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REVIEW

From Gene to Behavior: L-Type Calcium Channel Mechanisms Underlying Neuropsychiatric Symptoms

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Abstract The L-type calcium channels (LTCCs) $Ca_v1.2$ and $Ca_v1.3$, encoded by the *CACNA1C* and *CACNA1D* genes, respectively, are important regulators of calcium influx into cells and are critical for normal brain development and plasticity. In humans, *CACNA1C* has emerged as one of the most widely reproduced and prominent candidate risk genes for a range of neuropsychiatric disorders, including bipolar disorder (BD), schizophrenia (SCZ), major depressive disorder, autism spectrum disorder, and attention deficit hyperactivity disorder. Separately, *CACNA1D* has been found to be associated with BD and autism spectrum disorder, as well as cocaine dependence, a comorbid feature associated with psychiatric disorders. Despite growing evidence of a significant link between *CACNA1C* and *CACNA1D* and psychiatric disorders, our understanding of the biological mechanisms by which these LTCCs mediate neuropsychiatric-associated endophenotypes, many of which are shared across the different disorders, remains rudimentary. Clinical studies with LTCC blockers testing their efficacy to alleviate symptoms associated with BD, SCZ, and drug dependence have provided mixed results, underscoring the importance of further exploring the neurobiological consequences of dysregulated $Ca_v1.2$ and $Ca_v1.3$. Here, we provide a review of clinical studies that have evaluated LTCC blockers for BD, SCZ, and drug dependence-associated symptoms, as well as rodent studies that have identified $Ca_v1.2$- and $Ca_v1.3$-specific molecular and cellular cascades that underlie mood (anxiety, depression), social behavior, cognition, and addiction.

Keywords $Ca_v1.2$ · $Ca_v1.3$ · *CACNA1C* · *CACNA1D* · Mood · Social · Addiction

Introduction

Over the last 2 decades, work from multiple laboratories has established that $Ca_v1.2$ and $Ca_v1.3$ L-type calcium channels (LTCCs) are critical mediators of experience-dependent plasticity in the brain. More recently these channels have been identified to be key for various neuronal processes that are essential for normal brain development, connectivity, and function [1–3]. This is further underscored by the discovery of neuropsychiatric risk genetic variants in *CACNA1C*, which codes for the $Ca_v1.2$ $\alpha1$ subunit of LTCCs [4, 5], and *CACNA1D*, which codes for the $Ca_v1.3$ $\alpha1$ subunit [6, 7]. These variants can alter levels and function of the channels with consequences on neural processing and connectivity as revealed by human imaging studies [1, 8, 9].

The LTCCs belong to the family of voltage-gated Ca^{2+} channels, with $Ca_v1.2$ and $Ca_v1.3$ being the primary LTCC subunits expressed in the brain [10]. Although there is considerable overlap in their expression pattern, as revealed by *in situ* hybridization (Table 1), Fos expression, a measure of neuronal activity [21], and studies with genetic mutant mice ([1, 2] and as discussed below) have revealed differential contributions of these isoforms to neuronal function and behavior. These LTCC isoforms are present as heteromeric complexes with Ca_v1 encoding the $\alpha1$ pore-forming subunit that determines the physiological and pharmacological properties of these channels

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Table 1 $Ca_v1.2$ and $Ca_v1.3$ mRNA expression within mesocorticolimbic brain regions in rodents

Brain region	$Ca_v1.2$ mRNA	$Ca_v1.3$ mRNA	Reference
Hippocampus			[11]
CA1	*	**	
CA2	***	**	
CA3	***	**	
Dentate gyrus	***	***	
Hippocampus			[12]
Dentate gyrus	**	**	
Amygdala	*	*	
Hippocampus			[13]
CA1	NR	**	
CA3	NR	**	
Dentate gyrus	NR	***	
Hippocampus			[14]
Dentate gyrus	***	NR	
Amygdala	**	NR	
VTA	*	***	[15]
NAc			
Core	*	**	
Shell	**	***	
Hippocampus			[16]
CA	***	***	
Dentate gyrus	***	***	
VTA	*	*	
PFC	**	**	
Hippocampus			[17]
CA1	**	*	
CA3	***	*	
Dentate gyrus	***	*	
Amygdala			
BLA	**	*	
Hippocampus			[18]
CA1	*	**	
CA3	***	**	
Dentate gyrus	***	***	
Hippocampus			[19]
Hippocampal formation	***	NR	
Hippocampus			[20]
CA1	**	**	
CA3	**	**	
Dentate gyrus	**	***	
Amygdala			
CeA	*	**	
MeA	*	**	
BLA	*	**	
NAc			
Core	*	*	
Shell	**	**	
PFC			
Cing	*	**	
PreL	*	**	
IL	*	**	
OFC	*	**	

Comparison of $Ca_v1.2$ and $Ca_v1.3$ mRNA levels are made within and across brain regions for each study and not across different studies

NR = not reported; VTA = ventral tegmental area; NAc = nucleus accumbens; CA = hippocampal comus ammon regions CA1, CA2, and CA3; PFC = prefrontal cortex; BLA = basolateral amygdala; CeA = central amygdala; MeA = medial amygdala; Cing = cingulate cortex; PreL = prelimbic cortex; IL = infralimbic cortex; OFC = orbitofrontal cortex

*Low expression, **moderate, or ***strong expression

[2, 22]. The $Ca_v1.2$ and $Ca_v1.3$ subunits share a high degree of sequence and structural similarity resulting in lack of selectivity of LTCC pharmacological activators and blockers [2]. However, as we now know, $Ca_v1.2$ and $Ca_v1.3$ have different physiological characteristics [23–25] and associate with different proteins to form unique subunit-specific signaling complexes at the neuronal membrane [26–28], resulting in differential contributions to neuronal function and neuropathology underlying disease.

In this review we will first provide an overview of *CACNA1C* and *CACNA1D* genetic risk variants linked to neuropsychiatric disorders. As recent genetic findings have raised great interest in targeting LTCCs as a potential strategy for the treatment of neuropsychiatric disorders and drug dependence, as well as repurposing current clinically used LTCC medications [2, 6, 29, 30], we will next review clinical studies performed to date with LTCC blockers. We will then provide an overview of our current knowledge of the brain-region-specific contribution of $Ca_v1.2$ and $Ca_v1.3$ channels to neural and molecular mechanisms underlying the pathophysiology of neuropsychiatric and neurodevelopmental-associated behavioral endophenotypes, obtained using preclinical animal models (Fig. 1). Given the complex nature of neuropsychiatric disorders, we believe that understanding biological phenotypes in the context of behavioral endophenotypes, will greatly help both in better understanding neuropathology, as well as provide a framework for exploring new therapeutic targets for *CACNA1C*- and *CACNA1D*-associated disorders.

Functional Impact of *CACNA1C* and *CACNA1D* Genetic Risk Variants

As recently reviewed in detail in Heyes et al. [5], genome-wide association studies have identified multiple single nucleotide polymorphisms (SNPs) in *CACNA1C* to be significantly associated with bipolar disorder (BD) [31] and schizophrenia (SCZ) [32]. Additionally, risk SNPs within *CACNA1C* have also been linked to major depressive disorder (MDD) [33], autism

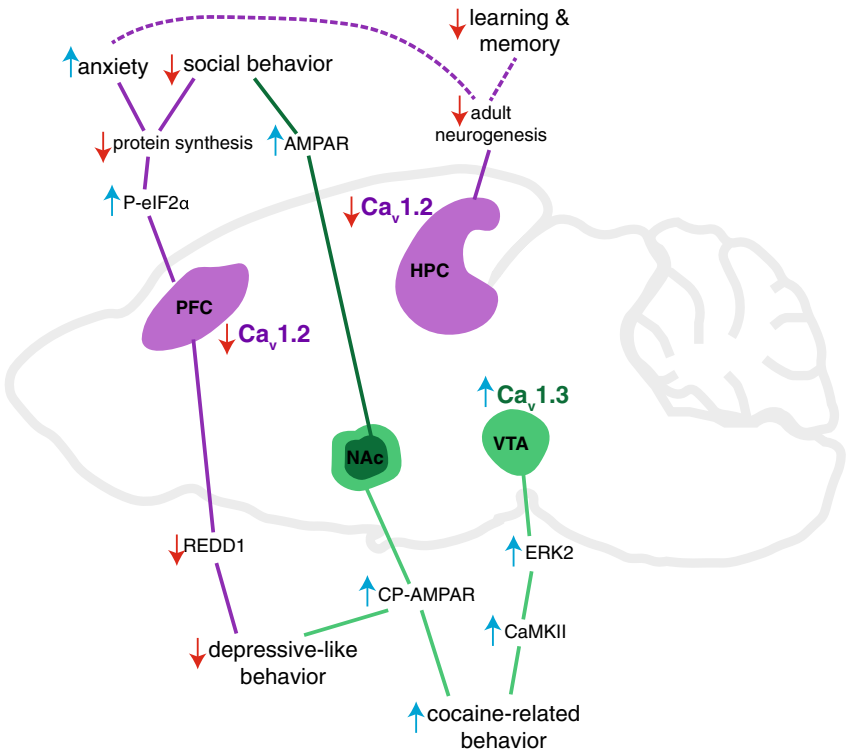

Fig. 1 $Ca_v1.2$- and $Ca_v1.3$-mediated anatomical and molecular pathways underlying the endophenotypes associated with neuropsychiatric disorders. Solid lines indicate pathways that have been identified for the respective behavioral endophenotypes and dotted lines indicate potential pathways that may be recruited AMPAR = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors; PFC = prefrontal cortex; HPC = hippocampus; NAc = nucleus accumbens; VTA = ventral tegmental area; REDD1 = regulated in development and DNA damage response 1; CP-AMPAR = Ca^{2+}-permeable AMPAR; ERK2 = extracellular regulated kinase 2; CaMKII = CaM-dependent protein kinase II

spectrum disorder (ASD) [34], and attention deficit hyperactivity disorder (ADHD) [35]. Furthermore, a meta-analysis study has linked disease-associated *CACNA1C* SNPs to all the abovementioned 5 disorders [35]. The majority of these SNPs are present in the intronic, 5' or 3' untranslated regions of *CACNA1C* [4, 5], in accordance with the growing body of literature establishing that large numbers of SNPs associated with complex diseases such as neuropsychiatric disorders, are present within noncoding regions [36]. Most of the *CACNA1C* risk SNPs associated with SCZ and BP, particularly SNP rs1006737 and those in linkage disequilibrium, are present in a large intron between exons 3 and 4 [5]. Functional studies to evaluate the impact of risk SNPs on gene expression are beginning to establish that these SNPs lie within regions that are under tight transcriptional control, with risk SNPs being able to alter gene expression by differentially binding nuclear proteins and also altering long-range intronic enhancer and promoter interactions within *CACNA1C* [37, 38]. Biological studies to measure levels of *CACNA1C* have found both increased [38–40] and decreased [37, 38, 40, 41] expression of *CACNA1C*, depending on the brain region and cellular system examined. This suggests that transcriptional control of *CACNA1C* is highly complex and most likely, differentially controlled at the level of brain region and cell type. Nevertheless, these studies demonstrate that intronic *CACNA1C* risk SNPs can alter levels of *CACNA1C* and that loss or gain of $Ca_v1.2$ can contribute to disease symptoms.

