1.1 The burden of depression-related symptoms: state of the art

Depression is the leading cause of disability worldwide and is a major contributor to the overall global burden of diseases, with high levels of suicide incidence (www.who.int, World Health Organisation website). According to the World Health Organization, it is estimated that 10% to 15% of the general population will experience clinical depression during their lifetime (Tsuang, Taylor, & Faraone, 2004). Currently, more than 350 million of people of all ages suffer from depression (www.who.int). Indeed, depressive disorders often start at young age, affecting lifestyle and usually becoming recurrent. The prevalence of depression is approximately doubled in females compared to males, and several studies suggest that the heritability of the disorder is significantly higher in women (Mill & Petronis, 2007). Depression core symptoms include depressed mood, anhedonia (reduced ability to experience pleasure from natural rewards), irritability, difficulties in concentrating, social withdrawal (withdrawal from social contact that derives from indifferance or lack of desire to have social contact) and abnormalities in appetite and sleep, the so called “neurovegetative symptoms” (Krishnan & Nestler, 2008).

Depression has shown to be comorbid with several neuropsychiatric diseases, such as schizophrenia, bipolar disorders, Alzheimer’s diseases, anxiety disorders, autism spectrum disorders (ASD) and stress-related diseases. In particular, anxiety-related disorders, such as obsessive-compulsive disorders and social anxiety disorder, are highly comorbid with depression, with up to 90% of patients experiencing clinical depression at some point in their lifetime (Ressler & Mayberg, 2007). Moreover, depression often occurs during the prodromic phase of Alzheimer’s disease, schizophrenia and bipolar disorders.

1.2 The impact of dietary factors on depressive-like symptoms

Lifestyle, particularly environmental and dietary factors, have a great influence on the pathogenesis of depression. In this regard, dietary Polyunsaturated Fatty Acids (PUFA) have received great attention during the last decades. PUFAs are a family of lipids that are identified by the position of the last double bond in their structure. Among them, n-3 and n-6 PUFAs are biologically important molecules that mediate several processes, such as signal pathways, membrane fluidity, neurotransmission, neuroinflammation and cell survival. N-3 and n-6 PUFA can be supplied either directly from diet or by metabolic conversion of their essential precursors, α-linolenic acid (18:3n-3) and linoleic acid (18:2n-6), respectively (Morgese & Trabace, 2016; 10
Morgese, Tucci, et al., 2017; Zuliani et al., 2009). N-3 PUFA include alpha linolenic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), while n-6 PUFA include linoleic acid (LA) and arachidonic acid (AA). N-3 PUFA, in particular DHA, are crucial for the brain development and to maintain correct central nervous system (CNS) functionality. Experimental evidence in animals has demonstrated that DHA deficiency during early brain development is deleterious and permanent (Lo Van et al., 2016; Lozada, Desai, Kevala, Lee, & Kim, 2017; Maekawa et al., 2017). During embryonal life and lactation, PUFA intake exclusively depends on maternal diet (Lafourcade et al., 2011). Indeed, it has been reported that maternal malnutrition plays a crucial role in development of psychiatric complications in later adulthood. In particular, evidence from human studies indicate that maternal metabolic state and diet influence dramatically the risk for behavioural disorders in progeny (Sullivan, Riper, Lockard, & Valleau, 2015). Unfortunately, it is quite appropriate to assume that this nutritional-poor diet will be later perpetuated, considering that represents part of a lifestyle acquired during early childhood.

