Dendritic Integration Dysfunction in Neurodevelopmental Disorders

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Abstract

Neurodevelopmental disorders (NDDs) that affect cognition, social interaction, and learning, including autism spectrum disorder (ASD) and intellectual disability (ID), have a strong genetic component. Our current understanding of risk genes highlights two main groups of dysfunction: those in genes that act as chromatin modifiers and those in genes that encode for proteins localized at or near synapses. Understanding how dysfunction in these genes contributes to phenotypes observed in ASD and ID remains a major question in neuroscience. In this review, we highlight emerging evidence suggesting that dysfunction in dendrites – regions of neurons that receive synaptic input – may be key to understanding features of neuronal processing affected in these disorders. Dendritic integration plays a fundamental role in sensory processing, cognition, and conscious perception, processes hypothesized to be impaired in NDDs. Many high-confidence ASD genes function within dendrites where they control synaptic integration and dendritic excitability. Further, increasing evidence demonstrates that several ASD/ID genes, including chromatin modifiers and transcription fac-

tors, regulate the expression or scaffolding of dendritic ion channels, receptors, and synaptic proteins. Therefore, we discuss how dysfunction of subsets of NDD-associated genes in dendrites leads to defects in dendritic integration and excitability and may be one core phenotype in ASD and ID.

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Introduction

Autism spectrum disorder (ASD) and intellectual disability (ID) are two of the most common neurodevelopmental disorders (NDDs), with an incidence of 1 in 54 births [1]. These NDDs have a strong genetic component, and substantial progress has been made to uncover the genetic architecture that contributes to impaired neurobiology and behavioral phenotypes. A key challenge for the field has been to translate these findings into an understanding of pathophysiology at the cellular and circuit level, with the goal of identifying key points of convergence across ASD/ID genes within the brain. Many excellent commentaries and reviews have advanced major themes of convergence in these disorders, including deficits in synaptic balance, connectivity, predictive processing, and in “top-down bottom-up” processing of stimuli relative to internal brain states [2–9]. Mechanistically,

considerable attention has been paid to how NDD-associated genes affect synapse function. Here, we discuss how extending beyond synapses to the dendrites in which they reside – and understanding how alterations in dendritic structure, excitability, and integration, either driven by or driving synaptic alterations – can help link theories of ASD/ID to cellular mechanisms affected in these disorders.

In this review, we focus primarily on neocortical regions and neuronal processing within pyramidal cell dendrites. As a site for higher order sensory processing, planning, and cognition, the neocortex has long been considered a key site for ASD/ID pathophysiology. Neocortical volume expands considerably across mammalian evolution, with parallel expansion in circuit complexity [10]. The neocortex is a multilayered structure, with each layer containing specific cell classes that have unique morphologies and synaptic connectivity. These synapses can be local, within regions that process similar information, or long-range, spanning regions to provide associative, contextual information to different regions of cortex. Pyramidal cells, which have dendrites spanning multiple layers, are uniquely positioned to integrate both local and long-range inputs, thereby acting as cellular structures that integrate disparate streams of input to help guide behavior. In particular, layer 5 pyramidal cells, which have dendrites that span all layers, have emerged as an important cell class for sensory discrimination and conscious perception [11]. Interestingly, coexpression network analysis from whole-exome sequencing data revealed that multiple high-confidence ASD genes are highly expressed in layers 5 and 6 glutamatergic projection neurons, highlighting these neurons as a central locus at which ASD risk genes converge [12–16]. Thus, a better understanding of how these neurons process information may shed light on the neurobiological mechanisms disrupted in NDDs. We note, however, that pyramidal cells are just one of many cell classes that are important for ASD/ID etiology and that many of the themes discussed here are broadly applicable across brain regions, including striatum, cerebellum, and other subcortical regions [17–25].

Main Text

Current Understanding of Pyramidal Cell Dendritic Function

Neocortical pyramidal cells in layers 2, 3, and 5 have characteristic dendritic morphologies. Basal dendrites in proximity to the soma are studded with spines that re-

ceive input from neighboring pyramidal cells as well as partners from similar cortical regions in the contralateral hemisphere [26–28]. These pyramidal cells also have one or more apical dendrites that arborize extensively in layer 1, a layer relatively devoid of somata but rich in neurites. Synapses made in layer 1 onto the apical tufts of pyramidal cells largely arise from long-range sources, including other regions of cortex, thalamocortical recurrent loops, and sources of neuromodulatory transmitters [29–31]. Thus, neocortex circuitry is organized to allow associative processing by making comparisons between local inputs and long-range inputs, reflecting circuit states in other brain regions (Fig. 1a). Within this framework, pyramidal cells play a central role, as their dendrites can sample both local sources in basal dendrites and long-range sources in their apical dendrites. In 1999, Larkum and colleagues provided the first empirical observations that dendrites of layer 5 pyramidal cells can perform such computations, allowing for coincidence detection between basal and apical regions [32]. In these experiments, they observed that pairing action potentials (APs) in the axon initial segment (AIS) with excitatory synaptic input into the apical tuft can lead to supralinear voltage responses in the dendrite that, in turn, result in enhanced neuronal output in the form of a high-frequency AP burst (Fig. 1b). This mechanism occurred only within a narrow temporal window, thereby serving as a coincidence detector for near-simultaneous activation of these two compartments. Furthermore, they showed that dendritic supralinearities can be vetoed by local inhibitory inputs. Remarkably, as discussed below, the cellular mechanisms that support each of these features have been shown to be disrupted in ASD/ID.