In addition to the noncoding variants, 2 truncating mutations in *CACNA1C* have been identified in a whole-exome sequencing study of SCZ that are predicted to cause loss of function [42], though this remains to be confirmed. As discussed in Heyes et al. [5], these truncation mutations in *CACNA1C* could exert a dominant negative effect through the interaction of truncated mutant proteins with the $Ca_v1.2$ channel, as has been reported for other voltage-gated subunits [43–45].

A coding *CACNA1C* variant has also been linked to ASD. A gain-of-function mutation in $Ca_v1.2$ causes Timothy syndrome (TS), an autosomal dominant developmental disorder [46]. This syndrome is a multiorgan disorder associated with malformations, cardiac symptoms (long QT), and neurological developmental defects [46–48], including manifestation of neuropsychiatric phenotypes [48]. The mutation in $Ca_v1.2$ that causes TS is a sporadic, dominant glycine-to-arginine mutation that is located at position 406 (G406R) in a mutually exclusive, alternatively spliced exon 8 or 8A of *CACNA1C* [46]. G406R in exon 8a causes TS1 and G406R or G402S in exon 8 causes a rare variant of TS, namely TS2 [46, 48]. TS1 has been associated with ASD [46, 48], whereas patients with TS2 additionally manifest with neuropsychiatric conditions [41, 48]. One patient with TS2 was reported to exhibit obsessive compulsive disorder and depression [48], while another patient with TS2 who carried the G402S mutation developed BD in adulthood [41].

Similar to *CACNA1C*, genetic variants in *CACNA1D* have also been identified in neuropsychiatric disorders. A SNP in *CACNA1D* (rs893363), which codes for $Ca_v1.3$, has been associated in the 5-disorder gene analysis, including BD, SCZ, ADHD, MDD, and ASD [35]. Separately noncoding variants [31] and 2 coding variants (A1751P and R1771W) have been

linked to BD [49]. However, a study in the Han Chinese population found no significant SNPs in *CACNA1D* associated with SCZ [50]. SNPs in *CACNA1D* have also been associated with cocaine dependence [51]. Furthermore, whole-exome sequencing studies have identified 2 *de novo* mutations (p.A749G and p.G407R) in *CACNA1D* in patients with sporadic autism and intellectual disability [52, 53]. Functional studies have identified these mutations as gain-of-function of $Ca_v1.3$ LTCCs [7, 54].

Thus, based on the above findings on the impact of *CACNA1C* and *CACNA1D* disease-associated genetic variants on gene expression and channel function, the available data suggest that higher or lower levels of Ca^{2+} influx in neurons can be detrimental. In addition, LTCCs can also regulate neuronal firing. For example, LTCCs can directly provide a depolarizing stimulus; this can stabilize upstates/plateau potentials (e.g. [55]), thus affecting neuronal firing. LTCCs can also couple to Ca^{2+}-activated K channels [56, 57], thus moderating neuronal firing. Therefore, decreased LTCC activity could actually increase firing in some neurons, which may trigger Ca^{2+} influx through other sources (other voltage-gated Ca^{2+} channels subtypes or glutamate *N*-methyl-D-aspartate receptors). Similarly, increase in LTCC activity as a result of gain of LTCC function could silence neurons. Thus, altered $Ca_v1.2$ and $Ca_v1.3$ LTCC levels or activity, in a cell-type-specific manner, can affect neuronal function in multiple ways that could negatively affect brain function and contribute to neuropsychiatric symptoms in disorders associated with *CACNA1C* and *CACNA1D*.

Targeting L-Type Calcium Channels in the Treatment of Neuropsychiatric Disorders and Drug Dependence

LTCC blockers have been used clinically for several decades in the treatment of cardiac conditions such as hypertension, arrhythmias, and cardiac ischemia [2]. Recently, with growing evidence of the association between LTCC genes and neuropsychiatric disorders [5], there has been increased interest in repurposing these drugs for the treatment of neuropsychiatric conditions and drug dependence [6, 29]. Since the 1980s several clinical studies have examined the efficacy of LTCC blockers using the 3 classes of LTCC pharmacological blockers—dihydropyridines (DHPs; nifedipine, amlodipine, felodipine, isradipine, nicardipine, nisoldipine, and nimodipine); phenylalkylamines (verapamil); and benzothiazepines (diltiazem)—to alleviate symptoms in patients presenting with neuropsychiatric conditions and drug dependence. Below, we review the findings of these studies (see Table 2). Of note, many of these clinical studies have utilized high systemic doses of LTCC blockers, particularly the DHPs and thus could have significant confounding effects on behavior, as demonstrated by rodent studies [105, 106]. Additionally, several of these studies have used the phenylalkylamine blocker, verapamil (Table 2). In addition to verapamil's nonspecific effects such as blocking other Ca^{2+} channels [107], potassium channels [108–110], and α-adrenergic receptors [111], studies examining how well verapamil enters the brain in humans have been sparse. Verapamil is a substrate for P-glycoprotein (P-gp) substrate, an efflux transporter found in several organs, including the blood–brain barrier, where it plays an important role for the entry of drugs, including verapamil, into the brain [112]. Verapamil can function as a stimulator of the P-gp activity at low concentrations, preventing brain entry, whereas at high concentrations it acts as an inhibitor of P-gp, allowing brain entry [113, 114]. However, verapamil at high concentrations, although capable of penetrating the blood–brain barrier, can have toxics effects [115].

BD

The efficacy of the LTCC blocker verapamil in alleviating acute mania observed in BD has been explored in several studies [116]. While some studies report a significant decrease in the severity of mania in patients with BD or manic patients [58, 59, 62–66, 68, 69], several others report no antimanic effects when verapamil was administered as a monotherapy [60, 61, 70–72]. However, when verapamil was administered in combination with the mood stabilizer lithium to patients with BD who were unresponsive to lithium [70] or in conjunction with the antipsychotic medication chlorpromazine [60] there was significant improvement in manic symptoms. This suggests that verapamil could have some potential for maintenance therapy of mania but only when administered in combination with other drugs. In addition to these findings, verapamil was found to improve significantly major psychotic depressive symptoms in 1 patient [67] and improve depressive symptom scores in patients prescribed verapamil for hypertension [73].

Although there are only a handful of studies with nimodipine and diltiazem, the findings are more consistent, though not as thoroughly investigated as verapamil. Bipolar manic patients treated with nimodipine either as a monotherapy [74–76] or in combination with lithium [77] or the antiseizure medication carbamazepine [74] showed significant improvements. Similar improvements in mood were reported when an adolescent with refractory, ultradian rapid cycling BD was treated with nimodipine [78]. Likewise, both bipolar manic patients [79] and treatment-resistant bipolar patients [80] treated with diltiazem had significantly decreased manic symptoms. However, in patients with no prior psychiatric history, the use of nifedipine to treat angina was associated with the onset of depression [81].

SCZ

Verapamil has also been tested in patients with SCZ. In patients with acute SCZ, verapamil treatment when administered

Table 2 Type of clinical study using L-type calcium channel blockers in neuropsychiatric disease

Neuropsychiatric disease treated	L-type calcium channel blocker used	Type of clinical study performed	Reference(s)
Bipolar disorder	Verapamil	Nonrandomized	[58–61]
		Randomized; patients received either verapamil or lithium and efficacy compared	[62]
		Randomized: crossover study; patients received either verapamil or lithium and then treatment switched	[63]
		Case report	[64–67]
		Randomized placebo-controlled within subject	[68]
		Nonrandomized placebo within subjects	[69]
		Randomized: phase I—lithium, phase II—nonresponders (verapamil or lithium); phase III—nonresponders (combined verapamil/lithium)	[70]
		Randomized placebo	[71, 72]
		Randomized; patients received verapamil or the antihypertensive drug atenolol and efficacy compared	[73]
	Nimodipine	Randomized placebo-controlled within-subjects	[74]
		Nonrandomized placebo within-subject	[75]
		Nonrandomized	[76]
		Case report	[77, 78]
	Diltiazem	Nonrandomized	[79, 80]
	Nifedipine	Case report	[81]
Schizophrenia	Verapamil	Case report	[82]
		Randomized placebo	[83, 84]
		Randomized placebo-controlled within subject	[85]
		Nonrandomized	[86]
		Nonrandomized placebo within subject	[87, 88]
	Nifedipine	Nonrandomized	[89]
		Randomized placebo	[90]
Cocaine dependence	Nimodipine	Randomized placebo-controlled within subject	[91]
	Isradipine	Randomized placebo-controlled within subject	[92, 93]
	Nimodipine	Randomized placebo	[94]
	Nifedipine	Randomized placebo-controlled within subject	[95]
	Amlodipine	Nonrandomized	[96]
	Isradipine	Randomized placebo-controlled within subject	[97]
Morphine dependence	Verapamil	Randomized placebo	[98]
	Diltiazem, verapamil, nimodipine	Randomized placebo-controlled within subject	[99]
	Nifedipine	Randomized; patients received nifedipine or the α-adrenoceptor blocker, clonidine; only nifedipine effects reported	[100]
Alcohol dependence	Verapamil, nimodipine	Randomized placebo	[101]
	Isradipine	Quasirandom placebo within subject; patients received 9 different combinations of ethanol or isradipine at different doses; only the first and second treatment was not randomly given	[102]
	Verapamil, nifedipine	Randomized placebo-controlled within subject	[103]
	Nimodipine	Nonrandomized	[104]