Modern western diets are characterized by deficiency in content of n-3 PUFA, in particular low consumption of fish in favour of baked and junk food has determined a dramatic increase of the n-6/n-3 PUFA ratio. Indeed, such ratio moved from 1, typical of early 20th century, up to 15 in industrialized countries (Simopoulos, 2009, 2011). Epidemiological evidences have established a negative correlation between n-3 PUFA consumption and development of anxiety and depressive symptoms as well as physiological distress (U. E. Lang, Beglinger, Schweinfurth, Walter, & Borgwardt, 2015; Larrieu, Madore, Joffre, & Laye, 2012; Ross, 2009). These findings were supported by clinical studies, indicating that the lack of n-3 PUFA in diet is linked to an increased susceptibility to neuropsychiatric disorders (Beydoun et al., 2015; Lucas, Kirmayer, Dery, & Dewailly, 2010; Murakami, Miyake, Sasaki, Tanaka, & Arakawa, 2010; Panagiotakos et al., 2010), while beneficial results with n-3 PUFA supplementation alone or in adjunctive therapies have been described in treatment of depressive-like disorders (Grosso, Pajak, et al., 2014; P. Y. Lin & Su, 2007).

Moreover, Evans and colleagues demonstrated that n-6 PUFA and their biosynthetic enzymes are useful biomarkers for measurements of depressive disorders and burden of diseases, suggesting that they should also be taken into consideration when n-3 PUFA role is investigated (Evans et al., 2015). However, studies involving humans are often polluted by uncontrollable variables and biases and some contrasting results and inconsistencies in clinical evaluations have also been
denounced (Grosso, Galvano, et al., 2014; Grosso, Pajak, et al., 2014). In this context, the use of animal model can be very useful, especially when diet-influenced outcomes need to be measured in offspring, since dosing, age of first assumption, along with duration of assumption are strictly monitored and are quite reliable.

Along with dietary deficiency, chronic stress is another environmental risk factor for the development of depressive symptoms and dysregulation of hypothalamic–pituitary adrenal (HPA) axis in response to chronic or repeated stressful events is a reported important mechanism (McEwen, Eiland, Hunter, & Miller, 2012). In this regard, low cerebral DHA content, secondary to poor diet, has been associated to increased anxiety-like behaviour induced by chronic mild stress paradigm in animals (Harauma & Moriguchi, 2011). Indeed, it has been reported that a diet poor in n-3 PUFA increased aggressive behaviour in rodents, while high n-3 PUFA diet was able to reduce the stress response (Fedorova & Salem, 2006; Ikemoto et al., 2001), indicating that n-3 PUFA deficiency plays a central role in the chronic stress modulation.

In this context, in chapter 2 and 3 of the present thesis, effects of n-3 PUFA deficient and n-3 PUFA enriched diets on female rat offspring have been investigated, in terms of depressive-like behaviours and alterations of neurochemical parameters related to chronic stress, anxiety and depression.

1.3 From neurobiology to neuropsychiatric symptoms: searching for new biomarkers

However, current nosology for the diagnosis of neuropsychiatric disorders classify each disorder into non-overlapping diagnostic categories. This separation is not based on their underlying etiology, but on convention-based clustering of qualitative symptoms of the disorder (Kas et al., Neuroscience & Biobehavioral reviews, submitted). Although these diagnostic categories are sufficient to provide the basis for general clinical treatments, they do not describe the underlying neurobiology that gives rise to individual symptoms. The ability to precisely link these symptoms to the underlying neurobiology would not only facilitate the development of better treatments, it would also allow physicians to help patients with a better understanding of the complexities and management of their illnesses (Kas et al., Neuroscience & Biobehavioral reviews, submitted). To realize this ambition, a paradigm shift is needed to raise awareness and to build an understanding of how neuropsychiatric diagnoses can be based on quantitative biological parameters. In this
regard, the main limit in the construction of biologically valid diagnoses is the lack of objective biomarkers. Moreover, the uncertain relationship between diagnosis and underlying etiology has created difficulties for the development of appropriate disease models and targeted treatments. Currently, there has been a rethinking of these diagnostic boundaries in regard to their usefulness in treatment and classification of neuropsychiatric disorders (Kas et al., Neuroscience & Biobehavioral reviews, submitted). This is partly based on the notion that there is more pathogenetic overlap between psychiatric and neurodegenerative disorders than previously thought, and that they might better be described as domains of cross-disorder-related traits rather than be classified into separate categories (Insel & Cuthbert, 2015; Kas et al., 2011; Krishnan & Nestler, 2008). To reach this purpose, animal models can be really helpful to longitudinally study behavioural alterations resembling human symptoms in a translational way, and ultimately investigate underlying neurobiology in order to deeper understand the etiology.

