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Prefrontal gene expression changes in mood disorders and suicide

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CHAPTER 1

GENERAL INTRODUCTION

When an individual is confronted with a threat or disturbance of its homeostasis, either real or perceived as such, his or her body and brain will respond and generally mount a stress response. This typically involves a variety of coordinated behavioural, bodily and hormonal responses that, working together, help the individual to adapt and cope with the aversive circumstance. When the stress response is not controlled, however, adaptation fails and the risk of developing psychopathology increases.

In line with this, an exaggerated response of the stress systems of the brain is commonly observed in both mood disorders and suicide (Bao et al., 2012; Lutz et al., 2017). The hypothalamus-pituitary-adrenal (HPA) system plays a central role and tends to show an exaggerated stress response in these disorders (Bao et al., 2008; Pandey, 2013; Turecki et al., 2012; Turecki and Meaney, 2016). In terms of its regulation, the HPA axis receives mostly inhibitory input from the hippocampus and the prefrontal cortex (PFC) (Narushima et al., 2003; Ongur and Price, 2000).

STRESS SYSTEM

Selye was the first who coined the "general adaptation syndrome" (GAS) as he realized that our body responds to stress or "noxious agents" (Szabo, 1998). He proposed three subsequent phases that occur in response to stress: (i) first there is an "alarm reaction", during which the organism prepares himself for fight or flight"; (ii) The next stage involves adaptation and resistance to stress, and (iii) the third stage, particularly of relevance during long term stress exposure, the body experiences advanced aging due to "wear and tear", which may lead to a state of exhaustion (Szabo, 1998).

An acute stress response is generally beneficial, as it prepares the body and brain for potential danger. It is directed to maintain homeostasis and allows the individual to adapt to the stressor. However, a prolonged and/or chronic activation of the stress system involves long-term exposure to glucocorticoid hormones that can have hazardous and deleterious effects on the body and, e.g., increase the risk of obesity, heart disease and a variety of other peripheral illnesses. Furthermore, chronic stress is notorious for increasing the risk of stress-related psychopathologies, such as major depression and other mood disorders (Tsigos and Chrousos, 2002).

HPA axis

The HPA axis is an important hub in mediating the stress response. Briefly, in response to a stressor, the paraventricular nucleus (PVN) of the hypothalamus releases corticotropin-releasing hormone (CRH), that is transported to the pituitary where it induces the release of adrenocorticotropin (ACTH) that travels through the blood and frees corticosteroid hormones (cortisol in humans and corticosterone in rodents) from the adrenal cortex. Cortisol is a powerful steroid hormone that prepares the body and brain for a flight or fight response, e.g. by focusing attention, increasing blood sugar levels, redistributing blood flow, suppressing the immune system, and altering the metabolism of fat, protein and carbohydrates. Notably, in addition to its peripheral effects, cortisol gives negative feedback to shut down the stress response after the threat has passed, by binding to specific stress hormone receptors in the same regions where the stress response was initiated. It does so by activating the pituitary and hypothalamus, via binding to the mineralocorticoid (MR) and glucocorticoid receptor (GR) (Bao et al., 2008; de Kloet, 2014). This inhibits CRH production.

The activity of HPA axis can further be modulated by other factors, such as the CRH receptors, by means of which CRHR1 stimulates CRH production (Karl et al., 2005; Muller and Wurst, 2004), whereas CRHR2 opposes this action. There are also opposite effects of MR and GR receptor activation (Muller and Wurst, 2004) and androgens and oestrogens affect the activity of the hypothalamic PVN in different ways (Bao et al., 2008; Wang et al., 2008). The ACTH-releasing effect of CRH on the pituitary is strongly potentiated by vasopressin (AVP) (Aguilera and Rabadan-Diehl, 2000; Gillies et al., 1982; Rivier and Vale, 1983), while inhibiting effects exist as well, such as the oxytocin (OXT) effect on ACTH release, which have been confirmed in various species (Legros, 2001). Furthermore, CRH neurons also project to other brain regions, and CRH in the PVN may thereby e.g. also affect mood through their direct central projections and/or through enhancing circulating levels of cortisol (Bao et al., 2005; Raadsheer et al., 1995),

Prefrontal cortex (PFC)

Anatomy

The PFC is the part of the frontal cortex that is situated in front of the motor and premotor areas. The PFC is a homogeneous structure and different subregions are distinguished according to their functional specialization, cytoarchitecture and

connectivity. There are four possible ways to define the PFC:

1) *As the "granular" frontal cortex*

The PFC has been defined based on its distinct cytoarchitecture, by, e.g. the presence of a granular layer IV. However, this definition only applies to primates, and not to non-primates where this layer IV is absent (Uylings et al., 2003).

2) *As the projection zone of the mediodorsal nucleus of the thalamus*

This definition is built on Rose and Woolsey who have identified projections running from the medio-dorsal nucleus to more anterior and ventral parts of the brain, at least in non-primates (Rose and Woolsey, 1948). The advantage of this definition is that the homologies between primates and non-primates (lack of a granular frontal cortex) can be established. The definition of the PFC based upon mediodorsal nucleus projection is still widely accepted (Fuster, 2008; Mitchell and Chakraborty, 2013).