as a monotherapy resulted in a significant decrease in psychotic symptoms [82]. These findings were confirmed in a separate study that reported a similar small, but significant, attenuation of psychotic symptoms with verapamil [83]. Similarly, patients with chronic SCZ treated with verapamil for 28 days displayed significant improvements in positive

and negative symptoms, as well as in anxiety and depression [86]. In contrast to these findings, other studies have reported an increase in paranoia in verapamil-treated patients with chronic schizophrenia who were recently withdrawn from neuroleptics [87], or no effect on the psychological state [88] and negative symptoms [84]. Similar to the results with verapamil, the effects of nifedipine on alleviating the psychotic symptoms are conflicting. While some studies showed that patients with chronic schizophrenia receiving nifedipine showed an improvement on the Dementia Scale [85] and the Brief Psychiatric Rating Scale [89], another showed no improvements based on the Psychiatric Symptom Assessment Scale ratings [90].

Cocaine Dependence

Evidence from rodent studies has identified an important role of LTCCs in multiple aspects of cocaine addiction, making these channels a potential target for the treatment of addiction. Over the last few decades, clinical studies have tested the efficacy of LTCC blockers on the subjective effects of cocaine, though the results have been mixed. While some studies report no effect with isradipine and nimodipine [91, 92], others have reported a reduction in the subjective response to cocaine with nifedipine [95]. In contrast, a recent study reported enhanced subjective effects with isradipine [93]. The effects of LTCCs have also been tested on cocaine craving, the primary cause of relapse to cocaine use, with nimodipine [94], amlodipine [96], and isradipine [97] reducing cocaine craving.

Morphine Dependence

The impact of LTCC blockers on the subjective effects of morphine are mixed. While 1 study reported a reduction in the subjective effect of morphine with verapamil [98], another study showed no influence of nimodipine, verapamil, and diltiazem on counteracting morphine's subjective effects in healthy humans [99]. Separately, it has been reported that nifedipine treatment caused confusion in individuals that were in morphine withdrawal [100]. These studies suggest that LTCC blockers may show selective effects in morphine-dependent individuals, having beneficial effects in some but detrimental effects in others.

Alcohol Dependence

With ethanol, LTCC blockers nimodipine and verapamil have been reported to have no effect on the subjective and psychomotor effects of the drug [101]. Similarly, isradipine had no effect on ethanol's acute effects on poor psychomotor performance [102], and failed to antagonize ethanol intoxication [103]. However, nimodipine has been found to be effective for the treatment of ethanol's withdrawal symptoms [104].

The discrepancies in the effects of LTCC blockers in the treatment of psychiatric disorder-associated symptoms and on the symptoms associated with drug dependence, as reviewed above, may be a consequence of a myriad of factors, including the high doses used; however, it highlights the complexity of neuropsychiatric disorders, as well as how dysregulated LTCCs may influence different psychiatric symptoms. Given our current knowledge of the varying impact of disease-risk variants to *CACNA1C* and *CACNA1D* levels (increase or decrease) and $Ca_v1.2$ and $Ca_v1.3$ function (gain or loss), it is not surprising that LTCC blockers may be efficacious in some individuals but not all and for some symptoms and not all those seen in *CACNA1C* and *CACNA1D*-linked neuropsychiatric conditions. Thus, understanding how $Ca_v1.2$ and $Ca_v1.3$ channel mechanisms contribute to neuropsychiatric-related symptoms can be greatly helpful. As progress on the development of new therapeutics for psychiatric disorders has been slow, understanding biological pathways in the context of disease symtoms (e.g., anxiety, social, depression, cognition) are key in identifying new targets for developing medications. We believe that this is particularly important given the complex nature of neuropsychiatric disorders *versus* the idea that they are sole entities as previously considered.

L-Type Calcium Channel Signaling in Neurons and Relevance to Neuropsychiatric Disorders

Several lines of evidence from both human and animal studies have unequivocally established a critical contribution of Ca^{2+} signaling pathways to the pathophysiology of both neuropsychiatric and neurodevelopmental disorder [1, 6, 117]. $Ca_v1.2$ and $Ca_v1.3$ channels are key mediators of Ca^{2+} signaling in neurons [26]. *In vitro* studies have established that depolarization-induced increase in local Ca^{2+} activates the calcium sensor calmodulin (CaM) at the synapse that subsequently activates a series of Ca^{2+}/CaM-dependent protein kinases (CaMKs) [118–122] and also the Ras/mitogen-activated protein kinase (MAPK) pathway [123–125], both of which transduce molecular cascades to the nucleus, activating gene expression via the extensively studied transcriptional factor cAMP response element-binding protein (CREB) (Fig. 2). CREB-activated genes are critically involved in synaptic, neuronal, and behavioral plasticity [126–130]. LTCC-induced kinase pathways are also recruited for phosphorylation of signaling molecules that activate other transcription regulators, including myocyte enhancer factor-2 [131–134] and MeCP2 (Fig. 2), key factors involved in neuronal development, behavioral alterations, and neurodevelopmental disorders. In addition to activation of the kinase pathways, LTCCs can also activate the phosphatase pathway that likewise modulates

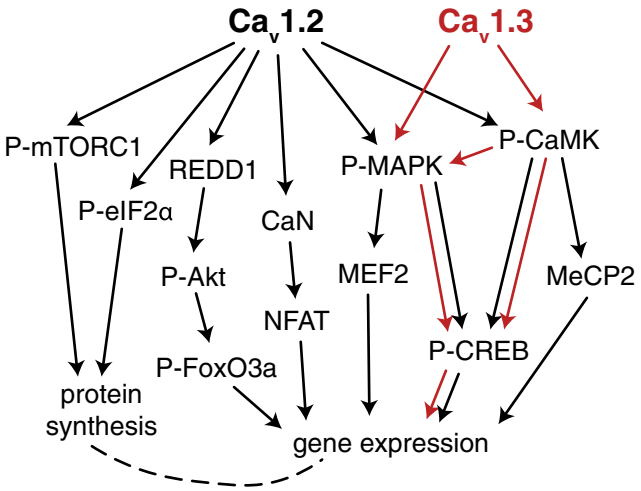

Fig. 2 $Ca_v1.2$ and $Ca_v1.3$ signaling mechanisms. Solid lines indicate pathways that have been directly linked to $Ca_v1.2$ or $Ca_v1.3$ channels and dotted line indicates potential pathway that may be recruited. Black arrows indicate $Ca_v1.2$-specific pathways; red arrows indicate $Ca_v1.3$-specific pathways. mTORC1 = mammalian target of rapamycin complex 1; REDD1 = regulated in development and DNA damage response 1; P-MAPK = phosphorylated mitogen-activated protein kinase; P-CaMK = phosphorylated CAM-dependent protein kinase; P-eIF2α = phosphorylated eukaryotic initiation factor 2 alpha; CaN = calcineurin; P-Akt = phosphorylated protein kinase B; MEF2 = myocyte enhancer factor 2; NFAT = nuclear factor of activated T cells; P-CREB = phosphorylated cAMP response element-binding protein

transcription factor function. This includes the nuclear factor of activated T cells (NFAT) family of transcription factors that is regulated by the LTCC-activated Ca^{2+}–calmodulin-dependent phosphatase calcineurin that dephosphorylates NFAT cytoplasmic 3 [135] and NFAT cytoplasmic 4 [136], inducing its translocation from the cytoplasm to the nucleus to regulate gene expression. Alteration of myocyte enhancer factor-2 and NFAT, as well as CREB signaling networks, has been linked to dendritic retraction as a consequence of elevated Ca^{2+} in induced pluripotent cells from patients with TS [132].

The significance of these LTCC-activated pathways to neuropsychiatric disease pathology is underscored by several pathway network analyses that have repeatedly identified significant association of the calcium signaling pathway to BD [137, 138], SCZ [138, 139], MDD [138], and ASD [140], highlighting the calcium pathway as a common dysregulated mechanism underlying the etiology of these disorders. This has also been observed using proteomic approaches with postsynaptic density fractions from the cortex of patients with SCZ [141] and BD [142] that have identified altered levels of proteins that are mediators of calcium signaling. Additionally, pathway analyses have identified significant enrichment of the MAPK/extracellular regulated kinase (ERK) pathway in ASD [140, 143], SCZ [141], and depression [144], and whole-exome sequencing has found rare and likely protein-damaging mutations in members of the MAPK/ERK and CREB-regulated intracellular signaling pathways in patients with BD [145]. Another pathway enriched in the proteomics-based pathway analysis from the postsynaptic density of patients with BD was the eukaryotic initiation factor 2α (eIF2α) signaling pathway [142], which is involved in mRNA translation [146] and a pathway we review below as a new candidate pathway linked to behavioral deficits in $Ca_v1.2$-deficient mice. In light of these findings, it is evident that dysregulation in LTCC and Ca^{2+} signaling can result in neuronal alterations that contribute to the pathogenesis of neuropsychiatric-related cellular [51, 147–150], physiological, synaptic [150, 151], and behavioral phenotypes [51, 150, 152, 153], all of which we discuss below.

