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REVIEW

The hypothalamus and neuropsychiatric disorders: psychiatry meets microscopy

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Abstract

The past decades have witnessed an explosion of knowledge on brain structural abnormalities in schizophrenia and depression. Focusing on the hypothalamus, we try to show how postmortem brain microscopy has contributed to our understanding of mental disease-related pathologic alterations of this brain region. Gross anatomical abnormalities (volume changes of the third ventricle, the hypothalamus, and its nuclei) and alterations at the cellular level (loss of neurons, increased or decreased expression of hypothalamic peptides such as oxytocin, vasopressin, corticotropin-releasing hormone, and other regulatory factors as well as of enzymes involved in neurotransmitter and neuropeptide metabolism) have been reported in schizophrenia and/or depression. While histologic research has mainly concentrated on neurons, little is currently known about the impact of non-neuronal cells for hypothalamus pathology in mental disorders. Their study would be a rewarding task for the future.

Keywords Hypothalamus · Histopathology · Schizophrenia · Depression · Neuropeptides

Introduction

For hundreds of years, the nature of mental illnesses remained enigmatic. Then, in 1837, the famous at that time psychiatrists ("mad doctors") Brigham and Browne independently of each other came up with the idea that "insanity" might be a brain organic disorder (Brigham 1837; Jarvis 1841). Even though the concept of a "brain-borne" origin of mental illnesses had eminent supporters like Kraepelin, it would be more than a century, before this assumption could be proven. Since the 1970s–1980s, with the availability of sophisticated microscopic, brain imaging and biochemical techniques, evidence has accumulated in favor of schizophrenia and major depressive disorder (MDD) being diseases of the brain, like Alzheimer's disease and Parkinson's disease (Torrey 2017). Nowadays, there is no doubt that the brains of individuals suffering from schizophrenia or MDD are measurably different from individuals who do not have these diseases, although it is (still) impossible to diagnose them solely based on brain structural or functional alterations. Focusing on the hypothalamus, the purpose of the present review is to show that postmortem human brain microscopy, despite some skepticism because of methodical limitations (Harrison 2000; Falkai and Schmitt 2016), has made and is still making valuable contributions to our understanding of mental disease-related brain pathology.

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Schizophrenia and MDD manifest themselves in brain structural abnormalities

Neuropathology of schizophrenia

Schizophrenia is a disabling mental illness that results from an interplay of genetic and environmental risk factors. It affects approximately 1% of the population world-wide. Clinically, schizophrenia is characterized by an array of symptoms, including delusions, hallucinations, disorganized speech or behavior and impaired cognitive ability. Disability often results from both negative and cognitive symptoms, such as impairments in attention, working memory, or executive function (Patel et al. 2014 and others). During the last years, research

has revealed that certain functional and structural brain changes are already present in drug-naïve patients at the onset of schizophrenia. Alterations seen in first-episode patients are different from those observed in chronic patients, which points to progressive brain changes. Of note, some of the alterations as observed in chronic schizophrenia may result from long-term antipsychotic treatment of the patients (for reviews, see Ellison-Wright et al. 2008; Huhtaniska et al. 2017). Brain abnormalities in schizophrenia affect both gray and white matter. According to a meta-analysis (Shepherd et al. 2012), replicated gross anatomical brain alterations in schizophrenia are (1) reduced whole brain volume; (2) enlargement of the lateral ventricles and cavum septum pellucidum; (3) reduced area of the mid-sagittal callosum; (4) reduced sizes of the frontal, parietal and temporal lobes; (5) reduced cerebellar subareas; (6) reduction in the anterior cingulate cortex; (7) bilaterally reduced insula; (8) reduced size of the thalamus; and (9) bilaterally reduced hippocampus, parahippocampus and amygdala. Further, larger basal ganglia and hypothalami as well as reduced habenular nuclei have been demonstrated (Heckers 1997; Schiffer et al. 2013; Zhang et al. 2017). These alterations may lead to functional deficits in certain neuronal circuits, whereby glutamatergic circuits are particularly concerned (Schmitt et al. 2011; Schwartz et al. 2012). At the cellular level, neuropathologic changes of neurons, glial cells and endothelial cells have been found. Morphometric analyses of the prefrontal cortex have shown increased density of pyramidal cells in schizophrenia patients (Rajkowska et al. 1998; Selemon and Goldman-Rakic 1999). In addition, decreased spine density was observed in this brain area (Glantz and Lewis 2000). Regarding interneurons, a decrease of the GABA-synthesizing enzyme, glutamic acid decarboxylase-67 (GAD67), has been revealed. Furthermore, reduction of the calcium-binding proteins parvalbumin and calbindin, which are expressed in subsets of GABAergic interneurons, has been reported (for overview see Jaaro-Peled et al. 2010). A further pathomorphologic sign of schizophrenia is disturbed adult neurogenesis in the hippocampus (Reif et al. 2006). Concerning glia, core findings are (1) fewer oligodendrocytes in various brain regions, together with decreased expression of myelin-related genes; (2) abnormal expression of a variety of astrocyte-related genes but no astrogliosis; and (3) increased densities of microglial cells and aberrant expression of microglia markers suggesting immunological/inflammatory processes in schizophrenia (reviewed in Uranova et al. 2007; Steiner et al. 2008; Schmitt et al. 2009; Bernstein et al. 2015a; Falkai et al. 2016).