3) *As cortex whose electrical stimulation does not evoke movements*

However, the electrically "silent" frontal cortex includes both granular and non-granular areas which can be a complication.

4) *As the part of the frontal lobe that is densely innervated by dopamine*

In rodents, the PFC receives an exceptionally dense dopaminergic innervation in comparison with other cortical areas (Beckstead, 1976; Divac et al., 1978). Furthermore, evidence for an extensive dopaminergic innervation of the primate and human PFC has been reported (Bjorklund et al., 1978; Gaspar et al., 1989).

While these different definitions show general agreement in the definition and location of a number of frontal areas, some areas differ markedly among the various maps. Neuroscientists have tended to rely almost exclusively on Brodmann's area (BAs) to localize prefrontal (and other) areas in the human brain. In the present thesis, we followed the definition of the PFC of Nieuwenhuys (Nieuwenhuys, 1978). The motor cortex and the PFC are the two main functional domains in the frontal cortex. The motor cortex lies rostral of the central gyrus (Nieuwenhuys, 1978).

The PFC is situated rostral to the precentral motor cortex and the premotor areas. The PFC can be divided into three major regions: lateral, medial and orbital.

Based upon the BAs brain map, the lateral PFC encompasses BAs 8, 9, 46, 10 and 47, the orbital PFC has been subdivided into two BAs, 11 and 47, and apart from medially extending portions of BAs 9, 10, the medial PFC includes BAs 24, 32 and 25 (Nieuwenhuys, 1978). It should be noted that the Brodmann areas vary widely between individuals (Uylings et al., 2005).

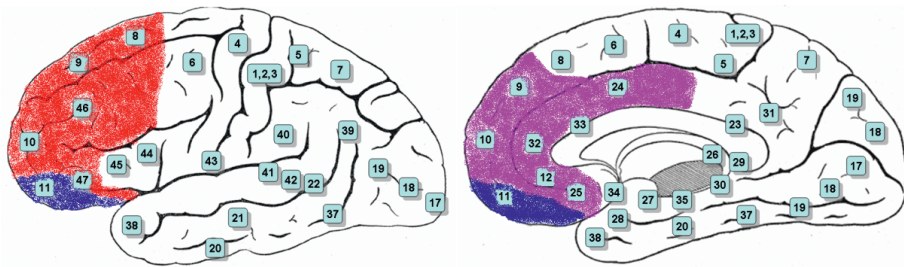


Figure 1 Prefrontal cortex (PFC) marked in colour in the left cerebral hemisphere. Subdivision according to Brodmann, lateral (left) and medial (right) views. The PFC is divided into the lateral PFC (red), orbital PFC (blue) and medial PFC (purple).

Physiology

The PFC has extensive reciprocal connections with several cortical sensory and motor systems, and also with other subcortical structures. Its primary functions involve planning, and inhibiting a person's response to complex and difficult problems. It acts as an "executor" for the decision-making process, integrating past events to present experiences in an optimal manner and thereby allow an individual to make the best choices. The anterior cingulate cortex (ACC; BA24, 32, 33), in particular the anterior and subgenual sites, are involved in emotion (Nieuwenhuys, 1978).

Interaction of HPA axis and PFC

Anatomical level

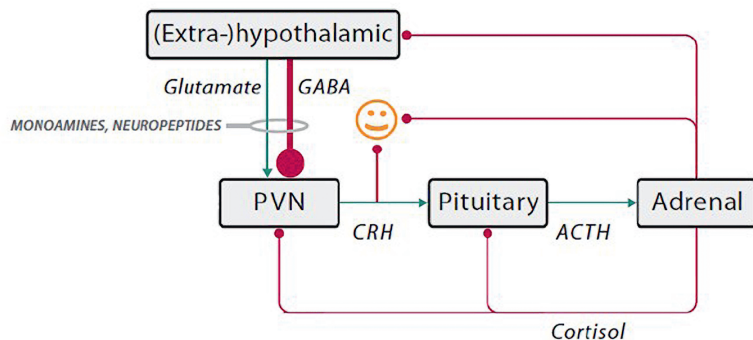
The bi-directional connections between the hypothalamus and PFC have been reviewed in different species (Saper, 2000). In rhesus monkey, the orbital, medial and lateral PFC receive projections from the hypothalamus. Injections of retrograde tracers in the lateral PFC areas labelled neurons in the lateral and medial posterior hypothalamus (Barbas and Rempel-Clower, 1997). In Macaque monkey, most of

the prefrontal projections to the hypothalamus arise from the medial prefrontal cortex in particular (Ongur et al., 1998). The subgenual cingulate cortex and ACC send strong projections especially to the anterior hypothalamic area and the ventromedial hypothalamic nucleus (Ongur et al., 1998). In contrast, the paraventricular-, supraoptic-, suprachiasmatic-, arcuate- and mamillary nucleus lack direct connections to the PFC. However, many PFC axons terminate around these nuclei and may still contact dendrites extending from them (Ongur et al., 1998). In the monkey, descending fibers from the orbitofrontal and medial PFC are involved in emotional regulation and provide both stimulatory and inhibitory actions on the autonomic nervous system (Barbas et al., 2003).