L-Type Ca^{2+} Channels and Neuropsychiatric-Related Phenotypes: Preclinical Animal Studies

Rodents have proved to be a useful tool to study human disease-related behavioral symptoms. Given the predominance of noncoding variants in *CACNA1C* that are predicted to affect transcriptional control and result in lower or higher levels of *CACNA1C*, studying gene knockout and overexpressing mice can be highly useful. Similarly, mice harboring coding mutations that cause either loss or gain of function can be informative. The $Ca_v1.2$ and $Ca_v1.3$ LTCC isoforms have structural similarities making them both equally sensitive to LTCC pharmacological agents [154], posing a challenge to study isoform-specific brain and behavioral alterations. To overcome this, several different laboratories have developed genetic mutant mouse models that have altered expression or function of either $Ca_v1.2$ or $Ca_v1.3$. The most common models used to study $Ca_v1.2$-specific mechanisms have been the heterozygous constitutive knockout mouse model (homozygous is embryonic lethal [155]), and temporal, spatial, and cell-type-specific conditional mouse models with restricted knockdown of *cacna1c* (encoding $Ca_v1.2$) in the brain using Cre-recombinase specific drivers (mouse lines and viral vectors). Constitutive $Ca_v1.2$ heterozygous knockout mice develop a cardiac phenotype, particularly following stress [156]; however, it is unlikely that this cardiac phenotype affects brain phenotypes at baseline [153, 157] or following stress [158]. For $Ca_v1.3$ studies, there exists the $Ca_v1.3$ knockout mouse, though because of the high expression of $Ca_v1.3$ in the hair cells of the ear are deaf and limit their use for behavioral studies. To overcome this and the lack of subunit-specific pharmacological agents, the Striessnig laboratory developed a $Ca_v1.2$ DHP-insensitive ($Ca_v1.2DHP^{-/-}$) mouse that harbors a single point mutation in the $Ca_v1.2\alpha1$ subunit at the DHP binding site, rendering $Ca_v1.2$ channels insensitive to DHPs [159], allowing the specific pharmacological manipulation of $Ca_v1.3$ channels [21, 51, 159–161]. Below we review studies that have utilized these preclinical mouse

models to examine behavioral and molecular phenotypes related to neuropsychiatric disorders.

$Ca_v1.2$ Channel Mechanisms and Neuropsychiatric-Related Endophenotypes

Anxiety

Symptoms of anxiety are one of the most prevalent endophenotypes of psychiatric disorders [162]. In mice with a 50% reduction of *cacna1c* ($Ca_v1.2$; $Ca_v1.2$ heterozygous mice), both females [153, 157] and males [153] display anxiety-like behavior. Similarly, restricted elimination of *cacna1c* ($Ca_v1.2$) in excitatory glutamatergic neurons of the forebrain (forebrain $Ca_v1.2$ conditional knockout mice), a cell type with high expression of $Ca_v1.2$, as well as selective elimination of $Ca_v1.2$ in the adult prefrontal cortex (PFC) has been found to result in anxiety-like behavior [150, 153].

These preclinical findings are supported by clinical studies that have identified generalized anxiety [163, 164] and trait anxiety [165] in *CACNA1C* risk allele (rs1006737) carriers together with structural [166] and functional alterations in the PFC of these individuals [167]. In contrast, male mice harboring the TS gain-of-function $Ca_v1.2$ mutation display no anxiety-like phenotype [168], suggesting that a loss, rather than a gain, of $Ca_v1.2$ function may mediate anxiety-like behavior.

Social Behavior

Impairments in social behavior are observed in a range of neuropsychiatric disorders [169] and represent a core domain in ASD [170]. Using rodents studies, it has become evident that dysregulated Ca^{2+} as a consequence of altered $Ca_v1.2$ channel function can influence social behavior [168]. The TS $Ca_v1.2$ gain-of-function mouse model displays a significant social deficit [168], demonstrating that excess Ca^{2+} can adversely affect social behavior. Similarly, mice with restricted deletion of $Ca_v1.2$ in glutamatergic neurons of the forebrain display a similar deficit in social behavior [150]. Focal knockdown of $Ca_v1.2$ in the adult PFC is sufficient to induce the social behavioral deficits [150], identifying the PFC as the common anatomical structure of $Ca_v1.2$'s effects on social function and anxiety-like behavior (Fig. 1). This is not surprising given that anxiety has been shown to negatively impact social function [171–173].

As loss of $Ca_v1.2$ results in both anxiety and social behavioral deficits, work from our laboratory has begun to dissect the mechanistic interaction between anxiety and social function by examining the biological pathways underlying these impairments. One mechanism that has received tremendous attention in recent years is dysregulation of dendritic mRNA translation and protein synthesis, being attributed to behavioral impairments. The role of LTCCs in regulating dendritic mRNA translation *versus* nuclear transcription remains largely unknown. One *in vitro* study has linked LTCCs to the mammalian target of rapamycin (mTOR) pathway [174], one of the most highly studied pathways regulating mRNA translation and protein synthesis [175]. In support of this, loss of $Ca_v1.2$ in glutamatergic neurons of the forebrain results in a significant decrease in levels of general protein synthesis in the PFC [150] (Figs. 1 and 2). Molecular studies have identified lower phosphorylated (at serine S2448) mTOR, indicating lower activity of mTOR complex 1 (mTORC1). In parallel, $Ca_v1.2$ deficiency also results in heightened levels of phosphorylated (at S51) eIF2α [150], a translational repressor. Both of these molecular findings support lower protein synthesis in $Ca_v1.2$-deficient mice. Altered protein synthesis, particularly heightened levels via the mTORC1 pathway has been implicated in both neurodevelopmental disorders, including ASD and neuropsychiatric disorders [176]. Preclinical mouse models with genetic manipulations of substrates of the mTORC1 pathway have been reported to display altered protein synthesis concurrent with neuropsychiatric-associated behavioral phenotypes, particularly social deficits [177–179]. Pharmacological manipulation of the mTOR pathway has been explored for treatment of neuropsychiatric disorders. For example, normalizing elevated protein synthesis with the mTOR inhibitor rapamycin [179] or inhibiting the mRNA translation factor, eIF4 [177, 178], has been shown to reverse social deficits. Supporting these preclinical findings a recent case study in a patient with the neurodevelopmental disorder, tuberous sclerosis complex (TSC), benefitted from the mTOR inhibitor everolimus. TSC in this patient resulted from a genetic deletion in *TSC2*, which increased mTOR activity, as seen *in vitro* experiments. Everolimus improved behavioral deficits (cognition, attention, social interaction, language development, and repetitive motor movements), seizures, and improved autism behavioral scores [180].

In contrast to the increase in general protein synthesis observed in several of the above mentioned models, $Ca_v1.2$-deficient mice, as also seen in MeCP2-deficient mice [181], display lower general protein synthesis, suggesting that any disruption in translational regulation may induce overlapping behavioral endophenotypes. In support of this, inhibiting the effects of elevated phosphorylated eIF2α S51 and lowering protein synthesis with ISRIB, a small molecule that potently inhibits the effects of eIF2α [182], is sufficient to not only normalize the social deficits, but also to reverse the elevated anxiety-like behavior in forebrain $Ca_v1.2$ conditional knockout mice [150]. Because of the lack of pharmacological agents that can elevate general protein synthesis via the mTORC1 pathway, ISRIB provides an alternative strategy to normalize the lower protein synthesis in mouse models such as forebrain $Ca_v1.2$ conditional knockout mice. It is interesting that despite lower active mTOR, targeting eIF2α is sufficient to normalize

behavioral deficits, suggesting cross-talk between the mTOR and eIF2α pathways [183].

These findings provide a unique role of $Ca_v1.2$ in protein synthesis via the eIF2α pathway and potentially the mTOR pathway (Fig. 2), and also identify a common $Ca_v1.2$-mediated molecular mechanism underlying social and anxiety-like behaviors (Fig. 1). Furthermore, it identifies a novel target in a $Ca_v1.2$-deficient mouse model that can be manipulated in the adult brain to rescue behavioral deficits. The contribution of eIF2α and its pathway to psychiatric and neurodevelopmental disease-associated symptoms remains unexplored but warrants further investigation. Increases in phosphorylation of eIF2α at S51 can not only decrease translation of most mRNAs [184], but can also induce translation of a subset of mRNAs containing short upstream open reading frames in an activating transcription factor 4-dependent manner [146], a member of the CREB family of transcription factors [185]. Thus, further studies to explore the specific proteins targeted by elevated phosphorylated eIF2α in the PFC of $Ca_v1.2$-deficient mice that are modulating both anxiety and social function will be informative.

Depressive-Like Behavior

In addition to the above mentioned endophenotypes, depression-related symptoms are also commonly observed in BD, MDD, and SCZ [162]. In the late 1980s, a role for LTCCs in regulating depression-related behavior was first realized using LTCC pharmacological agents demonstrating that the DHP LTCC blocker nifedipine has an antidepressant-like effect in rats [186]. This was further expanded in a later study that showed that, in addition to nifedipine, other DHP blockers, including nicardipine, nitrendipine, isradipine, felodipine, and nimodipine but not amlodipine, had a similar antidepressant-like effect [187]. More recently, in support of the pharmacological antidepressant-like effect, the use of genetic mutant mice has revealed that $Ca_v1.2$ heterozygous mice exhibit antidepressant-like behavior [152, 157]. Furthermore, focal knockdown of *cacna1c* ($Ca_v1.2$) in the adult PFC was sufficient to induce a similar antidepressant-like effect [152], consistent with antidepressants exerting their effects through cellular changes in the PFC [188].

In the context of *CACNA1C* SNPs the above findings suggest that gain of $Ca_v1.2$ function mutations would contribute to depression-related symptoms. In support of this, it has been shown that pharmacological activation of LTCCs with the DHP activator BayK8644 induces a depressive-like phenotype [189]. Although depression-related behavior has not been tested in the $Ca_v1.2$ gain-of-function TS mouse, there are case reports identifying 1 patient with TS with depression [48] and another patient with TS who developed BD in adulthood [41]. Together, these findings support the theory that gain of $Ca_v1.2$ function results in depression-related symptoms.