This landmark discovery brought forth more than a decade of research on cellular mechanisms present in dendrites that allow for “feature detection” in synaptic inputs. These features, which have been described in detail in excellent review articles [33–35], include (1) the generation of “dendritic spikes,” which occur when synaptic input paired with or without AP-mediated depolarization results in regenerative supralinearities within dendritic compartments, independent of APs initiated in the AIS (Fig. 1b, c) [36]; (2) detection of coincident synaptic input onto single dendritic branches, independent of the location of this branch within the overall dendritic arbor; (3) the directionality of activation of such inputs on single branches (i.e., in a cascade either toward or away from the soma; Fig. 1d) [37]; and (4) XOR (eXclusively OR) computations, where dendrites are capable of signaling the occurrence of one of

Fig. 1. Mechanisms of synaptic integration on layer 5 pyramidal neurons dendrites in neocortex. **a** Approximation of synaptic inputs to neocortical layer 5 pyramidal neurons, which tend to integrate long-range synaptic inputs onto apical tuft dendritic branches and local inputs on basal dendrites. **b** Coincidence detection between apical dendritic EPSPs and APs from basal regions generates supralinear depolarizations and axonal AP bursts. **c** High-frequency AP bursts onto apical tuft dendrites alone can evoke dendritic spikes and subsequent APs from the axon. **d** Synchronous synaptic input on dendritic branches drives individual EPSPs. When combined in a cascade of events from distal to more proximal parts of the soma, these EPSPs summate to generate events larger than their arithmetic sum (e.g., dendritic spike). EPSPs, excitatory postsynaptic potentials; APs, action potentials.

two inputs (X or Y), but not both (X and Y), a process previously thought to require a multicellular network [38]. These processes often result from coordinated synaptic engagement within a small region of dendrite, which allows synaptic depolarizations to accumulate, thereby relieving voltage-dependent magnesium block of N-methyl-D-aspartate (NMDA) receptors [39]. This, in itself, promotes further local depolarization, but NMDA receptor activation is often not the sole mechanism underlying dendritic supralinearities. As these dendrites depolarize, several voltage-gated channels can be recruited, including multiple sodium (Na_V) and calcium (Ca_V) channel proteoforms [40–42]. In addition, other channels can be inactivated, including potassium (K_V) and hyperpolarization-activated cyclic nucleotide-gated (HCN) channels [43–45]. Thus, any disruption in dendritically localized channels or receptors that contribute to dendritic excitability – whether localized to the synapse itself or instead in the dendritic shaft – could interfere with pyramidal cell processing and synaptic plasticity associated with dendritic supralinearities [46, 47].

Dendritic supralinearities are increasingly being recognized as critical for active perception and decision-making *in vivo*. Using calcium imaging approaches and direct electrophysiological recording from dendrites, the apical dendritic tuft of both layer 2/3 and layer 5 pyramidal cells has been shown to be engaged during sensory perception [48–50]. These dendritic spikes are often as-

sociated with a barrage of APs that, in turn, engages thalamocortical loops thought to be critical for neocortical processing [28, 51]. Causal manipulations that block the generation of dendritic spikes, often by engaging inhibitory networks that preferentially target the apical tuft, interfere with perception [52]. Furthermore, these dendritic tuft spikes appear to be critical for conscious perception, as they are some of the first subcellular events to be disrupted by anesthetics [53]. Together, these data identify a major role for pyramidal cell dendrites in higher order neocortical function. Furthermore, they highlight the complexity and convergence of multiple processes that regulate dendritic excitability, which includes intrinsic mechanisms within the dendrite, excitatory and inhibitory synaptic input to the apical tuft, and, as discussed further below, neuromodulatory pathways that alter signal processing in such regions.

Disruption in how dendrites process sensory input may fit into a mechanistic theory of ASD that proposes an altered balance in “top-down bottom-up” processing, with a bias toward bottom-up processing in ASD/ID. In terms of cognitive processes, this can be thought of as an inability to attend to specific stimuli (in the case of sensory processing), or specific streams of thought (in the case of associative, or internal state processing), due to a loss of “top-down” attentional control. Rather, “bottom-up” inputs are processed without filters, potentially resulting in sensory overload, thereby resulting in issues in identifying brain states that are relevant compared to

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Fig. 2. Multiple high-confidence ASD/ID genes converge on neocortical excitatory synapses. **a** Several NDD-associated genes encode for ion channels that are localized throughout the dendrites of neocortical pyramidal neurons. **b** Similarly, NDD-associated genes encode for a range of synaptic proteins essential for synaptic transmission that contribute to dendritic supralinearities. **c** “Covert” NDD-genes include the chromatin modifiers CHD2 and CHD8 and the transcription factor TBR1. They regulate the expression levels of

many “overt” NDD-genes as well as additional “covert genes,” which play critical roles in synaptic integration and dendritic processing. **d** FMRP is another “covert” regulator that suppresses the translation of multiple synaptic and dendritic proteins associated with NDDs. These include various ion channels (i.e., Na_v1.2 and multiple calcium channels), SHANK scaffolding proteins, SynGAP, neuroligins, and GluN2B. ASD, autism spectrum disorder; ID, intellectual disability; NDD, neurodevelopmental disorder.

those that instead should be ignored [54, 55]. Given the prominent role of neocortical pyramidal cells in coupling associative, top-down information with local, bottom-up signals, instantiated through interactions between apical and basal arbors, it is critical to consider whether such processes are disrupted in NDDs.

Impaired Dendritic Excitability and Synaptic Integration in NDDs

Recent work to understand the brain regions and cell types important for ASD has found that multiple genes converge onto pyramidal cells, with deep-layer pyramidal cells in prefrontal cortex of particular importance [56]. As discussed in detail above, dendrites of deep-layer pyramidal neurons play a central role in facilitating information

flow throughout the neocortex by functioning as coincidence detectors to integrate synaptic inputs from both local and long-range projections. Importantly, abnormal dendritic processing and synaptic integration within these neurons have been suggested to contribute to the social, cognitive, and communication deficits typically characteristic of NDDs [57].

The largest gene discovery effort to date identified approximately 102 genes highly associated with ASD [58]. Emerging from these large-scale genetic studies are “channelopathies” or dysfunction of various ion channels as causative factors in ASD pathogenesis [59–66]. A substantial number of these genes are of the Na_v, Ca_v, and potassium channel families, as well as HCN channels [66]. Interestingly, many of these channels are more com-

monly associated with dendritic function, rather than the synapse proper, and are abundantly expressed in neocortical pyramidal cell dendrites [67–71] (Fig. 2a). As such, pathogenic variants in genes that encode ion channels would likely have direct detrimental effects on dendritic excitability. Consistent with this, both rare variants and common polymorphisms are found within channelopathy-associated genes, some of the most prevalent include *SCN2A*, *SCN1A*, *KCNQ3*, and *CACNA1E* [66, 72–78]. In addition to overt effects on channel-related genes, a number of high-confidence ASD genes encode proteins found directly within synapses that regulate synapse structure, function, and connectivity, including *SHANK3*, *SYNGAP1*, *NLGN4*, and *GRIN2B* [66]. Given their prominent role in supporting synaptic activity, dysfunction in these genes could further impair dendritic excitability. Lastly, a number of ASD gene products that include chromatin modifiers, transcription factors, translation regulators, scaffolding proteins, and signaling molecules may also affect the expression, localization, and/or trafficking of ion channels, receptors, and other synaptic proteins [66]. Thus, dysfunction in these genes may indirectly disrupt dendritic function and coincidence detection. Below, we discuss how multiple high-confidence ASD genes are associated with altered dendritic structure, function, and integration in neocortical pyramidal neurons and high-light impaired dendritic excitability and coincidence detection as a central hub for ASD gene convergence.

