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REVIEW

Calcium and activity-dependent signaling in the developing cerebral cortex

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ABSTRACT

Calcium influx can be stimulated by various intra- and extracellular signals to set coordinated gene expression programs into motion. As such, the precise regulation of intracellular calcium represents a nexus between environmental cues and intrinsic genetic programs. Mounting genetic evidence points to a role for the deregulation of intracellular calcium signaling in neuropsychiatric disorders of developmental origin. These findings have prompted renewed enthusiasm for understanding the roles of calcium during normal and dysfunctional prenatal development. In this Review, we describe the fundamental mechanisms through which calcium is spatiotemporally regulated and directs early neurodevelopmental events. We also discuss unanswered questions about intracellular calcium regulation during the emergence of neurodevelopmental disease, and provide evidence that disruption of cell-specific calcium homeostasis and/or redeployment of developmental calcium signaling mechanisms may contribute to adult neurological disorders. We propose that understanding the normal developmental events that build the nervous system will rely on gaining insights into cell type-specific calcium signaling mechanisms. Such an understanding will enable therapeutic strategies targeting calcium-dependent mechanisms to mitigate disease.

KEY WORDS: Calcium signaling, Cortical development, Neurodevelopmental disorders

Introduction

Calcium, which lies at the hub of multiple signal transduction pathways, is uniquely situated to transduce dynamic biological inputs into distinct cell behaviors (reviewed by Berridge et al., 2003). Calcium influx in the embryonic brain occurs in response to multiple developmental signals, including electrical activity, and dynamic elevations in cytoplasmic calcium are linked to transcriptional programs that are crucial for development, homeostasis and plasticity (reviewed by Greer and Greenberg, 2008; Lyons and West, 2011). In this Review, we present evidence supporting the idea that spatiotemporally regulated and cell-specific functions of calcium signaling transducers underlie the earliest cellular behaviors that build the cerebral cortex. We focus on calcium entry in developing cortical cells, incorporating lessons gleaned from other developing neural populations. We also detail cell biological outputs influenced by the precise control of cytoplasmic calcium, placing special emphasis on stem/progenitor populations and immature neuroblasts. Moreover, we discuss genetic evidence suggesting that deregulation of intracellular calcium represents a potential node of convergence for neurodevelopmental disorders.

Mechanisms regulating intracellular calcium signaling

Calcium signaling involves both the sensing and transduction of extracellular calcium (Brown et al., 1993), as well as the transport of calcium across the plasma membrane (reviewed by Berridge et al., 2003). Homeostatic tuning of intracellular calcium employs an extensive repertoire of cell surface and organellar ion channels, transporters, pumps and buffers (Fig. 1, Box 1), each possessing distinctive properties (e.g. selectivity, conductance, calcium affinity, kinetics). These effectively stage a dynamic process of intracellular compartmentalization, wherein calcium abundance in different subcellular compartments (e.g. cytoplasm, intraorganellar calcium stores) changes across space and time. Movement of calcium into and out of these compartments enables activation of distinct sets of calcium-sensitive proteins, based on their levels and localization (reviewed by Berridge et al., 2003; Clapham, 2007). How distributed networks of calcium signaling proteins confer signaling specificity in various cellular contexts remains a fundamental question. Below, we briefly describe mechanisms of calcium regulation in developing neural cells. We emphasize spatiotemporal properties of calcium signals, alternative splicing of genes regulating calcium signaling, and cell type-specific expression of calcium-dependent effectors. Coupled with the cellular niche and environmental signals to which a cell is exposed, the intersection of these factors influences calcium dynamics, ultimately dictating the selective activation of gene expression programs (reviewed by Clapham, 2007; Rosenberg and Spitzer, 2011).

Spatiotemporal regulation of calcium signals

Calcium influx through different calcium-permeable channels engages distinct signaling cascades (Fig. 1), in part based on the localization of calcium-sensitive signaling proteins (Bading et al., 1993; Graef et al., 1999; reviewed by Parekh, 2008; West et al., 2001). Cytoplasmic calcium chelators, as well as ion pumps and exchangers that bind or extrude calcium (Fig. 1), create transient spatially-restricted high-calcium microenvironments within cells (reviewed by Parekh, 2008). This enables distinct contributions of local and global calcium elevations to intracellular signaling. Functional knock-in experiments and the use of calcium chelators with different affinities have revealed, for example, that local calcium elevations through L-type voltage-gated calcium channels (VGCCs) are transduced to the nucleus via a shuttle protein to promote activation of the transcription factor CREB (Deisseroth et al., 1996;

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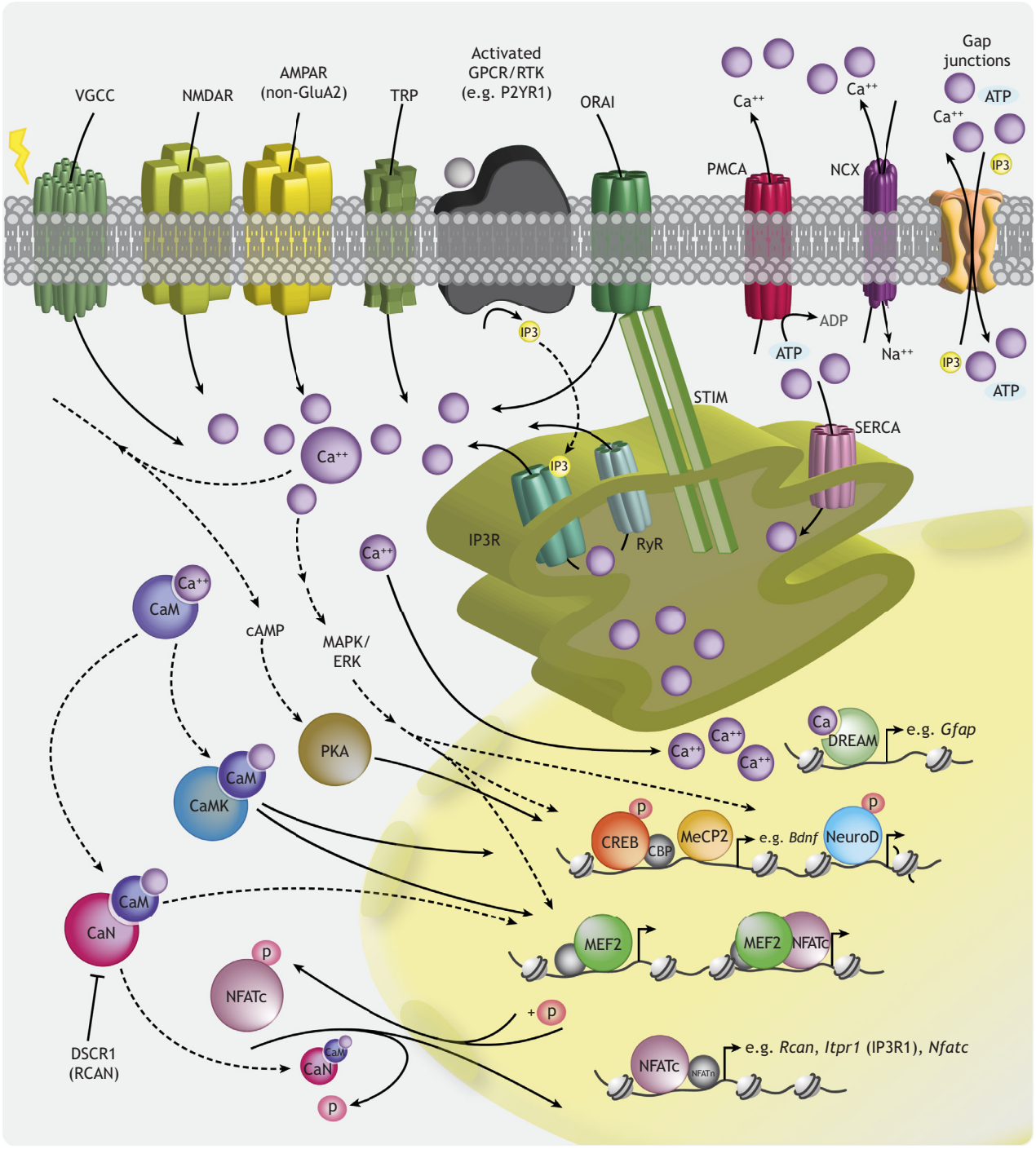

Fig. 1. Overview of intracellular calcium signaling. Schematic highlighting ion channels and pumps mediating cytoplasmic calcium homeostasis and select calcium-dependent pathways that transduce calcium signals to the nucleus. Low resting cytosolic calcium levels are maintained by plasma membrane calcium ATPases (PMCA1-4, encoded by *ATP2B1-4*), which extrude calcium out of the cell and display low calcium efflux capacity but high calcium affinity, and pumps on the surface of the sarco/endoplasmic reticulum (SR/ER) and mitochondria (e.g., the SR/ER calcium ATPases SERCA1-3, encoded by *ATP2A1-3*), which transport calcium into intraorganellar stores. Large calcium elevations are countered by sodium calcium exchangers (NCX1-4, encoded by *SLC8A1-4*) on the plasma membrane and mitochondrial and ER membranes. Calcium-permeable channels mediating calcium influx from the extracellular space include voltage-gated calcium channels (VGCCs), N-methyl-D-aspartate receptors (NMDARs), α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors (AMPARs), transient receptor potential (TRP) channels and ORAI channels. VGCCs are activated by membrane depolarization, whereas ORAI channels allow calcium influx upon ER calcium store depletion. Successive release of calcium from the ER, mediated by IP3R or RyR, depletes ER calcium, which in turn activates STIM calcium sensors (STIM1 and STIM2) to promote their interaction with ORAI channels (ORAI 1-3) and subsequent calcium influx. Gap junctions in the plasma membrane allow for intercellular propagation of calcium signals, through direct transfer of ions or small molecules that are crucial for intracellular signaling (e.g. IP3). Calcium-sensitive proteins in the cytoplasm (e.g. calmodulin; CaM) undergo a conformational change upon calcium binding, initiating distinct signaling cascades to the nucleus that culminate in calcium-dependent transcription. Note that only select calcium-dependent transcription factors with reported roles in the developing nervous system are highlighted; other factors and organellar calcium stores (e.g. mitochondria, lysosomes, Golgi apparatus) are not depicted.

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Box 1. Key mechanisms of calcium entry in developing neural cells

An overview of intracellular calcium signaling is depicted in Fig. 1. Here, we focus on channels mediating two types of calcium entry in immature neural cells that are dependent on environmental signals and result in downstream calcium-dependent signaling and transcription.

Voltage-gated calcium channels (VGCCs) are a primary route of calcium influx in developing neural cells (Fig. 1) in response to neural activity. By converting changes in membrane potential at the cell surface into intracellular calcium elevations, VGCCs couple electrical activity to cell biological processes, including phosphorylation and transcription (reviewed by Catterall, 2011; Zamponi et al., 2015). VGCCs consist of a pore-forming subunit, which allows calcium entry in response to depolarizing stimuli, and auxiliary subunits regulating channel localization and function (reviewed by Catterall, 2011; Zamponi et al., 2015). VGCCs are divided into families based on their physiological properties, and different channels display unique properties and localization. This enables distinct roles for VGCCs in different tissues and particular combinations of deficits associated with specific VGCC mutations (reviewed by Catterall, 2011; Zamponi et al., 2015).

Another major source of calcium influx is store operated calcium entry (SOCE), which is activated upon endoplasmic reticulum (ER) calcium store depletion in response to extracellular signals (Fig. 1) (reviewed by Prakriya and Lewis, 2015). SOCE is mediated by ORAI plasma membrane channels (ORAI1-3, also referred to as calcium release-activated calcium, or CRAC, channels) and the stromal interaction molecule (STIM) family of ER calcium sensors (reviewed by Putney et al., 2017). Activation of plasma membrane receptor tyrosine kinases or G-protein coupled receptors by extracellular ligands promotes inositol trisphosphate (IP3)- or ryanodine (Ry)-mediated release of calcium into the cytosol from the ER lumen (reviewed by Prakriya and Lewis, 2015). When intraluminal calcium is depleted, STIM proteins on the ER membrane oligomerize and translocate to ER-plasma membrane junctions, trapping and interacting with ORAI channels to modulate calcium influx (reviewed by Prakriya and Lewis, 2015). SOCE through ORAI channels can generate distinct patterns of intracellular calcium fluctuations to regulate various molecular events, including transcriptional activation (reviewed by Lewis, 2011).

Dolmetsch et al., 2001; Ma et al., 2014). In hippocampal neurons, it has been suggested that the calcium/calmodulin-activated phosphatase, calcineurin (CaN), is tethered to L-type VGCCs via an anchoring protein to contribute to the regulation of calcium influx through these channels (Oliveria et al., 2007, 2012).

Local translation of calcium signaling components can also influence calcium dynamics in specific cellular compartments, such as neuronal dendrites (Sun et al., 2021; reviewed by Holt et al., 2019). Moreover, emerging data reveal that calcium elevations near different intracellular calcium stores (e.g. lysosomes) regulate processes such as autophagy (Medina et al., 2015). In dendrites, endoplasmic reticulum (ER) stores participate in localized calcium signaling that is crucial for synaptic plasticity (Hirabayashi et al., 2017; O'Hare et al., 2022; Takechi et al., 1998). Mitochondrial calcium uptake, regulated by distinct mitochondrial morphologies in different neuronal compartments, can also modulate cytosolic calcium levels and processes such as neurotransmission (Lewis et al., 2018). Notably, spatial regulation of calcium is not restricted to individual cells, as propagation of calcium signals can occur across cohorts of coupled cells in the developing brain (Weissman et al., 2004).

Dynamic patterns of calcium fluctuations also enable signaling specificity, encoding information that is translated into long-lasting biochemical changes by cytosolic proteins with different calcium sensitivities (reviewed by Rosenberg and Spitzer, 2011). In T cells, for example, different patterns of calcium oscillations control transcriptional specificity (reviewed by Dolmetsch et al., 1997, 1998). Seminal studies of the developing *Xenopus* nervous system identified two types of spontaneous calcium transients contributing to distinct aspects of spinal neuron differentiation (Gomez and Spitzer, 1999; Gu and Spitzer, 1995; Gu et al., 1994). Recently, temporal waves of gene expression have been identified in cortical neurons, resulting from activity patterns of different durations (Tyssowski et al., 2018). The initial wave of early-response transcription factors induced by prolonged depolarization, including NPAS4 (Lin et al., 2008), corresponds to activity-dependent programs activated by brief stimulation. Other studies implicate Nuclear Factor of Activated T-cells (NFAT) transcription factors, previously linked to calcium influx through L-type VGCCs (Graef et al., 1999), as somatic calcium spike counters transducing dendritic VGCC activation to the nucleus (Wild et al., 2019). Dissecting how cell type-specific calcium transients encode information in the embryonic cortex will inform how these dynamics drive cell biological changes to impact developmental programs.

Coordination of routes of calcium entry

VGCCs and store-operated calcium entry (SOCE) are two major sources of calcium influx in developing neural cells (Box 1) (reviewed by Toth et al., 2016). Growing evidence indicates that these parallel entry mechanisms are reciprocally regulated (Park et al., 2010; Wang et al., 2010). In cortical neurons and vascular smooth muscle cells, the ER membrane protein STIM1 (Fig. 1), which activates ORAI channels to promote SOCE, attenuates calcium entry through the L-type VGCC $Ca_v1.2$ (Park et al., 2010; Wang et al., 2010). In the reverse direction, changes in membrane potential can alter calcium conductance through ORAI channels (Bakowski and Parekh, 2000). This bidirectional regulation may enable preferential use of store-operated or activity-dependent calcium entry in different cell types. In collaboration with calcium buffers, pumps and transporters, such crosstalk likely tunes calcium dynamics to control intracellular signaling. Much remains to be understood, however, about mechanisms coordinating calcium dynamics in the developing cortex to preferentially activate specific downstream transcriptional pathways.

Alternative splicing regulates calcium entry and homeostasis

Differentiation in the embryonic cortex is accompanied by global splicing changes (Zhang et al., 2016). Moreover, in different cell and tissue types, alternative splicing of calcium channels and calcium-dependent effectors regulates calcium signaling by generating functionally diverse isoforms (reviewed by Lipscombe et al., 2013). Precise isoform utilization in the embryonic cortex may, therefore, be an important contributor to cell- and region-specific calcium responses to developmental stimuli.

