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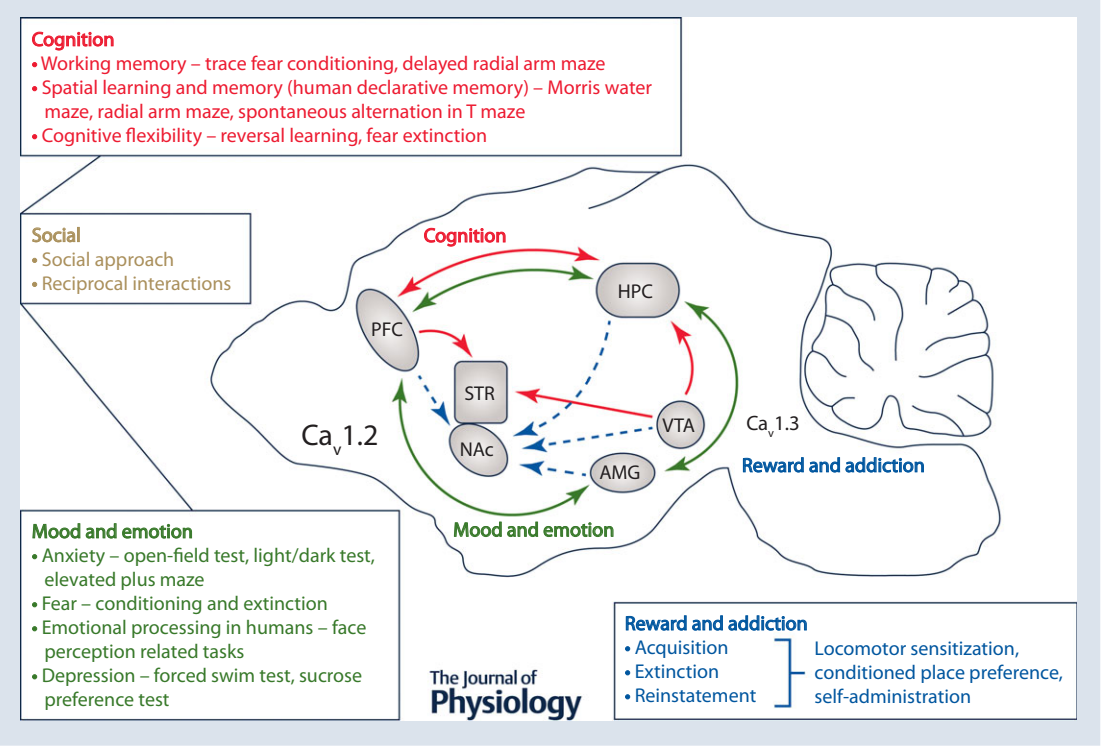
SYMPOSIUM REVIEW

# L-type $Ca^{2+}$ channels in mood, cognition and addiction: integrating human and rodent studies with a focus on behavioural endophenotypes

Z. D. Kabir[1,2,3], A. S. Lee[1,2,3] and A. M. Rajadhyaksha[1,2,3]

[1] *Division of Pediatric Neurology, Department of Pediatrics, Weill Cornell Medical College, New York, NY, USA*
[2] *Feil Family Brain and Mind Research Institute, Weill Cornell Medical College, New York, NY, USA*
[3] *Weill Cornell Autism Research Program, Weill Cornell Medical College, New York, NY, USA*




**Zeeba Kabir** is a postdoctoral fellow in the Rajadhyaksha Lab. Her interest is in the role of $Ca_v1.2$ and $Ca_v1.3$ L-type $Ca^{2+}$ channels in cognition and understanding the underlying anatomical and molecular processes. **Anni Lee** recently completed her PhD in the Rajadhyaksha Lab. Her work has contributed to describing the role of the neuronal $Ca_v1.2$ L-type $Ca^{2+}$ channel and its downstream molecules in anxiety, depression and addictive behaviours. **Anjali Rajadhyaksha** is a molecular neuroscientist with scientific interest in understanding the contribution of $Ca_v1.2$ and $Ca_v1.3$ L-type $Ca^{2+}$ channel mechanisms to behaviours related to neuropsychiatric disorders including addiction and mood disorders. The group's research methods include the use of genetically modified mouse models, stereotaxic techniques to generate site- and cell-type-specific knockouts coupled with biochemical studies and rodent behavioural tests that encompass a range of human neuropsychiatric-related phenotypes to better understand the molecular mechanisms underlying brain disorders in the context of behavioural deficits.

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**Abstract** Brain $Ca_v1.2$ and $Ca_v1.3$ L-type $Ca^{2+}$ channels play key physiological roles in various neuronal processes that contribute to brain function. Genetic studies have recently identified *CACNA1C* as a candidate risk gene for bipolar disorder (BD), schizophrenia (SCZ), major depressive disorder (MDD) and autism spectrum disorder (ASD), and *CACNA1D* for BD and ASD, suggesting a contribution of $Ca_v1.2$ and $Ca_v1.3$ $Ca^{2+}$ signalling to the pathophysiology of neuropsychiatric disorders. Once considered sole clinical entities, it is now clear that BD, SCZ, MDD and ASD share common phenotypic features, most likely due to overlapping neurocircuitry and common molecular mechanisms. A major future challenge lies in translating the human genetic findings to pathological mechanisms that are translatable back to the patient. One approach for tackling such a daunting scientific endeavour for complex behaviour-based neuropsychiatric disorders is to examine intermediate biological phenotypes in the context of endophenotypes within distinct behavioural domains. This will better allow us to integrate findings from genes to behaviour across species, and improve the chances of translating preclinical findings to clinical practice.

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**Corresponding author** A. M. Rajadhyaksha: 1300 York Avenue, Box 91, New York, NY 10065, USA. Email: amr2011@med.cornell.edu

**Abstract figure legend** Using rodent models to study behavioural endophenotypes with overlapping neurocircuitry in L-type $Ca^{2+}$ channel *cacna1c* ($Ca_v1.2$) and *cacna1d* ($Ca_v1.3$) associated neuropsychiatric disorders. AMG, amygdala; HPC, hippocampus; NAc, nucleus accumbens; PFC, prefrontal cortex; STR, striatum; VTA, ventral tegmental area.

