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► **To cite this version:**

Margaux Lebouc, Quentin Richard, Maurice Garret, Jérôme Baufreton. Striatal circuit development and its alterations in Huntington's disease. *Neurobiology of Disease*, 2020, 145, pp.105076. 10.1016/j.nbd.2020.105076 . hal-02988864

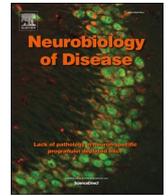
**HAL Id: hal-02988864**

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Submitted on 6 Nov 2020

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## Review

## Striatal circuit development and its alterations in Huntington's disease

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## ARTICLE INFO

## Keywords:

Striatal development  
Huntington's disease  
Spiny projection neurons  
Medium spiny neurons  
Neuronal excitability  
Striosomes  
Matrix  
Basal ganglia

## ABSTRACT

Huntington's disease (HD) is an inherited neurodegenerative disorder that usually starts during midlife with progressive alterations of motor and cognitive functions. The disease is caused by a CAG repeat expansion within the huntingtin gene leading to severe striatal neurodegeneration. Recent studies conducted on pre-HD children highlight early striatal developmental alterations starting as soon as 6 years old, the earliest age assessed. These findings, in line with data from mouse models of HD, raise the questions of when during development do the first disease-related striatal alterations emerge and whether they contribute to the later appearance of the neurodegenerative features of the disease. In this review we will describe the different stages of striatal network development and then discuss recent evidence for its alterations in rodent models of the disease. We argue that a better understanding of the striatum's development should help in assessing aberrant neurodevelopmental processes linked to the HD mutation.

## 1. Introduction

Huntington's disease (HD) is an inherited neurodegenerative disorder affecting around 1 in 10,000 people. This disease is caused by a CAG repeat expansion within the Huntingtin (*Htt*) gene on chromosome 4 (The Huntington's Disease Collaborative Research Group, 1993). This expansion leads to the translation of a mutated Htt protein (mHtt) with an expanded polyglutamine tract which becomes linked to a cascade of deleterious events leading to progressive alterations of motor and cognitive functions. The appearance of HD symptoms follows three consecutive stages. In the initial early stage, only subtle changes are observed in the form of mood disorders, sleep disturbances, poor motor coordination and cognitive deficits (Julien et al., 2007; Solomon et al., 2007; Wiegand et al., 1991). In the second stage, subjects with HD develop excessive and involuntary movements (chorea) with a deterioration of motor skills (gait, swallowing and speech) and cognitive capacities (decline in thinking and reasoning capacities). Finally, in the third stage, choreic movements are replaced by bradykinesia and rigidity (McColgan and Tabrizi, 2018). There is an accompanying general decline in health and death usually occurs about 15 to 20 years after disease onset. Concerning the neuropathology of the disease, HD is defined by a neurodegeneration of basal ganglia (BG), mainly the

striatum, and cortical atrophy.

People with a CAG expansion exceeding 39 repeats invariably develop HD, and the age of onset is inversely related to CAG repeats length with symptom onset most frequently occurring in middle age (Andrew et al., 1993; Ross and Tabrizi, 2011). However, many studies on premanifest HD patients have reported alterations occurring several years prior to conventional diagnosis. Imaging studies have highlighted changes such as altered brain volume and connectivity, especially in the striatum (Aylward et al., 2011; Harrington et al., 2015; Paulsen et al., 2010), raising the possibility that these early symptoms in HD are due to neurodevelopmental alterations. Indeed, children carrying the HD mutation have a smaller head size, suggesting a deficit in brain growth (Lee et al., 2012). Moreover, two recent neuroimaging studies performed on pre-HD children carrying the *Htt* mutation, estimated to be 35 years prior to clinical onset, showed impairments in striatal development, including striatal hypertrophy as well as hyperconnectivity of cerebellar-striatal circuitry prior to the age of 10 (Tereshchenko et al., 2020; van der Plas et al., 2019). These authors also observed an altered developmental trajectory of striatum growth, with a linear decline in striatal volume in pre-HD children, compared to a non-linear pattern of initial striatal growth (between 6 and 12 years old) and then a volume loss in non-HD children (van der Plas et al., 2019). As these alterations

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were observed in the earliest age assessed (6 years old), these findings suggest that striatal development could be impaired even earlier. In addition, this idea is in line with molecular and behavioral analyses in mouse models of HD showing early developmental deficits as well as early signs of alterations in several brain structures, including the striatum (Cepeda et al., 2019; Du et al., 2017; Du et al., 2016; Molero et al., 2009).

Given the obvious difficulties of studying human striatal development and its alterations in HD, and the resultant limited numbers of studies, most of this review will focus on research done on rodents. First, we will describe the physiological establishment of the striatal network through development, and second, we will discuss recent evidence showing early impairments of striatal neurodevelopment in mouse models of HD.

## 2. Overview of striatal network development

The striatum is usually subdivided into cytoarchitecturally close, but functionally distinct dorsal and ventral striatal components. As a whole, it constitutes the main input structure of the BG network because of its massive innervation by excitatory glutamatergic afferents from the cortex and thalamus.

The dorsal striatum, derived from the embryonic telencephalic vesicle, plays a central role in motor circuit function by sending projections into the BG output nuclei and then on to the thalamus and brainstem via poly-synaptic relays. Moreover, numerous feedback and re-entry loops are involved within this cortex-basal ganglia-thalamus-brainstem motor network so as to promote appropriate motor behavior according to the context (Kress et al., 2013; Reiner and Deng, 2018). In addition, the operation of the dorsal striatum is actively regulated by neuromodulatory afferents, notably dopaminergic and cholinergic inputs from the *substantia nigra pars compacta* (SNc) and the brainstem, respectively, which have been also shown to participate in proper striatal development (Fishell and Van Der Kooy, 1991; Lieberman et al., 2018).