1.4 Revisiting behavioural paradigms and rodent models for a translational approach

In this thesis, we focused on depressive-like symptoms that occur in several neuropsychiatric and neurodegenerative diseases, and, using different animal paradigms and models, we tried to disentangle the heterogeneous neurobiology behind these symptoms. In particular, the most used test to assess depressive-like behaviour is the Forced Swimming Test (FST). The FST is a reliable test widely used to evaluate depressive-like state and screen antidepressants activity in rodents (Li, Jiang, Song, Quan, & Yu, 2017). This test is based on learned helplessness that results in depressive-like symptoms, such as immobility increase and swimming and struggling decrease.

Disrupted sociability is an important behavioural aspect that needs to be taken into account to fully delineate a translational picture of symptoms related to depression. The currently available behavioural tests to assess sociability are the social interaction test and the three chamber or social preference test. In the social interaction test, interaction between two animals is evaluated, while, in the three chamber test, the animal can choose between one empty chamber and one chamber with a stimulus animal. Thus, in these tests only dyadic interactions can be analyzed. Hence, these behavioural tests are not able to investigate social dynamics in a translational way, due to the interactions with no more than two animals at the same time. For
this purpose, semi-natural habitats have been developed. In nature, rodents live in large groups with organized social structures and dominance hierarchies (So, Franks, Lim, & Curley, 2015). One of the most interesting systems for the behavioural analyses of social group dynamics is the Visible Burrow System (VBS), developed by the Blanchard group (D. C. Blanchard et al., 2012; D. C. Blanchard et al., 1995; R. J. Blanchard, Yudko, Dulloog, & Blanchard, 2001; Pobbe et al., 2010). The VBS is a semi-natural environment resembling rodent ecological appropriate environment. It consists of an open-arena that is connected to continuously dark tunnels with multiple nests in order to mimic the natural burrows. Research using the VBS has been primarily focused on aggression, dominance and hierarchies in rats (R. J. Blanchard, Dulloog, et al., 2001; R. J. Blanchard, Yudko, et al., 2001; Buwalda, Koolhaas, & de Boer, 2017). However, during the last decade, attention has shifted towards the use of mice, thus encouraging the study of transgenic and mutant mouse lines, resembling humane neuropsychiatric phenotypes. Among these lines, an interesting mutant strain is the BTBR T+tf/J (BTBR) inbred strain. The BTBR mice show deficits in social interaction, impaired communication, and repetitive behaviours, thus resembling the autism-like phenotype in humans (McFarlane et al., 2008). The BTBR behavioural deficits have been investigated in the VBS and subsequently validated using the Three Chamber test, by Pobbe et al. (Pobbe et al., 2010). In their VBS colonies, composed of four males, BTBR mice showed an impairment in all social behavioural domains, such as approach, aggressive behaviour and allo-grooming (Pobbe et al., 2010). Therefore, the BTBR strain appears to be a useful model to study social behavioural dysfunctions in a translational perspective.

In this regard, our group implemented a modified version of the VBS, adding two additional chamber in the burrows in order to have more nests. Moreover, to reproduce behaviours that naturally occur in colonies, we used mixed-sex colonies, using 2 females and 6 males for each VBS experiment. In chapter 4, we used the VBS to identify and validate behavioural readouts to assess sociability and social withdrawal features in BTBR and C57BL/6J control strain. In particular, C57BL/6J mouse strain has normal sociability and has been used as control strain in numerous preclinical studies (Cai et al., 2017; Hsieh, Wen, Miyares, Lombroso, & Bordey, 2017).