Sodium Channels

In several different neuron classes, the generation and propagation of dendritic potentials is dependent on voltage-gated sodium channels [79–85]. While the importance of sodium channels in dendritic excitability has been known for some time, only recently have we begun to understand the cellular and subcellular localization patterns of different sodium channel subtypes and their distinct roles in neuronal excitability. The predominant voltage-gated sodium channel alpha subunits expressed in the adult mammalian neocortex are *SCN1A*, *SCN2A*, and *SCN8A*, which encode $\text{Na}_V1.1$, $\text{Na}_V1.2$, and $\text{Na}_V1.6$, respectively [86, 87]. Each of these genes is associated with NDDs, including both ASD/ID and various forms of epilepsy. Reviews of alterations in sodium channel structure and function have highlighted how NDD-associated variants affect both biophysical properties as well as channel trafficking and modulation [88–95]. *SCN3A*, which encodes $\text{Na}_V1.3$, is expressed transiently during early development, and dysfunction in this gene affects cortical folding and is associated with epileptic encephalopathy

[96, 97]. Whether this in turn affects dendritic processing in more mature circuits has yet to be investigated.

SCN2A has repeatedly emerged from large-scale exome sequencing studies with some of the strongest association scores to ASD of any gene in the genome [66, 98–100]. *SCN2A* encodes $\text{Na}_V1.2$, which exhibits unique cell type and domain-specific expression patterns throughout development. In the neocortex, $\text{Na}_V1.2$ is expressed in glutamatergic pyramidal neurons along with $\text{Na}_V1.6$, whereas $\text{Na}_V1.1$ is the predominant sodium channel expressed in inhibitory interneurons [101–106]. Early in neocortical development, prior to 1–2 years of age in humans and postnatal day 7 in mice, $\text{Na}_V1.2$ is the only identifiable sodium channel isoform localized to the AIS [107–109]. In mature pyramidal neurons, $\text{Na}_V1.2$ is replaced by $\text{Na}_V1.6$ in the distal AIS and the nodes of Ranvier [110, 111]. $\text{Na}_V1.6$ has a lower voltage threshold for activation, making these sites more susceptible to spike generation. Later in development, $\text{Na}_V1.2$ appears to play a more dominant role in dendritic, rather than axonal, excitability throughout neocortex [112]. In hippocampus, freeze-fracture immunogold labeling has revealed that Na_V s are localized exclusively to dendritic shafts, not spines [113]. This may also be the case in neocortex. Human variants in *SCN2A* are broadly categorized into different classes of NDDs associated with increased or decreased channel function. Gain-of-function variants in *SCN2A* that enhance $\text{Na}_V1.2$ activity are associated with benign infantile familial seizures (BIFS) and epileptic encephalopathy (EE) [114–116]. By contrast, loss-of-function (LoF) variants in *SCN2A* are found in individuals with ASD and ID and consist of either missense variants that dampen $\text{Na}_V1.2$ function or protein truncating variants that result in haploinsufficiency [90, 93, 117]. In neocortical layer 5 pyramidal neurons, heterozygous LoF in *Scn2a* was shown to severely attenuate dendritic calcium transients evoked by backpropagating APs (bAP) [112]. This deficit was associated with a range of synaptic deficits: excitatory synapses had features more commonly observed in less mature cells, including an excess of silent synapses, and bAP-dependent synaptic plasticity was impaired [112]. Furthermore, other aspects of dendritic excitability, including the generation of local dendritic spikes, may be affected by *Scn2a* LoF. In hippocampus, for example, synaptic plasticity can be modulated by the generation of sodium-mediated dendritic spikes [118]. While these effects are likely mediated by $\text{Na}_V1.6$ in hippocampal neurons, $\text{Na}_V1.2$ may be similarly critical in neocortical dendrites [119].

Loss of function of *SCN8A*, in contrast to *SCN2A*, is not associated with ASD but instead with seizure-free ID [120, 121]. This may have to do with the different roles of these two sodium channels. In *SCN2A* LoF cases, dendritic excitability is impaired, but axonal excitability remains intact [112]. With *SCN8A* LoF, axonal excitability is impaired, both within pyramidal cells and also in the majority of inputs to neocortex that also rely on $\text{Na}_V1.6$ for axonal conduction [122]. Therefore, it is likely that *SCN8A* LoF results in profound synaptic impairments that make ID diagnoses most common.

Whether $\text{Na}_V1.6$ loss also affects neocortical dendritic processing is less clear. Current compartmental models of *Scn2a* haploinsufficiency best recapitulate empirical data when both $\text{Na}_V1.2$ and $\text{Na}_V1.6$ are expressed in equal densities in the somatodendritic domain [112]. By extension, *SCN8A* heterozygosity should have similar effects as *SCN2A* heterozygosity. While heterozygous conditions have not been examined, conditional knockout of *Scn8a* in neocortex has been studied [123]. In these conditions, AP-evoked dendritic calcium transients were unaffected by $\text{Na}_V1.6$ deletion; however, transients were imaged in dendritic regions relatively proximal to the soma, a region where $\text{Na}_V1.2$ heterozygosity also had little to no effect [112]. Whether more distal compartments have altered electrogenesis remains unknown. Furthermore, compensation for $\text{Na}_V1.6$ by $\text{Na}_V1.2$ was evident in the AIS of these neurons. It is therefore possible that $\text{Na}_V1.6$ loss was also compensated in dendrites [124].