**Abbreviations** ASD, autism spectrum disorder; BD, bipolar disorder; BDNF, brain derived neurotrophic factor; CPP, conditioned place preference; DHP, dihydropyridine; FST, forced swim test; GWAS, genome-wide association studies; LTCCs, L-type $Ca^{2+}$ channels; MDD, major depressive disorder; NAc, nucleus accumbens; PFC, prefrontal cortex; PTSD, post-traumatic stress disorder; SCZ, schizophrenia; SNP, single nucleotide polymorphism; SVF, semantic verbal fluency; VTA, ventral tegmental area.

## Introduction

Recent human genetic studies have raised tremendous interest and excitement for a role of brain voltage-gated $Ca_v1.2$ and $Ca_v1.3$ L-type $Ca^{2+}$ channels (LTCCs) in neuropsychiatric and neurodevelopmental disorders. Genome-wide association studies (GWAS) have linked multiple single nucleotide polymorphisms (SNPs) in the *CACNA1C* and *CACNA1D* genes to neuropsychiatric disorders (Bhat *et al.* 2012; Cross-Disorder Group *et al.* 2013; Heyes *et al.* 2015). Several *CACNA1C* SNPs, and in particular SNP rs1006737 (risk A allele), have been widely reproduced and strongly associated with bipolar disorder (BD) (Ferreira *et al.* 2008), major depressive disorder (MDD) (Green *et al.* 2010; Casamassima *et al.* 2010*b*), schizophrenia (SCZ) (Green *et al.* 2010; Nyegaard *et al.* 2010) and recently also autism spectrum disorder (ASD) (Li *et al.* 2015). *CACNA1D* SNPs have been linked to BD (Ament *et al.* 2015). Additionally, variants in coding regions of *CACNA1C* cause Timothy syndrome, a syndromic ASD (Splawski *et al.* 2004), and coding variants in *CACNA1D* have been associated with ASD (O'Roak *et al.* 2012; Pinggera *et al.* 2015). The contribution of *CACNA1C* and *CACNA1D* SNPs to the pathology of neuropsychiatric disorders is further underscored by their presence in biological pathways implicated in these disorders (Psychiatric GWAS Consortium *et al.* 2011; Network and Pathway Analysis Subgroup *et al.* 2015).

$Ca_v1.2$ and $Ca_v1.3$ channels are important mediators of $Ca^{2+}$ entry into excitable cells such as neurons. They are both expressed in neurons, with $Ca_v1.2$ expressed at higher levels compared to $Ca_v1.3$ in the forebrain (Hell *et al.* 1993) and $Ca_v1.3$ serving as the primary LTCC in the midbrain (Rajadhyaksha *et al.* 2004; Day *et al.* 2006). They shape neuronal firing and are present in signalling complexes (Calin-Jageman & Lee, 2008; Zamponi *et al.* 2015) primarily at the postsynaptic membrane (Di Biase *et al.* 2008; Jenkins *et al.* 2010), where they are poised for excitation–transcription coupling (Ma *et al.* 2012) by activation of $Ca^{2+}$ second messenger pathways (Simms & Zamponi, 2014) (Fig. 1). Because of these properties, LTCCs play an important role in neuronal plasticity related to neuronal development, learning and memory, drug addiction, and neuropsychiatric illness (Casamassima *et al.* 2010*a*; Bhat *et al.* 2012; Berger & Bartsch, 2014). Additionally, L-type activated signal transduction pathways crosstalk with dopamine and glutamate signalling pathways (Rajadhyaksha & Kosofsky, 2005), important mediators of neuronal processes underlying the neuropathology of multiple brain disorders. (For more in-depth information, readers are directed to Casamassima *et al.* 2010*a*; Bhat *et al.* 2012; Berger &

Bartsch, 2014; Simms & Zamponi, 2014; Striessnig *et al.* 2014; Zamponi *et al.* 2015).

Given the importance of $Ca_v1.2$ and $Ca_v1.3$ channels in brain function and the recent human genetic findings establishing *CACNA1C* and *CACNA1D* as risk genes for neuropsychiatric disorders, the time is prime to structure scientific studies to begin to identify the biological effects of human genetic variants that are reliable and eventually translatable back to the patient. This requires detailed analyses across multiple levels of complexity from gene to molecule to cell to circuit and behaviour. This is particularly important when studying neuropsychiatric disorders that clinically are behaviour-based disorders. Additionally, neuropsychiatric disorders (such as BD, SCZ and ASD), once considered unitary entities, share common behavioural phenotypic features most likely due to overlapping neurocircuitry (the primary focus of this review; Millan *et al.* 2012; Luthi & Luscher, 2014). Thus, the emphasis on utilizing behavioural domains (endophenotypes) as opposed to clinical diagnosis, as proposed in the Research Domain Criteria Framework (RDoC) by the National Institute of Mental Health (NIMH) (Insel, 2014), to explore the impact of *CACNA1C* and *CACNA1D* human polymorphisms on neuronal function and on neuronal circuits can be greatly helpful. We believe that such an approach will allow the integration of information from molecule to behaviour and increase the chance of translation of biological findings across species (human to mouse and back to human), towards better treatment outcomes in patients. Such an approach is already underway in multiple laboratories. The availability of new molecular and genetic technologies to study *cacna1c* and *cacna1d* in rodent models and the availability of samples derived from patients (such as patient brain tissue and patient-derived induced pluripotent cells) have already begun to shed light on the contribution of human *cacna1c* genetic variants on the pathophysiology of disease.

There have been several excellent recent reviews on $Ca_v1.2$ and $Ca_v1.3$ LTCCs in brain and brain disorders (Casamassima *et al.* 2010*a*; Bhat *et al.* 2012; Berger & Bartsch, 2014; Striessnig *et al.* 2014; Zamponi *et al.* 2015). In this review we aim to integrate recent human behavioural and neuroimaging data with information available from preclinical *cacna1c* and *cacna1d* rodent models to begin to gain insight on how dysfunction of $Ca_v1.2$ and $Ca_v1.3$ channels at the level of brain anatomy and circuitry can lead to behavioural phenotypes associated with neuropsychiatric disease. We hope that this will encourage electrophysiological, cellular and molecular studies in the context of neuropsychiatric-related behavioural deficits.