Furthermore, transgenic Knock-Out (KO) mice models for candidate genes involved in social pathways are becoming a growing field of research. In this context, cadherin superfamily, originally characterized as calcium-dependent cell-adhesion molecules, is now known to be involved in many biological processes, including cell recognition, cell signaling during
embryogenesis and formation of neural circuits (Bruining et al., 2015; Morishita & Yagi, 2007). In particular, protocadherin family, the largest subgroup within the cadherin superfamily, are predominantly expressed in the nervous system. Interestingly, recent evidence suggested that \textit{Protocadherin 9 (Pcdh9)} might be involved in schizophrenia and ASD pathogenesis (Hirabayashi & Yagi, 2014). Moreover, a recent study reported that the gene encoding \textit{Pcdh9} might be considered as a novel risk factor for Major Depressive Disorder (MDD) (Xiao, Zheng, et al., 2017). In this regard, in chapter 5 of this thesis, we investigated VBS colonies composed of 2 Homozygous (HOM) KO \textit{Pcdh9}, 2 Heterozygous (HET) KO \textit{Pcdh9} and 2 Wild Type (WT) \textit{Pcdh9} males, together with 2 WT \textit{Pcdh9} females, in order to evaluate sociability and social withdrawal features in relation to genotype differences.

1.5 Unraveling neurobiological alterations underlying depressive-like symptoms

Disentangle the etiology of depressive-like symptoms is a hard challenge. Indeed, available techniques to analyze the aberrant function of brain circuits is based on either \textit{post-mortem} studies, which have numerous limitations, or neuroimaging techniques, which rely on detecting changes in neuronal activity by using indirect markers of activation (Krishnan). Although these approaches have provided important insights into candidate brain regions, simple increases or decreases in regional brain activity are probably insufficient to explain the complex array of symptoms related to depression (Krishnan & Nestler, 2008). Therefore, neuropsychiatric symptomatology raises from heterogeneous neurobiology (Cummings, 2015), as a result of pathophysiological and biochemical alterations within several brain regions (Schiavone, Tucci, et al., 2017). This hypothesis is supported by several levels of evidence, in which neuropsychiatric symptoms are associated with underlying neurotransmitter system imbalances, including NA, DA, 5-HT, glutamate and gamma-aminobutyric acid (GABA), but also HPA axis dysfunctions, neurotrophins impairments and, recently, soluble beta amyloid involvement (Panza et al., 2010; Sweet et al., 2004; Wegener et al., 2004).

\textbf{The monoamine hypothesis of depression}

Depression has been associated with impaired neurotransmission of serotonergic, noradrenergic and dopaminergic pathways. This concept is now over fifty years old and arose from the empirical observation that depressive symptoms were influenced by the pharmacological manipulation of the monoaminergic system (Lanni, Govoni, Lucchelli, & Boselli, 2009; Sanacora, 2010). For
instance, reserpine, an antihypertensive first introduced in 1954, was found to deplete presynaptic stores of serotonin and noradrenaline and induce depression in some individuals (Lopez-Munoz, Bhatara, Alamo, & Cuenca, 2004). Moreover, iproniazid and imipramine had potent antidepressant effects in humans and were later shown to enhance central serotonin and noradrenaline transmission (Krishnan & Nestler, 2008). Since the catecholamine hypothesis of depression was first described, most antidepressant drug development has targeted the enhancement of monoamine neurotransmissions. For decades tricyclic antidepressants, that inhibit the reuptake of norepinephrine and serotonin, were the principal treatment choice for physicians. Therefore, monoamine hypothesis has been accepted as the most common hypothesis of major depression for a long period because of its simplicity and understandability (Boku, Nakagawa, Toda, & Hishimoto, 2017). Indeed, several evidence links depression to deficiencies in the neurotransmission of the monoamines 5-HT, NA and DA (D'Aquila, Collu, Gessa, & Serra, 2000; Popik et al., 2006). In this context, it has been suggested that a triple re-uptake inhibitor, resulting in an additive effect of enhancing neurotransmission in all three monoamine systems, might lead to improved efficacy and quicker onset of the antidepressant response (Marks, Pae, & Patkar, 2008). Although receiving considerable support, the monoamine hypothesis is considered restricted by several researchers (Joyce, 2007), as it does not provide a comprehensive explanation for the mechanism of actions of antidepressants and fails to explain why less than 50% of patients achieve full remission despite the numerous drugs available (Trivedi et al., 2006). For this reason, identification of new effective and safe treatment for depression is still a significant task and drugs targeting monoamine neurotransmissions alone are not able to fully cure all the behavioural symptoms and the different aspects and subtypes of depression.