Alternative splicing of VGCC transcripts yields channel variants with specialized roles in different tissues, cells and cellular compartments (reviewed by Abernethy and Soldatov, 2002; Lipscombe et al., 2013). *CACNA1C* (encoding the pore-forming subunit of the VGCC $Ca_v1.2$), for example, is extensively spliced to generate channels with distinct properties (Soldatov, 1994; Soldatov et al., 1997; Tang et al., 2004), and long-read sequencing confirms region-specific *CACNA1C* splicing in the adult human brain (Clark et al., 2020). Stereotyped use of specific exons also yields dominant tissue-specific *Cacna1c* isoforms, suggesting the presence of coordinated splicing events (Tang et al., 2007; Welling et al., 1997). Disease-causing mutations restricted to specific isoforms could thus give rise to channelopathies reflecting their expression pattern (reviewed by Abernethy and Soldatov, 2002; Lipscombe et al., 2013).

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Calcium channel splicing is also temporally regulated. Our studies and others point to developmental switches in *CACNA1C/Cacna1c* exon use in the brain, implying roles for different channel isoforms over time (Panagiotakos et al., 2019; Tang et al., 2009, 2011). For example, use of two mutually exclusive *CACNA1C* exons (8 and 8a), which are mutated in the syndromic autism spectrum disorder (ASD) Timothy Syndrome (TS), is developmentally controlled (Panagiotakos et al., 2019; Tang et al., 2011). In addition to impeding channel inactivation (Splawski et al., 2004), the TS mutation in exon 8a prevents a normal developmental splicing switch in patient cells (Table S1). This results in continued mutant exon inclusion in developing neurons and ensuing cellular phenotypes contributing to TS (Birey et al., 2017, 2022; Panagiotakos et al., 2019; Paşca et al., 2011; Table S1, discussed in more detail later). How channel subunit isoforms associate with one another, and how their expression is regulated across time, is unclear but likely influences cell type-specific calcium responses.

Tissue- and maturation state-specific PMCA (Fig. 1) isoform expression has also been reported (Brandt and Neve, 1992; Kip et al., 2006). Both neural activity and calcium regulate PMCA splicing (Carafoli et al., 1999; Zacharias and Strehler, 1996), supporting the idea that activity-dependent feedback influences calcium signaling via splicing regulation. Splice variants of many regulators of calcium homeostasis have been identified, including N-methyl-D-aspartate receptors (NMDARs) (An and Grabowski, 2007; Vallano et al., 1999), ORAI1 (Fukushima et al., 2012), STIM1 (Darbellay et al., 2011; Ramesh et al., 2021) and calcium-dependent transcription factors like NFAT (Vihma et al., 2008) and CREB (Walker et al., 1996). Mapping the cell type-specific expression of calcium channel and signaling protein isoforms across development is essential to understanding how calcium elicits specific responses in the embryonic cortex.

Calcium signaling is deregulated in neurodevelopmental disorders

Mutations in genes impinging on calcium signaling have been implicated in neuropsychiatric disorders of developmental origin. In this section, we discuss genetic evidence highlighting that disrupted calcium-dependent molecular networks may contribute to misregulation of cellular behaviors in the developing brain. To aid our discussion, we surveyed the Simons Foundation Autism Research Initiative (SFARI) Gene database for studies implicating regulators of calcium signaling in the etiology of neurodevelopmental disorders. We restrict our analysis (summarized in Table S1 and discussed below) to genes encoding proteins that either: (1) directly regulate calcium entry, signaling or homeostasis, or (2) indirectly modulate calcium signaling by altering membrane potential or excitability. Due to space constraints, we have not included synaptic structural proteins that regulate ion/calcium channel localization and function at synapses [e.g. ANK2 (Kline et al., 2014), NRXN1-3 (Luo et al., 2020; Missler et al., 2003)], which have been reproducibly implicated in ASD.

Genetic studies have associated mutations in VGCC subunits with increased risk for neuropsychiatric disorders (Table S1). For example, *CACNA1C* variants are associated with bipolar disorder, schizophrenia and ASD (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013; reviewed by Bhat et al., 2012). Classical TS, a syndromic ASD, is caused by a point mutation in *CACNA1C* (Table S1). This mutation impairs both voltage-dependent $Ca_v1.2$ channel inactivation, resulting in elevated depolarization-induced calcium, and channel splicing, leading to persistent mutant channel expression in immature neurons (Panagiotakos et al., 2019; Paşca et al., 2011; Splawski et al., 2004). The ensuing abnormalities in channel signaling yield a constellation of cellular phenotypes, including differentiation deficits, activity-dependent dendritic retraction and impaired interneuron migration (Birey et al., 2017; Krey et al., 2013; Panagiotakos et al., 2019; Paşca et al., 2011). Mutations in genes encoding other calcium-permeable channels, such as GluN2 NMDAR subunits, have also been linked to neurodevelopmental conditions (Endele et al., 2010) (Table S1). In addition, variants of *ATP2B2* (Iossifov et al., 2014), which encodes the PMCA2 calcium pump, and missense mutations in *ITPR1*, which encodes the IP3 receptor type 1 (IP3R1), are implicated in ASD (De Rubeis et al., 2014; Iossifov et al., 2014; Wang et al., 2016). In line with this, fibroblasts from individuals with syndromic and sporadic ASD display attenuated IP3-dependent calcium signaling (Schmunk et al., 2015, 2017).

Mutations in other ion channels and neurotransmitter receptors, which can indirectly influence voltage-dependent calcium influx, are also associated with neurodevelopmental disorders. Genetic variants in *SCN2A*, encoding the $Na_v1.2$ sodium channel, for example, are strongly linked to infantile epilepsy, ASD and intellectual disability (ID) (reviewed by Sanders et al., 2018) (Table S1). One such mutation (K1422E) in $Na_v1.2$ channels renders them calcium-permeable. $Scn2a^{K1442E/+}$ cortical neurons display larger action potential-evoked calcium transients compared with wild-type neurons, suggesting that this mutation impacts calcium signaling (Echevarria-Cooper et al., 2022). Similarly, potassium channel mutations that alter excitability (e.g. *KCNQ2* variants) and chromosomal abnormalities in loci containing γ-aminobutyric acid receptor (GABAR) genes (e.g. *15q11-13*) have been associated with neurodevelopmental phenotypes (Table S1) (Cook et al., 1998). Imbalances in GABAergic and glutamatergic signaling are postulated to contribute to the etiology of neurodevelopmental disorders (reviewed by Sohal and Rubenstein, 2019), and a recent study identifying genes with altered expression trajectories in ASD further hints at crucial roles for ion channels and GABAergic neurons in ASD pathophysiology (Berto et al., 2022).

In addition to ion channel mutations, activity-dependent transcriptional regulation, which is dependent on calcium, has been implicated in neurodevelopmental psychiatric disorders (Boulting et al., 2021; Sanchez-Priego et al., 2022). Altered activity-dependent splicing networks have also been reported in ASD cohorts (Gandal et al., 2018; Parikshak et al., 2016; Quesnel-Vallières et al., 2016). Finally, even in examples where known calcium signaling effectors are not mutated, alterations in calcium handling have been observed in cells from individuals with neurodevelopmental conditions. For example, cortical organoids from patients with *22q11.2* deletion syndrome, a highly penetrant cause of neuropsychiatric disease, exhibit calcium signaling deficits (Khan et al., 2020). Transplanted human induced pluripotent stem cell (iPSC)-derived astrocytes from ASD individuals also display elevated calcium responses (Allen et al., 2022). These observations suggest that calcium signaling may be a convergence point for multiple developmental neuropsychiatric disorders.

Calcium-dependent regulation of cellular behaviors in the developing cortex

Development of the cerebral cortex involves a series of spatiotemporally regulated cellular events, including neural stem and progenitor cell (NSPC) proliferation (reviewed by Libé-Philippot and Vanderhaeghen, 2021; Lin et al., 2021; Llorca and Marín, 2021), migration of newborn neuroblasts into the cortical plate (CP) (reviewed by Francis and Cappello, 2021; Silva et al., 2019) and the differentiation of these cells into mature, synaptically

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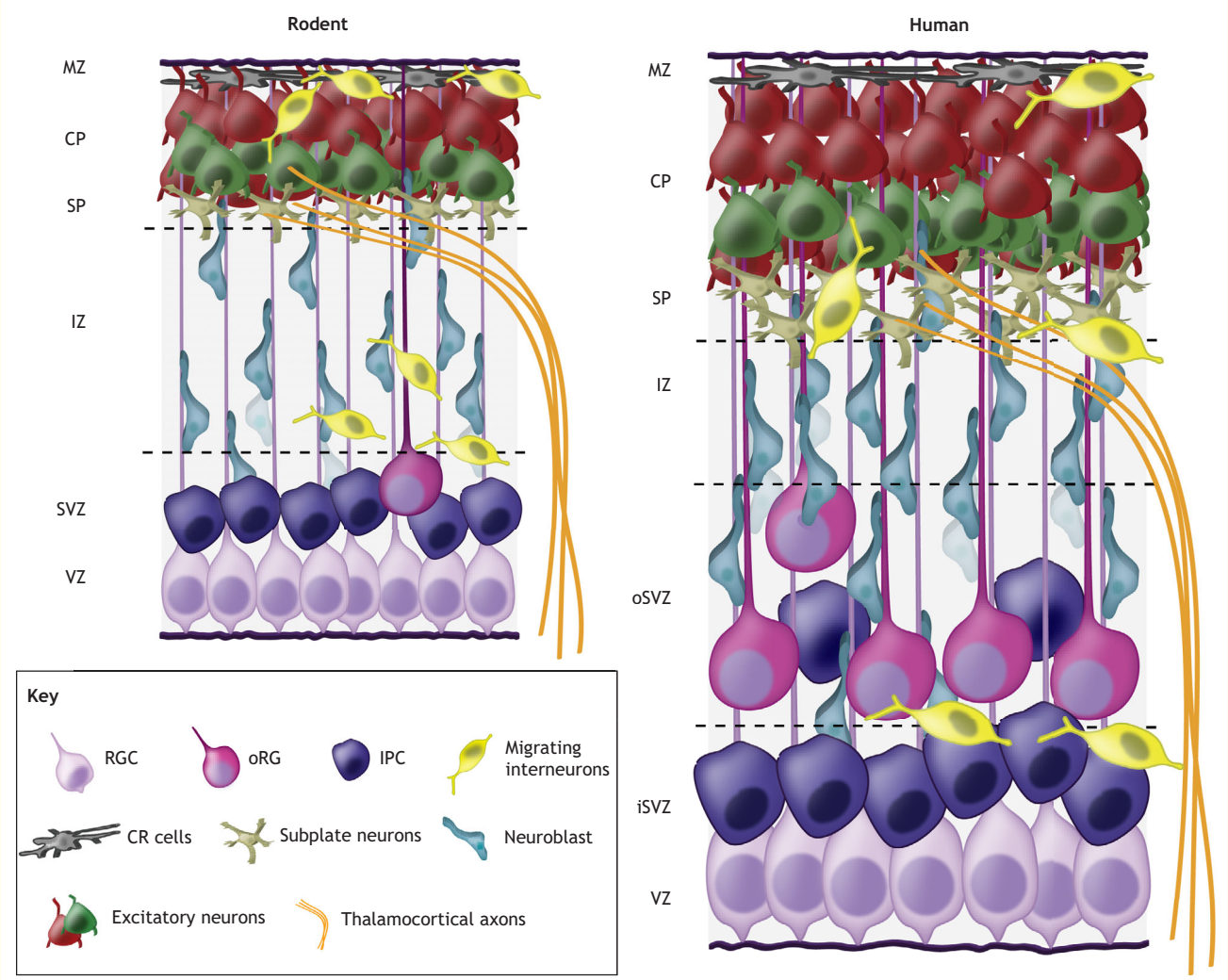
Box 2. Embryonic corticogenesis in rodents and humans

During early development, neuroepithelial cells give rise to radial glial cells (RGCs), proliferative neural stem cells that populate the cortex with neurons and astrocytes (reviewed by Libé-Philippot and Vanderhaeghen, 2021; Lin et al., 2021). RGCs initially divide symmetrically and subsequently switch to asymmetric divisions to generate postmitotic migratory neuroblasts and intermediate progenitor cells (IPCs; Haubensak et al., 2004; Noctor et al., 2004). Residing in the pseudostratified ventricular zone (VZ) adjacent to the ventricles, RGCs maintain contact with the overlying pia through a long radial fiber. Newborn neuroblasts exit the VZ and migrate along RGC fibers to reach their final laminar position. Newly generated IPCs detach from the ventricular surface and migrate into the subventricular zone (SVZ), where they divide symmetrically to produce daughter neurons. Young neuroblasts sequentially exit the VZ/SVZ to build the cortex in an inside-out fashion, terminally differentiating in the cortical plate (CP) (reviewed by Bonnefont and Vanderhaeghen, 2021). Early-generated subplate (SP) and Cajal-Retzius (CR) neurons, residing beneath the CP and in the marginal zone (MZ), respectively, are central to the development of cortical circuits (reviewed by Hoerder-Suabedissen and Molnár, 2015; Kanold, 2019; López-Bendito, 2018). In particular, the transient SP population plays an indispensable role in guiding thalamocortical axons innervating the developing cortex (reviewed by López-Bendito, 2018). Cortical interneurons are generated in the ventral telencephalon, tangentially migrating from their germinal centers into the cortex (reviewed by Lim et al., 2018; Silva et al., 2019). In humans, an expanded germinal zone overlying the VZ/SVZ (the outer SVZ; oSVZ) harbors outer radial glia (oRG), which generate cortical neurons and are thought to contribute to the evolutionary expansion of the human neocortex (Fietz et al., 2010; Hansen et al., 2010). Not depicted are less abundant cell types with important roles in cortical development, including microglia, endothelial cells and pericytes. iSVZ, inner SVZ; IZ, intermediate zone.



active neurons and glia (reviewed by Bonnefont and Vanderhaeghen, 2021; Taverna et al., 2014) (Box 2). Spontaneous and agonist-induced calcium elevations, neurotransmitter- and depolarization-evoked calcium influx, and SOCE have been observed at various stages of embryonic and adult NSPC lineage progression (reviewed by Toth et al., 2016; Uhlén et al., 2015). These different forms of calcium entry result in the induction of calcium-dependent transcriptional cascades (e.g. CREB-, MEF2-, NFAT- and NPAS4-dependent gene expression) that contribute to developmental regulation of cellular behaviors (reviewed by Greer and Greenberg, 2008). Achieving a granular picture of how cell type-specific calcium signaling impinges on lineage progression in the developing cortex is essential for understanding development and neurodevelopmental disease. Below, we link calcium responses in developing cortical cell populations with the cellular machinery mediating these signals and controlling different cellular behaviors.

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Cortical NSPC proliferation

Spontaneous calcium elevations

The proliferative NSPC compartment comprises radial glial cells (RGCs) and intermediate progenitor cells (IPCs) (Box 2), which give rise to cortical excitatory neurons and astrocytes. Residing adjacent to the ventricles, these cells are exposed to environmental stimuli impinging on calcium signaling during development, including growth factors and electrical activity (reviewed by Dehay and Kennedy, 2007; Fame and Lehtinen, 2020). Cortical NSPCs express ion channels, pumps and receptors that generate unique calcium dynamics to contribute to developmental cellular behaviors (Fig. 2). Different patterns of spontaneous calcium elevations are observed in the ventricular zone (VZ): slow rises are contained to individual cells, whereas coordinated transients (calcium waves) propagate across gap junction-coupled, mitotically-active RGCs (Bittman et al., 1997; Lo Turco and Kriegstein, 1991; Owens et al., 2000; Weissman et al., 2004).