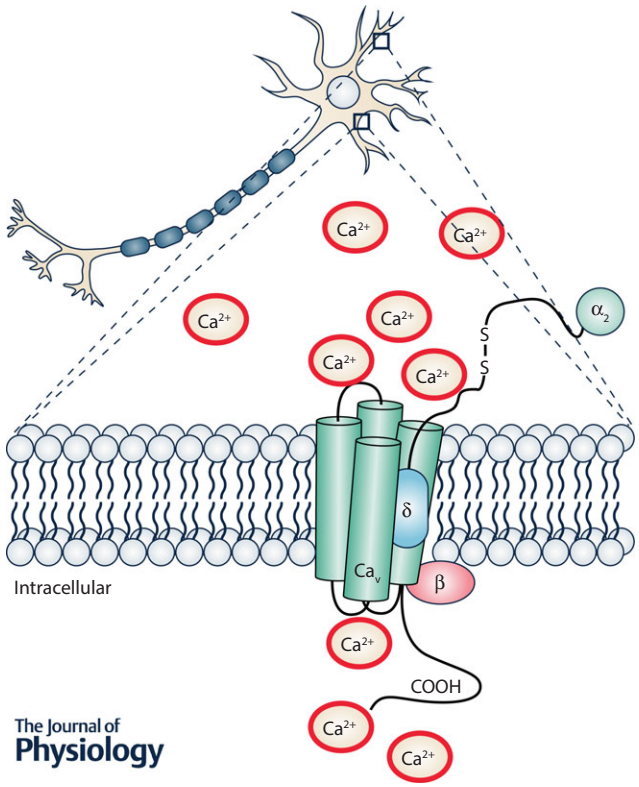


**Figure 1. Schematic diagram of the L-type $Ca^{2+}$ channels $Ca_v1.2$ and $Ca_v1.3$, and $\beta$ and $\alpha2\delta$ auxiliary subunits**

## Integrating human and mouse findings to understand pathological circuitry underlying intermediate phenotypes of psychiatric disorders

To date, the *CACNA1C* SNPs linked to neuropsychiatric disorders are present within non-coding regions (intronic, 5′ and 3′ untranslated regions) (Bhat *et al.* 2012) suggesting that they would affect *CACNA1C* gene expression. Consistent with this, both an increase (Bigos *et al.* 2010; Yoshimizu *et al.* 2015) and decrease (Gershon *et al.* 2014; Roussos *et al.* 2014; Yoshimizu *et al.* 2015) in *CACNA1C* mRNA have been reported in human samples (brain tissue and induced pluripotent stem cell (iPSC)-derived neurons), suggesting that gain or loss of $Ca_v1.2$ function can be detrimental. $Ca_v1.2$ gain of function mutation causes Timothy syndrome and *CACNA1D* single nucleotide variants identified in ASD (O'Roak *et al.* 2012) have recently been shown to be gain of function variants (Pinggera *et al.* 2015).

Brain imaging and clinical studies in the most replicated *CACNA1C* neuropsychiatric risk SNP rs1006737 has revealed altered brain structure and function in healthy carriers and patients (Bhat *et al.* 2012; Berger & Bartsch, 2014), underscoring the functional contribution of *CACNA1C* to the neuropathology underlying neuropsychiatric disorders.

Rodents (in particular mice) have proved to be useful in exploring human behavioural deficits, specifically for mapping circuitry that underlies behavioural phenotypes. Additionally humans and rodents share emotional behaviours and emotional circuitry that are conserved from mouse to human (Janak & Tye, 2015), thus allowing translation of human polymorphisms to mouse and back to the human. This has been elegantly demonstrated for a polymorphism in the *BDNF* gene (Glatt & Lee, 2015), a downstream molecular target of LTCCs (Tao *et al.* 1998; Tabuchi *et al.* 2000). At this time, studying *CACNA1C* non-coding variants in mouse models poses a challenge. However, studying loss of function (such as the use of knockout mice; Moosmang *et al.* 2005; Dao *et al.* 2010; Lee *et al.* 2012) or gain of function (such as the Timothy syndrome mouse model; Barrett & Tsien, 2008; Bader *et al.* 2011) can be informative.

To begin to gain a greater understanding of the $Ca_v1.2$ and $Ca_v1.3$ mediated neural mechanisms underlying the pathophysiology of psychiatric disorders, we attempt to integrate anatomical and circuit information that has been obtained from human neuroimaging and clinical studies with findings reported in *cacna1c* and *cacna1d* mouse models in the context of the major behavioural endophenotypes of neuropsychiatric disorders (mood and emotion, cognition, and social, in addition to addiction, a co-morbid endophenotype) associated with the *CACNA1C* and *CACNA1D* risk genetic variants.

## Mood and emotion

***CACNA1C.*** Changes in mood and emotion are core features that underlie psychiatric disorders. These can be manifested as anxiety and depression that are prominent components of the forms of neuropsychiatric disease in which *CACNA1C* has been implicated. Interestingly, healthy *CACNA1C* rs1006737 risk allele carriers had significantly higher scores for depression and anxiety on a self-report questionnaire (Erk *et al.* 2010, 2014*a*). These findings were replicated in a separate cohort of *CACNA1C* rs1006737 risk-allele healthy individuals who displayed increased trait anxiety and proneness to depression (Roussos *et al.* 2011).

