Aldrich, B9285) was dissolved in a sterile saline solution (0.9%) to inject a concentration of 100 mg/kg to the mice. The dissolved BrdU was kept at 4°C between each injection. Right before each injection, it was heated to 37°C. Mice were weighted and injected intraperitoneally (100 µL / 10 g) 3 times on the same day, 2 hours between each injection. The injections were done during the active phase of the mouse (dark). For basal proliferation and survival, the mice were injected with BrdU at 9 weeks old.

VII. Behavior

a) Open Space Forced Swim Test (OSFST)

This test was adapted from Stone et al., 2008 and Stone and Lin, 2011. The mice were placed in the middle of a rat tub cage (24 w × 43 h × 23 l cm) filled with 34 ±0.5°C tap water added with milk (approximately 10 mL). Mice were submitted to

individual daily swim session of 15 min during four consecutive days, and then twice per week for three weeks. All sessions were recorded with a camera, which was situated above the cage. Immobility time was defined when none of their four limbs nor tail were moving, and it was scored manually and blindly.

b) Novelty Induced Hypophagia (NIH)

Mice were trained for one hour twice a day for two days to drink sweetened milk in their home cage. The sweetened milk was contained in a polypropylene tube of 15 mL with a hole at the bottom closed by a glass bead (5 mm diameter) to make a sipper. On the third day, their home cage was placed in front of a camera, in a room with dim light (~27 lux), and they were presented with sweetened milk during 15 min. On the fourth day, the mice were put into an empty cage (no bedding) in a room with bright light (~1200 lux) and again the sweetened milk was presented to them during 15 min. Two parameters were recorded: the latency before they went to drink the milk for the first time and the total quantity drunk (weighing the tube before and after the session).

c) Chronic Restraint Stress (CRS)

For this test, C57BL/6J wild-type mice were purchased from Charles River Laboratories; they were housed four mice per cage and acclimated for one week to the animal facility. When the mice were 20-week-old, they were randomly divided into a control and stressed group, and the stressed mice were subjected to the CRS, while the control mice were submitted to daily handling. The stressed mice were immobilized in a polypropylene tube of 50 mL (115 mm length and 30 mm diameter) with the head turned to the bottom of the tube where there were three 0.4 cm air holes. All escape was prevented by blocking the opening of the tube with a piece of paper, the tail being out of the tube and free to move. They were immobilized during 2 hours per day for 21 days. Both groups could not access food and water during the two hours of testing. At the end of the two hours, the mice returned to their home cage immediately. They were sacrificed 48h after the last session of CRS.

d) Y-maze spontaneous alternation

This test has been performed as previously described (Holcomb et al., 1999; Richetin et al., 2020). *Crtc1* KO and WT mice were tested in a Y-maze apparatus made

of white acrylic, with 40 x 8 cm arms and 15 cm high walls. Each arm was randomly assigned a letter A, B and C. The mice were placed in the centre of the maze and could explore freely during 6 min. This test is based on the willingness of rodents to explore new environments, and the subject should show a tendency to enter a less recently visited arm. The entry is counted when the mouse has all four limbs in the arm. The whole procedure is recorded and analysed with ANY-maze: the number of arm entries are monitored, and the number of good alternations (triads) are counted. The percentage of triads is an indication for the spatial working memory of the mouse, a process that requires the implication of the hippocampus (Griffin, 2021).

e) Object recognition test

This test is based on the propensity for rodents to prefer novelty and the faculty they have to remember previously encountered objects (Dodart et al., 1997; Ennaceur and Delacour, 1988; Richetin et al., 2020). The day before the test, the mice were placed into an open-field arena (70 x 70 cm) for habituation and they explored it for 10 min. Their movement were tracked by ANY-maze to assess their motricity. The day after habituation, two same objects were placed into the open field, in the non-anxiogenic zone (10 cm from the walls). The mice were put into the arena and could explore during 15 min, before going back to their home cage for 4 min. One of the objects was changed, and the mice reintroduced into the open field for 6 min. Their exploration times were assessed manually to avoid any mistake from the software. Both the arena and objects were cleaned between two mice. The memory for the familiar object was calculated as a preference index for the new object: the percentage of time spent exploring the new object per total time spent exploring both objects.

f) Object location test

This test is based on the tendency of rodents that have been exposed to two identical objects to preferentially explore the one that has been displaced (Ennaceur et al., 1997; Richetin et al., 2020). This test was done the following day of the object recognition test, so no habituation to the open field was necessary. We did three versions of this test with three different distances between objects. For the first part of the task, the trial, the mice were placed in the open field with two objects never encountered before. These two objects were placed close to each other (15 cm), 10

cm from the back wall of the open field, and on one of the walls there was a grid printed on a piece of paper to serve as a visual cue for the mice to orient themselves in the open field. The mice were free to explore both objects for 15 min and then returned to their home cage where they stayed for 4 min. On the first test, one of the objects was displaced from 15 cm to 23 cm. On the second test, the object was displaced from 15 to 31 cm. On the third test, the object was displaced from 15 cm to 39 cm. For both trial and test, the time spent exploring both objects was manually recorded. As for the object recognition test, we calculated a preference index for the displaced object.

VIII. Sacrifices

a) Perfusion

Mice were weighted and injected with pentobarbital (300 mg/kg; diluted to inject 100 µL / 10 g) and their level of sleep assessed by pinching the limbs and tail. They were then placed under a hood, where they were perfused intracardiacally with a 0.9% saline solution, which was then changed for a 4% paraformaldehyde solution. The brain was then removed and let during 24h in a tube filled with the 4% paraformaldehyde solution. After 24h, the solution was changed for a 30% sucrose solution. After a few days in the sucrose, the brains were frozen with cold isopentane (-70°C) and then kept in freezer (-80°C) until further use.

b) Beheading

Mice were placed in a box with a tissue soaked with isoflurane until complete anesthesia. Their head was then cut with scissors, the brain quickly removed and thrown in cold isopentane to be frozen, or for the Golgi staining method, they were quickly rinsed in milli-Q water and put in the mix of A and B solution.

IX. Immunofluorescence

a) General procedure

Brains slices of 40 µm were cut with a cryostat. The slices were kept in a cryoprotectant solution: 30% Ethylene glycol, 30 % Sucrose, 40% Phosphate Buffer (0.1M) and stored in a -20°C freezer until further using. Slices were rinsed three times 10 min in PBS at room temperature. Only for slices prepared for CRTC1 immunolabeling, an antigen retrieval step was added and consisted in placing them in

a sodium citrate buffer (Sodium citrate 10 mM, 0.05% TX-100) at 80°C during 30 min, and then rinsing them again three times. They were then put in a blocking solution for one hour: 10% normal goat serum (NGS), 0.05% TX-100, 89.95%% PBS. They were then incubated with the primary antibodies (3% NGS, 0.5% TX-100, 96.5% PBS; see references in Table 2A) overnight at 4°C. On day two, slices were rinsed three times 10 min in PBS, and then incubated with secondary antibodies (3% NGS, 0.5% TX-100, 96.5% PBS; see references in Table 2B) during one hour at room temperature in the dark. Again, they were rinsed three times in PBS and incubating 10 min with 1/30000 DAPI (3% NGS, 0.5% TX-100, 96.5% PBS). They were finally rinsed two times 10 min in PBS and kept in PBS until mounting procedure. The slices were mounted on SuperFrost© slides (Thermo Scientific™) with Vectashield mounting medium (Vector laboratories, H-1000), covered with slide coverslips which was maintained with quick dry nail polish. The slides were let at room temperature in the dark during 24 hours before being stored at 4°C.

b) Specific procedure for BrdU

Procedure is the same as for the other antibodies except between the first rinsing and the blocking step. For cell count, one slice every 4 slices, both for the dDG and for the vDG were taken. After the slices were rinsed three times 10 min in PBS at room temperature, they were incubated during 2 hours in Formamide (2X SSC, 50% formamide, 40% distilled water) at 60°C and then washed twice 15 min at room temperature in saline-sodium citrate (SSC; 0.15M NaCl, 0.015M sodium citrate, distilled water). The slices were then incubated 30 min at 37°C in HCl (HCl 2N), rinsed once 15 min with borate buffer (0.1M pH 7; 2.38% boric acid, 1.27% Borax, 96.35% distilled water, pH 8.4) and washed six times 10 min in PBS. Then, slices are incubated 1 hour at room temperature in blocking buffer, and the same procedure as for the other antibodies is carried out according to the aforementioned protocol.

c) Antibodies

A. Primary

Targets	Species	Brand	Reference	Concentration
GFP	rabbit	Invitrogen	A6455	1/500
Myc Tag	mouse	Cell Signaling	9B11	1/1000
BrdU	rat	abcam	ab6326	1/500
NeuN	rabbit	abcam	ab177487	1/1000
CRTC1	rabbit	Cell Signaling	C71D11	1/500
RFP	rabbit	Rockland	600-401-379	1/500
Parvalbumin	mouse	Swant	PV 235	1/1000
GluR2/3	rabbit	Millipore	07-598	1/1000

B. Secondary

Targets	Species	Type, wavelength	Brand	Reference	Concentration
rabbit	goat	Alexa, 488	invitrogen	A11008	1/500
mouse	goat	Cy3, 550	Jackson IR	115-165-146	1/500
rat	donkey	Cy3, 550	Jackson IR	712-165-153	1/300

Table 2. References and concentrations of the different antibodies used for the immunofluorescence experiments. (A) Primary and (B) secondary antibodies list.

X. Punches, protein extraction and western blot

a) Punches

Non-perfused brains were cut with the cryostat in 300 µm slices and kept frozen on microscope slides. They were then placed at -20°C under binocular magnifier, and different brain regions were microdissected (Figure 10). The medial prefrontal cortex was collected with a 0.5 mm punch and all the hippocampal regions were collected with a scalpel. The tissues were placed in 1.5 mL tubes and stored at -80°C until further use.

b) Protein extraction

A RIPA solution was prepared: 50 mM Hepes, 150 mM NaCl, 1 mM EDTA, 2.5 mM EGTA, 10% Glycerol, 1% Nonidet P40, 1% Deoxycholate, 0.1% Sodium dodecyl sulfate. Right before use, a protease inhibitor cocktail (Sigma; 100 µL) and a phosphatase inhibitor cocktail (Roche, PhosSTOP™; one tablet) were added to 10 mL of the RIPA solution. The volume of RIPA solution added to the sample was adapted depending on the quantity of tissue (Table 3).

Region	RIPA volume (µL)
Medial Prefrontal Cortex (mPFC)	50
Dorsal Dentate Gyrus (dDG)	100
Dorsal Cornu Ammonis (dCA)	150
Ventral Dentate Gyrus (vDG)	100
Ventral Cornu Ammonis (vCA)	200

Table 3. RIPA volume added depending to the type of sample

The tissues were mechanically lysed with a plunger; the tubes were then shaken during 15 min at 4°C at 350 rpm before being centrifuged 15 min at 4°C at 10'000 rpm. The supernatant was transferred in a new tube and the quantity of protein was assessed with a BCA assay (ThermoFisher Scientific, BCA assay kit, 23225).

c) Western Blot

Samples were diluted in sample buffer (65.8 mM Tris HCl pH 6.8, 100 mM DTT, 2% SDS, 26.3 % Glycérol, 0.01% Bromophenol blue) so that the final volume deposed on the gel contained 20 µg of proteins (each sample was adjusted). Samples were heated 5 min at 95°C before they were deposed on a SDS-polyacrylamide gel, composed of a stacking gel (4%) and a resolving gel (8%) and migrated at 90V during 1h30. The proteins were then transferred on nitrocellulose membranes (Bio-rad, #1704158, 7 x 8.5 cm, 0.2 µm) with the Trans-Blot® Turbo™ Transfer System. Membranes were directly incubated in blocking solution (TBST, 1 mM Tris-base, 15 mM NaCl and 0.01% Tween 20, added with 5% milk) during 1 h at room temperature, before being quickly rinsed with TBST. Membranes were then incubated with primary antibodies (see references in Table 4) in TBST added with 5% bovine serum albumin overnight at 4°C on a shaker. The next day, membranes were rinsed three times 10 min in TBST and

then incubated with secondary antibodies (see references in Table 4) in TBST added with 5% milk 1 h at room temperature in the dark. Again, membranes were rinsed three times 10 min with TBST and kept in TBST until revelation. Membranes were scanned using Odyssey® CLx imaging system (LI-COR) and quantifications were done with the related software: Image Studio™ Software.

d) Antibodies

A. Primary

Targets	Species	Brand	Reference	Concentration
CRTC1	rabbit	Cell Signaling	C71D11	1/2000
β-actine	mouse	abcam	8226	1/10000

B. Secondary

Targets	Species	Type, wavelength	Brand	Reference	Concentration
Rabbit	Goat	IRDye800	Licor	611-132-122	1/10000
Mouse	Goat	IRDye700DX	Licor	610-130-121	1/10000

Table 4. References of the different antibodies used for the western blot revelation. (A) Primary and (B) secondary antibodies.

XI. Spine analysis

21 days after MMLV injections, mice were perfused, and their brains were cut to 40 µm slices. The signal of the red fluorescent protein was enhanced with immunofluorescence and, using a confocal microscope (Zeiss LSM 800), we used the biggest objective (x63, oil) to visualize the spines on the granular neuron dendrites. As many dendrite samples were imaged as possible in the granular cell layer and in the molecular layer, from as many different neurons as possible (from 3 to 5). Z stacks from black to black were taken with the microscope. The pictures were then analyzed in 3 dimensions using Imaris XT (Bitplane AG) software. The resolution was high enough not only to count the number of spines, but also to determine their type (Figure 7).

