Published in final edited form as:

Eur J Paediatr Neurol. 2020 January ; 24: 81–88. doi:10.1016/j.ejpn.2019.12.015.

Interneuron deficits in neurodevelopmental disorders: Implications for disease pathology and interneuron-based therapies

Rosalia Paterno¹, Mariana Casalia¹, Scott C. Baraban^{1,2}

¹Epilepsy Research Laboratory and Weill Institute for Neurosciences, Department of Neurological Surgery, University of California, San Francisco, San Francisco, CA, USA.

²Helen Wills Neuroscience Institute, University of California, Berkeley, Berkeley, CA, USA

Introduction

Excitatory and inhibitory (E/I) balance is a fundamental component of brain network dynamics. Indeed, reduced or enhanced inhibitory GABAergic neurotransmission is associated with epileptiform activity or cognitive impairment, respectively (Kaleueff & Nutt, 1997; Treiman, 2001). In the last decade, GABA-expressing interneurons (INs), a primary player in maintaining E/I balance, have been the focus of intense research. Although INs only represent 20–30% of the overall neuronal population and are extremely heterogeneous (Kelsom & Lu, 2013), they can form synapses with hundreds of neurons (Sik, et al., 1995) giving them the capability to synchronize many neurons and act as pacemakers of oscillatory activity.

Given their structure and function, it is not surprising that interneuron dysfunction contributes to neurological disease states. Indeed, several neurological disorders are now classified as “interneuronopathies” including schizophrenia, bipolar disorder, depression, and epilepsy (for more details ref to Chiapponi, et al., 2016; Knopp, et al., 2008; Luscher, et al., 2011; Nakazawa et al., 2012). Consistent with the overall theme of this issue, our review will focus on interneuronopathies leading to pathology in the *developing* brain, such as Rett syndrome, autism spectrum disorder, Down’s syndrome and neurofibromatosis type I. Despite the involvement of different genes, these neurodevelopmental disorders share some phenotypical features. Specifically, a unifying hallmark appears to be an E/I imbalance caused by a predominant GABAergic dysfunction (Ramamoorthi & Lin, 2011; Sohal & Rubenstein, 2019).

Here, we will review the current state of research linking interneuron dysfunction to neurodevelopmental disease. First, we summarize the origin, maturation, and migration of

Scott C. Baraban, Ph.D. (Corresponding author) Department of Neurological Surgery and Weill Institute of Neuroscience, University of California, San Francisco, 513 Parnassus Ave, Health Science East, E840, San Francisco, CA 94143, scott.baraban@ucsf.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

interneurons under physiological conditions. Then, we review circuit alterations during different developmental stages, in the context of aforementioned neurodevelopmental diseases. Finally, the technique, theory, and potential for interneuron-based cell transplantation is discussed as a possible treatment for neurodevelopmental disorders.

Maturation stages of interneurons

Discovery of interneuron involvement in neurodevelopmental disorders, and the fact that interneurons principally regulate large neural networks, suggest that disease states may directly result from abnormal circuit dynamics. Regarding neurodevelopmental diseases, network dynamics are further complicated by time, and developmental stage of the animal. For example, GABA exerts different actions – depolarizing vs. hyperpolarizing - depending on the specific stage of development (Ben-Ari, et al., 2012). As such, interneuronopathies may have different effects on network dynamics at different stages of development, which would suggest that symptoms of a neurodevelopment disorder are not constant over time. Mapping neural activity to symptoms at this level of detail will require unprecedented insight into the disease, but ultimately promises to lead to tailored and effective treatments. To that end, we begin with a brief discussion of the physiology of developing interneurons, focusing on origin and maturation stages.

Embryonic stage – origin and migration—Interneurons (INs) originate from the medial and caudal ganglionic eminence (MGE/CGE respectively) located in the embryonic subpallium (Pleasure et al., 2000; Wonders & Anderson, 2006). To reach cortex and hippocampus, CGE/MGE-derived INs migrate tangentially through the marginal (MZ) and subventricular zone (SVZ) entering hippocampus at embryonic day (E) 14.5 with a peak at E15-E18 (Danglot, Triller, & Marty, 2006; Tricoire et al., 2011). Similar to cortex, hippocampal circuit formation shows a laminar organization during development with principal neurons packed in the pyramidal cell layer and early born cells (MGE-derived INs) located in deeper structures such as stratum oriens and pyramidal and late born cells (CGE-derived INs) in superficial layers (stratum radiatum and lacunosum moleculare) (Tricoire et al., 2011). Once they reach hippocampus and cortex, INs differentiate through a complex maturation process into three main classes: parvalbumin-positive (PV+) and somatostatin-positive (SOM+) INs from MGE precursors, and vasoactive intestinal positive (VIP+)/5HT3a receptor-positive INs from CGE precursors (Lim, et al., 2018).

