From progenitors to progeny : shaping striatal circuit development and function

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Abstract

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. Lastly, 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.

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. Lastly, 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; Yu *et al.*, 2012; Tyler *et al.*, 2015; Kelly *et al.*, 2018; Ellender *et al.*, 2019; Guillamon-Vivancos *et al.*, 2019; Matsushima & 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 & Knowlton, 2006; Kravitz *et al.*, 2010; Cui *et al.*, 2013; Tecuapetla *et al.*, 2016), and it has been ascribed key computational roles in action selection, decision-making and reinforcement learning (Redgrave *et al.*, 1999; Reynolds *et al.*, 2001; Samejima *et al.*, 2005; Bogacz & 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 & Malenka, 2008; Tepper *et al.*, 2010; Tepper *et al.*, 2018). The SPNs are classically divided into the direct pathway dopamine D_1 receptor-expressing SPN (dSPN) and the indirect pathway dopamine D_2 receptor-expressing SPN types (iSPN), 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 globus pallidus (GPe) (Gerfen *et al.*, 1990; Day *et al.*, 2008; Gertler *et al.*, 2008). The resident striatal interneuron population can be subdivided into cholinergic interneurons 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 & 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 anatomical subregions of striatum (Graybiel & 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 anatomical subregion receiving innervation from different cortical and thalamic areas (McGeorge & 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 & Ragsdale, 1978; Herkenham & Pert, 1981; Graybiel, 1990; Crittenden & 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 & 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 (Rubenstein & Campbell, 2020).

A combination of morphogenetic movements and proliferation between embryonic day (E)9 and E11 in mice establish 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; Munoz-Manchado *et al.*, 2016), preoptic/anterior entopeduncular areas (POa/AEP) (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) (Figure 1A). Initial gradients of diffusible factors (Rallu *et al.*, 2002) and distinct transcription factor cascades (Schuurmans & 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 radial glial cells (RGCs), which divide at the ventricular wall to generate further progenitors that inhabit both the ventricular and subventricular zones (VZ and 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) (Figure 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-Cervino *et al.*, 2015) progressively differentiating towards 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 (Figure 1C). At approximately E18 in mice, the neurogenic divisions within the embryonic brain switch and become gliogenic, generating both astrocytes and oligodendrocytes (Anthony & Heintz, 2008; Minocha *et al.*, 2017; Turrero Garcia & Harwell, 2017). Although this review will mainly focus on progenitor-derived neurons, the extent to which 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 inhibit the VZ and SVZ (Halliday & Cepko, 1992; Sheth & Bhide, 1997; Olsson *et al.*, 1998; Stenman *et al.*, 2003; Gotz & Huttner, 2005; Mason *et al.*, 2005; Sousa & Fishell, 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 cell, of which two divide at the ventricular surface: classical 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 in the VZ have been shown to divide at subapical positions away from the ventricular surface; these have been named sub-apical 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 of more processes and resemble RGCs. The latter progenitors divide in the basal aspects of the LGE and are called basal radial glia cells (bRGC) (Pilz *et al.*, 2013) (Figure 1B). Detailed analysis of lineage progression amongst these progenitor types suggests that the majority of LGE RGCs generate 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 & Alvarez-Buylla, 2009) and suggests that most striatal SPNs are generated from IP. Indeed, lineage analysis suggests that LGE RGCs generates mainly additional RGCs, SNPs, or SAPs. In turn, the SNPs mostly generate further SNPs or SAPs, while SAPs generate further SAPs, BPs, or post-mitotic neurons (Pilz *et al.*, 2013) (Figure 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; Noctor *et al.*, 2004; Gal *et al.*, 2006; Kowalczyk *et al.*, 2009; Stancik *et al.*, 2010; Shitamukai *et al.*, 2011; Wang *et al.*, 2011; Franco & Muller, 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 & Haydar, 2013), whereas those in the LGE tend to have relatively short cell-cycle kinetics and produce further progenitors (Pilz *et al.*, 2013).