XII. Golgi staining

a) Slices' preparation

Brains were collected fresh from 12 weeks-old mice, rinsed in milliQ water before being plunged in a mix of solution A and B from the FD Rapid GolgiStain™ Kit (FD Neurotechnologies, Inc.). The mix was changed the day after, and they were then let in this mix for 10 days. The brains were then transferred in solution C and let there for 3 days. The brains were then cut with a vibratome in sections of 150 µm, mounted on gelatin-coated (3%) microscope slides. Slices were dried at room temperature. Staining procedure was made following the kit's instructions (Table 5). Slices were mounted with Permount™ (Fisher Chemical™ SP15-500) and the coverslips were fixed with "vernis cochon" (M.O. Cochon Vernis Protecteur Isolant Dermatologique) and dried at room temperature in the dark.

Solution	Time	Repetition
Milli-Q water	4'	2
Solution D/E	10'	1
Milli-Q water	4'	2
Ethanol 50%	4'	1
Ethanol 75%	4'	1
Ethanol 95%	4'	1
Ethanol 100%	4'	4
Xylene	4'	3

Table 5. List of steps for the staining procedure for a Golgi staining after the slices preparation.

b) Analyze

Slices were observed with an epifluorescence microscope. Neurons to analyze were chosen when they met these criteria:

- Cell body in the granular cell layer of the dentate gyrus and in the middle of the slice
- Ramifications intact

- Full cell isolated from any cluster

Once the cells were found, they were captured using the 40x objective in stack of pictures spaced of 1 µm. As many cells as possible were imaged: from 4 to 16 neuron per dDG or vDG per animal. The stacks created were then opened with Fiji (ImageJ). Contrasts were increased and the images were transformed in binary values. Then the “Simple neurite Tracer” plugin was used to trace every ramification on a 3D reconstruction. A Sholl analysis was done to complete the other measurements (intra software). To study the spines, one ROI was determined for each sublayer of the molecular layer per neuron, and the spines were counted and reported on the length of the dendrite sample analyzed.

XIII. Statistical analysis

All statistical analyses were done with GraphPad Prism 9.1.0 for Windows, GraphPad Software, La Jolla California USA. All data are presented as mean ± SEM. P-values of $p < 0.05$ were considered as statistically significant. All data were submitted to a Shapiro-Wilk test to check the normal distribution. When two groups were tested, a student t-test was performed when the data were normal, when not, a Mann-Whitney test was performed. When there were four groups tested, a two-way ANOVA (post hoc: Šidák) or a mixed effect analysis (post hoc: Tukey) was performed when the data were normal, when not, a Kruskal-Wallis was performed (post hoc: Dunn’s).

RESULTS

I. CRTC1 expression is decreased in brain regions relevant for depression after chronic stress

Our team previously showed that the CRTC1 KO mouse model exhibits a strong depressive-like behaviour (Breuillaud et al., 2012). We then wanted to know if inducing depression in a WT mouse would be associated with a downregulation of CRTC1 expression. Depression is not caused by the dysfunction of only one brain region, but is mainly due to the altered interaction between multiple brain regions, such as the frontal lobe, the hippocampus (HPC), the temporal lobe, the thalamus, the striatum and the amygdala (Zhang et al., 2008). Since our team previously showed decreased dopaminergic and serotoninergic turnover, as long with decreased *Bdnf* and CREB-regulated genes expression, both in the HPC and in the medial prefrontal cortex (mPFC; Breuillaud et al., 2012), we focused our investigations in these two brain regions. We subjected 20 weeks-old mice to a chronic restraint stress (CRS) paradigm: the mice were placed in a 50 mL Falcon tube with no escape possible during 2 hours per day for 21 days (Figure 10A). At the end of the 21 days, the mice were sacrificed and the CRTC1 protein levels were determined by western blot. We found lower CRTC1 levels both in the mPFC (p = 0.0499, unpaired t-test; Figure 10B) and in the ventral dentate gyrus (vDG; p = 0.0282, unpaired t-test; Figure 10D), but not in the dorsal dentate gyrus (dDG; p = 0.6952, unpaired t-test; Figure 10C), and the dorsal and ventral Cornu Ammonis (dCA and vCA; p = 0.5460 and p = 0.4497, unpaired t-test; Figure 10E et 10F), as compared to unstressed mice. These results suggest that chronic stress may impinge on CRTC1 levels both in the vDG and in the mPFC, which supports the involvement of CRTC1 in the pathophysiological cellular processes of stress-induced depression.

II. Is viral vector-mediated CRTC1 expression able to rescue the depressive-like phenotype of CRTC1 KO mice?

The CRTC1 KO mouse model showed a depressive-like phenotype that was accompanied by alterations in neurotransmitter turnover and gene expression both in the mPFC and in the HPC. Furthermore, in depressed WT mice, we saw a decreased expression of CRTC1 both in the mPFC and in the HPC. From these data, we hypothesized that a restoration of CRTC1 expression in the brain regions relevant for

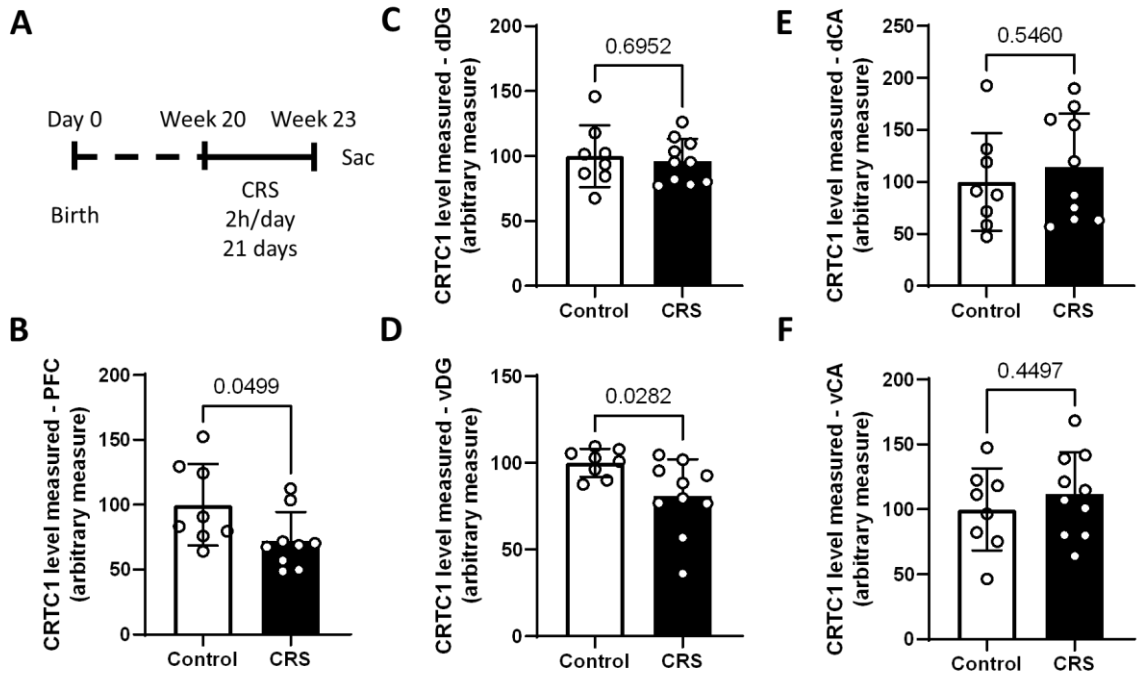


Figure 10. Expression of CRTC1 measured by western blot in different brain regions following a CRS paradigm. (A) Mice were subjected to CRS when they were 20 weeks-old, they were maintained in a Falcon tube during 2 hours per day for 21 days. At 23 weeks-old, they were sacrificed, and their brain processed to evaluate the CRTC1 protein levels by WB in the mPFC (B), dDG (C), vDG (D), dCA (E) and vCA (F). Unpaired t-test, n=8-10.

depression would be sufficient to rescue the phenotype. A group at the Universitat de Barcelona, led by Carlos Saura, used a viral vector overexpressing CRTC1 in two Alzheimer's disease mouse models, the double knock-out for presenilin genes (*PS* cDKO) and the β-amyloid precursor protein ($APP_{Sw,Ind}$) transgenic mouse (Parra-Damas et al., 2017, 2014). In both models they showed increased memory and increased expression of CREB-regulated genes *Nr4a1*, *Nr4a2* (in both) and *Arc* (only in $APP_{Sw,Ind}$). In addition, *PS* cDKO mice injected with the viral vector expressing CRTC1 showed an increase in total MAP2 staining (used to study the dendrites) and an increase in dendrite thickness in the CA3.

The viral vector used in these studies is an adeno associated virus (AAV) with an unspecific cytomegalovirus promoter (CMV). The control virus expressed only the green fluorescent protein (GFP), and the CRTC1 virus expressed CRTC1 with a *myc* tag and GFP (Figure 11A). As hippocampal injections of this AAV-CRTC1 construct improved the long-term memory of the Alzheimer's disease mouse models, we presupposed that this virus would be able to restore at least some of the depressive-like symptoms in our mouse model.

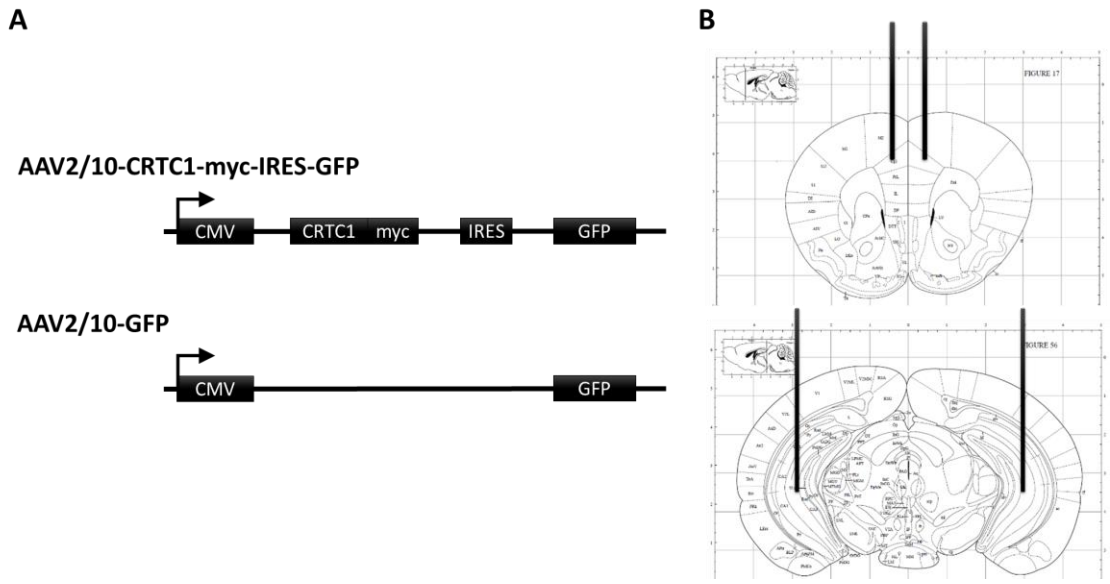


Figure 11. Viral vector injection. (A) Both vectors were under the control of the CMV promoter. The experimental virus expressed CRTC1 coupled with a *myc* tag and GFP, the control virus expressed only GFP. (B) The viruses were injected either in the mPFC (Upper panel; AP + 1.7 mm, ML ± 0.4 mm, DV – 1.4 mm) or in the vHPC (Lower panel; AP - 3 mm, ML ± 3 mm, DV – 3.6 mm).

We made two groups: one group injected in the mPFC, and the other one in the vHPC (Figure 11B). We injected these mice when they were 6 weeks old. Two weeks later, we subjected them to two paradigms: the open-spaced forced-swim test (OSFST) and the novelty induced hypophagia (NIH). For depressed patients, the effect of antidepressant is not immediate, but rather takes a few weeks. It is thus better to have a mouse model of depression that responds to chronic antidepressant treatment rather than acute treatment. Our team used this OSFS paradigm before (Breuillaud et al., 2012; Elsa M. Meylan et al., 2016), and saw that CRTC1 KO mice were much more immobile than WT mice.

Unfortunately, we did not observe the same results in our mice, because both groups (mice injected in the mPFC or in the vHPC; Figure 12A and 12B) displayed no statistical difference in the time spent immobile during this paradigm (mPFC: $F(3, 25) = 1.674$, $p = 0.1979$, mixed effect analysis; vHPC: $F(3, 24) = 1.012$, $p = 0.4044$, mixed effect analysis). There is an effect of time, meaning that all mice, as they are subjected to this test day after day, are more and more immobile over time (mPFC: $F(2.079, 46.67) = 13.85$, $p<0.0001$, mixed effect analysis; vHPC: $F(2.429, 48.85) = 36.26$, $p<0.0001$, mixed effect analysis), but there is no difference between the subgroups (*Crtc1*$^{-/-}$ mice injected with the control or CRTC1 virus, and *Crtc1*$^{+/+}$ mice injected with one or the other virus).

