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The Ventral Striatopallidum and Extended Amygdala in Huntington Disease

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1. Introduction

In the mammalian basal forebrain, two overlapping systems provide a complex morphological substrate for the investigation of emotion-associated functions (de Olmos et al., 2004; Heimer & Van Hoesen, 2006) and are, therefore, crucial for elucidating the pathophysiology of neuropsychiatric diseases. The ventral striatopallidum (VSP) consists of the nucleus accumbens, the olfactory tubercle, the ventral parts of the caudate nucleus and the putamen (caudatoputamen in rodents) and the ventral pallidum, which integrates emotional, cognitive and sensory information and is implicated in linking motivation to behaviour (Heimer et al., 2008; Waraczynski, 2006). The extended amygdala (EA) is a cell continuum emerging from the central or medial amygdaloid nuclei via the sublentiform region up to the bed nuclei of the stria terminalis. The medial EA has a strong influence on emotional, social and sexual behaviour and stress responses. The central EA is associated with fear-related behaviour, hormonal responses and the modulation of affective reactions to stress, and is also involved in alcohol dependence behaviour. The dysfunction of both systems is associated with various neurodegenerative and/or psychiatric diseases, including Parkinson's disease, Alzheimer's disease, schizophrenia, autism and Huntington's disease (HD). HD is a hereditary neurodegenerative disorder with early and marked striatal atrophy (Vonsattel et al., 1985) and the accumulation of huntingtin (htt) aggregates in selected brain areas (Difiglia et al., 1997; Gutekunst et al., 1999). The underlying pathogenesis is still a matter of debate. Clinically, HD is characterized by a triad of motor, cognitive and psychiatric impairments. The morphological correlates of psychiatric-associated symptoms are poorly defined in HD, but there is increasing evidence that the ventral striatum (Enzi et al., 2012; Majid et al., 2011) and the amygdala (Klöppel et al., 2010) are involved in the psychiatric affection of the disease. In this chapter, we introduce the structural components of the VSP and the EA and present the main characteristics of the disorder, with a focus on emotional affection. We include our previous

results in a rat transgenic for Huntington's disease (tgHD), which is unique in its limbic impact (Niescery et al., 2009; Petrasch-Parwez et al., 2007), and add recent results in the respective areas of the human HD brain (Petrasch-Parwez et al., 2012).

2. The Ventral Striatopallidal System

The ventral striatum is a term which was initially introduced in the rat on the basis of cytoarchitectural, chemoarchitectonic and projection studies which, clearly provide evidence, that the topographically organized corticostriatal input contains an overlapping ventral and dorsal division (Heimer & Wilson, 1975). The dorsal (motor) striatum receives input from the isocortex, while the ventral (limbic) striatum is mainly related to allocortical and nonisocortical areas including the piriform, entorhinal and anterior cingulate cortices, the insula as well as large parts of the orbitomedial prefrontal cortex and the hippocampus (Heimer & Van Hoesen, 2006). The ventral striatum comprises the nucleus accumbens as its major component, the olfactory tubercle, cell bridges connecting both parts and the ventrally located areas of the caudatoputamen in rodents and the putamen and caudate nucleus in primates respectively (Mai et al., 2008; Paxinos & Watson, 2007). The rodent nucleus accumbens with a centrally located core and a shell surrounding the core on its medial and ventrolateral aspects forms the main part of the ventral striatum and is continuous with the overlying caudatoputamen. The core is similar to the caudatoputamen and more associated with motor function such as movement initiation, whereas the shell is a crucial GABAergic output area to the ventral pallidum, which itself projects to the mediodorsal thalamus (Heimer et al., 1987) and is therefore associated with the prefrontal cortex. Functionally, the nucleus accumbens is related to somatic motor function, motivation and the control of vigor (Heimer et al., 2008). The continuity between the nucleus accumbens and the dorsolaterally located caudatoputamen is observed in Nissl sections (Fig. 1A) and clearly identified by various markers including tyrosin hydroxylase (TH; Fig. 1B), which is enormously enriched in these areas due to the strong dopaminergic input from the midbrain. Strong TH-immunoreactivity is also observed in the olfactory tubercle and the connecting cell bridges confirming the continuity of the VSP to the brain surface. The olfactory tubercle as a ventral extension of the VSP indicates the close association with olfactory-related areas, which has led to the term olfactostriatum initially introduced by Herrick (1926) and still used in the corresponding areas of nonmammalian vertebrates. The morphology of the rodent olfactory tubercle (Fig. 1) is intermediate between cortical, striatal and pallidal structures and obviously constitutes a relay station between olfaction and the VSP. It is trilaminated as the other olfactory cortices with an overall olfactory input, however, in nonprimates the dense cell layer exhibits a corrugated appearance with dwarf cell caps towards the molecular layer and the polymorph layer is penetrated by ventral pallidal extensions. Finally the area comprises the islands of Calleja, aggregations of small granule cells, which are characteristic for the ventral striatum of all mammals including humans. The ventral pallidum is located ventrally to the anterior commissure. It receives in addition to the ventral striatal input dopaminergic input from the ventral tegmental area, a pathway, which is functionally involved in addiction (Pierce & Kumaresan, 2006). The close relation of the ventral striatum

and ventral pallidum within the limbic loop of the basal ganglia led to the term VSP. The VSP may function as a crossroad between emotional content (amygdala), motivational behavior (dopaminergic input from the ventral tegmental area), locomotor behaviour (output to caudal mesencephalon), cognition and executive functions (via mediodorsal thalamic nuclei to the prefrontal cortex) and olfaction (olfactory bulb input).

