

Review

From Progenitors to Progeny: Shaping Striatal Circuit Development and Function

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Understanding how neurons of the striatum are formed and integrate into complex synaptic circuits is essential to provide insight into striatal function in health and disease. In this review, we summarize our current understanding of the development of striatal neurons and associated circuits with a focus on their embryonic origin. Specifically, we address the role of distinct types of embryonic progenitors, found in the proliferative zones of the ganglionic eminences in the ventral telencephalon, in the generation of diverse striatal interneurons and projection neurons. Indeed, recent evidence would suggest that embryonic progenitor origin dictates key characteristics of postnatal cells, including their neurochemical content, their location within striatum, and their long-range synaptic inputs. We also integrate recent observations regarding embryonic progenitors in cortical and other regions and discuss how this might inform future research on the ganglionic eminences. Last, we examine how embryonic progenitor dysfunction can alter striatal formation, as exemplified in Huntington's disease and autism spectrum disorder, and how increased understanding of embryonic progenitors can have significant implications for future research directions and the development of improved therapeutic options.

Key words: embryonic progenitors; lateral ganglionic eminence; medial ganglionic eminence; neuronal diversity; striatum; basal ganglia; spiny projection neurons; interneurons

Significance Statement

This review highlights recently defined novel roles for embryonic progenitor cells in shaping the functional properties of both projection neurons and interneurons of the striatum. It outlines the developmental mechanisms that guide neuronal development from progenitors in the embryonic ganglionic eminences to progeny in the striatum. Where questions remain open, we integrate observations from cortex and other regions to present possible avenues for future research. Last, we provide a progenitor-centric perspective onto both Huntington's disease and autism spectrum disorder. We suggest that future investigations and manipulations of embryonic progenitor cells in both research and clinical settings will likely require careful consideration of their great intrinsic diversity and neurogenic potential.

Introduction

Understanding how neuronal cell identity and precise synaptic circuits in the brain emerge during development remains a fundamental goal in neuroscience. The discovery of radial glial cells (RGCs) as the main progenitor cell in the developing nervous system, and observations that RGCs can give rise not only to neurons, but also to a diverse population of additional

progenitors, have made understanding the functional roles and contributions of progenitors to brain development a key focus for neuroscientists. Indeed, it is becoming increasingly clear that the remarkable diversity of embryonic progenitors is directly linked to the neuronal diversity, synaptic connectivity, and circuit function in a variety of regions in the adult brain (Yu et al., 2009; 2012; Tyler et al., 2015; Kelly et al., 2018; Ellender et al., 2019; Guillamon-Vivancos et al., 2019; Matsushima and Graybiel, 2020; van Heusden et al., 2021). This review will focus on the roles for diverse embryonic progenitors in shaping the development and properties of one brain region, the striatum.

The striatum is the main input nucleus of the basal ganglia, a group of interconnected subcortical nuclei that have critical functional roles in motor behavior, learning, and cognition (Graybiel et al., 1994; Grillner et al., 2005; Yin and Knowlton, 2006; Kravitz et al., 2010; Cui et al., 2013; Tecuapetla et al., 2016), and it has been ascribed key computational roles in action

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selection, decision-making, and reinforcement learning (Redgrave et al., 1999; Reynolds et al., 2001; Samejima et al., 2005; Bogacz and Gurney, 2007; Yartsev et al., 2018). The striatum is a relatively large brain nucleus, consisting of over a million neurons in the mouse. The neurons can be divided into the GABAergic spiny projection neurons (SPNs), which make up ~95% of all striatal neurons, and a diverse population of interneurons, which make up the remaining ~5% (Kreitzer and Malenka, 2008; Tepper et al., 2010, 2018). The SPNs are classically divided into the direct pathway dopamine D₁ receptor-expressing SPN (dSPN) and the indirect pathway dopamine D₂ receptor-expressing SPN (iSPN) types, respectively forming the striatonigral and striatopallidal pathways and sending major projections to the substantia nigra pars reticulata (SNr)/internal globus pallidus (GPi) or the external GP (GPe; Gerfen et al., 1990; Day et al., 2008; Gertler et al., 2008). The resident striatal interneuron population can be subdivided into cholinergic interneurons (CINs) and a diverse group of GABAergic interneurons.

At first glance, the striatum has a less obvious structure than other brain regions. For example, the cortex exhibits a distinct laminar organization with various layers forming sequentially during progressive embryonic periods, and each layer consisting of distinct cell types (Douglas and Martin, 2004). In contrast, the striatum seems to consist of vast numbers of intermingled dSPNs, iSPNs, and interneurons. However, several organizing principles of the striatum exist and are applicable to large populations of diverse striatal cells. These include distinct functional domains related to specific anatomic subregions of striatum (Graybiel and Ragsdale, 1978; Alexander et al., 1986; Graybiel, 1990; Haber, 2008; Pan et al., 2010; Oh et al., 2014; Hintiryan et al., 2016; Hunnicutt et al., 2016; McGregor et al., 2019; Lee et al., 2020). Indeed, one classical distinction divides the striatum into the dorsolateral striatum (DLS) and dorsomedial striatum (DMS), with each anatomic subregion receiving innervation from different cortical and thalamic areas (McGeorge and Faull, 1989; Voorn et al., 2004; Smith et al., 2014). Other distinctions are based on differential expression of a set of neurochemical markers, for example, the μ -opioid receptor, which segregates large populations of dSPNs, iSPNs, and associated interneurons into μ -opioid-rich striosome/patch compartments and μ -opioid-poor matrix compartments (Pert et al., 1976; Graybiel and Ragsdale, 1978; Herkenham and Pert, 1981; Graybiel, 1990; Crittenden and Graybiel, 2011), which are thought to differentially control reward-guided behavior (Gerfen, 1984, 1989; Fujiyama et al., 2011). This review will discuss the role of diverse embryonic progenitors in shaping these and other striatal subregions.

Aberrant development and integration of diverse striatal neurons into circuits can lead to a wide range of disorders with motor and cognitive symptoms (Arber et al., 2015; Peixoto et al., 2019). We further this discussion by addressing how embryonic progenitors generate diverse populations of striatal neurons as well as exploring a growing body of literature suggesting that pathologies such as Huntington's disease (HD) and autism spectrum disorder (ASD) arise from aberrant embryonic progenitor behavior. Furthermore, we discuss throughout the recent advances in technology that allow more sophisticated labeling and manipulation of embryonic progenitors, thus opening possibilities for both novel investigations and potential development of treatment options. Finally, where questions remain regarding the development of the striatum, we provide hypotheses and insights from studies in the cortex and other brain regions.

Embryonic progenitors of the ventral telencephalon

All neural progenitors descend from the neuroepithelial cells that form the neural tube in the developing embryo. After

closure of the neural tube, distinct rostral, medial, and caudal regions develop to ultimately give rise to the frontal, middle, and hindbrain regions of the brain (Stiles and Jernigan, 2010). This review mainly focuses on the developing rostral region, the telencephalon, in relation to the striatum; for a focus on basal ganglia development, see the study by Rubenstein and Campbell (2020).

A combination of morphogenetic movements and proliferation between embryonic day 9 (E9) and E11 in mice establishes further discrete proliferative regions in the rostral telencephalon, a dorsal region that gives rise to the cortex, a ventrolateral region that forms the lateral ganglionic eminence (LGE) and mainly gives rise to the SPNs of the striatum (Deacon et al., 1994; Olsson et al., 1998; Wichterle et al., 2001; Nery et al., 2002); and a ventromedial region forming the medial ganglionic eminence (MGE) that gives rise to the interneurons of the striatum, globus pallidus, and cortex, among others (Marin et al., 2000; Anderson et al., 2001; Rallu et al., 2002; Butt et al., 2005; Flandin et al., 2010; Dodson et al., 2015). In addition, adjacent ventral structures such as the caudal ganglionic eminence (CGE; Nery et al., 2002; Ma et al., 2012; Muñoz-Manchado et al., 2016), preoptic area (POA)/anterior entopeduncular area (Marin et al., 2000; Gelman et al., 2011), and septal neuroepithelium (SNE; Magno et al., 2017) also give rise to interneurons (Marin et al., 2000; Fig. 1A). Initial gradients of diffusible factors (Rallu et al., 2002) and distinct transcription factor cascades (Schuurmans and Guillemot, 2002; Silberberg et al., 2016) contribute to this dorsoventral regional patterning.

The first neuronal progenitor cells (NPCs) in each of these regions consist mainly of RGCs, which divide at the ventricular wall to generate further progenitors that inhabit both the ventricular zone (VZ) and subventricular zone (SVZ) and young neurons that migrate to the primordial striatum and other structures (Marin et al., 2000). The daughter progenitor cells consist of additional RGCs plus a diverse population of intermediate progenitors (IPs; Fig. 1B). These IPs can amplify the number of concurrently actively dividing cells in the developing brain (Noctor et al., 2004) and, as discussed later, convey unique properties to their daughter neurons. As progenitors divide, postmitotic neurons of the ventral telencephalon follow a well defined developmental sequence starting with their migration from their birthplace to their designated brain regions (Villar-Cerviño et al., 2015), progressively differentiating toward their final identity. During later postnatal stages, these immature neurons initially connect widely followed by periods of synaptic refinement and controlled apoptosis in maturing circuits (Fig. 1C). At approximately E18 in mice, the neurogenic divisions within the embryonic brain switch and become gliogenic, generating both astrocytes and oligodendrocytes (Anthony and Heintz, 2008; Minocha et al., 2017; Turrero Garcia and Harwell, 2017). Although this review will mainly focus on progenitor-derived neurons, the extent to which the diversity of embryonic progenitors is related to astrocyte and oligodendrocyte diversity is likely an interesting line of future research.