Neuropathology of MDD

Common features of all depressive disorders include the presence of sad or irritable mood, accompanied by somatic and cognitive changes that significantly affect the individual's capacity to function. MDD is characterized by a general feeling of sadness, anhedonia, avolition, worthlessness and hopelessness. Cognitive and neuro-vegetative symptoms, such as difficulty in concentrating, memory alterations, anorexia and sleep disturbances, are also present. The lifetime prevalence of MDD is estimated at around 2 to 20% (for an overview, see Ribeiro et al. 2017). Neuroimaging and postmortem studies have demonstrated widespread anatomical changes in fronto-subcortical regions. Volume deficits have been found in the ventral prefrontal cortex, striato-pallidal nuclei, mesiotemporal brain structures, thalamus, hypothalamus, habenula and brain stem areas (Bielau et al. 2005; Koenigs and Grafman 2009; Ranft et al. 2010; Bernstein et al. 2012a, b; Sambataro et al. 2018; and others). With regard to histopathologic changes, some authors consider MDD as a predominantly "glial disorder" (Rajkowska et al. 2001), with astrocytes being most often implicated. Cell counting studies report decreases in the packing density or number of astrocytes in various fronto-limbic brain regions. In addition, astrocytes are often functionally compromised in depression (reviewed in Rajkowska and Stockmeier 2013; Wang et al. 2017). However, oligodendrocyte deficits as well as impaired myelin integrity have also been described in affective disorders (Mosebach et al. 2013). In addition, microglia activation is implicated in the neuropathology of depression (Mechawar and Sawitz 2016; Brisch et al. 2017). Besides, neurons are important players in the neuropathology of MDD (for a recent review, see Boku et al. 2018). Neural plasticity, a fundamental mechanism of neuronal adaptation, is disrupted in depression and partially restored by antidepressant treatment (reviewed in Liu et al. 2017). Furthermore, nerve cell loss, atrophy and altered cell chemical composition of individual nuclei have been demonstrated in postmortem tissue from depressed subjects in the prefrontal cortex, hippocampus and other limbic brain areas, hypothalamus and brain stem (Manaye et al. 2005; Banasr et al. 2011; and others).

The hypothalamus in health at a glance

Anatomy

The hypothalamus is a small but complex brain structure encompassing numerous nuclei with different functions in the regulation of endocrine, autonomic and behavioral activities. The general organization of the hypothalamus is fairly uniform in most mammalian species including man (Sangruichi and Kowall 1991). The hypothalamus represents the ventral part of the diencephalon and is part of the limbic system. It is located above the midbrain and below the thalamus, forming the floor and part of the lateral wall of the third ventricle. Hypothalamic nuclei are organized into the anterior region, the tuberal region and the posterior (or mammillary)

region. The main nuclei within the anterior subdivision are the medial and lateral preoptic, periventricular, paraventricular (PVN), supraoptic (SON), suprachiasmatic (SCN) and anterior and lateral hypothalamic nuclei. To the tuberal region belong the ventromedial, dorsomedial, ventromedial, arcuate (ARC) and lateral nuclei. The medial portion of the posterior region contains the mammillary body (MB) and posterior nuclei, while its lateral portion is composed of the tuberomammillary and lateral nuclei (overview in Lechan and Toni 2016). Key functions of the hypothalamus are the coordination and integration of multiple biologic systems to maintain homeostasis. Consequently, the hypothalamus is highly interconnected with other parts of the CNS and the autonomous nervous system. The hypothalamus receives signals from the hippocampus, amygdala, septal nuclei, visual and olfactory pathways, the midbrain, brain stem and spinal cord. Main efferent projections from hypothalamic nuclei go to autonomic centers of brainstem and spinal cord but also to the thalamus, hippocampus and especially to the anterior and posterior hypophysis (reviewed in Lammers and Lohman 1974).

Functions

The functional roles played by the hypothalamus cannot be overestimated. Hypothalamic nuclei govern many vital physiologic functions, such as temperature regulation, thirst, hunger, sleep, mood, circadian and seasonal rhythms, sex drive and especially the production of some of the body's essential hormones, including those that stimulate or inhibit the release of other important hormones from extra-neural glands (for recent overview, see Xie and Dorsky 2017). As a rule, these hormones are peptides. The most important of these hypothalamic neuropeptides are oxytocin (OT) and arginine-vasopressin (AVP), which are produced in the PVN and SON and then transported to, and released from, the posterior pituitary into the blood stream. In addition, vasopressin is also generated in the SCN and at some places outside the hypothalamus. Both neuropeptides fulfill a plethora of important functions. The most prominent ones are contraction of the uterus and other smooth muscles (OT) and water retention in the kidney (AVP). Another class of hypothalamic neuropeptides control by stimulation or inhibit the release of hormones from the anterior hypophysis. Members of this peptide family are corticotropin-releasing hormone (CRH, synthesized in the parvocellular PVN), thyrotropin-releasing hormone (TRH, synthesized in the parvocellular PVN), growth hormone-releasing hormone (GHRH, synthesized in the ARC), gonadotropin-releasing hormone or luteinizing hormone-releasing hormone (GnRH or LHRH, synthesized in the neuroendocrine cells of the preoptic area) and growth hormone-inhibiting hormone or somatostatin, synthesized in the periventricular nucleus. Prolactin release from the anterior hypophysis is controlled by the amine dopamine, which is produced in the ARC (Vale et al. 1977; Seeburg et al. 1987; Barbosa et al. 2017; and others). Members of a third class of hypothalamic peptides are involved in the control of feeding, another essential regulatory function of the hypothalamus. Peptides that increase food intake are ghrelin, neuropeptide Y, agouti-related peptide, orexin (hypocretin), melanin-concentrating hormone and galanin. Peptides that decrease feeding behavior are leptin, cocaine and amphetamine transcript peptides (CART), CRH, cholecystokinin, insulin and glucagon-like peptide (summarized in Bouret 2017). However, the list of peptidergic and non-peptidergic bioactive hypothalamic factors is much longer than described here. We will introduce some of these compounds later on in case they are assumed to play roles in mental illnesses.

Neuropathology of the hypothalamus in schizophrenia

Until recently, there had only been limited interest among psychiatrists in putative morpho-functional alterations of the hypothalamus in schizophrenia (Bernstein et al. 2010a), even though since the mid-1950s evidence had accumulated in favor of disrupted neuroendocrine mechanisms in this disease (for history Bradley and Dinan 2010).

