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REVIEW

Development of Cortical Interneurons

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Inhibitory local circuit neurons (LCNs), often called interneurons, have vital roles in the development and function of cortical networks. Their inhibitory influences regulate both the excitability of cortical projection neurons on the level of individual cells, and the synchronous activity of projection neuron ensembles that appear to be a neural basis for major aspects of cognitive processing. Dysfunction of LCNs has been associated with neurological and psychiatric diseases, such as epilepsy, schizophrenia, and autism. Here we review progress in understanding LCN fate determination, their nonradial migration to the cortex, their maturation within the cortex, and the contribution of LCN dysfunction to neuropsychiatric disorders.
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INTRODUCTION

The cerebral cortex mediates higher-order cognitive processing, learning, and memory. These functions are made possible by intricate interactions of glia, excitatory projection neurons, and inhibitory interneurons. Most cortical interneurons, also termed local circuit neurons (LCNs), primarily use the neurotransmitter GABA (γ-aminobutyric acid) to modulate neural activity. LCNs comprise about 20% of the cortical neurons and can be subclassed based on neurochemical markers, connectivity, and physiological properties (Ascoli *et al*, 2008; DeFelipe *et al*, 2013; Kepecs and Fishell, 2014). Nearly all LCNs can be separated into three neurochemically distinct subgroups that express the calcium binding protein parvalbumin (PV), neuropeptide somatostatin (SST), or the ionotropic serotonin receptor 5HT3aR (Lee *et al*, 2010). The groups are biased for additional distinctions. For example, the PV subgroup tends to have a very rapid and nonaccommodating 'fast-spiking' firing response to injected current and to target pyramidal neuron somata, proximal dendrites, or axon-initial segments. The SST subgroup tends to have burst spiking or accommodating features and to target distal dendrites. The 5HT3aR subgroup includes vertically oriented, bipolar or bitufted LCNs that tend to target other interneurons. As we shall see below, the PV-SST-5HT3aR subgroupings also have biases for different spatial and temporal origins in the ventral forebrain.

LCNs have a vital role in the development and function of cortical networks. Dysfunction of LCNs has been associated with neurological and psychiatric diseases, such as epilepsy, schizophrenia, and autism. Here we review the progress in understanding LCN fate determination, their nonradial migration to the cortex, their maturation within the cortex, and the contribution of LCN dysfunction to neuropsychiatric disorders.

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SPATIAL AND TEMPORAL ORIGINS OF CORTICAL INTERNEURONS IN THE TELENCEPHALON

In general, the CNS develops from the neural tube by the radial migration of neurons from the proliferative zones along the tube's medial wall, to the mantle zones at the tube's periphery. Cortical projection neurons (glutamatergic, excitatory) follow this scenario. In contrast, cortical LCNs originate in subcortical areas of the telencephalon, in the same general region where the GABAergic projection neurons of the basal ganglia are being produced. The reason for this arrangement is not known, but in order to have a mixture of excitatory and inhibitory neurons in the evolving cerebral cortex the dorsal proliferative zone, generating glutamatergic neurons, could have been modified with the capacity to generate GABAergic ones. However, this would have been a highly complex adjustment as distinct extracellular signaling systems and transcription factor cascades are involved in glutamatergic *vs* GABAergic fate determination (Hebert and Fishell, 2008). Alternatively, GABAergic neurons could be imported into the evolving cortex from more ventrally located parts of the neural tube that were already producing these cells. Evolution chose importation, and although there has been some support for the notion that cortical LCN origins in primates may include the cortex itself (Jakovcevski *et al*, 2011; Letinic *et al*, 2002; Yu and Zecevic, 2011), the bulk of cortical LCN neurogenesis in

humans and other primates occurs in the ventral, subcortical forebrain (Hansen *et al*, 2013; Ma *et al*, 2013). The following section discusses the main spatial and temporal origins of cortical LCNs, based mainly on studies in rodents, and their relationship with LCN subgroup fate.