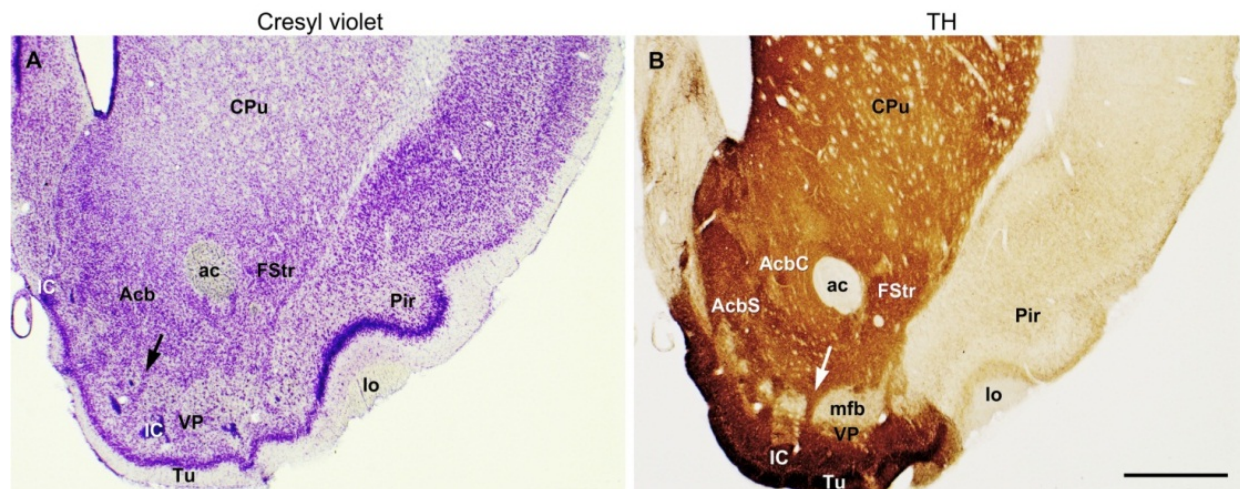


Figure 1. Cresyl violet stained (A) and Tyrosin hydroxylase (TH)-immunolabelled (B) frontal rat brain vibratome sections showing the main components of the ventral striatopallidum. The nucleus accumbens (Acb) and the fundus striati (FStr) are detected in the cresyl violet section (A) by dense accumulation of neurons in contrast to the overlying caudatoputamen (CPu). Note the continuum of the Acb and FStr with the olfactory tubercle (Tu) and the sharp medial and lateral border of the Acb and Tu in the TH-labelled section (B). The piriform cortex (Pir) lacks significant TH-immunoreactivity. The Acb can be distinguished into a shell (AcbS) and a core (AcbC) area. Cell bridges (arrow) traverse the medial forebrain bundle (mfb) and connect the Acb with the Tu. Islands of Calleja (IC) are dispersed in the Tu and associated with ventral pallidal extensions (VP). Anterior commissure (ac); lateral olfactory tract (lo); Bar in B for A and B = 1000 μ m..

In the primate brain the nucleus accumbens is located where the putamen and the caudate nucleus meet rostrally ventral to the anterior part of the internal capsule. It is impossible to define the boundaries between these three structures and therefore the nucleus accumbens and adjacent ventral parts of the caudate nucleus and putamen form together the main components of primate ventral striatum. Whereas the morphological, neurochemical and electrophysiological division into a shell and core region is widely accepted in rodents, in primates the core-shell dichotomy is more difficult to define. Attempts have been made for a differentiation of the area by comparing various primates including the human brain using Calbindin immunohistochemistry (Meredith et al., 1996). In humans, the shell begins rostrally as a narrow Calbindin-poor irregular outlined stripe, which expands at more caudal levels medially towards the ventricle and laterally towards the adjacent putamen to occupy the major part of the nucleus accumbens. However, the Calbindin immunoreactivity is unevenly distributed in both zones, therefore it can only be assumed that the core is generally Calbindin-rich and the shell Calbindin-poor. Furthermore, interspecific differences complicate the primate core-shell-dichotomy and may have led to a more topographically differentiation into a medial, central and lateral part as used by Mai et al., (2008).

The clear identification of the striatal, pallidal and olfactory structural components within the olfactory tubercle in primates and especially in the human brain is difficult. The olfactory tubercle is localized in the anterior perforated space caudally to the olfactory trigone, bordered laterally by the piriform cortex and medially by the diagonal band. It is continuous with the overlying nucleus accumbens more rostrally and with the ventral parts of the putamen and pallidum more caudally. Calleja islands are frequent, the major Calleja island between the nucleus accumbens and septal nuclei is the largest island among all mammalian brains.

The nucleus accumbens has attracted much interest in the field of psychiatry in recent years especially as the dysfunction of this area has been related with various disorders, including schizophrenia and obsessive-compulsive disorder. The nucleus accumbens is also an important target of antipsychotic drugs, which may respond differentially in the sub-territories, a matter which is frequently discussed in the neuronal circuit of addiction (Heimer et al., 2008).

3. The Extended Amygdala

Based on biochemical, morphological and ontogenetic criteria, the term EA was introduced for a system closely associated with the VSP in the overlapping limbic basal forebrain circuits. The first description of the EA dates back to Johnston (1923), who detected that the amygdala extends from caudolateral to rostromedial in the basal forebrain. Starting from the central and medial amygdaloid nucleus, the EA extends via the sublenticular region up to the bed nuclei of the stria terminalis and returns back to the central and medial amygdaloid nuclei. In consideration of morphological and functional aspects, the EA can be divided into a central and a medial part. The two divisions show a strongly pronounced symmetry between the medial and the central amygdaloid nuclei and the central and medial stria terminals respectively (Aldheid & Heimer, 1988; de Olmos et al., 2004; Heimer et al., 1997; 2008). The EA receives major afferents from the laterobasal amygdaloid complex and the cingulate cortex. Projections lead to autonomic and somatomotor centers in the hypothalamus and brain stem (central division) and to endocrine-associated areas in the medial hypothalamus (medial division).