The adult dorsal striatum is colonized by two neuronal cell types, namely spiny projection neurons (SPNs) and interneurons. Accounting for approximately 95% of all striatal neurons, SPNs (also known as medium spiny neurons) are GABA-releasing inhibitory neurons with a medium-sized cell body from which branched spiny dendrites radiate (Wilson and Groves, 1980). Striatal interneurons (SINs), known for modulating the activity of SPNs, are spiny neurons that make up the very small minority of the remaining 5% of striatal neurons. SINs can be divided into two broad classes: large neurons that release acetylcholine as their neurotransmitter, and GABAergic interneurons. In testament to their remarkable heterogeneity, GABAergic SINs can be further subdivided into several subclasses according to their differing molecular, morphological and electrophysiological profiles (Kawaguchi, 1993; Muñoz-Manchado et al., 2018). For a detailed description of the different subpopulations of SINs, refer to two recent reviews (Silberberg and Bolam, 2015; Tepper et al., 2018).

Dorsal striatal SPNs follow two distinct, yet complementary, basic organizational plans that define the intrinsic architecture of the striatal network. In terms of the network's functional organization, SPNs are subdivided into two neuronal subtypes according to the output nuclei of the BG to which they project and the molecular markers they express. On one hand, direct pathway SPNs (dSPNs) project monosynaptically to the internal segment of the Globus Pallidus (GPi) and to the *substantia nigra pars reticulata* (SNr) and promote the selection of wanted motor programs (Albin et al., 1989; Freeze et al., 2013). At the molecular level, they express dopamine D1 receptors (D1R) as well as the neuropeptides dynorphin and substance P (SP). On the other hand, indirect pathway SPNs (iSPNs) also target the GPi/SNr complex, but through a poly-synaptic relay, in the external segment of the globus pallidus (GPe), which in turn projects to the subthalamic nucleus (STN; Albin et al., 1989) and elsewhere (Smith et al., 1998). The activation of these

iSPNs promotes the suppression of motor programs (Kravitz et al., 2010). These neurons carry dopamine D2 receptors (D2R) and release the opioid peptide enkephalin (ENK; Reiner and Anderson, 1990). The maintenance of balance in the excitability and function of these two pathways, which is critical in the execution of controlled movements in time and space, is mainly ensured by dopamine released from SNc neurons. Dopamine helps to increase the excitability of the direct pathway (Lahiri and Bevan, 2020) and decrease that of the indirect pathway in order to facilitate proper voluntary motor skills (Planert et al., 2013).

The second organizational scheme of mature dorsal striatal architecture, which is superimposed upon the first, corresponds to the dorsal striatum's division into two neurochemically distinct compartments, namely the striosomes, similar to small cellular islands and also called patches, and the surrounding matrix (Graybiel and Ragsdale, 1978; Jain et al., 2001).  $\mu$ -opioid receptors (MOR) and calbindin are markers of striosomes and matrix, respectively (Gerfen et al., 1985; Pert et al., 1976). The size of the matrix is significantly larger than that of the striosomal compartment, such that a 4:1 ratio is usually observed. These two anatomically distinct compartments are colonized by both dSPNs and iSPNs. Furthermore, within each compartment, dSPNs and iSPNs are fully intermingled, giving rise to a cellular mosaic that is essential for maintaining a functional balance of striatal activity (Tinterri et al., 2018). Striosomal and matrix SPNs have been shown to be part of functionally distinct networks and so to be involved in diverse functions. Indeed, the former mainly receive inputs from the prefrontal cortex (Gerfen, 1989; Kincaid and Wilson, 1996) as well as from several midbrain regions and project in particular onto SNc dopaminergic neurons (Crittenden and Graybiel, 2011; Gerfen et al., 1985; Jimenez-Castellanos and Graybiel, 1987; McGregor et al., 2019; Watabe-Uchida et al., 2012). On the other hand, matrix SPNs receive massive inputs from the sensorimotor cortex (Donoghue and Herkenham, 1986; Gerfen, 1989; Gerfen, 1984; Hintiryan et al., 2016; Hunnicutt et al., 2016; Kincaid and Wilson, 1996) and in turn communicate synaptically with the basal ganglia output nuclei (Watabe-Uchida et al., 2012). As a result, striosomes seem to be preferentially involved in evaluation functions for decision-making as well as in motivational behaviors (Friedman et al., 2015), whereas in contrast, the matrix compartment is involved in the selection between specific motor tasks (Flaherty and Graybiel, 1994). Thus, the striosome/matrix compartmentalization is a crucial organizational plan as it defines output and input connectivity of the dorsal striatal network, as well as its different functions.

The ventral striatum, which is subdivided into the nucleus accumbens (NAc) and olfactory tubercle (OT), regulates limbic functions (Cansler et al., 2020; Castro and Bruchas, 2019). Specifically, the NAc is involved in a broad range of functions, including learning and memory, reward processing, addiction behavior, stress-related aversion and motivation (Carlezon and Thomas, 2009; Castro and Bruchas, 2019; Li et al., 2018; Ma et al., 2020).

Similarly to the dorsal striatum, the NAc is composed of 95% SPNs and 5% interneurons. These SPNs can be further subdivided into two neuronal subtypes: direct pathway cells expressing D1R that project monosynaptically to the ventral mesencephalon (VM), and indirect pathway cells expressing D2R, which also project to the VM by a relay via the ventral pallidum (VP) (Klawonn and Malenka, 2018). However, this dichotomy has been questioned by recent studies that have reported a substantial involvement of D1R-expressing SPNs in the indirect pathway and D2R-expressing SPNs in the direct pathway (Kupchik et al., 2015; Kupchik and Kalivas, 2017). Moreover, the NAc is also characterized by MOR-rich 'striosomes' and calbindin-rich 'matrix' compartments (Brimblecombe and Cragg, 2017; Zahm and Brog, 1992). Furthermore, it has been shown that SPNs in calbindin-diminished areas, recognized as striosomes, preferentially target VTA dopaminergic neurons, similarly to the identified innervation of SNc by striosomal SPNs in the dorsal striatum (Brimblecombe and Cragg, 2017; Watabe-

Uchida et al., 2012).