It is intriguing that loss of $Ca_v1.2$ in the PFC results in anxiety-like behavior but has an antidepressant-like effect. A deeper understanding of this differential effect of $Ca_v1.2$ deficiency has come from molecular studies that have identified separate mechanisms influencing anxiety and depression-related behaviors. In contrast to dysregulation of the mRNA translation pathway underlying anxiety in $Ca_v1.2$-deficient mice (described above), the regulated in development and DNA damage response 1 (REDD1; also known at DDIT4 or RTP801) pathway modulates depression-related behaviors (Fig. 1; [152]). $Ca_v1.2$ heterozygous mice that exhibit an antidepressant-like phenotype have lower levels of the depression-related protein REDD1 in the PFC, and increasing levels of REDD1 in this anatomical region of adult $Ca_v1.2$ heterozygous mice is sufficient to reverse the antidepressant-like phenotype [152]. This is consistent with present findings of higher REDD1 levels in the PFC of depressed patients [190].

Downstream of REDD1, the protein FoxO3a has been identified to play a role in modulating the antidepressant-like effect observed in $Ca_v1.2$ heterozygous mice (Fig. 2; [152]). FoxO3a belongs to the FoxO family of transcription factors with SNPs within the FoxO3a gene linked to BD [191]. In rodents FoxO3a has been identified as a modulator of depression-related behavior [192]. FoxO3a knockout mice exhibit an antidepressant-like phenotype, and the antidepressant imipramine [193] and the mood stabilizer lithium [194] have been found to decrease levels of nuclear FoxO3a, suggesting that higher levels of nuclear FoxO3a may be associated with depressive behavior. In support of this, elevated levels of nuclear FoxO3a in the PFC of $Ca_v1.2$ heterozygous mice, following REDD1 overexpression, has been associated with dampening the antidepressant-like phenotype seen in these mice [152]. These findings provide the first evidence of a role of the REDD1/FoxO3a signaling pathway in the PFC in regulating depression-related behavior in $Ca_v1.2$ heterozygous mice (Figs. 1 and 2), and a new framework to study $Ca_v1.2$-associated depressive behavior.

Cognitive Function

Although not as broadly recognized as a symptom in neuropsychiatric disorders as changes in mood and emotion, cognitive impairments are a prominent feature of the *CACNA1C*-associated psychiatric disorders, as well as ASD [195]. In particular, deficits within different aspects of learning and memory have been observed in BD, SCZ, MDD, ASD, and, to a lesser extent, ADHD [195]. Using rodent models, there is evidence that loss of $Ca_v1.2$ influences discrete forms of learning and memory. In the hippocampal-dependent Morris water maze (MWM) spatial memory task, $Ca_v1.2$ conditional knockout mice display normal acquisition and consolidation of the platform location with similar performance to the controls during the short- and long-term (24 hour) probe tests [150,

196], whereas during the remote 30-day probe trial $Ca_v1.2$ knockout mice display a significant deficit [196]. Recently, it has been demonstrated that by increasing the difficulty of the MWM task by decreasing the number of available spatial cues, $Ca_v1.2$ conditional knockout mice exhibit a delay in the acquisition of the platform location and a significant deficit in the long-term memory probe test [197]. A similar hippocampal-dependent deficit has been observed in the fear-associated context discrimination task [197]. This supports previous data by Moosmang et al. [198] demonstrating that $Ca_v1.2$ channels in the hippocampus (using hippocampus-specific conditional knockout mice) are necessary for a hippocampal-dependent discriminatory water-maze task. This is supported by a role of $Ca_v1.2$ in hippocampal long-term potentiation [198], a cellular model of learning and memory [199], as well as a role in adult hippocampal neurogenesis [149, 197], a cellular mechanism linked to learning/memory processes ([200, 201]; discussed below).

Similar to $Ca_v1.2$-deficient mice, the $Ca_v1.2$ gain-of-function TS mice display no deficit in learning and memory in the MWM spatial memory task or the Y-maze task [168]. However, when the hidden escape platform is moved to a different location to test reversal learning in both tasks, mice display a significant delay in determining the new platform location [168]. Because of this mild persistence in continuing to seek the original location of the platform in the MWM and repeatedly attempting to enter the arm of the Y-maze with the original platform, despite the presence of a physical obstruction, the authors interpret these observations as evidence of repetitive, restrictive, and perseverative behavior [168], and possibly a sign of lack of cognitive flexibility, seen in disorders such as SCZ [202]. In contrast to these findings, loss of $Ca_v1.2$ in the glutamatergic neurons of the forebrain appears to negatively impact learning and memory in the Y-maze hidden-platform task [150], an observation that begs further exploration on the anatomical and cell-type specificity of loss of $Ca_v1.2$ signaling.

Separately from studies in rodents, it is clear that the LTCCs also play an important role in fear-associated memories, the most common behavioral paradigm utilized to study the biological basis of emotion [203–205]. This is not surprising given that altered emotional processing has been reported in patients with SCZ, BD, and ADHD [206]. In rodents, it has been observed that systemic inhibition of LTCCs with nifedipine had no impact on the acquisition or long-term expression of cue-associated fear memories [207]. However, focal delivery of verapamil in the basolateral amygdala, a brain region involved in fear, of adult rats immediately prior to fear conditioning blocked cue-associated long-term fear memory but not the short-term memory [208]. Similarly, focal delivery of the LTCC blockers verapamil or nifedipine into the basolateral amygdala of adult rats immediately before cue extinction training impaired the long-term memory of fear extinction [209]. This is consistent with a previous study that showed impaired cue extinction with systemic administration of the LTCC blockers nifedipine and nimodipine [207]. These studies suggest that differential LTCC-mediated mechanisms are being recruited for acquisition *versus* extinction of cue-associated fear memories.

Using genetic mutant mice, recent studies have focused on dissociating the differential contribution of the $Ca_v1.2$ and $Ca_v1.3$ isoforms in fear processes. In agreement with pharmacological studies, brain-specific $Ca_v1.2$ knockout mice have no deficit in the consolidation and recall of a cue-associated fear memory [210]. However, selective conditional knockout of $Ca_v1.2$ in glutamatergic neurons of the forebrain display enhanced freezing during the long-term cue-associated fear memory test [150]. This discrepancy is most likely a result of compensatory upregulation of Ca^{2+}-permeable glutamate α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) in the amygdala [210]. Interestingly in the $Ca_v1.2$ gain-of-function TS mouse, an increase in freezing during the long-term cue-associated fear memory test has been reported [168], suggesting that too much or too little $Ca_v1.2$ signaling can have similar behavioral phenotypes in certain tasks. Interestingly, in contextual fear conditioning, loss of $Ca_v1.2$ in genetic mutant mice [197, 211] did not impact freezing during the context-associated fear memory test. In contrast, the $Ca_v1.2$ gain-of-function TS mice exhibited enhanced freezing during the context-associated fear memory test [168], identifying that loss and gain of function can have differential effects of certain brain region-specific tasks. In addition to the conventional fear-conditioning paradigms, LTCC inhibitors have been shown to block latent inhibition of conditioned fear [212] and fear-potentiated startle [213], suggesting a role of these channels in other forms of emotional learning and plasticity.

The mechanism underlying altered fear memories described above are not known. Late-phase long-term potentiation (LTP) at thalamic inputs to the lateral amygdala, a mechanism that requires LTCCs [198, 208, 214, 215], has been associated with cue fear conditioning [216]. One molecule that mediates LTP in the thalamoamygdala pathway is brain-derived neurotrophic factor (BDNF) [217], a downstream target of LTCCs [149, 218]. Induction of BDNF in the amygdala is required for consolidation of fear memories [219]. Supporting these findings, administration of the LTCC inhibitor verapamil blocks the induction of BDNF after cue-associated fear conditioning [220]. The findings from this study suggest that this occurs as a result of lack of activation of CaMKIV [220], a CREB kinase and a downstream target of LTCCs [221], resulting in decreased binding of phosphorylated CREB at the promoter regions of BDNF [220]. This is consistent with previous studies that have identified LTCCs as critical regulators of BDNF expression both *in vitro* [222] and *in vivo* [149]. Currently, the specific LTCC isoform

mediating this fear conditioning-induced LTP in the thalamoamygdalar pathway is unknown.

$Ca_v1.2$ Channels, Adult Hippocampal Neurogenesis, and Neuropsychiatric-Related Phenotypes

Adult hippocampal neurogenesis that involves addition of newborn neurons (granule cells) to the dentate gyrus of the hippocampus throughout life has been implicated in the pathology underlying SCZ, based on rodent models of the disorder [223–230], BD based on genes associated with the disorder [137, 231], and depression [232, 233], autism [234–237], and ADHD, based on rodent disease models [229, 235, 238]. Rodent behavioral studies suggest a role of adult hippocampal neurogenesis in many of the phenotypes related to these disorders that are also observed in $Ca_v1.2$-deficient mice described above, including memory formation [200, 201], context discrimination [239], modulation of anxiety and depressive-like behavior [240], as well as mediating the effects of antidepressants. In support of this, 2 independent studies have identified a deficit in adult hippocampal neurogenesis in mice with loss of $Ca_v1.2$ restricted to glutamatergic neurons of the forebrain [149] and in neurons of the entire brain [197]. This is consistent with a previous *in vitro* study identifying a role of LTCCs in activity-dependent regulation of adult-derived neural precursor cells [241].

The deficit in adult hippocampal neurogenesis in $Ca_v1.2$ conditional knockout mice is specific to survival and not proliferation of neural precursor cells (NPCs) [149]. This finding is supported by an *in vitro* study that has identified a role of LTCCs during the later neurogenic stages of survival and maturation of NPCs derived from adult rat hippocampus [242]. As adult hippocampal neurogenesis is a highly regulated process and results from a balance of proliferation of NPCs and the survival of young newborn neurons into which NPCs differentiate [243], the discovery of $Ca_v1.2$ channels in supporting the survival of newborn neurons suggests that this stage of adult neurogenesis may be important for certain aspects of neuropsychiatric disease.