The rostral forebrain, or telencephalon, consists of cortical and subcortical developmental domains. The subcortical (also termed subpallial or pallidal) telencephalon consists of five major subdivisions: the lateral ganglionic eminence (LGE), medial ganglionic eminence (MGE), caudal ganglionic eminence (CGE), septum (SE), and preoptic area (POA). Multiple studies in rodents, generally supported by additional studies in ferrets and primates (Anderson *et al*, 2002; Hansen *et al*, 2013; Ma *et al*, 2013), show that the MGE and CGE are the primary sources of cortical LCNs, with a small, diverse subset also originating in the POA (Gelman *et al*, 2009).

Medial Ganglionic Eminence

The ganglionic eminences can be divided into medial (MGE), lateral (LGE), and caudal (CGE) ganglionic eminence based on their dorsal–ventral and rostral–caudal locations within the subpallium. The MGE gives rise to about 60% of LCNs in rodents. Studies using transgenic mice found that both the somatostatin (SST)- and parvalbumin (PV)-expressing subgroups originate mainly in the MGE (Butt *et al*, 2005; Wonders and Anderson, 2006; Xu *et al*, 2004). On the basis of the study of human holoprosencephaly, in which the MGE-like region of the human ventral forebrain fails to form, this tissue also appears to generate PV- and SST-expressing LCNs in humans (Fertuzinhos *et al*, 2009).

Dissections and transplantations of subregions of rodent MGE found a strong bias for SST-expressing LCNs to be generated in the dorsal MGE, whereas PV-LCNs are generated by both dorsal and ventral MGE regions (Flames *et al*, 2007; Inan *et al*, 2012; Wonders *et al*, 2008). Thus far, only one LCN type has been identified as having a distinct MGE source. The axo-axonic (chandelier) cell, a fast-spiking subclass of LCN that also frequently expresses detectable levels of PV, has a strong bias for origination within the ventral-most region of the MGE at the end of cortical neurogenesis (Inan *et al*, 2012; Taniguchi *et al*, 2013).

In terms of birthdate, MGE LCNs follow the same general inside-out relationship of birthdating to laminar location in the cortex as do the projection neurons (Butt *et al*, 2005; Xu *et al*, 2004). Within a given layer, PV and SST LCNs have similar birthdates. However, as the ratio of PV to SST LCNs is roughly 1.5 : 1 in layers 5 and 6, but is closer to 3 : 1 in layers 2 and 3 (Xu *et al*, 2010b), a higher proportion of all SST LCNs are born earlier in the neurogenic period than is the proportion of all PV-LCNs.

In addition to location and time, retroviral lineage analysis suggests that PV and SST interneurons can be derived from the same radial glial cell (Brown *et al*, 2011). To connect this finding with spatial and temporal biases for differential origins of SST- and PV-expressing LCNs, evidence suggests that PV interneurons preferentially originate from intermediate progenitor divisions within the subventricular zone. This suggestion is based on the analysis of mice lacking cyclin D2, which is expressed in intermediate progenitors throughout the telencephalon and promotes their proliferation, and which have a reduction of PV but not SST interneurons in the neocortex and hippocampus (Glickstein *et al*, 2007a, b). Interestingly, there appear to be less cyclin D2-expressing cells in the dorsal-most MGE (Glickstein *et al*, 2007a).

Caudal Ganglionic Eminence

The CGE is the other main subpallial source of cortical LCNs (Anderson *et al*, 2001; Nery *et al*, 2002, 2003), generating at least 30% (Miyoshi *et al* 2010). Morphologically, the CGE exists as a caudal fusion of the MGE and LGE that begins at the coronal level of the mid-thalamus. Transplantation studies as well as genetic fate mapping have demonstrated that the CGE generates a remarkable diversity of LCN subclasses, variably overlapping, based on their expression of calretinin, vasoactive intestinal protein (VIP), reelin, and NPY (Butt *et al*, 2005; Miyoshi *et al*, 2007, 2010). Remarkably, nearly all of these subgroups express the 5HT3aR (Tricoire *et al*, 2010). An additional feature of the CGE is that LCNs from this region are born relatively late in neurogenesis, and do not follow the 'inside-out' relationship of birthdate to laminar location found for the MGE-derived cortical LCNs (Butt *et al*, 2005; Rymar and Sadikot, 2007; Xu *et al*, 2004).