Additionally, dysregulation of negative emotions, such as fear, also forms a core component underlying anxiety disorders (Dymond *et al.* 2014; Singewald *et al.* 2015). Human and rodent studies have revealed overlapping circuitry underlying fear, anxiety and depression. Fear-associative learning protocols have proven to be extremely useful to examine the neurocircuitry underlying anxiety disorders (Hijzen *et al.* 1995; Ohl *et al.* 2003; Singewald *et al.* 2015). In humans and rodents, fear conditioning is a form of emotional learning in which a naturally aversive stimulus (unconditioned) is paired either with a neutral context (contextual-associated) or tone (cue-associated) to elicit a fear response measured as freezing behaviour in rodents, or a physiological response in humans. Emotional responses to facial expressions (e.g. fearful faces, happy faces) are additionally used in humans to evaluate emotional processing (Ekman, 1992). In humans, a startle response is often used to measure negative emotional processing during visualization of unpleasant pictures (Lissek *et al.* 2007; Anokhin & Golosheykin, 2009; Fendt & Koch, 2013). In both humans and rodents, the inability to extinguish the conditioned context or cue fear response is additionally utilized to evaluate dysregulated fear (rodents) and emotional (humans) processing (VanElzakker *et al.* 2014) as observed in patients with SCZ and post-traumatic stress disorder (PTSD), an anxiety disorder.

Using fear-learning protocols, the amygdala, prefrontal cortex (PFC) and hippocampus have been established as the primary fear circuit in both humans and rodents (Phelps & LeDoux, 2005; Sehlmeyer *et al.* 2009). The amygdala is critical for the acquisition and expression of a conditioned fear response in rodents (LeDoux, 2003; Keifer *et al.* 2015) and humans (LaBar *et al.* 1995; Hamm & Weike, 2005). The PFC exerts a top-down regulation of the amygdala while the hippocampus, with its regional connectivity, can provide a modulatory effect on the amygdala either directly or via the PFC. The hippocampus functions to influence the context-dependent expression of fear (Knight *et al.* 2004; Sierra-Mercado *et al.* 2011; Sotres-Bayon *et al.* 2012), the extinction of cue-associated fear memories in rodents (Sierra-Mercado *et al.* 2011; Maren *et al.* 2013; Rosas-Vidal *et al.* 2014), and the extinction recall of contextual-associated fear memories in humans (Kalisch *et al.* 2006; Milad *et al.* 2007; Ahs *et al.* 2015). The use of optogenetic studies in rodents has also established the PFC, amygdala and hippocampus in regulating anxiety and depression (Covington *et al.* 2010; Tye *et al.* 2011; Warden *et al.* 2012; Ota *et al.* 2014; Bagot *et al.* 2015). In depressed patients, structural and functional alterations in these regions have been reported (Busatto, 2013).

Consistent with a role of the PFC–amygdala–hippocampus circuit in anxiety, depression and fear, neuroimaging studies in both healthy *CACNA1C* risk allele carriers (rs1006737 having been studied the most to date) and in patients, have identified structural and functional alterations within this circuit (Fig. 2). Structural neuroimaging studies have revealed that *CACNA1C* rs1006737 risk allele carriers have increased grey matter density in the PFC (Wang *et al.* 2011) and right amygdala (Perrier *et al.* 2011), and altered white matter microstructure in the right hippocampal formation (Dietsche *et al.* 2014). Functional imaging studies have found increased activation in the amygdala and ventral PFC of *CACNA1C* rs1006737 risk allele carriers during facial affect processing (Dima *et al.* 2013). Similar findings were

obtained in two other independent studies that observed increased activity in the left amygdala during a negative face matching task in both healthy individuals (Jogia *et al.* 2011; Tesli *et al.* 2013) and BD patients that carry the *CACNA1C* rs1006737 risk allele (Tesli *et al.* 2013). Additionally at the circuit level, Wang *et al.* (2011) reported decreased functional connectivity between the PFC and amygdala during a facial processing task (fearful and happy faces) in *CACNA1C* rs1006737 risk allele carriers (Wang *et al.* 2011). In BD patients that were carriers of the *CACNA1C* rs1006737 risk allele, Radua *et al.* (2012) reported decreased outflow of the medial frontal gyrus to the left putamen (part of the striatum) during perception of fearful faces, demonstrating hypo-connectivity between a prefrontal cortical region and a limbic structure during emotional processing (Radua *et al.* 2012).

Similarly in the hippocampus of *CACNA1C* risk allele carriers, Bigos *et al.* (2010) reported increased hippocampal activity in healthy individuals who were homozygote for the *CACNA1C* rs1006737 risk allele (AA), when measured during a facial processing task (Bigos *et al.* 2010). In a separate study Erk *et al.* (2010) showed a significant negative correlation between regional activation in the hippocampus and depression and anxiety scores (Erk *et al.* 2010) that was confirmed in a later study (Erk *et al.* 2014*a*). Data from these human neuroimaging studies provide clear evidence of structural and functional alterations in the PFC–amygdala–hippocampus circuit as a consequence of the *CACNA1C* risk allele. The dysregulation of this circuit has been suggested to be the underlying factor modulating the anxiety and depression intermediate phenotypes commonly observed in BD, SCZ and MDD (Erk *et al.* 2014*b*). With regard to the behavioural effects of the *CACNA1C* rs1006737 risk allele on emotional processing a study by Pasparakis *et al.* (2015) found reduced affective startle responses to pleasant pictures and exaggerated responses to negative pictures in healthy *CACNA1C* rs1006737 risk allele carriers (Pasparakis *et al.* 2015), further supporting the impact of the *CACNA1C* risk allele on the PFC–amygdala–hippocampus circuit.

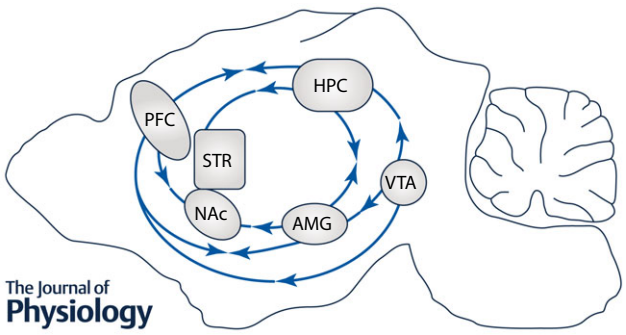


**Figure 2. Overlapping neurocircuitry of L-type $Ca^{2+}$ channels contributing to endophenotypes of psychiatric disorders**
Single arrow denotes unidirectional connectivity in the direction of the arrow and double arrow denotes bidirectional connectivity. PFC, prefrontal cortex; HPC, hippocampus; STR, striatum; NAc, nucleus accumbens; AMG, amygdala; VTA, ventral tegmental area.