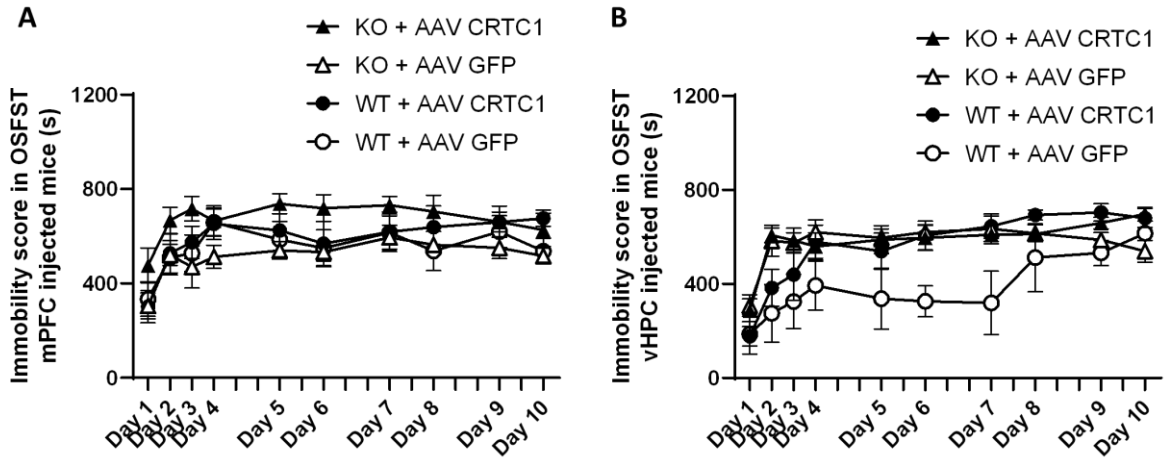


Figure 12. OSFST immobility time. Time spent not moving in the OSFST by the mice injected with the control virus (AAV GFP) or the CRTC1 virus (AAV CRTC1) in either the mPFC (A) or the vHPC (B). Mixed effects analysis, n=9.

All mice were then subjected to the NIH the week after the end of the OSFST. This test is based on the competition between the appetence for sweetened milk and the anxiety created by the anxiogenic environment. This test compares the latency to drink the sweetened milk in the home cage and in a novel environment. There were no differences in the latency to drink sweetened milk when the mice were in their home cage (mPFC: genotype F (1, 24) = 3.481, p = 0.0744, virus F (1, 24) = 1.142, p = 0.2958, two-way ANOVA; vHPC: genotype F (1, 21) = 0.1363, p = 0.7157, virus F (1, 21) = 0.001, p = 0.9752, two-way ANOVA; Figure 13A and 13C). Whether the mice were injected in the mPFC or in the vHPC, there were no statistical difference between the *Crtc1*$^{+/+}$ mice infected with the control virus or the CRTC1 virus, or between the

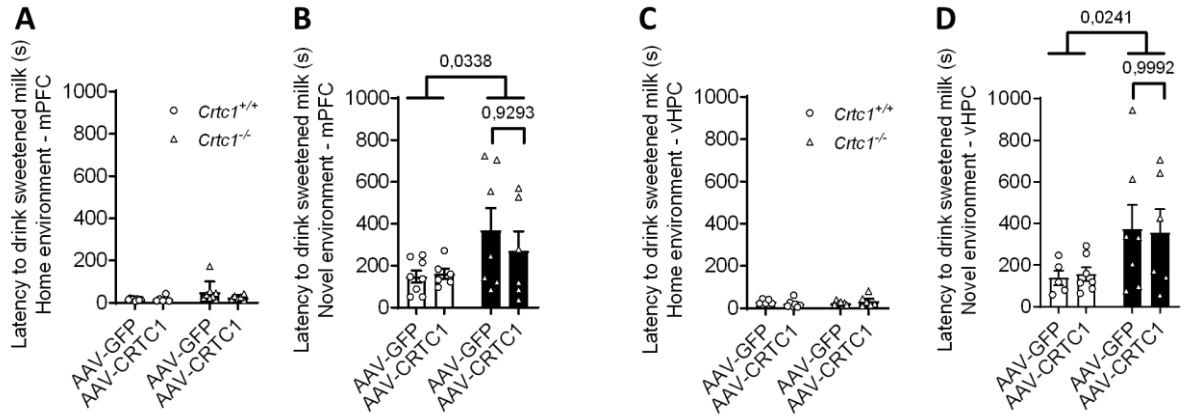


Figure 13. NIH results showed no difference between mice infected with the CRTC1 virus in comparison with the control virus. (A & B) Latency to drink milk while in their home cage (A) or in a novel environment (B) for the mice that received the viral injection in the mPFC. Two-way ANOVA, n=8-6-7-6. (C & D) Latency to drink milk while in their home cage (C) or in a novel environment (D) for the mice that received the viral injection in the vHPC. Two-way ANOVA, n=6-8-7-8.

Crtc1$^{-/-}$ mice infected with one or the other virus (mPFC: F (1, 23) = 0.3415, p = 0.5647; vHPC: F (1, 21) = 8.19x10^{-5}, p = 0.9929, two-way ANOVA; Figure 13B and 13D). However, the *Crtc1*$^{-/-}$ mice took overall more time to start drinking the milk as compared to the *Crtc1*$^{+/+}$ mice (mPFC: F (1, 23) = 5.093, p = 0.0338; vHPC: F (1, 21) = 5.912, p = 0.0241, two-way ANOVA).

We checked the infection site in those mice and found out a very different pattern of expression of CRTC1-myc compared to the expression of CRTC1 in *Crtc1*$^{+/+}$ mice (Figure 14 et 15). Indeed, CRTC1 in *Crtc1*$^{+/+}$ mice is expressed mostly in granular neurons in the DG, in the dendrite and around the nucleus, with a diffused expression in the hilus, but when we observed the infection of KO mice with the AAV-CRTC1, we see that the virus is expressed only in the hilus (diffusedly) and in some soma of hilar cells, but nothing in the granular neurons.

These observations suggest that the pattern of expression of AAV-CRTC1 is not the same as the endogenous CRTC1's one in WT conditions. This may explain why these experiments gave rise to inconsistent and inconclusive behavioural data. Therefore, we decided to let aside this experiment and explore another axis of the depression etiology, which is plasticity.

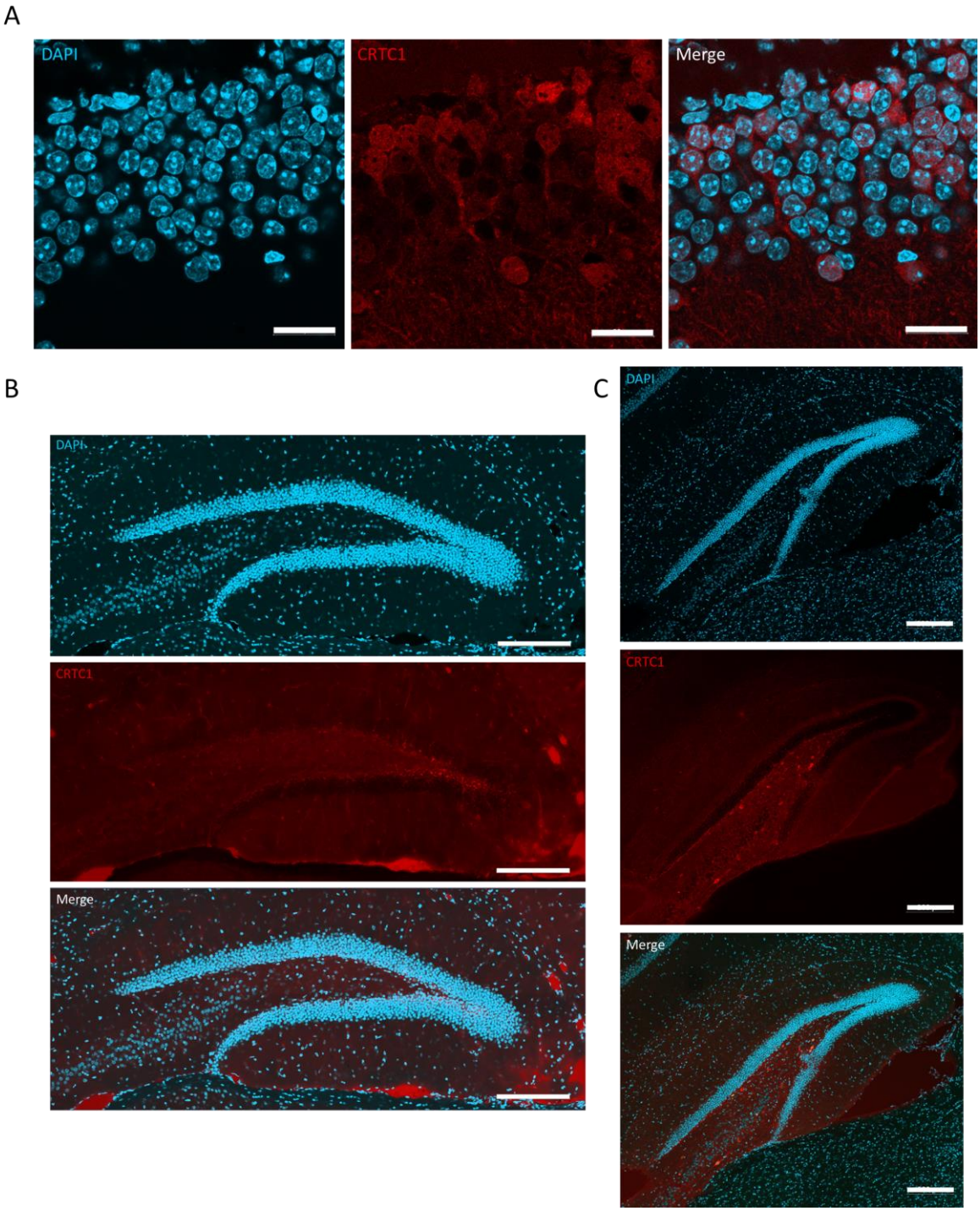


Figure 14. CRTC1's pattern of expression in the DG. (A) Close up on the granular cell layer of a naïve WT mouse, where CRTC1 is localised in the dendrites of the granular neurons, in the soma, and sometimes in the nucleus. Scale bar 20 µm. (B) Wide view of the DG of a naïve WT mouse in which CRTC1 is expressed in the inner granular cell layer and more diffusely in the hilus. Scale bar 200 µm. (C) Wide view of the DG of a KO mouse infected with the AAV-CRTC1, which did not express CRTC1 in the granular cell layer but showed some cells expressing CRTC1 in the hilus. Scale bar 200 µm.

III. Proliferation and survival of newborn neurons in the hippocampus is not altered in *Crtc1*$^{-/-}$ male mice, but is altered in *Crtc1*$^{-/-}$ female mice

CRTC1 is involved in plasticity processes, such as the maintenance of L-LTP, and BDNF-dependent dendritic growth in cortical neuron. Moreover, it is involved in the regulation of CREB-mediated transcription of genes involved in plasticity: *Bdnf*, *c-fos*, *Zif268/Egr1* and *Arc* (Breuillaud et al., 2012; Kovács et al., 2007; Li et al., 2009; Zhou et al., 2006). Therefore, we wondered if CRTC1 had a role in adult hippocampal neurogenesis, and more particularly, if the neurogenesis processes were altered in our *Crtc1*$^{-/-}$ mouse model. Mice were sacrificed 24h after 5-bromo-2'-deoxyuridine (BrdU) injection to evaluate the proliferation of progenitor cells, and 30 days after BrdU injection to evaluate the survival of these newborn cells. However, no differences were found in males, neither for proliferation (dorsal: $p = 0.5449$; ventral: $p = 0.1349$, unpaired t-test) nor for survival (dorsal: $p = 0.8520$; ventral: $p = 0.8171$, unpaired t-test) of newborn neurons (Figure 16).

It has been long known that women are more susceptible to depression than men (Noble, 2005) and growing evidences show differences at the molecular and cellular levels. Concerning neurogenesis, studies show that females, depending on their hormone cycle, have a different level of proliferation but not of survival. Also, the females response to stress is different than males (Yagi and Galea, 2019). Our group found that *Crtc1*$^{-/-}$ females were very aggressive when raising offspring (Breuillaud et al., 2012), but did not do supplementary experiment to clearly depict the female *Crtc1*$^{-/-}$ phenotype. But even without knowing exactly their phenotype, we thought it would be interesting to assess adult hippocampal neurogenesis status in *Crtc1*$^{-/-}$ females.

In female mice that we sacrificed 24 hours after BrdU injection, we found significantly less BrdU+ cells in the dorsal ($p = 0.0095$, unpaired t-test), but not in the ventral ($p = 0.1014$, Mann-Whitney) dentate gyrus of *Crtc1*$^{-/-}$ mice as compared with *Crtc1*$^{+/+}$ mice. However, this decreased proliferation in the dorsal DG did not result in a decrease of BrdU+ cells in the *Crtc1*$^{-/-}$ female mice sacrificed 30 days after BrdU injection ($p = 0.9307$, Mann-Whitney). This means that even if CRTC1 could have a

role in the proliferation of newborn neurons in the female DG, this number is evened after a few weeks.