Volumes of the third ventricle, hypothalamus and individual hypothalamic nuclei

A well-known abnormality in schizophrenia is the enlargement of the third ventricle, which was first found by postmortem brain volume analysis in drug-naïve, first-episode patients (Lesch and Bogerts 1984). Since this ventricle enlargement, which was replicated by neuroimaging investigations (Fannon et al. 2000; Tanskanen et al. 2010) might be based on tissue loss of the ventricle facing brain areas, investigators looked for hypothalamic structural deficits in schizophrenia. However, this search has yielded conflicting results. Histological studies on postmortem brains of schizophrenics revealed a reduction of the thickness of periventricular gray matter (Lesch and Bogerts 1984), while neuroimaging studies demonstrate reduced (Koolschijn et al. 2008), increased (Goldstein et al. 2007; Tognin et al. 2012; Schiffer et al. 2013) and unchanged (Klomp et al. 2012; Haijma et al. 2013) total hypothalamic volumes. Only few communications deal with the volumes of individual hypothalamic nuclei in schizophrenia. Two early histologic investigations (which do not meet criteria for modern morphometry) have reported no changes in volumes of hypothalamic nuclei (Hechst 1931; Wahren 1952). In postmortem studies, the volumes of the PVN, SON and the SCN were found to be unchanged in schizophrenia (Bernstein et al. 1998a, 2017a), while an increased volume of the PVN was reported in an MRI study (Goldstein et al. 2007). With regard

to MB in schizophrenia, again decreased (Briess et al. 1998), increased (Goldstein et al. 2007; Tognin et al. 2012 [ride MB only]), or unchanged (Bernstein et al. 2007a, b, c) volumes have been found. Lastly, no volume changes of the fornix, the main afferent system of the hippocampus to the septal nuclei and the hypothalamus, have been observed in two post-mortem and one neuroimaging studies (Chance et al. 1999; Brisch et al. 2008; Zahajszky et al. 2001), while reduced fornix volumes were found in other neuroimaging studies (Kuroki et al. 2006; Baumann et al. 2016).

Cell pathologic changes in the hypothalamus of schizophrenia individuals

Cell numbers and neurotransmitters

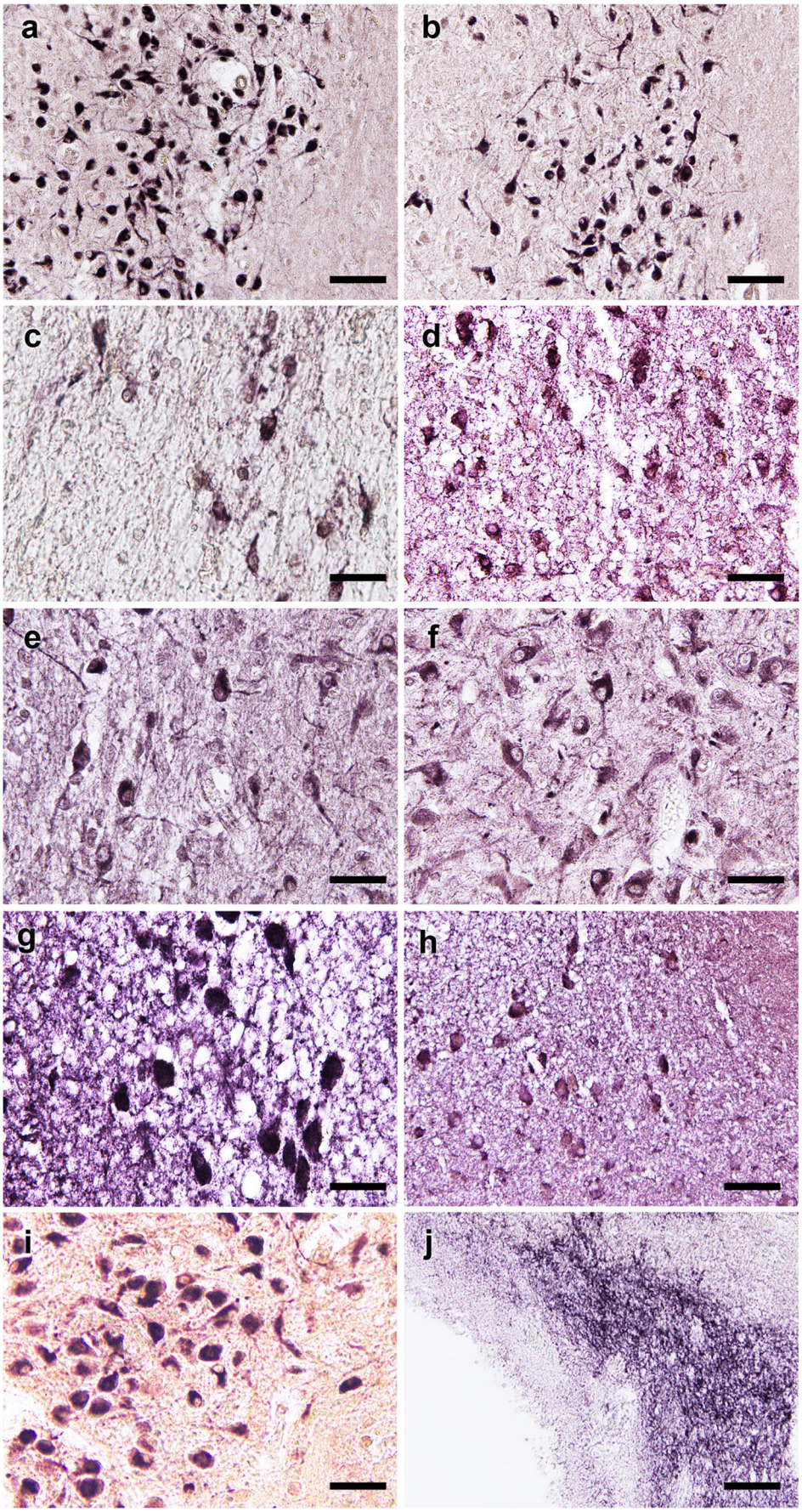
Studies on the hypothalamus in schizophrenia go back to 1931 (Hechst 1931). Investigating neurosecretory hypothalamic neurons on Nissl-stained brain sections of individuals with schizophrenia and controls, Hechst (1931) and later on Wahren (1952), did not observe disease-related peculiarities. More recently, Manaye et al. (2005) found that PVN and SON cell numbers are normal in schizophrenia. Numbers and densities of Nissl-stained MB neurons were reduced in schizophrenia, which is another evidence for limbic neuropathology in schizophrenia. This reduction was largely due to a decrease of the number of parvalbumin-immunoreactive (glutamatergic) neurons projecting to the anterior thalamus, which was reduced by more than 50% (Bernstein et al. 2007a). This circumscribed loss of glutamatergic neurons is the only available information about putative neurotransmitter alterations in the hypothalamus of individuals with schizophrenia. Concentrations of GABA, taurine, glycine-threonine, glutamate, aspartate, glutamine, tryptophan, alanine (Korpi et al. 1987), norepinephrine (Farley et al. 1978) and even dopamine and its metabolites (Haracz 1982) did not differ between schizophrenia hypothalami and controls.