Spontaneous calcium rises are dependent on internal calcium stores, as they persist in the absence of extracellular calcium but are eliminated upon ER calcium depletion (Owens and Kriegstein, 1998). VGCC activation, neurotransmitter signaling and depolarization are not necessary to promote spontaneous rises (Owens and Kriegstein, 1998; Weissman et al., 2004). Instead, initiation of these calcium transients requires purinergic signaling via metabotropic P2Y1 ATP receptors (P2Y1Rs) (Liu et al., 2008; Malmersjö et al., 2013; Owens and Kriegstein, 1998; Owens et al., 2000; Weissman et al., 2004), and NSPCs have been identified as a source of ATP eliciting pro-proliferative calcium responses (Lin et al., 2007). Calcium waves are activated by extracellular ATP in a temporally regulated fashion, occurring robustly at the peak of neurogenesis and propagating across dynamically coupled RGCs via connexin hemichannels at specific cell cycle stages (Bittman et al., 1997; Owens and Kriegstein, 1998; Weissman et al., 2004). Abrogating these waves by antagonizing P2Y1Rs or inhibiting gap junctions significantly reduces proliferation and promotes differentiation (Lin et al., 2007; Malmersjö et al., 2013; Weissman et al., 2004). Single cell RNA-sequencing (scRNA-seq) and calcium imaging studies demonstrate that P2Y1Rs are highly expressed in ventricular RGCs and IPCs of the rodent and human fetal cortex, and that P2Y1R agonists induce calcium rises in these cells (Mayer et al., 2019). P2Y1Rs are downregulated in neurons and, intriguingly, in human outer radial glia (oRG), a neural stem cell population abundant in humans that may contribute to evolutionary expansion of the neocortex, pointing to a conserved

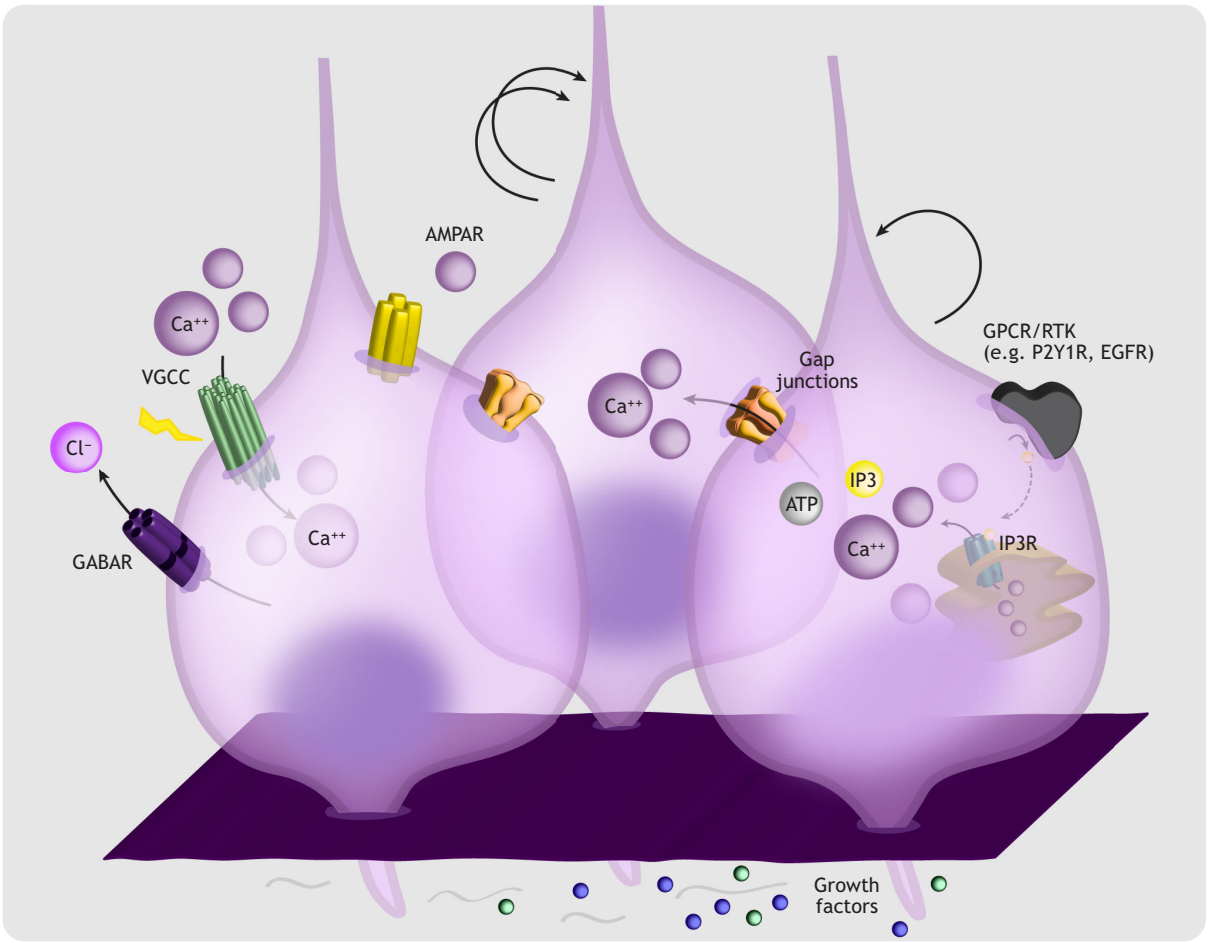

Fig. 2. Calcium-dependent regulation of proliferation during corticogenesis. Calcium imaging and electrophysiological recordings performed on embryonic rodent cortical slice cultures demonstrate that radial glial cells (RGCs) in the ventricular zone (VZ) exhibit spontaneous and induced calcium rises. Purinergic signaling through metabotropic P2Y1 receptors initiates calcium transients that propagate across VZ cells. These calcium waves, which modulate proliferation, require gap junctions and IP3-mediated calcium release. RGC primary cilia protrude into the ventricles, where they are exposed to diffusible growth factors in the CSF that initiate calcium rises and also influence RGC division. Finally, depolarization mediated by GABA and glutamate acting on GABARs and AMPARs, respectively, controls proliferation by inducing calcium rises through VGCCs.

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role for ATP-dependent calcium signaling in ventricular RGCs and IPCs (Liu et al., 2008; Mayer et al., 2019).

Links between calcium and growth factor signaling

Growth factors are important cell cycle regulators (reviewed by Dehay and Kennedy, 2007) that can induce calcium elevations in proliferative NSPCs. High concentrations of basic fibroblast growth factor (bFGF), for example, elicit robust cytoplasmic calcium rises in the apical end foot and cell body of RGCs, propagating in a sustained manner through the RGC fiber (Rash et al., 2016). bFGF can promote proliferation in concert with epidermal growth factor (EGF) (Tropepe et al., 1999), which stimulates ER calcium store depletion to activate SOCE and induce NFAT-dependent transcription in ganglionic eminence (GE)-derived ventral progenitors and adult subventricular zone (SVZ) cells (Somasundaram et al., 2014). NFATs have been linked to cell cycle regulation (Carvalho et al., 2007; Teixeira et al., 2016) and progenitor proliferation in the neural tube and postnatal neural cultures (Huang et al., 2011; Serrano-Pérez et al., 2015). In GE progenitors, inhibiting SOCE using genetic and pharmacological approaches decreases proliferation (Somasundaram et al., 2014). Although the function and upstream activators of SOCE in cortical NSPCs remain unknown, spontaneous calcium waves in the VZ are partially mediated by intracellular calcium stores and IP3-dependent calcium release (Weissman et al., 2004). Application of the IP3 receptor antagonist 2-aminoethoxydiphenyl borate, at doses that inhibit SOCE, reduces the amplitude and duration of calcium transients in cortical RGCs (Rash et al., 2016), pointing to potential roles for SOCE in proliferative NSPCs.

Neurotransmitter signaling and calcium

Neurotransmitter signaling also influences cortical NSPC calcium elevations to regulate cell division. In the embryonic brain, upon binding to $GABA_A$Rs, the neurotransmitter GABA depolarizes immature cells (reviewed by Ben-Ari et al., 2007). $GABA_A$R-dependent depolarization results from unopposed developmental activity of the Na^+-K^+-$2Cl^-$ transporter NKCC1 (also known as SLC12A2), which yields elevated chloride concentrations in embryonic neural cells (Owens et al., 1996, 1999; reviewed by Ben-Ari et al., 2007). The postnatal emergence of the K^+-Cl^- co-transporter KCC2 (SLC12A5) induces a developmental switch in GABA activity from depolarizing to hyperpolarizing (reviewed by Ben-Ari et al., 2007). This maturation of inhibition is regulated by the activity of the largely transient subplate (SP) neuron population (Kanold and Shatz, 2006), by GABA (Ganguly et al., 2001) and by growth factor signaling (Rivera et al., 2004). The role of neural activity in developmental regulation of intracellular chloride and the transition to GABA inhibition is supported by studies demonstrating that manipulating excitatory input or sensory experience modulates KCC2 expression (He et al., 2010; Kanold and Shatz, 2006; Sernagor et al., 2003). Activity and cytosolic calcium also alter chloride gradients in immature hippocampal neurons (Fiumelli et al., 2005), whereas activity-dependent neurotrophins modulate KCC2 expression and GABAergic inhibition (Aguado et al., 2003; Ludwig et al., 2011).

Embryonic cortical NSPCs express functional $GABA_A$ receptors (Lo Turco et al., 1995; Mayer et al., 2019; Owens et al., 1996) and GABA-induced depolarization elicits calcium transients in NSPCs through VGCC activation (Lo Turco et al., 1995; Mayer et al., 2019; Owens et al., 1996, 1999; Panagiotakos et al., 2019). GABA depolarization inhibits DNA synthesis, decreasing cortical NSPC proliferation (Antonopoulos et al., 1997; Lo Turco et al., 1995). This effect can be rescued by application of chloride transport blockers, suggesting that the depolarizing activity of GABA underlies its ability to suppress NSPC proliferation (Lo Turco et al., 1995). Importantly, separately dissecting the effects of GABA in the VZ and SVZ reveals that GABA inhibits SVZ progenitor proliferation but has pro-proliferative effects in the VZ, shortening the cell cycle to promote mitotic re-entry (Haydar et al., 2000). This suggests that GABA exerts cell type-specific effects on RGCs and IPCs, although how they are transduced to influence calcium in each cell type remains unknown. Understanding how developmental GABAergic activity is linked to the electrical properties of progenitor types, which can change across developmental time (Vitali et al., 2018), represents an exciting avenue for future studies.

Likewise, the excitatory neurotransmitter glutamate depolarizes NSPCs, promoting calcium rises that control proliferation. Although NMDARs are expressed in the developing brain (Henson et al., 2008; Lo Turco et al., 1991; Monyer et al., 1994), a confluence of data points to NMDARs playing an outsized role in post-mitotic neurons compared with NSPCs (Behar et al., 1999; Lo Turco et al., 1991, 1995; Maric et al., 2000; Mayer et al., 2019). In the rat VZ, NMDA does not elicit currents in NSPCs, whereas in human RGCs and oRG, NMDA elicits magnesium-insensitive currents at resting membrane potentials (Lo Turco et al., 1991, 1995; Maric et al., 2000; Mayer et al., 2019). Calcium imaging of human fetal cells identified a small fraction of VZ cells responding to NMDA, but scRNA-seq reveals that these cells are predominantly excitatory neurons and mostly absent from NSPC clusters (Mayer et al., 2019).

In contrast, ionotropic α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) and kainate (KA) receptors are expressed in VZ/SVZ cells (Haydar et al., 2000; Lo Turco et al., 1995; Maric et al., 2000). Four main subunits, GluA1-4, compose heteromeric AMPA receptors (AMPARs) (reviewed by Traynelis et al., 2010), and the presence of GluA2 renders AMPARs calcium impermeable (Sommer et al., 1991). Intriguingly, GluA2 abundance increases postnatally, suggesting that embryonic neural cells are more likely to express calcium-permeable AMPARs (Kumar et al., 2002; reviewed by Behm and Öhman, 2016). In line with this, AMPA induces calcium elevations in isolated NSPCs completing their final division (Maric et al., 2000), and AMPA/KA antagonists block calcium elevations elicited by glutamate in rat cortical VZ cells (Lo Turco et al., 1995). AMPAR stimulation in isolated human fetal cortical NSPCs also promotes differentiation (Mayer et al., 2019; Whitney et al., 2008). Consistent with these findings, glutamate and KA (but not NMDA) significantly inhibit DNA synthesis in VZ cells (Lo Turco et al., 1995). Once again, separating RGCs from IPCs reveals a more complex picture: glutamate increases proliferation in the VZ and decreases SVZ proliferation, highlighting differential responses of distinct progenitor populations to neurotransmitter signaling (Haydar et al., 2000). It will be important to dissect these responses across development, particularly in light of data demonstrating progressive RGC hyperpolarization during cortical neurogenesis as a key regulator of RGC output (Vitali et al., 2018). Notably, among the channels upregulated to promote this developmental change in RGC membrane potential are several calcium-activated K^+ channels (Vitali et al., 2018). Although dynamic changes in K^+ channel expression and membrane potential have been linked to the control of proliferation (reviewed by Blackiston et al., 2009), how such changes influence NSPC calcium signaling remains unclear.

The neurotransmitters serotonin (5-HT) and acetylcholine (Ach) also induce NSPC calcium transients. Maternally-derived 5-HT is reported to regulate proliferation in the developing brain (Côté et al., 2007); however, stimulation of the 5-HT receptors HTR2A and

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HTR2C promotes rat cortical progenitor survival without affecting proliferation (Dooley et al., 1997). HTR2A is highly expressed in human cortical germinal zones, and the HTR2A agonist TCB-2 induces robust calcium rises in human NSPCs (Mayer et al., 2019). HTR2A inhibition alters fiber length in proliferating human RGCs but does not impact division, positing a human-specific role for serotonergic signaling in maintaining RGC structural integrity during proliferation (Mayer et al., 2019). In contrast, muscarine and Ach stimulate calcium influx in cortical NSPCs via muscarinic Ach receptor (mAchR) activation, and mAchR antagonists and calcium chelators attenuate NSPC proliferation (Atluri et al., 2001; Ma et al., 2000). In GE-derived progenitors, Ach, like EGF, stimulates SOCE via mAchRs, and abrogating SOCE reduces proliferation, pointing to potential links between cholinergic activity, SOCE and NSPC divisions (Somasundaram et al., 2014).

It is possible that agonist-induced SOCE and depolarization-induced calcium entry represent mechanisms that antagonistically regulate NSPC proliferation. Understanding the coordination of different modes of calcium entry and how their interplay impacts proliferative NSPCs is thus essential. Moreover, as calcium influx via VGCCs and SOCE can contribute to calcium oscillations, it will be crucial to determine how cellular responses are encoded in patterns of calcium transients and how these dynamics enable signaling specificity in NSPCs.

Calcium-dependent cellular motility

NSPC motility

Proliferative RGCs undergo interkinetic nuclear migration (INM) – dynamic somatic movements in phase with the cell cycle (reviewed by Taverna et al., 2014). During G1, the somata of RGCs move away from the ventricle to complete S-phase, whereas they move apically during G2, initiating mitosis at the ventricular wall. Pharmacological inhibition of connexin hemichannels suppresses RGC calcium waves (Liu et al., 2010; Weissman et al., 2004) and significantly attenuates INM (Liu et al., 2010). Chelating intracellular calcium also reduces INM distance and speed (Liu et al., 2010), suggesting that calcium propagating through coupled RGCs plays a role in the dynamic changes associated with RGC motility.

IPCs do not exhibit INM, instead delaminating from the VZ and moving into the SVZ along RGC fibers (Noctor et al., 2004; reviewed by Taverna et al., 2014). Pharmacological inhibition of purinergic signaling or P2Y receptor knockdown reduces calcium transient frequency in proliferative IPCs, preventing their migration into the SVZ (Liu et al., 2008). Thus, ATP-mediated calcium signaling is not only necessary for NSPC proliferation, but also for the dynamic progenitor movements that shape the developing cortical cytoarchitecture (Liu et al., 2008).

Spontaneous calcium rises in postmitotic migratory cells

Spontaneous calcium rises have been linked to the radial migration of excitatory neuroblasts (Box 2; Fig. 3). Newborn neuroblasts exiting the VZ exhibit the highest frequency of somatic bursting calcium transients in the developing cortex (Rash et al., 2016). It has also been postulated that calcium transients in RGC fibers, which act as a scaffold for radial migration (Box 2), signal to neuroblasts to influence their calcium dynamics and migratory behavior (Rash et al., 2016). It remains unclear, however, how calcium dynamics in RGCs and neuroblasts intersect, and what the functional contribution of bursting transients in migratory neuroblasts is to radial migration.