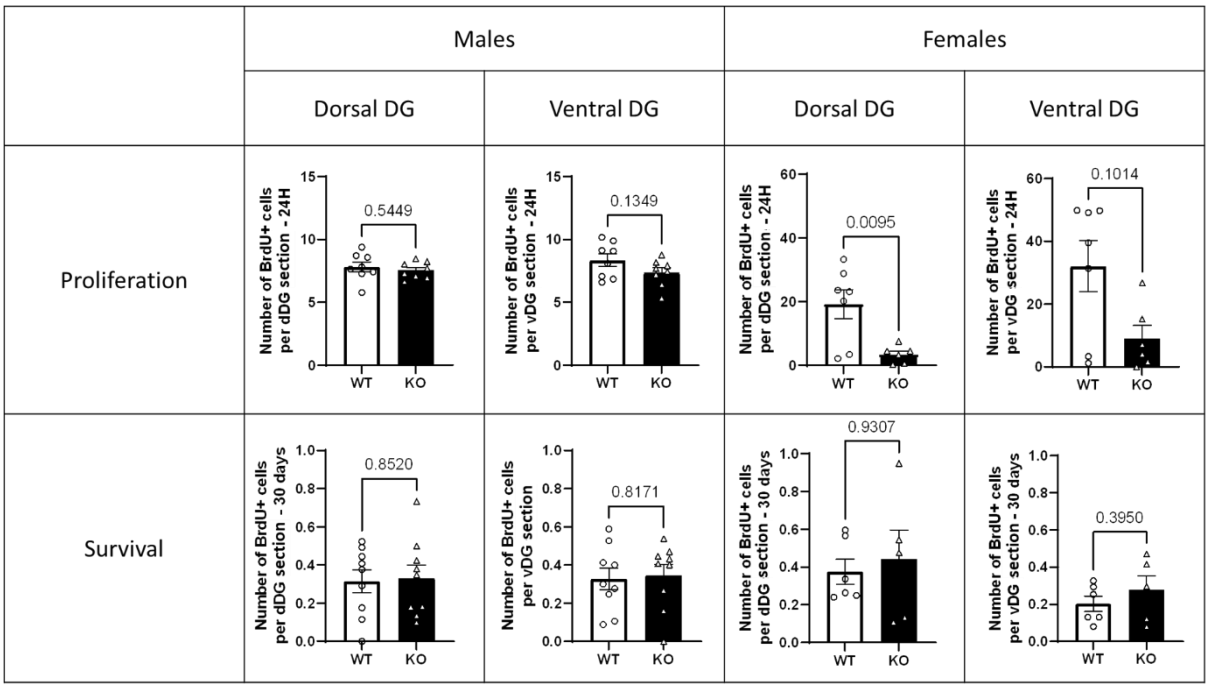


Figure 16. Neurogenesis study in *Crtc1*$^{-/-}$ mice. Counting of BrdU+ cells in both dorsal and ventral dentate gyrus, either 24h (up) or 30 days (down) after BrdU injection, in males (left) and females (right). Male, proliferation, unpaired t-test, n=7-8. Male, survival, unpaired t-test, n=9. Female, proliferation, unpaired t-test, n=7-6. Female, survival, unpaired t-test, n=6-5.

IV. Physical exercise has mixed effects on proliferation and survival in *Crtc1*$^{-/-}$ mice

Since the basal state of adult hippocampal neurogenesis is not affected in *Crtc1*$^{-/-}$ male mice, we hypothesized that a difference could be revealed in conditions that would normally increase neurogenesis. van Praag and colleagues, in 2005, showed a considerable increase of the number of BrdU+ cells in mice with an access to a running wheel in their home cage (van Praag et al., 2005). Accordingly, we incorporated a running wheel in the home cage of our mice and let them run freely while monitoring their physical activity. To evaluate the effect of running on proliferation, we let 14 weeks-old mice run for 5 consecutive days, on the 5th day, we injected them with BrdU, let them run again for 24 hours, and sacrificed them. To

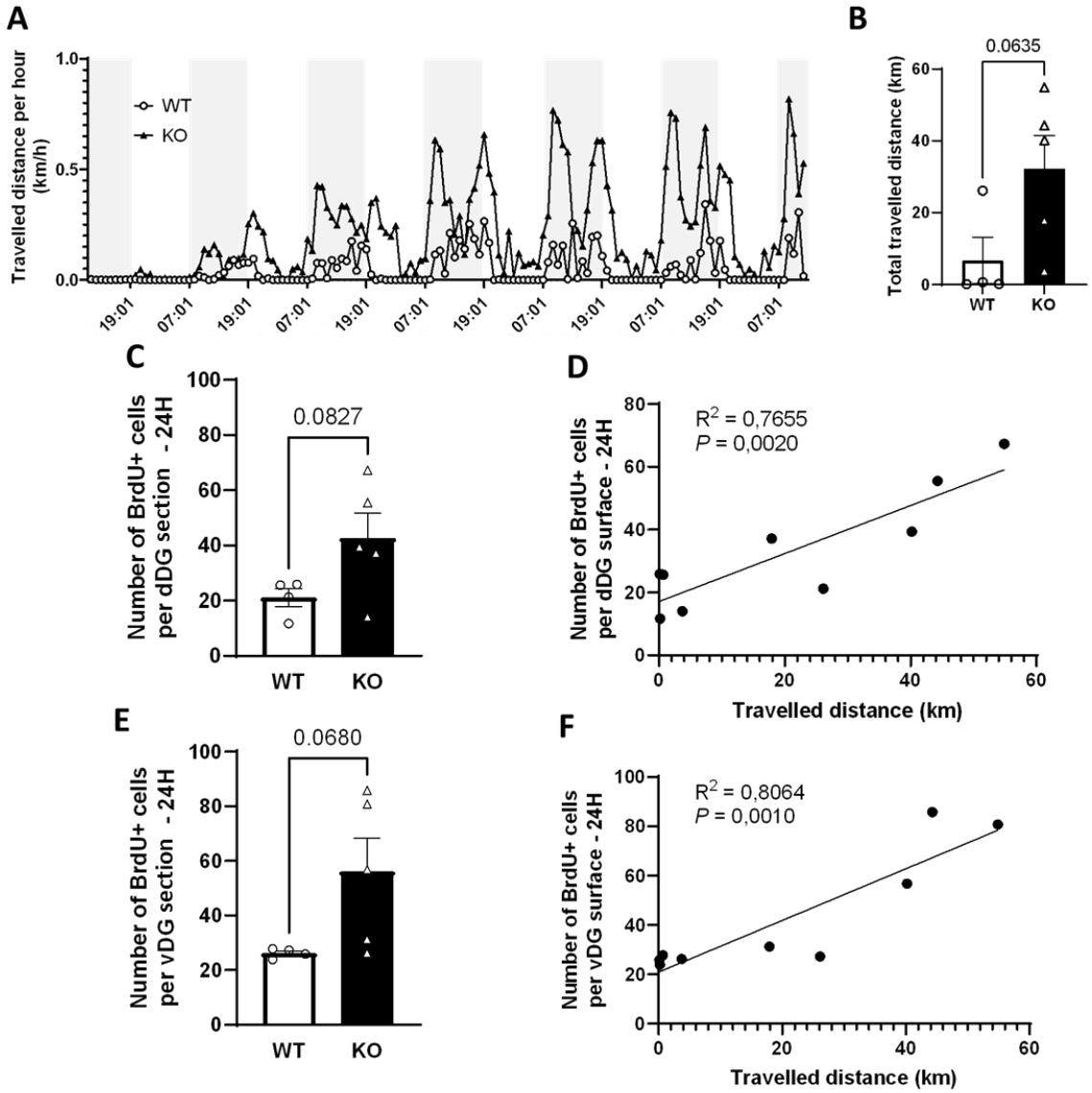


Figure 17. Effect of running on proliferation in the mice DG. (A) Mean of the number of kilometres run each day by WT and KO mice. Two-way ANOVA, n=4-5. (B) Sum of the total distance travelled during 6 days by both groups. Mann-Whitney, n=4-5. (C) Number of BrdU+ cells counted in the dDG, and (D) correlated with the distance travelled by each mouse. (E) Number of BrdU+ cells counted in the vDG and (F) correlated with the distance travelled by each mouse. Unpaired t-test and Pearson correlation, n=4-5.

evaluate the effects of running on survival, we let 8 weeks-old mice run for 5 days before the BrdU injections and let them run for 30 more days before sacrificing them.

We know from studies performed by our team that *Crtc1*$^{-/-}$ mice tend to be more active during the light phase than *Crtc1*$^{+/+}$ mice, but they reach approximately the same levels of activity during the dark phase (Rossetti et al., 2017). However, with a running wheel in the home cage, *Crtc1*$^{-/-}$ mice ran a lot more (Mean = 32.200 km) than *Crtc1*$^{+/+}$ mice, which barely ran (Mean = 6.775 km; p = 0.0635, Mann-Whitney), three out of the four mice tested ran less than 1 km in 6 days (Figure 17A and 17B). Nevertheless,

no significant difference in the number of BrdU+ cells between KO and WT mice could be observed, both in the dDG (p = 0.0827, unpaired t-test; Figure 17C) and in the vDG (p = 0.0680, unpaired t-test; Figure 17E), although the number of BrdU+ cells in each region was nicely correlated with the travelled distance in the running wheel (dDG: p = 0.0020, R = 0.7655; vDG: p = 0.0010, R^2 = 0.8064, Pearson correlation; Figure 17D and 17F).

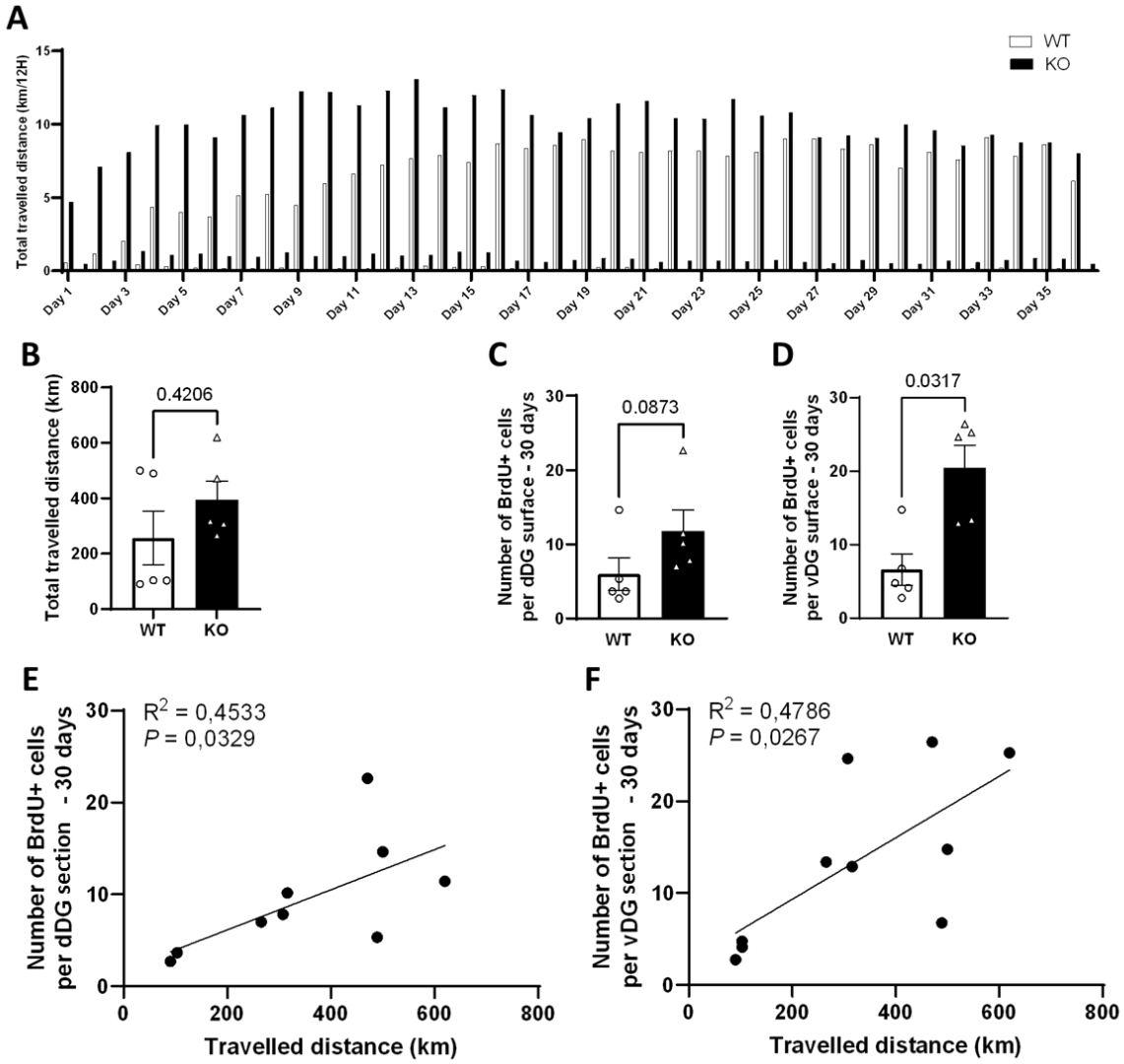


Figure 18. Effect of running on survival of BrdU+ cells in the mice DG. (A) Mean of the number of kilometres run each day by WT and KO mice. Mixed-effects analysis, n=5. (B) Sum of the total distance travelled during 6 days by both groups. (C) Number of BrdU+ cells counted in the dDG, and (E) correlated with the distance travelled by each mouse. (D) Number of BrdU+ cells counted in the vDG and (F) correlated with the distance travelled by each mouse. Unpaired t-test and Pearson correlation, n=5.

When the mice had access to the running wheel for 36 days, they ran between 100 and 600 km in total (Figure 18B), which is quite a lot. The KO mice ran more than the WT mice during the 10 first days, but then this difference slowly disappeared

(Figure 18A), and overall, there was no statistical difference in the total distance travelled between the two groups (p = 0.4206, Mann-Whitney; Figure 18B). At the level of adult hippocampal neurogenesis, the number of BrdU+ cells remaining 30 days after BrdU injection was not statistically different in the dDG (p = 0.0873, Mann-Whitney; Figure 18C), whereas it was significantly increased in the vDG of KO mice as compared to WT (p = 0.0317, Mann-Whitney; Figure 18D). As for the assessment of proliferation 24 hours after BrdU injection, we observed a nice correlation between the distance travelled and the number of BrdU+ cells both for the dDG (p = 0.0329, R = 0.4533; Figure 18E) and vDG (p = 0.0267, R = 0.4786; Figure 18F), thus suggesting that the number of newborn cells correlated to the physical activity of the mice irrespective of their genotype.