Postnatal stage (birth to 2 weeks)—At *birth*, GABAergic neurons *in hippocampus and cortex* play a role in synchronized neuronal activity known as *spontaneous plateau assemblies* (SPAs) (Allene et al., 2008, 2012). This activity is generated by activation of membrane conductance in groups of neurons connected by gap junctions (Crépel et al., 2007). *During the first postnatal week, in hippocampus*, as GABAergic neurons gradually mature (Allene et al., 2012), SPAs are replaced by *giant depolarizing potentials* (GDPs) driven by formation of synaptic connections (Ben-Ari, Cherubini, Corradetti, & Gaiarsa, 1989; Garaschuk, Linn, Eilers, & Konnerth, 2000). Somatargeting INs originating from MGE (Flossmann et al., 2019; Wester & McBain, 2016) seem to be critical for GDP generation with GABA acting via a GABA_A receptor that depolarizes postsynaptic cells (Ben-Ari, et al., 2007; Ben-Ari, et al., 2012). *In cortex*, on the other hand, the first

spontaneous activity is known as *early network oscillations* (ENOs), which is exclusively dependent on glutaminergic release. At the end of the first postnatal week, ENOs are replaced by GDPs (Allene et al., 2008), further suggesting that different mechanisms are involved in ENO/GDP generation. Taken together, these results highlight the hypothesis that GABA influences developing neural networks differently in separate brain regions, which suggests that altering GABA-mediated signaling may cause region-dependent circuit alterations.

During the second post-natal week, GABA shifts from depolarizing to hyperpolarizing (Ben-Ari et al., 2012) in concomitance with expression of a potassium-chloride co-transporter, KCC2 (Rivera, et al., 1999). As GABAergic neurotransmission matures, GDPs disappear (Ben-Ari et al., 1989) and interneurons acquire an adult functional role to hyperpolarize neurons. Thus, around postnatal day (P) 15–17 a more mature oscillatory pattern is observed in cortex and hippocampus (Brockmann, et al., 2011; Minlebaev, et al., 2011; Mohns & Blumberg, 2008).

Juvenile stage—The next maturation step is a “period of plasticity”. During this period, animals in the P25–27 range map external sensory stimuli to specific network activity (Gao et al., 2018; Hensch, 2005). Several studies performed during this “critical period” in visual cortex highlight the importance of E/I balance and a potential role for PV+ basket cell INs during this stage of development (Hensch, 2005).

Adult stage—In the adult brain, more than 20 different cortical/hippocampal IN sub-types have been identified and numerous reviews focus on their morphology, location, physiological function, and biochemical profile (for more details ref to Lim et al., 2018; Pelkey et al., 2017). For simplicity, we here classify INs into three main categories (PV+, SOM+ and ionotropic VIP/5HT_{3A}R INs).

PV+ INs represent the largest and best characterized class of cortical/hippocampal interneurons. They are characterized by a fast-spiking high frequency train of action potentials, lowest input resistance and fastest membrane time constant of all INs (Cauli et al., 1997; Gibson, et al., 1999; Kawaguchi & Kubota, 1997; Xu & Callaway, 2009). They include *basket cells and chandelier cells or axo-axonic cells*. Importantly, in addition to these intrinsic properties, their function seems to correlate to axon projection patterns. PV+ basket cells synapse with soma and proximal dendrites of excitatory pyramidal neurons, whereas PV+ chandelier cells project to the initial segment of pyramidal cells axons (Kawaguchi & Kubota, 1997). SOM+ INs represent the second largest interneuron sub-population. They are characterized by regular spiking and morphologically they form a heterogeneous group (Beierlein, et al., 2003; Reyes et al., 1998). The largest SOM subgroup is represented by Martinotti cells in cortex and OLM INs in hippocampus. Their axons branch for several subfields to make synapses with the most distal apical dendrites of excitatory pyramidal cells (Kawaguchi & Kubota, 1997). Together, SOM+ and PV+ INs, which derive from MGE progenitors, control excitatory pyramidal cell activity through a combination of dendritic and somatic inhibition, respectively (Miles, et al., 1996). Interneurons that express the serotonin receptor 5HT_{3A}R represent a quite heterogeneous group that derive from CGE progenitors. Most 5HT_{3A}R+ INs also express vasoactive intestinal peptide (VIP) and reelin.