Finally, unlike the dorsal striatum, the NAc displays a distinct organizational plan in comprising a central core that is surrounded by an outer shell (Voorn et al., 1989). On one hand, the NAc core receives inputs mainly from the cortex (prelimbic, orbital and insular cortices), the olfactory areas, basolateral amygdala (BLA), subiculum and thalamus and seems to be preferentially involved in reward-cue associations and the initiation of reward-related motor actions. On the other hand, the NAc shell receives projections mostly from the hippocampus, lateral hypothalamus, thalamus, BLA and VP, and is preferentially responsible for reward prediction and reward learning (Klawonn and Malenka, 2018; Li et al., 2018; Scofield et al., 2016; Shiflett and Balleine, 2011).

The developmental origins as well as the relationship between these two striatal organization schemes (striosome/matrix compartmentalization and SPNs specification into dSPNs and iSPNs) remain elusive. However, knowledge of this physiological situation is of paramount importance to better understanding and eventually confronting the neurodevelopmental abnormalities observed in HD. Thus, we propose here firstly to review the current state of knowledge in the literature concerning the proper embryonic and postnatal development of the striatal network.

### 2.1. Mechanisms underlying striosome/matrix compartmentalization and SPN specification

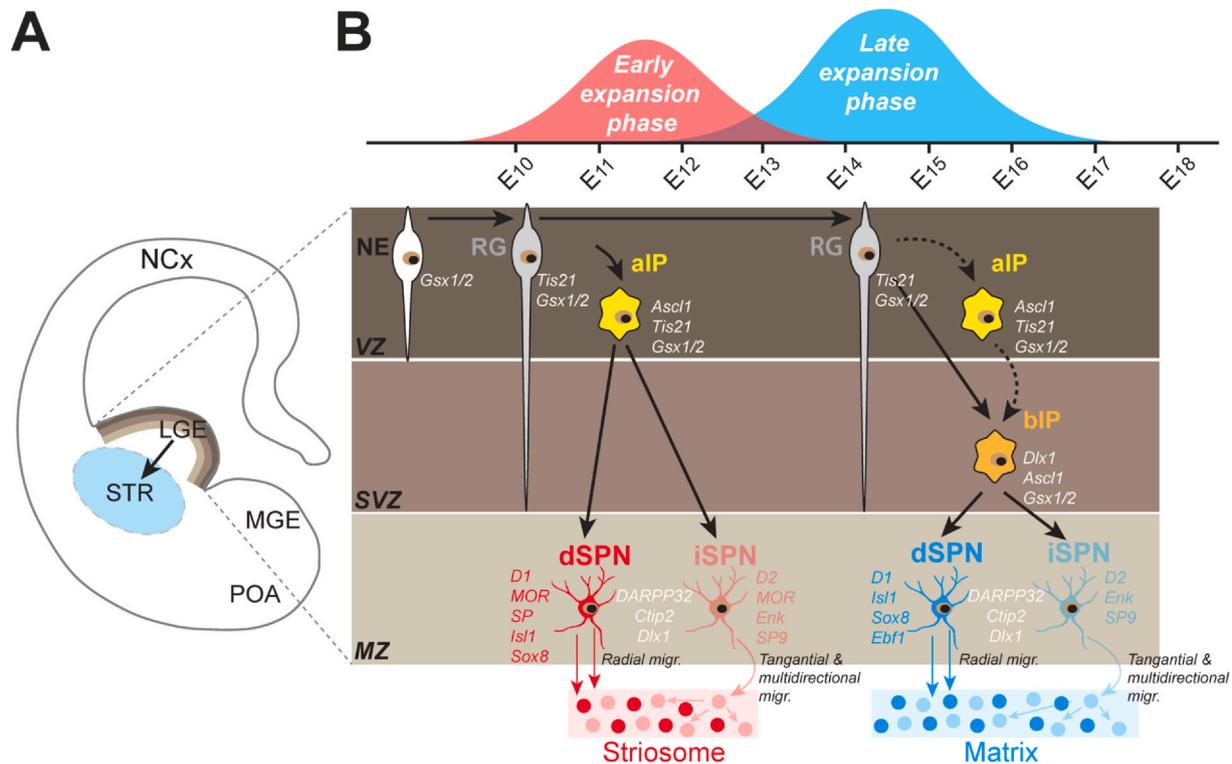
In mammals, the dorsal striatum is derived from the embryonic ventral telencephalon, which contains the lateral ganglionic eminence (LGE) (Fig. 1A). The LGE, which forms at embryonic day 9.5 (E9.5), is an intense neurogenic zone containing a pool of neural epithelial (NE) progenitor cells in the ventricular region. These NE cells first give birth to cells which send projections into the subventricular region of the LGE and thus shape radial glia. The latter are the radial glial (RG) cells from which all SPNs originate (Sousa and Fishell, 2010). The same pool of RG cells then differentiate sequentially into two distinct subpopulations of intermediate progenitors (IP) during striatal neurogenesis, first into apical (aIP) then into basal IP (bIP) cells, although the link between these two types of neuronal progenitors and the two SPN subpopulations has not yet been established (Pilz et al., 2013; Turrero Garcia and Harwell, 2017) (Fig. 1B). Indeed, this lack is why our understanding of the mechanisms underlying the assembly of the embryonic striatal architecture and consequently its functional input and output connectivity is currently so sparse.