Preoptic Area

The preoptic area (POA) is a telencephalic region ventral to the MGE that also expresses Nkx2.1 in progenitor cells (Flames *et al*, 2007). Using *in utero* electroporation as well as genetic fate mapping from Nkx5.1-expressing cells, the POA was recently shown to give rise to a small number of LCNs (Gelman *et al*, 2009). These were found mainly in the superficial cortex, and about a third expresses NPY but not SST, and tended to have a distinctive, rapidly adapting electrophysiological property. Interestingly, these preoptic-derived LCNs, unlike those developing from Nkx2.1+ progenitors in the MGE, do not express the transcription factor Lhx6 that, in the MGE, lies downstream of Nkx2.1 in the specification of PV- and SST-expressing LCNs.

CORTICAL INTERNEURON FATE DETERMINATION

As genetic fate-mapping and transplantation studies find clear biases for the generation of distinct cortical LCN subclasses from distinct subcortical progenitor domains, LCNs appear to be fate committed either at or shortly after cell cycle exit. Fate determination of the MGE-derived LCNs requires the transcription factor Nkx2.1 (Sussel *et al*, 1999; Xu *et al*, 2004, 2005). Upstream of Nkx2.1, the morphogen sonic hedgehog (SHH) is required for initial patterning of

the Nkx2.1 domain in the MGE (Fuccillo *et al*, 2004), and to maintain Nkx2.1 expression in progenitors during neuronogenesis (Xu *et al*, 2005, 2010b). Downstream of Nkx2.1, Lhx6, a direct target of Nkx2.1 (Du *et al*, 2008), is expressed permanently in most MGE-derived LCNs from around the time of cell cycle exit (Lavdas *et al*, 1999; Liodis *et al*, 2007). Little is known about the transcriptional cascades leading to terminal maturation of cortical LCNs in the postnatal cortex, although Sox6 appears to be an important effector of Lhx6 signaling (Azim *et al*, 2009; Batista-Brito *et al*, 2009), and Satb1 also has a role downstream of Lhx6 (Close *et al*, 2012).

The molecular mechanisms underlying the differential fate determination of SST- *vs* PV-expressing LCNs in the MGE are not clear. It has been proposed that there are distinct progenitor domains within the MGE that give rise to different classes of LCNs (Flames *et al*, 2007). However, transplantation studies in which cells are labeled with markers that indicate they were still in the cell cycle shortly prior to transplantation, thus controlling for postmitotic migration within the proliferative zone, do not support the existence of such clear demarcations of domains committed to the generation of distinct LNC subclasses (Inan *et al*, 2012). Although the dorsal MGE is strongly biased for generating SST-expressing interneurons, PV-expressing LCNs are generated throughout the MGE.

To date, there has been relatively little progress in determining how distinct subclasses of LCNs become specified. In the MGE, SST-expressing LCNs appear to be specified at higher levels of Shh signaling, which appear to be present in the dorsal-most MGE, whereas PV-expressing LCNs require lower levels (Xu *et al*, 2010a). The putative transcription factor LMO4 may also promote PV-LCN fate (Au *et al*, 2013), but a connection between Shh signaling and LMO4 expression, not to mention factors responsible for interneuron subtype fate determination, has yet to be established.