Feedback inhibition mediated by corticosteroids

The PFC is well known for its inhibitory action on corticotropin-releasing hormone (CRH) release in the PVN. Animal experiments have shown that PFC lesions activate the HPA axis (Diorio et al., 1993). An important study on stroke patients has shown that the severity of post-stroke depression correlated negatively with the distance between the stroke lesion and the frontal pole of the PFC of the patient (Narushima et al., 2003). This indicates that the PFC is crucially involved also in mood regulation in humans. Moreover, there are receptors for both glucocorticoids and CRH in the PFC, and both these stress-related compounds are increased in depression (Raadsheer et al., 1994; Raadsheer et al., 1995; Wang et al., 2008). On the other hand, hypercortisolism, which occurs in MDD and BD patients, will also inhibit PFC activity and together these two effects might even reinforce each other (Bao et al., 2008). In mood disorders and Alzheimer's disease (AD), the interaction between the PFC and the HPA axis therefore seems to be of crucial importance. Inhibition of PFC activity in AD will cause a chronic rise of CRH and cortisol levels that produce mood changes through their action on the brain (Gao and Bao, 2011; Herbert and Lucassen, 2016).

Control



Depression

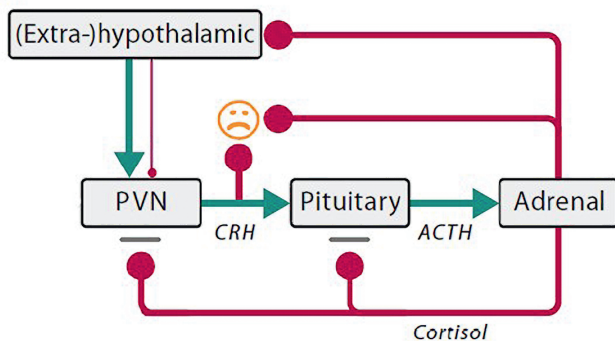


Figure 2 Pathogenetic hypothesis on the relationship between extra-hypothalamic (e.g., the prefrontal cortex, PFC) and hypothalamic changes.

→ : stimulate
 -●: inhibition

The thickness of the lines indicates the strength of the effects (Based upon Bao et al., 2012).

Several studies further show that hypofrontality correlates with disease severity in both major depressive disorder (MDD) and bipolar disorder (BD) (Bao et al., 2008; Galynker et al., 1998). In addition, imaging studies have revealed differential patterns of neural activity between MDD patients with suicide attempt history and MDD patients per se (Pan et al., 2011). A recent study showed that the reduced fronto-subcortical circuit of structural connectivity plays a role in suicidal ideation in MDD patients. This includes regions associated with executive function and impulsivity (Myung et al., 2016). In addition, it was reported that functional connectivity of the anterior cingulate is associated with past suicidal ideation and

depressive behaviour in psychotic MDD (Minzenberg et al., 2016). Patients with bipolar disorder (BP) are further characterized by a pronounced impairment in several PFC related tasks (Zihl et al., 1998). Furthermore, in both MDD and BD, glucose metabolism in both the dorsolateral PFC (DLPFC) and ACC, is strongly reduced (Price and Drevets., 2010). In addition, a reduction of grey matter volume has been reported in the DLPFC in both MDD and BD, When followed up postmortem, this volume reduction appeared related to reduced densities and sizes of both neurons and glial cells (Price and Drevets., 2010; Rajkowska et al., 1999; Rajkowska et al., 2001). Finally, transcranial magnetic stimulation (TMS) and electrical deep brain stimulation, when applied to the PFC, have been shown to be effective in the treatment of refractory depressive patients (Burt et al., 2002; Temel and Lim, 2013). Furthermore, during TMS treatment of depression there are several regions that subsequently increased in volume, and the increases in the ACC with TMS correlated with improvement in depression severity (Lan et al., 2016).

MOOD DISORDERS

Clinical features and epidemiology

In general Diagnostic and Statistical Manual for Mental Disorders (DSM) terms, mood disorders include: MDD, BD, persistent depressive disorder, cyclothymia and seasonal affective disorder. The life-time prevalence of MDD is estimated to be 16% (Kessler et al., 2003), while the prevalence estimate for BD is 4.4% (Merikangas et al., 2007). According to the DSM III-R (APA, 1987) and DSM IV (APA, 1995), which were used for the diagnosis in the present thesis, the essential feature of MDD is a profound sadness and/or loss of interest or the ability to enjoy pleasure in almost all activities. Together with associated symptoms, these symptoms should be present for at least two weeks. Of the associated symptoms, 5 should be present during the disorder, they include eating disorder, weight change, sleep changes, psychomotor agitation or retardation, reduced energy levels, feelings of worthlessness or extreme, often inappropriate guilt, thinking or concentration problems, and thoughts of death or suicide.

Risk factors involved in mood disorders

Several risk factors have been identified for mood disorders. Female gender, age, polymorphisms in genes for the glucocorticoid or mineralocorticoid receptor, the

presence of a CRH1 and CRH2 receptor, but also having been abused as a child and early maternal separation are risk factors for later depression. Stressful life events, often in combination with specific genetic risk factors, may trigger depression in vulnerable individuals (Bao et al., 2008).