To address this question, Kelly and co-workers have recently traced the developmental trajectory of LGE RG cells in mice up until the ultimate stage of their differentiation into SPNs by genetic fate mapping (Kelly et al., 2018). In this study of major interest, the authors highlighted the existence of a developmental program integrated within these neural cells, which runs sequentially in time and space in two major phases: an early phase extending from ~E10 to ~E13.5 during which the pool of RG cells is restricted to the production of aIPs that in turn give rise almost exclusively to striosomal SPNs, and a later and longer phase beginning at ~E12.5 and ending at ~E17, which generates almost all matrix SPNs, from the same pool of RG cells after an intermediate differentiation step into bIPs (Fig. 1B) (Kelly et al., 2018). Thus, these results are in line with those of previous studies demonstrating that striosomal and matrix striatogenesis occur sequentially, with the generation of the former compartment preceding the latter, albeit in partial temporal overlap (Liao et al., 2008; Mason et al., 2005; Newman et al., 2015; van der Kooy and Fishell, 1987). Moreover, a differential gene expression profile is associated with each cell type. NE cells express the transcription factor (TF) GS homeobox 1/2 ( $Gsx1/2$ ), while RG cells express  $Gsx1/2$  and the TF Tis21 ( $Gsx1/2^+/Tis21^+$ ). Regarding IP cells, two neurogenic factors appearing sequentially during striatal neurogenesis allows aIPs from bIPs to be distinguished. Specifically, aIPs express the TF achaete-scute family bHLH 1 ( $Ascl1$ )

but not the TF distal-less homeobox 1 ( $Dlx1$ ), whereas bIPs express both ( $Ascl1^+/Dlx1^+$ ) (Fig. 1B). This sequential gene expression is proposed to be involved in the chronological production of the two SPN subtypes, where  $Dlx1$  would act downstream from  $Ascl1$  within the bIPs to give rise to matrix SPNs (Kelly et al., 2018; Martín-Ibáñez et al., 2012; Yun et al., 2002). In contrast, the molecular mechanisms underlying this biphasic differentiation of RG cells into aIPs and then into bIPs remains an open question and requires further studies.

In parallel with, but independently from, the developmental program defining striosome/matrix compartmentalization, many other transcriptomic programs are activated in these same IPs, downstream from  $Ascl1$  and  $Dlx1$ , to induce SPN neurogenic specification into dSPNs and iSPNs. The identity of direct pathway neurons is specified by three main TFs, namely Insulin gene enhancer protein Islet-1, Early B-Cell Factor ( $Ebf1$ ) and SRY-Box Transcription Factor 8 ( $Sox8$ ), which are expressed as early as E11 and required for the proper development and survival of these neurons (Fig. 1B). More broadly, these factors ensure the normal development of the direct projection pathway by promoting the development of embryonic and early postnatal functional striatonigral connectivity (Ehrman et al., 2013; Garel et al., 1999; Lobo et al., 2008; Lobo et al., 2006; Lu et al., 2014; Merchan-Sala et al., 2017). Regarding  $Ebf1$  specifically, this TF has been shown to be involved in the proper differentiation of matrix compartment dSPNs (Lobo et al., 2008; Lobo et al., 2006). For its part, the TF SP9 is instrumental for the normal development of indirect pathway neurons by driving the striatopallidal progenitor differentiation into iSPNs and also by participating in ensuring the survival of these post-mitotic differentiated neurons (Fig. 1B) (Xu et al., 2018; Zhang et al., 2016). While dSPNs and iSPNs are derived from both aIPs and bIPs, which produce striosomal and matrix SPNs, respectively, the relationship between the developmental origins of these two organizational schemes remains to be understood. Nonetheless, several hypotheses have been proposed, including one according to which the aIPs and bIPs sub-groups could exist within these (striosomal/matrix) subpopulations, some of which being committed to generating dSPNs and others to producing iSPNs (Kelly et al., 2018). To confirm this hypothesis, however, more detailed studies on the specific fate of these neural precursor subpopulations are necessary.

Despite a substantial literature on the molecular profile of the developing striatum, a core issue remains to be deciphered, namely the SPN migratory processes that shape the striatal mosaic. Following their specification in the LGE subventricular zone (SVZ), both dSPNs and iSPNs migrate alongside the radial glia towards the mantle zone to integrate the different compartments under formation (early migration towards the striosomes and later migration towards the surrounding matrix). Within the striatal mantle, dSPNs and iSPNs then actively intermix to shape the mosaic cell architecture that is vital for the striatum's function. While it is commonly accepted that SPNs migrate radially to colonize the entire striatum (Halliday and Cepko, 1992; Hamasaki et al., 2003; Song and Harlan, 1994), this assumption has recently been questioned. Indeed, by analyzing the iSPN migration profile within the embryonic striatum by two-photon time-lapse imaging, Tinterri and co-workers revealed that after the early specification of dSPNs/iSPNs, iSPNs gradually invade the striatal mantle, laterally and then medially, by a dSPN-dependent tangential and multi-directional migration (Fig. 1B) (Tinterri et al., 2018). However, tangential migration, which is characteristic of MGE-derived interneurons, a neuronal population specified later during striatal neurogenesis (Kelly et al., 2018; Marin et al., 2000; Nóbrega-Pereira et al., 2008), is also common to other LGE- and MGE-derived neuronal populations such as globus pallidus neurons (Dodson et al., 2015; Nóbrega-Pereira et al., 2010). Thus tangential migration is thought to actively participate in the intermixing of dSPNs and iSPNs within both compartments, in association with the classical radial migration profile of dSPNs (Hagimoto et al., 2017; Tinterri et al., 2018). The mechanisms governing this iSPN migration pattern are still unknown. However,  $Ebf1$  would appear to



**Fig. 1.** Current model of embryonic mechanisms underlying striatal architecture and the ontogenesis of SPNs. A: Schematic representation of a coronal hemisection of the developing brain in which are represented the neocortex (NCx), striatum (STR), lateral ganglionic eminence (LGE), medial ganglionic eminence (MGE) and the preoptic area (POA). B: Enlargement of the LGE region indicating the different expansion phases of neuroepithelial (NE) cells leading to the formation of striosomal and matrix striatal compartments. In the early (E10-E13.5) expansion phase, NE cells give rise to radial glial (RG) cells that generate apical intermediate precursors (aIP), which in turn give rise to striosomal dSPNs and iSPNs. A second wave of expansion takes place between E12.5 and E17, during which RG cells give rise directly or indirectly through aIP (dashed arrows) to basal intermediate precursors (bIP) which will produce matrix dSPNs and iSPNs. While striosomal and matrix dSPNs eventually reach their final destination in the developing striatum following radial migration, iSPNs reach their targets through a tangential and multidirectional migration process.

The molecular identity of the different neuronal progenitors is indicated by the expression of transcription factors (*Gsx1/2*; *Tis21*; *Ascl1*; *Dlx1*), whereas the molecular identity of mature striosomal and matrix SPNs appears in red and blue, respectively.