**GABAergic and glutamatergic neurotransmissions in depressive-like symptoms affecting the social sphere**

During last decades, a number of evidence suggested that altered function of the amino acid neurotransmitter systems, especially GABA and glutamate systems, might contribute significantly to the etiology of neuropsychiatric disorders (Sanacora, 2010).

In this regard, glutamate is the major mediator of excitatory synaptic transmission in the mammalian brain (Maletic et al., 2007). Abnormal function of the glutamergic system has been implicated in the pathophysiology of several neuropsychiatric disorders, such as Huntington's chorea, epilepsy, Alzheimer's disease, schizophrenia and anxiety disorders (Hashimoto, Malchow,
Increasing evidence indicated that abnormal activity of the glutamatergic system observed in patients affected by mood disorders is likely to contribute to impairments in synaptic and neural plasticity found in these patients (Lanni et al., 2009). Moreover, preclinical studies demonstrated a negative correlation between glutamatergic tone and sociability, reporting an increase in social interactions following suppression of glutamatergic neurotransmission, while activation of prefrontal cortex led to reduced social interactions (Kendell, Krystal, & Sanacora, 2005), suggesting that attenuation of glutamatergic tone might ameliorate depressive-like symptoms affecting sociability, such as social withdrawal.

Conversely, GABA is the most widely distributed inhibitory neurotransmitter in the mammalian central nervous system (Celio, 1986). GABAergic tone is involved in the synaptic transmission of 5-HT, NA and DA, and has been shown to act as a modulator of several behavioural processes, such as sleep, appetite, aggression, sexual behaviour, pain, thermoregulation and mood. In this regard, reduced GABA concentrations have been observed in plasma and cerebrospinal fluid of depressed patients (Bhagwagar & Cowen, 2008). Accordingly, neuroimaging data has shown lowered levels of GABA in the occipital cortex of depressed subjects (Price, Lee, Garvey, & Gibson, 2010) and patients suffering from schizophrenia, depression, ASD and bipolar disorders appear to have lowered central and peripheral GABA levels when compared to healthy controls (Lewis, 2014; Romeo, Choucha, Fossati, & Rotge, 2017). In particular, this lowered functionality is visible during the prodromal stage of the diseases, concomitantly with behavioural dysfunctions, such as disrupted sociability (Minzenberg et al., 2010). In this view, recent studies showed that decreasing GABA neurotransmission in prefrontal cortex and amygdala led to decreased sociability (Paine, Swedlow, & Swetschinski, 2017). Thus, changes in GABA signaling might mediate sociability dysfunctions, such as social withdrawal, which is an important early symptom of several neuropsychiatric diseases.

In conclusion, drugs aim to potentiate GABAergic and attenuate glutamatergic neurotransmissions might be helpful to treat depressive-like symptoms, particularly in relation to the social sphere.