$\text{Na}_V1.1$ (*SCN1A*) is the predominant sodium channel expressed in GABAergic inhibitory interneurons [125]. Variation in *SCN1A* is well known for its causative link to Dravet's syndrome (DS) and genetic epilepsy with febrile seizures plus (GEFS+) [126–128]. Haploinsufficiency of *Scn1a* in mice dampens interneuron excitability, resulting in disinhibition of the cortical network and in turn seizures, premature death, and cognitive deficits, as observed in DS patients [125, 129–134]. *SCN1A* is also associated with ASD through exome sequencing and familial studies [66, 135, 136]; however, the mechanisms by which dysfunction of $\text{Na}_V1.1$ contributes to ASD are not as well understood. Interestingly, recent work has shown that excitability deficits in parvalbumin-positive interneurons resolve by postnatal day 50 in *Scn1a*^{+/-} mice, whereas deficits in vasoactive intestinal polypeptide (VIP)-expressing interneurons persist [137]. These VIP neurons form disinhibitory circuits with pyramidal cell apical tuft dendrites through somatostatin interneurons [138]. As such, the regulation of dendritic excitability may be indirectly affected in *Scn1a*^{+/-} condi-

tions. Such hypotheses are explored in detail in a companion manuscript in this issue [139].

Calcium Channels

Ca_V s play fundamental roles in dendritic excitability and synaptic integration. Activation of Ca_V s promotes regenerative depolarizations that generate both linear and nonlinear dendritic spikes [140, 141]. AP backpropagation into the apical dendrites of neocortical pyramidal neurons also engages Ca_V s, which then modulate other ion channels and receptors, stimulate various signaling cascades, and regulate gene expression [142–144]. These active dendritic processes increase the probability of AP firing, mediate dendritic neurotransmitter release, and regulate synaptic plasticity, such as spike timing-dependent plasticity (STDP) and long-term potentiation (LTP) [145, 146]. Therefore, dendritic Ca_V s have profound effects on synaptic integration and coincidence detection in neocortical pyramidal neurons, and dysfunction of Ca_V s due to genetic variation would have severe effects on dendritic excitability and neocortical processing [147].

Voltage-gated calcium channels are broadly classified into two groups based on electrophysiological properties: high voltage-activated channels consist of L-, N-, P-/Q-, and R-type calcium channels and low-voltage-activated channels include T-type channels [148]. The L-type calcium channels are encoded by *CACNA1S*, *CACNA1C*, *CACNA1D*, and *CACNA1F* and include $\text{Ca}_V1.1$, $\text{Ca}_V1.2$, $\text{Ca}_V1.3$, and $\text{Ca}_V1.4$, respectively. P/Q-, N-, and R-type calcium channels correspond to $\text{Ca}_V2.1$, $\text{Ca}_V2.2$, and $\text{Ca}_V2.3$ and are products of *CACNA1A*, *CACNA1B*, and *CACNA1E* [148]. Last, T-type channels include $\text{Ca}_V3.1$, $\text{Ca}_V3.2$, and $\text{Ca}_V3.3$ encoded by *CACNA1G*, *CACNA1H*, and *CACNA1I* [148]. Electrophysiological and immunohistochemical studies have shown that all calcium channel subtypes are present within dendrites [149, 150]. However, the distribution patterns of each subtype are heterogeneous across brain regions, cell types, and even different neuronal domains [151, 152]. Ca_V1 channels are found on the soma, proximal dendritic shafts, and within spines of hippocampal and deep-layer neocortical neurons [153, 154]. These channels are known to play an important role in triggering intracellular cascades related to synaptic plasticity [155–159]. In parallel, neocortical dendritic excitability can also be supported by $\text{Ca}_V2.x$ and $\text{Ca}_V3.x$ channel isoforms [160–162]. $\text{Ca}_V2.2$ isoforms, in particular, appear highly expressed in layer 5 pyramidal dendrites [163]. Their density is highest in proximal apical dendrites, gradually decreasing into the distal dendritic arbors.

Dysfunction of multiple Ca_v s may contribute to ASD [164–166]; ASD gene variants are found in loci that encode for almost all Ca_v alpha subunits and their associated beta subunit partners [167]. Somewhat confusingly, both gain- and loss of function variants in Ca_v s are associated with ASD. Gain-of-function (GoF) variants were found in genes that encode for Ca_v1 channels including *CACNA1C*, *CACNA1D*, and *CACNA1F*, resulting in excess calcium influx due to impaired voltage-dependent inactivation [168–171]. By contrast, loss-of-function variants were identified in *CACNA1A* ($\text{Ca}_v2.1$) and *CACNA1H* ($\text{Ca}_v3.2$), both of which reduce voltage-dependent activation and channel conductance [172, 173]. Thus, it is likely that dendritic calcium electrogenesis is altered in many of these cases. Moving forward, a central question will be to determine how neocortical dendritic impairments contribute to ASD pathophysiology in particular cases, or if Ca_v function in other brain regions or neuronal compartments is more important. For example, $\text{Ca}_v2.1$ channels, which are common to dendrites, are also critical for neurotransmitter release at presynaptic terminals across the brain [174–179]. Thus, dysfunction in these channels may have an indirect effect on dendritic function, altering synaptic input to dendritic regions, but also may have profound effects on axonal integration and short-term synaptic plasticity in presynaptic boutons [180–183].

Hyperpolarization-Activated Cyclic Nucleotide-Gated Channels

HCN channels are expressed broadly in neocortical neurons. In general, HCN channels are expressed at a higher density in thick-tufted pyramidal cells of the pyramidal tract compared to thin-tufted pyramidal cells that project within the telencephalon [184]. Within thick-tufted cells, HCN channels are expressed at increased density in more distal parts of the dendrite, including the apical dendritic tuft [185]. These nonselective cation channels have relatively unique voltage dependence and kinetics: they are open at hyperpolarized potentials and close slowly with depolarization. This can create conditions in which the channels contribute to resonant oscillations in membrane potential [186]. Moreover, since they are gated by cyclic nucleotides, HCN current amplitude can be regulated by second messengers. Of note, HCN channels are tightly coupled to and regulated by group 1 metabotropic glutamate receptors (mGluRs) present in the primary apical dendrite of deep-layer pyramidal cells, and depolarizations mediated by group 1 mGluRs in apical dendritic shafts are driven in part by

reduced HCN function [187, 188]. Thus, these channels can play a major role in regulating coupling between apical and basal compartments in neocortical dendrites.