In conclusion, these data suggest that *Crtc1*$^{-/-}$ mice tend to be more active than *Crtc1*$^{+/+}$ mice, and this increased physical activity is indeed associated with increased neurogenesis. CRTC1 does not seem to be required both for proliferation and survival of newborn cells in the DG, either in basal state or in conditions increasing adult hippocampal neurogenesis.

V. Granular neurons of *Crtc1*$^{-/-}$ mice have an increased number of spines when compared to *Crtc1*$^{+/+}$ mice

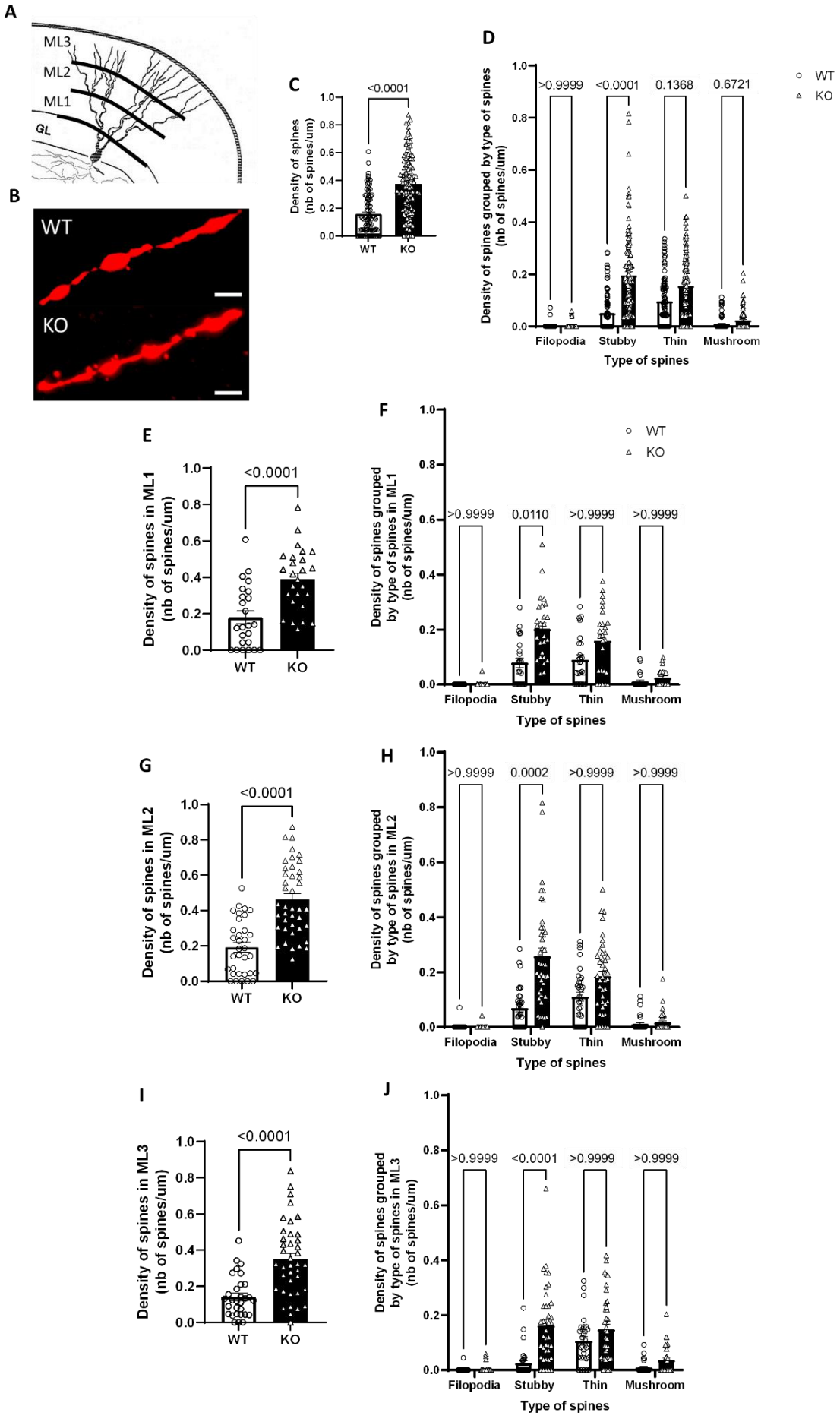
Although CRTC1 doesn't seem to be necessary for proliferation and survival of newborn cells, it may be involved in other plasticity processes. Ch'ng and his colleagues showed that CRTC1 is localised in the post-synaptic site, and that synaptic activity triggers its translocation to the nucleus through an active transport system involving the motor protein dynein moving along microtubules (Ch'ng et al., 2012). CRTC1 modulates the expression of the CREB-regulated gene *bdnf*, and BDNF is known to be involved in the number, structure, and plasticity of the spines (Zagrebelsky et al., 2020). Therefore, we hypothesized that in absence of CRTC1, the spines in newborn cells could be altered. To evaluate the spines in newborn cells in our mouse model, we used a Moloney murine leukaemia virus (MMLV) system. We injected this virus in the DG of KO and WT 11-week-old mice and waited 21 days before sacrificing them. This virus will make newborn cells (not necessarily neurons) express the red fluorescent protein (RFP) and allow us to study the number of spines

of newborn neurons (Figure 19B). We used three mice for each genotype, and for each mouse, we used two slices of 40 µm. On each slice, we found as many neurons RFP+ as possible (from one to five) and took Z-stack of fractions of dendrite from 11.5 to 29.3 µm.

The molecular layer of the DG can be divided into 3 sub-layers (Figure 19A): one which is the closest to the granular cell layer, the inner molecular layer (ML1), one which is the furthest to the granular cell layer, the outer molecular layer (ML3) and one between those two, the middle molecular layer (ML2). We studied fractions of dendrites in all three of these layers. While we were expecting a lower number of spines in the *Crtc1*$^{-/-}$ mice, we were quite surprised to see an important increase in the density of spines on the granular cell dendrites (p<0.0001, Mann-Whitney; Figure 19B and 19C). This increase was mainly due to the increased number of stubby spines, while we saw no differences in the number of filopodia, thin and mushroom types (filopodia p>0.9999, thin p = 0.1368, mushroom p = 0.6721, stubby p<0.0001, Kruskal-Wallis, multiple comparisons).

We analysed the number of spines for each molecular layer and saw that the increased number of spines in KO mice was observable in every sub-layer (p<0.0001, Mann-Whitney; Figure 19E, 19G and 19I), and this increase was always due to the increase of stubby spines (p<0.0001, Kruskal-Wallis; Figure 19F, 19H and 19J). Therefore, it appears that the absence of CRTC1 in mice results in an increase of the number of spines in the granular neurons of the DG.

Figure 19. Number of dendritic spines of the granular cells in the DG. (A) Division of the molecular layer in three sublayers. (B) Representative picture of the dendrite fractions studied to determine the number of spines. Scale bar = 5 µm. (C) Total density of spines observed. Mann-Whitney, n=98-116. (D) Density of spines grouped by type of spines. Kruskal-Wallis, n=98-116. (E, G, and I) Density of spines observed by sublayer. Mann-Whitney, ML1, n=24-26; ML2, n=33-41; ML3, n=30-39. (F, H, and J) Density of spines grouped by the type of spine. Kruskal-Wallis, ML1, n=24-26; ML2, n=33-41; ML3, n=30-39.


A
ML3
ML2
ML1
GL
B
WT
KO
C
<0.0001
Density of spines (nb of spines/um)
WT
KO
D
>0.9999
<0.0001
0.1368
0.6721
WT
KO
Density of spines grouped by type of spines (nb of spines/um)
Filopodia
Stubby
Thin
Mushroom
Type of spines
E
<0.0001
Density of spines in ML1 (nb of spines/um)
WT
KO
F
WT
KO
>0.9999
0.0110
>0.9999
>0.9999
Density of spines grouped by type of spines in ML1 (nb of spines/um)
Filopodia
Stubby
Thin
Mushroom
Type of spines
G
<0.0001
Density of spines in ML2 (nb of spines/um)
WT
KO
H
>0.9999
0.0002
>0.9999
>0.9999
Density of spines grouped by type of spines in ML2 (nb of spines/um)
Filopodia
Stubby
Thin
Mushroom
Type of spines
I
<0.0001
Density of spines in ML3 (nb of spines/um)
WT
KO
J
>0.9999
<0.0001
>0.9999
>0.9999
Density of spines grouped by type of spines in ML3 (nb of spines/um)
Filopodia
Stubby
Thin
Mushroom
Type of spines

VI. Golgi staining study revealed an altered neuronal morphology in *Crtc1*$^{-/-}$ mice associated with an increased number of spines

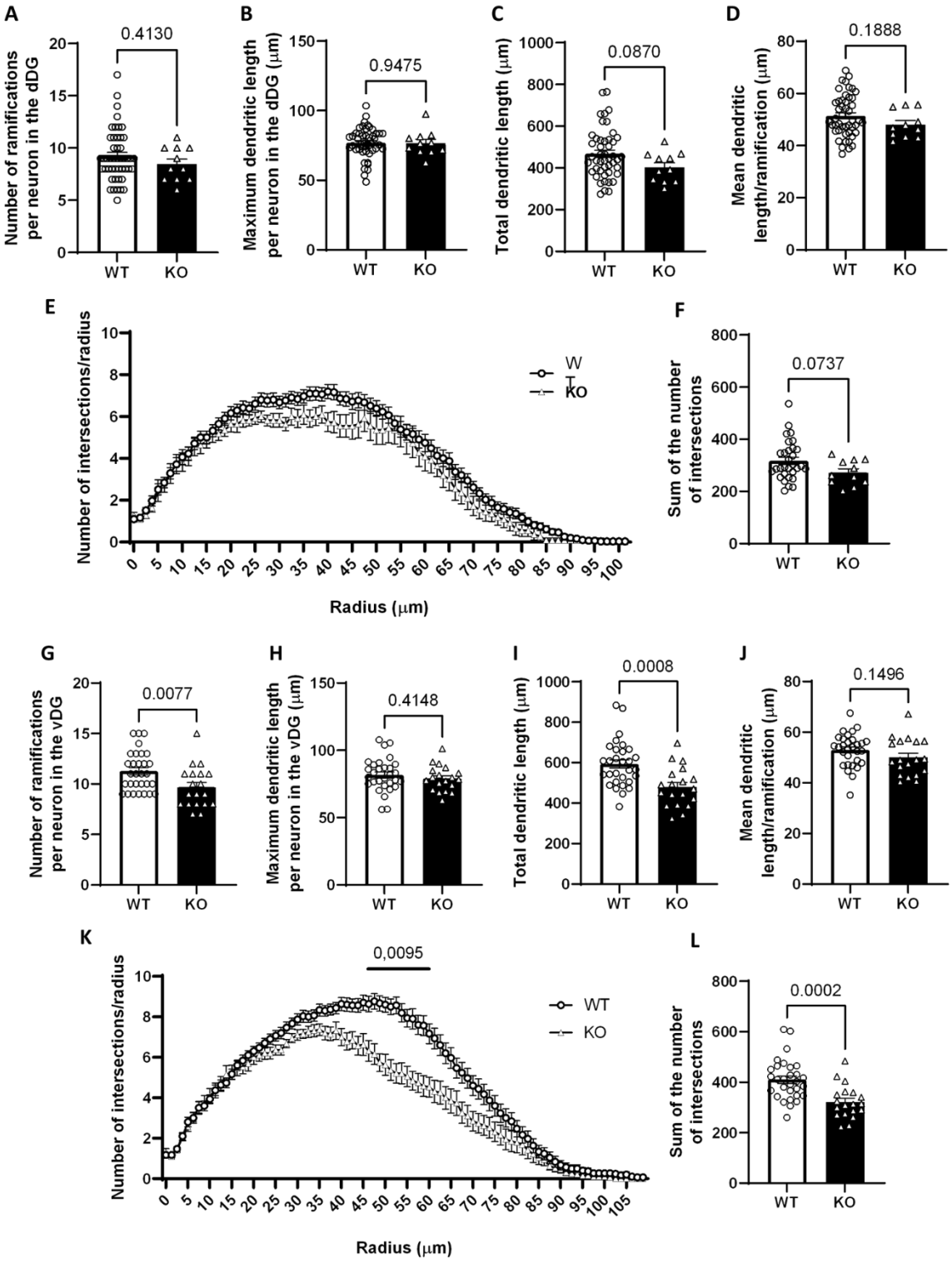
The increased number of spines in the 21-day-old newborn granular neurons of the *Crtc1* KO mice may be transient. Alternatively, this could be a durable effect and the mature granular neurons may stay with a high number of spines in our KO model. The spines connectivity could also be related to the morphology of the granular neurons. To assess the spines number in the general population of the granular neurons, as well as their morphology, we used a Golgi staining on 8 weeks old mouse brains.

We first studied the general morphology of the granular neurons both in the dDG and in the vDG. We monitored different parameters such as the number of ramification per neuron (Figure 20A and 20G), the maximum dendritic length from the soma to the end of the longest dendrite (Figure 20B and 20H), the sum of all dendritic lengths (Figure 20C and 20I), and the mean dendritic length per ramification (Figure 20D and 20J). We also performed a Sholl analysis to evaluate the complexity of the dendritic tree for each neuron (Figure 20E and 20K) and summed the total number of ramifications (Figure 20F and 20L).