Cell chemical changes in oxytocin-and vasopressin-expressing neurons

OT, AVP, neurophysin(s)

The hypothalamus is known to abundantly express various regulatory neuropeptides, of which some play roles in schizophrenia (LaCrosse and Olive 2013). Efforts have therefore been directed toward identifying alterations in the disease-related cellular expression of these chemical compounds. A wave of information suggests that OT and AVP are prominently involved in the regulation of social and cognitive processes that are abnormal in schizophrenia. Moreover, treatment of schizophrenia patients with either OT or AVP (or their synthetic analogues) is, in addition to having a therapeutic effect on positive symptoms of schizophrenia, beneficial in attenuating negative symptoms and cognition problems. Furthermore, genes coding for OT and AVP and some OT and AVP pathway genes are associated with schizophrenia. Lastly, reduced OT and/or AVP levels in the peripheral blood, CSF, pituitary and brain are found in individuals with schizophrenia (for reviews, see Frank and Landgraf 2008; Marazzati and Catena dellósso 2008; Uhrig et al. 2016; Bernstein et al. 2017). Pioneering work with regard to the possible involvement of the classical hypothalamo-hypophysial neurosecretory system in schizophrenia was carried out by Gerber (1965), who investigated hypothalamic neurons after applying Gömöri's trichrome stain. He observed reduced cellular content of neurosecrete in many neurons of neuroleptic-treated individuals with schizophrenia. Later on, Mai et al. (1993), by using antisera that recognize both neurophysins I and II, performed a morphometric analysis and found a decreased number of neurophysin immunoreactive neurons in the PVN but not SON in individuals with schizophrenia. Since neurophysins are the carrier proteins of OT and AVP (Fig. 1a), their results should be taken as an indication for the relevance of OT and AVP neurons in schizophrenia. However, since biochemical work had shown that the OT-neurophysin and the AVP-neurophysin systems are differently affected in schizophrenia (Legros et al. 1992), further cytochemical analysis had to be done. Immunocytochemical analysis revealed that both the number of AVP-expressing SON neurons and the hypothalamic concentration of this peptide are normal in schizophrenics without polydipsia (Malidelis et al. 2005) but reduced in the SCN of schizophrenia individuals (Bernstein et al. 2005b). The latter finding is in good accordance with data of Legros et al. (1992), showing decreased vasopressinergic function in schizophrenia. It must

Fig. 1 **a**–**j** Immunolocalization of peptides and enzyme proteins in human hypothalamus using the nickel-enhanced streptavidin-biotin technique as described earlier (Bernstein et al. 2008). **a** Immunodetection of neurophysin immunoreactivity in PVN neurons. Bar = 120 μm. Neurophysin expression is reduced in the PVN and SCN in schizophrenia. **b** IRAP immunopositive neurons in the PVN. Bar = 120 μm. IRAP expression is decreased in the PVN in schizophrenia but decreased in MDD. **c** IRAP expression in the SCN. Bar = 40 μm. IRAP expression is reduced in SCN neurons in schizophrenia. **d** VGF–immunoreactive neurons in the PVN. Bar = 60 μm. VGF expression in the PVN is reduced in schizophrenia and MDD. **e** Beacon-like peptide-immunopositive PVN neurons. Bar = 60 μm. Beacon expression in hypothalamic neurons is elevated in schizophrenia. **f** Beacon-like peptide-immunopositive SON neurons. Bar = 60 μm. **g** Agouti-related peptide immunolocalization in ARC neurons. Bar = 25 μm. In schizophrenia, Agouti expression is normal in the hypothalamus but its concentration is increased in the pituitary. **h** Weak Cat K expression in ARC neurons (control case). Bar = 35 μm. **i** Strong increase in hypothalamic Cat K expression in a haloperidol-treated schizophrenia individual. Bar = 35 μm. **j** GAD immunoreactive neuropil in the SCN. Bar = 100 μm. In MDD, GAD expression is reduced in the PVN but increased in the SCN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be emphasized, however, that SCN neurons do not send information to the pituitary but mainly to other hypothalamic nuclei and the pineal gland. Alterations as described above may result from changes in OT or AVP synthesis, posttranslational processing of these peptides and/or their degradation. In addition, antipsychotic treatment might influence the expression of these peptides in schizophrenia (Kiss et al. 2010). However, neither Mai et al. (1993) and Malidelis et al. (2005) nor we (Bernstein et al. 1998a, b, 2005b) could find a correlation between neurophysin and/or neuropeptide expression and treatment with neuroleptics.

Insulin-regulated aminopeptidase (*EC* 3.4.11.3)

Since enzymatic degradation might influence OT and AVP levels, we looked for the cellular distribution of insulin-regulated aminopeptidase (IRAP), which is the main OT- and AVP-degrading enzyme (Wallis et al. 2007), in hypothalami of individuals with schizophrenia and controls. Strong immunoreaction was observed in the PVN, SON, periventricular, SCN and accessory neurosecretory nuclei (Fig. 1b, c). Interestingly, the cellular distribution pattern of IRAP protein was similar to, if not identical with, that of neurophysin(s). Double immunostaining demonstrated partial co-distribution of IRAP with OT and AVP. In addition, the median eminence, infundibulum and the posterior lobe stood out by intense immunostaining (Bernstein et al. 2017a). In schizophrenia, a significant reduction in numerical density of IRAP-expressing neurons was found in the right PVN and SCN (i.e., those hypothalamic nuclei with altered OT and AVP expression in schizophrenia), which again was not correlated with antipsychotic treatment (Bernstein et al. 2017a). These findings indicate, together with data of others (Wallis et al. 2007; Fernández-Atucha et al. 2015), that IRAP might well contribute to altered hypothalamic and peripheral OT and AVP levels in schizophrenia.