In contrast to the human literature there have been few, but significantly important, animal studies that have begun to dissect the role of *cacna1c* ($Ca_v1.2$) in anxiety, depression and fear and their underlying neurocircuitry. To study anxiety in rodents, behavioural protocols that use approach–avoidance conflict to inhibit an ongoing behaviour that is characteristic for the animal have been utilized (Bailey & Crawley, 2009) and include the open-field test, light–dark test and the elevated plus maze test (Ohl *et al.* 2003). Using these tests, constitutive heterozygous *cacna1c* knockout female (Dao *et al.* 2010) and male mice (Bader *et al.* 2011; Lee *et al.* 2012) have been shown to exhibit increased anxiety-like behaviour. The anxiety phenotype was recapitulated in conditional *cacna1c*-deficient male mice that had *cacna1c* knocked out specifically in excitatory neurons of the forebrain (Lee *et al.* 2012). Additionally consistent with altered PFC function in *CACNA1C* risk allele carriers, focal deletion of *cacna1c* in the PFC of adult mice resulted in an anxiogenic phenotype (Lee *et al.* 2012). Interestingly, the knock-in $Ca_v1.2$ gain of function TS mouse displayed no alteration in anxiety (Bader *et al.* 2011). As human studies have revealed altered function of the amygdala and hippocampus in *CACNA1C* risk allele carriers, additional rodent studies using strategies such as focal deletion of $Ca_v1.2$ in these regions would be greatly helpful in elucidating the *cacna1c* neural circuitry underlying anxiety.

Studying depression in rodents is accomplished using behavioural protocols like the Porsolt forced swim test (FST) (Porsolt *et al.* 1977; Can *et al.* 2012), tail suspension test (Bergner *et al.* 2010) and the sucrose preference test (Katz, 1982; Strekalova *et al.* 2004) that target the core components of depressive-like behaviour such as despair (FST and tail suspension test) and anhedonia (sucrose preference test). So far, only one study has been published reporting an anti-depressive phenotype in constitutive *cacna1c* heterozygous mice using FST and the tail suspension test (Dao *et al.* 2010). We have replicated this finding using FST and the sucrose preference test (authors' unpublished observations) and ongoing studies in our laboratory are currently examining the anatomical and molecular mechanisms mediating the anti-depressive phenotype in constitutive *cacna1c* heterozygous mice.

As the behavioural paradigm and underlying neurocircuitry in fear-learning has been well established, several researchers have focused their attention on the role of $Ca_v1.2$ channels in fear processing. Interestingly, conditional knockout of *cacna1c* in the excitatory neurons of the forebrain had no effect on the conditioning

or extinction of a contextual-associated fear memory (McKinney *et al.* 2008). Langwieser *et al.* (2010) similarly found no deficit in the consolidation and recall of a cue-associated fear memory in brain specific *cacna1c* knockout mice and identified that the lack of this particular phenotype was a result of compensatory upregulation of $Ca^{2+}$ permeable glutamate AMPA receptors in the amygdala (Langwieser *et al.* 2010). Thus, compensatory adaptations in developmental knockout mouse models may override the influence of $Ca_v1.2$ LTCCs in fear conditioning protocols and may not be the most appropriate option to study the role of these channels in fear processing. This is highlighted from pharmacological studies where acute inhibition of LTCCs with an LTCC blocker (isradipine or verapamil) delivered either into the intracerebroventricular compartment (Langwieser *et al.* 2010) or directly into the lateral division of the amygdala (Bauer *et al.* 2002) of the adult animal was sufficient to induce a deficit in recall of a cue-associated fear memory. Similarly repeated inhibition of LTCCs with verapamil or nifedipine in the basolateral amygdala of the adult rat impaired cue fear extinction, demonstrating that LTCCs can mediate fear processing (Davis & Bauer, 2012). As pharmacological blockers to date do not differentiate between the two LTCC isoforms, $Ca_v1.2$ and $Ca_v1.3$, we encourage alternative strategies such as the use of focal brain knockout of $Ca_v1.2$ in the adult brain using viral vectors (Lee *et al.* 2012) to directly test the role of the $Ca_v1.2$ LTCCs in fear memory recall. This suggestion is underscored by the finding that knockout of $Ca_v1.2$ channels using viral vectors specifically in the anterior cingulate cortex, a brain region that has increased activity during the observation of others' fear (Olsson *et al.* 2007), impaired observational fear learning in mice (Jeon *et al.* 2010). This further suggests that the $Ca_v1.2$ isoform can be recruited during fear learning and highlights the importance of examining site-targeted deletion of these channels. Further support of the role of $Ca_v1.2$ in fear processing is provided from the knock-in Timothy syndrome mouse that displayed significantly increased contextual- and cue-associated fear memories that persisted up to 2 weeks postconditioning (Bader *et al.* 2011).

Contextual-associated fear memories are dependent not only on the amygdala but also on the hippocampus that is recruited to form a representation of the fear-associated context (Phillips & LeDoux, 1992). Since conditional *cacna1c* knockout mice display a deficit in recall of a hippocampal-dependent spatial memory 30 days after training (White *et al.* 2008), it begs the question on whether these mice have a similar deficit in long-term contextual-associated fear memories, an area of study that has not been as extensively explored but is highly relevant with regard to PTSD.