In the dDG, we observed no difference in the granular neuron morphology between *Crtc1*$^{-/-}$ and *Crtc1*$^{+/+}$ mice, for each parameter studied. However, in the vDG there were differences in the number of ramifications per neuron (p = 0077, Mann-Whitney; Figure 20G), the total dendritic length (p = 0.0009, Mann-Whitney; Figure 20I), and both in the Sholl analysis (F (1, 47) = 16.10, p = 0.0002, two-way ANOVA; Figure 20K) and the total number of ramifications (p = 0.0002, unpaired t-test; Figure 20L). Each of these parameters were decreased in the KO mice, mirroring a lower complexity in the granular neuron morphology in the vDG of KO mice compared to WT mice.

We then explored the spines on these neurons, also using the Golgi staining. The resolution was high enough to count the number of spines, but it was not sufficient to determine the type of spines (Figure 21A and B). We had three WT mice and KO mice, we found between 5 and 13 neurons on which we were able to take Z-stack of dendrites. As for the newborn neurons, we divided the molecular layer in three sublayers for the total DG: ML1, ML2 and ML3. There was no difference in the number of spines in the ML2 (p = 0.6460, unpaired t-test; Figure 21D), but we did observe an increase of the number of spines both in ML1 (p = 0.0144, unpaired t-test; Figure 21C) and ML3 (p = 0.0326, Mann-Whitney; Figure 21E) for the KO mice compared to the WT mice.

Figure 20. Morphology study of granular neurons of both the dDG and the vDG. (A) Number of ramifications per neuron, (B) maximum dendritic length, (C) sum of dendritic length, (D) mean dendritic length per ramification (unpaired-t-test for all), (E) Sholl analysis representation (Two-way ANOVA) and (F) total number of ramifications for granular neurons (unpaired t-test) of the dDG. n=31-11. (G) Number of ramifications per neuron, (H) maximum dendritic length, (I) sum of dendritic length, (J) mean dendritic length per ramification (unpaired t-test for all), (K) Sholl analysis representation (Two-way ANOVA) and (L) total number of ramifications (unpaired t-test) for granular neurons of the vDG. n=30-19.


A
Number of ramifications per neuron in the dDG
0.4130
WT
KO
B
Maximum dendritic length per neuron in the dDG (μm)
0.9475
C
Total dendritic length (μm)
0.0870
D
Mean dendritic length/ramification (μm)
0.1888
E
Number of intersections/radius
Radius (μm)
F
Sum of the number of intersections
0.0737
G
Number of ramifications per neuron in the vDG
0.0077
H
Maximum dendritic length per neuron in the vDG (μm)
0.4148
I
Total dendritic length (μm)
0.0008
J
Mean dendritic length/ramification (μm)
0.1496
K
0,0095
Number of intersections/radius
Radius (μm)
L
Sum of the number of intersections
0.0002

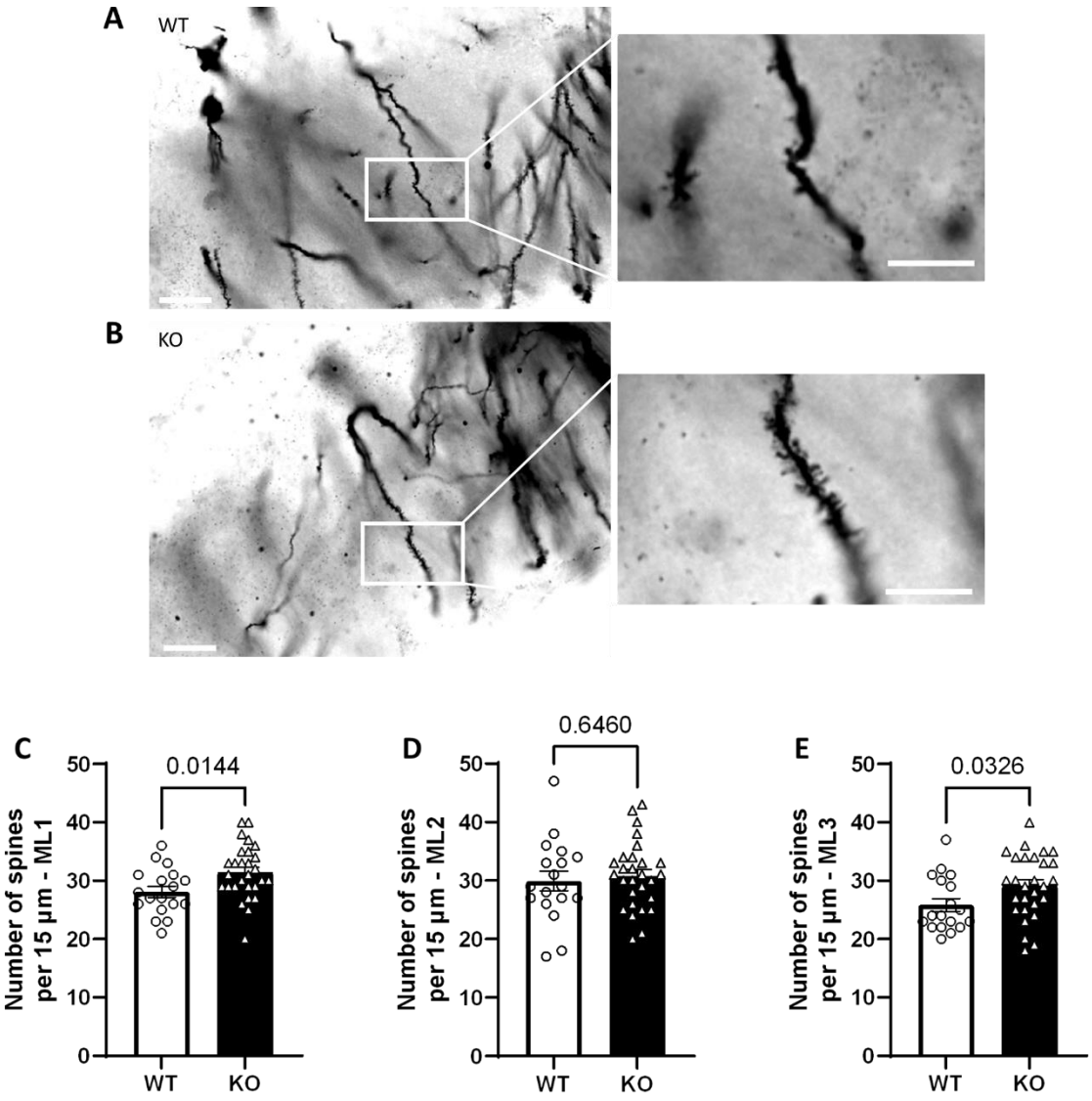


Figure 21. Spines counting on Golgi-stained granular neurons of the dentate gyrus. Representative picture of the dendrite fractions studied to determine the number of spines in WT (A) et KO (B) mice. Scale bar left panels = 20 µm; scale bar right panels = 10 µm. Number of spines counted by dendritic fractions observed in either the ML1 (C; unpaired t-test), ML2 (D; unpaired t-test) or ML3 (E; Mann-Whitney). n=18-28.

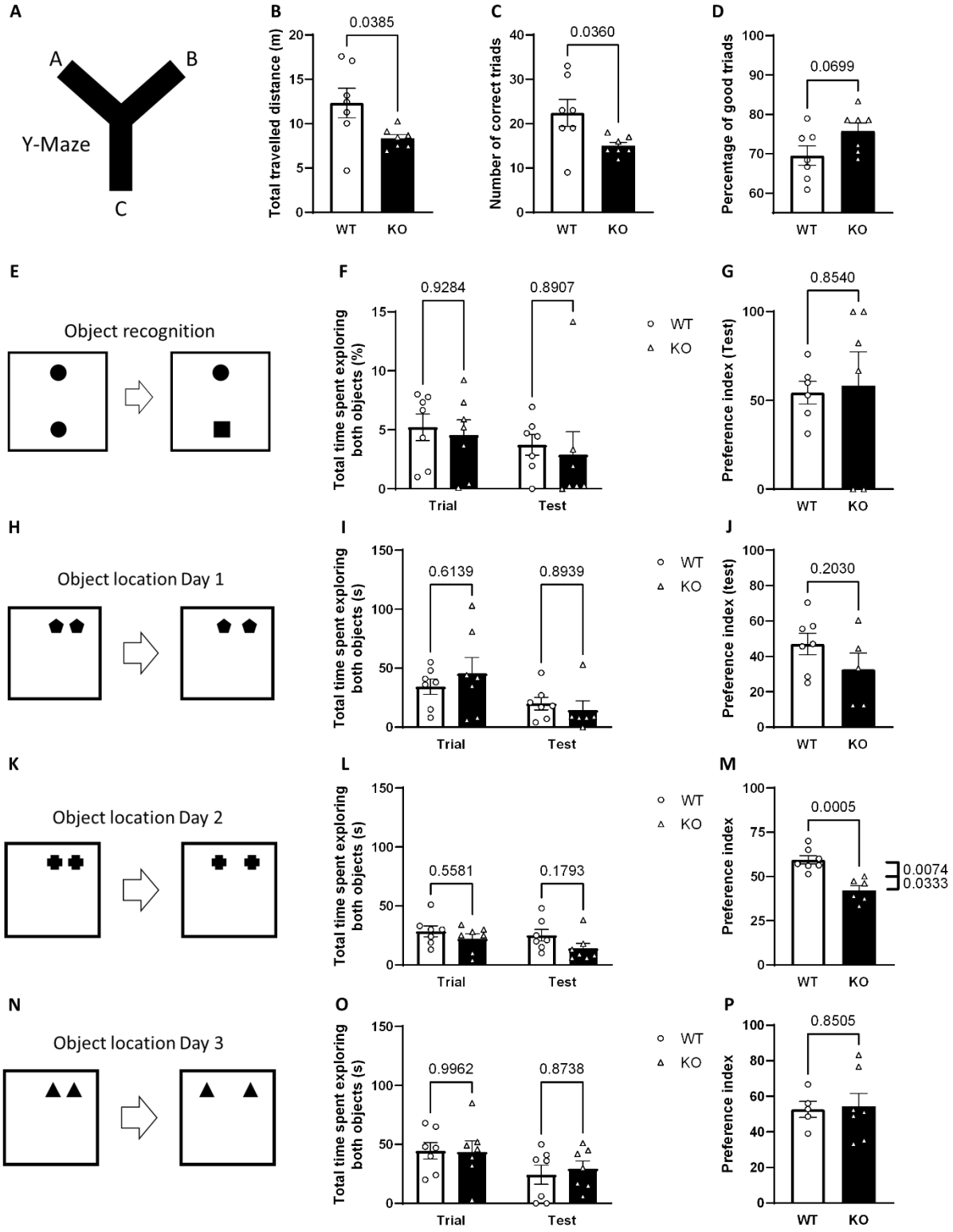
VII. *Crtc1*$^{-/-}$ mice do not have learning and memory impairment

The spines dynamic being a key process in learning and memory (Kasai et al., 2010; McCann and Ross, 2017), we wondered if this increased number of spines in the hippocampus of *Crtc1* KO mice could lead to better (or lower) memory performances. To explore this hypothesis, we subjected 10 weeks-old KO and WT mice to three memory tasks: the Y-maze with spontaneous alternation (Figure 22A) that is used to assess the working memory performance of rodents; the object recognition (Figure 22E) to assess short term recognition memory, and the object location (Figure 22H, K and N), with three different tests where the object is displaced a bit further each time, to assess the pattern separation performances of the mice. We chose these three tasks because the hippocampus is involved in all of them (Axmacher et al., 2007; Hammond et al., 2004; Poch et al., 2011; Yassa and Stark, 2011).

For each test, we recorded the total distance travelled to ensure that the results observed were not due to a difference in the global locomotor activity of the mice. There was a difference in the distance travelled by the mice in the Y-maze ($p = 0.0385$, unpaired t-test; Figure 22B), the KO mice being less active than the WT, which led to a difference in the number of triads (correct alternation of the three arms; $p = 0.0360$, unpaired t-test; Figure 22C). However, when these data are reported as a percentage of triads out of the total number of alternations, there was no statistical difference ($p = 0.0699$, unpaired t-test; Figure 22D). For the object recognition and object location tests, we recorded the total time spent exploring both objects in each of the situation to avoid a bias caused by any potential preference for one of the two objects presented each time. There wasn't any statistical difference in the exploration of both objects for each task (Figure 22F, I, L, O). We then calculated a preference index, expressed as the percentage of time spent exploring the new or displaced object per total time spent exploring both objects. Our first observation was that the WT mice never preferred the new or the displaced object in each task (One sample t-test, $p = 0.5280$, $p = 0.6442$, $p = 0.5931$; Figure 22G, J, P) except for the second day of the object location, when they finally showed a preference for the displaced object (One sample t-test, $p = 0.0074$; Figure 22M). To evaluate the preference for one object or the other, we perform a statistical test that evaluates the difference from 50% (which is the absence of preference). Surprisingly, we observed the same results for the KO mice: they had

no preference for either object in the object recognition task (One sample t-test, p = 0.6864; Figure 22G), nor in the object location on day 1 and on day 3 (One sample t-test, p = 0.1344, p = 0.5601; Figure 22J and P), but they did prefer the non-displaced object on day 2 of the object location task (one sample t-test, p = 0.0333; Figure 22M). For the day 2 of the object location, the result observed both with WT and KO could be due to a preference in the object used that day. Unfortunately, regarding the differences in the travelled distance and the absence of preference for the displaced or changed object, we cannot draw any clear conclusion concerning the memory in our mouse model.