The components of the medial division of the EA include the medial amygdaloid nucleus, the medial and intraamygdaloid bed nucleus of the stria terminalis, the medial sublenticular EA and the medial division of the supracapsular bed nucleus of the stria terminalis. The medial amygdaloid nucleus is located medially to the nucleus of the lateral olfactory tract and expands caudally to the temporal horn of the lateral ventricle. Laterally it extends to the basolateral amygdala. Based on the cytoarchitectural criteria, the medial amygdaloid nucleus can be subdivided into a principal body, a smaller anteroventral part and a posterodorsal part at the caudal end. Functionally, it may be involved in odor discrimination and in mediating sexual behavior (delBarco-Trillo et al., 2009; Holder et al., 2010). The medial bed nucleus of the stria terminalis can be divided into an anterior, a ventral and a posterior part. The medial nucleus may influence social approach between individuals, as well as social

aversion (Goodson & Wang, 2006) via Vasotoxin-positive neurons. The intraamygdaloid bed nucleus of the stria terminalis contains only a few cells bordering the dorsal part of the medial nucleus laterally. It is interspersed by fibers projecting to the stria terminalis. The medial sublenticular EA is a homogeneous complex of medium-sized neurons that borders the globus pallidus dorsally. Due to its prominent projections to dopaminergic neurons in the substantia nigra pars compacta, the medial sublenticular EA has been suggested to influence the dopamine metabolism (Fudge & Emiliano, 2003). The neurons of the medial division of the supracapsular bed nucleus of the stria terminalis form a cell continuum that follows the stria terminalis and penetrates the dorsal part of the internal capsule. This subnucleus receives afferents from the medial (endocrine-associated) hypothalamus (Shammah-Lagnado et al., 2000).

Comparable to the medial division of the EA, the central EA contains the central amygdaloid nucleus, the lateral bed nucleus of the stria terminalis, the central sublenticular EA, the central division of the supracapsular bed nucleus of the stria terminalis and the interstitial nucleus of the posterior limb of the anterior commissure (IPAC). The IPAC is a general term for neurons being located above and below the posterior part of the anterior commissure ventral to the striatum in rodents (Paxinos & Watson, 2007) and primates (Fudge & Tucker, 2009). The IPAC, which may also be subdivided into a lateral and medial part, is considered as part of the VSP and also of the EA (Shammah-Lagnado et al., 2001), as this area receives afferents from various autonomic and limbic areas as the insular cortex, the amygdala, lateral hypothalamus and the bed nucleus of the stria terminalis suggesting the close limbic association.

The central amygdala is a continuum of cells in the dorsocentral part of the amygdala. It is located between the striatum (amygdalostriatal transition area) dorsolaterally and the interstitial nucleus of the ansa lenticularis at its dorsomedial side. The central nucleus can further be subdivided into a medial, lateral and lateral capsular central nucleus. Functionally, the central nucleus is involved in mediating the behavioral and physiological responses associated with fear and anxiety, it modulates hormonal responses to stress and plays an important role in learning Pavlovian conditioning (Kalin et al., 2004; Liubashina et al., 2000). It has recently been proposed, that while the central nucleus of the amygdala is involved in acute fear responses, the bed nucleus of the stria terminalis is more related to anxiety responses (Pitts et al., 2009). The lateral bed nucleus of the stria terminalis is a heterogeneous cell continuum expanding from the internal capsule on the medial side to the nucleus accumbens rostrally, it borders the caudate nucleus dorsally and reaches the IPAC at its caudal end. Based on morphological, structural and immunohistochemical data, the lateral division of the bed nucleus of the stria terminalis can be separated into a dorsal, posterior, ventral, intermediate and juxtacapsular part. It seems to be important for the expression of anxiety and fear through the integration of autonomic and behavioral responses as well as by modulation of affective responses to stress (Bartfai et al., 1992; Davis & Shi, 1999). The central sublenticular EA expands from the lateral bed nucleus of the stria terminalis in a dorsomedial and ventrolateral direction until it borders the central nucleus. With regard to their neurochemistry, the medial and central sublenticular subdivisions are

very similar to each other, which suggests that the majority of cells interact with the medial central nucleus (Fallon et al., 1992). The central division of the supracapsular bed nucleus of the stria terminalis borders the lateral bed nucleus of the stria terminalis rostrally and the central amygdaloid nucleus caudally.

The EA is functionally associated with emotion, motivation and social behavior because of its morphological and neurochemical composition as well as its projections and pathways. Therefore, it is not surprising that the EA is involved in diverse psychiatric and neurodegenerative diseases such as depression, anxiety and chronic stress, schizophrenia and HD. In recent years scientists discussed the role of the amygdala in terms of addiction, loss of control in limiting drug intake as well as dysphoria and anxiety after drug abuse. Therefore, they often focused on the central amygdaloid nucleus, as it has a key function in reinforcing actions of drug abuse. In the rat, lesions of this nucleus block oral self-administration of alcohol and the cocaine self-administration can be blocked by microinjections of dopamine D1 receptor antagonists into the area (Caine et al., 1995; McGregor & Roberts, 1993). Additionally, closely related functional effects could be detected for the central EA in terms of withdrawal and negative affects after drug abuse. Especially an acute withdrawal may lead to an increased release of norepinephrine (brain stress system) in the bed nucleus of the stria terminalis and an inactivation of Neuropeptide Y (antistress system), which may cause a negative emotional state (Kobb, 2008). Accessorily, changes in the gene expression of alcohol-preferring rats within the EA have been detected (McBride et al., 2010).

In summary, the EA comprises a complex system of multiple subdivisions with a close crucial pharmacological relationship, which makes this area a valuable target for investigating pathophysiological pathways and pharmacological approaches.

4. Huntington Disease

HD is a hereditary neurodegenerative disorder caused by a cytosine-adenine-guanine (CAG) repeat expansion in exon 1 of the *huntingtin* gene (*HTT*), (Huntington's Disease Collaborative Research Group, 1993). Patients with 36 to 39 CAG repeats have an increasing risk to develop HD, repeats of 40 and more will always lead to the disorder within a normal lifespan (Bates, 2003). The mean age of onset is around 35-50 years with marked individual variations; the duration is around 15-20 years with no differences between the sexes (Hayden, 1981). The most characteristic brain pathology is the atrophy of the caudate nucleus and putamen, which is accompanied by a secondary enlargement of the lateral ventricles (Roos et al., 1985; Vonsattel et al., 1985). The striatal atrophy is due to the progressive loss of medium-sized GABAergic striatal neurons (Heinsen et al., 1994), which comprise approximately 90% of all neurons in the striatum. Cortical, subcortical and brainstem areas with grey and white matter changes are also affected (de la Monte et al., 1988; Dumas et al., 2012; Heinsen et al., 1996; Heinsen et al., 1999; Rosas et al., 2003; Rüb et al., 2009; Schmitz et al. 1999; Tabrizi et al., 2011). Up to now, there is no cure for HD.