***CACNA1D.*** Mouse models of *cacna1d* have been utilized to study the role of the $Ca_v1.3$ LTCCs in anxiety (Lee *et al.* 2012), depressive-like behaviour (Sinnegger-Brauns *et al.* 2004) and fear processing (McKinney & Murphy, 2006). We have previously shown that focal knock-down of $Ca_v1.3$ in the PFC does not impact anxiety (Lee *et al.* 2012), ruling out the role of these channels in the PFC in mediating anxiety-like behaviour. When tested in FST, $Ca_v1.3$ knockout mice exhibit an antidepressive-like phenotype. Using $Ca_v1.2$ dihydropyridine (DHP)-insensitive mutant mice that have a point mutation in the DHP-binding pocket of the $Ca_v1.2$ subunit eliminating the sensitivity of the $Ca_v1.2$ channels to DHP blockers, when treated with the DHP LTCC activator BayK8644 resulted in a depressive-like behavioural phenotype (Sinnegger-Brauns *et al.* 2004), suggesting a role for $Ca_v1.3$ LTCCs in the modulation of depressive-like behaviour. In contextual fear conditioning, homozygous *cacna1d* knockout mice display impaired consolidation of fear memory but normal extinction (McKinney & Murphy, 2006). Given the recent finding of compensatory adaptation in *cacna1d* knockout mice (Poetschke *et al.* 2015), the $Ca_v1.2$ DHP insensitive mutant mouse line is an excellent mouse model to further explore the role of $Ca_v1.3$ channels in fear processing, in addition to the use of viral vectors expressing $Ca_v1.3$ short hairpin (sh)RNA (Schierberl *et al.* 2011*a*; Lee *et al.* 2012).

## Cognition

Although alterations in mood and emotion form the main components in neuropsychiatric disorders, deficits in cognition are commonly observed and can be equally debilitating to the lifestyle of an individual (Millan *et al.* 2012). Several human studies have shown an association between the *CACNA1C* rs1006737 risk variant and cognitive function. In healthy individuals there are conflicting results over the influence of this gene on cognitive function. Some studies report lower verbal fluency performance (Krug *et al.* 2010), deficits in attention (Thimm *et al.* 2011), impaired working memory (Zhang *et al.* 2012) and poorer learning performance (Dietsche *et al.* 2014). In contrast, others have reported no significant association between the rs1006737 risk allele in the *CACNA1C* gene and verbal learning and memory, verbal intelligence (Erk *et al.* 2010, 2014*a*; Roussos *et al.* 2011), recognition memory (Dietsche *et al.* 2014), working memory (Paulus *et al.* 2014) and overall cognitive function (Hori *et al.* 2012; Soeiro-de-Souza *et al.* 2013). However, in BD and SCZ patients, all studies to date have reported a negative effect of the *CACNA1C* rs1006737 risk allele on executive function (Arts *et al.* 2013; Soeiro-de-Souza *et al.* 2013) and working memory (Zhang *et al.* 2012).

Abnormal neural activity in cortical anatomical regions and concurrent dysregulation in their connectivity to other brain regions have been suggested to be responsible for deficits in cognitive function (Millan *et al.* 2012) (Fig. 2). From animal studies, it has been shown that the PFC is the central anatomical structure mediating high-order cognitive function by exerting a top-down executive control on subcortical structures including the hippocampus, striatum, thalamus and amygdala (Miller, 2000; Riga *et al.* 2014). Depending on the subcortical structure innervated, the impact of the PFC on distinct cognitive domains varies.

Several functional imaging studies in *CACNA1C* rs1006737 risk allele carriers have identified alterations in brain activation during multiple cognitive behavioural tasks. During an n-back working memory task, healthy *CACNA1C* risk AA homozygote individuals displayed significantly increased activity in the PFC, which they suggested indicated an inefficiency of the PFC (Bigos *et al.* 2010). In contrast to these findings two separate studies showed that healthy carriers of the *CACNA1C* rs1006737 risk allele had significantly reduced activation in the dorsolateral PFC during an associative episodic memory task (Erk *et al.* 2014*a*) and the n-back working memory task (Paulus *et al.* 2014) with altered connectivity between the dorsolateral PFC and hippocampus (Paulus *et al.* 2014). In the hippocampus, three independent studies have reported significantly lower activation of the hippocampus in healthy carriers of the *CACNA1C* rs1006737 risk allele during an episodic memory recall test (Erk *et al.* 2010, 2014*a*,*b*; Krug *et al.* 2014) with diminished functional coupling between the left and right hippocampal regions (Erk *et al.* 2010). Concurrent with this the authors reported decreased activation in the subgenual part of the perigenual anterior cingulate, a brain region that is implicated in mood regulation as well as memory processing (Erk *et al.* 2014*a*,*b*). Consistent with lower verbal fluency in *CACNA1C* rs1006737 risk allele carriers (Krug *et al.* 2010), a test used to measure executive control (Shao *et al.* 2014), the same study reported increased activation in the left inferior frontal gyrus and left precuneus during a semantic verbal fluency (SVF) task in risk carriers (Krug *et al.* 2010), while in depressed patients with the *CACNA1C* rs1006737 risk allele there was increased SVF task-related activation in the left middle/inferior frontal gyrus and enhanced functional coupling between the left middle/inferior and right superior/middle frontal gyri (Backes *et al.* 2014).

In the last several decades, distinct behavioural tasks have been developed in animal models to study the underlying neurocircuit and molecular pathways mediating different domains within cognition. To relate these animal models to the deficits in executive function observed in human neuropsychiatric patients, researchers have designed behavioural protocols to mimic the behaviours often used in human studies. Using behavioural tasks in which stimuli are separated in time such as trace fear conditioning (Gilmartin *et al.* 2013) and the delayed radial arm maze (Floresco *et al.* 1999), working memory has been shown to be mediated by the prefrontal modulation of the striatum and thalamus (Floresco *et al.* 1999; Gilmartin *et al.* 2013). With regard to spatial learning and memory, which has been considered to be equivalent to human declarative abilities (Morellini, 2013), a form of memory that is often disrupted in SCZ (Cirillo & Seidman, 2003), BD (van Gorp *et al.* 1999) and MDD (Austin *et al.* 2001), animal behavioural tasks like the Morris water maze, the radial arm maze and spontaneous alternation in the T maze have been utilized to demonstrate the involvement of the PFC, hippocampus and dorsal striatum (Morellini, 2013; Pooters *et al.* 2015). Another domain within cognition that has often been reported in neuropsychiatric disorders is cognitive flexibility, defined as the ability to flexibly alternate one's behaviour in response to changing environmental contingencies. In humans, this has been measured using the Wisconsin card-sorting task (Miyake *et al.* 2000) and the Stroop test (Jensen & Rohwer, 1966) while in animal models this has been tested through reversal learning in a Y maze (Trinh *et al.* 2012) or operant task (Brady & Floresco, 2015), as well as through extinction of a conditioned fear (Trinh *et al.* 2012).