Four HCN isoforms are expressed in the brain [189]. In neocortex, HCN1 is most heavily expressed in dendrites. HCN2 is also expressed in distal apical dendrites, but HCN3 and HCN4 are not found in neocortex [190]. Despite the expression of both HCN1 and HCN2, to date, only variants in *HCN1* have been shown to associate with NDDs, including epileptic encephalopathy, ASD, and ID [191]. Similar to *SCN2A*, variant genotype-phenotype correlations are emerging, with GoF variants more commonly associated with epilepsy and LoF more commonly associated with ASD/ID [192]. Consistent with these direct effects on neocortical HCN channels, similar reductions in HCN expression are observed with other ASD-associated genes, including mouse models of *Fmr1* and *Shank3* [193–196].

Potassium Channels

Potassium channels are ubiquitously expressed in pyramidal cell dendrites, helping to set resting membrane potential and the time-course of dendritic electrogenesis [197–201]. There are conflicting reports regarding potassium channel density in the apical dendrite relative to the soma, with some studies reporting low ratios [202], whereas others report high ratios [203], possibly due to differences in experimental approach. Regardless, both transient (I_A) and sustained (I_{KD}) potassium currents are observed throughout the dendrite. The precise isoforms that generate such currents have been difficult to dissect, in large part due to significant diversity in the channel proteoforms that can produce similar currents. For example, I_A can be produced by homotetramers of $\text{K}_v1.4$, $\text{K}_v3.4$, $\text{K}_v4.1$, $\text{K}_v4.2$, or $\text{K}_v4.3$ or by heteromeric channels containing a mix of these subunits [204].

While I_A - and I_{KD} -related genes have not been shown to be associated with ASD/ID, two other potassium channel genes have been identified: *KCNQ3* and *KCNMA1* [66]. *KCNQ3* is a member of the K_v7 family of potassium channels that produces a slow outward current, with expression best characterized in axonal domains [205, 206] and therefore likely falling outside the framework proposed here. *KCNMA1* encodes a calcium-activated potassium current (BK) found throughout pyramidal cell arbors, including the apical tuft, where it regulates the duration of dendritic spikes [207]. Interestingly, in contrast to many other genes, ASD association stems exclusively from missense variants for both *KCNQ3* and *KCNMA1*, with no evidence that protein truncation contributes to

such conditions. This contrasts markedly with cases of epileptic encephalopathy where LoF stemming from protein truncation is common, at least for *KCNQ3* [208, 209]. Such conditions mirror observations for the sodium channel *SCN2A*, where GoF and LoF largely associate with epilepsy and ASD/ID, respectively. Of note, current gene discovery methods for NDDs rely heavily on identifying protein truncations, as it is clear that such truncations impair protein function. Missense variants, by contrast, may have little to no effect on channel function, and without proper electrophysiological validation, it is difficult to have confidence that such variants contribute to disease. One hint that a particular missense variant is indeed pathogenic is recurrence. Missense variants in the same location, identified in patients with similar conditions, can increase confidence. This is the case for *KCNQ3* [210], but fewer recurrent variants have been identified to date in other potassium channel genes. Given the opposing roles of Na_V and K_V channels in dendritic excitability, one could envision that ASD-associated variants would result in GoF conditions in dendritically localized K_V s (i.e., missense variants). Potential discovery of such cases will require far larger genetic cohorts than currently available.

Glutamate Receptors

The overwhelming majority of synaptic inputs onto neocortical layer 5 pyramidal neurons occur on distal dendritic tufts, basal dendrites, and oblique dendrites of the main apical shaft, making these domains key sites for synaptic integration [211–215]. Within these regions, the coordinated activation of multiple glutamatergic synapses produces a local “NMDA spike,” which is a summation of regenerative events that require AMPA and NMDA receptor activation [216, 217]. NMDA spikes are high amplitude, long duration events (several hundred milliseconds) capable of depolarizing the local dendritic domain for sustained periods of time and are even able to drive somatic depolarization [218]. NMDA spikes regulate synaptic integration by modulating the dendritic environment to promote active synaptic input, spatiotemporal information processing, and to regulate LTP and depression – processes hypothesized to be impaired in ASD/ID [219–221]. In addition, excitable dendritic spines on layer 5 pyramidal neurons are necessary for regulating AP backpropagation, and changes in spine function and morphology significantly influence AP backpropagation efficacy [222]. Glutamatergic synapses and dendritic spines are major contributors to synaptic integration and dendritic excitability of layer 5 pyramidal neurons. Consistent with this, impairments in glutamatergic synapses

are strongly implicated in the pathophysiology of ASD and ID [223–225].

NMDA receptors are ionotropic glutamate receptors critical for fast excitatory neurotransmission and NMDA spike initiation [226]. *GRIN2B*, which encodes the GluN2B subunit of NMDA receptors, is one of the most strongly associated genes to ASD, and hundreds of variants in *GRIN2B* are found in individuals with NDDs including both ASD and ID [66, 99, 227–229]. Large cohort studies identified numerous LoF variants in *GRIN2B* as causative for ASD and ID [230–232]. NMDA receptor subunits undergo highly regulated spatiotemporal expression patterns, magnifying the detrimental effects LoF variants in *GRIN2B* would have on normal neurodevelopment. The GluN2B subunit is highly expressed throughout the brain during prenatal development and gradually decreases during postnatal development, becoming predominantly expressed in forebrain neocortical neurons where it plays an essential role in dendritic function [233]. Therefore, LoF ASD variants in *GRIN2B* would be expected to severely disrupt layer 5 pyramidal neuron development and synaptogenesis. Consistent with this, multiple LoF variants in *GRIN2B* cause significant reductions in glutamatergic transmission, with decreased excitatory postsynaptic current and impaired excitatory neuron maturation [234–237]. While human variants in *GRIN2B* severely disrupt glutamatergic synapse function, the effects of *GRIN2B* loss on NMDA spike initiation and dendritic excitability have, to our knowledge, not been investigated in the neocortex. However, one could easily foresee severe disruptions in dendritic excitability that may contribute to associated disorders in activity-dependent neuronal development.