Histopathological hallmark is the accumulation of htt aggregates in affected brains (Difiglia et al., 1997; Gutekunst et al., 1999; Maat-Schiemann, 2007) which can be identified by immunohistochemistry with the so-called EM48, a widely used antibody which specifically detects N-terminal htt aggregates in brains of HD individuals and HD animal models (Gutekunst et al., 1999; Hodgson et al., 1999; Li et al., 1999; 2001; Nguyen et al., 2006; von Hörsten et al., 2003). The role of htt aggregates and neurodegeneration is still controversial. They may be toxic by a direct influence on cellular processing (Bates, 2003) or, conversely, could also be neuroprotective by sequestering toxic fragments into an insoluble form in order to prevent them from interacting with key cellular proteins (Arrasate et al., 2004).

Clinically, HD is characterized by cognitive impairments, motor dysfunctions and psychiatric changes, the latter often preceding the onset of the other symptoms. The early detection of psychiatric affection is essential in HD, as these changes are mainly accessible to symptomatic treatment. Psychiatric symptoms have been reported to affect 35-75% of HD individuals (van Duijn et al., 2007). They are more variable than motor and cognitive impairments and do not follow a progressive course, except apathy (with loss of initiation and motivation), which is discussed to be the most frequent personality change in HD (Caine et al., 1978; Craufurd & Snowden, 2003; Paulsen et al., 2001; Thomson et al., 2002). Depression is also a common feature; irritability, aggression and outbursts are frequent (Burns et al., 1990) and often observed in presymptomatic HD patients (Klöppel et al., 2010). Anxiety and reduced ability to recognize negative face expressions as disgust, fear and anger have also been reported in several studies (Hayes et al., 2009; Johnson et al., 2007; Sprengelmeyer et al., 2006). Heining et al. (2003) found an increase in the activity of the ventral striatum in response to disgusting odors in HD patients. Interestingly, HD patients exhibit lower fear and higher anger ratings in response to fear stimuli than control individuals, reflecting dysfunctions within the frontostriatal circuit and the amygdala (Eddy et al., 2011).

Neuropathological analyses of limbic associated regions in human HD brains (such as the nucleus accumbens and the amygdala) are relatively sparse, areas as the olfactory tubercle, the bed nucleus of the stria terminalis and the IPAC are rarely mentioned. Striatal degeneration occurs gradually, starting dorsomedially and extending ventrolaterally. The caudate nucleus is initially more affected than the putamen, the nucleus accumbens appears relatively preserved (Vonsattel et al., 1985; Kassubek et al., 2005). However, when compared with control brains, the nucleus accumbens shows significant volume shrinkage already at preHD stages as detected by magnetic resonance imaging (MRI) and voxel based morphometry (van den Bogaard et al., 2011a; 2011b; Majid et al., 2011). These methods can be applied in large cohorts of HD-affected patients in presymptomatic and early stages as well as follow-up studies and are therefore valuable tools for detecting changes of and in specific brain areas.

In HD individuals the amygdaloid complex is also affected. Cross section analysis of the amygdala has shown a reduced area (Mann et al., 1993) and amygdaloid volume atrophy was detected by MRI studies, which may occur at a very early stage of the disease (Van den

Bogaard et al., 2011; Rosas et al., 2003). It should be noted that the reduction of D2/D3 receptor binding and a microglia activation has been observed in the bed nucleus of the stria terminalis, the ventral striatum and the amygdala of premanifest and symptomatic HD gene carriers (Politis et al., 2011). In contrast, Enkephalin, Neuropeptide Y and Neurotensin immunohistochemistry in the central nucleus of the amygdala showed no obvious changes (Zech et al., 1986). In addition, a reduction in the activity of Cholinacetyltransferase in the olfactory tubercle has been reported in some HD cases (Simpson et al., 1984).

In summary, the human HD individuals show a broad spectrum of psychiatric symptoms which may occur at all stages of the disease, often prior to movement and cognitive disturbances. Structural alterations in the nucleus accumbens and amygdala have also been described, suggesting that their dysfunction may explain some of the psychiatric symptoms. To date, the distribution of htt aggregates has not been investigated in the VSP and EA.

5. The Transgenic Huntington Rat - a 'Limbic Huntington Model'

As HD occurs only in humans, the creation of genetically engineered HD animal models represents an important step for elucidation of genetic and behavioral aspects as well as testing new therapeutic strategies. Since the mutation that causes HD was identified in 1993, numerous rodent models for HD have been generated all of which reproducing more or less HD-like behavioral and/or neuropathological features of the disease.

The first transgenic mouse model, the R6/2 mouse, expresses an exon 1 of the human HD gene containing around 141 to 157 CAG repeats (Mangiarini et al., 1996). From the third week after birth, R6/2 mice develop an early phenotype with severe behavioral and motor dysfunctions. Tremors, lack of coordination and enormous loss of weight is accompanied by a severe general atrophy of the brain leading finally to death within 12 - 15 weeks of age (Crook & Housman, 2011; Heng et al., 2008). The R6/2 mice show an early and overall distribution of htt aggregates in many brain areas including the hippocampus, the cerebellum and the spinal cord as detected by the EM48 antibody (Li et al., 1999; 2001). A focus on the limbic associated areas did not reveal any special abnormalities. According to the rapid and reproducible phenotype, the R6/2 mice have been extensively studied and gave important results on the pathogenesis, however, R6/2 mice mimic the juvenile form of HD, which only affects approximately 10% of all HD individuals with onset before age 20 and repeats typically exceeding 50 CAGs (Rasmussen et al., 2000).

Another well studied and widely used transgenic HD animal model is the yeast artificial chromosome mouse model YAC128 (Hodgson et al., 1999; Slow et al., 2003). The YAC128 transgenic mouse expresses the full-length human *HTT* gene with 128 CAG repeats under the control of the endogenous *HTT* promoter. This animal model also exhibits motor abnormalities and cognitive dysfunction. In YAC128 mice, the HD-like phenotype progresses slowly, and is fully developed over the course of 12-18 months. Mild cognitive impairments and motor deficits begin with hyperactivity at two month of age followed by hypokinesia from the fourth month onwards. Behavioral abnormalities can also be detected at the age of two months followed by a depressive-like behavior at the early stage of three

months of age. Between nine to twelve months of age, animals show an atrophy of the striatum, the globus pallidus and the cortex, which extends to a global atrophy at the age of two years. Htt aggregates are localized in various brain areas including the striatum, the cortex and the hippocampus with a prominent nuclear localization (Hodgson et al., 1999; Van Raamsdonk et al., 2005).