While there is significant, though limited, evidence of the negative relationship between the *CACNA1C* risk allele and cognition in humans, not much has been done in identifying the neuroanatomical basis of these deficits. To date, only one study has identified a deficit in long-term (30 day) recall of a spatial memory in mice that had a conditional knockout of *cacna1c* in the excitatory neurons of the forebrain (White *et al.* 2008), suggesting a role of these channels in cognition. Similar evidence of a role of these channels in cognition has been obtained through studies done in the knock-in Timothy syndrome mouse (Bader *et al.* 2011) that displayed normal learning and memory but significant deficits in reversal learning (Bader *et al.* 2011). Additional studies need to further explore *cacna1c* animal models to understand the role of $Ca_v1.2$ channels in cognitive deficits.

We believe that it is of high priority to explore $Ca_v1.2$ as a potential target for treating cognitive impairments in neuropsychiatric patients particularly since the current drugs used to treat the mood-related symptoms in psychiatric disorders fail to alleviate the cognitive deficits (Millan, 2006; Hill *et al.* 2010). Unpublished data from our lab suggest a role for $Ca_v1.2$ channels in mediating different aspects of cognition that is interactive with distinct neurotransmitter systems.

## Social behaviour

Deficits in social behaviour and communication are observed in a range of neuropsychiatric disorders, including SCZ and depression, and represents a core feature observed in ASD (Kennedy & Adolphs, 2012; APA, 2013). In humans, social interaction is complex and heavily dependent on appropriate cognitive and emotional function. Interestingly, in healthy individuals the *CACNA1C* rs1006737 risk allele was significantly associated with low extraversion, a personality trait that is characterized by reduced social activities and interactions (Roussos *et al.* 2011).

As with all the other endophenotypes discussed above social behaviour is mediated by a network of brain regions that function in an interdependent manner (Fig. 2). These include the fusiform gyrus that mediates face perception, the amygdala and anterior cingulate cortex that are involved in processing facial expressions of fear, and the PFC that is required for interpreting others' intentions and motives (Grady & Keightley, 2002). In *CACNA1C* rs1006737 risk allele carriers, there is increased activation of the fusiform gyrus during a facial affect-processing task (Dima *et al.* 2013), suggesting dysregulation within the circuitry that is recruited for facial processing in social interaction.

Rodents, being innately social creatures, have been used to study social behaviour. Through lesion and optogenetic studies, certain key anatomical regions mediating social behaviour in rodents have been delineated and includes the hippocampus (Felix-Ortiz & Tye, 2014; Hitti & Siegelbaum, 2014; Stevenson & Caldwell, 2014), amygdala (Martel *et al.* 2008; Katayama *et al.* 2009), PFC (Jodo *et al.* 2010; Yizhar *et al.* 2011; Felix-Ortiz *et al.* 2015), nucleus accumbens (NAc) and ventral tegmental area (VTA) (Gunaydin *et al.* 2014). In rodents, social behaviour is most commonly studied using the social approach test in a 3-chamber apparatus in which the time that the test mouse spends interacting with a stranger mouse *versus* an inanimate object is measured. Reciprocal interactions between pairs of mice are also studied in which a variety of parameters, including nose-to-nose interactions, anogenital sniffing, allogrooming and play, are measured (Silverman *et al.* 2010).

Although the *CACNA1C* gene has been implicated in ASD and SCZ, both of which show significant impairments in social behaviour, no study to date has tested social behaviour in *cacna1c* deficient mice. However, the knock-in Timothy syndrome mouse displays a severe deficit in social behaviour (Bader *et al.* 2011), demonstrating that $Ca_v1.2$ channels can regulate social behaviour. The lack of studies points to a need for additional work to further explore the role of *cacna1c* in social behaviour. Similarly, because of the recent finding of the association between the *CACNA1D* gene and ASD (O'Roak *et al.* 2012; Pinggera *et al.* 2015), preclinical studies need to be pursued using *cacna1d* mouse models to identify the impact of this gene on social behaviour.

## Reward and addictive behaviour

Altered reward processing and reward brain circuitry is often associated with multiple psychiatric disorders (Pechtel *et al.* 2013; Whitton *et al.* 2015). Importantly, substance abuse disorders are often co-morbid with neuropsychiatric disorders (Post & Kalivas, 2013; Luthi & Luscher, 2014; Lai *et al.* 2015). Cocaine use in particular has been associated with higher incidence of mood and anxiety disorders (Falck *et al.* 2004; Post & Kalivas, 2013; Luthi & Luscher, 2014). In a study conducted by Herrero *et al.* (2008), over 40% of young cocaine users recruited in non-clinical settings presented psychiatric co-morbidity, with 27% diagnosed with mood disorders and 13% diagnosed with anxiety disorders (Herrero *et al.* 2008). Furthermore, the severity of anxiety disorders such as PTSD, MDD and BD may be increased when co-morbid with substance use disorder (Kessler *et al.* 2005). Conversely, patients with psychiatric disorders may have an increased vulnerability to abuse drugs. Patients with anxiety disorders, BD and SCZ have an increased likelihood of cocaine and stimulant use (Volkow, 2009; Post & Kalivas, 2013; Tang *et al.* 2014).