They represent ~30% of all cortical INs and are preferentially found in superficial layers (Miyoshi et al., 2010). This IN population preferentially targets other GABAergic neurons such as PV+ and SOM+ cells and tend to mediate network disinhibition (Dávid, Schleicher, Zuschratter, & Staiger, 2007; Pfeffer, Xue, He, Huang, & Scanziani, 2013).

Despite relatively modest overall numbers in the brain, interneurons exhibit exquisite diversity in location, electrophysiological properties, and output targets. This diversity makes them capable of regulating large amounts of information processing in neural circuits (Francavilla et al. 2018; Hu, et al., 2014) and places them at a crucial juncture for maintaining normal network processes - conversely, dysfunction of one, or more, IN subgroups can lead to pathological conditions. In the following section, we discuss a few examples of these pathologies with a focus on neurodevelopmental disorders.

Interneurons in neurodevelopmental disorders

Autism spectrum disorder (ASD) is a complex and heterogeneous neurodevelopmental disorder characterized by a common behavioral phenotype consisting of stereotyped behavior patterns, impaired social skills, and communication/language alterations (Kleijer, et al., 2014). The diagnosis is usually established in early infancy when network remodeling takes place. Despite many ASD-risk genes identified, a common hallmark of this disease is an E/I imbalance (Gogolla et al., 2009; Ramamoorthi & Lin, 2011; Rubenstein & Merzenich, 2003). Specifically, in many mouse models of ASD-risk genes (Shank1, Shank3B, Cntnap2), PV+ INs defects are a common finding (Mao et al., 2015; Penagarikano et al., 2011). and an MGE-based interneuron cell transplantation approach focused on introducing new PV+ INs early in development could prove therapeutic in this disorder.

Cntnap2 (contactin-associated protein like 2) is a gene localized on chromosome 7 that encodes the CASPR 2, a protein of the neurexin family that mediates synaptic cell-adhesion (Poliak et al., 1999, 2003). A mutation of this gene has been associated with autism and cortical dysplasia-focal epilepsy syndrome (CDFE) (Strauss et al., 2006). *Cntnap2* expression starts in the embryo (Poliak et al., 1999; Rodenas-Cuadrado, et al., 2014) supporting its role in neurodevelopment. Indeed, at P14, *Cntnap2* knockout mice show a neuronal migration abnormality and delayed maturation of PV+ INs in different brain regions including hippocampus, striatum, and sensory-motor cortex (Laubert, et al., 2018; Penagarikano et al., 2011). Given the critical function of GABAergic neurotransmission during this developmental stage (as summarized above), an interneuron deficit mostly likely will cause an E/I imbalance that persists through the “critical period” and into adulthood. Indeed, *in vitro* studies report impaired inhibitory neurotransmission in hippocampus and somatosensory cortex correlated with PV+ IN dysfunction (Antoine, Langberg, Schnepel, & Feldman, 2019; Jurgensen & Castillo, 2015; Scott et al., 2019). Interestingly, Antoine et al. found *in vivo* under whisker stimulation, a decreased firing rate of FS units in layer II/III in somatosensory cortex but a normal firing rate under baseline recording conditions. Those results suggest a decreased feedforward inhibition and further support a dynamic function of INs in neural networks (Antoine et al., 2019). In contrast, in mPFC circuit, in addition to an inhibitory deficit, pyramidal cells showed a decreased excitatory drive leading to a reduced preferred-phase to delta and theta rhythm during locomotion (Lazaro et al., 2019; Scott et

al., 2019). The opposite findings in some brain areas may highlight different functions of the *Cntnap2* protein in distinct circuit (Table 1) and suggest a more nuanced approach to IN-based transplantation is warranted.