Embryonic progenitors of the LGE and their progeny

The formation of the LGE as a clearly visible structure in the subpallium occurs around E11 in mice and is followed by the onset of neurogenesis by a diverse population of neurogenic progenitors that inhabit the VZ and SVZ (Halliday and Cepko, 1992; Sheth and Bhide, 1997; Olsson et al., 1998; Stenman et al., 2003; Gotz and Huttner, 2005; Mason et al., 2005; Sousa and Fishell,

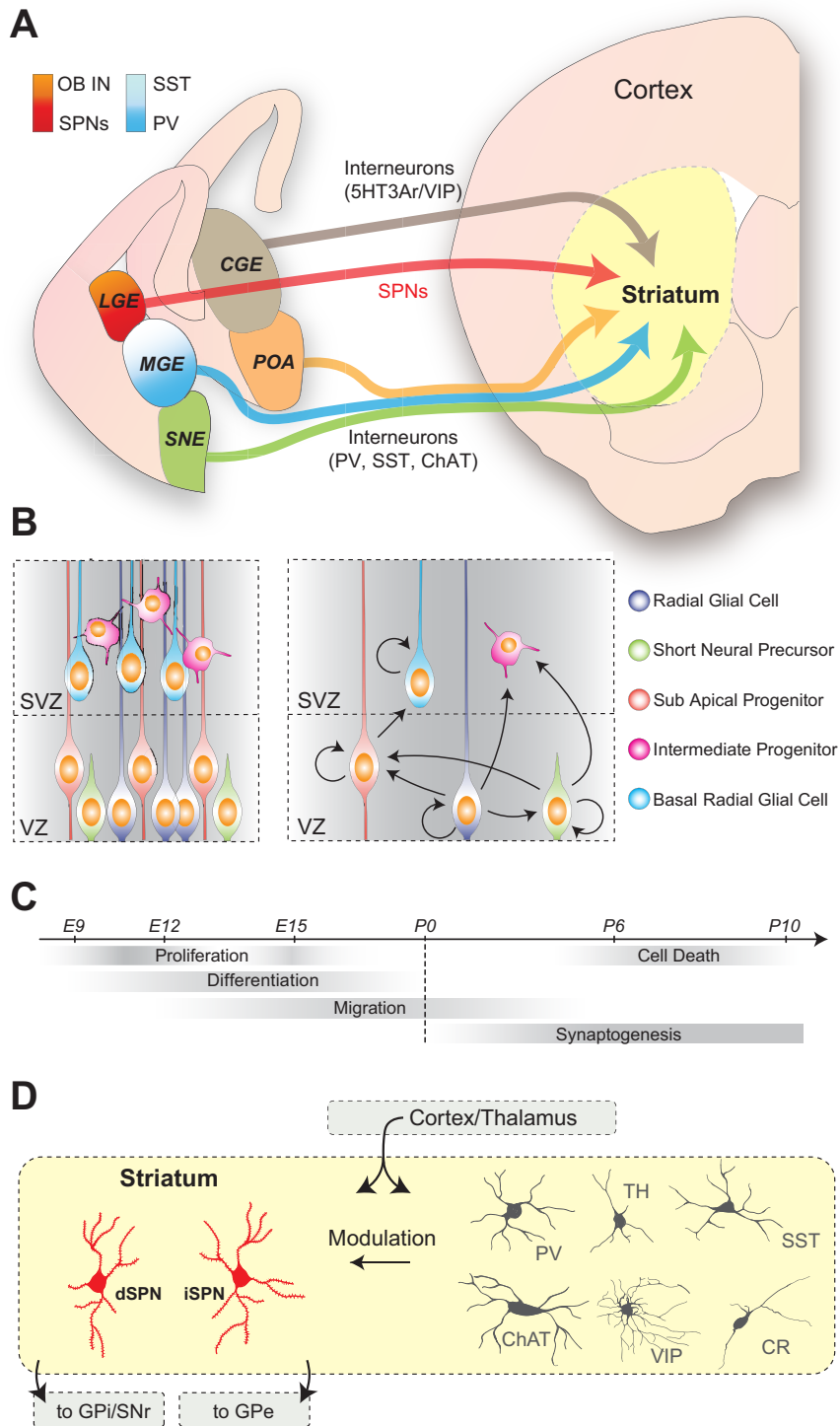


Figure 1. Striatal cells arise from diverse progenitor populations in the ganglionic eminences and neighboring structures. **A**, The embryonic domains that give rise to striatal fated cells include the LGE, MGE, CGE, POA, and SNE. Further gradients can be found within the eminences (e.g., dorsal LGE is a major source of OB interneurons and ventral LGE gives rise to SPNs), and SST interneurons are preferentially derived from dorsal MGE, while PV interneurons are preferentially derived from ventral MGE. **B**, Left, Embryonic progenitors can be segregated into different groups: the apical progenitors of the VZ, including radial glial cells; subapical progenitors and short neural precursors; and the basal progenitors of the SVZ, which can be separated into bRGCs and other IPs (e.g., basal progenitors). Right, The arrows represent the possible outcomes of progenitor division. **C**, Cells undergo broadly conserved steps of maturation, including proliferation, differentiation, and migration followed by refinement of circuitry through synaptogenesis and controlled apoptosis. **D**, The main excitatory inputs to striatum come from cortex and thalamus, which innervate both the SPNs (left) and interneurons (right). SPNs include both the dSPNs (in red) and the iSPNs (in red), which send axonal projections to downstream basal ganglia nuclei including, respectively, the SNr/GPi and GPe. The local populations of diverse interneurons are integrated within the striatum and can modulate the activity of SPNs. VIP, Vasoactive intestinal polypeptide.

2010; Pilz et al., 2013; Kelly et al., 2018; van Heusden, 2021, #6256). The VZ of the LGE is thought to contain several types of embryonic progenitor cells, of which the following two divide at the ventricular surface: classic RGCs with a bipolar morphology that exhibit a basal and apical process during division; and short neural precursors (SNPs), which exhibit a rounded morphology and tend to lack processes during division. Other progenitors (OPs) in the VZ have been shown to divide at subapical positions away from the ventricular surface; these have been named subapical progenitors (SAPs; Pilz et al., 2013). Finally, the SVZ contains progenitor types that lack a process during division and resemble basal progenitors (BPs), as well as progenitors that retain one or more processes and resemble RGCs. The latter progenitors divide in the basal aspects of the LGE and are called basal RGCs (bRGCs; Pilz et al., 2013; Fig. 1B). Detailed analysis of lineage progression among these progenitor types suggests that the majority of LGE RGCs generates daughter progenitor cells, which continue to divide without directly generating postmitotic neurons (Pilz et al., 2013). This is unlike RGCs in the cortex and MGE (Kriegstein and Alvarez-Buylla, 2009) and suggests that most striatal SPNs are generated from IPs. Indeed, lineage analysis suggests that LGE RGCs generate mainly additional RGCs, SNPs, or SAPs. In turn, the SNPs mostly generate further SNPs or SAPs, while SAPs generate further SAPs, BPs, or postmitotic neurons (Pilz et al., 2013; Fig. 1B). Many of these embryonic progenitors are not unique to the LGE and have also been characterized in detail in proliferative zones of the cortex (Noctor et al., 2001, 2004; Gal et al., 2006; Kowalczyk et al., 2009; Stancik et al., 2010; Shitamukai et al., 2011; Wang et al., 2011; Franco and Müller, 2013; Taverna et al., 2014), although their properties can differ between these structures. For example, cortical SNPs tend to have relatively long cell cycle kinetics and often generate neurons directly (Gal et al., 2006; Stancik et al., 2010; Tyler and Haydar, 2013), whereas those in the LGE tend to have relatively short cell cycle kinetics and produce further progenitors (Pilz et al., 2013).

The morphologic diversity of LGE progenitors coexists alongside broader divisions of LGE based on differential transcription factor expression. For example, the transcription factor *ETV1/Er81* delineates the dorsal regions of the LGE, which can be further subdivided into a lateral subregion, with high expression of the transcription

factors paired-box protein 6 (*Pax6*) and Genetic-Screened Homeobox 2 (*Gsh2*) and bordering the cortex (Yun et al., 2001; 2003), and a more medial region with low *Pax6* expression but high *Gsh2* expression (Flames et al., 2007). Other studies have revealed that the dorsally situated *Etv1/Er81*⁺ progenitors tend to generate olfactory bulb (OB) fated interneurons, whereas the more ventrally located *Isl1*⁺ progenitors supply SPNs of the striatum, thus providing the first evidence that distinct progenitor domains generate distinct neuron populations (Yun et al., 2001; Stenman et al., 2003; Fig. 1A).

Specific transcription factors, such as GS Homeobox 1/2 (*Gsx1/2*), achaete-scute homolog 1 (*Ascl1*), and Distal-Less Homeobox 1/2 (*Dlx1/2*), as well as Notch signaling, mediate cell-autonomous and nonautonomous regulation of neurogenesis in the LGE and control ordered production of striatal neurons (Yun et al., 2002; Mason et al., 2005). These can further delineate different LGE VZ and SVZ regions (Puelles et al., 2000; Toresson et al., 2000; Yun et al., 2001; Stenman et al., 2003; Flames et al., 2007; Petryniak et al., 2007; Wang et al., 2013). Key in this process are the *Gsx* (Corbin et al., 2000; Toresson et al., 2000; Yun et al., 2001; 2003; Wang et al., 2013; Roychoudhury et al., 2020; Salomone et al., 2021) and *Dlx* gene families expressed during the maturation of both progenitors and neurons in the LGE (Porteus et al., 1991; 1994; Anderson et al., 1997; Liu et al., 1997; Eisenstat et al., 1999) and governing further downstream transcriptional networks controlling LGE and striatal development (Long et al., 2009; Lindtner et al., 2019). Indeed, it has been suggested that the early LGE contains *Gsx1/2*⁺ neuroepithelial cells that produce multiple progenitor types characterized by *Ascl1* and *Dlx* expression (Yun et al., 2002; Martín-Ibáñez et al., 2012). The *Ascl1*⁺/*Dlx1/2*⁻ and *Ascl1*⁺/*Dlx1/2*⁺ progenitors are inferred to emerge in sequence (Martín-Ibáñez et al., 2012) and interact through Notch-mediated lateral inhibition to coordinate both proliferation and neurogenesis (Mason et al., 2005). The progenitors within the LGE can be further distinguished through differential transcription factor expression from those found in neighboring eminences. For example, the MGE expresses the transcription factors NK2 Homeobox 1 (*Nkx2.1*) and LIM/homeobox protein 6 (*Lhx6*), whereas the LGE does not (Chen et al., 2017; Mayer et al., 2018).