The precise mechanism of the deficit in survival of newborn neurons remains unknown. Given that $Ca_v1.2$ expression is restricted to mature young hippocampal neurons in adult mice [244], one potential mechanism is via the neurotrophic factor, BDNF. LTCCs mediate BDNF production in glutamatergic neurons of the hippocampus [149], release of which acts on both the secreting neuron and neighboring neurons [245]. LTCCs serve as a primary Ca^{2+} source for *Bdnf* transcriptional regulation, particularly at the promoter of *Bdnf* exon IV, a splice variant critically involved in experience-dependent neuronal plasticity [246–249]. Multiple LTCC-activated transcription regulators, including CREB, Ca^{2+} response factor, and MeCP2, which are also involved in regulating adult hippocampal neurogenesis [127, 237, 250, 251], control *Bdnf* expression by binding to *Bdnf* exon IV promoter in hippocampal neurons [222, 252–255]. Thus, it is plausible that lack of activation of these factors in the hippocampus results in lower BDNF and thus lowers survival of newborn neurons. This mechanism may also contribute to the LTP deficit observed in hippocampal-specific $Ca_v1.2$ knockout mice [198] as BDNF signaling and adult newborn neurons are required for hippocampal-dependent learning and memory processes [256]. Additionally, BDNF is a key player in regulating mood-related phenotypes [257]. Thus, collectively, it is plausible that the lower survival of adult born neurons as a result of $Ca_v1.2$/BDNF deficiency could contribute to the neuropsychiatric-related phenotypes observed in $Ca_v1.2$-deficient mice, a mechanism to be confirmed in future studies.

Another key question is whether restoring reduced survival of newborn neurons is sufficient to rescue phenotypes observed in $Ca_v1.2$-deficient mice. Using the neuroprotective aminopropyl carbazole P7C3-A20, a small molecule that blocks neuronal cell death [258–264] and thus increases cell survival of hippocampal newborn neurons [243, 265, 266], it has been found that this compound is capable of restoring hippocampal neurogenesis to normal levels in forebrain $Ca_v1.2$ conditional knockout mice [149]. This therapeutic effect occurred despite a lack in the normalization of BDNF levels. Given that BDNF-enhancing agents have not proved to be effective therapeutically to date, P7C3-A20 offers an alternative therapeutic mechanistic route to restore impaired adult neurogenesis in $Ca_v1.2$-deficient mice that circumvents lower BDNF signaling. If P7C3-A20 is able to rescue behavioral deficits, this work may provide new treatment opportunities for patients suffering from *CACNA1C*-associated neuropsychiatric symptoms. Additionally the identification of a previously unidentified role for $Ca_v1.2$ channels in neuronal cell survival may provide novel insight and approaches to treating neuropsychiatric disease, particularly in situations of decreased $Ca_v1.2$ or loss of $Ca_v1.2$ function.

$Ca_v1.2$, Excitatory/Inhibitory Imbalance and Neuropsychiatric Phenotypes

One emerging hypothesis for the pathophysiological mechanisms underlying the behavioral impairments in neuropsychiatric disorders is altered synaptic excitation (E) to inhibition (I) balance [151, 267], a cellular perturbation reported in multiple mouse models exhibiting anxiety-like behavior, altered social behavior, and impaired cognitive function [150, 177, 178, 267–269]. However, the impact of loss or gain of LTCC function on synaptic E/I balance and its impact on behavior remains largely unknown. *In vitro* pharmacological studies have provided evidence that LTCC-mediated mechanisms modulate synaptic plasticity in a homeostatic fashion

[270]. Cortical neurons treated for 24 hours with the LTCC blocker nifedipine have been shown to increase both frequency and amplitude of miniature excitatory postsynaptic currents [271]. Furthermore, in hippocampal neurons, 24-hour blockade of LTCCs with nifedipine has been found to decrease the expression of synaptic γ-aminobutryic acid A receptors [272], which mediate inhibitory neurotransmission, suggesting that LTCCs can modulate E/I balance. This is supported by an *in vivo* study, which found that loss of $Ca_v1.2$ in glutamatergic neurons of the forebrain results in higher frequency and amplitude of miniature excitatory postsynaptic currents in layer-5 neurons of the PFC, suggesting an increase in the overall E/I balance in this region [150], supporting other mouse models of neuropsychiatric disorders with higher E/I associated with neuropsychiatric-related behaviors.

These *in vivo* and *in vitro* studies suggest that chronic loss of LTCC signaling can have long-term consequences on synaptic scaling and, subsequently, function. The precise mechanism underlying this synaptic plasticity is not known. There are, however, 2 possible mechanisms that may be involved. First, impaired LTCC signaling may impact on nuclear transcriptional processes that can subsequently affect dendritic synaptic protein changes. This possibility is supported by an *in vitro* study that found that 24-hour inhibition of LTCCs results in increased (as opposed to the expected decrease) CREB-dependent transcription of the GluA1 subunit of the excitatory AMPARs [271]. Second, loss of LTCC signaling can negatively affect the mRNA translation machinery within spines and alter the composition of synaptic proteins [150]. These findings add to the growing literature that neuropsychiatric disorders are disorders of the synapse and that altered $Ca_v1.2$ signaling, even though shown not to impact spine and dendritic architecture [198, 210] as opposed to $Ca_v1.3$ channels [28, 273], can impact synaptic function via secondary homeostatic effects.

$Ca_v1.3$ Channels and Neuropsychiatric-Related Phenotypes

Anxiety-Like, Depressive-Like, and Social Behavior

Using rodent preclinical models, $Ca_v1.3$ channels, although less studied than $Ca_v1.2$ channels, also modulate neuropsychiatric-related endophenotypes. $Ca_v1.3$-deficient mice demonstrate an anxiolytic-like phenotype [274], although this effect may be attributed to the congenital deafness observed in these mice [275]. This is supported by recent findings in $Ca_v1.2DHP^{-/-}$ mice wherein treatment with the LTCC activator BayK8644, which selectively activates $Ca_v1.3$ channels, does not induce anxiety-like behavior [51]. In contrast to this, $Ca_v1.3$ regulates depressive-like behavior with $Ca_v1.3$ deficiency resulting in an antidepressant-like phenotype [274], whereas systemic activation of the $Ca_v1.3$ channels induces a depressive-like phenotype [159]. $Ca_v1.3$ channel activation with BayK8644 has also been found to induce a deficit in social behavior [51], in support of $Ca_v1.3$ gain-of-function mutations associated with ASD [7, 54]. The systemic effect of $Ca_v1.3$ channel activation on depression-related and social behaviors has been attributed to its role in the ventral tegmental area (VTA) [51], supporting the role of dopaminergic neurotransmission in both depressive and social behavior (discussed below).

Cognitive Function

Rodent studies have identified a role of $Ca_v1.3$ in certain forms of learning and memory. Although $Ca_v1.3$-deficient mice displayed no deficit in the MWM spatial memory task [276], these mice have significantly impaired object location memory in a discrimination test [244], suggesting that $Ca_v1.3$ channels may be recruited in specific spatial memory tasks. However, given the findings of Temme et al. [197] that $Ca_v1.2$ is recruited when the difficulty of the MWM is increased, it would be interesting to test $Ca_v1.3$-deficient mice in a similar task, particularly given the deficit in adult hippocampal neurogenesis observed in these mice ([244]; reviewed below). In the contextual fear-conditioning test, $Ca_v1.3$ channels are not required during acquisition or extinction of the conditioned memory [106, 276], but play an important role in the consolidation of the context-associated fear memory [276]. This has been attributed to reduced LTP in the basolateral amygdala [277].

Adult Hippocampal Neurogenesis

In contrast to the high expression of $Ca_v1.2$ LTCCs in the hippocampus, $Ca_v1.3$ channels are expressed at much lower levels [278]. Despite this, loss of $Ca_v1.3$ channels has a profound effect on adult hippocampal neurogenesis [244]. $Ca_v1.3$ knockout mice display a deficit in both proliferation of neural progenitor cells and survival of newborn hippocampal neurons [244], an effect not observed following deletion of $Ca_v1.2$ channels that only impacts survival [149]. These differential roles of $Ca_v1.2$ and $Ca_v1.3$ may be a consequence of the differential expression of $Ca_v1.2$ and $Ca_v1.3$ channels in the adult neurogenic regions [244]. While $Ca_v1.2$ is expressed exclusively in mature young hippocampal neurons, $Ca_v1.3$ is expressed in both newly formed immature NPCs, as well as mature young hippocampal neurons [244]. The contribution of reduced adult hippocampal neurogenesis to mood and learning/memory behaviors as a result of deficient $Ca_v1.3$ remains currently unknown, but it is plausible that it could contribute to the mood and memory deficits associated with dysregulated $Ca_v1.3$ Ca^{2+} signaling.

L-Type Ca^{2+} Channels and Drug Dependence

LTCCs have been demonstrated to play a role in mediating the effects of multiple drugs of abuse, including psychostimulants (cocaine, amphetamine), opioids (morphine), alcohol, and nicotine. To date, no genetic studies have been reported linking *CACNA1C* to drug dependence; however, *CACNA1C*-risk SNP carriers have altered reward processing [279], and a recent study has weakly linked *CACNA1C* to food addiction [280]. In contrast, recent work has identified a significant association between *CACNA1D* and cocaine dependence [51]. Below we review both LTCC pharmacological studies (summarized in Table 3) and LTCC isoform-specific contribution to drug dependence-specific phenotypes in rodent models.

Cocaine

In rodents, pharmacological studies have established an important role of LTCCs in various aspects of cocaine's effects. LTCC blockers, nimodipine, nifedipine, and diltiazem have been shown to attenuate the development and expression of cocaine behavioral sensitization [160, 283, 284], a model of drug-induced plasticity [320–322]. Using cocaine-conditioned place preference (CPP), a model used to study the rewarding effects of drugs [281], isradipine [282, 285] and nifedipine [51, 286, 287] diminish the rewarding effects of cocaine. Additionally, using cocaine self-administration, a model of the reinforcing effects of drugs [323], isradipine and nimodipine attenuate the reinforcing effects of cocaine [288].