En: embryonic day n; MZ: mantle zone; SVZ: subventricular zone; VZ: ventricular zone.

play an important role in this process as its inactivation leads to an altered dSPN/iSPN intermixing (Tinterri et al., 2018). This therefore implies that although the specification of these two neuronal subtypes is largely independent, their intermixing within the different compartments is conditioned by the proper development of both dSPNs and iSPNs, which cooperate and interact together to shape a mature and functional striatal network. Another TF, Forkhead box P1 (FoxP1), which is expressed in both dSPNs and iSPNs, could also be involved in this migration process since it has recently been shown to be necessary for the correct migration of iSPNs generated during the early phase of striatogenesis (i.e. those cells intended to colonize the striosome compartment) (Anderson et al., 2020).

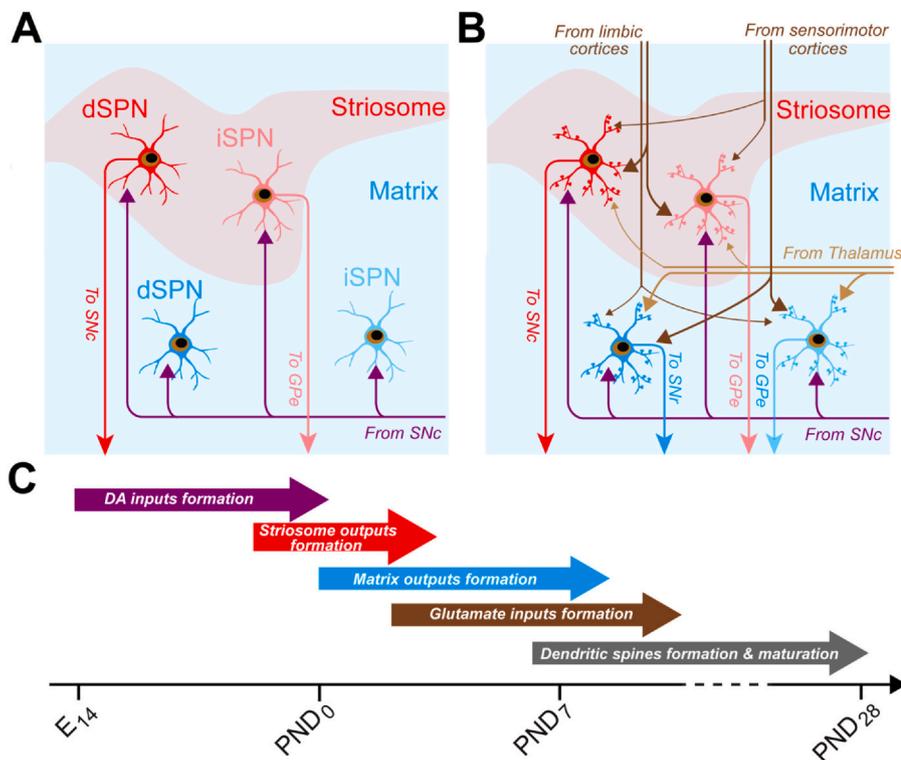
Concerning NAc development, little is known about the precise mechanisms leading to the NAc architecture formation. Indeed, it is still unclear whether neurons in the dorsal and ventral striata are derived from a common pool or from different cell lineages, and therefore might share the same developmental processes (Chen et al., 2020). Previous studies have shown that neurons of the dorsal striatum are produced between E13 and P3 whereas NAc neurons are born between E15 and P3 in the rat brain (Bayer, 1984; Bayer and Altman, 1987). Moreover, Chen and co-workers have shown that *Dlx1/2* is directly related to the migration of SPNs to the ventral part of the striatum, suggesting its crucial role in NAc neuron formation (Chen et al., 2020). From these findings, one hypothesis proposed is that the early-born progenitor cells (aIPs), expressing only *Ascl1*, produce striosomal SPNs of the dorsal striatum, while the late-born progenitor cells (bIPs), expressing both

*Ascl1* and *Dlx1*, produce matrix neurons of the dorsal striatum and NAc neurons (Chen et al., 2020; Kelly et al., 2018). Given that the NAc is probably implicated in psychiatric symptoms in HD (Hirano et al., 2019), further investigations are needed to shed light on the mechanisms at the origin of NAc architecture formation.

Embryonic striatal development involves a critical period during which the shaping of striatal circuitry takes place. This developmental window brings into play a host of specification, migration and interaction processes as well as numerous transcriptomic programs, all tightly regulated in time and space. An abnormal development of this architecture will subsequently have adverse consequences for proper postnatal striatal maturation, which could lead years later to the appearance of debilitating pathologies, as is the case in HD whose pathogenesis is increasingly being thought to comprise a neurodevelopmental component (Barnat et al., 2020; Cepeda et al., 2019; Humbert, 2010; Kerschbamer and Biagioli, 2016).

## 2.2. Postnatal maturation of the striatal circuit

After the embryonic proliferation and migration of the SPNs, the early postnatal period is crucial as it is defined by the establishment of striatal inputs and output connectivity as well as the maturation of SPN properties. Regarding their outputs, it has been shown in rats that striosomal SPNs send their projections to the SN as early as E17, while matrix SPNs do so mostly during the first postnatal week (Fig. 2A, C) (Fishell and van der Kooy, 1989; Fishell and van der Kooy, 1987). In



**Fig. 2.** Establishment and maturation of the developing striatum. A–B: Schematics depicting the sequential maturation of the striatum. A: Dopaminergic inputs and axonal projections of striosomal SPNs develop principally between E14 and birth (PND0). B: During the first postnatal week, matrix SPNs make connections with their targets (the SNr and the GPe) and glutamatergic inputs from the cortex and thalamus are formed. Between the first and fourth postnatal weeks, the striatal microcircuit becomes fully functional with a strengthening of glutamatergic inputs and the formation and maturation of SPN dendritic spines. C: Timeline showing the different key steps involved in the maturation of the developing striatum. En: embryonic globus pallidus; PNDn: postnatal day n; SNc: *substantia nigra pars compacta*; SNr: *substantia nigra pars reticulata*.

addition, during the first postnatal week, the striatum normally undergoes a physiological cell death period. In rats, between PND2 and PND7, around 30% of striatal neurons die independently of their location in the striosomes or matrix suggesting that their birthdate has no impact on their subsequent survival. However, it has been shown that striatal neurons that have already sent projections to the SN or the GPe at PND2 survive more during this cell death period, suggesting that the development of early striatofugal axons ensures SPN survival (Fishell and Van Der Kooy, 1991).