In addition, several hormonal factors may be involved in the risk for depression. Oestrogens stimulate CRH transcription, whereas androgens inhibit this process. This may explain why the prevalence of MDD is twice as high in females as in males (Bao and Swaab, 2007). Smoking during pregnancy, may increase the risk to develop depression (Clark et al., 1996; Clark, 1998). In addition, associations exist between a low birth weight, a permanently increased activity of the HPA axis, a higher response of cortisol, and an increased risk to develop MDD (Thompson et al., 2001). Studies have also shown that MDD is commonly observed after stroke (Narushima et al., 2003) and in hypertension (Everson et al., 2000), where the CRH neurons are strongly activated (Goncharuk et al., 2007).

SUICIDE

Suicide is a serious public health concern worldwide. According to the World Health Organization, every year there are about 800 000 persons die due to suicide worldwide. Risk factors for suicide can be categorized as distal and proximal factors (Hawton and van Heeringen, 2009; Lutz et al., 2017; Turecki et al., 2012). Distal risk factors' include genetic background and earlier suicide in the family, stressful or traumatic early life-events, epigenetic alterations, as well as specific personality traits and cognitive styles (Hawton and van Heeringen, 2009; Turecki et al., 2012). In addition, more 'proximal risk factors' exist that can act as triggers for the induction of a depressive episode. These include e.g. the existence of psychiatric and/or general comorbidity, recent life events that induce acute stress and/or the presence of financial or relational problems (Hawton and van Heeringen, 2009; Turecki et al., 2012). In addition, moderators are distinguished of the relationship between distal and proximal risk factors, that involve age, education, religious and spiritual beliefs, sex, employment and income, and the quality of one's social environment and level of psychological and moral support (Qin et al., 2003; Turecki et al., 2012). Based on evidence from numerous empirical studies, over 90% of suicide victims present with a diagnosable psychiatric illness (Singhal et al., 2014; Wasserman et al., 2012; Whiteford et al., 2013).

While postmortem studies in mood disorders and suicide victims allow a direct investigation of neurotransmitters and related molecules, such as neurotransmitter transporters and receptors, the results in the literature are often inconsistent, which is why the exact molecular mechanisms underlying the etiology and pathophysiology of mood disorders and suicide have so far remained obscure. Notably, although a large proportion of suicides occur in mood disorder sufferers, a specific proportion of these patients have never shown any suicidal behaviour and have never attempted suicide. Furthermore, the presence of suicides in the family is at least partly independent from the presence of mental disorders in the family (Qin et al., 2002). These observations suggest that suicide is probably not the outcome of the psychiatric disease, but rather a disorder in itself (Aleman and Denys, 2014). However, in the available postmortem studies, most depression research was carried out in mood disorder patients who died due to suicide and, so far, little attention has been paid to the comparison of mood disorders with and without suicide separately (see Chapter 2) and it is thus often not clear whether the changes found are characteristic for mood disorders or for suicide.

NEUROTRANSMITTERS AND THEIR RECEPTORS IN THE PFC

The HPA axis is innervated and regulated by a large number of neurotransmitter systems (monoamines, amino acids, acetylcholine and neuropeptides) that all are altered in mood disorders. Here, we give a very brief introduction on these neurotransmitters and neuromodulators in general, and then focus on GABA and glutamate, NOS, retinoic acid and BDNF.

Neuropeptides

Several studies (Bao et al., 2008) imply that (hypothalamic) neuropeptides such as CRH, AVP and OXT are very important not only for neuroendocrine-, autonomic- and higher functions of the brain, they also contribute to depressive symptoms. Intracerebral injection of CRH in the rodent brain e.g. induces depressive-like symptoms and increased anxiety (Holsboer, 2001). Furthermore, part of the parvocellular neurons in the PVN secrete both CRH and AVP as neurohormone. Since AVP potentiates the effects of ACTH and hence of the corticosterone production (Engelmann et al., 2004), AVP is important, in close interaction with

CRH, in stimulating HPA axis activity. Unlike AVP, OXT was found to inhibit basal HPA axis activity and to diminish HPA activity in humans as well as in many other species (Legros, 2001). Activation of OXT neurons also occurs in mood disorders and is presumed to be related to the disturbances in eating behaviour and weight loss in these disorders (Dai et al., 2017; Gimpl and Fahrenholz, 2001; Meynen et al., 2007a; Purba et al., 1996). Enhanced OXT production in the PVN was especially found in postmortem material of melancholic MDD patients (Meynen et al., 2007a). It should be noted that, since neuropeptides such as OXT, AVP and CRH can be secreted into the circulation, but are also expressed in a wide variety of brain areas, measuring peripheral circulating hormonal alterations does not necessarily give information on their central effect.

Monoamines

Serotonin (5-HT)

The serotonergic system is widely studied in relation to several aspects of brain function. It has obtained most attention in relation to studies on suicide and depression (Pandey, 2013; Pompili et al., 2010). The concept that a dysfunction of 5-HT transmission may contribute to a depressed mood and possibly even suicide, started with the observed clinical benefits of selective serotonin reuptake inhibitors. These commonly used antidepressants increase serotonergic neurotransmission. In addition, CSF-5HIAA levels were found to be related with depression and suicide (Asberg et al., 1976; Traskman-Bendz et al., 1989).