Unlike excitatory neurons, inhibitory cortical interneurons are generated in subpallial structures, including the medial and caudal ganglionic eminences (MGE and CGE, respectively), undertaking saltatory tangential migration to reach the cortex (reviewed by Buchsbaum and Cappello, 2019; Contractor et al., 2021; Lim et al., 2018; Silva et al., 2019). Within the cortex, interneurons undergo both tangential and radial migration to their appropriate laminar destination (Box 2) (Tanaka et al., 2006; reviewed by Silva et al., 2019). Migratory interneurons exhibit spontaneous calcium transients characterized by oscillatory bursts or individual spikes (Bortone and Polleux, 2009; Martini and Valdeolmillos, 2010). Chelating intracellular calcium or pharmacologically blocking VGCC activity significantly disrupts cytoskeletal dynamics and impairs interneuron migration (Bortone and Polleux, 2009; Martini and Valdeolmillos, 2010). Caffeine-induced ER calcium release also promotes cytoskeletal changes to stimulate interneuron motility (Martini and Valdeolmillos, 2010). Interestingly, SOCE is attenuated in migratory neuroblasts isolated from the GE (Somasundaram et al., 2014), again raising the question of how different modes of calcium entry intersect in developing neurons to coordinate migration.

Agonist-induced calcium rises in migratory neuroblasts

Tyrosine receptor kinase B (TrkB; Ntrk2), canonically bound by brain derived neurotrophic factor (BDNF), has been linked to embryonic cortical neuroblast migration (Bartkowska et al., 2007; Behar et al., 1997) (Fig. 3). BDNF stimulates calcium transients and increases cortical neuroblast migration, which can be blocked by application of Trk inhibitors or calcium chelators (Behar et al., 1997). This suggests that TrkB activation promotes migration partly by inducing downstream calcium signaling, although it should be noted that EGF robustly transactivates TrkB *in vivo* to stimulate cortical neuroblast migration (Puehringer et al., 2013).

TrkB is also involved in tangential interneuron migration (reviewed by Contractor et al., 2021; Silva et al., 2019). BDNF and neurotrophin 4 (NTF4) activate interneuron TrkB receptors, and Trk inhibitor application reduces the fraction of MGE-derived cells migrating into the cortex. In mice lacking *Trkb*, the number of calbindin-positive interneurons that reach the cortex is attenuated (Polleux et al., 2002). In contrast to TrkB-mediated activation of PLCγ and MAP kinase in excitatory neuroblasts, BDNF activates PI3-kinase signaling in interneurons to control tangential migration (Polleux et al., 2002). Intriguingly, BDNF- and NTF4-dependent TrkB activation has been implicated in KCC2 regulation, positing a link between growth factor signaling and excitability in developing neurons (Rivera et al., 2004).

Neurotransmitter-induced calcium signaling in migrating neuroblasts

Intracellular calcium modulation via GABAR-mediated signaling also impacts radially migrating cortical neurons. In excitatory neuroblasts, GABA induces calcium transients and stimulates migration (Fig. 3) (Behar et al., 1996). BAPTA blocks these effects, suggesting that calcium transduces GABA stimulation into migratory behavior (Behar et al., 1996). Indeed, $GABA_A$ and $GABA_B$ receptors are functionally expressed in migratory cortical neurons (López-Bendito et al., 2002; Owens et al., 1996, 1999). Pharmacological studies in embryonic rat cortical slices indicate that activation of different GABARs plays distinct region-specific roles across the cerebral wall (Behar et al., 2000). Similar observations have been replicated *in vivo*, where local application of $GABA_AR$ antagonists or chronic administration of desensitizing levels of $GABA_AR$ agonists attenuate spontaneous calcium transients, resulting in cortical heterotopias (Heck et al., 2007). Notably, although GABA has been reproducibly implicated in migration, mice lacking *Gad65* (*Gad2*) and *Gad67* (*Gad1*) do not

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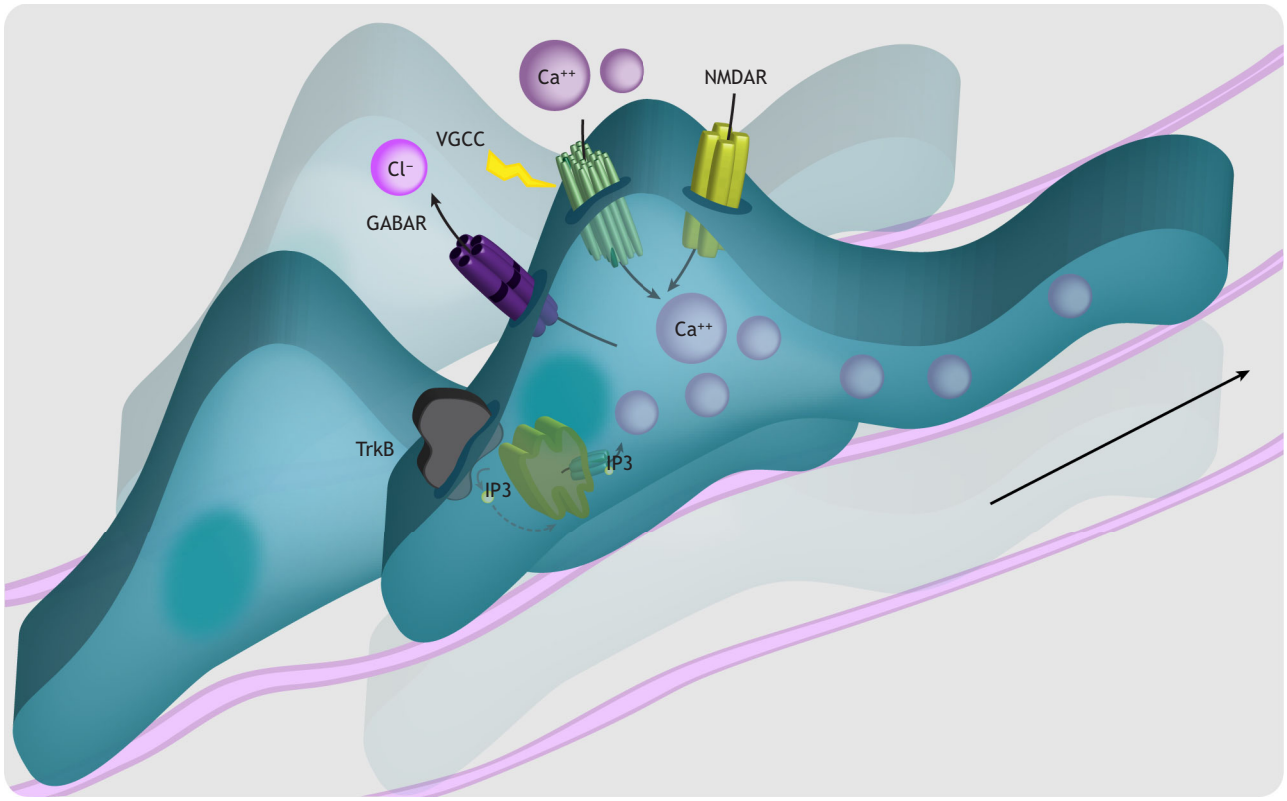

Fig. 3. Calcium and excitatory neuroblast migration. Excitatory neuroblasts undergo radial migration along RGC fibers to reach their final laminar destination. Migratory neuroblasts exiting the VZ display high frequency spontaneous calcium transients. As they enter the SVZ, neuroblasts adopt a multipolar morphology and exhibit low amplitude calcium events. Calcium transients during neuroblast migration are largely mediated by extracellular agonists like BDNF, which activates TrkB, by neurotransmitter receptors (e.g. NMDARs, GABARs), and by downstream activation of VGCCs. Glutamate influences radial migration by inducing calcium influx primarily through NMDARs. Depolarization via GABARs and calcium influx via VGCCs also control radial migration. Emerging evidence suggests that calcium transients propagating through RGC fibers may also contribute to the regulation of neuroblast migration into the cortical plate.

display major cortical malformations (Ji et al., 1999), and radial migration is not significantly altered in *Gad67* knockout mice (Furukawa et al., 2014). Other endogenous activators of $GABA_A$Rs (e.g. taurine) have thus been proposed to control neuronal migration (Furukawa et al., 2014).

Tangentially migrating cortical interneurons also display GABAR-mediated calcium transients (Soria and Valdeolmillos, 2002). As immature interneurons migrate from the MGE, GABA exerts a depolarizing effect via $GABA_A$Rs (Bortone and Polleux, 2009; Cuzon et al., 2006), and antagonizing $GABA_A$Rs results in accumulation of migrating interneurons at the pallial-subpallial boundary (Cuzon et al., 2006). GABA depolarization activates VGCCs to promote calcium influx, acting as a pro-migratory signal, presumably via calcium-dependent pathways to the cytoskeleton (Bortone and Polleux, 2009). During the first postnatal week in mice, KCC2 upregulation renders GABA hyperpolarizing, leading to decreased calcium transients and reduced interneuron motility to terminate migration (Bortone and Polleux, 2009). Suppressing the activity of CGE-derived interneurons at distinct developmental stages does not affect tangential migration but reveals essential contributions of activity-dependent signaling in the radial migration of specific subpopulations into their final laminar positions in the CP (De Marco García et al., 2011).

Glycine receptor (GlyR) activation by endogenous ligands (e.g. glycine, taurine) is also depolarizing in cortical neuroblasts, eliciting calcium rises that may modulate migration (Avila et al., 2013; Flint et al., 1998; Yoshida et al., 2004). Although cortices from mice lacking the developmentally enriched α2 GlyR display no gross morphological defects (Young-Pearse et al., 2006), genetic deletion of these receptors results in impaired interneuron migration (Avila et al., 2013). In migratory cortical interneurons, extrasynaptic glycine acting on α2 GlyRs stimulates dynamic calcium fluctuations via VGCCs, promoting motility through calcium-dependent tuning of actomyosin contractions (Avila et al., 2013). In excitatory neuroblasts, the role of GlyRs is less clear (Furukawa et al., 2014), although GlyR activation in organotypic slice cultures, in the presence of glycine uptake inhibitors, impedes radial migration (Nimmervoll et al., 2011).

Seminal experiments in cerebellar granule cells first demonstrated calcium-dependent roles for glutamate in neuroblast migration (Komuro and Rakic, 1993). In the developing cerebral cortex, glutamate released by post-mitotic neurons induces calcium transients in radially migrating neuroblasts, modulating their motility primarily through NMDARs (Fig. 3) (Behar et al., 1999; Hirai et al., 1999). NMDARs are heteromers, the majority consisting of two GluN1 and two GluN2 subunits. Whereas GluN1 subunits are expressed before and after birth in the cortex, GluN2 subunit expression is dynamically regulated during development, resulting in NMDARs with markedly different physiological properties. Compared with those containing GluN2B subunits, GluN2A-containing NMDARs have faster deactivation kinetics, higher open probabilities and lower sensitivity to agonists. Although both

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NMDAR subtypes display similar calcium permeability, their unique gating properties shape the dynamics of their contribution to calcium influx to influence downstream signaling (Erreger et al., 2005; Sheng et al., 1994; reviewed by Paoletti et al., 2013; Wyllie et al., 2013). In humans, *GRIN2B*, encoding GluN2B, is highly expressed in postmitotic embryonic neurons, whereas *GRIN2A*, encoding GluN2A, is expressed in embryonic RGCs and neurons after birth (Mayer et al., 2019). This developmental subunit switch, which occurs in early postnatal life in the rodent and can be regulated by neural activity (reviewed by Yashiro and Philpot, 2008), results in enriched GluN2B abundance during the peak of neuroblast migration. Consequently, shRNA-dependent GluN2B and GluN1 knockdown in embryonic rodent cortices delays neuronal migration, whereas manipulating GluN2A does not affect neuroblast motility (Jiang et al., 2015). Pharmacological NMDAR inhibition or calcium chelators in the presence of NMDA also abrogate neuroblast migration (Behar et al., 1999; Hirai et al., 1999; Reiprich et al., 2005; Yuryev et al., 2018). More recently, transient glutamatergic transmission from SP neurons onto excitatory neuroblasts was shown to regulate neuroblast migration in an NMDAR-dependent manner (Ohtaka-Maruyama et al., 2018). Although these studies suggest that NMDARs are essential for radial migration, genetic inactivation of *Grin1*, encoding GluN1, reveals no major deficits in neuronal distribution (Messersmith et al., 1997; Iwasato et al., 2000). This may result from mechanisms compensating for long-term GluN1 loss of function (reviewed by Luhmann et al., 2015; Medvedeva and Pierani, 2020). In tangentially migrating cortical interneurons, NMDA and Kainate also induce calcium transients (Soria and Valdeolmillos, 2002), and activation of NMDARs or AMPARs positively regulates interneuron motility in a VGCC-dependent manner (Bortone and Polleux, 2009). Within the intermediate zone (IZ), tangentially migrating interneurons continue to express calcium-permeable AMPARs (Métin et al., 2000) and, in CGE-derived interneuron subtypes, 5-HT3A receptor activation induces calcium transients required for proper migration (Murthy et al., 2014).

VGCCs in neuroblast migration

A function for VGCCs in neuronal migration was initially described in cerebellar granule cells (Komuro and Rakic, 1992). In the embryonic cortex, L-type VGCCs are highly expressed in cortical neurons, and migrating upper layer neurons exhibit spontaneous L-type VGCC-mediated calcium transients (Kamijo et al., 2018). *In utero* $Ca_v1.2$ overexpression in excitatory neurons destined for upper cortical layers impairs radial migration, and a severe calcium influx-dependent migratory defect in this population results from electroporation of $Ca_v1.2$ channels bearing the TS mutation (Kamijo et al., 2018).

L-type VGCCs, and to a lesser extent N-type VGCCs, are also essential for interneuron motility (Bortone and Polleux, 2009). Depolarization of immature interneurons by GABA or glutamate activates VGCCs to promote tangential migration into the cortex (Bortone and Polleux, 2009). Assembloid models using human iPSCs further support a role for $Ca_v1.2$ in human cortical interneuron migration, demonstrating that inhibitory neurons from TS patients display abnormal migratory behaviors (Birey et al., 2017). Dissecting these migratory phenotypes demonstrates that VGCC-dependent calcium signaling impinges on distinct molecular networks to influence cellular motility (Birey et al., 2022).

Calcium and programmed cell death

Developing cortical circuits are refined by precisely regulated apoptosis, which scales down NSPC, pyramidal cell and cortical interneuron populations. Approximately 12% of cortical pyramidal cells undergo apoptosis in the early postnatal period in rodents (Wong et al., 2018), and a substantial fraction of cortical interneurons also undergo postnatal cell death (Priya et al., 2018; Southwell et al., 2012). In both developing populations, a central regulator of apoptosis is neuronal activity and intracellular calcium signaling.

In vitro studies in the 1990s first implicated activity-dependent calcium signaling in cortical pyramidal neuron survival (Ghosh et al., 1994; Voigt et al., 1997). Stimulation of embryonic cortical cultures with potassium chloride (KCl) enhances cell survival by promoting neurotrophin expression, an effect that can be eliminated by chelating calcium or pharmacologically blocking L-type VGCCs (Ghosh et al., 1994). NMDARs contribute to developmental apoptosis of pyramidal cells during discrete temporal windows, as early postnatal NMDAR inhibition promotes cell death. This effect can be rescued by concurrent VGCC activation, suggesting that VGCCs and NMDARs have overlapping roles in promoting calcium-dependent survival (Ghosh et al., 1994; Heck et al., 2008; Ikonomidou et al., 1999). The contribution of GABA to cortical neuron survival is again linked to its depolarizing or hyperpolarizing activity. Global NKCC1 inactivation reduces developmental cell death of transient layer 1 Cajal-Retzius (CR) neurons (Blanquie et al., 2017a), and hyperpolarization promotes subtype-specific survival of CR neurons (Riva et al., 2019). Inhibiting activity altogether in developing pyramidal cells significantly reduces their survival (Voigt et al., 1997), and regional variations in apoptosis *in vivo* are partly regulated by corresponding differences in endogenous activity (Blanquie et al., 2017b). *In vitro* evidence suggests, however, that it is not simply the presence or absence of activity that regulates apoptosis in developing cortical neurons; rather, distinct activity patterns may modulate survival, further supporting the notion that information encoded in the frequency of calcium signals can drive changes in cell behavior (Golbs et al., 2011; Wong Fong Sang et al., 2021). Investigating how ion channel subunit composition and localization contribute to activity patterns *in vivo* and how these patterns activate specific calcium-dependent signaling pathways in developing cortical neurons to regulate survival is an essential next step.