Rett Syndrome is characterized by a mutation in the gene encoding for methyl CpG-binding protein 2 (*MECP2*) on chromosome X. It is characterized by partial or complete motor, cognitive, and communication skill loss after a normal development period (Smeets, et al., 2018). Even if the gene is ubiquitously expressed, a mouse model restricting gene deletion to the central nervous system recreated RTT-like phenotypes highlighting a key function for *Mecp2* in the brain and more precisely in GABAergic neurotransmission (Chao et al., 2010). In particular, using Cre-specific promoters, PV+ and SOM+ interneurons were identified as neurons responsible for these phenotype and each of those interneurons causes unique features in Rett syndrome (Ito-Ishida, Ure, Chen, Swann, & Zoghbi, 2015) highlighting the importance of interneuron-type specificity of this disease.

One salient aspect of the effect of the *Mecp2* gene mutation in the brain seems to be a region-specific circuit alteration (Table 2). For example, in mutated *Mecp2* animals, hippocampus becomes hyperexcitable and hyper-synchronized as a result of an impaired inhibition (Calfa, Hablitz, & Pozzo-Miller, 2011; Lu et al., 2016; Zhang, He, Jugloff, & Eubanks, 2008) secondary to the involvement of PVBC+ INs (Calfa, et al., 2015). *In vivo*, such hyperexcitability translates to spatial memory dysfunction (D'Cruz et al., 2010). In particular, mice failed to form place field stability during familiar environmental exposure likely due to a memory consolidation defect (Kee, et al., 2018). The somato-motor cortices, on the other hand, are characterized by an abnormal anatomical structure and pyramidal cell hypoactivity in part due to an increased inhibitory drive (Dani et al., 2005; Fukuda, Itoh, Ichikawa, Washiyama, & Goto, 2005; Morello et al., 2018). The region-specific E/I imbalance found in *Mecp2* animal models, makes treatment investigation difficult. Should treatments focus on the loss of inhibition of the medial temporal lobe, or the increased inhibition of the somato-motor cortices? It is clear that there is not a single neuroactive “pill” that can solve the spatially and functionally diverse effects of Rett syndrome.

Instead, therapies capable of modulating neural circuits in different directions at the same time may be needed. Consistent with that approach, one attractive option involves INs cell transplantation, which can be tailored to inject different interneuron subtypes in different regions to decrease (VIP/5HT_{3A}R+ INs) or increase (PV+ and SOM+) inhibition.

Trisomy of chromosome 21 (also known as Down's syndrome, DS) is associated with a significant delay in cognitive function leading to mental retardation, seizures and early onset dementia (Lott & Dierssen, 2010). Due to involvement of cognitive behaviors, hippocampal circuitry has been implicated in DS and extensively studied using a transgenic mouse model (Ts65Dn) developed in 1993 (Davisson & Schmidt, 1993). In adult animals, decreased long term potentiation (LTP) in the dentate gyrus (Kleschevnikov, 2004; Fernandez et al., 2007) and CA1 (A. C. S. Costa & Grybko, 2005; Scott-McKean et al., 2018) has been reported. Although morphological and spine density abnormalities are restricted to excitatory principal neurons, studies have also shown enhanced GABA-mediated synaptic inhibition onto granule cells in the dentate gyrus (Kleschevnikov et al., 2004) and increased

interneuron density in PV+ and SOM+ subtypes (Chakrabarti et al., 2010; Hernández-González et al., 2015; Hernández et al., 2012; Pérez-Cremades et al., 2010). Indeed, treatment with GABA receptor antagonist rescued LTP and associated cognitive impairments (Rueda et al., 2008; A. C. S. Costa & Grybko, 2005; Kleschevnikov, 2004; Kleschevnikov et al., 2012; Fernandez et al., 2007; Colas et al., 2013; Rueda et al., 2008; Scott-McKean et al., 2018), and reached clinical trial investigation (ACTRN12612000652875). However, systemic GABA antagonist treatment can also lead to unwanted side effects such as an increased risk of seizure activity or interference with physiological synaptic inhibition. An alternative therapeutic strategy would instead be the introduction of VIP/reelin+ INs using CGE progenitor cell transplantation. As described above, this class of neurons preferentially targets PV+ and SOM+ INs and, offers an alternative approach to decrease inhibition specifically in the brain region involved. Moreover, if these cells are introduced early during postnatal neurodevelopment, when the brain is more prone to plasticity, there could a less severe progression of the syndrome through adulthood.