5-HT innervation is present in nearly all brain areas, and originates exclusively from neurons in the raphe nucleus. Mann and colleagues reported a decrease of serotonin binding sites in the PFC (Mann et al., 1996) and ventrolateral PFC (Arango et al., 1995) in suicide victims. In addition, a diminished serotonin transporter density has been found in the PFC (Austin et al., 2002), although exceptions exist as well (Bligh-Glover et al., 2000; Hrdina et al., 1993). There is one study also showing that, during the chronic citalopram treatment, the dopamine-related stress response was preferentially controlled by an upregulation of 5-HT_{1A} receptor signalling, particularly in the PFC (Kaneko et al., 2016). Increased levels of prefrontal 5-HT₂ receptors were reported (Hrdina et al., 1993), but this was not replicated by others (Cheetham et al., 1988; Lowther et al., 1997). Using a larger sample, no differences between groups were observed in 5-HT₂ receptors in the cortex (Lowther et al., 1994). Many microarray studies have determined

the transcription levels of 5-HT related genes in the frontal cortex of both suicide and MDD patients (Sequeira et al., 2012; Tochigi et al., 2008), but most failed to find serotonergic gene expression differences between suicide and controls (Ernst et al., 2009). There are families in which SNPs in the 5-HT transporter are related to the risk for mood disorder, but this concerns only a small minority of patients (Kiyohara and Yoshiimasu, 2009). In addition, the serotonin levels in the brain go up on the days when SSRIs are given, whereas it takes week for mood to improve (Bao et al., 2012). These observations do not support the concept that for most cases the 5-HT system is the primary cause of mood disorders.

DA

The major dopaminergic innervation of the brain originates from the ventral tegmental area and substantia nigra in the mesencephalon. To date, there is little evidence to implicate (changes in) dopaminergic transmission in suicide. Dopamine levels were not significantly different between suicide and matched controls (Allard and Norlen, 2001). Nonetheless, it is common knowledge that dopamine can regulate the stress system and that stress exposure, combined with elevated levels of glucocorticoids does enhance dopamine release (Dunn, 1988; Piazza and Le Moal, 1996; Rouge-Pont et al., 1998; Thierry et al., 1976). Dopamine release in the nucleus accumbens is disturbed in MDD patients and seems to be related to anhedonia (Pizzagalli et al., 2009; Willner et al., 1992). The impaired PFC-dependent working memory after acute stress (Arnsten, 2007; Srikumar et al., 2007) is probably mediated by an excessive release of dopamine in the PFC (Arnsten and Goldman-Rakic, 1998; Arnsten et al., 2000; Morrow et al., 2000). Furthermore, an animal study indicates that hyperactivation of dopamine D1 receptors may mediate stress-induced deficits of emotional learning and memory (Wang et al., 2012).

Adrenaline and noradrenaline

Adrenaline and noradrenaline are produced by the adrenal medulla in response to stress, while noradrenaline is also synthesized in the brain. Both monoamines as well as adrenergic transmission in general are thought to contribute to both mood disorders and suicide (Lipinski et al., 1987; Maletic et al., 2017) and studies have reported a relation between morphological features of the locus coeruleus, the small adrenergic nucleus located in the brainstem, and the presence or absence of suicide (Gos et al., 2008; Poulter et al., 2010; Roy et al., 2017). Furthermore, the

receptors for adrenaline and noradrenaline have been extensively studied in this respect. In the CNS, two metabotropic adrenergic receptor subtypes exist: the α - and β -subtype (Hein, 2006). Several studies have reported that in the hypothalamus and frontal cortex of depressed suicide patients, α_2 -adrenergic receptors are increased when compared to matched control subjects (Escriba et al., 2004; Garcia-Sevilla et al., 1999), but not in all of them (De Paermentier et al., 1997; Gross-Isseroff et al., 2000). Furthermore, one study showed that abnormal α_2 -adrenergic receptor signalling pathways are involved in the pathogenesis of depression (Valdizan et al., 2010), and are critical for the antidepressant-like effects of desipramine (Zhang et al., 2009).

Glutamate and gamma-aminobutyric acid (GABA)