Notably, the emergence of synchronous calcium transients within populations of cortical pyramidal and hippocampal neurons is positively correlated with survival (Heck et al., 2008; Murase et al., 2011; Voigt et al., 1997). Such synchronous transients in neuronal domains are partially mediated by gap junctions (Kandler and Katz, 1998; Yuste et al., 1992), and pharmacological gap junction inhibition preserves spontaneous asynchronous activity but increases neuronal apoptosis (Heck et al., 2008). In line with this, multiple calcium-dependent transcription factors have been linked to neuronal survival, including MEF2 (Liu et al., 2003; Mao et al., 1999) and NFATc4 (Benedito et al., 2005; Quadrato et al., 2012).

Increased activity also correlates with improved postnatal survival of cortical interneurons (Denaxa et al., 2018; Priya et al., 2018; Wong et al., 2018, 2022). Interneurons that die are less likely to participate in coordinated network events, displaying fewer synchronized calcium fluctuations *in vivo* compared with cells that survive (Duan et al., 2020; Wong et al., 2018). Accordingly, artificially hyperpolarizing interneurons decreases their survival, whereas increasing their activity promotes survival (Denaxa et al., 2018; Priya et al., 2018). Interestingly, the contribution of activity-dependent signaling to interneuron survival, thought to be mediated at least partly through the calcium-sensitive CaN/NFAT pathway (Priya et al., 2018), is

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subtype-specific (Denaxa et al., 2018; Priya et al., 2018). The activity of maturing neuronal populations also non-cell autonomously regulates interneuron subtype survival to shape developing circuits (Wong et al., 2018, 2022). Glutamatergic signaling is required for activity-dependent survival of neurogliaform and basket cells, whereas bipolar cells rely on serotonin to modulate activity-dependent survival (Wong et al., 2022). It will be interesting to determine the calcium-dependent pathways that link electrical signals to the survival of specific neuronal subtypes.

Differentiation

Calcium and electrical activity play central roles in regulating aspects of neuronal identity. We restrict our focus here to a brief discussion of calcium functions in early events underlying cortical neuron differentiation, namely the acquisition of fate determinants and initial elaboration of neurites. The involvement of activity-dependent signaling in later events, such as synaptogenesis, circuit integration, maturation and plasticity, have been extensively reviewed elsewhere (Antón-Bolaños et al., 2018; Greer and Greenberg, 2008; Molnár et al., 2020; Pan and Monje, 2020; Rosenberg and Spitzer, 2011).

Pioneering studies in *Xenopus* spinal neurons demonstrated that intracellular calcium elevations regulate distinct aspects of differentiation, including neurotransmitter specification, maturation of ionic conductances and synaptic development (Borodinsky and Spitzer, 2007; Gu and Spitzer, 1995). In the developing cortex, expression of neuronal fate determinants may be calcium-regulated. Elevated calcium in differentiating human iPSC-derived TS cortical neurons biases neuronal production *in vitro* (Paşca et al., 2011). Moreover, *in vivo* gain and loss of function of the L-type VGCC $Ca_v1.2$ in differentiating NSPCs bidirectionally modulates the relative abundance of cells expressing markers of callosal or subcerebral projection neurons in a calcium-dependent manner (Panagiotakos et al., 2019). $GABA_AR$-dependent activation of L-type VGCCs also controls the morphological differentiation of pyramidal cells (McAllister et al., 1996; Redmond et al., 2002; Wayman et al., 2006; reviewed by Chen and Ghosh, 2005), and premature KCC2 expression *in vivo* reveals that GABA depolarization is necessary for dendritic maturation of cortical neurons (Cancedda et al., 2007). In addition, elevating neuronal activity and spontaneous calcium transient frequency in migratory neurons arrests migration and induces precocious dendritic branching (Bando et al., 2016). Consistent with this, thalamocortical afferent activity is indispensable for proper development of neuronal morphology (Callaway and Borrell, 2011; Li et al., 2013), as well as barrel column formation in mice (Antón-Bolaños et al., 2019; Li et al., 2013). Recently, a small molecule chemical screen in human iPSC-derived cortical neurons identified epigenetic modifiers and calcium signaling activators as enhancers of neuronal maturation, including neurite elaboration, further supporting that facilitating calcium-dependent gene expression can promote terminal differentiation of cortical neurons (Ciceri et al., 2022 preprint; Hergenreder et al., 2022 preprint).

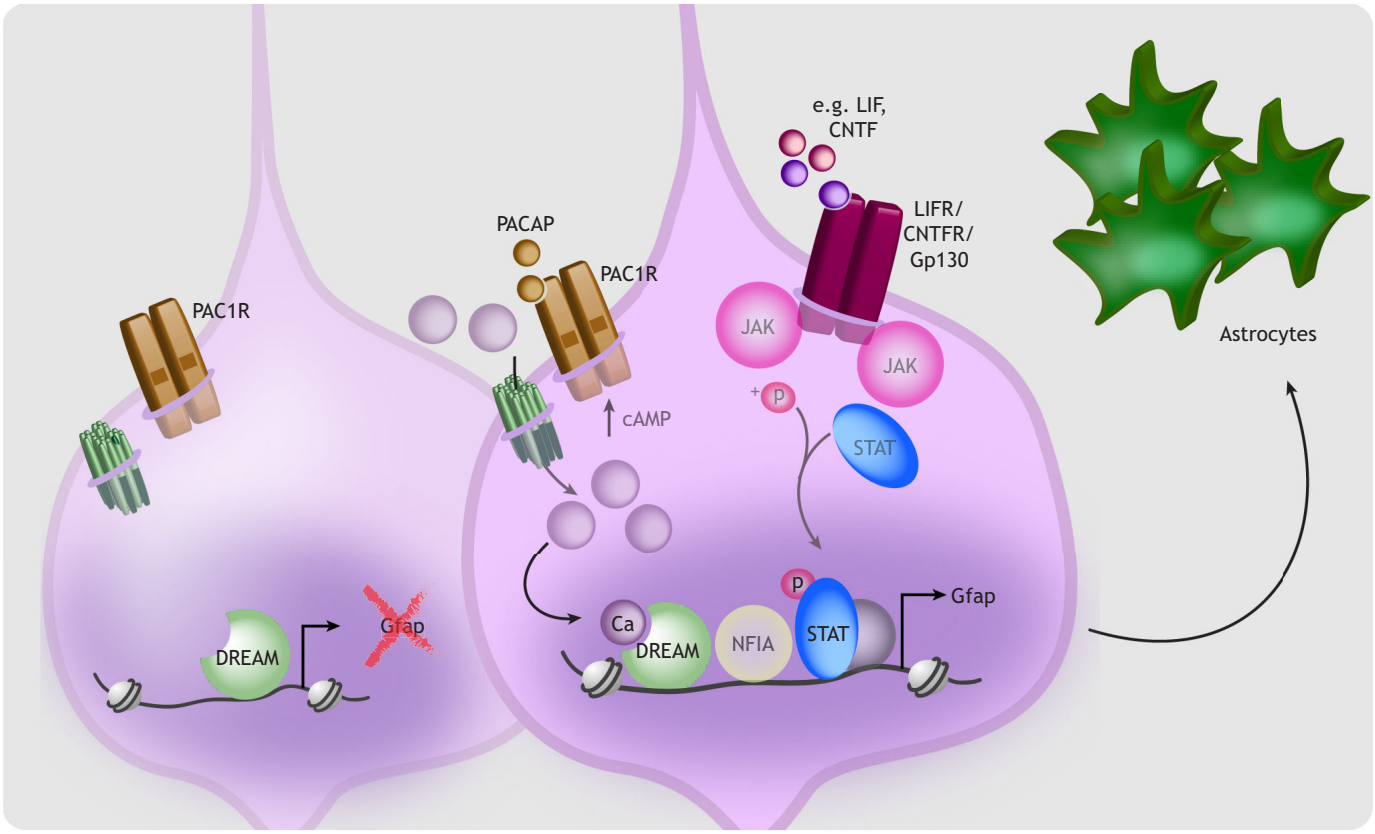

Fig. 4. Calcium and astrogliogenesis. Although microglia and embryonic oligodendrocytes originate largely outside of the cortex, RGCs (light purple) transition from making neurons to generating cortical astrocytes (green) during mid-to-late gestation in the rodent. This gliogenic switch begins at approximately embryonic day 17 in mice and continues postnatally. Activation of plasma membrane receptors [glycoprotein 130 (Gp130; Il6st), ciliary neurotrophic factor receptor (CNTFR) and leukemia inhibitory factor receptor (LIFR)] regulates *Gfap* transcription and astroglial differentiation via JAK/STAT signaling. In parallel, pituitary adenylate cyclase activating polypeptide (PACAP)-mediated activation of its receptor, PAC1R, generates cAMP-dependent calcium elevations. Calcium binds DREAM to promote expression of astrocyte-specific genes and astrogliogenesis.

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Calcium-regulated transcription factors or transcriptional activators, including CREB (Redmond et al., 2002; Wayman et al., 2006), NEUROD (Gaudillière et al., 2004) and CREST (Aizawa et al., 2004), have also been implicated in dendrite development. In addition, a CREB-dependent microRNA (miR132) positively regulates cortical neuron neurite outgrowth (Vo et al., 2005). Callosal axon outgrowth in the developing cortex is impeded by suppressing neuronal activity (Mizuno et al., 2007; Rodríguez-Tornos et al., 2016; Suárez et al., 2014; Wang et al., 2007), and axonal pathfinding has been linked to intracellular calcium signaling involving kinases and phosphatases with distinct calcium sensitivities (reviewed by Gomez and Zheng, 2006). How these calcium-dependent mechanisms cooperate to control axonal and dendritic elaboration in the developing cortex remains unclear. Intriguingly, a calcium-independent interaction between $Ca_v1.2$ and RhoA was shown to regulate dendritic morphogenesis (Krey et al., 2013), highlighting additional roles for VGCCs as anchors for large signaling complexes at the membrane.

Electrical activity and neurotransmitter signaling regulate cortical interneuron differentiation in a calcium-dependent manner. BDNF, in conjunction with depolarization, enhances dendritic branching and electrophysiological maturation of parvalbumin (PV)-expressing interneurons (Berghuis et al., 2004). Postnatal electrical activity mediated by ionotropic glutamate receptors is also required for morphological maturation of calretinin- and reelin-expressing cortical interneurons (De Marco García et al., 2011). The activity-regulated DNA binding protein SATB1, which is associated with postnatal survival of somatostatin (SST)-expressing MGE-derived interneurons, is necessary for their maturation and terminal differentiation (Close et al., 2012; Denaxa et al., 2012). KCl-induced SATB1 upregulation is dependent on both calcium influx through L-type VGCCs and GABAR activation (Denaxa et al., 2012). More recently, the calcium-dependent transcription factor MEF2C was found to be required for the differentiation of PV-expressing cortical interneurons (Mayer et al., 2018). Activity-dependent splicing regulators such as the ASD-relevant RNA binding protein RBFOX1 (Table S1), which promote neuronal differentiation of cortical NSPCs (Zhang et al., 2016), also regulate distinct aspects of PV- and SST-expressing interneuron maturation and connectivity (Wamsley et al., 2018). These data reveal that activity-dependent calcium signaling is essential for the acquisition of molecular identity and morphology in developing pyramidal and interneuron populations.

Calcium and gliogenesis

To ensure that neurogenesis proceeds faithfully during early cortical development, RGCs actively inhibit intrinsic mechanisms of astrogliogenesis, including transcription of astrocyte-specific genes (reviewed by Miller and Gauthier, 2007). Extrinsic signals acting via neurotrophic factors later stimulate cortical RGCs to become gliogenic (Qian et al., 1997; Song and Ghosh, 2004), in part via JAK/STAT pathway activation (Bonni et al., 1997). G protein signaling initiated by pituitary adenylate cyclase-activating polypeptide (PACAP, encoded by *Adcyap1*) and transduced via calcium has been identified as a complementary mechanism involved in the onset of astrogliogenesis (Fig. 4) (Nishimoto et al., 2007; Vallejo and Vallejo, 2002). Activation of PAC1 receptors by PACAP induces cyclic AMP (cAMP) production, which promotes astrocyte differentiation (Cebolla et al., 2008; McManus et al., 1999; Vallejo and Vallejo, 2002). PACAP stimulation elicits gradual intracellular calcium rises in NSPCs, whereas cAMP antagonism eliminates these rises and blocks astrocyte differentiation (Cebolla et al., 2008). During astrogliogenesis, calcium binding to the downstream regulatory element antagonist modulator (DREAM) is required for expression of the astrocyte-specific glial fibrillary acidic protein (*Gfap*) gene (Cebolla et al., 2008). These data indicate that PACAP induces cAMP-dependent calcium entry, enabling calcium-dependent astrocyte-specific gene transcription (Cebolla et al., 2008; McManus et al., 1999; Vallejo and Vallejo, 2002). PACAP signaling in mice lacking *Dream* (*Kcnip3*) fails to induce astrocyte differentiation, but this can be rescued by JAK/STAT activation, suggesting that calcium-regulated DREAM signaling works in parallel to JAK/STAT signaling during astrogliogenesis (Cebolla et al., 2008).

Neural activity and downstream calcium signaling is also implicated in the development and function of cortical oligodendrocyte precursor cells (OPCs) and microglia (Box 3). Dissecting how activity-dependent calcium signaling facilitates communication between developing neurons and glia will enhance our understanding of how the cortex is built.

Box 3. Calcium and embryonic glial cells originating outside the cortex

Embryonic oligodendrocyte precursor cells (OPCs) initially populate the cortex through two waves of migration from the ganglionic eminences (Kessaris et al., 2006). A third group of OPCs is generated in the postnatal cortex, replacing a subset of ventrally-derived OPCs (Kessaris et al., 2006). During these developmental windows, OPCs begin to express ion channels and neurotransmitter receptors that enable them to respond to activity-dependent signals (De Biase et al., 2010; Fulton et al., 2010; Spitzer et al., 2019; reviewed by Bergles and Richardson, 2015). It was first demonstrated in the rodent optic nerve that inhibiting electrical activity reduces the number of mitotic OPCs (Barres and Raff, 1993). Pharmacological, electrophysiological and optogenetic manipulations in the cortex have since reinforced the notion that neuronal activity regulates OPC proliferation and myelination (Demerens et al., 1996; Gary et al., 2012; Gibson et al., 2014; Mitew et al., 2018). The effects of electrical activity on OPCs are likely at least partly transduced via VGCCs, as $Ca_v1.2$ loss of function results in impaired OPC proliferation, axon-OPC interactions and myelination (Cheli et al., 2015, 2016). Live imaging of the developing zebrafish spinal cord also reveals that neuronal activity induces different patterns of calcium signals to regulate myelination (Baraban et al., 2017; Krasnow et al., 2018). What initiates these dynamics and how they influence genetic programs driving OPC differentiation and myelination remains unclear. Although OPCs differentially respond to activity-dependent signals in the spinal cord (Marisca et al., 2020), such OPC functional heterogeneity in the developing cortex remains poorly understood.

Microglia originate outside the CNS and migrate into the cortex during embryonic development (Ginhoux et al., 2010; reviewed by Thion and Garel, 2017), where they play important roles in regulating progenitor abundance and sculpting developing circuits (Cunningham et al., 2013; Squarzoni et al., 2014; Ueno et al., 2013; reviewed by Thion and Garel, 2020). Although various neurotransmitters, immune molecules and ligands for purinergic receptors induce microglial calcium rises *in vitro* (reviewed by Umpierre and Wu, 2021), it remains less clear how calcium influences the functions of cortical microglia. Neuronal activity regulates microglial-mediated synaptic pruning (Schafer et al., 2012), and microglia sensitive to GABA preferentially remodel inhibitory synapses in the postnatal cortex (Favuzzi et al., 2021). In the developing zebrafish spinal cord, activity-dependent myelin phagocytosis by microglia is characterized by spontaneous calcium transients in microglial processes contacting myelin (Hughes and Appel, 2020). Future studies probing how activity and calcium facilitate neuron-glia communication during development will aid our understanding of how different cell types function in concert to build the cortex.