The first tgHD rat model harbors a human cDNA fragment with 51 CAG repeats in a truncated htt spanning exon 1 to exon 15 under the control of the native rat htt promoter (von Hörsten et al., 2003). TgHD rats show adult-onset neurological HD-like phenotype with an early reduced anxiety, followed by later onset of cognitive impairments and slowly progressive motor dysfunction (von Hörsten et al., 2003; Cao et al., 2006) closely resembling the adult-onset neurological phenotype of human HD. Among all Huntington animal models generated until now (and including the two extensively studied R6/2 and YAC128 mice), the tgHD rat is unique as it shows most prominent accumulation of htt aggregates in structures of the VSP and the EA (Niescery et al., 2009; Petrasch-Parwez et al., 2007). Moreover, it presents very early and ongoing emotional changes, which partly may be associated with dysfunctions of the VSP and EA (Bode et al., 2008; Faure et al., 2011; Nguyen et al., 2006). The distribution of htt accumulates in the medioventral striatum including the olfactory tubercle (Fig. 2A-C), which receives topographically organized input from the ventral tegmental area in the midbrain. In detail, at advanced age htt aggregates are abundantly expressed in the nucleus accumbens (more expressed in the shell than in the core), in the ventral parts of the caudatoputamen, in the cell bridges and in the olfactory tubercle, more expressed in the medial part. The prominent distribution of htt in the medial olfactory tubercle and the medial shell may reflect two mesolimbic dopamine reward circuitries to the accumbens-olfactory tubercle complex (Ikemoto, 2007). According to the midbrain input, the htt-rich medial olfactory tubercle is a continuum of the medial shell, whereas the lateral olfactory tubercle with minor aggregates is related to the core and lateral shell of the nucleus accumbens. Furthermore, the special htt distribution in the olfactory tubercle corresponds to the subdivision into a medial striatal-associated and a lateral more olfactory-related part, as has been reported in various studies (Ikemoto et al., 2007; Meyer & Wahle, 1986; Wahle & Meyer, 1986).

The htt composition in the ventral striatum shows highly heterogeneous aggregates varying in size suggesting that htt is localized in all cell compartments, whereas in the projection area (the ventral pallidum) it is homogeneously and finely structured and mainly localized in synaptic terminals, suggesting a production in the ventral striatum and a projection to the ventral pallidum (Petrasch-Parwez et al., 2007). The pronounced localization of htt aggregates in the ventral (limbic) striatum, lacking in the dorsal (motor) striatum, suggests a strong neuropathological affection of the ventral striatum in the tgHD rat. This observation correlates with the behavioral phenotype of the tgHD rat, which shows early onset of emotional changes followed later by motor dysfunction and cognitive decline.

Blunting of emotional oro-facial perception, which were recently described in tgHD rats (Faure et al., 2011), may also be related to ventral striatal circuits.