Relative to MGE-derived LCNs, even less is known about the fate determination of the highly diverse subclasses of CGE-derived LCNs. On the top of the transcriptional hierarchy are two homeobox genes, Gsx1 and Gsx2. The transcription factors generally function in the specification of neuronal subclasses from LGE and CGE (Waclaw *et al*, 2009). Consistent with this role, elimination of Gsx2 results in a selective reduction of the CGE-derived vertically oriented CR+ population (Xu *et al*, 2010a). CoupTF2 is an additional transcription factor that controls the generation of CGE-derived interneurons (Lodato *et al*, 2011b), although many more, particularly those involved in interneuron subtype fate determination, remain to be discovered.

REGULATION OF CORTICAL INTERNEURON MIGRATION

Motogens

In their sojourn from the subcortical telencephalon into the cerebral cortex, LCNs face a variety of environments, for which a variety of chemorepulsion, chemoattraction, migratory substrates, and motogens contribute to the guidance process (Guo and Anton, 2014). First, multiple transplantation and culture studies have demonstrated that the LCN precursors (postmitotic, fate committed) have a strong migratory drive. Hepatocyte growth factor/scatter factor (HGF/SF), GDNF, BDNF, and NT4 are expressed by cells within the paths of migrating LCNs and have all been shown to stimulate tangential (nonradial glial-guided) migration (Polleux *et al*, 2002; Powell *et al*, 2001; Pozas and Ibáñez, 2005). Dopamine D1 receptor signaling also appears to promote LCN migration (Crandall *et al*, 2007). With a strong drive to migrate, the LCN precursors then use a combination of attractive and repulsive cues, together with permissive substrates, to guide their way into and across the overlying cortex.

Guidance Cues

To push the LCN precursors away from the proliferative zones lining the lateral ventricle, both Eph-ephrin and Slit-Robo signaling appears to function (Rudolph *et al*, 2010; Zhu *et al*, 1999; Zimmer *et al*, 2008). As the LCNs approach the developing striatal mantle zone, semaphorin-neuropilin-mediated chemorepulsion comes into play. Cortical LCNs express the Sema receptor, Neuropilin-2, and therefore migrate away from the semaphorin-expressing striatum, whereas striatal LCNs, which also derive mainly from Nkx2.1-expressing progenitors in the MGE, are neuropilin-2-negative (Le *et al*, 2007; Marín *et al*, 2001; Nobrega-Pereira *et al*, 2008). Interestingly, in contrast to cortical MGE-derived LCNs, Nkx2.1 expression is maintained in striatal LCNs (Marin *et al*, 2000; Nobrega-Pereira *et al*, 2008) and this expression prevents the expression of NPN2 and hence prevents the chemorepulsion away from striatum.

At least two chemoattractants affect the migration of LCN precursors into and within the cortical plate. First, a membrane-bound form of neuregulin1 appears to form a preferential track for ErbB4-expressing LCNs as they migrate from the striatum to the cortex (Flames *et al*, 2004). Neuregulin-ErbB4 signaling also functions to attract migrating LCNs into the cortex. In the cortex, SDF (Cxcl12) signaling via the Cxrc4 receptor on migratory LCNs results in a preference for their migration to track above and below the developing cortical plate (Stumm *et al*, 2003; Tiveron *et al*, 2006). Netrin signaling also contributes as attraction to cortical migratory streams, particularly the one that courses in layer 1, just below the pial surface (Sanchez-Alcaniz *et al*, 2011). The migratory drive to move in a generally lateral to medial direction across the cortex is not clear, but may involve LCN chemorepulsion of each other. This effect may be mediated by GABA (Cuzon *et al*, 2006), such that LCNs would tend to migrate down their own density gradient.