From this transcriptional and morphologically diverse population of embryonic progenitors in the LGE, the vast majority of postmitotic neurons become GABAergic striatal SPNs, with a smaller population maturing into OB interneurons (Wichterle et al., 1999; Corbin et al., 2001; Wichterle et al., 2001; Stenman et al., 2003). The generation of SPNs starts at approximately E10.5 and continues until birth, E19.5, in mice (Deacon et al., 1994; Sheth and Bhidé, 1997; Matsushima and Graybiel, 2020; Fig. 2B), although some are also born during early postnatal stages (Das and Altman, 1970; Bayer, 1984; Wright et al., 2013). The orderly production of early- and late-born SPNs within the LGE is regulated in part through various downstream transcription factors (e.g., *Ebf1*, *Isl1*, *Sp9*; Zhang et al., 2016; Merchan-Sala et al., 2017), which can regulate SPN subtype generation and survival, as well as allowing for their selective labeling during early development (Merchan-Sala et al., 2017). Indeed, for the generation of dSPNs it has been shown that the transcription factor *Isl1* is important (Ehrman et al., 2013; Lu et al., 2014), with conditional loss leading to early cell death of newly born dSPNs (Ehrman et al., 2013), likely through loss of *Foxo1* expression (Waclaw et al., 2017). Additional factors such as *ebf1* also play a role in SPN survival (Lobo et al., 2006; 2008), but with loss mainly affecting dSPNs during later stages of neurogenesis. For the generation

and survival of iSPNs, it has been shown that the transcription factors *Ikaros* and *Helios* are important and also regulate the expression of the iSPN marker enkephalin (Martín-Ibáñez et al., 2010, 2012). In addition, the expression of the transcription factors *sp8* and *sp9* (Long et al., 2009; Zhang et al., 2016) are further required for iSPN survival as double knockout (KO) results in a nearly complete loss of iSPNs (Xu et al., 2018), similar to KO of their downstream transcription factor *six3* (Song et al., 2021).

Embryonic progenitors of the MGE and their progeny

Striatal interneurons, which exert a strong regulatory control over SPN activity and consequently striatal output, are derived primarily from the MGE (Fig. 1A). Therefore, we will first outline what is currently known about MGE progenitors and subsequently introduce the progenitors in other structures that produce the remaining striatal interneurons.

Like the LGE, the MGE arises from the ventral region of the neural tube at approximately E9.5 and is divided into the VZ and SVZ progenitor zones. In the VZ, the primary progenitor is the RGC, which, in addition to self-replication, can give rise to other progenitors and neurons (Turrero Garcia and Harwell, 2017). Other progenitors in the MGE include SAPs and SNPs of the VZ, in addition to other IPs and bRGCs of the SVZ (Turrero Garcia and Harwell, 2017; Fig. 1B). The generation of such progenitors occurs in a lineage-specific manner; for example, SNPs arise from the direct division of RGCs, whereas the generation of bRGs is achieved through SAP intermediates (Pilz et al., 2013; Petros et al., 2015; Fig. 1B).

As in the LGE, the morphologic diversity of embryonic progenitors in the MGE is accompanied by heterogeneity in the combinatorial expression of different transcription factors (Flames et al., 2007; Flandin et al., 2010; Lopes et al., 2012). *In situ* hybridization studies for multiple target genes such as *Dlx2*, *Pax6*, *Nkx2.1*, *Lhx6*, and *Lhx7* have revealed subdomains formed by groups of transcriptionally similar progenitors that are localized to specific regions of the MGE (Flames et al., 2007). Each of these genes plays a distinct role in the control of cell identity within the subdomains. For example, *Dlx* genes drive the upregulation of the GABA-synthesizing enzyme glutamic acid decarboxylase and delineate the GABAergic interneurons (Stuhmer et al., 2002; Le et al., 2017). Local populations of APs and BPs can also be further divided into subpopulations based on their transcriptional identity, which controls their metabolism, cell cycle dynamics, or overall neurogenic role. For example, one population of APs displays high expression of the genes required for oxidative phosphorylation (*Atp5e* and *Cox6c*), whereas another population of APs highly expresses DNA replication genes (*Mcm5*, *Mcm6*, and *Mcm7*) and translation regulators (*Eif4g1*, *Eif2s1*, and *Eif3b*; Chen et al., 2017). On the other hand, BPs can be divided into two populations based on the expression levels of glutamic acid decarboxylase 2 (*Gad2*) and aristaless-related homeobox (*Arx*), which represses the inhibition of cell cycle progression (Lim et al., 2019). Coexpression of *Coup-TF1* and *Coup-TF2* in distinct progenitor subdomains of the MGE directly controls cell cycle dynamics and neurogenic differentiation (Hu et al., 2017). Upon *CoupTF2* ablation, cell proliferation is perturbed, and the resulting cell fate is shifted. Thus, distinct progenitors in the MGE show different transcriptional and functional properties, which likely contribute to the generation of striatal interneuron diversity.

MGE progenitors give rise to a widely heterogeneous and dispersed population of interneurons that populate brain areas such

as the cortex, hippocampus, globus pallidus, and nucleus accumbens (Marin et al., 2000), and can be differentiated based on their chemical, electrical, and morphologic properties. The primary striatal interneuron subtypes are identified by their expression of parvalbumin (PV), somatostatin (SST), or choline acetyltransferase (ChAT) and are diverse regarding their connectivity patterns and intrinsic properties. For example, PV⁺ fast-spiking interneurons form short-range connections with SPNs and exert strong inhibition that can regulate action potential initiation in both dSPNs and iSPNs, thus mediating feedforward inhibition over striatal output (Mallet et al., 2005; Gittis et al., 2011; O'Hare et al., 2017; Owen et al., 2018). These fast-spiking interneurons receive dense innervation from the cortex, with smaller inputs from both thalamic projections and striatal ChAT⁺ CINs, and output to multiple SPNs with firing rates of up to 400 Hz through their dense axonal field (Kita, 1993). In contrast, SST⁺ interneurons coexpress one or both of the neurochemical markers neuropeptide Y (NPY) and nitric oxide synthase, and are commonly referred to as low-threshold spiking interneurons (Kawaguchi et al., 1995; Muñoz-Manchado et al., 2016, 2018). These neurons are also primarily innervated by monosynaptic, excitatory inputs coming from cortex, but they differ from PV⁺ interneurons in that they form longer-range connections with SPNs and show significantly lower levels of connectivity (Assous et al., 2019). Moreover, these neurons are innervated by CINs and mediate cholinergic-mediated feedforward inhibition (English et al., 2011). Finally, the CINs display a range of transcriptional, morphologic, and physiological properties (Magno et al., 2017; Muñoz-Manchado et al., 2018). For example, it has been shown that the transcription factors *Lhx6* and *ETV1/Er81* segregate striatal CINs into functional subtypes (Lozovaya et al., 2018; Ahmed et al., 2019, 2021). In particular, the *Lhx6*-expressing CINs, also called cholinergic-GABAergic interneurons (Lozovaya et al., 2018), display different physiological properties with higher firing rates and larger dendritic fields compared with other CINs. Indeed, coexpression of neurotransmitters such as acetylcholine, glutamate, and GABA in different CINs further highlights their functional diversity (Nelson et al., 2014; Granger et al., 2016). Newly developed approaches [e.g., adeno-associated virus (AAV)-based tools; Vormstein-Schneider et al., 2020; Table 1] will help to selectively label and further study these diverse interneurons.

Other embryonic progenitors and their progeny

While most striatal interneurons are derived from the MGE, smaller populations originate from other embryonic structures, including the POA and SNE, which are both situated ventrally to the MGE, as well as the CGE (Marin et al., 2000; Ma et al., 2012; Fig. 1A). The CGE is a chemically distinct proliferation domain originating from the caudal merging of the MGE and LGE, and is classically defined by the expression of the 5HT_{3a} serotonin receptor (Nery et al., 2002; Lee et al., 2010; Fig. 1C). The peak proliferation of CGE-derived NPCs occurs 3 d after that of MGE-derived progenitors (Miyoshi et al., 2010). Approximately 20% of the CGE-derived neurons contribute to a population of striatal PV⁺ fast-spiking interneurons (Miyoshi et al., 2010) and specifically express 5HT_{3a} (Muñoz-Manchado et al., 2016). The remaining interneurons include a unique population of late-spiking neurogliaform cells and low-threshold spiking cells, both of which lack the expression of known interneuron markers (Muñoz-Manchado et al., 2018). Other striatal interneuron subtypes include a substantial population of tyrosine hydroxylase-

positive (TH⁺) interneurons comprising electrophysiologically distinct cell subtypes (Mao et al., 2019). Striatal TH⁺ interneurons are not dopaminergic, but rather are a type of GABAergic interneuron that expresses TH without the other requisite enzymes or transporters to operate as dopaminergic neurons. These interneurons play an important role in striatal function through fast GABAergic synaptic transmission. They respond to local or cortical stimulation with glutamatergic EPSPs and exert widespread GABAergic inhibition onto both dSPNs and iSPNs, and between CINs (Xenias et al., 2015; Dorst et al., 2020). Modulation of the properties of TH⁺ interneurons by dopamine and acetylcholine may play important roles in mediating the striatal effects of these neuromodulators, with potentially important implications in disorders affecting the striatum (Ibáñez-Sandoval et al., 2015). The positional fate, morphology, and neurochemical identity of CGE-derived interneurons in cortex were shown to be dependent on the progenitor domain from which they arise (Torigoe et al., 2016), but no evidence has directly reported whether this extends to the CGE-derived interneurons of the striatum.

Interestingly, progenitors of the POA and SNE express the transcription factor *Nkx2.1* and also generate neurons expressing ChAT⁺, PV⁺, and SST⁺ (Marin et al., 2000; Fig. 1A). As smaller contributors to the overall interneuron populations in the cortex and striatum, these regions have been somewhat neglected, so further investigation is needed. This is highlighted by the fact that the morphologic properties of SNE and POA progenitors are not yet clearly defined within the literature. Yet, it is known that POA progenitors are transcriptionally distinct from those in the MGE, expressing transcriptional markers such as brain homeobox protein 1 (*Dbx1*) and sonic hedgehog (*Shh*; Gelman et al., 2009).

Finally, a small subpopulation of Empty Spiracles Homeobox 1-lineage (*Emx1*) cells originating in the cortical proliferative zones seem to migrate into the developing striatum during early prenatal development (Willaime-Morawek et al., 2006) and differentiate primarily into DARPP-32⁺ SPNs and a small number of calretinin-positive (CR⁺) striatal interneurons (Cocas et al., 2009). In addition, a small population of SPNs has also been shown to arise from the CGE (Nery et al., 2002).

It is largely unknown how the heterogeneity of embryonic progenitors based on their location of division (e.g., VZ and SVZ), morphology, and cell cycle kinetics maps onto the transcriptional heterogeneity seen in the ganglionic eminences. This is important to understand, not only to further our understanding of progenitor diversity and lineage progression, but also because it might reveal a cohesive framework for labeling and tracking these populations of progenitors during embryogenesis, as well as following their development and neuronal progeny. Endeavors to map the genetic diversity within the ganglionic eminences at the single-cell level (Mayer et al., 2018; Mi et al., 2018) will further these efforts but is complicated because of the highly dynamic nature of their transcriptional profiles (Li et al., 2020).