Neuronal nitric oxide synthase (*EC* 1.14.13.39)

Neuronal NOS generates about 90% of brain nitric oxide (NO). Since NO, besides having a plethora of other functions in healthy and diseased CNS (Bernstein et al. 2005a), is supposed to play a regulatory role in the expression of OT and AVP in and their release from, hypothalamic neurons (Kadowaki et al. 1994; Reis et al. 2007; Orlando et al. 2008), we immunolocalized this enzyme in human hypothalamus. NOS containing nerve cells were detected in several hypothalamic nuclei. The vast majority of hypothalamic nNOS-immunoreactive neurons was found in the PVN. Both magno- and parvocellular paraventricular neurons contained the enzyme. NOS immunoreactive neurons were also found in the SON and SCN (Bernstein et al. 1998a; Bernstein et al. 2000; Bernstein et al. 2005b). Cell counts of paraventricular NOS-positive neurons in schizophrenia and controls revealed a significant reduction of cell density in the right PVN in schizophrenia. Further, it was found that the total amount of NOS-immunoreactive PVN and SCN neurons was smaller in schizophrenic patients. We speculated that fewer nitrergic SCN neurons might contribute to sleep disturbances in schizophrenia (Bernstein et al. 2010b). Interestingly, the expression of AVP mRNA but not OT mRNA was reduced in the PVN of mice lacking neuronal nitric oxide synthase (nNOS) (Orlando et al. 2008), while neurophysin immunoreactivity was unchanged in these mice (Bernstein et al. 1998b).

Hypothalamic releasing and inhibiting factors

Evidence suggests disturbances of the hypothalamic-pituitary-adrenal (HPA) axis in schizophrenia (Altamura et al. 1999; Guest et al. 2011; Berger et al. 2016; Riecher-Rössler 2017; and others), which can already be observed in drug-naïve first-episode patients (Belvederi Murri et al. 2012; Borges et al. 2013). Interestingly, people with schizophrenia can experience both hyper- and hypofunction of the HPA axis (Bradley and Dinan 2010). In addition, deregulation of the hypothalamic-pituitary-thyroid axis (Othman et al. 1994; Santos et al. 2012) and the hypothalamic-pituitary-gonadal axis (Rajkumar 2014; Heringa et al. 2015; Riecher-Rössler 2017) has been described in schizophrenia. Since these disturbances may originate from functionally compromised neuroendocrine hypothalamic neurons, it is ingenious to search for altered expression of releasing and inhibiting factors in schizophrenia. Amazingly, little efforts have been directed toward reaching this goal. Early biochemical work suggests that CRH (Frederiksen et al. 1991), GHRH (Peabody et al. 1990) and somatostatin (Nemeroff et al. 1986) concentrations are not reduced in hypothalami of schizophrenics. The latter finding is in accordance with results from our laboratory (Bernstein and Heinemann, unpublished), showing that the density of somatostatin-immunopositive neurons in the periventricular nucleus is normal in schizophrenia.

Peptides involved in the regulation of food intake and satiety

Many patients with schizophrenia suffer from "metabolic syndrome," which is characterized by visceral obesity, type 2 diabetes, increased lipid levels and hypertension and reduced sensitivity to insulin (summarized in Bernstein et al. 2010a). Weight gain and metabolic disturbances are common side effects of treatment with atypical neuroleptics but some of the metabolic problems can already be observed in drug-naïve first-episode patients (for recent review see Steiner et al. 2018). Weight gain in patients suffering from schizophrenia is often accompanied by increased food intake. Three primary neuroendocrine components are thought to control food intake: (1) the afferent peripheral system that is stimulated in

response to a meal, (2) the CNS food intake integrating unit and (3) the efferent system (Bernstein et al. 2010a). Hormonally, feeding behavior and body weight homeostasis are regulated by a number of peptides released from either hypothalamic neurons (neuropeptide Y, CRH, orexins/hypocretins, cocaine- and amphetamine-regulated transcript, agouti-related peptide melanocortin, VGF and others, see chapter hypothalamus) or peripheral sites (insulin, leptin, ghrelin; reviewed in Kalra et al. 1999; Mastorakos and Zapani 2004; Bernstein et al. 2009). Unfortunately, our knowledge about food intake-controlling hypothalamic peptides in schizophrenia is still limited. We could show that the neuronal expression of VGF precursor (Fig. 1d), a large neuropeptide probably linked to impaired factor signaling and energy homeostasis, is significantly reduced in the PVN and SON of individuals with schizophrenia (Busse et al. 2012). Beacon-like/ubiquitin-5-like peptide (Figs. 1e, f), another neuropeptide involved in the control of energy balance and body weight by regulating food intake (Collier et al. 2000; Bozaoglu et al. 2006), was found to be up-regulated in PVN and SON neurons in schizophrenia and a rat paradigm of schizophrenia (Bernstein et al. 2008). Lastly, the hypothalamic expression of agouti-related peptide (Fig. 1g), another peptide candidate to be studied under aspects of metabolic disturbances, was found to be normal in haloperidol-treated patients (unpublished data), while others found elevated concentrations of this peptide in pituitary tissue of schizophrenics (Krishnamurthy et al. 2013) and rat hypothalami after exposure to olanzapine (Fernø et al. 2011). Curiously, the hypothalamic expression of peptides belonging to the orexin/hypocretin system, which is central to weight gain induced by antipsychotics (Tiwari et al. 2016), has never been studied.