Neurofibromatosis type I is a single gene disorder caused by mutations in NF1 gene producing loss of function of Neurofibromin, a negative regulator of the RAS pathway (Shilyansky, et al., 2010). At first, it was identified as neurocutaneous disorder (Canale, 1972), however, the expression of NF1 in pyramidal neurons, INs and glia in the cortex and hippocampus and the presence of cognitive deficits (Rosman & Pearce, 1967)(Millichap, 2012)(Levine, Materek, Abel, O'Donnell, & Cutting, 2006)(Ullrich, Ayr, Leaffer, Irons, & Rey-Casserly, 2010) highlighted brain and cortical involvement. Using CRE-expressing mice to specifically deplete NF1 from INs, studies have shown impaired GABAergic inhibition of hippocampal CA1 pyramidal neurons, as well as decreased activity of layer II/III cortical pyramidal neurons and striatal medium-sized spiny neurons. However, the direct implication of increased GABA inhibition associated with these deficiencies was later confirmed by the use of a GABA receptor antagonist to rescue cognitive dysfunction (Cui et al., 2008; Carrie Shilyansky et al., 2010). It was suggested that increased inhibitory drive could be attributed to different factors in a region specific manner since increased GABA levels were found in the prefrontal cortex and striatum but not in the hippocampus, while increased GABA receptors levels were found in the DG and CA1/CA3 but not in cortex or striatum of NF1^{+/-} adult mice (Gonçalves et al., 2017). While no specific IN subtype has been specifically implicated in NF1^{+/-} deficits, the overall increase in network GABA-mediated inhibition was consistently showed to cause LTP and cognitive impairments in NF1. Like DS, transplantation of CGE-derived progenitors that will integrate as VIP+ INs innervating PV+ and SOM+ INs offers a potential therapeutic treatment to ameliorate these circuit deficits and restore cognitive function.

Conclusions

In neurodevelopmental diseases, interest in a strategy to manipulate circuits is increasing. Indeed, interventions that can reliably alter E/I balance during a developmental “critical period” hold therapeutic potential for these disorders. Optogenetic activation or inhibition of selected interneurons is one approach that has received considerable attention, but it is unclear precisely how this experimental strategy can be translated to the clinic or applied

during early neurodevelopmental stages. A promising alternative is the generation of functionally integrated interneurons via transplantation of embryonic MGE or CGE progenitors. MGE-derived progenitor transplantation has already been shown, at a functional level, capable of altering E/I balance. Indeed, in host brain cortex or hippocampus, transplanted MGE progenitors migrate widely and functionally integrate in a synapse-specific manner consistent with their interneuron cell type e.g., MGE-derived SOM+ INs innervate the dendrites of pyramidal neurons and PV+ INs innervate soma (Howard & Baraban, 2016; Hsieh & Baraban, 2017). Once established, MGE-derived INs appear to be stable for the life of the animal (Casalia, et al., 2017). From a therapeutic perspective, preclinical studies using rodent models of genetic and acquired epilepsies have consistently demonstrated a dramatic reduction in spontaneous seizure activity following cortical or hippocampal transplantation of embryonic MGE progenitors. These effects were also shown, in an adult rodent model of acquired epilepsy, to improve behavioral deficits namely those associated with hippocampal-mediated cognitive function (Casalia, et al., 2017; Hunt, et al., 2013). CGE-derived interneurons can also be transplanted into hippocampal or cortical circuits where they hold the capacity to innervate other interneurons, as expected (Larimer et al., 2016). With experimental tools now in place to generate functional PV+ and SOM+ (from embryonic MGE progenitors) or VIP/5HT_{3A}R+ (from embryonic CGE progenitors) INs it is now possible to examine whether this strategy will restore E/I balance and exert therapeutic effects in a variety of neurodevelopmental disorders where it has been disrupted.