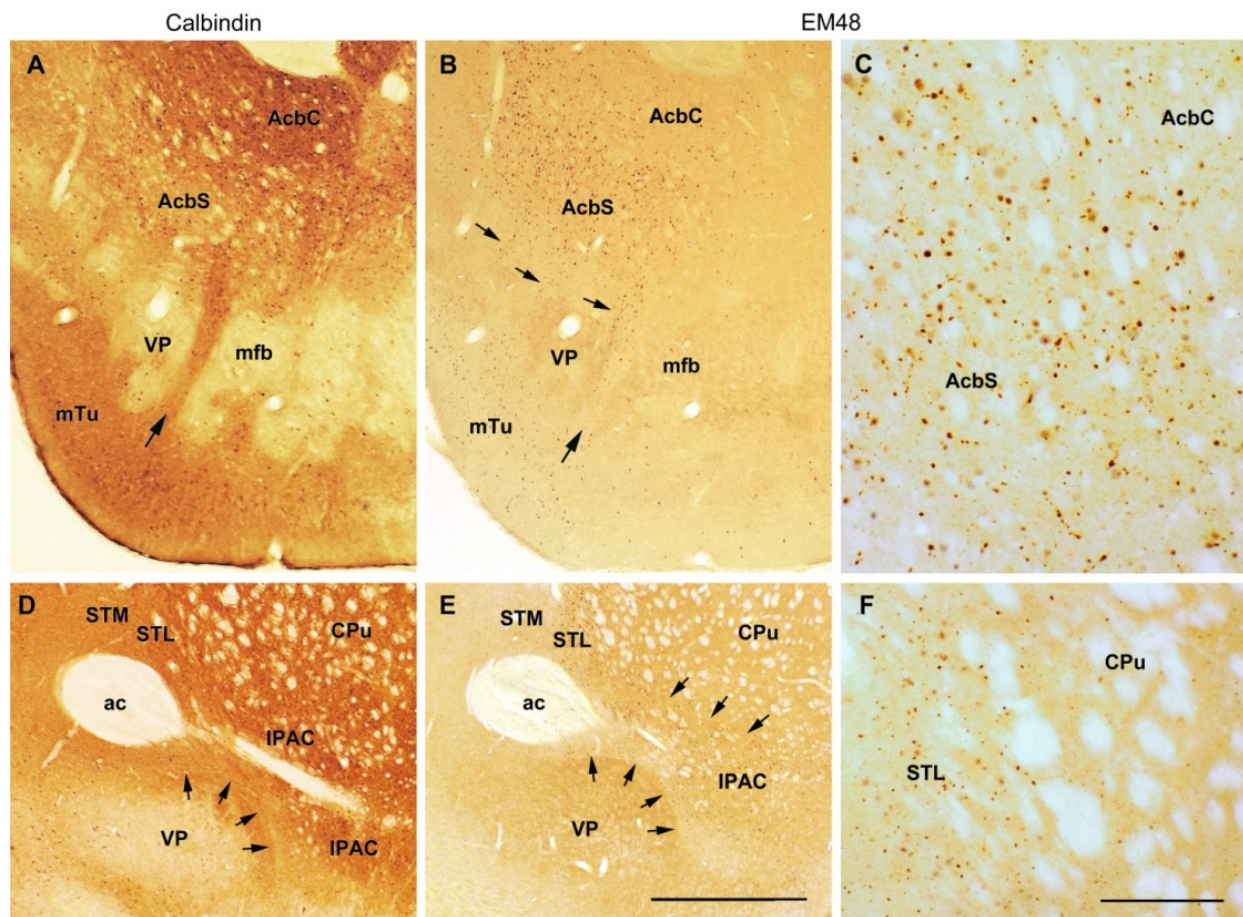


Figure 2. Calbindin (A, D) and EM48 (B, C, E, F) immunostained adjacent vibratome sections showing structures of the ventral striatopallidum (A, B, C) and the extended amygdala (D, E, F) of a tgHD rat, 19 months of age. The Calbindin section shows the nucleus accumbens with the shell (AcbS) and core region (AcbC), the medial olfactory tubercle (mTu) and the connecting cell bridges (arrow) traversing between the medial forebrain bundle (mfb). B. Note the strong huntingtin (htt) immunoreactivity in the AcbS, the cell bridges (arrows) and the mTu. C. Aggregates are less abundant in the AcbC than in the AcbS. D. The medial (STM) and lateral bed nucleus of the stria terminalis (STL) and the interstitial nucleus of the posterior part of the anterior commissure (IPAC) adjacent to the anterior commissure (ac) are distinguished by Calbindin immunohistochemistry and display abundant htt aggregates as detected in the EM-48-stained section (E). F. Higher enlargement shows the dense accumulation of aggregates in the STL as compared with the caudatoputamen (CPu). Ventral pallidum (VP). Bar in E for A, B, D, E=1000 μ m; bar in F for C and F=100 μ m.

Htt has also been shown in the EA, more precisely in the bed nuclei of the stria terminalis adjacent to the lateral ventricle (Fig. 2 D, E, F). The distribution follows the posterior part of the anterior commissure and ends in the central amygdaloid nucleus, where aggregates are abundantly expressed (Fig. 3). The dichotomy of the medial and central part of the EA is also reflected by the htt distribution. The aggregates in the central part are larger and more heterogeneously, whereas the aggregates of the medial part are smaller and more homogeneously distributed (Niescery et al., 2009; Petrasch-Parwez et al., 2007).

In the tgHD rat, the special affection of the central amygdaloid nucleus is also supported by a recent investigation of Faure et al. (2011), who assessed a significant shrinkage of the

central nucleus at 15 months of age. Additionally, the central EA has prominent projections to autonomic and somatomotor centers in the hypothalamus and brainstem (Heimer & Van Hoesen, 2006) and may therefore elucidate the autonomic dysfunction observed in HD patients (Andrich et al., 2002). Within the medial EA, the aggregates are very fine and tiny. The emotional blunting and hypersensitivity to negative situations observed in tgHD rat (Faure et al., 2011) may reflect corresponding emotional blunting and dyscontrol observed in HD patients (Paradiso et al., 2008; Snowden et al., 2008; Spengelmeyer et al., 1996).

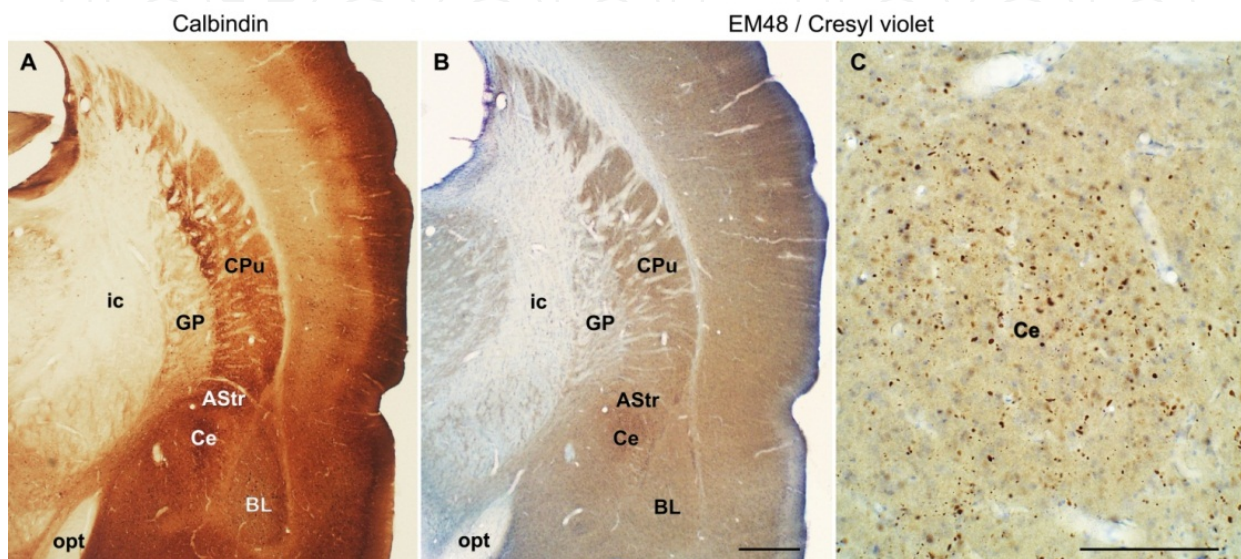


Figure 3. Calbindin (A) and EM48 immunohistochemistry, the latter counterstained with Cresyl violet (B, C) of a tgHD rat brain vibratome section of the central amygdaloid nucleus (Ce). A. The strongly Calbindin-stained Ce ventrally to the amygdalostriatal transition area (AStr) is also detected in the adjacent EM48 section by the dense accumulation of aggregates, clearly identified at higher enlargement in C. Basolateral amygdala nucleus (BL); caudatoputamen (CPu); globus pallidus (GP); internal capsule (ic); optic tract (opt). Bar in B for A and B=1000 μ m; bar in C=100 μ m.

In conclusion, the pronounced accumulation of htt in the VSP and EA observed in the tgHD rat is unique among the HD animal models. The tgHD rat is therefore an extremely valuable model to investigate behavioral and neuropathological aspects of emotional dysfunction in HD.