The morphological 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; Yun *et al.*, 2003), and a more medial region with low *Pax6* 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) (Figure 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 non-autonomous 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; Yun *et al.*, 2003; Wang *et al.*, 2013; Roychoudhury *et al.*, 2020; Salomone *et al.*, 2021) and *Dlx* gene families expressed during maturation of both progenitors and neurons in the LGE (Porteus *et al.*, 1991; Porteus *et al.*, 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; Martin-Ibanez *et al.*, 2012). The *Ascl1*$^{+}$*/Dlx1/2*$^{-}$ and *Ascl1*$^{+}$*/Dlx1/2*$^{+}$ progenitors are inferred to emerge in sequence (Martin-Ibanez *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 post-mitotic 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 embryonic day E10.5 and continues until birth, E19.5, in mice (Deacon *et al.*, 1994; Sheth & Bhide, 1997; Matsushima & Graybiel, 2020) (Figure 2B), although some are also born during early postnatal stages (Das & 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 though loss of *Foxo1* expression (Waclaw *et al.*, 2017). Additional factors such as *ebf1* also play a role in SPN survival (Lobo *et al.*, 2006; Lobo *et al.*, 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 (Martin-Ibanez *et al.*, 2010; Martin-Ibanez *et al.*, 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 KO results in a near 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 medial ganglionic eminence (MGE, **Figure 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 & Harwell, 2017). Other progenitors in the MGE include SAPs and SNPs of the VZ, in addition to other IPs and bRGC of the SVZ (Turrero Garcia & Harwell, 2017); **Figure 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); **Figure 1B**).

As in the LGE, the morphological 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 apical progenitors (AP) and BP can also be further divided into sub-populations based on their transcriptional identity which controls their metabolism, cell-cycle dynamics or overall neurogenic role. For example, one AP population displays high expression of 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). Co-expression 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 *CoupTF-2* 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 contributes 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 morphological 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 $ChAT^+$ cholinergic interneurons (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 co-express one or both of the neurochemical markers neuropeptide Y (NPY) and nitric oxide synthase (NOS) and are commonly referred to as low-threshold spiking (LTS) interneurons (Kawaguchi *et al.*, 1995; Munoz-Manchado *et al.*, 2016; Munoz-Manchado *et al.*, 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, morphological, and physiological properties (Magno *et al.*, 2017; Munoz-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; Ahmed *et al.*, 2021). In particular, the *Lhx6*-expressing CINs, also called cholinergic-GABAergic interneurons (Lozovaya *et al.*, 2018), display different physiological properties with higher firing rate and larger dendritic field compared to other CINs. Indeed, co-expression of neurotransmitters such as acetylcholine, glutamate, and GABA in different CINs further highlight their functional diversity (Nelson *et al.*, 2014; Granger *et al.*, 2016). Newly developed approaches e.g. AAV-based tools (Vormstein-Schneider *et al.*, 2020) (Table 1) will help to selectively label and further study of 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 caudal ganglionic eminence (CGE) (Marin *et al.*, 2000; Ma *et al.*, 2012) (Figure 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 5HT3a serotonin receptor (Nery *et al.*, 2002; Lee *et al.*, 2010) (Figure 1C). The peak proliferation of CGE-derived NPCs occurs 3 days 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 5HT3a (Munoz-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 (Munoz-Manchado *et al.*, 2018). Other striatal interneuron subtypes include a substantial population of Tyrosine Hydroxylase (TH) positive 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 excitatory postsynaptic potentials (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 (Ibanez-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) (Figure 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 morphological 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-positive SPNs and a small number of calretinin (CR) positive 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 due to 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 circuits. From the LGE, postmitotic cells migrate predominantly radially over a short distance, following a number of migratory cues towards the striatum (Bayer, 1984; Halliday & Cepko, 1992; Song & 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 & 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-Cervino *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-Cervino *et al.*, 2015). The rapid downregulation of *Nkx2.1* acts as a post-mitotic transcriptional switch (**Figure 3B**) in cortical-fated cells, as it transcriptionally inhibits cortical migration cues such as Nrp2 (Butt *et al.*, 2008; Nobrega-Pereira *et al.*, 2008). In contrast, striatal-fated cells maintain *Nkx2.1* expression into adulthood, preventing cortical migration (Villar-Cervino *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 caudo-rostral 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 (**Figure 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) (**Figure 2B**)**.** Similarly, different types of CR^+ interneurons do not distribute homogeneously; for example, those co-expressing the Ca^{2+} 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 & Walsh, 2002; Ciceri *et al.*, 2013; Turrero Garcia *et al.*, 2016) (**Figure 2A**; **Table 1**). However, other studies analyzing the same data set 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 & Hickey, 1982; van der Kooy & Fishell, 1987; Song & 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 & Graybiel, 2020) (**Figure 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 IP, both derived from a RGC lineage. During early stages of neurogenesis (E9.5-12.5), apical IPs express the transcription factor *Ascl1* and have limited capacity to produce striosomal SPNs. During later phases of neurogenesis (E13.5-18.5), basal IPs expressing both *Ascl1* and *Dlx1* produce matrix SPNs. It is possible that *Ascl1*, in conjunction with *Gsx2*, in SAPs inhibit 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, by Tinterri and colleagues, used a combination of transgenic animals and time-lapse video imaging to provide insight into the seemingly uniform distribution of both dSPNs and iSPNs (Tinterri *et al.*, 2018). 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).