Bibliography

- Allene C, Cattani A, Ackman JB, Bonifazi P, Aniksztejn L, Ben-ari Y, & Cossart R (2008). Sequential Generation of Two Distinct Synapse-Driven Network Patterns in Developing Neocortex. *Journal of Neuroscience*, 28(48), 12851–12863. 10.1523/JNEUROSCI.3733-08.2008 [PubMed: 19036979]
- Allene C, Picardo MA, Becq H, Miyoshi G, Fishell G, & Cossart R (2012). Dynamic Changes in Interneuron Morphophysiological Properties Mark the Maturation of Hippocampal Network Activity. *Journal of Neuroscience*, 32(19), 6688–6698. 10.1523/jneurosci.0081-12.2012 [PubMed: 22573691]
- Antoine MW, Langberg T, Schnepel P, & Feldman DE (2019). Increased Excitation-Inhibition Ratio Stabilizes Synapse and Circuit Excitability in Four Autism Mouse Models. *Neuron*, 101(4), 648–661. 10.1016/j.neuron.2018.12.026 [PubMed: 30679017]
- Asaka Y, Jugloff DGM, Zhang L, Eubanks JH, & Fitzsimonds RM (2006). Hippocampal synaptic plasticity is impaired in the Mecp2-null mouse model of Rett syndrome. *Neurobiology of Disease*, 21(1), 217–227. 10.1016/j.nbd.2005.07.005 [PubMed: 16087343]
- Beierlein M, Gibson JR, & Connors BW (2003). Two Dynamically Distinct Inhibitory Networks in Layer 4 of the Neocortex. *J Neurophysiol*, 90(5), 2987–3000.
- Ben-Ari Y, Cherubini E, Corradetti R, & Gaiarsa J-L (1989). Giant synaptic potentials in immature rat CA3 hippocampal neurones. *Journal of Physiology*, 416(1), 303–325. [PubMed: 2575165]
- Ben-Ari Y, Gaiarsa J-L, Tyzio R, & Khazipov R (2007). GABA: A Pioneer Transmitter That Excites Immature Neurons and Generates Primitive Oscillations. *Physiological Reviews*, 87(4), 1215–1284. 10.1152/physrev.00017.2006 [PubMed: 17928584]
- Ben-Ari Y, Khalilov I, Kahle KT, & Cherubini E (2012). The GABA excitatory/inhibitory shift in brain maturation and neurological disorders. *Neuroscientist*, 18(5), 467–486. 10.1177/1073858412438697 [PubMed: 22547529]
- Bridi MS, Park SM, & Huang S (2017). Developmental Disruption of GABAAR-Mediated Inhibition in Cntnap2 KO Mice. *ENeuro*, 4(5), 1–14.