Figure 22. Memory tasks. (A) Schematic representation of the Y-maze, (B) total travelled distance in the Y-maze, (C) number of correct triads, (D) percentage of correct triads. Unpaired t-test, n=7. (E) Schematic representation of the object recognition, (F) total time spent exploring both objects in the object recognition trial and test, (G) preference index for the object recognition test. (H) Schematic representation of the first day of the object location task, (I) total time spent exploring both objects on the first day of object location trial and test, (J) preference index for the object location day 1 test. (K) Schematic representation of the second day of the object location task, (L) total time spent exploring both objects on the second day of object location trial and test, (M) preference index for the object location day 2 test. (N) Schematic representation of the third day of the object location task, (O) total time spent exploring both objects on the third day of object location trial and test, (P) preference index for the object location day 3 test. Two-way ANOVA, unpaired t-test and one sample t-test, n=7.


A
A
B
C
Y-Maze
B
Total travelled distance (m)
0.0385
WT
KO
C
Number of correct triads
0.0360
D
Percentage of good triads
0.0699
E
Object recognition
F
Total time spent exploring both objects (%)
0.9284
0.8907
Trial
Test
G
Preference index (Test)
0.8540
H
Object location Day 1
I
Total time spent exploring both objects (s)
0.6139
0.8939
J
Preference index (test)
0.2030
K
Object location Day 2
L
0.5581
0.1793
M
Preference index
0.0005
0.0074
0.0333
N
Object location Day 3
O
0.9962
0.8738
P
0.8505

VIII. Mossy cells to parvalbumin neurons ratio is altered in the DG of *Crtc1*$^{-/-}$ mice

Because *Crtc1* KO mice exhibited differences in granular neuron morphology and spines number, we hypothesized that this could be due to an intrinsic dysregulation of the granular cells, or to the different inputs received by these neurons. The granular neurons form an intricate circuit with parvalbumin interneurons and mossy cells, which participate to the regulation of neuronal activity (Milstein and Soltesz, 2017; Rovira-Esteban et al., 2020). Using immunofluorescence, we studied these two cell populations in 10 weeks-old mice. We divided the dentate gyrus in three parts: the hilus, the granular cell layer (GCL) and the molecular layer. We used antibodies directed against parvalbumin (PV) and AMPA receptor subunits 2 and 3 (GluR2/3) to study parvalbumin interneurons and mossy cells, respectively. However, the signal for GluR2/3 made the counting difficult, except for the most medial part of the hilus. Therefore, we counted GluR2/3+ cells in this part, and for all the other parts, we measured optical density. The staining of PV+ cells was much clearer and thus they were easier to count.

For both PV and GluR2/3 optical density, there was no difference between KO and WT mice. However, we noticed a decrease in the density of PV+ cells in the GCL (p = 0.0109, unpaired t-test; Figure 23C) of the dDG and an increase of GluR2/3+ cells in the hilus of KO mice (p = 0.0142, unpaired t-test; Figure 23D). Furthermore, when we combine the total cell density of the DG and calculate a ratio of the number of PV+ cells to the number of GluR2/3+ cells, there is a decrease of this ratio in both the dDG and the vDG of KO mice (dDG: p = 0.0069, Mann-Whitney; vDG: p = 0.0030, unpaired t-test; Figure 23G and H). These data suggest a diminution in the number of PV interneurons and an increase of mossy cells in the DG of KO mice, probably associated with an imbalance between inhibition and excitation in those regions.

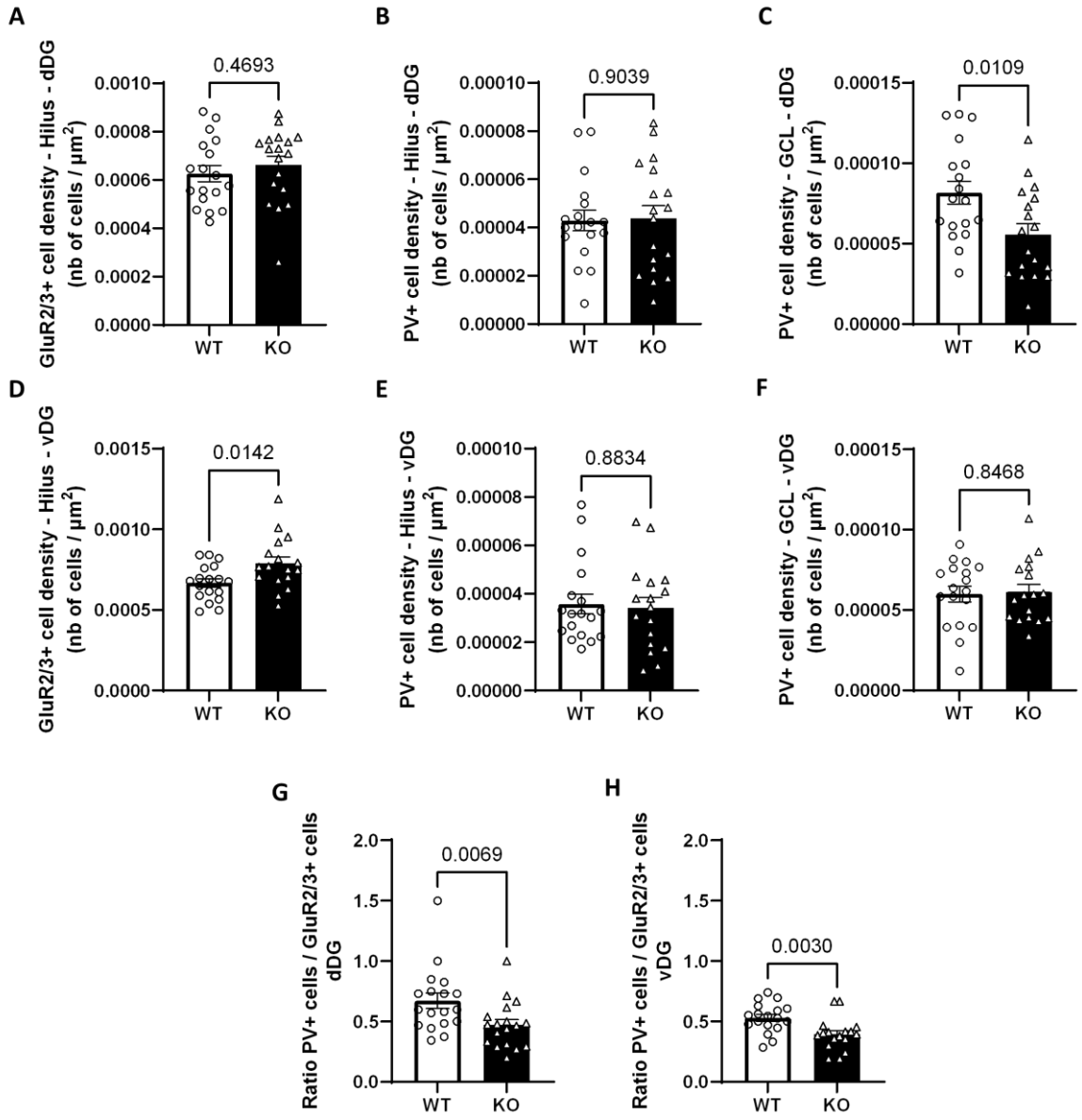


Figure 23. GluR2/3+ and PV+ cell density in DG. GluR2/3+ cell density in the hilus of the dDG (A) and the vDG (D). PV+ cell density in the hilus of the dDG (B) and the vDG (E), and in the GCL of the dDG (C) and the vDG (F). Ratio of the number of PV+ cells to the number of GluR2/3+ cells in the dDG (G) and in the vDG (H). Unpaired t-test, n=18.

DISCUSSION

In the first part of this project, we showed that mice exposed to a chronic stress had diminished expression of CRTC1 both in the prefrontal cortex and in the dentate gyrus of the ventral hippocampus. These results are in accordance with previous studies (Jiang et al., 2019; Liu et al., 2020), adding more evidence to the role of CRTC1 in the etiology of depression. However, this observation has only been made in mice and, if we want to have a translational perspective, it should be showed in humans. A biobank in the USA (The Stanley Medical Research Institute) is collecting brains from psychiatric patients and proposing the samples for this kind of analyses. It would be very interesting to investigate the levels of CRTC1 and SIK2 in depressed patients to compare them with non-ill people and to prove a direct link between mood disorders and CRTC1 expression levels.

In the second part of this project, the objective was to restore CRTC1 levels in the hippocampus of *Crtc1*$^{-/-}$ mice using a viral vector and assess the behavioural effects of this rescued CRTC1's expression. This vector proved its efficiency in Alzheimer's mouse models (Parra-Damas et al., 2017, 2014), in which it improved memory and increased CREB-regulated gene expression when injected into the hippocampus (AP: -2 mm; ML: ±1.8 mm; DV: -1.8 mm). However, the authors of these studies did not explore the pattern of expression of CRTC1 in the injected mice. They showed that CRTC1 is overexpressed (mRNA and protein levels) in the whole hippocampus, and they wrote that it is overexpressed in CA1, CA3, stratum oriens and hilus of the DG without showing these results (Parra-Damas et al., 2014). In our model, we saw that, in the DG, the pattern of CRTC1's expression induced by AAV-CRTC1 is different from the pattern of CRTC1's expression in WT mice, suggesting that this virus induces CRTC1 overexpression, but not in the cells where it is supposed to be expressed, resulting in an ectopic expression. According to the work of Carlos Saura's team, this ectopic expression was sufficient to cause behavioural effects in their Alzheimer mouse models, but, in our model, it was not sufficient.

Furthermore, the abnormal ectopic expression of CRTC1 or the AAV-mediated protein overexpression may have had unforeseen effects that may explain the quite puzzling behavioural data of the OSFST. Indeed, when comparing them to previous studies with our mouse model (Breuillaud et al., 2012; Elsa M. Meylan et al., 2016),

there should be a clear difference in immobility time between *Crtc1*$^{-/-}$ and *Crtc1*$^{+/+}$ mice from the third day of OSFST, and this was not the case in our experiment. With our mice, there was absolutely no significant difference between the 4 groups at each of the ten swim sessions. We think that there could have been a problem with our mouse breeding: there seems to be an increased mobility for the WT mice compared to previous experiments, that could be due to the breeding or/and to the stress related to the intracranial injection procedure. In the NIH paradigm, we see an increased anxiety in the KO compared to the WT but no influence of the virus, showing that the ectopic expression of CRTC1 induced by the AAV was not sufficient to induce an anxiolytic effect in our mouse model.

Considering the work already done on the implication of CRTC1 in different plasticity processes such as dendritic growth, L-LTP or the regulation of CREB regulated genes (Breuillaud et al., 2012; Briand et al., 2015; Finsterwald et al., 2010; Fukuchi et al., 2015; Kovács et al., 2007; Li et al., 2009; Nonaka et al., 2014; Uchida et al., 2017; Zhou et al., 2006), we considered that it would be interesting to evaluate the possibility that adult hippocampal neurogenesis might be altered in the *Crtc1*$^{-/-}$ mouse model. The injection of BrdU is widely used to evaluate the proliferation and survival of newborn cells in mouse brain (Kuhn and Cooper-Kuhn, 2007; Wojtowicz and Kee, 2006). BrdU is incorporated into the DNA as a thymidine analogue into dividing cells and can then be studied with immunofluorescence assays. When mice are sacrificed 24 hours after the injection, the proliferation can be evaluated through the number of cells that incorporated BrdU. During the whole process of neurogenesis, neuronal precursor cells (NPC) divide into other NPCs and into neuroblast that become immature neurons. Immature neurons have dendrites that are not fully grown yet and with a very little number of spines. During its maturation, the neuron will develop its dendritic arborisation and will grow spines to connect to the neuronal network and to be fully integrated into this network. The whole process lasts approximately 4 weeks to have a fully interconnected neuron. However, a vast majority of the newborn neurons die by apoptosis during the first four days, during the transition from progenitor to neuroblast (Kempermann et al., 2004; Sierra et al., 2010). We thus chose two different time points post-BrdU injection to evaluate the state of adult hippocampal neurogenesis in the *Crtc1*$^{-/-}$ mouse model: 24h to study the proliferation,

and 30 days to study the survival of the newborn cells. We hypothesized that both proliferation and survival would be decreased in the KO mice. However, we observed absolutely no difference between WT and KO male mice, both for proliferation and survival. Of course, the absence of difference is no proof, but it is still a clear indication that both processes are not impacted by the absence of CRTC1 in the organism. For the females, we found a significant difference for the proliferation in the dDG and a tendency in the vDG, and this difference is not visible 30 days after BrdU injection anymore. These results suggest that CRTC1 may be important for the proliferation process in the female mice, but the decreased proliferation has little influence on the number of cells that survived and integrated into the circuitry. There could also be a compensatory mechanism in place to end up with a great number of survival adult born neurons.