Lastly, using a combination of transgenic *Dlx1*-Cre recombinase mice under the control of a fast-acting version of Tamoxifen (4-OHT), Matsushima and colleagues 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 surrounded by increasingly later-born SPNs (Matsushima & Graybiel, 2020). They found that this center-surround rule was universal and was employed in both anterior and posterior parts of the striatum, despite absolute differences in the birthdate of SPNs in these distinct parts. Moreover, they found that a key anatomical structure, the so-called striosome-dendron bouquet, forms during a very specific period of neurogenesis in the mouse (i.e. around E12-13; (Matsushima & Graybiel, 2020); Figure 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 “peri-striosomal boundaries” (Prager & Plotkin, 2019). CINs and SST^{+} interneurons located at the interface between striosomes and matrix have dendrites and axons that traverse across compartmental borders (Kubota & Kawaguchi, 1993; Bernacer *et al.*, 2012; Brimblecombe & 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 inter-compartmental 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 anatomical subregion (e.g. DLS and DMS). These distinct anatomical domains contain a mixture of dSPNs and iSPNs that are 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; Krajeski *et al.*, 2019). These anatomical domains are thought to be part of larger parallel functional pathways through the basal ganglia (Graybiel & 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 & Silberberg, 2014) or diverge and form biased synaptic connections on either dSPNs or iSPNs (Wall *et al.*, 2013; Johansson & 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 alpha1 (Tα1) promoter (Table 1). Interestingly, different tubulin isotypes 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 van Heusden study combined a Tα1-Cre recombinase construct with a reporter construct incorporating a flexible excision (FLEx) CβA-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 Tα1) in the VZ had characteristic 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 (pH3) but new technology, with for example FUCCI (Sakaue-Sawano *et al.*, 2008) will allow for more detailed insights (Table 1). Conversely, the progenitors that expressed TdTomato (i.e. not expressing Tα1 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^+ Tα1-expressing progenitors were collectively referred to as apical IPs (aIP) and the $TdTomato^+$ non-Tα1-expressing progenitors simply as other progenitors (OPs) (Figure 2A). This also conforms to nomenclature of similar cortical (Tyler & 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 (Figure 2A). The van Heusden study, together with recent observations in cortex (Ellender et al., 2018; Ellender et al., 2019), suggest that a neuron's lineage 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 how progenitor identity relates to final function.