From ganglionic eminences to postnatal striatum

The LGE and MGE generate the majority of the neurons found in the postnatal striatum. From these embryonic domains, postmitotic cells must first migrate through the mantle zone, the superficial layer beyond the SVZ that contains neurons at various stages of migration and differentiation, before proceeding to the primordial striatum, where they integrate into functional striatal

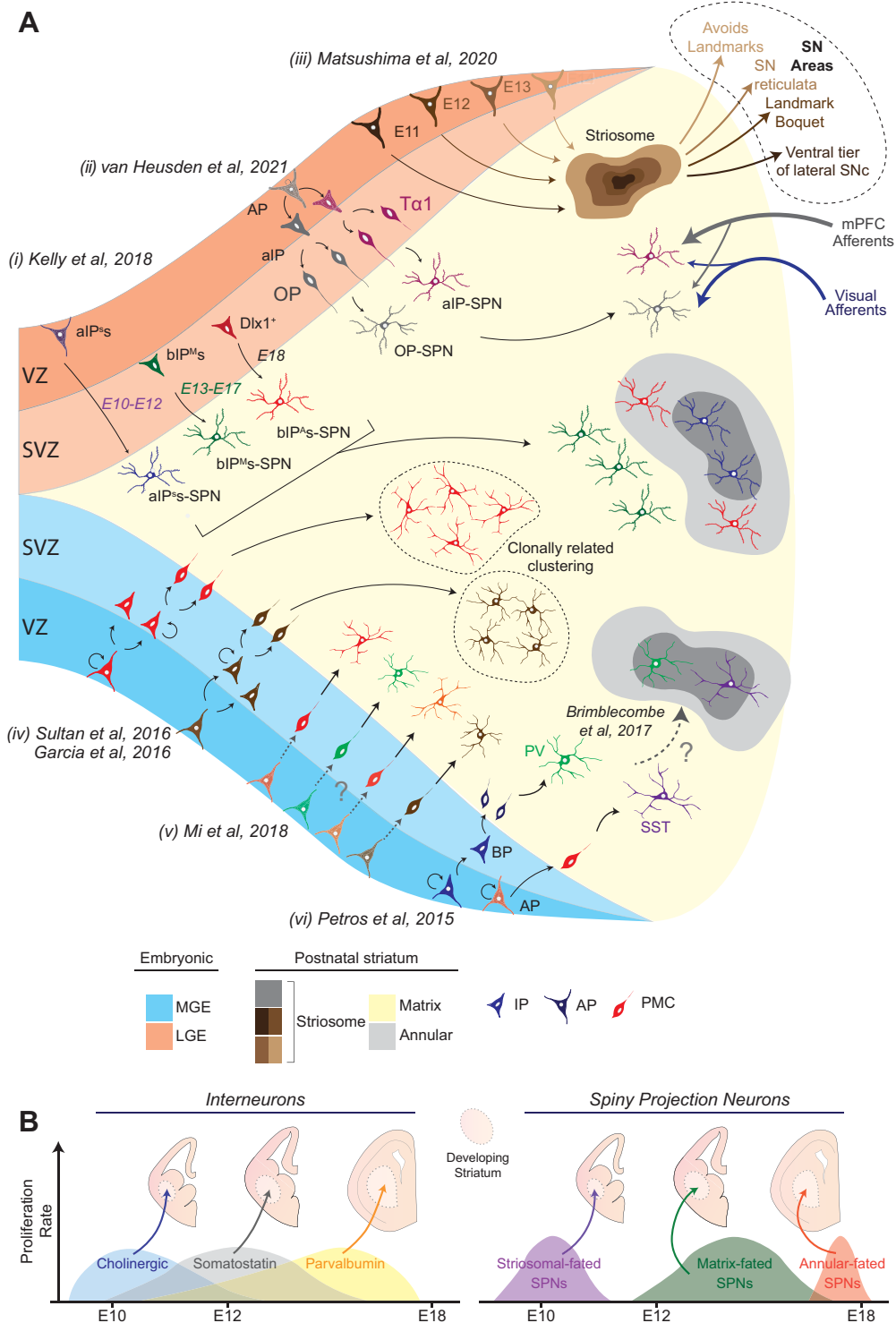


Figure 2. Embryonic progenitor origin controls many aspects of mature striatal neuron position and connectivity. **A**, *i*, LGE aIPs and bIPs generate SPNs fated to the striosomes (aIP^s-SPN) and matrix (bIP^Ms-SPN) compartments of the adult striatum. SPNs fated for the annular region (bIP^As-SPN) are generated later in development from specific bIPs expressing the transcription factor *Dlx1*. *ii*, IPs expressing *Tα1* in the LGE generate SPNs that receive stronger innervation from the mPFC, whereas OPs, which do not express *Tα1*, generate SPNs that receive stronger innervation from visual cortex afferents. *iii*, The time of birth of SPNs in the LGE determines their spatial arrangement within striosomes and, consequently, facilitates the formation of different long-range synaptic connections with the SN. *iv*, It is debated whether lineage and/or clonal relationships govern the spatial distribution of MGE-derived neurons. *v*, The transcriptional identity of mature MGE-derived interneurons is reflected in early postmitotic cells (PMCs); however, whether the underlying progenitor cells predetermine this is not known. *vi*, Apical neurogenesis in the MGE biases toward the generation of SST interneurons, whereas basal neurogenesis preferentially generates PV interneurons. Unlike the SPNs, it is not known whether this bias extends to the spatial distribution between striosomes and matrix neurochemical compartments in the striatum. **B**, For both MGE- and LGE-derived neurons, the time of birth appears to be a critical factor that facilitates the generation of the chemical identity and spatial distribution of a neuron.

circuits. From the LGE, postmitotic cells migrate predominantly radially over a short distance, following a number of migratory cues toward the striatum (Bayer, 1984; Halliday and Cepko, 1992; Song and Harlan, 1994; de Carlos et al., 1996; Hamasaki et al., 2003; Newman et al., 2015; Kelly et al., 2018; Xu et al., 2018; Chen et al., 2020), where they actively intermix (Tinterri et al., 2018). From the MGE, interneurons migrate longer distances to both the cortex and the striatum, again relying on differential expression of guidance molecules and receptors. For example, it is known that migration to cortical regions is guided by chemoattraction of semaphorin ligands (Sema3A and SemaF), and neuropilin receptors (Nrp1, Nrp2; Marin and Rubenstein, 2001; Andrews et al., 2017) expressed in cortical fated cells, whereas migration to the striatal region is regulated by neuregulin 1 and ErbB4 receptor tyrosine kinase 4 signaling (Villar-Cerviño et al., 2015). Any change in the expression of these transcription factors in postmitotic cells will redirect cells fated to a specific brain region (Villar-Cerviño et al., 2015). The rapid downregulation of *Nkx2.1* acts as a postmitotic transcriptional switch (Fig. 3B) in cortical fated cells, as it transcriptionally inhibits cortical migration cues such as Nrp2 (Butt et al., 2008; Nóbrega-Pereira et al., 2008). In contrast, striatal fated cells maintain *Nkx2.1* expression into adulthood, preventing cortical migration (Villar-Cerviño et al., 2015).

The smaller populations of cells derived from the CGE, SNE, and POA must also migrate to the striatum; however, they follow different migratory routes, regulated by different genetic cues. Unlike the MGE and LGE, the CGE has two separate caudorostral migratory routes that cells use to invade the striatum, hippocampus, and cortex (Nery et al., 2002; Touzot et al., 2016). These cells regulate migration through specificity protein 8 (Sp8), Prox1, and CoupTF-I/TF-II signaling, which when perturbed, disrupts the ability of cells to successfully integrate into these diverse circuits (Touzot et al., 2016). In the next section, we explore how certain organizational aspects of striatum are governed by embryonic progenitor origin (Fig. 2).

Progenitors shaping striatal neuron positioning. How is the position of a neuron in the striatum related to the embryonic progenitor it is derived from? It is known that early-born SPNs are located in the caudal parts of the striatum, while later-born SPNs are found in more rostral parts (Newman et al., 2015; Kelly et al., 2018). The differential localization of these SPNs must, to some extent, be related to the populations of progenitors that are actively dividing during early and later stages of neurogenesis. As the proportion of IPs is greater at later stages of neurogenesis, this would suggest a larger contribution of certain IPs (e.g., BPs) to the generation of rostral SPNs (Pilz et al., 2013; Newman et al., 2015; Kelly et al., 2018). Both dSPNs and iSPNs are found intermingled throughout the striatum in a mosaic (Gangarossa et al., 2013), which, at least for the matrix compartment, seems to arise from active intermingling of newly born SPNs (Tinterri et al., 2018). This intermingling suggests that clonal clusters of SPNs might be spread out more extensively throughout the striatum than clones found in the cortex (Yu et al., 2009; Brown et al., 2011; Shi et al., 2017), although this has not been systematically tested. Further positional information of SPNs in the striatum can be related to differential gene expression. For example, clear gradients of expression of the genes *Crym* and *Cnr1* in SPNs can be observed from ventrolateral to dorsomedial striatum (Stanley et al., 2020). However, whether these gradients result from different developmental origins of the SPNs is currently unknown.

Like SPNs, striatal interneurons do not distribute homogeneously within the striatum. Interneuron migration follows a ventral to dorsal gradient and interneurons sequentially populate the lateral and medial regions of the striatum (Chen et al., 2020). In particular, early-born interneurons such as the PV⁺ interneurons and CINs tend to accumulate in the lateral part of the striatum (Marin et al., 2000; Fig. 2B). Similarly, different types of CR⁺ interneurons do not distribute homogeneously; for example, those coexpressing the Ca²⁺ binding protein secretagogin and Sp8 are preferentially located in the rostral parts of the striatum, while other subsets of CR⁺ interneurons are located more uniformly (Garas et al., 2018). Interestingly, the expression of secretagogin also defines a subpopulation of PV⁺ interneurons found in more caudal parts of the striatum (Garas et al., 2016). A direct link between progenitor identity and the final location of MGE-derived cells is yet to be elucidated, and the extent of spatial distribution of lineage-related interneurons is a current matter of debate. It has been proposed that lineage relationships do not determine interneuron allocation to particular regions (Mayer et al., 2015) and that clonally related interneurons can be widely dispersed (Harwell et al., 2015). Indeed, studies tracing clonally related neurons (predominantly after retrovirus labeling of progenitors embryonically) reveal that they disperse across the cortex, hippocampus, and striatum, with no apparent clustering (Reid and Walsh, 2002; Ciceri et al., 2013; Turrero Garcia et al., 2016; Fig. 2A, Table 1). However, other studies analyzing the same dataset suggest that lineage (i.e., clonal or progenitor origin) does form clusters of neurons in the postnatal brain (Sultan et al., 2016). Further studies of clonally related striatal interneurons from different embryonic regions and different progenitor cell types are likely necessary to unambiguously answer this question.

