Neuropsychiatric disease is the globally leading cause of non-fatal disease burden [1, 2], and approximately 46% of Americans will meet the American Psychiatric Association’s criteria for a mental disorder at some point in their lives [3]. The poorly understood pathophysiology of psychiatric disorders makes them difficult to diagnose and has broadly precluded development of mechanism-based treatments [5]. In recent genetic studies, the gene *CACNA1C* has consistently emerged as a risk factor for neuropsychiatric disease, including bipolar disorder [6-13], schizophrenia [7, 14-17], and major depressive disorder [18, 19]. Most notably, the largest genome-wide association study to date identified *CACNA1C* as one of only two collective risk genes among patients with bipolar disorder, schizophrenia, autism spectrum disorders, major depressive disorder, and attention-deficit/hyperactivity disorder [15, 20]. Nearly a decade after first being implicated in psychiatric disorders, the role of *CACNA1C* in psychopathology remains unclear.

*CACNA1C* encodes Cav1.2, which comprises 85% of voltage-gated L-type calcium channel (LTCC) alpha subunits in the mammalian brain and confers much of the whole channel’s functional properties, including drug sensitivity, selectivity, and composition of both the pore-forming unit and voltage-sensing domain [21-23]. Cav1.2 has a well-established role in coupling postsynaptic membrane depolarization with expression of genes involved in long term potentiation and concomitant memory formation [24-30]. Previously, our research group assessed the consequences of forebrain-specific elimination of *Cacna1c* on mouse postnatal hippocampal neurogenesis. Using this model, we identified a two-fold increase in young hippocampal neuron death, providing evidence for Cav1.2 as a key regulator of neuronal survival in postnatal hippocampal neurogenesis (Figure 1) [4].

Figure : Forebrain-specific knockout of Cav1.2 reduces the survival of newborn neurons.

Mice were given a single injection of bromodeoxyuridine (BrdU) and sacrificed 30 days later. Brains were serially sectioned and the number of BrdU-positive (BrdU+) neurons were quantified between genotypes. \*\*p<0.01 [4]

Cell death is a prominent feature of many forms of neuropsychiatric illness [31] and can result from an array of mechanisms, including necrosis, autophagy, and apoptosis [32]. Importantly, loss of mitochondrial calcium homeostasis predisposes neurons to activation of cell death programs, placing mitochondria as pivotal regulators in neuronal life and death [33-39]. Energy-demanding tissues in the nervous system require tightly regulated mitochondrial calcium (Ca2+)for efficient production of adenosine triphosphate (ATP) [35, 40, 41].

Cav1.2 activity itself increases mitochondrial metabolism and reactive oxygen species (ROS) levels, likely due to allosteric activation of Ca2+-sensitive tri-carboxylic acid (TCA) cycle dehydrogenases and ATP synthase [42]. Persistently elevated Ca2+ levels push ROS production beyond tolerable signaling levels and lower the threshold for opening of the mitochondria permeability transition pore (PTP), priming mitochondria cytochrome C release and apoptosis [33-36]. In renal tubular cells, blockade of LTCCs reduces both mitochondrial Ca2+ accumulation and mitochondria-mediated apoptosis [43-46]. In addition, patients with bipolar disorder, schizophrenia, and major depression show deficits in neuronal oxidative phosphorylation [47, 48]. The links between Cav1.2 and mitochondria in calcium flux and cell death raise the possibility that altered Cav1.2 signaling in psychiatric disorders could disrupt intracellular calcium (Ca2+) handling in mitochondria and prime neurons for apoptosis.

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