Glutamate is the main excitatory, and GABA the main inhibitory neurotransmitter in the brain. Glutamate is mainly synthesized by projection neurons, whereas GABA is the predominant and fast acting neurotransmitter found in interneurons. For the synthesis of both glutamate and GABA, glutamine is essential. Within the nerve terminals, the enzyme glutaminase converts glutamine to glutamate. Subsequently, glutamate is used to synthesize GABA via conversion by glutamic acid decarboxylase. Glutamine synthetase is present in glial cells and involved in the synthesis of glutamine from the re-uptake of either glutamate or GABA (Weiler et al., 1979). Recently, more and more evidence has been accumulating about the importance of the role that amino acid neurotransmitters may play in the pathogenesis of mood disorders. In most of depression, GABA levels in the cerebral cortex, plasma and CSF were found to be decreased (Gao and Bao, 2011). Based on their pharmacological and molecular differences, two distinct receptors exist; i.e. the GABA-A and GABA-B receptor. The GABA-A receptor is a pentameric, ligand-gated ion channel, whereas the GABA-B receptor is a G-protein-coupled heterodimer. GABA-ergic neuronal density was found to be decreased in the PFC of mood disorder patients (Cotter et al., 2002b; Rajkowska et al., 2007). GABA-A receptors or GABA receptor-associated binding proteins are further changed in many brain areas of suicide victims with MDD (Sequeira et al., 2009) (especially in the PFC). Two major classes of glutamate receptors exist: ionotropic glutamate receptors (NMDA, AMPA, kainate receptors) and metabotropic glutamate receptors (mGluR). They are located on the pre- and post-synaptic located membrane of neurons and glial cells. AMPA receptors consist of 4 subunits (GluR1 4, Wisden and Seeburg, 1993), whereas NMDA receptors are

tetramers of two NR1 and two NR2A, NR2B, NR2C, or NR2D subunits (Wenthold et al., 2003). The family of metabotropic receptors consists of 8 different members, i.e. mGluR1-mGluR8 (Duvoisin et al., 2005).

GABAergic and glutamatergic pathways are significantly altered in the PFC, as was extensively studied in depressed patients, the majority of which died due to suicide (Choudary et al., 2005; Cotter et al., 2002a; Cryan and Kaupmann, 2005; Guidotti et al., 2000; Krystal et al., 2002; Rajkowska et al., 2007). In BD, the glutamate content is increased in the ACC and DLPFC relative to healthy controls (Frye et al., 2007; Lan et al., 2009), while in MDD, both NR1 and NR2A expression was decreased in the DLPFC (Beneyto and Meador-Woodruff, 2008). On the other hand, several microarray-based investigations have shown indications for strong GABAergic and glutamatergic dysfunction when comparing suicide victims with and without major depressive disorder (MDD) (Choudary et al., 2005; Klempan et al., 2009; Merali et al., 2004; Sequeira et al., 2007; Sequeira et al., 2009).

Glutamate-Glutamine cycle

Glutamate can be synthesized in two ways: (i) de novo from glucose and (ii) from glutamine that is obtained from glial cells. After its release into the synapse, glutamate is cleared by excitatory amino acid transporters (EAAT1 and EAAT2) that are located on neighbouring glial cells. Also neuronal EAAT3 and EAAT4 exist, but their role is less prominent. Glutamate is converted to glutamine by glutamine synthetase in glial cells. Glutamine is subsequently released by System N transporters and taken up by neurons through System A sodium-coupled amino acid transporters (Rose et al., 2013; Zhou and Danbolt, 2014).

During the past decade, pathology of glial cells has become accepted as important contributors to MDD and BD. There is e.g. a marked reduction in glial cell number and density in the PFC of mood disorder patients (Cotter et al., 2002b; Lucassen et al., 2014; Ongur et al., 2008; Rajkowska and Miguel-Hidalgo, 2007). Also, glial fibrillary acidic protein (GFAP) is decreased in the PFC of depressed patients (Miguel-Hidalgo et al., 2000; Miguel-Hidalgo et al., 2010; Webster et al., 2001). Such changes are thought to be associated with the altered GABA and glutamate levels found in depressed patients (Sanacora et al., 1999; Sanacora et al., 2004).

NO

Nitric oxide (NO) may also contribute to the pathogenesis of mood disorder and

suicide. NO is an unconventional, gaseous neurotransmitter, that diffuses between neurons and directly affects intracellular components. There are 3 different subtypes of NO synthase (NOS) that convert L-arginine into NO: NOS1 (neuronal NOS, nNOS), NOS2 (inducible NOS, iNOS), and NOS3 (endothelial NOS, eNOS; (Grijth and Stuehr, 1995). NOS1 is found in human neocortex, cerebellum and hippocampus (Egberongbe et al., 1994) while NOS2 and NOS3 are also expressed in the human brain (Broholm et al., 2003; Vodovotz et al., 1996).

In the human cortex, NOS1 is found in both glutamatergic pyramidal cells and GABAergic interneurons (Judas et al., 1999; Kwan et al., 2012). Diminished ACC-NOS1 expression and decreased CSF-NO_x levels were found in mood disorder patients (Gao et al., 2013). Constitutive NOS activity, reflecting both NOS1 and NOS3, was found to be significantly decreased in the DLPFC of MDD patients (Xing et al., 2002). The observations that the locus of NOS1 on chromosome 12q24 is linked to MDD (Ewald et al., 1998; Fallin et al., 2005; McGujn et al., 2005), and that polymorphisms in the 3 subtypes of NOS are related to an increased susceptibility or relapse risk for depression (Galecki et al., 2011; Yu et al., 2003), support the involvement of NOS in the pathogenesis of depression.