Progenitors shaping striatal neurochemical compartments. As mentioned in the Introduction, striatal dSPNs and iSPNs are intermingled within several functionally and anatomically distinct subregions. SPNs born in the early phases of neurogenesis become preferentially incorporated into striosomes/patches and the later-born SPNs settle in the surrounding matrix (Graybiel and Hickey, 1982; van der Kooy and Fishell, 1987; Song and Harlan, 1994; Mason et al., 2005; Newman et al., 2015). Whether there is further fine-scale organization within these compartments and to what extent this relates to the diversity of embryonic progenitors in the LGE was until recently largely unknown. Several recent studies have started to provide some key insights, however (Kelly et al., 2018; Tinterri et al., 2018; Matsushima and Graybiel, 2020; Fig. 2).

The first study used elegant fate-mapping experiments to provide insight into the roles of distinct types of progenitor cells in the LGE in generating SPNs fated to either the striosome/patch or matrix compartments (Kelly et al., 2018). In this study, the authors used lineage-tracing analysis of embryonic progenitors [using tamoxifen-inducible, NGF-inducible protein (*Tis21*)- and *Ascl1*-Cre recombinase mouse driver lines] and demonstrated that the LGE contains two types of IPs, both derived from a RGC lineage. During early stages of neurogenesis (E9.5 to E12.5), apical IPs (aIPs) express the transcription factor *Ascl1* and have limited capacity to produce striosomal SPNs. During later phases of neurogenesis (E13.5 to E18.5), basal IPs (bIPs) expressing both *Ascl1* and *Dlx1* produce matrix SPNs. It is possible that *Ascl1*, in conjunction with *Gsx2*, in SAPs inhibits neurogenesis and promotes initial proliferation of these large numbers of basal IPs (Roychoudhury et al., 2020). Both types of embryonic progenitor (apical and basal IPs) were shown to generate both dSPNs and iSPNs (Kelly et al., 2018).

The second study (Tinterri et al., 2018) used a combination of transgenic animals and time-lapse video imaging to provide insight into the seemingly uniform distribution of both dSPNs and iSPNs. Indeed, they were able to show that late-born iSPNs actively intermix with early-born dSPNs and that this, at least for the matrix compartments, depends on the expression of the transcription factor *ebf1* in dSPNs (Tinterri et al., 2018).

Last, using a combination of transgenic *Dlx1*-Cre recombinase mice under the control of a fast-acting version of tamoxifen (4-OHT), Matsushima and Graybiel (2020) revealed that the striosomes/patches are formed through a center-surround rule, in which early-born SPNs are predominantly found in the center of the striosomes/patch compartments and are surrounded by increasingly later-born SPNs. They found that this center-surround rule was universal and was used in both anterior and posterior parts of the striatum, despite absolute differences in the birth date of SPNs in these distinct parts. Moreover, they found that a key anatomic structure, the so-called striosome-dendron bouquet, forms during a very specific period of neurogenesis in the mouse (i.e., approximately E12 to E13; Matsushima and Graybiel, 2020; Fig. 2).

Striatal interneurons also allocate differently between the striosome/patch and matrix compartments, which affects how these local microcircuits of SPNs are modulated (Banghart et al., 2015; Friedman et al., 2015). Often found at higher density in the matrix, CINs, PV, NPY, and CR-expressing interneurons are frequently located along striosomal borders in anatomically and functionally defined areas called “peristriosomal boundaries” (Prager and Plotkin, 2019). CINs and SST⁺ interneurons located at the interface between striosomes and matrix have dendrites and axons that traverse across compartmental borders (Kubota and Kawaguchi, 1993; Bernacer et al., 2012; Brimblecombe and Cragg, 2015; Matamales et al., 2016). Such interneurons might provide a functional bridge and modulate activity in both compartments (e.g., as demonstrated for the CINs; Crittenden et al., 2017). Yet, the precise roles of many other striatal interneurons in functionally linking striosome/patch and matrix microcircuits and intercompartmental communication remain poorly explored and form an interesting area for future study (Amemori et al., 2011).

Progenitors shaping striatal long-range excitatory synaptic circuits. How does embryonic progenitor origin shape the specificity of synaptic connections in the striatum? As mentioned in the Introduction, the striatum can be split into distinct functional domains depending on anatomic subregion (e.g., DLS and DMS). These distinct anatomic domains contain a mixture of dSPNs and iSPNs that is thought to process and integrate excitatory inputs from distinct brain regions and also interact with each other via lateral inhibitory connections (Taverna et al., 2008; Planert et al., 2010; Chuhma et al., 2011; Burke et al., 2017; Krajewski et al., 2019). These anatomic domains are thought to be part of larger parallel functional pathways through the basal ganglia (Graybiel and Ragsdale, 1978; Alexander et al., 1986; Graybiel, 1990; Haber, 2008; Pan et al., 2010; Oh et al., 2014; Hintiryan et al., 2016; Hunnicutt et al., 2016; McGregor et al., 2019; Lee et al., 2020). At a more local level, the clear segregation of these functional pathways is less clear. Indeed, individual SPNs exhibit considerable heterogeneity in their afferent connectivity patterns (Pan et al., 2010), and populations of SPNs with diverse excitatory inputs are intermingled in striatum (Oh et al., 2014; Hintiryan et al., 2016; Hunnicutt et al., 2016). Moreover, it has been shown that long-range glutamatergic synapses from

different cortical regions can converge onto single SPNs (Reig and Silberberg, 2014) or diverge and form biased synaptic connections on either dSPNs or iSPNs (Wall et al., 2013; Johansson and Silberberg, 2020). Considering that young SPNs exhibit complex migratory pathways and intermix in striatum during development (Tinterri et al., 2018), a question remains regarding how these precise striatal excitatory synaptic circuits develop and whether there is a role for distinct progenitor lineages.

A recent study has provided the first evidence that synapse specificity, of at least corticostriatal afferents, can arise from the embryonic origin of SPNs (van Heusden et al., 2021). In this study, the authors used *in utero* electroporation of a combination of constructs to label two active pools of embryonic progenitor in the VZ of the LGE at E15.5, based on the differential expression of the tubulin $\alpha 1$ ($T\alpha 1$) promoter (Table 1). Interestingly, different tubulin isoforms can shape the properties of proliferating cells and might therefore provide a good target for future delineation of further progenitor types (Ramos et al., 2020). The study by van Heusden et al. (2021) combined a $T\alpha 1$ -Cre recombinase construct with a reporter construct incorporating a flexible excision (FLEX) $C\beta A$ -FLEX cassette, so that Cre recombination permanently switches expression from the fluorescent protein TdTomato to GFP (Franco et al., 2012). Using this methodology, the authors showed that progenitors labeled with GFP (i.e., expressing $T\alpha 1$) in the VZ had characteristics of both the SNP and SAP populations of LGE progenitors, including a rounded morphology during division, location of division, and fast cell cycle kinetics (Pilz et al., 2013; Kelly et al., 2018; van Heusden et al., 2021). Measures of cell cycle kinetics in this and previous studies (Stancik et al., 2010) were evaluated through labeling with the mitotic marker phosphohistone-3, but new technology [e.g., FUCCI (fluorescence ubiquitination cell cycle indicator); Sakaue-Sawano et al., 2008] will allow for more detailed insights (Table 1). Conversely, the progenitors that expressed TdTomato (i.e., not expressing $T\alpha 1$ and likely consisting of a more heterogeneous population of progenitors) resembled the population of RGCs in that they had slower cell cycle kinetics and frequently exhibited a radial morphology during division (Pilz et al., 2013; Kelly et al., 2018; van Heusden et al., 2021). As many SAPs derive from SNPs and hence are closely lineally related (Pilz et al., 2013), and as both divide in the apical aspects of the LGE proliferative zone, the GFP⁺ $T\alpha 1$ -expressing progenitors were collectively referred to as “apical intermediate progenitors,” and the TdTomato⁺ non- $T\alpha 1$ -expressing progenitors simply as “other progenitors” (Fig. 2A). This also conforms to nomenclature of similar cortical (Tyler and Haydar, 2013; Ellender et al., 2019) and embryonic LGE progenitors (Kelly et al., 2018).

Using this approach, the authors followed the progeny of labeled cells and found that both progenitor pools predominantly generated striatal GABAergic SPNs; they referred to these cells as aIP- and OP-derived SPNs. Notably, both progenitor pools generated both dSPNs and iSPNs, which were intermingled, mostly in the DMS, and had similar properties (van Heusden et al., 2021). The authors explored whether aIP- and OP-derived SPNs differentially sample excitatory input coming from distinct cortical regions using local injections of AAV1-ChR2 in two different regions that send strong projections to DMS [Pan et al., 2010; Oh et al., 2014; Guo et al., 2015; Hunnicutt et al., 2016; i.e., the medial prefrontal cortex (mPFC); Laubach et al., 2018] and visual cortex (VC; Khibnik et al., 2014); this allowed optogenetic activation of afferents and whole-cell patch-clamp recordings of aIP- and OP-derived striatal SPNs. Strikingly, they found that embryonic progenitor origin conveyed significant biases in the strength of the long-range synaptic inputs coming from cortex, in that mPFC strongly innervated the aIP-derived SPNs, whereas

the VC strongly innervated the OP-derived SPNs (Fig. 2A). The study by van Heusden et al. (2021), together with recent observations in cortex (Ellender et al., 2019), suggest that the lineage of a neuron may be a key contributor to synapse specificity. *In utero* electroporation and other techniques such as Flash-Tag (Telley et al., 2016; Govindan et al., 2018) are powerful approaches to label progenitors and follow their progeny (Table 1) to further our understanding of how progenitor identity relates to final function.

Unlike for SPNs, no study has yet investigated the correlation between the identities of progenitor cells (transcriptional, morphologic, or otherwise) and the subsequent excitatory synaptic connectivity pattern of mature striatal interneurons in detail. However, it is possible to infer a link between the two, based on current knowledge of striatal development. Indeed, distinct classes of striatal interneurons receive different glutamatergic inputs along the mediolateral axis. For example, CINs in the DMS receive more inputs from the pedunculopontine nucleus than the CINs in DLS (Assous et al., 2019), and, similarly, PV⁺ interneurons in the DMS, and not those in the DLS, receive glutamatergic inputs from the cingulate cortex (Monteiro et al., 2018). In the MGE, newly postmitotic, late-born CINs can be defined by the expression of the *Gbx2* transcription factor (Chen et al., 2010), which might be related to their preferred pedunculopontine innervation in the DMS CINs. However, the extent to which the identity of the newly formed postmitotic cell is controlled by the transcriptional profile of the underlying progenitor is only beginning to be understood (for review, see Mi et al., 2018; Fig. 2).