6. The Ventral Striatopallidum and Extended Amygdala in Huntington Brains

Though animal models are valuable tools for investigating the mechanism of a disease and their generation have led to great progresses during the last decades, the pathogenetic pathway from the HD gene mutation to neurodegeneration and neuronal dysfunction is still unknown. An important criterium for the validity of an animal model is whether and how far the pathological features in the animal models may represent the corresponding pathological features in human HD. In order to determine whether the accumulation of aggregates in the tgHD rat forebrain reflects a pathological feature of human HD, the distribution of htt aggregates were investigated in the VSP and EA of HD brains by EM48 immunohistochemistry. Post-mortem study of human HD brains showed abundantly

distributed htt aggregates in the nucleus accumbens and the most ventral parts of the caudate nucleus and putamen (Fig. 4). The aggregates accumulate in patches, but are neither consistent with the distribution of Calbindin-poor nor with Calbindin-rich areas. The localization and heterogenous form and size closely resemble the pattern of aggregates, which were observed in the tgHD rat. In the dorsal caudate nucleus and putamen, where atrophy is mostly expressed, aggregates were sparse. The pronounced distribution of htt aggregates in the ventral striatum is in agreement with a previous report (Kümmerle et al., 2003), though not shown before. Some patch- or stripe-like accumulations of aggregates were also identified in the olfactory tubercle, but not in the ventral pallidum nor in the globus pallidus.

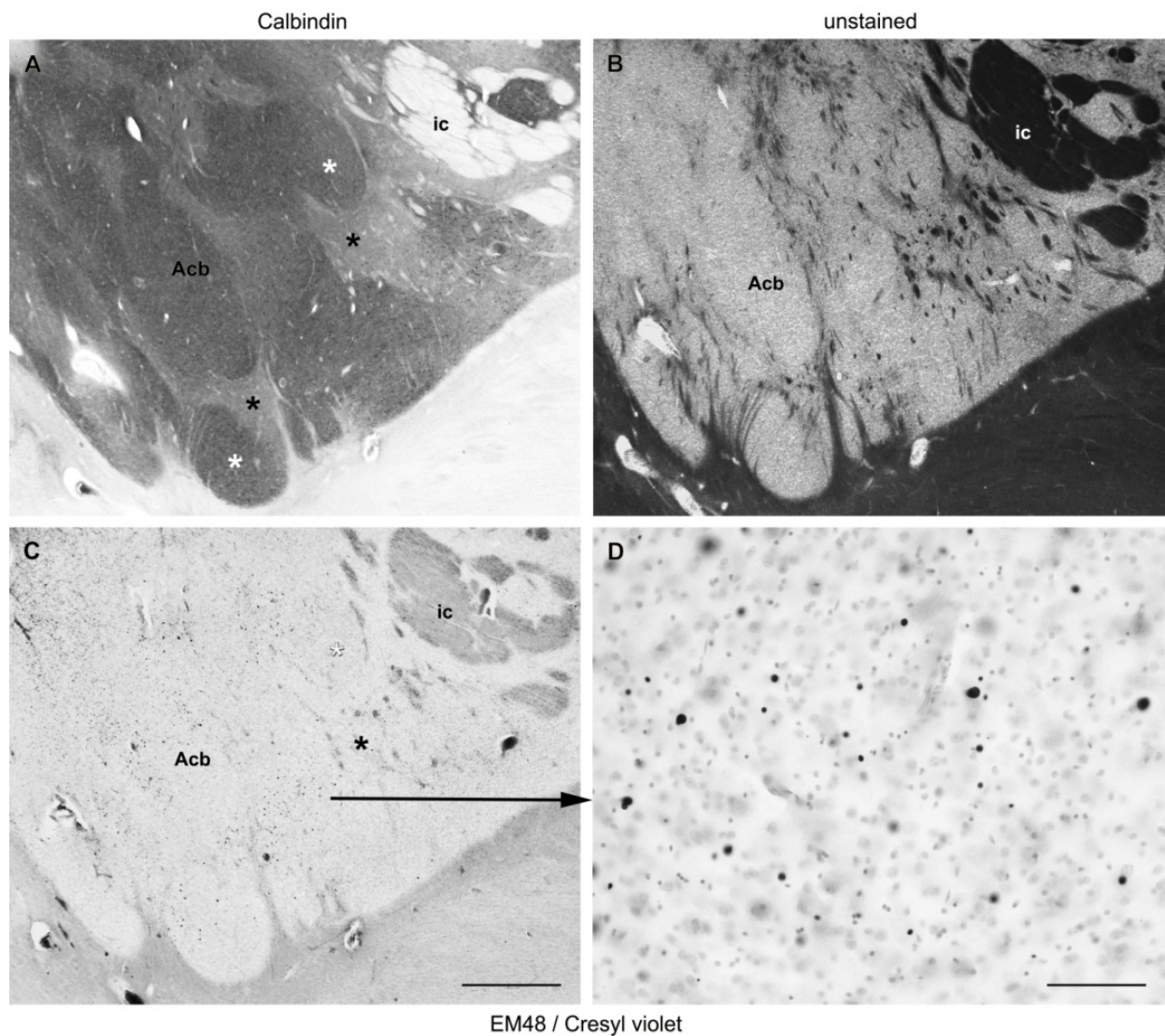


Figure 4. Micrographs of adjacent vibratome sections of the human HD nucleus accumbens (Acb). A. Calbindin-poor (black asterisks) and Calbindin-rich zones (white asterisks) are distinguished. B. The unstained section prior to Calbindin immunohistochemistry shows the fiber distribution. C. The adjacent EM48-immunostained section exhibits the patch-like distribution pattern of huntingtin (htt) aggregates in the Acb, which does not match neither to Calbindin-rich nor Calbindin-poor areas in A. D. Enlargement of a htt-rich area (arrow) shows numerous aggregates varying in size and form. Internal capsule (ic). Bar in C for A-C=1000 μ m; bar in D=200 μ m.