Cortical Plate Invasion and Migration Stoppage

Downregulation of SDF-CxCr4 signaling permits LCN invasion of the cortical plate from their migratory streams,

both below the pial surface and in the cortical intermediate zone (Sanchez-Alcaniz *et al*, 2011; Wang *et al*, 2011). How the LCNs determine their final position is not known, but it is clear that at least the MGE-derived LCNs are following cues generated by the cortical pyramidal neurons (Hevner *et al*, 2004; Lodato *et al*, 2011a; Pla *et al*, 2006). Finally, GABA signaling may form an important stop signal for the LCNs, as upregulation of the Kcc2, which results in a shift of GABA-A receptor effects from depolarizing to hyperpolarizing, is associated with the termination of MGE-derived LCN migration (Bortone and Polleux, 2009). Genetically introduced hyperpolarization also can result in stoppage of CGE-derived LCN migration (De Marco Garcia *et al*, 2011). However, the extent to which this effect is due to altered intrinsic signaling, for example by changing mitochondrial dynamics, *vs* altered ability to respond to extrinsic depolarizing signals, remains to be determined.

Postmigratory Maturation

The final stage of LCN maturation involves terminal, postmigratory differentiation within the cortical plate, and can be divided into two stages. In the first stage, LCN attains their mature fates, defined by their distinctive connectivities, neurochemistries, and firing properties, which culminate in their attaining distinct functions within juvenile cortical circuits (Ascoli *et al*, 2008). A detailed discussion of this process is beyond the scope of this review, but interacting influences of transcription factors (Close et al, 2012; Cobos *et al*, 2005), neurotransmitters (Eggan *et al*, 2012), neurotrophins (Huang *et al*, 1999), cell adhesion molecules (Pillai-Nair *et al*, 2005), and their activities are clearly in play (Bartolini *et al*, 2013; Batista-Brito and Fishell, 2009). The second stage of LCN maturation occurs in concert with cortical circuitry maturation, a process that begins in the early postnatal time period but is not finally achieved in all cortical regions until adolescence or young adulthood. For example, PV expression by chandelier LCN axon terminals reaches a peak in monkey prefrontal cortex just prior to the initiation of excitatory axon pruning, raising the possibility that interneuron maturation may be directing the refinement of cortical circuitry (Anderson *et al*, 1995). Indeed, studies in GABA-deficient transgenic mice clearly demonstrate a role of LCN function in the alterations of excitatory connectivity that accompany critical period plasticity (Hensch, 2005). As we shall discuss below, recent evidence links a specific system, neurogulin-Erbb4 signaling, in regulating both PV-LCN synaptogenesis and cortical excitatory neuron pruning in a manner that may shed light on an etiology of schizophrenia (Del Pino *et al*, 2013).

NEURODEVELOPMENTAL DISORDERS ARISING FROM DYSFUNCTIONAL CORTICAL INTERNEURONS

As reviews of the associations between disruption of LCN function and neuropsychiatric disorders have been published recently (Inan *et al*, 2013; Lewis *et al*, 2012; Marin, 2012), this section will focus on a few LCN–mental illness links to schizophrenia that are bolstered by data from mouse models and that also relate to developmental points discussed above (Figure 1).

22q11.2 Deletion Syndrome (22qDS)

One of the best-established genetic factors underlying the risk of developing schizophrenia is the microdeletion in chromosomal region 22q11.2 (Bassett *et al*, 2010). 22qDS (DiGeorge syndrome, velocardiofacial syndrome) occurs in roughly 1 in 3000 births (Shprintzen *et al*, 2005). Patients display impairments in a variety of cognitive tasks (Karayiorgou *et al*, 2010) and roughly 30% will receive the diagnosis of schizophrenia (Murphy *et al*, 1999; Pulver *et al*, 1994). In fact, this mutation constitutes ~1–2% of the sporadic cases of schizophrenia (Bassett *et al*, 2008; Xu *et al*, 2008).