Retinoid signalling

Retinoids are composed of vitamin-A and its derivatives. There are involved in brain development. Vitamin A (Retinol) is either esterified by lecithin retinol acetyltransferase and stored, or oxidized reversibly into retinaldehyde. Subsequently, it is oxidized by retinaldehyde dehydrogenases (RALDH1 to RALDH3) to retinoic acid (RA), which acts as a ligand for specific nuclear receptors (i.e., heterodimers of RA receptors (RARs) and retinoid X receptors (RXRs)) in order to regulate the transcriptional activity of specific target genes. Also involved in this pathway are the cellular retinol binding proteins (CRBPs) and cellular retinoic acid binding proteins (CCRABPs). In cells expressing cytochrome P450 26 (CYP26) enzymes, RA is transformed into more polar compounds, metabolized and eliminated (Tafti and Ghyselinck, 2007). Brain functioning during adulthood probably requires retinoid signaling as well (Lane and Bailey, 2005). Based on case reports, retinoid use was found to be involved in the onset/offset of depressive symptoms in severe acne patients (Bremner and McCaffery, 2008; Bremner et al., 2012). Retinoid application to animals also affects structural plasticity measures such as neurogenesis, as seen in many animal models for depression, which closely correlates with depression-like behaviour (Hu et al., 2016).

BDNF

Tropomyosin receptor kinase B (TrkB) is a transmembrane receptor that binds Brain-Derived Neurotrophic Factor (BDNF) with high affinity. This growth factor supports the survival of existing CNS neurons, as well as the growth and differentiation of new neurons and synapses. Full-length TrkB and TrkB.T2 are located in neurons, whereas TrkB.T1 is mainly found in astrocytes. Both BDNF and TrkB have received considerable attention in studies on MDD and suicide and some reported lower serum levels of BDNF in MDD patients (Brunoni et al., 2008; Ray et al., 2014; Thompson Ray et al., 2011). In addition, also prefrontal BDNF and/or TrkB levels were found to be decreased in suicide cases (Ernst et al., 2009; Maussion et al., 2014; Pandya et al., 2014).

ALZHEIMER'S DISEASE (AD)

More than 35 million people worldwide suffer from AD, a common neurodegenerative disorder that is characterized by progressive memory loss and disturbances in other cognitive domains.

Depression in AD

One of the most common psychiatric complications and comorbidities in AD is depression, affecting up to 50% of the AD patients (Lyketsos and Lee, 2004; Zubenko et al., 2003). When AD patients become depressed, this may seriously affect their daily functioning and activities, as it decreases their cognitive functioning and increases their mortality rate (Duru Asiret and Kapucu, 2015). In addition, it means an increased burden for caregivers, as well as an increased likelihood of being eligible for admission to a nursing home (Mohamed et al., 2010).

It is complex to diagnose depressive disorder in AD patients. Firstly, based on the DSM-III-R and DSM-IV classification, depression in AD does not belong to MDD as depression in this case occurs during the course of a neurodegenerative disease process. Secondly, depression and AD have many overlapping symptoms (Burke et al., 1988; Teng et al., 2008) such as a loss of interest and anhedonia. Therefore, the Cornell scale for depression in dementia was designed (Alexopoulos et al., 1988). This instrument contains 19 items, and is a validated method for assessing depression in demented subjects.

A hypothesis to explain the high prevalence of depression in AD is that of a decreased cortical metabolism (Arendt et al., 2015) that might lead to a hyper-

activation of the HPA axis (Bao et al., 2008; Meynen et al., 2007b; Swaab et al., 2000). Neuritic plaques and neurofibrillary tangles, the two major hallmarks of AD brains, are indeed present in higher amounts in depressed AD patients than in non-depressed AD patients (Caraci et al., 2010). Another study has shown that the Cornell scores is correlated with the number of neuritic plaques in the entire cortex and in particular in the temporal cortex of AD patients (Meynen et al., 2009).

The epidemiology and brain changes in AD

AD is a multifactorial disease. with advancing age as its principle risk factor. From 65 years of age onwards, the incidence of AD doubles every 5 years (Querfurth and LaFerla, 2010). Although data on centenarians suggest that AD may not necessarily be the outcome of aging per se (den Dunnen et al., 2008), the AD diagnosis applies to one in three people over 85 years (Alzheimer's, 2014). The presence of the apolipoprotein E (ApoE) e4 risk allele is responsible for some 17% of the cases. Mutations in the amyloid precursor protein, presenilin 1 or 2 genes, are risk factors for familial and often early onset dementia, but together, these patients contribute no more than 1% to the total prevalence of AD (Bettens et al., 2013). Female gender, low sex hormone levels, a low level of education and obesity are also risk factors for AD (Bao et al., 2008).

The PFC is strongly affected, particularly in late-stage AD, as appears from its atrophy and the accumulation of plaques and tangles (Bossers et al., 2010; Braak and Braak, 1991; Schaeffer and Gattaz, 2008). Since most studies on aging and AD focus on regions that are affected early on in the AD process, such as the medial temporal lobe – mainly entorhinal cortex and hippocampus – and that are linked to encoding declarative memories, much less is known about the AD process in the PFC (Leuba et al., 2008). Without disregarding the importance of AD related lesions such as A β senile plaques and neurofibrillary tangles (Bossers et al., 2010), the functional changes in the aging or AD PFC could be related to changes in synaptic and cytoskeletal plasticity, as the loss of synaptic proteins was found to be greater in the frontal than in the parietal cortex of AD patients (La Joie et al., 2012; Reddy et al., 2005). A characteristic functional change in the PFC in these conditions is hypometabolism, which may trigger the hyperactivity of HPA axis. In turn, the resulting hypercortisolism may inhibit the PFC even more (Fulham et al., 1995; Klupp et al., 2015), leading to further activation of the HPA axis. Whether the metabolic changes in the cortex of AD patients are cause or

effect of a hyperactive HPA axis remains a matter of debate (Swaab et al., 2005).