Searching for answers in the cortex

Many questions remain regarding the role of embryonic progenitors in shaping postnatal striatal neuronal identity and circuits. For example, how do specific progenitor-derived cells map onto modern transcriptomic classifications of striatal neurons? What is the contribution of progenitor types other than the ones studied so far? We will now discuss some of these outstanding questions in light of the relevant literature, mainly from studies in the cortex, and discuss how these may guide future research in the striatum.

What is the contribution of other embryonic progenitors to the striatum? As discussed above, the LGE contains a heterogeneous mix of progenitor types including those that divide in the apical aspects of the LGE (e.g., RGC and aIP) and those that divide in the basal aspects of the LGE (e.g., bRGCs and BPs; Olsson et al., 1998; Stenman et al., 2003; Pilz et al., 2013; Kelly et al., 2018; van Heusden et al., 2021). Although a recent study has started to provide insight into the contribution of the apically dividing progenitors to the striatal cellular and circuit organization (van Heusden et al., 2021), much less is known about the contribution of other more basally dividing progenitors. It has been proposed that the number and relative proportion of basal progenitors are responsible for the extensive growth of the neocortex in humans (LaMonica et al., 2013; Florio and Huttner, 2014; Lewitus et al., 2014) and have underpinned an evolutionary step driving our unique cognitive abilities. However, bIPs may not solely exist to increase brain size, but instead offer alternative contributions to the development of cortical as well as striatal circuits.

In the striatum, the striosome and matrix compartments differ substantially in size, but their approximate 1:4 size ratio is conserved across many mammalian species (Brimblecombe and

Cragg, 2017). The findings that distinct IP types with different neurogenic capacities are fate restricted to generate SPNs destined for either striosome or matrix compartments provide a plausible explanation for this observation (Kelly et al., 2018). Indeed, Kelly et al. (2018) demonstrated that larger numbers of bIPs are generated from RGCs during a long, late phase in embryogenesis and that individual bIPs undergo more rounds of transitory amplification compared with early aIPs. This results in early aIPs generating many of the striosome SPNs, and later bIPs generating many of the matrix SPNs (Fig. 2A,B). Moreover, these authors demonstrated that the progeny of distinct types of bIPs at various stages of embryonic development inhabit distinct matrix compartments (Kelly et al., 2018), suggesting that bIP diversity can also inform the formation of distinct regions in striatum. What further properties, if any, are conveyed by bIPs is currently largely unknown.

In cortex, *in utero* electroporation of T-box brain protein 2 (*Tbr2*) Cre-recombinase constructs and fate mapping of their progeny made it possible to show that the cortical progeny of *Tbr2*⁺ bIPs had distinctive electrical and morphologic properties compared with neurons derived from other progenitors (Tyler et al., 2015). It might be possible to label bIPs in the LGE using similar approaches, as *Tbr2* is embryonically expressed in the LGE (Kimura et al., 1999). Considering that the MGE gives rise to both striatal and cortical interneurons, it is possible that the mechanisms demonstrated for cortical neurogenesis can be extended to the striatum.

Interestingly, bIPs have been shown to selectively contribute to interneuron diversity (Petros et al., 2015). Indeed, apical progenitors appear to preferentially generate SST⁺ interneurons, whereas bIPs contribute to PV⁺ interneurons, confirming a distinct role for bIPs in the MGE (Fig. 2A). Especially during later stages of embryonic development, bIPs become the primary proliferative cells in both ganglionic eminences (Smart, 1976), and it will be interesting to explore whether they might convey further characteristics related to cell identity, synaptic connectivity, and/or intrinsic electrical properties.

Do diverse embryonic progenitor types map onto defined postnatal neuron populations? The advent of single-cell RNA sequencing (sc-RNAseq) technology has provided great insight into the vast diversity of postnatal neurons in the brain, including the striatum (Table 1). Indeed, this has provided evidence for SPN types beyond the classical distinction of dSPNs and iSPNs (Saunders et al., 2018; Martin et al., 2019), additional subdivisions within the dSPNs or iSPNs (Gokce et al., 2016; Zeisel et al., 2018; Stanley et al., 2020), and gradients of transcriptional heterogeneity correlating with SPN position in the striatum (Stanley et al., 2020). Whether and to what extent this great diversity of SPN types maps onto distinct embryonic progenitor pools is largely unknown. It has been shown that different progenitor pools in LGE, such as aIP and OP (van Heusden et al., 2021), and bIP (Kelly et al., 2018), can each generate both dSPNs and iSPNs. It seems that dSPN and iSPN share common progenitors (i.e., both AP and BP) and that lineage commitment is established during the postmitotic transition, as shown in humans as well (Bocchi et al., 2021). This suggests that factors beyond the embryonic pool of origin likely contribute to the generation of SPN transcriptional subtypes (Tepper et al., 1998; Lobo et al., 2006; Franco et al., 2012; Kelly et al., 2018; Anderson et al., 2020; Sharma et al., 2020). Many other factors could act on progenitors and young neurons, including epigenetic modifications (Yoon et al., 2018; Zahr et al., 2018; Telley et al., 2019), factors related to migration (Lim et al., 2018), or further differential transcription

Table 1. Recent technological advances in embryonic progenitor research

Methods	Key findings and references
Analysis of gene expression	
sc-RNAseq Quantification of RNA transcripts with single-cell resolution	Uncovered new MGE-derived NPC subtypes and transcriptionally defined cortical interneurons (Tasic et al., 2016; Mayer et al., 2018; Mi et al., 2018; Saunders et al., 2018; Tasic et al., 2018) AP and BP populations divide into two subtypes (Chen et al., 2017) Further subdivisions within dSPN and iSPN and additional striatal SPN types (Gokce et al., 2016; Saunders et al., 2018; Zeisel et al., 2018; Martin et al., 2019) Uncovered gradients of transcriptional heterogeneity correlating with positional information of SPNs (Stanley et al., 2020) Whole-exome sequencing identifying ASD risk genes and the critical importance of interneurons within ASD etiology (Satterstrom et al., 2020) sc-RNAseq of human striatal progenitors and young neurons (Bocchi et al., 2021)
Patch-Seq Investigating transcriptional profiles and physiological properties of single cells	Reveals seven main classes of striatal SPNs and interneurons with gradients of gene expression that vary from cortical and hippocampal interneurons (Muñoz-Manchado et al., 2018) Transcriptional classification of aIP- and OP-derived cortical neurons (Ellender et al., 2019)
Spatial transcriptomics Visualizing RNA transcripts in specific areas with spatial resolution (50 μm)	Spatial transcriptomics enables generation of a whole-brain atlas and uncovers new spatial domains in the striatum (Lein et al., 2017; Ortiz et al., 2020)
MERFISH Visualizing RNA transcripts with subcellular compartmentalization	MERFISH enables spatial RNA profiling of individual cells in different subcellular compartments and in transcriptionally distinct cell cycle phases. This technique is useful to study cell fate and regulation of gene expression (Xia et al., 2019)
Lineage tracing and cell fate assays	
MADM MADM provides genetic dissection of intrinsic gene function	This genetic mosaic strategy enables sparse altering of single cells while maintaining a “normal” local microenvironment. This study showed that <i>Lgl1</i> is a critical regulatory element for embryonic cortical neurogenesis and cell-autonomous control of RGC-mediated glia genesis and postnatal NPCs (Beattie et al., 2017)
FlashTag Label, track and isolate isochronic cohorts of newborn cells in the CNS	This powerful technique, first described in the neocortex, can be used in many brain regions to date the birth of and isolate any type of progenitor in contact with the VZ and to follow cell migration of newly born neurons (Telley et al., 2016; Govindan et al., 2018)
<i>In utero</i> electroporation Label embryonic progenitors and track their progeny through prenatal and postnatal periods	<i>In utero</i> electroporation of constructs driving recombinase systems (e.g., Cre) under the control of promoter sequences specific for certain progenitors in combination with reporter constructs allows for labeling of progenitors and progeny. Used to label apical IPs in striatal and cortical proliferative regions (Gal et al., 2006; Stancik et al., 2010; Tyler and Haydar, 2013; Ellender et al., 2019; van Heusden et al., 2021), and basal IP cells and/or bRGCs in cortical proliferative regions (Tyler et al., 2015; Li et al., 2020)
Transplantation assays Human pluripotent stem cell-derived neurons	In this study, the authors reveal a differentiation protocol to direct hPSCs to mature neurons in 37 d <i>in vitro</i> (Comella-Bolla et al., 2020). Transplantation experiments show that NPCs survive and differentiate (for at least 3 months) in the mouse striatum (Martínez-Cerdeño et al., 2010; Noakes et al., 2019; Comella-Bolla et al., 2020)
FUCCI Fluorescence ubiquitination cell cycle indicator analyzes the temporal dynamics of cell cycle progression (live cell imaging)	Genetically encoded fluorescent probes to visualize cell cycle transition from G1 to S phase (individual G1 phase nuclei in red, S/G2/M phases in green; Sakaue-Sawano et al., 2008)
Clonal relationships Dispersion of clonally related interneurons	Study the clonal or progenitor origin that influences the spatial distribution of mature interneurons (Ciceri et al., 2013; Harwell et al., 2015; Mayer et al., 2015; Sultan et al., 2016; Turrero Garcia et al., 2016)
Connectivity and cell activity	
Viral transfections RV: retrograde monosynaptic tracing	Mapping of synaptic inputs to projection neurons and cholinergic interneurons in the dorsal striatum using modified rabies virus tracing (Guo et al., 2015)
AAV: labeling of distinct neuronal subtypes	Identification of multiple new enhancers to target functionally distinct neuronal subtypes in mice, primates, and humans (Vormstein-Schneider et al., 2020)
Studying progenitors in humans	
Brain organoids <i>In vitro</i> models that replicate some developmental processes of the human brain	Study of the transcriptional regulation of progenitor fate that is altered in ASD—for example revealing that the overexpression of <i>FoxG1</i> leads to the overproduction of interneurons (Mariani et al., 2015)
Perturb-Seq Introduction of mutations in specific genes by gene editing (e.g. knock-out candidate genes in mice embryos), followed by single-cell transcriptomic analysis	Alteration of cortical lineages in the developing mouse brain and analysis of 35 ASD risk genes in five cells classes, including projections neurons, inhibitory neurons, astrocytes, oligodendrocytes and microglia. They revealed that cell type composition remains unaffected, but cell state is affected (Jin et al., 2020). This method can be applied across diseases from diverse tissues, such as human PSCs or brain organoids

MERFISH, Multiplexed error-robust FISH; MADM, mosaic analysis with double markers; FUCCI, fluorescence ubiquitination cell cycle indicator.