Endogenous opioid peptides (endorphins and enkephalins)

Endogenous opiates are involved in the pathophysiology of schizophrenia but it is still a matter of debate whether a "hypermorphinergic" or a "hypomorphinergic" pathology is typical for the disease (discussed in Schmauss and Emrich 1985; Bernstein et al. 2002a; Lendeckel et al. 2009; Laux-Biehlmann et al. 2013). We studied the cellular localization of the peptide in ARC neurons as well as the beta-endorphinergic innervation of PVN neurons in postmortem hypothalami of individuals with schizophrenia and controls and showed that the number and the density of beta-endorphin-containing neurons was significantly decreased in schizophrenia. Moreover, the number of beta-endorphin-innervated PVN neurons was also reduced (Bernstein et al. 2002a; Lendeckel et al. 2009). Radioimmunoassay measurements did not reveal altered hypothalamic concentrations of beta-endorphin in schizophrenia but showed increased levels of alpha- and gamma-endorphin, two metabolites of beta-endorphin. This might be an indication for a deviant beta-endorphin metabolism in schizophrenia (Wiegant et al. 1988). Remarkably, the protease cathepsin K (CatK; EC. 3.4.22.38) was shown to be involved in beta-endorphin metabolism by liberating met-enkephalin from beta-endorphin (Lendeckel et al. 2009). This unique enzyme property, which was demonstrated both in human brain tissue and tissue culture, might contribute to altered beta-endorphin metabolism in schizophrenia. The expression of CatK is low in normal brains but becomes up-regulated after neuroleptic treatment as is the case in schizophrenia (Figs. 1h, i; Bernstein et al. 2007b; Lendeckel et al. 2009). In support of a role of the formation of met-enkephalin at the expense of beta-EP, increased numbers of Cat K immunoreactive cells but diminished numbers of both beta-endorphin-positive cells and double-positive (CatK/beta-endorphin) cells were found in the ARC of schizophrenics (Lendeckel et al. 2009).

Non-neuronal cells

Massive fibrous gliosis was seen in the hypothalamus in schizophrenia (Stevens 1982), which was interpreted as indicating previous or low-grade inflammation. This finding has not been replicated yet. No information is available on hypothalamic oligodendrocytes, microglial cells, or endothelial cells in schizophrenia. Taking into account the great importance of inflammatory/immune processes for the pathophysiology of schizophrenia, studies on these cell types are urgently required.

Neuropathology of the hypothalamus in MDD

Since the 1950s, most psychiatrists accept that "endogenous" depression comes from within the body (Kraines 1957, 1966). This insight paved the way for the search of brain alterations in depression, including those in the hypothalamus.

Volumes of the third ventricle, hypothalamus and of individual hypothalamic nuclei

Planimetric measurements of CSF spaces in CT scans revealed enlarged third ventricles in MDD (Scott et al. 1987; Baumann et al. 1997 [in females only])). Third ventricle enlargement in MDD was confirmed in more recent studies (Zhao et al. 2017), giving rise to the bold hypothesis that MDD is a "disease of the third ventricle" (Hendrie and Pickles 2010). Morphometric analysis of postmortem brains of individuals with MDD did not reveal significant volume differences between MDD and control cases (Bielau et al. 2005). However, when differentiating between non-suicidal and suicidal MDD patients, volume reduction can be found in the group of non-suicidal patients, whereas suicide victims had normal hypothalamus volumes (Bielau et al. 2013). In vivo studies yielded conflicting results. While Dupont et al. (1995) reported

normal hypothalamus volumes in MDD, Pinilla (2009) did find reductions in depression (reviewed in Schindler et al. 2012). Concerning hypothalamic nuclei, it has been found that PVN, SON and SCN volumes are normal (Bernstein et al. 1998a, 2005a, b, 2017b), while MB volume reductions were found in MDD (Bernstein et al. 2012a, b). The volumes of the fornix did not differ between patients with MDD and control subjects (Brisch et al. 2008).

Cell pathologic changes in the hypothalamus of individuals with MDD

Cell numbers and neurotransmitters

Using Nissl-stained brain sections, Manaye et al. (2005) found a reduction of 50% in total neuron number in the PVN for MDD, compared with age-matched controls, with no differences in neuron numbers in the SON. No group differences in the total neuronal number or neuronal density were found for MB (Bernstein et al. 2012a, b). Abnormalities of the GABAergic system have been registered in MDD: reduced immunoreactivity of the GABA synthesizing enzyme GAD 65/67 (Fig. 1j) was registered in the PVN (Bernstein et al. 2007c; Gao et al. 2013), while strongly increased expression of GAD mRNA and immunoreactivity was detected in the SCN in MDD (Wu et al. 2017). Despite its enormous significance for MDD, little is known about glutamate in the hypothalamus (Gao and Bao 2011). However, disbalances of the glutamate system have recently been demonstrated in a mouse model of depression, (Rao et al. 2016). Elevated serotonin transmission to and within the hypothalamus was reported for MDD patients and for a rodent model of melancholia (Andrews et al. 2015), which might in patients be influenced by antidepressant treatment with SSRIs. A decrease of hypothalamic tuberoinfundibular dopamine-containing neurons was seen in a rat model of depression (Sugama and Kakinuma 2016). In situ hybridization studies showed reduced hypothalamic expression of the histamine degrading enzyme histamine-*N*-methyltransferase in MDD (Shan et al. 2013).