Unlike for SPNs, no study has yet investigated the correlation between the identities of progenitor cells (transcriptional, morphological or otherwise) with 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 medio-lateral 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 post-mitotic, 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 post-mitotic cell is controlled by the transcriptional profile of the underlying progenitor is only beginning to be understood; see for example (Mi *et al.*, 2018) **Figure 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. bRGC and BP) (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 & 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 & 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 and colleagues 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 to early aIPs. This results in early aIPs generating many of the striosome SPNs, and later bIPs generating many of the matrix SPNs (Kelly *et al.*, 2018); Figure 2A and 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 morphological 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 (Figure 2A). Especially during later stages of embryonic development, bIPs become the primary proliferative cells in both ganglionic eminences (Smart, 1976) and it will 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 technology (sc-RNAseq) 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 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 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 (Munoz-Manchado *et al.*, 2018; Mahfooz & Ellender, 2021) (Table 1) to transcriptionally map aIP- and OP-progenitor-derived cortical neurons to a published large-scale sc-RNAseq neuronal classification of cortex (Tasic *et al.*, 2018). They found that the cortical aIP progenitors, as defined by the selective expression of the Tα1 promoter during early development, were more restricted in the types of cortical neurons they generated than OP progenitors, 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 (Martinez-Cerdeno *et al.*, 2006; Tyler & Haydar, 2013; Taverna *et al.*, 2014; Guillamon-Vivancos *et al.*, 2018) 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 & Muller, 2013; Taverna *et al.*, 2014). Lastly, the data indicates 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 longstanding 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 & Walsh, 2002). As previously described, postmitotic transcriptional switches such as *Nkx2.1* can determine cortical versus striatal fate (Villar-Cervino *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 & Kaznowski, 1991; Desai & 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 & Molnar, 2015) (Figure 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 & 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 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 to 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 (Figure 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 & 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 & 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 scRNA-seq 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; Krajeski *et al.*, 2019) and FS 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 birthdate 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) (Figure 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 amongst SPNs with similar birthdates, 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 (Krajeski *et al.*, 2019), suggesting they could result from synaptic plasticity driven by early neural activity (Cinotti & 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 towards 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 Huntington's disease (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 & 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 a HD mouse model, it was shown that mHtt affects levels of neurogenesis and can result in increased numbers of embryonic progenitors (Lorincz & Zawistowski, 2009), something that also has been observed in post-mortem 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 & Folstein, 1995; Friedman *et al.*, 2020); given that striosomal SPNs are generated mainly from aIP 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 recent Review on altered striatal development in HD (Lebouc *et al.*, 2020).

Autism spectrum disorder (ASD) is a group of neurodevelopmental pathologies that cause significant social and communication challenges and restrictive/repetitive behaviors. Evidence from human post-mortem 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; Griesi-Oliveira *et al.*, 2020; 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^+ post-mitotic interneurons (Close *et al.*, 2012), and Ephrin type-B receptor 1 (Ephb1), a regulator of striatal and cortical interneuron migration (Villar-Cervino *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 further research is needed on 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 & Kriegstein, 2017; Pollen *et al.*, 2019), air-liquid interface cerebral organoids from mouse or human iPSC (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 neurological 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 & 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 papers and would like to refer also this recent Review (Bjorklund & 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 E12.5-13.5 or E14.5 MGE progenitor cells can differentiate into interneurons and integrate into early postnatal circuits (Alvarez-Dolado *et al.*, 2006; Martinez-Cerdeno *et al.*, 2010). Moreover, transplantation of embryonic progenitor cells into the postnatal brain has been successfully trialed in pre-clinical models as potential replacement strategies for the treatment of disorders such as Parkinson's disease and epilepsy (Martinez-Cerdeno *et al.*, 2010; Hunt & Baraban, 2015; Upadhya *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 (Figure 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 (hPSC) grafted into 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 (Quattrocolo *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) have 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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Figure legends

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 lateral ganglionic eminence (LGE), medial ganglionic eminence (MGE), caudal ganglionic eminence (CGE), preoptic area (POA) and septal neuroepithelium (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 basal radial glia (bRGC), and other intermediate progenitors (IP) (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 striatal projection neurons (SPNs, left) and interneurons (right). SPNs include both the direct-pathway dopamine D_1-receptor-expressing SPNs (dSPNs; in red) and the indirect-pathway dopamine D_2-receptor-expressing SPN types (iSPN; in red), which send axonal projections to downstream basal ganglia nuclei including, respectively, the substantia nigra pars reticulata (SNr)/internal globus pallidus (GPi) and external globus pallidus (GPe). The local populations of diverse interneurons are integrated within the striatum and can modulate the activity of SPNs. PV: Parvalbumin, TH: Tyrosine Hydroxylase, SST: Somatostatin, CR: Calretinin, VIP: Vasoactive Intestinal Polypeptide, ChAT: Choline Acetyltransferase.