An imbalance between GABA and glutamate was also reported in the PFC in AD: a significant decrease in GABA without glutamate changes was found, e.g., in the DLPFC in depressive patients with AD, while the glutamate/GABA ratio correlated with the depressive state (Garcia-Alloza et al., 2006). A connection was also found between depression and decreased glucose metabolism in the DLPFC and ACC in early AD (Hirono et al., 1998; Marano et al., 2013). The possible relationship between GABA and glutamate changes in the PFC and depression in AD is currently under investigation in our group.

ANIMAL MODELS

AD patients with comorbid depression show higher levels of cortical plaque and tangle accumulation than AD patients without comorbid depression (Meynen et al., 2009; Rapp et al., 2008). We therefore wondered whether mouse models for AD could also be used as a model for depression in AD. There are two hallmark lesions in AD: 1) diffuse and neuritic plaques, mainly composed of A β peptide, and 2) neurofibrillary tangles, composed of filamentous aggregates of hyperphosphorylated tau protein.

One of the most commonly used models for AD is the APP/PS1 mouse line, which overexpresses the Swedish APP mutation and the PSEN1 L166P mutation as human transgenes (Radde et al., 2006). As a consequence, these mice produce elevated levels of A β and are considered a model for familial AD. The APP/PS1 mice have several features in common with familial AD patients, including the development of amyloid plaque deposition, a loss of spines and memory impairment at advanced age, mainly in their neocortex. These mice generally exhibit cognitive impairments by 7 months of age (Serneels et al., 2009), and learning impairments by 8 months (Radde et al., 2006). In the hippocampal CA1 region, microglia activation is present and long-term potentiation (LTP), an *in vitro* model for learning and memory formation, is impaired. These changes also start around 7-8 months (Gengler et al., 2010; Hoeijmakers et al., 2017). Interestingly, exposure to stress during the early life period modified longterm survival of the mice and amyloid pathological levels (Green et al., 2006; Lesuis et al., 2016; Lesuis et al., 2017). Notably, this can be rescued by application of blockers of the GR (Baglietto-Vargas et al., 2013, Lesuis et al., 2018).

Animal model has, however, clear discrepancies with human AD. For instance, the congophilic amyloid deposits in APP/PS1 mice are surrounded by phosphorylated tau-positive, neuritic processes, but not by fibrillary tau inclusions, or full-fledged neurofibrillary tangles, as seen in human AD brain (Radde et al., 2006; Rupp et al., 2011). Also, it is important to note that in these mice, the neuropathological alterations follow, rather than precede, the functional disturbances (Radde et al., 2006; Rupp et al., 2011). Animal models may thus be a formidable tool in the investigation of the etiology of AD, its course and potential treatment (Collado 2010; Lanzas 2010), and for the study of the neurobiology of behaviour (McKinney 2001), but the validity of a model should be proven by comparison to the human disorder.

SCOPE OF THE PRESENT THESIS

Most postmortem studies on depression have been carried out in mood disorder patients that died due to suicide, while most postmortem studies on suicide were comparing these subjects to healthy controls, even though most suicide patients have a psychiatric background. Therefore, it is often not clear whether the reported changes in the literature are related to depression, suicide or both. This problem is first illustrated in a short communication of the literature in Chapter 2. The **central question** of the present thesis is, therefore, whether changes in the postmortem PFC are related to depression or rather to suicide. For this question, we studied, in the ACC and in the DLPFC, components of the two major neurotransmitter pathways, i.e. glutamate and GABA (Chapter 3 and 4), and a series of stress-related neurotransmitters, neuropeptides and related compounds (Chapter 5), as well as possible changes in the glutamate-glutamine cycle and neuronal/glial glutamate transporters (Chapter 6).

For the second research question, we hypothesized that, in AD, the presence of amyloid plaques in the frontal cortex may induce alterations in the GABAergic and glutamatergic pathways, thereby causing activation of the HPA axis, and in this way contributing to the high prevalence of depression in AD. Thus, the **second question** in this thesis is whether AD-related depression is accompanied by such changes in the glutamate and GABA pathways, as also observed in mood disorders and what the relation of these changes is to hyperactivity of the HPA axis in AD. Finally, the APP/PS1 mouse model for AD was studied, in order to see whether it also displays depression-related changes and might thus be useful for studies on

depression in relation to AD pathology (Chapter 7).

In Chapter 8, I provide an overview of my main findings, and a discussion of recent literature in relation to future research. To summarize, our research has shown that, both in ACC and DLPFC, mood disorder patients who committed suicide have a different molecular fingerprint than mood disorder patients who died of natural causes. Specifically, our data indicate that the increase in glutamate related gene expression in the ACC may be linked to suicide, rather than to MDD per se.

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