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Conclusions

As we have reviewed here, the coordinated spatiotemporal regulation of calcium signaling directs cellular behaviors that underlie early cortical development, including aspects of NSPC function. Calcium is a key mediator of activity-dependent gene expression, serving as a hub linking environmental cues to the cytoskeleton, metabolic pathways and other biochemical cascades. Underscoring these crucial developmental roles, genetic studies reveal that mutations in genes encoding calcium signaling modulators contribute to the pathophysiology of neurodevelopmental disorders. There remain, however, open questions about how activity and calcium-dependent processes are regulated at a cell type-specific level and how this regulation coordinates cellular behaviors during corticogenesis. In other cell and tissue types, properties of intracellular calcium dynamics have been linked to activation of specific downstream transcription factors. It is thus tempting to hypothesize that distinct cell type-specific patterns of electrical signals and calcium elevations in the embryonic cortex may subserve specific developmental roles. A natural corollary to this hypothesis is that disrupting calcium signaling and patterned electrical activity in specific cortical populations during development may promote neurodevelopmental disease.

Much remains to be elucidated about how calcium signaling is initiated and transduced in developing cortical cells. Titration of calcium signaling is not only achieved through dynamic regulation of ion channels and signaling proteins but also via coordination of extrinsic cues, including maternal hormones and metabolic regulation (Rash et al., 2018; Tyzio et al., 2006), which indirectly influence calcium homeostasis. How then do extrinsic signals converge to shape calcium entry in different cortical cell populations? How do different modes of calcium entry work cooperatively to direct gene expression programs across cell types? And how might intracellular calcium signals in one population influence dynamic interactions with other cell types? For example, do compartmentalized calcium signals that propagate across polarized cells, as reported in RGCs, influence local cellular processes (e.g. translation)? Single-cell, long-read and spatial sequencing technologies, organoid modeling, subcellular calcium and voltage imaging approaches, optogenetic and chemogenetic tools, and advances in labeling and isolating developing cortical cell populations will hopefully allow us to address these and other questions with unprecedented cellular resolution.

Determining how disease-relevant mutations affect intracellular signaling and cell type-specific developmental behaviors across space and time (reviewed by Panagiotakos and Pasca, 2022) will also enable the development of therapeutic approaches for neurodevelopmental diseases targeting calcium and activity-dependent mechanisms. Of special interest is determining how early disruption of activity-dependent signaling might cascade into later developmental events to promote disease. Recent findings support the notion that neurodevelopmental mechanisms may be reactivated to promote adult and aging-related disease states (Boxes 4 and 5), reinforcing the significance of exploring how calcium signals are normally regulated to coordinate the development of functional circuits. Looking ahead, it will be important to consider how changes at the organismal level (e.g. immune function, metabolism, gut-brain axis) may contribute to the regulation and misregulation of calcium in the embryonic and adult cortex to better understand normal development and the emergence of neurological disorders.

Box 4. Reactivation of developmental calcium signaling mechanisms in glioma

In primary glioma specimens from adult human patients, stem-like glioma cells display molecular signatures reflecting neural stem and progenitor cell (NSPC) identity (Bhaduri et al., 2020; Venteicher et al., 2017; Wang et al., 2020), and their morphology, behavior and lineage trajectory resembles that of embryonic radial glial cells (RGCs) (Bhaduri et al., 2020; Couturier et al., 2020; Wang et al., 2020). Similarities between cortical RGCs and stem-like glioma cells extend into calcium signaling dynamics, suggesting that calcium-regulated developmental mechanisms may be reused to promote glioma initiation and maintenance. For example, patient-derived glioblastoma xenografts in mice display synchronous calcium transients (Venkataramani et al., 2019; Venkatesh et al., 2019) and, as in cortical radial glia, calcium and electrical activity modulates glioma cell proliferation (Urso et al., 2019; Venkatesh et al., 2019; Zhang et al., 2012). Adjacent glioma cells are connected via 'microtubes' composed of gap junctions (Osswald et al., 2015), and calcium propagates across coupled cells in a manner reminiscent of calcium waves in the developing cortical ventricular zone (Osswald et al., 2015; Venkataramani et al., 2019). It is plausible that unraveling the calcium signaling mechanisms directing embryonic NSPC proliferation and migration will provide crucial insights into glioma cell biology to identify potential therapeutic targets for the management of glioma invasion and progression.

Box 5. Implications for neurodegenerative diseases

Calcium signaling deregulation has been implicated in neurodegenerative disorders, including Alzheimer's disease (AD) (reviewed by Pchitskaya et al., 2018; Verkhratsky, 2019). In human induced pluripotent stem cell models of AD and frontotemporal lobar degeneration-tauopathy, activity-dependent calcium elevations are abnormally high (Imamura et al., 2016; Park et al., 2018). Neurons and glia also display elevated basal calcium in AD mouse models (reviewed by Pchitskaya et al., 2018; Verkhratsky, 2019), and genes related to increased cytosolic calcium are enriched in patients with heightened risk for sporadic AD (Heck et al., 2015). Intriguingly, calcium- and activity-dependent pathways altered in neurodevelopmental diseases are thought to be affected in AD (Ivashko-Pachima et al., 2021; Mencer et al., 2021). Key calcium signaling effectors like DYRK1A (Table S1) are deregulated both in neurodevelopmental disorders and cortices of sporadic AD patients (Ferrer et al., 2005). Consistent with this, aging and AD rodent models exhibit aberrant calcium-dependent CaN/NFAT signaling (Foster et al., 2001; Norris et al., 2005), and blocking CaN/NFAT in AD models improves synaptic function, amyloid pathology and astrogliosis (Furman et al., 2012).

Emerging studies also suggest that individuals with neurodevelopmental disorders such as autism spectrum disorder (ASD) and Down syndrome (DS) have increased risk of developing AD and related dementias early in life (Vivanti et al., 2021; reviewed by Lott and Head, 2019). Although, in the case of DS, association with early-onset dementia is related to increased amyloid precursor protein (APP) resulting from trisomy of all or part of chromosome 21, multiple genetic and environmental factors likely contribute to increased AD susceptibility. Deregulation of electrical activity, which impinges on calcium, represents one possible contributing mechanism common to neurodevelopmental and neurodegenerative disorders. In DS and ASD mouse models, abnormalities in NKCC1/KCC2 expression promote persistent depolarizing activity of GABA, akin to the developing brain, in adult and postnatal hippocampal neurons (Deidda et al., 2015; Tyzio et al., 2014). Consequently, administration of the NKCC1 antagonist bumetanide in these models restores chloride gradients and rescues cognitive and behavioral abnormalities (Deidda et al., 2015; Tyzio et al., 2014). Intriguingly, bumetanide was recently shown to improve pathological and behavioral deficits in an AD rodent model (Taubes et al., 2021). Furthermore, APP has been linked to the regulation of KCC2, GABAR and VGCC expression (Chen et al., 2017; Doshina et al., 2017; Yang et al., 2009), implicating it as a regulator of electrical activity and calcium homeostasis.

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Competing interests
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Table S1. Developmental disease-associated mutations intersect with calcium signaling.
Select genes from the SFARI Gene Database encode protein products that either directly regulate calcium homeostasis and signaling or indirectly impinge on calcium by modulating neuronal excitability or altering membrane potential. We restricted our survey to genes defined as either Category 1 (high confidence) or Category 2 (strong candidate) (see: https://gene.sfari.org/about-gene-scoring/ for the SFARI gene scoring criteria) and list the developmental functions of their gene products and the functional effects (when known) of select disease-associated mutations. This Table only highlights selected genes and is not exhaustive in scope. Notably, due to space constraints, we have not included synaptic structural proteins that regulate ion/calcium channel localization and function at synapses [e.g., ANK2 (Kline et al., 2014), NRXN1-3 (Luo et al., 2020; Missler et al., 2003)], which have been reproducibly implicated in ASD.