The postnatal maturation of SPNs is also strongly related to the establishment of their dopaminergic, cortical and thalamic inputs. Dopaminergic innervation is the earliest to develop, with SNc neurons sending their axonal projections to the striatum as soon as E14 in rats, although their terminals release dopamine only around E18–PND0 in mice, suggesting that most nigrostriatal synapses are functional at birth (Fig. 2A, C) (Ferrari et al., 2012; Specht et al., 1981; Voorn et al., 1988). In mice, dopamine release was shown to be crucial for the maturation of dSPNs as the lack of nigrostriatal dopaminergic transmission prevents the decrease in dSPNs excitability (Lieberman et al., 2018). In parallel, mouse cortical neurons send their axonal projections to the striatum from PND3 (Sohur et al., 2014) but only 75% of SPNs respond to cortical stimulation between PND3 and PND6, indicative of ongoing corticostriatal synaptogenesis (Hurst et al., 2001; Krajeski et al., 2019). From PND9, all SPNs receive cortical innervation and the amplitude of postsynaptic currents induced by cortical stimulation continue to increase progressively, especially between PND10 and PND18, suggesting an ongoing strengthening of corticostriatal synapses (Fig. 2B, C) (Hurst et al., 2001; Krajeski et al., 2019; Peixoto et al., 2016). Cortex and striatum development appear to be strongly interdependent as an alteration in either striatal or cortical activity during this period has a strong impact on corticostriatal connectivity (Kozorovitskiy et al., 2012; Peixoto et al., 2016). Finally, thalamic neurons send their projections from PND3 as 75% of SPNs respond to a thalamic stimulation at this stage, but the establishment of thalamo-striatal synapses could start even earlier as VGLUT2-positive axons are already found at birth in the mouse striatum (Nakamura et al., 2005). Similarly to the cortical inputs, all SPNs receive thalamic inputs from PND9 and the amplitude of

postsynaptic currents generated by a stimulation of these inputs increase progressively until PND28, also suggesting a continued strengthening of thalamostriatal synapses (Krajeski et al., 2019). As described earlier, striosomal and matrix striatogenesis occur sequentially, with an early production and migration of striosomal SPNs followed by matrix ones (see § II.1.). Consequently, these striosomal SPNs are more susceptible to receiving early inputs from cortex, thalamus and SNc. Indeed, early-forming dopaminergic innervation of the striatum occurs first in the patch compartment before its expansion into the matrix (Edley and Herkenham, 1984; Fishell and van der Kooy, 1989; Graybiel, 1984; Prager and Plotkin, 2019). Similarly, early cortical and thalamic innervation labeling by Vglut1 and Vglut2, respectively, appear to match with the striosomes' location (Nakamura et al., 2005).

Regarding SPN morphology and excitability, it has been shown that during the first postnatal week, neonatal SPNs express immature characteristics as indicated by an absence or slight presence of dendritic spines as well as the presence of thin and varicose dendrites (Fig. 2B, C) (Sharpe and Tepper, 1998). In terms of their electrophysiological properties, SPNs exhibit immature patterns of activity compared to the adult state, with a lower level of spontaneous activity *in vivo*, and an hyperexcitability observed both *in vivo* and *ex vivo* (Dehorter et al., 2011; Krajeski et al., 2019; Tepper and Trent, 1993). This elevated intrinsic excitability of immature neurons during development, which is found in many brain structures and across many species, has been shown to be crucial to developmental processes such as neuronal growth and synapse formation (Spitzer, 2006). After the first postnatal week, SPNs undergo a maturation to attain their adult-like activity state and morphology. Regarding morphology, this maturation involves the development of the dendritic arbor and the formation of dendritic spines, with their density increasing gradually especially between PND10 and PND12 (Fig. 2B, C). SPN activity also increases from P10, with an overall increase in spontaneous firing rate and burst frequency observed *in vivo* (Krajeski et al., 2019; Peixoto et al., 2016). Conversely, the intrinsic excitability of SPNs progressively decreases caused by an hyperpolarization of their resting membrane potential and a longer latency to spike firing (higher rheobase and action potential threshold

seen *ex vivo*) (Dehorter et al., 2011; Krajcski et al., 2019; Peixoto et al., 2016). This change in excitability is essentially due to the acquisition of inwardly rectifying potassium channel (Kir) currents (Krajcski et al., 2019; Tepper et al., 1998). During this critical PND10-PND12 period, the AMPA/NMDA receptor ratio starts to increase, resulting in a bias towards AMPA receptor recruitment, which is usually related to synapse maturation (Krajcski et al., 2019; Peixoto et al., 2016; Petralia et al., 1999). By the end of the fourth postnatal week (PND28), SPNs have morphological and electrophysiological properties that closely resemble those of adult neurons.

Thus, during the postnatal period between PND0 and PND28, SPNs undergo a strong maturation in their morphologies, electrophysiological properties and synaptic wiring (Dehorter et al., 2012; Dehorter et al., 2011). This maturation involves several mechanisms that occur concomitantly and are interdependent. From PND35, the striatal network appears to be fully mature, concurrently with mouse sexual maturity (Krajcski et al., 2019).