Cell chemical changes in OT- and AVP-expressing neurons

OT, AVP neurophysin(s)

Neuroendocrine abnormalities are a core feature in MDD. Thanks to research efforts of Swaab's group (Netherlands), the crucial role of oxytocin- and vasopressin-expressing neurons in depression has been well characterized. By using immunocytochemical techniques, this group reported increased numbers of vasopressin- and oxytocin-immunoreactive neurons in the PVN in MDD (Purba et al. 1996). Since both AVP and OT potentiate the effects of CRH, this finding was interpreted as sign of activation of the HPA axis (Purba et al. 1996). Interestingly, in MDD, there is a strong increase in the number of PVN neurons that co-express AVP and CRH (Raadsheer et al. 1994). Further, after having demonstrated that formalin-fixed paraffin-embedded sections can be used for quantitative analysis of in situ hybridization for AVP and OT mRNAs (Lucassen et al. 1995; Meynen et al. 2007), Swaab's group revealed increased AVP and OT expression in PVN and SON in MDD (Hoogendijk et al. 2000; Meynen et al. 2006; Meynen et al. 2007). Elevated number of AVP-immunoreactive neurons, together with a decreased AVP mRNA expression, was found in the SCN of depressed individuals (Zhou et al. 2001), which might suggest both reduced synthesis and release of AVP in the SCN. However, our group observed a decreased density of neurophysin-containing SCN neurons in depression (Bernstein et al. 2005a, b). In addition, Wu et al. (2013) showed that the number of vasoactive intestinal peptide-immunoreactive cells (forming the other large peptide cell population in the SCN) is increased in MDD. It should be emphasized, however, that pronounced diurnal and seasonal changes in SCN neuropeptide expression make it difficult to reveal mood disorder-related alterations of this nucleus (discussed in Bernstein et al. 2017b).

Insulin-regulated aminopeptidase

A report about a role of insulin-regulated aminopeptidase (IRAP) in mediating the antidepressant-like effects of oxytocin (OT) in mice (Loyens et al. 2012) prompted us to look for IRAP expression in hypothalami of depressed patients. In contrast to schizophrenia, significantly increased cellular IRAP expression was found in the left PVN (Müller et al. 2013). Since increased numbers of AVP- and OT-expressing neurons were found in the PVN in MDD (Purba et al. 1996; Meynen et al. 2007), we assume that that hypothalamic IRAP expression might be closely associated with the neuropeptide–neurophysin system (discussed in detail in Bernstein et al. 2017a).

Neuronal nitric oxide synthase

The amount of NOS-immunoreactive PVN neurons was smaller in MDD patients than in controls (Bernstein et al. 1998a, b). Reduced NOS expression in PVN neurons was also found in an animal model of depression (chronically stressed rats, Gao et al. 2014). The number of NOS-immunoreactive SCN neurons was also reduced in depression (Bernstein et al. 2002b, 2005a, b). While decreased NOS expression in the PVN as part of the disturbed cross-talk between NO, CRH and hypothalamic other factors might contribute to the hyperactivity of the HPA axis in MDD (reviewed in Bernstein et al. 2007c),

reduced NO levels in the SCN might contribute to sleep disturbances in MDD patients (Vadnie and McClun 2017).

Hypothalamic releasing and inhibiting factors

One of the best replicated findings is activation of the HPA axis in a subset of MDD patients, which can already be found in unmedicated patients (for recent review see Fischer et al. 2017). By elevating ACTH secretion, activating the expression of CRH receptor 1, estrogen receptor-alpha, AVP receptor 1 and mineralocorticoid receptor and reducing the expression of androgen receptor (Wang et al. 2008), increased CRH signaling significantly contributes to HPA axis abnormalities in MDD (Waters et al. 2015; and many others). Increased CRH mRNA levels were measured in the PVN of depressed patients (Raadsheer et al. 1995), whereby the mean total number of CRH-expressing neurons of the depressed patients was four times higher than in controls (Raadsheer et al. 1994). This strong increase is partly due to an increased co-expression of CRH and AVP in PVN neurons (Raadsheer et al. 1994). Despite disrupted HPA axis, MDD is characterized by abnormalities of the hypothalamo-pituitary-gonadal axis affecting reproduction (overview in Young and Korszun 2002). Since agonists of the releasing factor GnRH agonists exhibit anxiolytic- and antidepressant-like effects, whereas GnRH antagonists induce anxiogenic-like behavior (Parhar et al. 2016), it would be ingenious to look for peculiarities of its hypothalamic expression in MDD. Unfortunately, no such studies have been done yet. The same holds true for LHRH. Functional alterations of the hypothalamo-pituitary-thyroid axis are known in depression, which affect sleep (Staner et al. 2003) and eating behavior (Brambilla et al. 2006) of the patients. Since testing the release of TRH may predict the clinical outcome/recurrence of depression (Tsuru et al. 2013), it is important to know TRH concentrations in the hypothalamus of MDD patients. A strong decrease in TRH mRNA expression is present in the PVN of patients with MDD (Fliers et al. 2006). At the end of this chapter, one question remains unanswered. On the one hand, Manaye et al. (2005) reported a reduction by 50% of PVN neurons in MDD; on the other hand, Swaab's group demonstrated increases in AVP-, OT- and CRH-expressing PVN cells in MDD, which together represent the by far largest cell populations of this nucleus. The correctness of these findings prompted: what then might be the cell chemical signature of Manaye's "lost" PVN neurons?

Peptides involved in the regulation of food intake and satiety

Depression increases the risk of suffering from metabolic syndrome and obesity (Ghanei Gheshlagh et al. 2016; Milaneschi et al. 2018; and many others). The reasons for this are complex and not fully understood yet but undoubtedly involve dysregulation of hypothalamic satiety factors (Sestan-Pesa and Horvath 2016). Of the many known appetite-regulating factors, only a few have been studied with regard to their hypothalamic expression in MDD. The cellular expression of CRH, which besides many other functions is involved in energy homeostasis control (Bali and Jaggi 2016 and others), is elevated in MDD (see above). A striking increase in the amount of hypocretin immunoreactivity was seen in female but not in male depressed patients (Lu et al. 2017) and in a mouse model of depression (male animals; Jalewa et al. 2014).

VGF, which is prominently involved in the regulation of energy metabolism, was decreased in the right PVN of male individuals with MDD (Bernstein et al. 2015b).