Gene	Mutation type	Disease	Relationship to calcium/activity dependent signaling	Electrophysiological characterization of select variants and/or select developmental phenotypes	References
CALCIUM CHANNELS					
ATP2B2	missense, nonsense, truncating variants,	ASD, epilepsy	encodes the PMCA2 ATPase calcium pump	> LoF mutations predicted to result in excess intracellular calcium; > ASD associated variants (e.g., Cys756*, Trp1064* - predicted to lead to nonsense mediated decay); > heterozygous LoF mice: heightened amplitude AMPAR-mediated calcium transients in cerebellar Purkinje cells; increased expression of P/Q-type VGCCs; increased amplitude depolarization-induced calcium influx, decreased Purkinje cell numbers; > KO mice: reduced growth rate, balance and movement problems, deafness and vestibular problems	***Select genetic studies:*** *Carayol et al. 2011; Takata et al., 2018; Iossifov et al. 2014; Yang et al., 2013; Prandini et al., 2012* ***Select functional references:*** *Smits et al., 2019; Fakira et al., 2012; Kozel et al., 1998*
CACNA1A	missense, frameshift, stop-gain and LoF variants	ASD, ID, epilepsy (e.g., EE, primary generalized epilepsy), paroxysmal movement disorders; FHM	encodes the pore forming subunit of the VGCC Cav2.1	> GoF mutations (e.g. R192Q mutation implicated in FHM): knock-in mice exhibit elevated calcium current density in cerebellar granule cells, increased neurotransmitter release at neuromuscular synapses, enhanced induction of cortical spreading depression; > epilepsy related mutations: dominant negative, impaired channel function (e.g. C5733T, E147K); > KO mice: ataxia, dystonia and early death, irregular corticothalamic activity; > interneuron-specific LOF: epilepsy, abnormal GABA release from PV+ cells; > pyramidal neuron specific LOF: attenuates excitability	***Select genetic studies:*** *Gulsuner et al., 2020; Epi4k Consortium 2016; Hamdan et al., 2017; Damaj et al., 2015; Jiang, 2015; Jouvenceau et al., 2001; Imbrici et al., 2004; Stam et al., 2009; commentary in Noebels et al., 2002* ***Select functional references:*** *Bomben et al., 2016; Rossignol et al., 2013; Llinás et al., 2007; Todorov et al., 2006; van den Maagdenberg et al., 2004; Kaja et al., 2005; commentary in Noebels et al., 2002*
CACNA1C	missense variants, G406R point mutation in *exon 8a*	classical TS, SCZ, BPD	encodes the pore forming subunit of the VGCC Cav1.2	> GoF TS mutation: impaired channel splicing, loss of voltage-dependent channel inactivation, increased depolarization-dependent calcium elevations, altered cortical projection neuron differentiation, activity-dependent dendritic retraction, deficits in cortical excitatory and inhibitory neuron migration	***Select genetic studies:*** *Splawski, et al. 2004; SCZ Psychiatric GWAS consortium 2011; Cross-disorder group of Psychiatric Genomics Consortium, 2013; SCZ Working Group of the Psychiatric Genomics Consortium, 2014; Ripke, et al. 2013; Ferreira et al, 2008; Purcell, et al. 2014, Green et al., 2010; Green et al., 2013* ***Select functional references:*** *Splawski, et al. 2004; Barrett & Tsien, 2008; Pasca et al., 2011; Krey et al., 2011; Birey et al., 2017; Kamijo et al., 2018; Panagiotakos et al., 2019; reviewed by Bhat et al., 2012*
CACNA1D	missense, LOF, and GoF variants	ASD, epilepsy	encodes the pore forming subunit of the VGCC Cav1.3	> GoF mutations: impaired/irregular voltage-dependent channel inactivation (e.g., G407R, G403D, G403R, Q547H, P1336R, A769G, V401L and S652L); hyperpolarized voltage dependence of activation (e.g., V259D, F747L, I750M, V1153G, A769G, V401L and S652L); increased current density (e.g. V401L); > LoF mutations: increased sensitivity to dihydropyridine inhibition (e.g. S652L); > ASD-associated mutation A760G: reduced calcium dependent inactivation, altered channel gating leading to increased intracellular calcium > KO mice: deafness, cardiac irregularities	***Select genetic studies:*** *O'Roak et al., 2012; Klassen et al., 2011* ***Select functional references:*** *Pinggera et al., 2015, 2017, 2018; Hofer et al., 2020; reviewed by Ortner et al., 2020; Baig et al. 2011; Scholl et al. 2013; Limpitikul et al., 2016; Platzer et al., 2000*
CACNA1E	missense, synonymous, and GoF/LoF variants	ASD, DEE	encodes the pore forming subunit of the VGCC Cav2.3	> G1209S: top de novo ASD risk mutation; > GoF mutations: slow inactivation, hyperpolarizing shifts in voltage dependent activation, increased current density (e.g. majority of DEE variants in pore domains, S6 variants: F698S, I701V, A702T; S4-5 variant: I603L); > KO mice: CA1 pyramidal cells from KO mice exhibit increased excitability, and altered action potential properties; neurons of the reticular thalamus have significantly reduced high voltage activated calcium currents, and suppressed rhythmic burst discharges.	***Select genetic studies:*** *O'Roak et al., 2012; Takata et al., 2016; Helbig et al., 2018; comment in Carvill et al., 2019; Neale et al., 2012* ***Select functional references:*** *Helbig et al., 2018, Zaman et al., 2011, Neale et al., 2012; comment in Carvill et al., 2019; Gutzman et al., 2019*
CACNA1H	missense and LoF/GoF variants	ASD, epilepsy (e.g. CAE)	encodes the pore forming subunit of the VGCC Cav3.2	> missense LoF ASD mutations in voltage sensor (e.g., R212C, R902W), pore-forming domains (e.g., W962C), and c-terminus (e.g., R1871Q + A1874V): significantly reduced Cav3.2 (T-type) calcium currents; > CAE associated variants result in GoF and LoF (e.g., C456S, G773D, R788C, V831M, E282K: altered voltage dependence of activation; F161L, P648L, G773D, R788C: altered voltage dependence of inactivation; C456S, A748V, D1463N: faster activation kinetics; G773D, G784S, R788C, V831M: slower activation kinetics; F161L: faster inactivation kinetics; G499S, P648L, G773D, R788C, V831M, G773D, V831M, G848S, R788C, G773D, R788C: slower inactivation/deactivation kinetics); > modeling predicts net GOF/enhanced burst firing of thalamic neurons for CAE associated variants (e.g., C456S, P648L, G773D, R788C, G773D-R788C, A748V, G784S, G848S, and D1463N); > modeling predicts decreased thalamic neuron burst firing for CAE associated variants (e.g., E282K and V831M); > KO mice have anxiety-like phenotypes and impairments in memory	***Select genetic studies:*** *Chen et al., 2003; Splawski et al., 2006; Vitko et al., 2005; Heron et al., 2007* ***Select functional references:*** *Khosravani et al., 2004; reviewed by Perez-Reyes 2006; Vitko et al., 2005; Vitko et al., 2007; Heron et al., 2007; Gackiere et al., 2008, Tao et al., 2008; Becker et al., 2008; Powell et al., 2009; Hu et al., 2009; Gangarossa et al., 2014; Splawski et al., 2006*
CACNA2D3	missense variants, splice site mutations, deletions	ASD, epilepsy	encodes the auxiliary α2δ3 VGCC subunit	> deletion of *CACNA2D3* homolog *unc-36* in c-elegans: altered axon termination; > *Cacna2d3* KO mice: impaired hearing, increased anxiety-related behaviors, reduced sensitivity to thermal pain	***Select genetic studies:*** *Iossifov et al., 2012; Girirajan et al., 2013; De Rubeis et al., 2014; C Yuen et al., 2017* ***Select functional references:*** *Buddell et al., 2019; Peng et al., 2021; Landmann et al., 2019; Pirone et al., 2014; Neely et al., 2010*
CACNB2	various missense variants	ASD	encodes the auxiliary β2 VGCC subunit	> GoF ASD-associated mutations (e.g., G167S, S197F): slower time dependent inactivation, altered sensitivity of voltage dependent inactivation, enhanced peak current densities; > LoF ASD-associated mutations (e.g., F240L): accelerated time-dependent inactivation	***Select genetic studies:*** *Cross disorder group of the psychiatric genomics consortium 2013; Ripke et al., 2013; Cross disorder group of the psychiatric genomics consortium 2017; Pardinas et al., 2018, Yuen et al., 2015* ***Select functional references:*** *Breitenkamp et al., 2014; Graziano et al, 2021; Despang et al., 2020*
TRPC6	translocations, missense variants, premature stop variant	ASD	encodes a calcium permeable cation channel from the transient receptor potential family	> neural progenitor cells from ASD patient-derived iPSCs: reduced calcium influx; > neurons from ASD patient-derived iPSCs: reduced TRPC6 protein levels, reduced dendritic spine density, altered synaptic properties; > transgenic *Trpc6* GOF: increased dendritic spine density, enhanced spatial memory	***Select genetic studies:*** *Griesi-Oliveira et al., 2014* ***Select functional references:*** *Griesi-Oliveira et al. 2015; Zhou et al., 2008*
TRPM1	CNVs, deletions	ASD	encodes a calcium permeable cation channel from the transient receptor potential family	> *Trpm1* KO mice: hyperactive, attenuated anxiety-related behaviors, altered fear memory, abnormal social behavior	***Select genetic studies:*** *Girirajan et al., 2013; Matsunami et al., 2014* ***Select functional references:*** *Hori et al., 2021*
OTHER ION CHANNELS THAT IMPINGE ON CALCIUM ENTRY AND ACTIVITY DEPENDENT SIGNALING					
CHRNA7	copy number variants, missense variants, microdeletion	Epilepsy, SCZ, DD, ID, ASD	encodes a calcium permeable nicotinic cholinergic receptor	> KO mice: phenotypes dependent on background strain due to differences in endogenous *Chrna7*; > C3H KO mice: impaired LTP, abnormal auditory processing; > C3H Het mice: reduced GAD65 levels, reduced GABAA receptors in male mice; > reduced *CHRNA7* transcription and function (e.g., *CHRNA7* promoter variants); decreased calcium influx through CHRNA7 (e.g., both 15q13.3 deletions and duplications); increased ER stress (e.g., 15q13.3 duplications)	***Select genetic studies:*** *Mikhail et al., 2011; Shinawi et al,. 2009; Soler-Alfonso et al., 2014; Gillentine et al., 2017; Hoppman-Chaney et al., 2013; Leonard et al., 2002; Gault et al., 2003; Stephens et al., 2009* ***Select functional references:*** *Yin et al., 2017; Freund et al., 2016; Adams et al., 2012; Leonard et al., 2002; Sinkus et al., 2011; Gillentine et al., 2017*
KCNJ10	missense variants, synonymous variants, LoF/GoF variants	Seizures, ASD	encodes an ATP-sensitive potassium channel	> KO mice: motor impairments, hypomyelination, axonal abnormalities, retarded growth, dehydration, abnormalities in renal salt handling, premature death; > astrocyte- and oligodendrocyte-specific cKO: seizures, premature death, ataxia, hindleg paralysis, retarded growth, abnormal astrocyte depolarization, impaired uptake of glutamate and potassium, reduced spontaneous neuronal activity, abnormalities in post-tetanic potentiation and short-term potentiation; > oligodendrocyte-specific cKOs: mitochondrial abnormalities, axonal degeneration, loss of axonal integrity, neuronal loss, visual deficits, retinal abnormalities, motor problems, functional abrnomalities including slow potassium clearance, delayed axonal recovery post stimuation, seizures; > GoF mutations: enhanced membrane expression; increased current density (e.g., R18Q); pH-dependent current inhibition (e.g., R348H); increased current amplitudes (e.g., R18Q, V84M); increased unit conductance (e.g. V84M); > homozygous missense mutations affecting transmembrane domain (e.g., G65P, G77R) modeled in *Xenopus*: decreased potassium currents	***Select genetic studies:*** *Ferraro et al.,2004; Buono et al., 2004; Sicca et al., 2011; Bockenhauer et al., 2009* ***Select functional references:*** *Bockenhauer et al., 2009; Neusch et al., 2001; Djukic et al., 2007; Schirmer et al., 2018; Larson et al., 2018; Sicca et al., 2011*
KCNMA1	missense variant, frame shift variant, GoF variants, LoF variant	Epilepsy, ASD, paroxysmal dyskinesia	encodes the pore-forming α-subunit of the large conductance calcium and voltage-activated potassium channel	> LoF mutations: altered resting membrane potential, decreased channel activity; > KO mice: alterations in suprachiasmatic nucleus function and circadian rhythm, progressive hearing loss, cerebellar abnormalities, motor coordination dysfunction, reduced activity of Purkinje neurons, dysfunctional astrocyte/arteriolar smooth muscle communication; > GoF mutations: enhanced voltage dependent activation and enhanced voltage sensitivity (e.g. N536H); in *Xenopus* oocytes: increased voltage- and calcium-dependent activation, faster activation kinetics in response to depolarizing voltage (e.g., D434G mutation); in CHO cells: increased sensitivity to calcium, activation at lower voltages, increase in open-channel probilitity (e.g., D434G)	***Select genetic studies:*** *Laumonnier et al., 2006; Neale et al., 2012; Liang et al., 2019; Zhang et al., 2020b; Satterstrom et al., 2020; Zou et al., 2021; Bailey et al., 2019; Du et al., 2005; Tabarki et al., 2016; Zhang et al., 2015* ***Select functional references:*** *Plüger et al., 2000; Díez-Sampedro et al., 2006; Meredith et al., 2006; Ruttiger et al., 2004; Sausbier et al., 2004; Filosa et al., 2006; Zhang et al., 2020b; Du et al., 2005*
GRIA2	nonsense variant, missense variant, deletions	ASD, ID, seizures, DEE, DD	encodes the GluA2 AMPAR subunit, whose inclusion in AMPARs renders them calcium-impermeable	> LoF mutations: decrease current amplitudes compared to wild type (WT) channels (e.g., G47E, D302G, del528-530, G609R, A639S, F644L, T646N); > GoF mutations: increase current amplitudes compared to WT channels (e.g., Q607E); > KO mice: increased calcium permeability in hippocampal neurons lacking GluA2, alterations in LTP, impaired exploratory behavior, alterations in reward behaviors	***Select genetic studies:*** *De Rubeis et al., 2014; Deciphering Developmental Disorders Study 2017; C Yuen et al., 2017; Hackmann et al., 2012* ***Select functional references:*** *Salpietro et al., 2019; Lu et al., 2009; Jia et al., 1996; Hackmann et al., 2012; Mead et al., 2003*
GRIN1	missense variants	ASD, Polymicrogyria, Epilepsy, ID, DD	encodes the GluN1 subunit of calcium permeable NMDARs	> LoF missense variants in or adjacent to a transmembrane domain (e.g., P557R, S560dup, G618R, G620R, Y647S, G815R, F817L, Q556*, G827R); > GoF mutations: increased calcium currents through NMDARs (e.g., E662K); > *Grin1* KO mice: significantly attenuated NMDA-induced calcium rises, abnormal social behaviors; > *in utero* knockdown in developing cortex: deficits in radial migration; > conditional *Grin1* deletion in PV+ cells: reduced LTP induction and maintenance, impaired social behavior; > interneuron-specific *Grin1* deletion: attenuated NMDA currents; > conditional *Grin1* deletion in pyramidal cells: increased social approach behavior; > *Dlx5/6*-Cre mediated deletion *in utero*: abnormal morphological maturtion of Re+ interneurons and improper circuit integration	***Select genetic studies:*** *Epi4K Consortium et al., 2013; Hamdan et al, 2011; Jiang, 2015* ***Select functional references:*** *Hamdan et al, 2011; Gandal et al., 2012; Saunders et al., 2013; Lemke et al. 2016; commentary in Lemke, 2020; Forrest et al., 1994; Ferri et al., 2020; Billingslea et al., 2014; De Marco Garcia et al., 2015; Fry et al., 2018; reviewed by Vieira et al,. 2021*
GRIN2A	copy number variants, nonsense mutation, chromosome translocation breakpoints, missense variant	ASD, various epileptic syndromes (e.g., Landau-Kleffner syndrome, EE, childhood epilepsy, infantile onset EE), polymicrogyria, SCZ	encodes the GluN2A subunit of calcium permeable NMDARs	> GoF mutations: increased GluN1/GluN2A current density (e.g., R1067W); increased sensitivity to glutamate and/or glycine agonists (e.g., P552R, M817V, L812M, V452M, K669N, N447K, V506A, P699S); decreased magnesium block, increased current density (e.g., N447K); impaired zinc inhibition, normal current amplitude, glutamate and glycine affinities and open-state probabilities (e.g., A243V); increased total surface expression (e.g., K590N, K879R, R1067W); > LoF mutations (e.g., R518H, T531M, D731N, V685G, G483R, A716T, C436R, C231Y, A548T, P79R, I694T, M705V, A727T, V734L, K772E, R370W); loss of magnesium block and decreased calcium permeability (e.g., N615K); > *Grin2A* KO mice: altered NMDA/AMPA receptor currents in hippocampal neurons, impairments in LTP and LTD, increased locomotion, deficits in fear conditioning; > *in utero* knock down: no effect of cortical radial migration	***Select genetic studies:*** *Barnby et al., 2005; Endele et al 2010; Lemke et al., 2013; Yoo et al., 2012; Liu et al., 2021; Singh et al., 2022* ***Select functional references:*** *Liu et al., 2021; Endele et al 2010; Strehlow et al., 2019; Kannagara et al., 2015; Sakimura et al. 1995; Kiyama et al. 1998; Chen et al., 2017; Ogden et al., 2017; Yuan et al., 2014; Marwick et al., 2019; Bertocchi et al., 2021; Xu et al., 2018; Swanger et al., 2016; Gao et al., 2017; Addis et al., 2017; Serraz et al., 2016; reviewed by Vieira et al., 2021*
GRIN2B	splice site variants, non-synonymous variants, LoF variants, *GRIN2B* GoF (West syndrome), chromosome translocation breakpoints, frameshift mutations, missense mutations,	ASD, SCZ, West Syndrome, ID, DD, Epilepsy	encodes the GluN2B subunit of calcium permeable NMDARs	> GoF mutations: loss of voltage dependent magnesium block (e.g., N615I, V618G); reduced calcium permeability (e.g., N615I); > LoF GluN2B-724 truncation mutant: attenuated calcium influx, impaired trafficking to cell membrane, impaired dendritic morphogenesis; > LoF mutations: mutation in ligand binding domain, impaired glutamate binding, higher glutamate concentrations required for activation (e.g., G689S, G689C), poor expression of G689C variant at cell membrane; overexpression in hippocampal neurons: decreased frequency of NMDAR-dependent mEPSCs with faster deactivation kinetics, no change in frequency of AMPAR-dependent mEPSCs; > KO GluN2B to GluN2A "replacement" mouse: altered synaptic plasticity/development, reduced social exploration, hyperlocomotion; > MADM-mediated *Grin2b* KO: impaired dendritic pruning and patterning in DG granule cells and spiny stellate cells; > Dlx5/6-Cre mediated *Grin2b* deletion: abnormal morphological maturation of Re+ interneurons > GluN2B overexpression in mice: altered synaptic function, enhanced memory/learning	***Select genetic studies:*** *De Rubeis et al., 2014; Iossifov et al., 2015; Ohtsuki et al., 2001; Myers et al., 2011; Lemke et al., 2014; Epi4K Consortium et al., 2013; Endele et al., 2010; Zhao et al.,2011; Tarabeux et al., 2011; O'Roak et al., 2011; O'Roak et al., 2012; Kellner et al., 2021* ***Select functional references:*** *Lemke et al., 2014; Swanger et al., 2016; Tang et al., 1999; Freunscht et al., 2013; Fedele et al., 2018; Akashi et al,. 2009; Wang et al., 2009; Wang et al., 2011; Kellner et al., 2021; Bahry et al., 2021; Sceniak et al., 2019; De Marco Garcia et al., 2015; Jiang et al., 2015a; Espinosa et al., 2009; reviewed by Vieira et al., 2021*
GABRB2	missense variants, LoF mutations	ASD, epilepsy (e.g., CAE, DEE, EME)	encodes the β2 subunit of the GABAA receptor, activation elicits calcium influx in cortical NSPCs	> LoF disease-associated variants in N-terminal and transmembrane regions: reduced GABA-induced current amplitudes (e.g., I246T, V282A, I288S, P252L); > *Gabrb2* KO mice: increased susceptibility to seizures and epilepsy, altered startle response, reduced anxiety/depression behaviors, hyperlocomotivity, social behavioral abnormalities, memory deficits	***Select genetic studies:*** *Srivastava et al., 2014b; Iossifov et al. 2014; Satterstrom et al., 2020; Yang et al., 2020; Hamdan et al., 2017* ***Select functional references:*** *el Achkar et al, 2021; Yeung et al., 2018*