The nuclei of the stria terminalis also showed abundantly distributed htt aggregates in HD brains, which were detected in the angle between the anterior commissure and the internal capsule (not shown). More laterally adjacent and ventrally to the posterior part of the anterior commissure, many aggregates were present in the so-called amygdalostriatal transition area, which extends far ventrally adjacent to the amygdaloid complex. Inspecting the amygdaloid complex of HD individuals, aggregates were mainly distributed in the central amygdaloid nucleus, and most prominently in the lateral subdivision (Fig. 5).

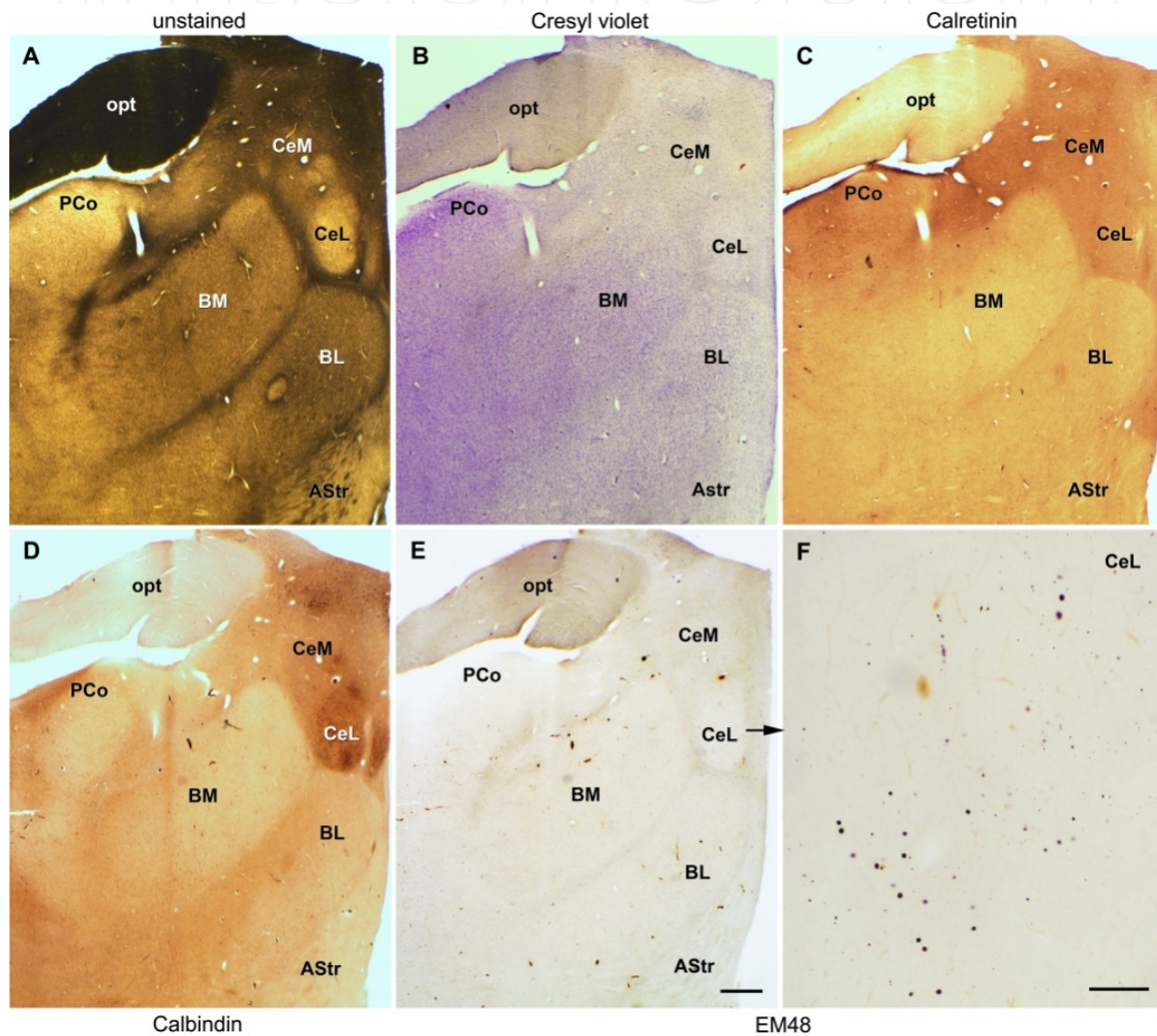


Figure 5. Micrograph of vibratome sections of a human HD amygdala. The overviews show adjacent sections unstained (A), stained for Cresyl violet (B), immunolabelled for Calretinin. (C) Calbindin (D) and EM48 (E) at the level of the medial (CeM) and lateral part of the central amygdaloid nucleus (CeL). F. Higher enlargement of the CeL shows many unevenly distributed htt aggregates. Amygdalostriatal transition area (AStr); basomedial amygdaloid nucleus (BM); basolateral amygdaloid nucleus (BL); posterior cortical amygdaloid nucleus (PCo); optic tract (opt). Bar in E for A-E=500 μ m; bar in F=100 μ m.

In summary, the distribution pattern of htt aggregates in the human HD brain is comparable to the pattern reported in the tgHD rat (Fig. 2; 3); Petrasch-Parwez et al., 2007). The pronounced localization within defined limbic forebrain structures give hints for affected circuits, which demand further investigations.

7. Conclusion

The introduction of the two interacting basal forebrain systems VSP and EA four decades ago paved the way for better understanding the complex organization of the mammalian forebrain. Both systems are now accepted as functional-anatomical entities and may act as an interface between motor, limbic and olfactory areas. The discovery had an enormous impact in the field of psychiatry, as both systems are involved in personality and behavioral changes, which are common in neurodegenerative disorders. HD is a neurodegenerative disease characterized by motor dysfunction, cognitive decline and a broad spectrum of psychiatric impairments. The disease is often seen as a motor-related illness, but a majority of patients develop psychiatric symptoms long before motor dysfunction can be detected. To date, the areas associated with motor functions are intensively investigated, but morphological correlates to psychiatric disturbances are poorly understood. Our studies on HD brains have shown a clear and important accumulation of N-terminal htt aggregates in the VSP and EA, which closely resemble the distribution pattern previously published in the tgHD rat. The affection of both limbic forebrain systems may help elucidating the emotional regulation and the psychiatric aspects of HD disorder.

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