### 3. Huntingtin plays a key role in striatal development

#### 3.1. Huntingtin is ubiquitous and involved in many key cellular processes

Htt is a widely distributed protein with a higher expression in the central nervous system than in peripheral tissues. Its expression occurs very early during embryonic development and is maintained throughout adulthood (Bhide et al., 1996; Landwehrmeyer et al., 1995; Marques Sousa and Humbert, 2013; Nasir et al., 1995). Htt is known to be expressed throughout the brain, including the cortex and striatum, although its precise distribution during development is still unknown. Wild-type Htt protein interacts with a large number of partners with which it forms complexes and regulates many cellular functions (Shirasaki et al., 2012). Among these processes, wild-type Htt regulates vesicular trafficking of organelles along microtubules, cell division by controlling the assembly and orientation of the mitotic spindle, the transcription of many key genes such as p53 and also ciliogenesis (for a detailed description of these Htt-regulated cellular processes, see Cattaneo et al., 2005; Saudou and Humbert, 2016).

At the cortico-striatal circuit level, which is primarily affected and dysfunctional in HD, Htt plays a vital role since it promotes striatal neuron survival by regulating several mechanisms. Htt initially stimulates cortical synthesis of the brain-derived neurotrophic factor (BDNF) gene by positively regulating its transcription and then promotes its anterograde vesicular transportation to cortico-striatal synapses as well as its release into the synaptic cleft. In a second step, once BDNF binds to the Tropomyosin receptor kinase B (TrkB) receptor located on the dendrites of post-synaptic striatal neurons, the activated BDNF-TrkB complex is then endocytosed and transported to the somata of these neurons under the action of Htt to activate pro-survival signaling pathways (Gauthier et al., 2004; Liot et al., 2013; Zuccato et al., 2001). Furthermore, it has been shown that Htt exerts this neuroprotective function by repressing caspases-3 and -9-mediated apoptosis (Rigamonti et al., 2001; Zhang et al., 2006). However, while the impact of the HD mutation on the functional integrity of the adult striatum has been widely analyzed, much less is known about the importance of wild-type Htt in normal striatal architecture establishment. The following section thus reviews current knowledge about Htt's involvement throughout striatal development.

#### 3.2. Huntingtin is crucial for striatal neuron specification, survival and motor function

Several studies, in which deletion of wild-type *Htt* was performed, have enabled a better understanding of the multiple functions of the protein in the developing brain and especially in the striatum. First, it has been shown that Htt is crucial for normal embryonic development as its homozygous deletion induces an early mortality of mouse

embryos (Duyao et al., 1995; Nasir et al., 1995; Zeitlin et al., 1995). Moreover in mice with disrupted *Htt* from a later embryonic stage (E15), progressive alterations in subsequent adulthood are observed, including neurodegeneration in the striatum, motor deficits, and early mortality, thereby recapitulating impairments found in the HD phenotype (Dragatsis et al., 2000). Second, analyses of chimeric embryos have suggested that Htt is essential for neuronal survival in the striatum (Reiner et al., 2001). Third, in mice with a specific deletion of *Htt* in *Gsx2* lineages (lineage described § II.1 and Fig. 1B), similar striatal neurodegeneration and motor deficits are observed (Mehler et al., 2019). These latter findings have also been confirmed by a recent study in which a cell-type specific deletion of *Htt* in SPNs was performed around E16 using striatal-pathway specific transgenic mice (Burrus et al., 2020). The loss of *Htt* in iSPNs leads to a dramatic reduction of GABAergic synapses in the GPe, associated with behavioral hyperactivity, in 2-month-old mice. Conversely, the loss of *Htt* in dSPNs leads to an increased inhibition of the SNr with an associated hypoactivity in mice at the same age. These results therefore suggest that Htt is required for the maintenance of basal ganglia circuit integrity. Moreover, these specific deletions of *Htt* either in dSPNs or iSPNs induce HD-like alterations in adulthood, evidenced by SPN loss, motor alterations, and reactive gliosis observed in 10 month-old mice (Burrus et al., 2020).

Together these findings suggest that the adult alterations are caused, at least in part, by the loss of function of the protein during the earlier developmental period. However, as Htt is normally reduced or depleted constantly throughout life, the results obtained in the above studies could also be due to the continuous loss of the protein's function. To address this possibility, a recent paper studied the specific role of Htt during neural development by reducing Htt expression for a limited period, from embryonic stages until PND21 (Arteaga-Bracho et al., 2016). This experiment induced striatal developmental alterations with ectopic tissue masses observed in the striatum both in the embryo and postnatal stages. In the embryonic stage, the cells within these masses expressed both SPN progenitor markers, *Isl1* and *Ctip2*, and the interneuron marker, *Nkx2.1*. In addition, at PND10 these cells expressed both calbindin and  $\mu$ -opioid receptors, which are specific markers of matrix and striosomes, respectively. These results indicated that the loss of Htt induces early deficits in the specification, migration and organization of striatal circuitry, thereby underlining the crucial role Htt plays in striatal development. Moreover, the same progressive HD-like phenotype is observed in the adult stage, with striatal neurodegeneration and astrogliosis as well as motor deficits (gait disturbances and motor coordination alterations) occurring. These latter results therefore suggest that a loss of Htt during neural development is also involved in the neurodegeneration observed in later life. These findings are also consistent with studies on induced pluripotent stem cells (iPSCs) from HD patients in culture, which revealed a deregulation of genes such as *Ctip2*, *DARPP-32* and *Isl1* involved in striatal development (Conforti et al., 2018; Ring et al., 2015; The HD iPSC Consortium, 2017; for review: Wiatr et al., 2018). One explanation proposed is that the lack of Htt during development increases the subsequent vulnerability of striatal neurons to cell death (Arteaga-Bracho et al., 2016; Fu et al., 2018; Mehler and Gokhan, 2001; Rikani et al., 2014). This idea is consistent with the role of Htt in striatal neuron survival through its actions on cortico-striatal pathways (see § III.1.). Finally, it has been shown that a deletion of *Htt* in the developing cortex leads to an aberrant increase in cortico-striatal synapse formation and SPN dendritic spine maturation, suggesting that cortical Htt is important for negatively regulating synaptic connectivity between the cortex and striatum (McKinstry et al., 2014).