Overlapping neurocircuitry and common genetic risk factors have been suggested to underlie the high co-morbidity in mood and drug abuse disorders (Nestler & Carlezon, 2006; Luthi & Luscher, 2014). Many studies reveal convergence of neuronal circuits (Fig. 2) and molecular mechanisms involved in mood disorders and reward systems (Peters & Buchel, 2009; Russo & Nestler, 2013; Luthi & Luscher, 2014). The NAc is the key nucleus that modulates reward and motivation for drug seeking (Kelley, 2004; Kalivas & Volkow, 2005), by integrating information from other brain regions within the mesolimbic reward circuitry that include, but are not limited to, dopaminergic inputs from the VTA and glutamatergic inputs from the basolateral amygdala, medial PFC and hippocampus (Koob & Volkow, 2010), identical brain regions also recruited for the intermediate phenotypes discussed above. The VTA additionally projects to the medial PFC, hippocampus and basolateral amygdala (Fig. 2).

In rodents, three commonly used behavioural protocols to assess the addictive potential of drugs of abuse are behavioural sensitization, conditioned place preference (CPP) and self-administration. Behavioural sensitization is a model of drug-induced long-term synaptic and behavioural plasticity (Robinson & Berridge, 1993; Pierce & Kalivas, 1997; Vanderschuren & Pierce, 2010). Interestingly, increased behavioural drug responsivity also occurs as a result of repeated stress and repeated

occurrence of episodes of BD (Post & Kalivas, 2013). CPP is a simple, non-invasive procedure wherein animals are trained to associate a specific environment with the rewarding effects of a drug (Bardo & Bevins, 2000). Subsequently when animals are allowed to freely explore the drug-paired and non-drug-paired environment, they prefer the drug-paired environment, indicating drug–reward associations. The conditioned response is thought to be relevant to human drug-seeking behaviour and to drug- and cue-induced relapse (Stewart, 2008). The operant reinstatement model of cocaine seeking using the self-administration procedure wherein animals volitionally respond for delivery of a drug such as cocaine, possesses greatest face validity as a model of addiction, as it most closely resembles human self-administered drug taking behaviour (Panlilio & Goldberg, 2007).

Using the above behavioural protocols, pharmacological studies have established an important role of LTCCs in addictive behaviour (reviewed in Bhat *et al.* 2012; Berger & Bartsch, 2014). Below we specifically highlight what has been found for *CACNA1C* and *CACNA1D* in human and mouse.

***CACNA1C.*** To the best of our knowledge, to date human *CACNA1C* genetic studies in a drug-dependent population have not been reported. However, as outlined above, several of the brain regions that comprise the brain's reward pathway have altered function in *CACNA1C* rs1006737 risk allele carriers as revealed by neuroimaging. Two studies have examined reward response in *CACNA1C* rs1006737 risk allele carriers. Lancaster *et al.* (2014) found that *CACNA1C* risk allele carriers had a blunted behavioural response in a reward-based task compared to non-carriers (Lancaster *et al.* 2014). Wessa *et al.* (2010) tested reward reversal learning and reported increased amygdala activity in *CACNA1C* rs1006737 risk allele carriers in response to delivery of reward (Wessa *et al.* 2010). Using conditional *cacna1c* knockout mice in the behavioural sensitization protocol, we have found that $Ca_v1.2$ channels in the NAc mediate the long-term expression of the sensitized response (Schierberl *et al.* 2011*a*). Using the CPP protocol we find that constitutive heterozygous *cacna1c* mice have a potentiated cocaine reward response (Schierberl *et al.* 2011*b*). Ongoing studies are currently examining the neural circuitry and molecular mechanisms that underlie the enhanced reward response in constitutive heterozygous *cacna1c* mice.

***CACNA1D.*** A new study from our group has identified *CACNA1D* SNPs in cocaine dependent individuals. Examination of 947 *CACNA1D* SNPs has identified three significant SNPs associated with cocaine dependence (Martinez-Rivera *et al.* 2015). To date, this is the only human genetic study that has been reported in a cocaine-dependent population.

Using *cacna1d* knockout mice and $Ca_v1.2$ DHP-insensitive mutant mice (Sinnegger-Brauns *et al.* 2004), we have demonstrated a role for $Ca_v1.3$ channels in the VTA in the development of behavioural sensitization (Schierberl *et al.* 2011*a*), in mediating dopamine D2 receptor-induced molecular changes in the striatum (Schierberl *et al.* 2012) and in the acquisition of cocaine CPP (Martinez-Rivera *et al.* 2015). A new study supporting our data finds that the LTCC blocker isradipine, injected directly into the rat VTA, blocks acquisition of cocaine CPP (potentially via $Ca_v1.3$ channels as $Ca_v1.3$ is the predominant subunit expressed in VTA neurons; Rajadhyaksha *et al.* 2004). They further extend these findings to demonstrate that isradipine can enhance extinction of cocaine CPP and block cocaine-induced reinstatement (Degoulet *et al.* 2016), a model of relapse to drug taking behaviour. Similarly, the LTCC blockers nifedipine and isradipine, infused into the VTA, attenuate cue-induced cocaine seeking in the rat cocaine self-administration model (Nunes *et al.* 2015). Based on our human genetic findings and a role for *cacna1d* in addictive behaviour in rodents, additional studies to explore *CACNA1D* in mood disorders is warranted.

## Conclusion

Several recent human genetic studies have identified L-type $Ca^{2+}$ channel genes *CACNA1C* and *CACNA1D* as candidate risk genes in neuropsychiatric and neurodevelopmental disorders. Human neuroimaging studies, along with cellular and mouse studies, have established an important role for $Ca_v1.2$ and $Ca_v1.3$ channels, encoded by *cacna1c* and *cacna1d*, respectively, in intermediate phenotypes relevant to neuropsychiatric disorders. In this review we have integrated human behavioural and neuroimaging data with neuropsychiatric-related behavioural domains and endophenotypes, to allow a platform to pose experimental questions towards gaining a better understanding of neural mechanisms that underlie neuropsychiatric disorders in which *CACNA1C* and *CACNA1D* have been implicated. Within this framework, the time is ideal to exploit the newly developed genetic, cellular and molecular tools for neuroscience research to move forward in our understanding of the impact of the newly discovered *CACNA1C* and *CACNA1D* human polymorphisms on the brain and behaviour.

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## Additional information

### Competing interests

None declared.

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