Nerve Growth Factor in depressive-like symptoms

Nerve growth factor (NGF), a key neurotrophin for the development of the nervous system, was initially discovered by Cohen and Levi-Montalcini, who won the Nobel Prize for this amazing discovery (Cohen, Levi-Montalcini, & Hamburger, 1954). Since first being discovered in 1979, NGF has been studied in different areas, such as neurology, angiogenesis, immunology, urology, and
others (Y. W. Chen et al., 2015). In the searching for neurobiological substrate involved in depressive-like states, NGF also play a significant role. NGF is an important member of the neurotrophins groups and is produced mainly in the cortex, hippocampus and hypothalamus, but also in the peripheral nervous system and immune system (Martino et al., 2013; Xiong et al., 2011). Evidence from animal studies reported decreased levels of NGF in specific brain areas of different mouse models, such as anxiety-related models, stress-induced diseases, learned helplessness and threatening treatment. All those mouse models are believed to represent forms of depressive-like models (Y. W. Chen et al., 2015). Accordingly, clinical studies have detected reduced levels of NGF in patients with major depression when compared with healthy individual controls (Diniz et al., 2014; Xiong et al., 2011). In addition, treatment with certain antidepressants has increased NGF levels in both clinical and experimental studies (Hassanzadeh & Rahimpour, 2011; Wiener et al., 2015). Furthermore, a significant decrease in serum NGF has been observed in patients with mild cognitive impairment, suggesting that the availability of NGF might be reduced at the onset of several neurodegenerative process (Schaub, Anders, Golz, Gohringer, & Hellweg, 2002). Since the identification of peripheral biomarkers to help in the diagnosis or to monitor the progression of mental diseases is still a field open to future research, NGF might be further investigated as a putative biomarker related to neurodegenerative disorders.

In addition, NGF and 5-HT are close and reciprocally regulated signals, thus the changes in NGF levels, acting through modifications of the 5-HT system, might help to disentangle the neurobiological mechanisms that give rise to depressive-like symptoms (Colaianna et al., 2010; Garcia-Alloza et al., 2004; Tapia-Arancibia, Aliaga, Silhol, & Arancibia, 2008).

**HPA axis parameters related to depressive-like states**

Chronic stress is generally known to exacerbate the development of a wide variety of neuropsychiatric diseases, such as depression, fear and anxiety disorders (Z. P. Liu et al., 2014). In this regard, HPA axis hyperactivation is a crucial response to chronic stress. HPA axis hyperactivation is featured by increased hypothalamic corticotropin-releasing factor (CRF) expression and consequently elevated plasmatic glucocorticoid concentrations (T. Chen, Li, & Chen, 2009; Wang et al., 2010; Zhang et al., 2017). In regard to depressive-like symptoms, it has long been hypothesized that cortisol secretion is an important neurobiological characteristic of depressive disorders (Lee & Rhee, 2017). Moreover, a number of studies supported the hypothesis of HPA axis involvement in depression, reporting an increase in hypothalamic CRF in depressed
patients (Raadsheer, Hoogendijk, Stam, Tilders, & Swaab, 1994; Raadsheer et al., 1995), or a decrease of CRF receptors in the frontal cortex (Nemeroff, Owens, Bissette, Andorn, & Stanley, 1988), or a decreased sensitivity to negative feedback (Halbreich, Asnis, Shindledecker, Zumoff, & Nathan, 1985; Pfohl, Sherman, Schlechte, & Winokur, 1985; Young et al., 2004). However, HPA axis dysfunctions have been found only in a subset of depressed patients (Varghese & Brown, 2001), suggesting that not all the depressive disorders share the same pathogenic pathways. Interestingly, HPA axis hyperactivity is highly related to anxiety disorders (Herman & Tasker, 2016; Y. T. Lin et al., 2017). In this regard, recent studies indicated that optogenetic inhibition of parvalbumin CRF neurons reduces anxiety-like behaviour, while stimulation induces anxiety-like behaviour (Fuzesi, Daviu, Wamsteeker Cusulin, Bonin, & Bains, 2016; Herman & Tasker, 2016).