Figure 2: Embryonic progenitor origin controls many aspects of mature striatal neuron position and connectivity. (A) (*i*) LGE apical IPs (aIPs) and basal IPs (bIPs) generate SPNs fated to the striosomes (aIP^Ss-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 tubulin α1 (Tα1) in the LGE generate SPNs that receive stronger innervation from the medial prefrontal cortex (mPFC), whereas other progenitors (OP), 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 substantia nigra (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 (PMC), however whether the underlying progenitor cells predetermine this is not known. (*vi*) Apical neurogenesis in the MGE biases towards the generation of somatostatin (SST) interneurons, whereas basal neurogenesis preferentially generates parvalbumin (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 a neuron's chemical identity and spatial distribution.

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-Cervino *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 & Jabaudon, 2020). These two models could also co-exist 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 down-regulates 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 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.

TABLE 1: Recent technological advances in embryonic progenitor research.	
METHODS	**KEY FINDINGS and REFERENCES**
ANALYSIS OF GENE EXPRESSION	
Single-cell RNA sequencing (sc-RNAseq) Quantification of RNA transcripts with single-cell resolution	• Uncovered new MGE-derived neuronal progenitor cell (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 sub-types (Chen *et al.*, 2017) • Further subdivisions within dSPN and iSPN and additional striatal SPN types (Zeisel *et al.*, 2018) (Gokce *et al.*, 2016; Saunders *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 (Munoz-Manchado *et al.*, 2018) • Transcriptional classification of aIP and OP-progenitor derived cortical neurons (Ellender *et al.*, 2019)
Spatial Transcriptomics Visualizing RNA transcripts in specific areas with spatial resolution (50 μm)	• Spatial transcriptomics enables to generate 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	• Multiplexed Error-Robust FISH (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 Mosaic Analysis with Double Markers provides genetic dissection of intrinsic gene function	• This genetic mosaic strategy enables to sparsely alter single cells whilst maintaining a "normal" local microenvironment. This study showed that *Lgl1* is a critical regulatory element for embryonic cortical neurogenesis and cell-autonomous control of RGC-mediated glia genesis and postnatal NPC (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 birthdate and isolate any type of progenitor in contact with the VZ and to follow cell migration of newly born neuron (Telley *et al.*, 2016; Govindan *et al.*, 2018)
In utero electroporation Label embryonic progenitors and track their progeny through prenatal and postnatal periods	• *In utero* electroporation of constructs driving recombinase systems (e.g. Cre) under the control of promoter sequences specific for certain progenitors in combination with reporter constructs allow for labeling of progenitors and progeny. Employed to label apical IPs in striatal and cortical proliferative regions (Gal *et al.*, 2006; Stancik *et al.*, 2010; Tyler & Haydar, 2013; Ellender *et al.*, 2019; van Heusden *et al.*, 2021), and basal IP cells and/or bRGC 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 human pluripotent stem cells (hPSCs) to mature neurons in 37 days in vitro (Comella-Bolla *et al.*, 2020). Transplantation experiments show that NPCs survive and differentiate (for at least 3-months) in the mouse striatum (Martinez-Cerdeno *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 and 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 AAV: Labeling of distinct neuronal subtypes	• Mapping of synaptic inputs to projection neurons and cholinergic interneurons in the dorsal striatum using modified rabies virus tracing (Guo *et al.*, 2015) • 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 *In vitro* 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 *FoxG1* 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 analyzed 35 ASD risk genes in 5 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