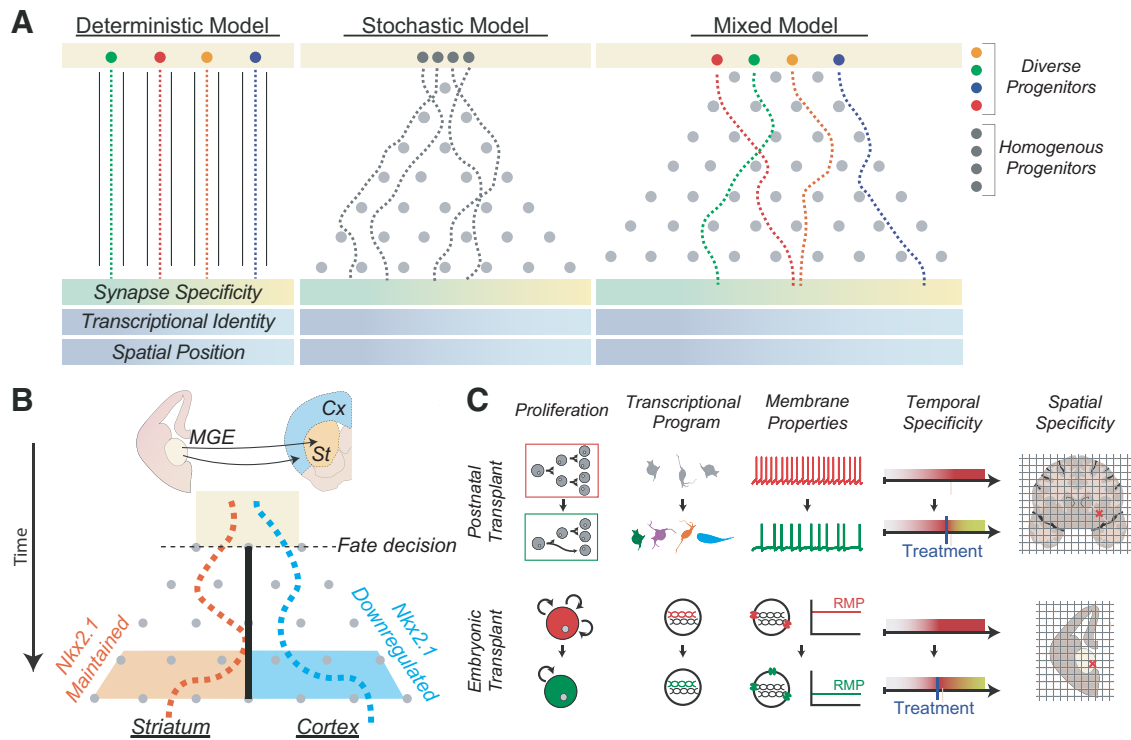


Figure 3. The relationship between diversity in embryonic progenitors and diversity in postnatal neurons. **A**, Different models have been proposed to explain the neuronal diversity observed in the postnatal brain. In the deterministic model (left), different progenitor pools (different colors; Villar-Cerviño et al., 2015) generate neurons that have specific characteristics (e.g., biased synaptic inputs, transcriptional identity, and/or spatial positioning). In the stochastic model (middle), these characteristics are mainly attained shortly after birth through a seemingly random process (Llorca et al., 2019; Klingler and Jabaudon, 2020). These two models could also coexist for distinct progenitor populations, and they are not mutually exclusive: a mixed model (right) is possible. **B**, It is possible that some developmental cues are irreversible, permanently shifting the outcome of a stochastic system. In this example, the dark line represents a restriction within the stochastic system: after a cell downregulates the transcription factor *Nkx2.1*, it becomes fated for the cortex instead of striatum. The result cannot be reversed, regardless of intrinsic or extrinsic cues. **C**, Top, To effectively restore neural physiology with cell transplants in the postnatal brain, multiple factors must be considered, including transplanting a sufficient number of cells with appropriate transcriptional identities and intrinsic properties (Noakes et al., 2019). Bottom, Because neurodevelopmental pathologies can arise from dysfunctional progenitors, modulation of existing progenitors *in situ* or transplanting progenitors prenatally might restore a healthy developmental trajectory. This will also necessitate the generation of progenitors with appropriate cell cycle dynamics (Wang et al., 2020), transcriptional states (Satterstrom et al., 2020), and other intrinsic properties, including resting membrane potential (RMP; Vitali et al., 2018). Both adult and embryonic transplants would require transplanting cells at the correct time within a developmental or disease process, as well as in the correct location in the brain.

factor expression (Lu et al., 2014; Zhang et al., 2016; Bocchi et al., 2021), to prime or post-transcriptionally regulate protein expression (Nowakowski et al., 2013; Zahr et al., 2018; Li et al., 2020).

Despite the above findings, there is some early evidence linking transcriptionally defined cortical neurons to defined populations of embryonic progenitor (Ellender et al., 2019). In this study, the authors used a modified Patch-seq approach (Muñoz-Manchado et al., 2018; Mahfooz and Ellender, 2021; Table 1) to transcriptionally map aIP- and OP-derived cortical neurons to a published large-scale sc-RNaseq neuronal classification of cortex (Tasic et al., 2018). They found that the cortical aIPs, as defined by the selective expression of the *Ta1* promoter during early development, were more restricted in the types of cortical neurons they generated than OPs, which consisted of a more heterogeneous population of progenitors (Ellender et al., 2019). This restricted output from aIPs supports the idea that intermediate progenitors emerged to increase the representation of particular postmitotic cell types (Martínez-Cerdeño et al., 2006; Tyler and Haydar, 2013; Taverna et al., 2014; Guillamon-Vivancos et al., 2019) and also supports the idea that VZ neuronal progenitors can exhibit different degrees of lineage restriction (Franco et al., 2012; Gil-Sanz et al., 2015; Llorca et al., 2019). At the same time, as aIPs are derived from RGCs, these findings are compatible with a general model in which a single neuronal progenitor cell type ultimately gives rise to the full complement of excitatory

cortical neuronal cell types (Franco and Müller, 2013; Taverna et al., 2014). Last, the data indicate that multiple excitatory progenitor pools, and intermediate progenitor pools in particular, have not simply evolved to expand brain structure volume, but can also contribute to cell diversity.

How progenitor cell diversity in the MGE shapes interneuron transcriptional diversity in the mature brain has been a long-standing question in neural development. Of particular interest is whether a single MGE-derived progenitor can generate both striatal and cortical interneurons (Reid et al., 1995; Reid and Walsh, 2002). As previously described, postmitotic transcriptional switches such as *Nkx2.1* can determine cortical versus striatal fate (Villar-Cerviño et al., 2015); but it is not known whether this is predetermined at a progenitor level. Currently, two distinct models have been suggested. In one model, across its proliferative life span, a single progenitor can generate both cortical and striatal fated neurons, which, when mature, can have vastly different functional properties (McConnell and Kaznowski, 1991; Desai and McConnell, 2000; Llorca et al., 2019). Alternatively, a single progenitor may be fate locked to the generation of either striatal or cortical cells. In this latter paradigm, progenitor cell diversity directly drives neuron heterogeneity (Franco et al., 2012; Garcia-Moreno and Molnar, 2015; Fig. 3). Both possible mechanisms raise questions. For example, if cortical and striatal interneurons are derived from

different progenitors, are these progenitors spatially segregated within the VZ of the MGE (Flames et al., 2007; Mi et al., 2018)? Or are they randomly distributed, with a stochastic system of probabilistic decisions delineating striatal from cortical MGE-derived interneurons, as has been shown for excitatory neurons in the cortex (Llorca et al., 2019; Klingler and Jabaudon, 2020). Alternatively, specific molecules could separate progenitors giving rise to both striatal and cortical interneurons. For example, the *ETV1/Er81* transcription factor is expressed from E10.5 in the MGE and segregates subtypes of progenitor cells in the VZ and SVZ. It has been shown to play a critical role during development, impacting several properties, including neuronal identity (Flames et al., 2007; Doitsidou et al., 2013) and excitability of cortical (Dehorter et al., 2015), as well as striatal interneurons (Ahmed et al., 2021). However, how the *ETV1/Er81* transcription factor relates to the distinct progenitor cells discussed so far is largely unknown. It would be interesting to further investigate whether this specific molecule dictates MGE-derived cell fate and participates in the emergence of functional diversity within the striatum.

The question of transcriptional identity is closely related to the more general question: to what extent is embryonic progenitor diversity related to neuronal diversity (Fig. 3)? Because cortical development has been studied to a greater extent than that of other brain regions (including striatum), it may provide some insight into this question. Recently, it was shown that the progenitors that give rise to cortical pyramidal neurons follow a stochastic system of differentiation, wherein their random exposure to different developmental cues differentiates subsequent cellular properties (Llorca et al., 2019; Klingler and Jabaudon, 2020). Indeed, stochastic modeling could predict the clonal size, spatial distribution, and volumetric heterogeneity of cortical pyramidal neurons. This model provides an explanation for how diverse progeny can arise from a relatively homogenous group of progenitors (Klingler and Jabaudon, 2020). However, a completely homogenous population of progenitors that followed a stochastic mechanism did not fully explain all experimental observations. Indeed, the authors had to trace the progeny from two distinct progenitors, which could then accurately predict the laminar position and their clonal size. This implies that even under a stochastic system, having multiple types of progenitor cells in the embryonic brain is required to generate the required cellular diversity of the postnatal brain (Llorca et al., 2019). Longitudinal sc-RNAseq studies encompassing extended periods of perinatal development, as recently achieved for cortical structures (Di Bella et al., 2021; La Manno et al., 2021), will allow for deeper probing of these questions.

What controls the local connectivity among striatal neurons? We previously discussed how embryonic progenitor origin generates biases in the long-range excitatory connectivity from different cortical regions onto SPNs and could contribute to the generation of separate functional striatal pathways. Within the striatum, the SPNs (and associated interneurons) form local inhibitory synapses with which they regulate each other's activity; these have also been shown to be selective and biased. For example, iSPNs form more frequent and stronger synaptic connections than dSPNs (Taverna et al., 2008; Planert et al., 2010; Chuhma et al., 2011; Cepeda et al., 2013; Burke et al., 2017; Krajcski et al., 2019), and fast-spiking interneurons make more frequent connections onto dSPNs than onto iSPNs (Gittis et al., 2010; Planert et al., 2010). What rules govern these observed biases in local inhibitory connectivity? Is there evidence for involvement of progenitors?