Using a mouse model of 22q11.2 deletion syndrome, Meechan *et al.* showed that the distribution of PV + cortical LCNs is altered in the 22qD mouse cortex, although the total number of PV + neurons is not changed (Meechan *et al*, 2009). The presence of this pathology in mouse prefrontal

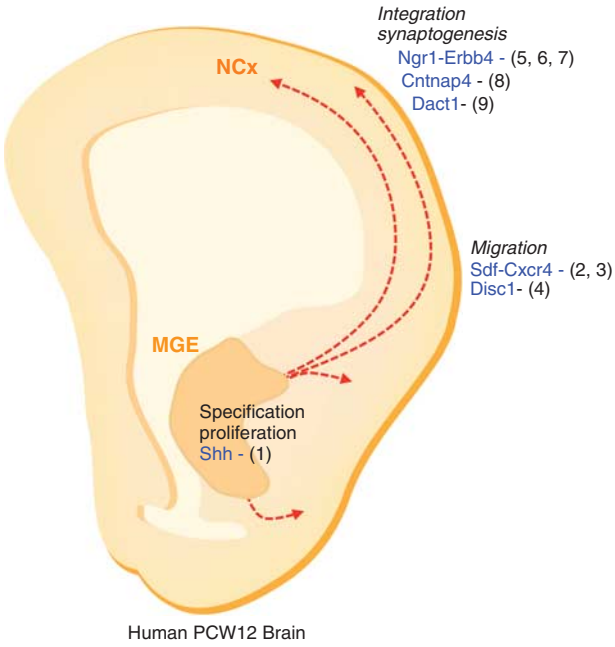

Figure 1. Development of cortical LCNs in humans in relation to proposed LCN-related disruptions that contribute to neuropsychiatric disorders. This schema shows a human coronal-plane hemisection at roughly 12 weeks of gestation. Basic stages of cortical LCN development are highlighted, including proliferation and fate determination, nonradial migration, and then initial integration into cortical circuitry. References link these stages with studies, mainly in rodents, that examine the functions disease-related genes in relation to these developmental stages. (1)—Maynard *et al*, 2013; (2)—Toritsuka *et al*, 2013; (3)—Meechan *et al*, 2012a; (4)—Steinecke *et al*, 2012; (5)—Del Pino *et al*, 2013; (6)—Yang *et al*, 2013; (7) —Tai *et al*, 2014; (8)—Karayannis *et al*, 2014; (9)—Arguello *et al*, 2013. Ncx, neocortex; MGE, medial ganglionic eminence.

cortex, along with multiple behaviorial deficits associated, like schizophrenia, with PFC dysfunction, also supports the validity of this model (Meechan *et al*, 2013). Both Shh and Cxcr4 signaling are also altered in these mice, raising the possibility that altered LCN subtype fate determination along with migrational abnormalities may contribute to the schizophrenia-related phenotypes in both mice and people with 22qDS (Marin, 2012; Maynard *et al*, 2013; Meechan *et al*, 2012b).

Neuregulin-ErbB4 Signaling in Schizophrenia

Numerous studies identified ErbB4 as a candidate susceptibility gene for schizophrenia (for reviews, see Buonanno, 2011; Rico and Marin, 2011). ErbB4 protein is a receptor tyrosine kinase preferentially expressed by PV- and SST-expressing cortical LCNs (Neddens *et al*, 2011). The Nrg1-ErbB4 interaction has a prominent role in many aspects of neuronal development, including neuronal migration, axon guidance and synapse formation, and plasticity (Mei and Xiong, 2008; Rico and Marín, 2011). ErbB4 mutant mice display hyperactivity, impaired working memory, and decreased PPI (Barros *et al*, 2009; Golub *et al*, 2004; Stefansson *et al*, 2002). Early disruption of ErbB4 using GFAP-Cre (all neural cells) or Dlx5/6-Cre (all forebrain GABAergic cells) mice decreased excitatory synapses, spine density, chandelier axon synapses, synaptic transmission between cortical LCNs and projection neurons, and also impaired prepulse inhibition (PPI) (Barros *et al*, 2009; Fazzari *et al*, 2010). Elimination of ErbB4 with PV-Cre decreased GABAergic transmission, induced locomotor hyperactivity, and caused impairments in PPI, working memory and fear conditioning (Chen *et al*, 2010; Wen *et al*, 2010). Importantly, targeting the ErbB4-signaling pathway with a small-molecule inhibitor of the PI3 kinase improved behavioral phenotypes in two mouse models of schizophrenia-related behavioral deficits, suggesting that ErbB4 signaling could be a medication target for a subset of patients with schizophrenia (Law *et al*, 2012).