We found the difference between males and females quite interesting. From the very beginning, both sexes of our *Crtc1*$^{-/-}$ mouse model were studied. However, the females showing a more subtle phenotype (e.g. they were aggressive only when they were lactating ; Breuillaud et al., 2012), our group focused primarily on the males. Studying females has also been considered quite difficult because of the hormonal cycle, requiring a cycle synchronisation that can be quite tedious. Here, we decided to study both, because this difference between sexes could help us understand the global role of CRTC1 in the etiology of the depressive-like phenotype observed in our model, and also because there is increasing evidence that the etiology of major depression might be different for men and women. Although there were no observed differences in basal proliferation and survival between *Crtc1*$^{-/-}$ and *Crtc1*$^{+/+}$ male mice, we still thought that CRTC1 could be involved in the regulation of these processes. We thus used a known factor, physical activity, to induce an increase in adult hippocampal neurogenesis (van Praag et al., 2005). To study proliferation, we let the mice run freely with a running wheel in their home cage for 6 days. Even though the total distance travelled between the WT and the KO mice was not statistically different, we observed that 3 out of the 4 WT mice studied ran less than 1 km, making the interpretation of cell count difficult. However, we did see a very nice correlation between the total distance travelled and the number of newborn cells, confirming previous studies about the effect of physical activity on neurogenesis (Huang et al., 2012; van Praag et al., 2005) and suggesting that CRTC1 is not involved in those

effects. Furthermore, we confirmed that KO male mice are more active during the light phase than the WT, which is consistent with the previous findings of our group (Rossetti et al., 2017).

For the study of the survival of newborn cells, mice had access to a running wheel in the home cage for 36 days. There was still no statistical difference for the total travelled distance between WT and KO mice, even though the WT mice tended to run less. Again, the number of BrdU+ cells 30 days after injection was correlated with the distance travelled, and there was no significant difference in the number of cells in the dDG, but there was a difference in the vDG. However, this difference in the number of cells did not correspond to what we were expected: indeed, the number of BrdU+ cells in the KO was increased compared to WT. This means that, upon favourable neurogenesis conditions and in the absence of CRTC1, the survival rate of newborn cells is increased. Programmed cell-death is a common mechanism in neurogenesis; it is triggered in neurons that had failed to construct solid connectivity (Oppenheim, 1991). Maybe CRTC1 could be involved in the apoptotic processes indirectly. Apoptosis is triggered by cellular stress, leading to cysteine-dependent aspartate proteases (caspases) activation, and followed by DNA fragmentation and cell death. In this process, pro- and anti-apoptotic signals are integrated by the Bcl-2 family. BDNF has been shown to regulate the antiapoptotic Bcl-2 protein through the Akt pathway in the striatum (Pérez-Navarro et al., 2005) and to have a crucial role in neurogenesis (Rossi et al., 2006; Scharfman et al., 2005). However, one study showed that in BDNF mutant mice, the proliferation rate is increased without affecting the survival, and the new neurons are not able to mature completely (Chan et al., 2008). The authors' conclusion is that BDNF must be essential for terminal differentiation of newborn neurons in the hippocampus. In our *Crtc1*$^{-/-}$ mouse model, the levels of BDNF are decreased (Breuillaud et al., 2012), so it would be very interesting to check if these neurons fully matured and are indeed integrated into the circuitry.

CRTC1, when inactive, is located in the cytoplasm, up until the post-synaptic compartment, and under synaptic activation it will be dephosphorylated, transported and translocated into the nucleus, where it will bind to CREB (Ch'ng et al., 2012). Spines are very dynamic: their formation, disappearance and stabilization is regulated

by neuronal activity and developmental age (Runge et al., 2020). They can appear and disappear in less than ten minutes, which is the case for filopodia (Ziv and Smith, 1996), or be stable for months, which is the case for large headed-mushrooms (Grutzendler et al., 2002). It has been admitted that the mushrooms are the most mature spines. However, time-lapse studies showed that upon stimulation, mushroom spines had a neck-length reduction ending in looking like stubby spines, which means that stubby could be mushroom spines with very short neck (Tønnesen et al., 2014). The thin spines can acquire fully functional synapse (Matsuzaki et al., 2004), but the presence of synapse in small spines does not predict their future stability: some spines can form temporary synapse and then be eliminated (Cane et al., 2014). In our mouse model, we injected a virus expressing RFP only in the newborn cells. When looking at the dendritic spines on the granular neurons of the DG 21 days after viral injection, we saw an increased number of spines (principally thin and stubby) in the KO mice compared to the WT mice. We then checked the dendritic spines of the granular neurons in adult mice with a Golgi staining, with no information on the maturity of these neurons, and again the number of spines was similarly increased in the KO mice. We did not anticipate these results, because it was known that stressed and MDD subjects have a reduced number of spines in the hippocampus (Kang et al., 2012; Patel et al., 2018). Spine reduction is even a converging point of study for several psychiatric diseases such as schizophrenia (Xu et al., 2013), intellectual disabilities (Purpura, 1974), bipolar disorders (Konopaske et al., 2014) and a certain form of autism (Dindot et al., 2008; Yashiro et al., 2009). To our knowledge, the only disease with an increased number of dendritic spines is the Fragile X syndrome, which is a disability caused by the mutation of the *Fmr1* gene (on the X chromosome) leading to intellectual disability, as well as behavioural and learning challenges (National Fragile X Foundation, 2021). Increased number of spines is observed on L5 cortical neurons in Fragile X subjects, and these spines are immature and abnormally elongated (Comery et al., 1997; Galvez and Greenough, 2005; Irwin et al., 2001; Nimchinsky et al., 2001). However, other studies failed to reproduce these results (Harlow et al., 2010; Till et al., 2012; Wijetunge et al., 2014). Two teams showed that *Fmr1* knock-out mice had increased spine turnover and that they did not decrease the spine dynamics after 2 week of age like in WT mice (Cruz-Martín et al., 2010; Pan et al., 2010): the spines failed to mature and to stabilize. Pan and colleagues also showed that a chessboard whisker trimming, a phenomenon that normally induces the formation of new

persistent synaptic connections, had no effect on the *Fmr1* KO mice (Holtmaat et al., 2006; Pan et al., 2010). More so, these mice failed to learn a motor task needing spine formation (Padmashri et al., 2013), and they did not form new spines in an enriched environment (Arroyo et al., 2019). The *Fmr1* mutation in mice prevented the spine dynamic related to lived experiences, making them unable to adapt to the external world.

What we observed in our mouse model is from two different time points and two different techniques but says nothing about the dynamics of the spines. One possibility could be that *Crtc1* KO mice have a disrupted dynamic of the dendritic spines of DG granular neurons, leading to an increased number of spines that could be potentially immature, as well as unable to mature and to stabilize. It would be interesting in the future to check if these spines are functional or not, if they are mature, and of course it would be very interesting to explore their dynamic.

It has been years since the first theories about the link between memory and synaptic formation have been developed (Hebb, 1949; Milner, 1957; Stent, 1973). This link has been experimentally showed with activity-dependent long-lasting changes in the synapse, such as LTP, long-term depression (LTD) and long-term facilitation (LTF; Bliss and Collingridge, 1993; Glanzman, 2010; Roberts and Glanzman, 2003). LTP is a consequence of a high-frequency electrical stimulation of a neuronal pathway, or repeated pairing of presynaptic and postsynaptic cell firing. The synchronisation of these inputs is determining the formation of LTP, strengthening the synapse, or LTD, weakening a synapse (Abraham et al., 2019). The modification of the synapse is correlated with the shape and the molecular composition of the spine (Matsuzaki et al., 2004): the LTP has for consequence a widening of the spine, correlated with an increased number of AMPA receptors (Kasai et al., 2010). These spine structures can be stable for years *in vivo* (Zuo et al., 2005), hence the idea of structural plasticity supporting the memory formation and sustainability. In our model, we did not see a clear alteration, or amelioration, of the memory performances. Even though we had confusing observation with the WT mice, whose memory does not seem very efficient, it was clear that the KO did not show an obvious preference for the new or displaced object, nor for the old or non-displaced object. The only exception was for the second day of object location, where the WT mice finally showed a preference for the displaced object and the KO for the non-displaced object. If anything, these data

mainly support the idea that the increased number of spines in KO mice's DG does not support increased memory performance for these mice. This is in line with the previous idea, which stated that although they have an increased number of spines, these spines are not necessarily functional or well-integrated into the neuronal network.

A very recent paper highlighted the role of CRTC1 in autophagy processes following LTD (Pan et al., 2021). Calcineurin, the enzyme responsible for the dephosphorylation of CRTC1, has been known to be involved in the LTD process (Kameyama et al., 1998; Mulkey et al., 1994). CRTC1 is activated and then translocated into the nucleus upon LTP, and in this paper the authors show that LTD induces stronger CRTC1 dephosphorylation, nuclear translocation and binding to CREB than LTP (Pan et al., 2021). LTD triggers autophagy processes, and this study showed that CRTC1 is involved in the pathway triggering autophagy upon LTD. The authors conclude that CRTC1 plays an important role in the autophagy processes provoked by LTD in the post-synaptic site. Another paper showed that the lack of autophagy in pyramidal neurons has for consequence an increased spine density (Tang et al., 2014). Taken together, these studies suggest that the absence of CRTC1 in our mouse model might lead to decreased autophagy processes, which would explain the increased spine density. To verify this hypothesis, a way could be to assess the expression of some autophagy-related genes, such as *Atg3, Atg5, Atg7, Atg12, Ulk* and *LC3* in the DG of WT and KO mice. We tried to set up a viral strategy to re-express CRTC1 specifically in the newborn neurons, which could also be used to assess the role of CRTC1 in these processes. *Crtc1*$^{-/-}$ mice were generated in our laboratory following a genetrap strategy. The inactivating splice acceptor site of the genetrap is flanked by two loxP sites, and therefore it should be excised by the Cre recombinase, which should silence the genetrap and rescue *Crtc1* expression. Hence, we attempted to target newborn neurons by injecting the DG of *Crtc1*$^{-/-}$ mice with a MMLV expressing Cre recombinase. This strategy looks promising, but unfortunately, we have not yet been able to confirm the rescued expression of *Crtc1* in infected newborn neurons.

Moreover, the synaptic homeostasis is synchronized with the circadian rhythm: plastic processes occurring during wakefulness strengthen the synapses, whereas during sleep, these processes are downscaled (Tononi and Cirelli, 2006). During

development, spine pruning is essential to the refinement of neuronal connections following daytime experiences (Yu et al., 2013). However, during adulthood, both synapse weakening/pruning and strengthening/synaptogenesis happen during sleep phases, consistent with long-term modifications of synapses (Li et al., 2017; Yang et al., 2014). In our mouse model, it has been shown that the circadian rhythm is disrupted: the male KO mice tend to be more active during light phase (when they normally sleep) than the WT mice (Rossetti et al., 2017). This disruption could probably have for consequence to modify the correct homeostasis regulation that happens during sleep, hence the increased spine density. Also, recent experiments, led by Clara Rossetti and for which the results haven't been published yet, showed that depending on the exact time of sacrifice of the mouse, certain protein expression levels can be very different. Since we had this information very recently, we did not plan the sacrifices of the mice accordingly and we just did them one after the other, and during their sleep phase. Presumably, we could have observed different spines density with mice sacrificed at the end of their sleep phase or at the end of their wake phase.

The observed modifications in the granule cells morphology could be due to the absence of CRTC1 inside these cells, but it could also be a consequence of the absence of CRTC1 in the other cells of the dentate gyrus, connected to the granule cells. The granule cells receive their inputs from the entorhinal cortex (EC), which form the perforant path (Amaral et al., 2007). These inputs can be divided in two components: one from the medial portion of the EC, carrying spatial information and connecting to the granule cells' dendrites in the middle molecular layer, and one from the lateral portion of the EC, carrying sensory information and connecting to the granule cells' dendrites in the outer molecular layer (Hunsaker et al., 2007). In the dentate gyrus, the main source of excitation and inhibition are glutamatergic and GABAergic synapses, respectively (Amaral et al., 2007; Coulter and Carlson, 2007). Granule cells receive glutamatergic inputs from the entorhinal cortex's cells (Witter, 2007) and from mossy cells in the inner molecular layer (Buckmaster et al., 1992). Mossy cells send glutamatergic inputs to the PV neurons, which send GABAergic inputs to the soma of the granule cells, and the granule cells send glutamatergic inputs to the mossy cells (Rovira-Esteban et al., 2020). This is only a part of the dentate gyrus

connectivity. These connections are finely tuned to orchestrate a precise balance of excitation and inhibition in the hippocampus, along with a dynamic excitation-inhibition delay crucial for the signal transmission, and decisive to determine the survival or not of a connection and to the cognitive consequences. In our model, we showed that there is an increased density of mossy cells in the dentate gyrus, combined with a decreased density of PV neurons: this means that the excitation-inhibition balance is disturbed. To investigate the functional significance of our observations, the next steps would be to explore the number of functional GABAergic and glutamatergic synapses in the dentate gyrus, and to evaluate the excitability of the granule cells.

Excitation-inhibition imbalance has been widely associated with schizophrenia and autism (Gao and Penzes, 2015; Rubenstein and Merzenich, 2003). However, there are many studies linking a deficit in GABAergic transmission to MDD (Luscher et al., 2011). Depressed patients show reduced brain concentration of GABA (Bhagwagar et al., 2008; Gerner and Hare, 1981; Hasler et al., 2007; Honig et al., 1988), and studies suggest that antidepressant drugs ultimately act to counteract GABAergic deficits (Luscher et al., 2011). GABA transmission is tightly connected to CREB and BDNF and a deficit in GABAergic transmission in mice was sufficient to cause a MDD phenotype (Luscher et al., 2011). All this suggesting that the GABAergic transmission is playing an important role in the neurobiology of MDD.

The imbalance of excitation-inhibition, combined with the increased granule cells' spine density, suggest that *Crtc1*$^{-/-}$ mice may have disrupted hippocampal connectivity and plasticity that would support their depressive-like phenotype. Although our findings require a functional assessment of the implications of all these structural alterations possibly leading to cognitive and behavioural deficits, we have uncovered a perplexing, but interesting, involvement of CRTC1 in hippocampal plasticity.

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