Endogenous opioid peptides (endorphins and enkephalins)

Endorphins have rewarding and reinforcing properties and are reported to be involved in stress response and in stress-related psychiatric disorders like depression (reviewed in Hegadoren et al. 2009; Merenlender-Wagner et al. 2009). Immunohistochemical analysis revealed that in MDD, there is a similar situation as in schizophrenia: fewer beta-endorphin expressing ARC neurons and reduced beta-endorphinergic innervation of PVN neurons were found (Bernstein et al. 2002a). Enkephalins are also important modulators of the stress response. While preproenkephalin knockout mice exhibit abnormal stress reactivity and show increased anxiety behavior in acute stress situations, enkephalin knockout mice are resistant to chronic mild stress (Melo et al. 2014). Unfortunately, there is no work on hypothalamic encephalin expression in MDD. A third group of endogenous opioid peptides, which might play roles in MDD, are prodynorphin-derived peptides. They are involved in the regulation of stress and anxiety and have a function in ACTH release control. So, prodynorphin knockout mice show a 30% reduction in corticotropin-releasing hormone (CRH) mRNA expression in the hypothalamic PVN nucleus and an accompanying 30–40% decrease in ACTH serum levels (Wittmann et al. 2009). Data on hypothalamic dynorphin expression in MMD are not available yet.

Non-neuronal cells

Although glial cells are known to play pivotal roles in MDD pathophysiology (including regulation of neuroinflammation), there is no work dealing with hypothalamic astroglia, oligodendroglia, or microglia in MDD. The same holds true for endothelial cells.

Main histopathologic findings are summarized in Table 1.

Table 1 What is under the microscope? Hypothalamic abnormalities in schizophrenia and MDD revealed by microscopy

Parameter	Schizophrenia	MDD
Volume changes	Enlargement of the third ventricle (Lesch and Bogerts 1984) Reduced periventricular tissue (Lesch and Bogerts 1984) Normal volumes of PVN, SON and SCN (Hechst 1931; Wahren 1952; Bernstein et al. 1998a, 2017a). Decreased volume of the mb (Briess et al. 1998). Normal volumes of the mb (Bernstein et al. 2007a). No volume changes of the fornix (Chance et al. 1999; Brisch et al. 2008)	Volume reduction in non-suicidal MDD cases (Bielau et al. 2013) Normal volumes of PVN, SON and SCN (Bernstein et al. 1998a, 2005). Decreased volume of the mb (Bernstein et al. 2012a, b). No volume changes of the fornix (Brisch et al. 2008)
Cell counts/Nissl	Normal cell numbers in PVN and SON (Manaye et al. 2005). Reduced cell density in the mammillary bodies (Bernstein et al. 2007a)	Reduced cell density in the PVN, SON normal (Manaye et al. 2005). Normal cell densities in the mb (Bernstein et al. 2012a, b)
Neurotransmitters	Reduced parvalbumin-positive (glutamatergic) neurons in the mb (Bernstein et al. 2007a)	Reduced GAD 65/67 immunoreactivity in the PVN (Bernstein et al. 2007c; Gao et al. 2013). Increased expression of GAD in the SCN (Wu et al. 2017). Reduced cellular expression of histamine-*N*-methyltransferase (Shan et al. 2013)
OT, AVP, neurophysins	Reduced neurosecrete in hypothalamic neurons (Gerber 1965). Reduced number of neurophysin immunoreactive PVN neurons (Mai et al. 1993). Normal AVP expression in the SON (Malidelis et al. 2005). Reduced neurophysin cells in the SCN (Bernstein et al. 2005b)	Increased numbers of AVP-and OT-expressing neurons in the PVN (Purba et al. 1996; Hoogendijk et al. 2000; Meynen et al. 2006, 2007). Elevated number of AVP-immunoreactive, neurons; but decreased AVP mRNA, in the SCN (Zhou et al. 2001). Reduced number of neurophysin-expressing SCN neurons (Bernstein et al. 2005a, b). Increased co-expression of AVP and CRH in the PVN (Raadsheer et al. 1994)
IRAP	Reduced density of IRAP expressing neurons in the right PVN and the SCN (Bernstein et al. 2017a)	Increased IRAP expression in the left PVN (Müller et al. 2013)
nNOS	Reduced cell density in the right PVN (Bernstein et al. 1998a) and SCN (Bernstein et al. 2010b)	Reduced cell density in the PVN (Bernstein et al. 1998a) and SCN (Bernstein et al. 2002b, 2005). Reduced expression in the PVN, rat model (Gao et al. 2014)
Releasing and inhibiting factors		Increased number of CRH immunoreactive PVN neurons (Raadsheer et al. 1994) and CRH mRNA levels in the PVN (Raadsheer et al. 1995)
Satiety peptides	Reduced expression of VGF in PVN and SON (Busse et al. 2012). Increased density of beacon-like peptide in PVN and SON (Bernstein et al. 2008)	Reduced expression in right PVN in males (Bernstein et al. 2015b). Increased hypocretin expression in females (Lu et al. 2017) and in a rat model (Jalewa et al. 2014)
Endogenous opiates	Reduced number and the density of beta-endorphin-containing ARC neurons; reduced number of beta-endorphin-innervated PVN neurons (Bernstein et al. 2002a; Lendeckel et al. 2009). Up-regulation of Cat K (Lendeckel et al. 2009)	Fewer beta-endorphin expressing ARC neurons, reduced beta-endorphinergic innervation of PVN (Bernstein et al. 2002a)
Non-neuronal cells	Massive astrogliosis (Stevens 1982)	

Conclusions

1. By using postmortem brain microscopy, multiple hypothalamic abnormalities have been revealed in schizophrenia and MDD, which are more pronounced (and better studied) in MDD than in schizophrenia.
2. Alterations are present at the gross anatomical level (hypothalamic volume) and at the cellular level (cell loss,

increased or decreased expression of hypothalamic peptides and certain enzymes).

3. Some alterations in schizophrenia and MDD point in the same direction (reduced expression of neurophysin in the SCN, decreased expression of neuronal nitric oxide synthase nNOS, reduced expression of VGF, reduced expression of beta-endorphin), while others point in opposite directions (total cell numbers in PVN and SON, decreased expression of neurophysin in the PVN in schizophrenia, increased OT- and AVP-expression in the PVN in MDD; reduced number of IRAP-containing neurons in schizophrenia; elevated number in MDD).
4. An unaccomplished field is revealing possible abnormalities of non-neuronal cells. Since glial cells are prominently involved in the pathophysiology of schizophrenia and MDD, their study would be a rewarding task.

Compliance with ethical standards

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of interest The authors declare that they have no conflict of interest.

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