Hence, future medications, pointing towards the modulation of HPA axis parameters, should be considered for the treatment of depressive-like disorders comorbid with anxiety states. **Soluble Amyloid Beta (Aβ1-42) peptide in depressive-like states**

During the last decade the soluble Aβ1-42 peptide has gained great attention in the study of depression insurgence, also considering that such neuropsychiatric disease is highly comorbid with Alzheimer’s Disease (AD) and other neurodegenerative illnesses (Colaianna et al., 2010; Morgese, Schiavone, & Trabace, 2017; Pomara & Sidtis, 2007; Schiavone, Tucci, et al., 2017; Sun et al., 2008). More recently, depressive signs have been potentially linked, in part, to the presence of soluble Aβ in the brain. Aβ peptides are physiologically produced from the Aβ protein precursor through beta and gamma secretase cleavage (Zetterberg, Mattsson, Shaw, & Blennow, 2010). They possess different brain area-selective neuromodulatory actions (Morgese, Schiavone, et al., 2017; Morgese et al., 2014; Mura et al., 2010; Trabace et al., 2007). Although the relationship among soluble Aβ, brain neurochemistry and depression remains complex, several studies have demonstrated an increased risk for the development of AD in individuals with late-life depression, indicating a prodromal state of AD (Dal Forno et al., 2005; Steffens et al., 1997; Sun et al., 2008). Similarly, it has been reported that depressed individuals are nearly twice as likely to develop dementia, often in the form of AD, compared with non-depressed individuals (Jorm, 2001). Aβ might have an effect on mood not limited to AD patients, indeed depressive-like states might precede or accompany dementia (Starkstein, Mizrahi, & Power, 2008). In this regard, our group has previously shown that central Aβ 1-42 administration in male rats was able to evoke a
depressive-like phenotype (Colaianna et al., 2010), characterized by increased immobility frequency in the Forced Swimming test and reduced cortical 5-HT and neurotrophins, such as NGF and Brain-Derived Neurotrophic Factor (BDNF). Since behavioural and neurochemical alterations were observed at a time at which amyloid plaques were not visible in the rat brain (Trabace et al., 2007), we could hypothesize that cerebral injection of soluble Aβ induced long-lasting neuronal circuits disruption ultimately responsible of depressive-like symptomatology (Schiavone, Tucci, et al., 2017).

1.6 Thesis aims and outline
The knowledge of the pathophysiology of depressive-like symptoms has evolved substantially from Galen’s speculations in antiquity about an excess of black bile (“melancholia”) to current evidence that incorporate lifestyle factors, genetic, endocrine, neurochemical and metabolic mediators, and cellular, molecular and epigenetic alterations. In this regard, considering the polysyndromic nature of depression, a multifactorial approach to better explore the etiopathogenesis of different depressive-like symptoms is warranted (Krishnan & Nestler, 2008).

Hence, the overall aim of this thesis was to investigate neurobiological determinants related to depressive-like symptoms. More specifically, by using different animal models and behavioural paradigms resembling human depressive-like symptoms, we evaluated the underlying neurobiological pathways, including monoamine system impairments, alterations in amino acids neurotransmissions, neurotrophin changes and HPA axis dysfunctions.

In particular, in chapter 2 and 3, we assessed the effect of n-3 PUFA in adult female offspring fed from conception with a diet poor in n-3 PUFA, or rich in n-3 PUFA, or a control diet. From a behavioural point of view, we performed Forced Swimming test to assess depressive-like behaviour and Open Field test to evaluate locomotor activity and anxiety-like behaviour. Moreover, we analyzed monoamine contents, in particular NA, DA, 5-HT and 5-HT turnover, HPA axis parameters, in particular hypothalamic CRF and plasmatic corticosterone, cortical NGF levels, plasmatic soluble Aβ levels, and, the last but not the least, GABA and glutamate levels.

Furthermore, we evaluated the effects of n-3 PUFA supplementation on a model of Aβ-induced depressive-like phenotype in adult female rats, performing the behavioural tests and neurochemical analyses listed above.
Moreover, in chapter 4 and 5 of this thesis, we implemented a modified version of the Visible Burrow System to study group-housed social dynamics and ultimately identify and validate behavioural readouts to assess sociability and social withdrawal features in mutant BTBR strain, transgenic *Pcdh9* line and C57BL/6J control strain. In addition, we investigated the neurobiological alterations underlying social behaviours, particularly focusing on GABA and glutamate neurotransmission.