LTCC blockers have also demonstrated efficacy in rodent models of relapse to cocaine-seeking behavior, one of the central clinical problems in treating cocaine addiction. In a self-administration model of relapse following extinction of cocaine-seeking behavior, diltiazem treatment in the nucleus accumbens (NAc) has been shown to block the effects of cocaine-primed seeking behavior [289]. Similarly, blocking LTCCs with isradipine in the VTA has also shown efficacy in attenuating cocaine-seeking behavior following exposure to drug-associated cues in drug-abstinent rats [324], another model of relapse. Of clinical significance, this study found that isradipine had no effect on sucrose-seeking behavior, suggesting that isradipine could be directly targeted in cocaine-dependent individuals without affecting their natural reward processing.

Studies addressing the specific role of the individual LTCC isoforms have identified a critical role of the $Ca_v1.3$ LTCCs in dopaminergic neurons of the VTA in the development of cocaine behavioral sensitization [325] and the acquisition of cocaine CPP [51]. Given that $Ca_v1.3$ channels are the primary L-type subunit in VTA dopamine neurons [15], the effects of isradipine in the VTA on attenuation of cocaine CPP [282] and cocaine-seeking behavior [324] are most likely due to its effects on $Ca_v1.3$ channels. However, VTA $Ca_v1.2$ channels may also play a role as they mediate acute responses [326] and VTA physiology [327]. In contrast, $Ca_v1.2$ channels play a role in mediating the long-term effects of cocaine via its effects in the NAc [160, 161].

Molecular studies find that $Ca_v1.3$ channels activate the CamKII/ERK pathway in the VTA and $Ca_v1.2$ channels in the NAc activate CamKII (Fig. 2), which increases GluA1 phosphorylation and elevates surface expression of GluA1 [161]. Recently, these findings have been extended to demonstrate that Ca^{2+}-permeable AMPARs (CP-AMPARs) in the NAc mediate the long-term effects of cocaine (Fig. 1) [51], and add to the growing body of evidence that long-lasting addiction-related behaviors are mediated by an increase in NAc CP-AMPAR neurotransmission [328].

Morphine

LTCCs have also been shown to play a role in the rewarding effects of morphine. The LTCC blockers nimodipine, nifedipine, and verapamil attenuate the development of morphine sensitization [290]. Similarly, isradipine and nifedipine attenuate the rewarding effects of morphine using CPP [286, 287, 291], and isradipine and nimodipine suppress the reinforcing effects of morphine using self-administration [288].

A major aspect of morphine and opioids, in general, is the manifestation of physical withdrawal symptoms [329]. This can be modeled in rodents by precipitating withdrawal symptoms with the use of the compound naloxone [330, 331]. Multiple studies have also shown that LTCC blockers when administered prior to (nifedipine, nimodipine, verapamil [292]), along with (diltiazem, nimodipine, nifedipine [293, 294, 298–300]) or after morphine treatment (verapamil, nimodipine, diltiazem, nicardipine [295–297]) can alleviate physical withdrawal symptoms, suggesting that LTCC blockers may be helpful in easing withdrawal symptoms following onset.

The molecular mechanisms by which LTCCs mediate the effects of morphine remain unknown. However, there is evidence of increased $Ca_v1.2$ and $Ca_v1.3$ protein levels in the frontal cortex and limbic forebrain regions of mice exposed to morphine [287, 332]. Separately, it has also been reported that chronic morphine treatment results in a decrease in $Ca_v1.3$ but not $Ca_v1.2$ protein levels in midbrain regions (pons, midbrain, and medulla [333]). Together, these findings suggest that morphine may regulate $Ca_v1.2$ and $Ca_v1.3$ in a brain region-specific manner.

Ethanol

Pharmacological studies provide evidence that LTCCs are important mediators of the effects of ethanol. Verapamil, isradipine, nifedipine, felodipine, nimodipine, nicardipine, nitrendipine, diltiazem, and verapamil reduce ethanol

Table 3 L-Type calcium-channel pharmacological studies and its contribution to drug dependence-specific phenotypes in rodent models

Drug	Behavioral paradigm	LTCC blocker	Behavioral outcome	Reference
Cocaine	Behavioral sensitization	Nimodipine	Suppressed development [157, 281] and expression [157, 282] of sensitization	[283]
		Nifedipine		[160]
		Diltiazem		[284]
	Conditioned place preference	Isradipine	Decreased conditioned place preference	[282, 285]
		Nifedipine and verapamil		[286]
		Nifedipine		[51, 287]
	Self-administration	Isradipine and nimodipine	Decreased self administration	[288]
	Self-administration: cocaine-primed reinstatement	Diltiazem	Decreased reinstatement of cocaine seeking following extinction	[289]
Morphine	Behavioral sensitization	Nimodipine, nifedipine, and verapamil	Suppressed development of sensitization	[290]
	Conditioned place preference	Nifedipine, verapamil	Decreased conditioned place preference	[286]
		Nifedipine		[287]
		Isradipine		[291]
	Self-administration	Isradipine and nimodipine	Decreased self-administration	[288]
	Naloxone-induced withdrawal	Nifedipine, nimodipine and verapamil (prior to morphine)	Attenuated the withdrawal effects	[292]
		Diltiazem (along with morphine)	Attenuated the withdrawal effects	[293, 294]
		Verapamil (after morphine but before naloxone)		[295]
		Verapamil, nimodipine (after morphine but before naloxone)		[296]
		Verapamil, nicardipine and diltiazem (after morphine but before naloxone)		[297]
	Withdrawal after chronic morphine	Nimodipine (along with morphine)	Attenuated some of the withdrawal effects	[298, 299]
		Nifedipine (along with morphine)		[300]
Ethanol	Consumption	Nifedipine	Decreased ethanol intake	[301]
		Verapamil		[302]
		Nifedipine, verapamil and isradipine		[303]
		Nifedipine, felodipine, nimodipine, isradipine, nicardipine, nitredipine and diltiazem		[304]
		Isradipine and nifedipine	No effect	[305]
		Nimodipine		[306]
	Locomotor activity	Nifedipine	Decreased locomotor activity induced by low dose of ethanol (2.5 g/kg) exposure	[301, 307, 308]
		Verapamil and diltiazem		
		Nifedipine and verapamil	No effect after chronic treatment of the blockers	[309]
	Self-administration	Verapamil	Prevented cue-primed reinstatement following 21 days of abstinence	[20]
	Withdrawal following chronic ethanol consumption	Nitrendipine	Reduced withdrawal symptoms	[310, 311]
	Withdrawal following chronic ethanol inhalation	Nitrendipine	Reduced withdrawal symptoms	[310, 311]
		Nimodipine, nitrendipine and isradipine	Reduced convulsive behavior during withdrawal	[310]
	Withdrawal following binge drinking	Nimodipine	Reduced withdrawal symptoms following binge drinking	[312]
	Chronic alcohol-induced seizures	Nifedipine	Reduced chronic alcohol-induced seizures	[313]
		Nifedipine and nimodipine		[314]
Nicotine	Locomotor activity	Nimodipine	Reduced acute nicotine induced locomotor activity	[315]
	Behavioral sensitization; Locomotor activity	Nimodipine, verapamil and diltiazem	Suppressed development and expression of behavioral sensitization	[316]
		Nifedipine		[16]

Table 3 (continued)

Drug	Behavioral paradigm	LTCC blocker	Behavioral outcome	Reference
			Suppressed expression of behavioral sensitization	
	Mecamylamine-induced withdrawal	Nimodipine, verapamil and diltiazem	Reduced withdrawal symptoms	[317]
	Withdrawal from acute nicotine	Nimodipine, verapamil and diltiazem	Attenuated withdrawal- induced anxiety	[315, 318]
	Withdrawal from chronic nicotine treatment	Nimodipine and verapamil	No effect on withdrawal-induced anxiety	[319]

consumption [301–304], and nifedipine, verapamil, and diltiazem decrease the heightened locomotor activity induced by low doses of ethanol [301, 307, 308]. In contrast, a study reported that nifedipine and verapamil had no impact on the ethanol-induced increase in locomotor activity [309], nor did isradipine, nifedipine or nimodipine on ethanol consumption [305, 306]. This discrepancy in findings may rely mainly on the different doses of LTCC blockers used. Verapamil has also been shown to block alcohol-seeking behavior in response to alcohol-associated cues following abstinence using self-administration [20], and mice deficient in $Ca_v1.2$ in forebrain glutamatergic neurons show a deficit in alcohol-seeking behavior [20]. These behavioral findings are consistent with the previous report showing that protracted abstinence from alcohol increases $Ca_v1.2$ but not $Ca_v1.3$ in the amygdala and hippocampus [20], 2 brain regions involved in mediating the effects of alcohol [334–336].

Separately, nitrendipine has been shown to reduce withdrawal symptoms when administered during chronic ethanol exposure [310, 311]. Excessive ethanol consumption in a short period of time (also referred to as "binge drinking") can be mimicked in rodents, with nimodipine reducing the withdrawal effects resulting from binge drinking [312]. Furthermore, nifedipine and nimodipine have been found to reduce seizures that occur during withdrawal from chronic alcohol [313, 314], a symptom suggested to be driven, in part, by increased LTCC currents [337]. Similarly, nimodipine, nitrendipine, and isradipine can also decrease the convulsive behavior associated with chronic ethanol withdrawal [338].

Nicotine

As with other drugs of abuse, the continuous use of nicotine results in dependency and adverse withdrawal symptoms while in abstinence [339]. Acute nicotine treatment in mice increases forebrain $Ca_v1.3$ mRNA levels 24 hours after exposure, while chronic nicotine treatment alters $Ca_v1.2$ mRNA levels [16]. Additionally, cortical neurons exposed to long-term nicotine, enhances $Ca_v1.2$ and $Ca_v1.3$ protein levels [340]. This was later confirmed by chronic nicotine treatment for 7 days in mice that led to an increase in $Ca_v1.2$ and $Ca_v1.3$ protein levels in the cortex [341]. Behaviorally, LTCC blockers have been shown to attenuate acute nicotine-induced locomotor activity (nimodipine [315]), as well as decrease the development (nimodipine, verapamil, diltiazem [316]) and expression (nimodipine, verapamil, diltiazem, nifedipine [16, 316]) of nicotine behavioral sensitization. Similarly, treatment with nimodipine, diltiazem, and verapamil reduced the rewarding effects of nicotine using CPP [316]. Moreover, nimodipine was capable of attenuating nicotine-induced drug seeking using the self-administration paradigm [318].