A recent paper used Lhx6-Cre to eliminate ErbB4 expression selectively from MGE-derived LCNs shortly after cell cycle exit (Del Pino *et al*, 2013). Although the SST-expressing subgroup was not affected, PV-expressing LCNs had a significant reduction of excitatory inputs. In addition to behavioral deficits that phenocopy some aspects of schizophrenia-related cognitive deficits, these mice, with an interneuron-selective loss of ErbB4 function, also showed a marked reduction of dendritic spines on prefrontal cortical pyramidal neurons. As this reduction also phenocopies a frequently reported finding in schizophrenia and related mouse models (Faludi and Mirnics, 2011), this study supports the possibility that interneuron alterations may be causative, rather than downstream (Lewis *et al*, 2012), of an etiology of schizophrenia. That said, given the heterogeneity of this disorder, etiologies are very likely to occur where LCN dysfunction is downstream of the causative process.

Ventral Hippocampal Hyperactivity

Given the role of GABAergic LCNs, particularly the PV-expressing subgroup, in PFC functions that are frequently found to be disrupted in patients with schizophrenia, it is understandable that most studies on an LCN-related pathophysiology of schizophrenia have focused on the PFC (Lewis *et al*, 2012). However, a connection between LCN dysfunction and hippocampal abnormalities in schizophrenia bears mention. Psychosis has long been associated with enhanced dopamine signaling in the striatum (Abi-Dargham, 2004; Kellendonk *et al*, 2009). Multiple lines of evidence indicate that ventral hippocampal activity, via a circuit that includes the nucleus accumbens and ventral tegmentum, enhances striatal release of DA (Lisman *et al*, 2008). Multiple studies have also documented a remarkable correlation between patients' report of psychosis and their level of hyperactivation of the ventral hippocampus (Schobel *et al*, 2013, 2009; Small *et al*, 2011). These studies raise the possibility that a disease state-producing ventral hippocampal hyperactivation would also produce psychosis. In fact, in contrast to most post-mortem findings in PFC, where PV, GAD67, and other LCN-related measures are reduced but not in a manner consistent with actual cell loss, an excellent study of LCN numbers in hippocampus does report reduced numbers of cortical LCNs (Konradi *et al*, 2011). Remarkably, in a rodent model that produces, among other abnormalities, a reduction of hippocampal LCNs and enhanced striatal DA release, transplantation of LCN precursors into the adult hippocampus corrected the striatal phenotype and the correlating behavioral abnormality (Perez and Lodge, 2013). This finding has been replicated and extended using a transgenic mouse model, in which there is a developmental loss of PV-expressing LCNs in the hippocampus (Gilani *et al*, 2014). Hippocampal transplants into adults of LCN precursors enriched for those committed to PV-expressing fates corrected multiple psychosis-related alterations in this model. Some of these corrections include the increased hippocampal blood flow, the increased ventral tegmental DA neuron firing, and the increased locomotor response to amphetamine. These studies suggest that medication development targeting the enhancement of hippocampal LCN function, if not actual transplants in cases of severe treatment resistance with fMRI confirmation of hippocampal hyperactivity, warrants serious consideration (Gill and Grace, 2013).

Summary and Conclusions

Cortical LCN development involves stages of proliferation, nonradial migration, and cortical integration, and disruptions at each of these stages has been associated with neuropsychiatric disorders. At the same time, improved understanding of how embryonic or neonatal insults can result in later manifestations of cortical dysfunction provides the opportunity to devise novel therapies. Although correcting the initial problem as it happens may not be

realistic, improved understanding of how these problems relate to later cortical dysfunctions, which may themselves shift throughout the maturation process, can allow us to identify windows of opportunity for interventions intended to balance or normalize the downstream pathological sequelae of earlier insults.

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