In addition to ionotropic glutamate receptors, changes in the function of group 1 mGluRs have long been associated with ASD/ID [238, 239]. The bulk of studies focused on their role in synaptic transmission and regulation of plasticity [240, 241]. This in and of itself will have effects on dendritic integration, but there may also be more direct ways in which mGluRs can regulate neocortical dendritic excitability. These metabotropic receptors are expressed at high density in the apical dendritic shaft connecting the soma with the apical tuft. In sensory cortices, such mGluRs receive input from thalamus and result in membrane depolarization that improves cooperativity between apical and basal arbors during sensory discrimination [242, 243]. This thalamic activation of mGluRs is hypothesized to act as a gate for sensory responses [244]. Thus, loss of mGluR function commonly observed in ASD/ID models may interfere with this process.

Dendritic Scaffolding and Maintenance Proteins

The recruitment and localization of ionotropic and mGluRs is essential for normal synaptic integration. Several proteins involved in AMPA and NMDA receptor (as well as ion channel) localization, spine maintenance, synaptic connectivity, and plasticity are associated with ASD and ID, including *NLGN1*, *NLGN3*, *CNTNAP2*, *SHANK3*, and *SYNGAP1* (Fig. 2b) [66, 245–248]. Thus, impairments in synaptic function and dendritic integration are not limited to direct deficits of dendritic receptors and ion channels discussed above, but can also result from dysfunction in scaffolding and maintenance proteins that keep those channels in place. As seen below, the majority of work on these proteins has focused on essential synapse function, and to date, “downstream” effects on dendritic excitability have yet to be tested. This is an enticing area of investigation in the future, potentially tying scaffold function in the synapse to broader dendritic deficits observed with other NDD-associated genes.

SHANKs are a family of scaffolding proteins highly enriched within the postsynaptic density (PSD) of dendritic spines, with significant associations to syndromic and idiopathic ASD as well as ID [66, 249–253]. Here, they are regarded as major organizers of excitatory synapse structure and function and directly interact with numerous proteins within the PSD, including the GluR1 subunit of AMPA receptors, PSD-95-associated proteins, Homer, and other SHANK family members [253]. As seen with other cytoskeletal proteins important for spine formation and maintenance, genetic deletion of SHANK proteins reduces the levels of AMPA and NMDA receptors [254]. This, in turn, results in significant morphological and functional deficits as well as reductions in spine density in neocortical neurons of SHANK-deficient mice [255–257]. In addition, ASD variants in *SHANK3* result in reduced mGluR group 1 receptor expression and disrupt mGluR-dependent synaptic plasticity [258].

ASD-associated variants are found within *NLGN1*, *NLGN3*, and *NLGN4*, which encode NLGN1, NLGN3, and NLGN4 members of the neuroligin family of cell adhesion molecules [259]. Neuroligins are localized within postsynaptic domains of dendritic spines and form transmembrane connections with presynaptic neurexin proteins that promote synapse development, function, and maintenance [260]. In addition, neuroligins interact with PSD-95, SHANKs, and AMPA and NMDA receptors within spines to regulate excitatory synaptic formation and transmission in hippocampal neurons [261, 262]. Mouse models of *Nlgn1* and *Nlgn3* knockout as well as LoF missense variants display behavioral phenotypes

characteristic of ASD, including social interaction deficits and repetitive behaviors [263–266], but these behaviors are likely attributed to multiple brain regions including neocortex, hippocampus, and striatum.

Genetic variants in *CNTNAP2* are found in individuals with ASD [267–270]. Contactin-associated protein-like 2 (CASPR-2), product of the *CNTNAP2* gene, is a member of the neurexin family. CASPR-2 is a presynaptic transmembrane protein known to control glutamatergic synapse connectivity and spine formation, dendritic arborization, and synaptic transmission [271]. *Cntnap2* knockout mice demonstrate malformations of neocortical development with upper layer glutamatergic neurons mislocalized into layers 5 and 6, which would be expected to have severe effects on integration and neocortical processing [272]. *Cntnap2* knockdown in mouse prefrontal neocortical pyramidal neurons caused reduced excitatory synaptic transmission, abnormal network activity, and synaptic dysfunction, which resulted in behavioral phenotypes similar to those found in ASD [273, 274]. Furthermore, *Cntnap2* null mice have reduced numbers of parvalbumin-positive (PV+) interneurons and the remaining PV+ cells exhibited abnormal intrinsic physiological properties [275]. These findings highlight a key role for *CNTNAP2* in regulating synaptic communication between both excitatory and inhibitory neurons throughout the neocortex.

SYNGAP1 is a significant risk gene for ID, ASD, and epileptic encephalopathy [66, 232, 276–278]. Heterozygous, de novo LoF variants in *SYNGAP1* are causative in approximately 1% of individuals with ID and developmental delay, demonstrating its essential role in brain development and function [279, 280]. *SYNGAP1* encodes the synaptic Ras GTPase-activating protein (SynGAP), which is highly enriched in the PSD of mature neocortical and hippocampal pyramidal neurons [281]. SynGAP negatively activates the small GTPases Ras- and Rap-GAP to promote AMPA receptor trafficking, membrane incorporation, and synaptic LTP and depression (LTD) [282, 283]. In addition to its role in synaptic plasticity, SynGAP is fundamental for dendritic spine maturation. In neocortical neurons, SynGAP expression levels rise dramatically during postnatal development, around postnatal day 14 in mice [284]. Normal SynGAP function is critical during this developmental window as haploinsufficient *Syngap1* mice display aberrant dendritic spine maturation; however, knockout of *Syngap1* late in development had no significant effect on synaptic function [285, 286]. Therefore, human variants that disrupt SynGAP function during critical periods of synaptogenesis

would be expected to have permanent effects on excitatory integration and synaptic plasticity in developed neurons. However, a recent study by Creson et al. demonstrated that re-expression of SynGAP in adult *Syngap1* heterozygous mice restored neuronal excitability deficits, memory impairments, and seizure thresholds [Creson Colgin, 2019, DOI: 10.7554/eLife.46752]. These findings offer insight on the development of new treatment strategies that rescue expression or function of SynGAP to treat SYNGAP-associated NDDs in adult patients.