Nicotine dependent individuals undergo physical withdrawal that can be modeled in rodents using the compound mecamylamine [342]. Nimodipine, verapamil, and diltiazem have been shown to attenuate the mecamylamine-induced withdrawal symptoms [317]. Anxiety is one of the most common features observed in nicotine-dependent individuals when they abstain from smoking [343]. Nimodipine, verapamil, and diltiazem reduced the anxiogenic effects during withdrawal resulting from acute nicotine treatment [318]. However, one study found that nimodipine and verapamil administered during withdrawal from nicotine had no impact on the anxiogenic effect of chronic nicotine treatment [319]. These studies suggest that LTCCs can modulate nicotine-induced anxiety only if the blocker is administered before nicotine dependency.

Model of Comorbid Mood and Substance Use Disorders

Genetic factors significantly influence susceptibility to mood disorders and substance abuse that are often comorbid, particularly as seen for BD and cocaine dependence [344], conditions linked to *CACNA1D* [31, 49, 51]. Overlapping neural circuitry and convergent cellular and molecular mechanisms have been suggested to underlie such comorbidity [345–347]. As reviewed above, emerging data on the impact of *CACNA1D* mutations on $Ca_v1.3$ physiology [7, 54], together with animal studies, suggest that enhanced $Ca_v1.3$ activity (resulting from gain-of-function mutations or increased gene expression from noncoding variants) may contribute to co-

occurring mood and drug-dependence phenotypes. Recent rodent studies have found that common molecular mechanisms can regulate depressive-like behavior, deficits in social behavior, and cocaine-related behaviors [348–352]. In support of the human genetic findings, work from our laboratory has identified that repeated activation of $Ca_v1.3$ channels in the VTA in $Ca_v1.2DHP^{-/-}$ mice, with high $Ca_v1.3$ expression [15], is sufficient to induce depressive-like behavior, social deficits, and cocaine-related behaviors [51]. A potential mechanism could be via $Ca_v1.3$ channels increasing burst firing of VTA dopamine neurons [327], a neuronal property known to mediate depressive-like behavior [353–355], social behavior [356], and reward-related behavior [357].

The NAc is another key brain reward region that mediates the effects of all 3 behaviors, and molecular adaptations within this region drive long-term behavioral changes [347, 358, 359], a crucial problem in substance abuse disorders and possibly depressive behavior and social impairments, particularly following stressful insults. In fact, it has been shown that the NAc mediates the effects of $Ca_v1.3$ channel activation in the VTA [51]. This is not surprising as the VTA–NAc mesolimbic pathway has a central role in mediating the effects of depressive-like behavior [353, 354], social behavior [356], and cocaine [360], with glutamatergic signaling in the NAc driving many of these behaviors [328]. In support of this, depressive-like and cocaine behaviors resulting from VTA $Ca_v1.3$ activation are mediated by increased CP-AMPARs in the NAc shell, whereas social deficits are mediated by increased GluA1/GluA2 AMPARs in the NAc core [51], 2 subregions demonstrated to play distinct roles within the brain's reward pathway [361]. This is consistent with studies that have identified CP-AMPARs as a key synaptic mechanism underlying cocaine-behaviors [328] and heightened AMPAR activity in the NAc as a mediator of depressive [362–364] and social behaviors [365]. Together, these findings provide evidence of a useful, disease relevant model to study mechanisms of co-occurring mood- and cocaine-dependence-related behavioral phenotypes.

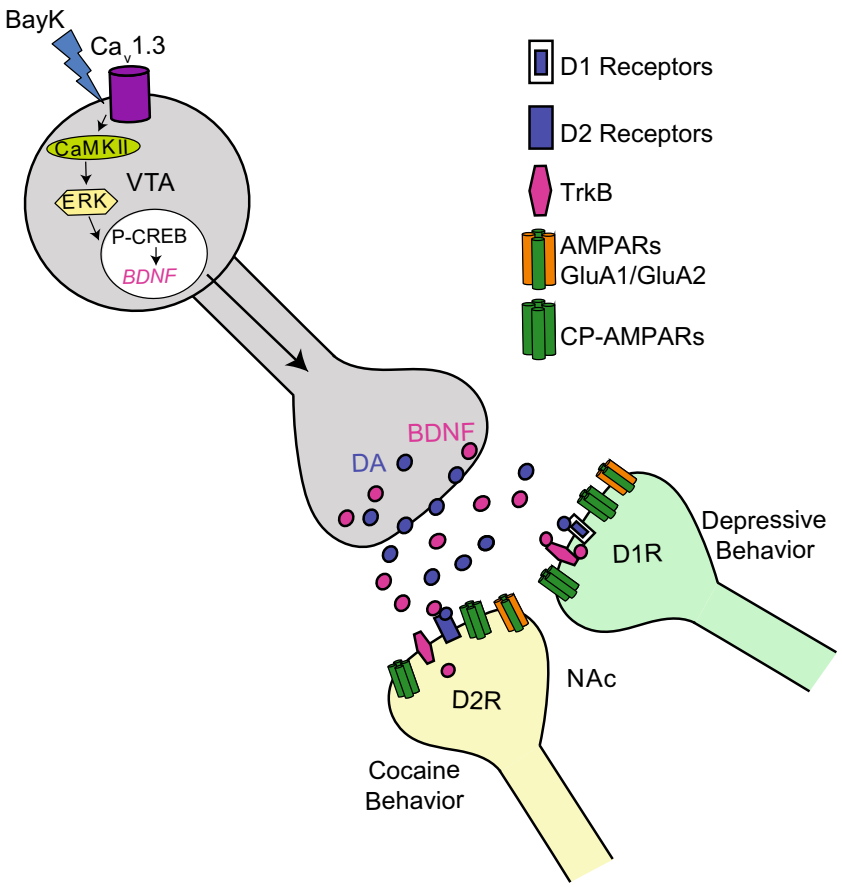

Fig. 3 Proposed mechanistic model for ventral tegmental area (VTA) $Ca_v1.3$ activation, which leads to depressive-like and cocaine-related behaviors. VTA $Ca_v1.3$ channel activation by BayK 8644 promotes CAM-dependent protein kinase (CaMK)II/extracellular regulated kinase (ERK)/ cAMP response element-binding protein (CREB) signaling, which results in the production of the neurotrophic factor, brain-derived neurotrophic factor (BDNF). Subsequently, BDNF gets transported from the VTA to the nucleus accumbens (NAc), which may mediate both depressive-like and cocaine behaviors, via increase in Ca^{2+}-permeable α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (CP-AMPARs). We propose that depressive like-behavior is mediated by a BDNF/tropomyosin receptor kinase B (TrkB) mechanism in NAc dopamine (DA) D1 receptor-expressing cells [350] and cocaine-related behaviors in NAc DA D2 receptor-expressing cells [351]

How VTA $Ca_v1.3$ channel activation can simultaneously promote depression- and cocaine-related behaviors remains an unanswered question. Given that $Ca_v1.3$ activation is expected to increase VTA dopamine burst firing [327] and thus increase dopamine release in the NAc that is expected to increase cocaine behaviors but decrease depressive symptoms, opposite of what is seen in patients and animal models, dopamine alone is not sufficient to explain the emergence of both behaviors. A potential candidate that could be mediating both these behaviors is BDNF. It has been found that BDNF via its receptor, tropomyosin receptor kinase B (TrkB) in the NAc mediates both depressive behavior [366] and cocaine behaviors [367]; however, it exerts its effects on the 2 behaviors in a cell-type-specific manner. The NAc is composed of 2 primary populations: the dopamine D1 receptor-containing and dopamine D2 receptor-containing cells [368, 369]. BDNF/TrkB in D1 receptor cells have been shown to mediate depressive behavior [366], whereas BDNF/TrkB in D2 receptor cells mediate cocaine behaviors [367]. As BDNF is a downstream target of LTCCs it is plausible that BDNF is generated following $Ca_v1.3$ activation in the VTA, most likely via activation of the CaMKII/ERK/CREB pathway [325] that is transported to the NAc (Fig. 3).

Conclusions

From these studies, it is clear that dysregulation of both brain-specific LTCC isoforms $Ca_v1.2$ and $Ca_v1.3$ can contribute to neuropsychiatric-associated endophenotypes and that LTCC blockers have the potential for alleviating some, if not all, psychiatric symptoms resulting from *CACNA1C* and *CACNA1D* dysfunction. Targeted anatomical approaches and molecular studies in preclinical animal models provide evidence that dysfunction of $Ca_v1.2$ and $Ca_v1.3$ channels alter distinct signaling cascades in separate anatomical structures that influence behavioral outcomes. This underscores the complexity of neuropsychiatric disorders and the cell-type- and brain-region-specific influence of *CACNA1C* and possibly *CACNA1D* risk SNPs on disease symptoms. Another factor to consider as studies continue to examine potential mechanisms of *CACNA1C*- and *CACNA1D*-associated disorders, as well as treatment options, is the impact of secondary effects as a result of persistent dysregulated Ca^{2+} in neurons on neuropsychiatric symptoms. We now know that dysregulated Ca^{2+}-mediated molecular and transcriptional gene networks [370], as well as the inability to maintain neuronal homeostasis [371], can disrupt normal development of neuronal circuits and lead to brain disease. Thus, by identifying biological pathways underlying specific symptoms and discovering novel substrates that are altered as a consequence of dysregulated $Ca_v1.2$ and $Ca_v1.3$ may provide better targets for therapeutics.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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