A recent study investigated whether embryonic progenitor origin affected the strength of local inhibitory connections

among SPNs and found no evidence (van Heusden et al., 2021). In this study, an optogenetic circuit-mapping approach was used to study the strength of inhibitory synaptic connections from aIP-derived SPNs to either aIP-derived or OP-derived SPNs and found no difference in their strength. Instead of progenitor origin, the birth dates of SPNs influenced the strength of connections, in that SPNs tended to form strong inhibitory synaptic connections with SPNs born during similar stages of neurogenesis, over and above SPNs born at other developmental stages (van Heusden et al., 2021; Fig. 2B). This is in contrast to recent findings in cortex where embryonic progenitor origin was shown to impact the incidence of local synaptic connectivity among the excitatory neurons in both layer 4 and layer 2/3 of the somatosensory cortex (Ellender et al., 2019). Here, the authors demonstrated that neurons tended to make preferential synaptic connections with other neurons derived from a different embryonic progenitor pool (Ellender et al., 2019).

The results in striatum described above are a first indication of increased interactions among SPNs with similar birth dates, but they do not provide insight into the emergence of preferred connectivity between dSPNs and iSPNs. It is known that the preferred connectivity patterns between SPNs emerge early in postnatal development (Krajcski et al., 2019), suggesting that they could result from synaptic plasticity driven by early neural activity (Cinotti and Humphries, 2021; Lopez-Huerta et al., 2021) and neuromodulation (Goffin et al., 2010). Regarding striatal interneurons, a recent study revealed that in the absence of the *Er81* transcription factor, striatal CINs shifted toward less PV–CIN and CIN–CIN synaptic connections (Ahmed et al., 2021). Considering the MGE contains a population of progenitors expressing *Er81*, it is possible that the cholinergic interneurons derived from these progenitors are fated to a specific connectivity pattern.

Embryonic progenitors and striatal pathology. Understanding the role of embryonic progenitors in relation to striatal development has the potential to further our understanding of striatal dysfunction in both neurodevelopmental and neurodegenerative disorders. Indeed, recent evidence suggests that defects in the division and differentiation of these progenitors are associated with diseases such as Huntington's disease and autism spectrum disorder.

The earliest symptoms of HD are often subtle, including problems with mood or cognition; these are followed by a general lack of coordination and an unsteady gait. As the disease advances, uncoordinated, involuntary body movements worsen. The cause of HD is typically genetic: a mutation in the *huntingtin* gene (*HTT*) is inherited from an affected parent (Barnat et al., 2020) or arises from *de novo* mutations. The resulting mutant protein (mHtt) leads to the eventual death of striatal cells, particularly affecting the iSPNs (Zheng and Kozloski, 2017). Recent findings have suggested that mHtt can affect progenitor cells during embryonic periods (Wiatr et al., 2018; Barnat et al., 2020). Indeed, using an HD mouse model, it was shown that mHtt affects levels of neurogenesis and can result in increased numbers of embryonic progenitors (Lorincz and Zawistowski, 2009), something that also has been observed in postmortem samples from humans with HD (Curtis et al., 2003). More recently, it was established that these mutations also severely affect the developing cortex, causing mislocalization of both mHtt and junctional complex proteins, defects in embryonic progenitor cell polarity and differentiation, abnormal ciliogenesis, and changes in mitosis and cell cycle progression in both humans and mice (Barnat et al., 2020). In addition, there are

suggestions that mature striosomes exhibit increased vulnerability in HD (Hedreen and Folstein, 1995; Friedman et al., 2020); given that striosomal SPNs are generated mainly from aIPs during early stages of neurogenesis (Kelly et al., 2018), the selective impact of mutations in HTT in this population of progenitors could be interesting to study and to test novel treatments (Lin et al., 2015). Together, these recent findings suggest that HD has a substantial neurodevelopmental component and is not solely a neurodegenerative disorder. See also a recent review on altered striatal development in HD (Lebouc et al., 2020).

ASD is a group of neurodevelopmental pathologies that cause significant social and communication challenges and restrictive/repetitive behaviors. Evidence from human postmortem brain studies (Cheffer et al., 2020) and human-derived iPSCs identify early embryonic development as a critical period for this disorder (Cheffer et al., 2020; Griese-Oliveira et al., 2021; Hohmann et al., 2020). Stem cells derived from people with autism show higher rates of proliferation (Cheffer et al., 2020; Adhya et al., 2021), reduced differentiation potential, and a different genetic profile than those from control donors (Grunwald et al., 2019; Shen et al., 2019; Wang et al., 2020; Adhya et al., 2021). Recent whole-exome sequencing studies of ASD risk genes have shed light on the critical importance of interneurons in ASD etiology (Satterstrom et al., 2020). For example, striatal interneurons show reduced expression of postmitotic neural differentiation factors (Close et al., 2012), including SATB Homeobox 1 (SatB1), which regulates the survival of SST⁺ and PV⁺ postmitotic interneurons (Close et al., 2012), and Ephrin type-B receptor 1 (Ephb1), a regulator of striatal and cortical interneuron migration (Villar-Cerviño et al., 2015). Although interneuron numbers might normalize during development, the early alterations can lead to long-lasting changes in neuronal circuit function that affect behavior (Magno et al., 2021). Further work is necessary to directly attribute early alterations in neural progenitor cells and neural circuit formation to the disease mechanisms in ASD.

These studies highlight a clear role for embryonic progenitors in two different disorders and suggest that further research is needed into the impact of the altered behavior of progenitors on the developing brain. One opportunity is the growing use of *in vitro* models to further dissect disease mechanism and etiology. Despite the limitations (e.g., reproducibility, scalability, and long-term survival; Quesnel-Vallieres et al., 2019; Wang et al., 2020; Pintacuda et al., 2021), the “disease-in-a-dish” approach allows for precisely timed analyses and offers an opportunity to further probe the cellular and molecular alterations in brain development in health and disease (Chan et al., 2020). Stem cell-derived model systems, such as three-dimensional organoids (Di Lullo and Kriegstein, 2017; Pollen et al., 2019), air–liquid interface cerebral organoids from mouse or human iPSCs (Giandomenico et al., 2019), and combining different organoids in “assembloids” (Miura et al., 2020) have opened new experimental avenues for investigating aspects of development and pathology of the human brain (Table 1). Notably, determining how brain cells derived from diverse human genetic backgrounds respond to specific drugs might ultimately allow for personalized medicine approaches for disorders such as HD and ASD (Mariani et al., 2015; Maussion et al., 2019; Wang et al., 2020).

Progenitors supporting neurologic restoration. As outlined above, remarkable progress has been made in our understanding of progenitors, stem cells, and their progeny, allowing us to shape progenitor cell development to generate many functional mature neural cell types (Arber et al., 2015). A major objective is to

reproduce the maturation steps of brain cells and provide new insights into the pathophysiology of various disorders *in vitro* (Tyson and Anderson, 2014; Mariani et al., 2015; Noakes et al., 2019; Comella-Bolla et al., 2020; Wang et al., 2020). A further objective is to harness this knowledge and develop new cell-based treatment options, including cell transplantation, which would allow for restoration (or modulation) of neural circuit defects in brain disorders. Below, we highlight a few recent articles and would like to refer also this recent review (Bjorklund and Parmar, 2020).

So far, transplantation studies of embryonic progenitor cells in animals and humans have generated some positive results with regard to the ability of delivering cells that become functionally integrated into the postnatal brain. For example, it has been shown that isolated E12.5 to E13.5 or E14.5 MGE progenitor cells can differentiate into interneurons and integrate into early postnatal circuits (Alvarez-Dolado et al., 2006; Martínez-Cerdeño et al., 2010). Moreover, transplantation of embryonic progenitor cells into the postnatal brain has been successfully trialed in preclinical models as potential replacement strategies for the treatment of disorders such as Parkinson’s disease and epilepsy (Martínez-Cerdeño et al., 2010; Hunt and Baraban, 2015; Upadhyaya et al., 2019; Doi et al., 2020; Guo et al., 2021). However, accurate programming of induced cells into specific progenitors, striatal neurons, or mixtures of neurons (Reddington et al., 2014) is likely critical when considering cell transplantation as a possible treatment option for HD or ASD and other disorders.

Directing human stem cells into specific neuronal types is complex and will require accurate differentiation protocols that mimic endogenous neuronal development, integrating aspects of cell maturation (e.g., morphology and electrical properties) and circuit formation (Fig. 3C). Indeed, this will also likely require consideration of the distinct transcriptional programs and developmental sequential events that guide newborn neurons (Telley et al., 2016; Vitali et al., 2018). Recent work has started to examine the properties of human pluripotent stem cells (hPSCs) grafted onto the postnatal mouse (Comella-Bolla et al., 2020) and rat (Noakes et al., 2019) striatum. The cells adopted cellular profiles similar to those found in the human striatum (Table 1). In the latter study, CR⁺ interneurons were the predominant cells; CINs, while present within the graft, were absent in the *in vitro* culture; and SST⁺ and PV⁺ cells, originally absent in the graft, were detected in the culture. Potential reasons for the differences in cellular composition between the graft and cell culture could be a subtype-dependent survival bias or environment-driven redirection of interneuron fate, creating a shift in the subtype composition to match the region where the cells were grafted (Quattrocchio et al., 2017). Further elucidation of the survival and subtype composition achieved by the grafts is necessary to shed light on the relative influence of intrinsic and extrinsic cues on neuronal fate. The degree of fate commitment present at the progenitor stage could potentially be tested by transplanting hPSC-derived progenitors from a specific ganglionic eminence into the neonatal striatum using neuron type-specific hPSC reporter lines or reprogramming of endogenous cells into neurons (Weinberg et al., 2017). Recent sequencing of mouse (Mayer et al., 2018; Mi et al., 2018; Loo et al., 2019) and human striatal progenitors and young neurons (Bocchi et al., 2021) has provided insight into their lineages and can facilitate the development and the efficacy of cell replacement, showing great potential to improve therapeutic avenues.

Conclusions

The postnatal striatum is a highly complex brain structure with multiple levels of organization, some aspects of which, as outlined in this review, are related to embryonic progenitor cell origin. Here, we highlighted recent studies delineating the crucial importance of progenitor origin in shaping the spatial position, cellular identity, and synaptic connectivity of both striatal spiny projection neurons and interneurons during development. Understanding these novel roles of diverse embryonic progenitors in shaping striatal development provides a useful framework through which to view the vast complexity of neuronal circuits in the postnatal brain, and it can help shape future research directions and the development of cell-based therapies.

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