GABRB3	de novo LoF mutations, missense mutations, intronic variants, synonymous mutations	ASD, epilepsy (e.g., CAE)	encodes the β3 subunit of the GABAA receptor; activation elicits calcium influx in cortical NSPCs	> LoF CAE variants: reduced current densities compared to wild type channels (e.g., P11S, S15F, G32R); reduced peak current amplitudes and reduced surface expression (e.g., P11S)	***Select genetic studies:*** *Epi4K Consortium et al., 2013; Chen et al., 2014; De Rubeis et al., 2014; Yang et al., 2017; Urak et al., 2006; Tanaka et al., 2008; Sanders et al., 2015; Jiang, 2015* ***Select functional references:*** *Delahanty et al., 2012; Urak et al., 2006; Tanaka et al., 2008; Tanaka et al., 2012*
KCNB1	LoF mutations, missense mutation, nonsense variant	DD, epilepsy (e.g., EE, West Syndrome), ASD	encodes the voltage-gated potassium channel Kv2.1	> V378A: altered subcellular localization, altered electrophysiological properties (retained voltage dependent activation with faster inactivation kinetics), altered ion selectivity; > EE-associated mutations (e.g. S347R, G379R, T374I): deficits in ion selectivity; > epilepsy-associated mutations (e.g. R306C, G401R): R306C - altered voltage sensitivity, reduced neuronal firing; G401R - dominant negative mutation in channel pore, G401R abolishes Kv2.1 currents and reduces neuronal firing; > *Kcnb1* KO mice: hyperactivity, abnormalities in spatial learning, accelerated progression of seizures	***Select genetic studies:*** *de Kovel et al., 2017; Torkamani et al., 2014; Parrini et al., 2017; Thiffault et al., 2015; Srivastava et al., 2014a; Allen et al., 2016; Saitsu et al., 2015* ***Select functional references:*** *Torkamani et al., 2014; Thiffault et al., 2015; Speca et al., 2014; Saitsu et al., 2015*
KCNQ2	splice site variant, LoF mutations, missense variants, frameshift variants	ASD, BPD, epilepsy (e.g. DEE, benign familial neonatal seizures)	encodes the voltage gated potassium channel Kv7.2	> LoF mutations largely implicated in BFNS; > voltage sensor S4 transmembrane segment mutations: impaired channel function, dominant negative effect at subthreshold voltages, depolarizing shift in activation curve (e.g., I205V and R213Q); reduced current amplitudes, increased channel protein levels (e.g., R213Q); > pore forming S5 and S6 domain mutations: impaired channel function, dominant negative (e.g., A265P, T274M, G290D); > c-terminal mutations: reduced potassium current amplitude (e.g., R532W, M518V); > *Kcnq2* heterozygous null mice (modeling LoF pathogenic mutations): increased susceptibility to seizures and behavioral abnormalities including reduced sociability and hyperactivity; > homozygous null *Kcnq2* LOF: increased pyramidal neuron excitability	***Select genetic studies:*** *Singh et al., 1998; Jiang et al., 2013; Milh et al., 2013; Judy et al., 2013, Borsotto et al., 2007; Lee et al., 2019; Jiang, 2015* ***Select functional references:*** *Biervert et al., 1998; Borsotto et al., 2007, Zhang et al., 2020a; Soh et al., 2014; Orhan et al., 2014*
KCNQ3	translocation mutations, missense variant	ASD, epilepsy (e.g., benign familial neonatal seizures)	encodes the voltage gated potassium channel Kv7.3	> LoF variants largely implicated in BFNS; > GoF mutations linked to ASD and DD: channel GOF, not associated with seizures in patients (e.g., R230C, R230H, R230S, R227Q); voltage sensor mutations (e.g., R227 and R230); > LoF mutations: voltage sensor mutations (e.g., M240R; homomeric channels not functional, mutation affects voltage sensitivity, predicted increase in channel resting state stability and destabilization of active state); significantly reduced current density, impaired channel function (e.g., R330L, R330C)	***Select genetic studies:*** *Hirose et al., 2000; Epi4K Consortium et al., 2013; Miceli et al., 2020; Grinton et al.,2015; Gilling et al., 2013; Charlier et al., 1998* ***Select functional references:*** *Miceli et al., 2015; Miceli et al., 2020; Gilling et al., 2013; Sands et al., 2019*
P2RX5	gene disrupting mutations, LoF variants	ASD	encodes a calcium permeable purinergic receptor	unknown?	***Select genetic studies:*** *Sanders et al., 2015; Iossifov et al. 2014* ***Select functional references:*** *Bo et al., 2003*
SCN1A	protein truncation mutations (LoF), frameshift, nonsense, splice-donor, missense mutations	Asperger Syndrome, ASD, FHM, epilepsy (Dravet Syndrome, Severe myoclonic epilepsy of infancy, GEFS+)	encodes the α subunit of the voltage-gated sodium channel Nav1.1	> *SCN1A* LoF mutations: Dravet syndrome; > LoF mutations: reduced current amplitude, hypersensitivity to steady-state inactivation (e.g., S1328P); abolished sodium currents in HEK cells (e.g., E78X, W384X, E1587K, and R1596C); partial LOF, abnormal recovery after inactivation, reduced sodium current density (e.g., E788K and M909K); slow inactivation recovery, hyperpolarizing shifts in activation/inactivation (e.g., D249E); reduced current density, slow recovery after inactivation (e.g., T1934I), slow recovery from inactivation (e.g., E78D); > interneurons from iPSCs derived from individuals with Dravet Syndrome (heterozygous S1328P mutations): sodium current and AP firing deficits; no electrophysiological abnormalities in excitatory neurons; > mutations causing GEFS+ mainly missense mutations; > select mutations linked to GEFS+ (functional effects influenced by cell type/expression system): increased Nav1.1 channel function in HEKs (D188V), increased Nav1.1 function in *Xenopus* oocytes (W1204R, R1648H, D1866Y); decreased Nav1.1 channel function in *Xenopus* oocytes (R859C, T875M); decreased Nav1.1 channel function in tsA201 (V1353L, I1656M, R1657C, A1685V); > LoF in mice: epileptic seizures	***Select genetic studies:*** *Weiss et al. 2003; Escayg et al., 2000; Barela et al., 2006; Epi4K Consortium et al., 2013; Claes et al., 2001; Osaka et al., 2007; O'Roak et al., 2011; O'Roak et al., 2012; De Rubeis et al., 2014; C Yuen et al., 2017; Hamdan et al., 2017; Jiang et al., 2015b; Kluckova et al., 2020* ***Select functional references:*** *Weiss et al., 2003; Sun et al., 2016; Ogiwara et al., 2007; Barela et al., 2006; reviewed by Escayg and Goldin, 2010; Kluckova et al., 2020*
SCN2A	LoF variants (often associated with ASD), missense variants, GoF variants, protein truncating variants (ASD)	ASD, ID, epilepsy (infantile EE, benign infantile seizures), SCZ	encodes the α subunit of the voltage gated sodium channel Nav1.2	> Effects of mutations differ in mature and immature neurons owing to changes in subcellular distribution and splicing; > LoF mutations: often associated with ASD and ID, impaired excitability in immature neurons and altered dendritic dendritic excitability in mature neurons; > GoF mutations: mostly associated with infantile epilepsies, increased neuronal excitability; > K1422E: mutation in selectivity filter, renders channel calcium permeable; > R1902C: ASD-associated mutation, allows calcium-dependent conformational change in Nav1.2 when complexed with CaM; > homozygous KO mice: perinatal lethality; > heterozygous *Scn2a* LoF mice: impaired excitability and action potential initiation in immature neurons; impaired dendritic excitability and disrupted synaptic function and plasticity in mature neurons, with presence of immature dendritic spines; normal PV and SST neuron APs; hyperactivity, absence-like seizures, and learning delays	***Select genetic studies:*** *Hamdan et al., 2017; Jiang et al., 2015b; Sanders et al., 2012; Tavassoli et al., 2014; Jiang et al., 2013; Sundaram et al., 2013; Carroll et al., 2016* ***Select functional references:*** *Begemann et al., 2019; Spratt et al., 2019; Spratt et al., 2021; Zhang et al., 2021; Ben-Shalom et al., 2017; Heinemann et al., 1992; Echevarria-Cooper et al., 2022; Fromer et al., 2014; Kim et al., 2004; reviewed by Sanders et al., 2018*
SCN8A	various missense mutations	ASD, DD, ID, epilepsy (e.g. E1EE13)	encodes the voltage-gated α8-subunit of the sodium channel Nav1.6	> majority of patient mutations are GoF: increased channel activity due to alterations in opening and inactivation kinetics; > LoF mutations: cognitive impairment, movement disorders; > GoF mutations: heterozygous missense, increased neuronal excitability in postnatal rat hippocampal neuronal cultures (e.g., N1768D); enhanced channel activation in neurons in vitro, increased excitabillity and spontaneous activity (e.g., T767I); altered voltage dependence of activation, predicted to yield premature neuronal firing (e.g., N984K); > heterozygous knock-in N1768D mice: seizures and sudden unexpected death in Epilepsy, dose dependent effects (homozygous knock-in mice: earlier onset of seizures and death); > LoF mutations: abolishes sodium currents (e.g., G964R, E1218K); reduces protein abundance (e.g., E1218K); significantly reduced channel activity in HEKs, protein product stable and expressed at similar levels to WT, possible off target effects of mutant protein product (e.g., G1451S); > *in vitro* LoF but possible *in vivo* GoF (e.g, R223G: reduced current density and at 37C reduces protein stability; similar activation/inactivation kinetics as WT at 30C with increased ramp current - possible GoF > Conditional *Scn8a* deletion in inhibitory cells using Dlx5/6-Cre: absence epilepsy; no absence seizures with excitatory neuron-specific deletion	***Select genetic studies:*** *Epi4K Consortium et al., 2013; Veeramah et al., 2012; Blanchard et al., 2015; Estacion et al., 2014; de Kovel et al., 2014* ***Select functional references:*** *Veeramah et al., 2012; Wagnon et al., 2015; Blanchard et al., 2015; Estacion et al., 2014; Wagnon and Meisler 2015; de Kovel et al., 2014; Makinson et al., 2017*
SLC6A1	truncating variants, missense variants, splice site variants CNVs, insertions, deletions and synonymous variants, nonsense variant	epilepsy (myoclonic atonic, genetic generalized, non-acquired focal, Lennox-Gastaut syndrome), DD, ASD, ID, speech delay, SCZ	encodes the voltage-dependent GABA transporter protein type 1 responsible for sodium-dependent GABA reuptake	> LoF mutations associated with Lennox-Gastaut syndrome: reduced total protein levels in HEKs and rat cortical neurons, reduced cell surface expression, impaired GABA uptake (e.g., G234S); > P361T: heterozygous LoF mutation associated with epilepsy and autism, lower total protein levels, mutant protein abnormally localized in ER, reduced protein function and surface expression; > KO mice: homozygous LoF yields increased tonic inhibition, reduced phasic inhibition, reduced quantal GABA release, no change in GABA receptor density, tremor, walking abnormalities, decreased strength, seizures, and anxious behaviors; heterozygous LoF yields diminished GABA reuptake	***Select genetic studies:*** *Sanders et al., 2012, Satterstrom et al., 2020, Satterstrom et al., 2019; Cai et al., 2019; Carvill et al., 2015; Rees et al., 2020; Wang et al., 2020* ***Select functional references:*** *Cai et al., 2019; Carvill et al., 2015; Jensen et al., 2003; Cope et al., 2009; Chiu et al., 2005*
SELECT CALCIUM-INTERACTING PROTEINS, CALCIUM SIGNALING MODULATORS, AND ACTIVITY-DEPENDENT PROTEINS					
CREBBP	coding variants, point mutations, deletion, duplications, frameshift mutation, missense mutations, splice site mutations	ASD, Rubinstein-Taybi syndrome	encodes the calcium regulated transcriptional coactivator CBP, a CREB co-factor critical for activity-dependent gene expression	> CH1 domain mutant mice: deficits in social interaction, ASD-relevant repetitive behaviors, hyperactivity, and abnormal synaptic plasticity; > *Gfap*-cre mediated cKO mice: microcephaly, behavioral anomalies, reduced embryonic NSPC proliferation, deficits in NSPC migration, impaired postnatal neurogenesis, and abnormal pyramidal cell morphology	***Select genetic studies:*** *Petrij et al., 1995; Roelfsema et al., 2005; Barnby et al., 2005; Wincent, et al. 2016; Coupry et al., 2002* ***Select functional references:*** *Merk et al., 2018; Zheng et al., 2016; Schoof et al., 2019; Valor et al., 2011*
CASK	missense variants, splice site variant, premature stop variants	ASD	encodes a calcium/calmodulin-dependent serine protein kinase	> iPSC-derived neurons from *CASK* mutation carriers: reduced CASK levels, alterations in presynaptic development, reduced spontaneous calcium events; > neurons from *Cask* KO mice: increased frequency of spontaneous excitatory miniature synaptic events, decreased frequency of spontaneous inhibitory miniature synaptic events	***Select genetic studies:*** *Iossifov et al., 2014; Najm et al. 2008; Stessman et al. 2017; Becker et al., 2020; Mukherjee et al., 2020* ***Select functional reference:*** *Atasoy et al., 2007; Becker et al., 2020*
CIB2	copy number variants	ASD	encodes a calcium binding protein that mediates calcium signaling processes	> *Cib2* KO mice: hearing loss, loss of auditory hair cell currents; > CIB2 down regulation in zebrafish and *Drosophila*: deafness and vision deficits	***Select genetic studies:*** *Prasad et al., 2012; Riazuddin et al., 2012* ***Select functional references:*** *Wang et al., 2017; Riazuddin et al., 2012*
DYRK1A	truncating variants, nonsense mutations, missense variants, frameshift mutations, splice site variants, copy number variants (DS), translocation	ASD, ID, microcephaly, DD	encodes a kinase that regulates localization and/or activity of calcium-dependent transcription factors (e.g. NFAT, CREB)	> *DYRK1A* in Down syndrome (DS) critical region, copy number increase implicated in DS; > LoF *DYRK1A* mutations: microcephaly, ID and ASD; > kinase domain mutations alter catalytic activity; R467Q: predicted function in protein stability; L245R: prevents DYRK1A autophosphorylation; > LoF mutations (e.g., E396ter: protein product degraded by ubiquitin proteasome pathway, inactive kinase, no dominant negative effect; other predicted LoF mutations: I48K(fs*2), A498P(fs*94), E414V(fs*76) (loss of exon 11, kinase domain mutation); > *in ovo* GoF in chick spinal cord: reduced proliferation; pharmacological LoF: increased proliferation and apoptosis; > embryonic overexpression upregulates p27Kip1 in the embryonic chick spinal cord and mouse cortex; > *in utero* GoF in mouse cortex: reduced proliferation, abnormal radial migration, enhanced neuronal differentiation, phenotypes dependent on timing and degree of over-expression; > Trisomy of *Dyrk1a* (in mBAC TgDyrk1a mice): lengthened G1 and RG cell cycle length, altered numbers of neurons and IPCs during embryonic neurogenesis; > *minibrain* (*Drosophila* ortholog): GoF promotes cell cycle exit, facilitates neuronal differentiation; haploinsufficiency results in microcephaly > *Dyrk1a* homozygous KO mice: growth delays, die at midgestation; *Dyrk1a* heterozygous +/- mice: reduced brain size, increased neuronal density; > cortex-specific *Dyrk1a* deletion: decreased cortical mass, reduced neuronal size, disrupted growth factor signaling; heterozygous mutants: changes in axonal projections and deeper layer neuron morphology; increased ASD-related behaviors; > *in vitro* knockdown: altered dendritic growth and spine development	***Select genetic studies:*** *De Rubeis et al., 2014; Iossifov et al. 2015; Bronicki et al., 2015; Ji et al., 2015; Dang et al., 2018; Moller, et al. 2008; van Bon et al., 2016; Courcet, et al. 2012; van Bon et al., 2011; Lee et al., 2020; Iossifov et al. 2015; Deciphering Developmental Disorders 2015; Iossifov et al., 2012; Ruaud et al., 2015* ***Select functional references:*** *Tejedor, 1995; Dang et al., 2018; Fotaki, et al. 2002; Lee et al., 2020; Yabut et al., 2010; Evers et al., 2017; Shaikh et al., 2016; Fotaki et al., 2004; Hammerle et al., 2011; Levy et al., 2021; reviewed by Park and Chung, 2013; Guimera et al., 1996; Najas et al., 2015; Chakrabarti et al., 2007; Kurabayashi and Sanada, 2013*
MEF2C	nonsense mutation, deletions	ASD, DD, mental retardation	encodes a calcium-dependent member of the MADS box family of TFs	> genome wide analyses for TF binding sites: MEF2 controls many activity-dependent genes > LoF mutations in hiPSC-derived cortical neurons: aberrant electrophysiological properties, including elevated synaptic activity and increased excitation; > conditional *Mef2c* deletion in developing interneurons: reduced PV+ cell density, deficits in PV cell maturation; > *Mef2c* cKO in excitatory lineage: attenuated cortical network activity and ASD-, ID- and schizophrenia-related behaviors; > *Gfap*-Cre mediated *Mef2c* KO: increased excitatory synapse numbers, upregulated synaptic transmission, impairments in learning and memory; > *Mef2c* cKO in NSPCs (*Nestin*-cre): abnormal cytoarchitecture/compaction of cells in CP, altered cortical organization; > Mef2c KO mice: immature electrophysiological properties, reduced excitability; > expression of superactivating MEF2C: decreased frequency of mEPSCs	***Select genetic studies:*** *Novara et al., 2010; Neale et al., 2012* ***Select functional references:*** *Mayer et al., 2018, Allaway et al., 2021; Harrington et al., 2016; Trudler et al., bioRxiv 2020; Li et al., 2008; Barbosa et al., 2008; Flavell et al., 2008*
RBFOX1	copy number variants	ASD, ID, epilepsy	encodes an RNA binding protein and activity-dependent splicing regulator	> encodes member of a family of splicing factors that regulate ion channels and synaptic proteins (e.g. *Cacna1c*); > 160kb deletion in first exon and intron: reduced expression of *Rbfox1* mRNAs; > knockdown: abnormal alternative splicing, abnormal neuroblast migration, impaired axon extension, impaired dendritic arborization, abnormal membrane and synaptic properties, increased neuronal excitability; > interneuron specific cKO: abnormal alternative splicing, increased PV- and SST-expressing interneuron density, impaired interneuron activity (i.e., decreased mIPSC frequency and amplitude, increased cFos expression), increased seizure susceptibility, altered synaptic connectivity; > CNS-specific knockdown: increased seizure susceptibility, increased neuronal excitability, and abnormal splicing	***Select genetic studies:*** *Hamada et al., 2016; Sebat et al., 2007; Martin et al., 2007; Bhalla et al., 2004; Mikhail et al., 2011; Davis et al., 2012; Zhao, 2013; Gandal et al., 2018; Davies et al., 2015* ***Select functional references:*** *Wamsley et al., 2018; Gehman et al., 2011; Martin et al., 2007; reviewed by Bill et al., 2013; Tang et al., 2009*
SRCAP	de novo LoF variants, truncating variants, frameshift variants, missense variants	ASD, FHS	encodes an activator of the calcium-sensitive transcriptional coactivator CREBBP	> FHS variants map to last two exons of SRCAP (33 and 34), DNA methylation profiles vary depending on the location of the mutation	***Select genetic studies:*** *Hood et al, 2012; Iossifov et al., 2014; Stessman et al., 2017; C Yuen et al., 2017; Rots et al., 2021; reviewed by Alonso-Gonzalez et al., 2018*

Footnote: Autism Spectrum Disorders (ASD); Benign Familial Neonatal Seizures (BFNS); Epileptic Encephalopathy (EE); Schizophrenia (SCZ); Intellectual Disability (ID); Developmental and Epileptic Encephalopathy (DEE); Childhood Absence Epilepsy (CAE); Developmental and Epileptic Encephalopathy (DEE); Developmental Delay (DD); Floating-Harbor syndrome (FHS); Timothy syndrome (TS); Bipolar Disorder (BPD); Episodic Ataxia Type 2 (EA2); Familial Hemiplegic Migraine (FHM); Generalized Epilepsy with Febrile Seizures Plus (GEFS+); Early-infantile EE Type 13 (EIEE13); Early Myoclonic Encephalopathy (EME)

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