Gamma-Aminobutyric Acid Receptors

Gamma-aminobutyric acid (GABA) is the primary inhibitory neurotransmitter in the adult mammalian brain. Dysfunction of inhibitory microcircuits within the neocortex has been linked to ASD and other NDDs through a variety of mechanisms including abnormal development, migration, intrinsic properties, or connectivity [275, 287, 288]. Different subtypes of GABAergic interneurons synapse onto discrete domains of excitatory neurons, including layer 5 pyramidal neurons in the mPFC, where they play unique roles in modulating pyramidal cell excitability and plasticity. PV-positive interneurons target the somatodendritic domain and AIS of pyramidal neurons, whereas SOM cells primarily synapse onto the dendrites [289–291]. Martinotti SOM+ interneurons synapse onto distal apical dendrites of layer 5 pyramidal neurons, where they tightly control dendritic activity [292]. Specifically, they inhibit pyramidal cell firing during sustained periods of high activity and are also capable of effectively blocking the generation of dendritic spikes [293]. Last, VIP interneurons are found in layer 2/3 and preferentially target other neocortical interneurons including PV and SOM neurons in layer 5 [294–296]. Therefore, pathogenic variants in genes involved in GABAergic interneuron subtype function or in genes that encode GABA receptor subunits could potentially impair neocortical neuron dendritic processing. Several genes that encode GABA receptors have been implicated in NDDs, including ASD [297–300]. Whole-exome sequencing studies revealed *GABRB2* and *GABRB3*, which code for the GABA_A receptor beta-2 and beta-3 subunits, are among the top 102 high-confidence ASD genes [66]. Familial studies identified single nucleotide polymorphisms within genes that encode additional GABA receptor subunits including *GABRA4* (alpha-4), *GABRB1* (beta-1), and *GABRB3* (beta-3) in patients with ASD [301, 302]. In addition, a recent study found a 2.4 Mb duplication of 4p12 to 4p11 that consists of GABA receptor subunit gene clusters that include *GABRA4*, *GABRA2*,

GABRB1, and *GABRG1* in 4 siblings with ASD [303]. A similar duplication of this GABA receptor gene cluster has been reported in other individuals with ASD who present with a range of behavioral phenotypes [304–307]. Consistent with genetic studies, multiple GABA receptor subunits were found at significantly lower expression levels in postmortem brain of ASD individuals as compared to neurotypical controls [308, 309]. While GABAergic interneurons and multiple GABA receptor subunits are involved in ASD pathophysiology, it will be important for future work to determine how GABAergic circuitry functions in tandem with glutamatergic receptors to control dendritic excitability and integration and how this is altered in ASD. In addition, pathogenic variants in several ASD-associated genes mentioned throughout this review, such as *CNTNAP2*, *TBR1*, and *PTEN*, result in both glutamatergic and GABAergic deficits, which could further potentiate impairments in dendritic processing. Taken together, these findings suggest that although the etiology of ASD is heterogeneous, excitatory synapse dysfunction and impaired neocortical dendritic processing may be one core feature among some individuals with ASD and ID.

“Covert” Mechanisms in ASD/ID That Regulate Dendritic Impairments

Efforts to identify convergence between ASD genes have broadly separated high-confidence ASD genes into two main groups: synaptic function and transcriptional regulation. However, evidence suggests that these two groups intersect at multiple levels, perhaps leading to dysfunction of shared downstream processes [310–312]. In support of this, recent work by Jing et al. used PerturbSeq, a novel high-throughput genetic screen that allows for single-cell resolution of phenotypic changes caused by introducing an array of genetic perturbations. This technique allows for the identification of points of convergence between multiple seemingly diverse ASD/NDDs in unique cell types and transcriptomic networks across the developing brain [313]. Here, we have discussed how dysfunction of multiple NDD-associated genes that encode for various subtypes of ion channels, receptors, and scaffolding proteins impairs dendritic excitability and synaptic integration in neocortical pyramidal neurons. We term these particular genes “overt” genes, as loss or dysfunction of their protein products directly results in neocortical dendritic deficits. By contrast, an additional pool of NDD-associated genes that encode chromatin modifiers, transcriptional and translational regulators, and trafficking proteins may function in a more “covert”

way to also affect dendritic integration, in part through their regulation of “overt” mechanisms discussed above. Below, we highlight emerging evidence of such interactions in select NDD-associated genes.

Fragile X syndrome is the single most common form of inherited ID and monogenic cause of ASD [314]. Fragile X syndrome is caused by the expansion of a CGG repeat in the 5' UTR region of *FMR1*, which results in the loss of *FMR1* and, in turn, its protein product FMRP (fragile X mental retardation protein) (Fig. 2d) [315]. FMRP is an RNA-binding protein that suppresses the translation of numerous mRNA targets including multiple *Shanks*, *Scn2a*, multiple calcium channel genes, *Synap1*, *Nlgns*, and *Grin2b*, which are essential for normal dendritic excitability [316, 317]. FMRP shuttles mRNA from the nucleus throughout the cytoplasm, but it is also highly enriched within dendritic spines, where it colocalizes with many of its mRNA targets [315]. The loss of FMRP would therefore likely lead to aberrant expression of multiple proteins involved in dendritic morphology and integration. Consistent with this, neocortical neurons of individuals with Fragile X syndrome, including layer 5 neurons, have abnormally long, immature spines [318]. In addition, the activation of mGluRs upregulates FMRP expression within spines. This demonstrates a functional link between mGluR stimulation and local translation in spines, a process necessary for excitatory synapse function, morphology, and plasticity [319, 320]. The reciprocal relationship also exists as FMRP controls the translation of mGluR, and the loss of FMRP causes increased mGluR signaling, a process known as the mGluR hypothesis of fragile X syndrome [321]. Ultimately, the dendritic phenotypes observed in the Fragile X syndrome patients and animal models of *FMR1* loss overlap with animal models of haploinsufficiency of multiple FMRP mRNA targets (i.e., *Scn2a*^{+/-} and *Synap1*^{+/-} mice), further highlighting impaired neocortical dendrites as a point of convergence between genes with the strongest association scores.