All these studies in which Htt expression levels have been manipulated therefore shed light on the functions of the protein with respect to the development of the striatum. Importantly, Htt appears to be crucial for the correct cytoarchitectural organization of striatal circuitry into striosomes and matrix.

### 3.3. Evidence for abnormal striatal neurodevelopment in mouse models of HD

Following identification of the mutation of the gene that encodes the Htt protein, a number of mouse models of HD have been developed. These models can be classified into 3 major groups, the transgenic fragment models, the transgenic full-length models and the knock-in models. Each model displays a range of HD-like characteristics with various time frames of manifestation (Pouladi et al., 2013). It is of note that the loss of expression described in the section above is distinct from the dominant nature of the expression of the mutated Htt in mouse models of HD. Compared to the numerous studies focusing on the neurodegenerative alterations in HD, few studies have provided lines of evidence on the neurodevelopmental aspect of HD. These latter studies showed that several characteristics of striatal development appear to be impaired in HD mice models. A first study using Htt-Q111 mice, a knock-in model in which the murine *Htt* gene exon 1 was replaced by the corresponding human mutant form with a 111 poly-Q stretch, showed alterations in different steps of striatal development from embryonic SPN specification to striatal organization (Molero et al., 2009). In this transgenic line, spatio-temporal striatal neurogenesis is altered with a delayed cell cycle exit of striatal IPs leading to reduced number of striatal NeuN+ neurons at E17.5. This delay in turn impacts on physiological neurogenesis and the formation of early striosomal and matrix cells. Moreover, the volume of progenitor cells appears enhanced and most of these cells express abnormal morphologies with irregular and invaginated nuclei. As a consequence, this abnormal specification profoundly affects the striatal cytoarchitecture in the postnatal period with the expression of the striosomal marker,  $\mu$ -opioid receptor, being reduced at PND2 whereas the matrix marker, calbindin, displays an altered mosaic pattern at PND7. These defects were only observed in the striatum, suggesting a specific altered maturation and enhanced vulnerability of striatal neurons (Molero et al., 2009). In this context, it is noteworthy that *in vitro* analyses of induced pluripotent stem cells derived from HD patients (Mathkar et al., 2019) or human embryonic stem cells bearing the HD mutation (Ruza et al., 2018) also display delayed progenitor differentiation as well as an increased volume of progenitors cells with abnormal morphologies. Moreover, in zQ175 mice, a full length knock-in model with a poly-Q stretch ranging between 175 and 200, the maturation of striatal dendritic spines appears to be accelerated at PND21 without any significant change in either cortical or thalamic striatal synapse numbers (McKinstry et al., 2014). However, in Q140 mice, a knock-in model with 140 CAG repeats inserted into the mouse gene, the number of VGLUT2-positive axodendritic thalamic terminals is decreased by 40% in the striatum at 1 month compared to wild-type mice (Deng et al., 2013). These studies thus suggest that striatal circuit maturation is impaired in a dynamic and complex manner during the first post-natal weeks. Interestingly, a recent study has shown that a selective expression of mHtt only during development, from the embryonic phase to PND21, is sufficient to induce an HD-like phenotype in later adult stages, specifically involving striatal neurodegeneration, motor coordination impairments, altered corticostriatal connectivity and striatal electrophysiological activity changes (Molero et al., 2016). Together these findings are therefore consistent with the conclusion that the *Htt* mutation induces developmental changes that will, in part, lead to the progressive neurodegenerative features of the disease.

### 3.4. Concluding remarks/Future directions

The various studies discussed in this review highlight the complexity of the striatum's normal development as well as the deleterious effects of a loss of wild-type Htt function or *Htt* mutation on striatal development and HD pathogenesis (Burrus et al., 2020; Lopes et al., 2016). Indeed, strong alterations in striatal cytoarchitectural and corticostriatal connectivity are observed when Htt expression is decreased.

Similarly, the expression of mHtt induces a delayed specification of striatal progenitors resulting in striatal network modification. Moreover, both low levels of Htt or the expression of mHtt restricted to the embryonic and early postnatal period, when striatal neurogenesis occurs, are sufficient to induce an HD-like phenotype in adulthood. It has been suggested that striatal developmental alterations induced by the decreased expression of Htt and/or expression of mHtt may enhance the vulnerability to cell death of striatal neurons and lead to neurodegeneration and motor alterations later in life (Fu et al., 2018; Rikani et al., 2014). However, whether developmental defects or HD pathogenesis are due to a gain-of-function of mHtt or a loss-of-function of wt Htt is unclear (Arteaga-Bracho et al., 2016). Clearly, a better understanding of the specific mechanisms underlying such disruptions of striatal development is needed before realistic attempts can be made to reverse these processes and potentially avoid the neurodegenerative features observed in later life.

Since a striatal hypertrophy was observed in human studies on pre-HD children (van der Plas et al., 2019), it would be interesting to determine whether striatal neuron numbers are also increased in HD mice models during the early postnatal period. As mentioned earlier, during the first postnatal week, the striatum undergoes a cell death period during which 30% of striatal neurons die. Therefore, it is possible that the number of striatal neurons dying during this period is reduced in the HD-phenotype, leading to a striatal hypertrophy. Moreover, it was shown that striatal neurons with already projecting striatofugal axons survive more during this cell death period (Fishell and Van Der Kooy, 1991). It is thus tempting to hypothesize that the striatal hypertrophy observed in humans is due to an enhanced maturation of striatal neurons that project their striatofugal axons earlier. In this perspective, it could also be instructive to look at a possible precocious establishment of striatofugal outputs in mice models of HD during the embryonic and postnatal periods.

The different aspects discussed in this review reinforce the conclusion that the neurodevelopmental aspect of HD should be considered in HD treatments. Given the paucity of studies both in HD patients and rodent models of HD, further investigations are needed to confirm results already obtained and to shed new light on the mechanisms leading to striatal development defects.

### Acknowledgements

M.L. is supported by a PhD fellowship from the Association Huntington France. This work was supported by the Labex Brain (ANR-10-LABX-43). University of Bordeaux and Centre National de la Recherche Scientifique (CNRS) provided infrastructural support.

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