In addition to genes that regulate translation, damaging variants in genes that control transcription can also affect genes directly involved in dendritic excitability (Fig. 2c). The chromatin modifiers, *CHD2* and *CHD8*, each carrying strong ASD association, are both expressed in human deep-layer neocortical neurons, where they regulate the expression of several other genes involved in brain development [56, 66, 322]. Further, *CHD8* and *CHD2* targets include numerous ASD-linked genes, including *SCN2A*, *GRIN2B*, *SHANK2*, *POGZ*, *TBR1*, and *ANK2* [323]. Therefore, haploinsufficiency of *CHD2* and

CHD8 could impair dendritic excitability and integration by affecting target genes involved in transcription, dendritic scaffolding, and excitability. Consistent with this, *Chd8* knockdown in mice causes delayed neocortical neuron migration and reduced dendritic outgrowth [324].

TBR1 is another ASD-associated transcriptional regulator gene that controls the expression of several other genes involved in the etiology of ASD [325]. *Tbr1* controls the transcription of *Grin2b*, *Scn2a*, and *Ank2* genes involved in excitatory synaptic function, dendritic excitability, and protein localization in axonal structures, respectively [326]. TBR1, a T-box transcription factor, is regarded as a master regulator of cortical development as it plays a fundamental role in the differentiation and identity of deep-layer neocortical pyramidal neurons [327–329]. *Tbr1* mutant mice have fewer excitatory and inhibitory synapses onto neocortical dendrites that are partially due to reduced WNT signaling [330, 331]. Both excitatory and inhibitory synaptic deficits can be rescued with WNT agonists [332]. Interestingly, *Tbr1* heterozygosity in layer 6 pyramidal neurons converts their dendritic arborization into layer 5-like apical dendrites, where ectopic growth of the apical dendrite extends into layer 1 instead of their typical termination with little arborization in layer 4 [333]. How these ectopic dendritic tufts impact the function of affected neocortical areas remains unclear. Interestingly, these conditions may serve as an excellent model in which to test the relative function of different deep-layer pyramidal cells, as this would create situations where layer 6 neurons may have typical basal inputs but vastly different apical inputs. One major question would be to test whether such neurons now adopt processing features more commonly associated with layer 5 cells, rather than those ascribed to layer 6 (e.g., gain control of cortical columns) [334].

PTEN encodes the protein PTEN, a phosphatase strongly associated with ASD and ID [335, 336]. PTEN is highly expressed in both glutamatergic and GABAergic neurons, where it acts as an inhibitor of PI3K/AKT signaling through the activation of receptor tyrosine kinases (RTKs) [337–339]. Conditional knockout of *Pten* in neocortical glutamatergic pyramidal neurons results in aberrant dendritic and axonal arborization and somatic overgrowth, due to heightened β -catenin expression, causing macrocephaly and deficits in social behaviors [340–342]. Homozygous loss of *Pten* weakened excitatory synaptic transmission and plasticity in hippocampal neurons [342]. The effects of *Pten* loss on dendritic excitability in neocortical neurons remain unclear [342–344]. In addi-

tion, PTEN loss in mouse cortical GABAergic interneurons results in reduced somatostatin cell number shifting the ratio of PV/somatostatin interneurons, which, in turn, may lead to abnormal dendritic function and integration [345].

Here, we have discussed only a few “covert” genes that have been shown to directly regulate the expression or localization of “overt” genes in dendrites of neocortical pyramidal neurons. This is likely the tip of an iceberg that will be better revealed as deep genetic phenotyping of multiple ASD-associated models emerges in the coming years. Loss-of-function of these “covert” genes results in functional, morphological, and organizational deficits on neocortical neurons, particularly in layer 5. Of note, many of these transcriptional regulators modify expression levels of multiple “overt” genes at once, making predictions about the final effects on synaptic and dendritic function difficult without empirical tests.

Conclusion and Future Directions

As mentioned at the outset, this review focused primarily on the role of dendritic integration in neocortical areas for several reasons. First, our understanding of neocortical dendritic function is relatively refined both in terms of cellular mechanisms and *in vivo* function, with clear models emerging for the role of dendritic integration in conscious perception and decision-making. Second, neocortical pyramidal cells appear to be a point of convergence for several ASD/ID-associated genes acting both overtly and perhaps covertly to affect dendritic integration. As highlighted recently for the function of psychedelics [346], our hope is that future studies take dendritic excitability into consideration in parallel with key experiments examining molecular, cellular, systems, and behavioral consequences of ASD/ID-associated variation in such genes.

ASD and ID are brain-wide disorders, and while neocortex is thought to be important for ASD/ID etiology, it is not affected in isolation. A wealth of studies have highlighted the importance of other key circuits, including basal ganglia, amygdala, hippocampus, and cerebellum [87, 347–365]. Importantly, many of the concepts discussed above, including the mechanisms supporting dendritic nonlinearities, are relevant across these structures. Thus, while we highlight neocortex here, these themes likely extend to other structures, each with their own rules governing how dendritic excitability shapes the processing of relevant information.

Moving forward, several areas of investigation will be critical to better understand how dendrites are affected in ASD/ID. First, more complete genotype-phenotype correlations of genes known to regulate dendritic function will help to better identify the precise conditions in which aspects of dendritic integration are affected. For example, in both *SCN2A* and *GRIN2B*, a large number of missense variants can be associated with a range of disorders, likely due to differential effects in channel biophysics, ligand affinity, trafficking, etc. While a great deal can be done in heterologous expression systems, it can often be difficult to understand the end effects of such variation in non-native systems. Second, deep phenotyping of the neuronal proteome, perhaps focusing on “overt” dendritic excitability genes, in animal models with “covert” gene disruption may help us to better understand how chromatin modification and other forms of gene regulation affect the dendrite. Last, the development of ASD/ID-relevant behavioral approaches that are amenable to simultaneous imaging, recording, and ideally, manipulation of dendritic activity in ASD/ID-relevant models will not only be key to understanding the role of dendrites in NDDs, and also may shed light on components of dendritic function necessary for neurotypical processing.

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Conflict of Interest Statement

The authors have no conflicts of interest to disclose.

Author Contributions

A.D.N. and K.J.B. contributed equally to this work.

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