- Brockmann MD, Pöschel B, Cichon N, & Hanganu-Opatz IL (2011). Coupled oscillations mediate directed interactions between prefrontal cortex and hippocampus of the neonatal rat. *Neuron*, 71(2), 332–347. 10.1016/j.neuron.2011.05.041 [PubMed: 21791291]
- Calfa G., Hablitz JJ., & Pozzo-Miller L. (2011). Network hyperexcitability in hippocampal slices from Mecp2 mutant mice revealed by voltage-sensitive dye imaging. *J Neuophysiol*, 105(4), 1768–1784. 10.1152/jn.00800.2010.
- Calfa G, Li W, Rutherford JM, & Pozzo-miller L (2015). Excitation/Inhibition Imbalance and Impaired Synaptic Inhibition in Hippocampal Area CA3 of Mecp2 Knockout Mice. *Hippocampus*, 25(2), 159–168. 10.1002/hipo.22360 [PubMed: 25209930]
- Canale DJ (1972). Von Recklinghausen disease of the nervous system. *Handbook of Clinical Neurology*, 14, 132–162.
- Casalia ML, Howard MA, & Baraban SC (2017). Persistent seizure control in epileptic mice transplanted with gamma-aminobutyric acid progenitors. *Annals of Neurology*, 82(4), 530–542. 10.1002/ana.25021 [PubMed: 28833459]
- Cauli B, Audinat E, Lambolez B, Angulo MC, Ropert N, Tsuzuki K, ... Rossier J (1997). Molecular and physiological diversity of cortical nonpyramidal cells. *The Journal of Neuroscience*, 17(10), 3894–3906. [PubMed: 9133407]
- Chakrabarti L, Best TK, Cramer NP, Carney RSE, Isaac JTR, Galdzicki Z, & Haydar TF (2010). Olig1 and Olig2 triplication causes developmental brain defects in Down syndrome. *Nature Neuroscience*, 13(8), 927 10.1038/nn.2600 [PubMed: 20639873]
- Chao H-T, Chen H, Samaco RC, Xue M, Chahrour M, Yoo J, ... Zoghbi HY (2010). Dysfunction in GABA signalling mediates autism-like stereotypies and Rett syndrome phenotypes. *Nature*, 468(7321), 263–269. 10.1038/nature09582 [PubMed: 21068835]
- Chiapponi C, Piras F, Piras F, Caltagirone C, & Spalletta G (2016). GABA system in schizophrenia and mood disorders: A mini review on third-generation imaging studies. *Frontiers in Psychiatry*, 7, 1–10. 10.3389/fpsy.2016.00061 [PubMed: 26903886]
- Colas D., Chuluun B., Warriar D., Blank M., Wetmore DZ., Buckmaster P., ... Heller HC. (2013). Short-term treatment with the GABAA receptor antagonist pentylentetrazole produces a sustained pro-cognitive benefit in a mouse model of Down's syndrome. *British Journal of Pharmacology*, 169(5), 963–973. 10.1111/bph.12169 [PubMed: 23489250]
- Cope EC, Briones BA, Brockett AT, Martinez S, Opendak M, Wang SS, & Gould E (2016). Immature Neurons and Radial Glia, But Not Astrocytes or Microglia, Are Altered in Adult Cntnap2 and Shank3 Mice, Models of Autism. *ENeuro*, 3(5), 1–15.
- Costa ACS, & Grybko MJ (2005). Deficits in hippocampal CA1 LTP induced by TBS but not HFS in the Ts65Dn mouse: A model of Down syndrome. *Neuroscience Letters*, 382(3), 317–322. 10.1016/j.neulet.2005.03.031 [PubMed: 15925111]
- Crépel V, Aronov D, Jorquera I, Represa A, Ben-Ari Y, & Cossart R (2007). A Parturition-Associated Nonsynaptic Coherent Activity Pattern in the Developing Hippocampus. *Neuron*, 54(1), 105–120. 10.1016/j.neuron.2007.03.007 [PubMed: 17408581]
- Cui Y, Costa RM, Murphy GG, Elgersma Y, Zhu Y, Gutmann DH, ... Silva AJ (2008). Neurofibromin Regulation of ERK Signaling Modulates GABA Release and Learning. *Cell*, 135(3), 549–560. 10.1016/j.cell.2008.09.060 [PubMed: 18984165]
- D'Cruz JA, Wu C, Zahid T, El-Hayek Y, Zhang L, & Eubanks JH (2010). Alterations of cortical and hippocampal EEG activity in MeCP2-deficient mice. *Neurobiology of Disease*, 38(1), 8–16. 10.1016/j.nbd.2009.12.018 [PubMed: 20045053]
- Danglot L, Triller A, & Marty S (2006). The development of hippocampal interneurons in rodents. *Hippocampus*, 16(12), 1032–1060. 10.1002/hipo [PubMed: 17094147]
- Dani VS, Chang Q, Maffei A, Turrigiano GG, Jaenisch R, & Nelson SB (2005). Reduced cortical activity due to a shift in the balance between excitation and inhibition in a mouse model of Rett Syndrome. *PNAS*, 102(35), 12560–12565. [PubMed: 16116096]
- David C., Schleicher A., Zuschratter W., & Staiger JF. (2007). The innervation of parvalbumin-containing interneurons by VIP-immunopositive interneurons in the primary somatosensory cortex of the adult rat. *European Journal of Human Genetics*, 25(8), 2329–2340. 10.1111/j.1460-9568.2007.05496.x

- Dávid C, Schleicher A, Zuschratter W, & Staiger JF (2007). The innervation of parvalbumin-containing interneurons by VIP-immunopositive interneurons in the primary somatosensory cortex of the adult rat. *European Journal of Neuroscience*, 25(8), 2329–2340. 10.1111/j.1460-9568.2007.05496.x [PubMed: 17445231]
- Davisson M, & Schmidt C (1993). Segmental trisomy as a mouse model for Down syndrome. *Progress in Clinical and Biological Research*, 384, 117–133. [PubMed: 8115398]
- Fernandez F, Morishita W, Zuniga E, Nguyen J, Blank M, Malenka RC, & Garner CC (2007). Pharmacotherapy for cognitive impairment in a mouse model of Down syndrome. *Nature Neuroscience*, 10(4), 411 10.1038/nn1860 [PubMed: 17322876]
- Flossmann T, Kaas T, Rahmati V, Kiebel SJ, Witte OW, Holthoff K, & Kirmse K (2019). Somatostatin Interneurons Promote Neuronal Synchrony in the Neonatal Hippocampus. *Cell Reports*, 26(12), 3173–3182. 10.1016/j.celrep.2019.02.061 [PubMed: 30893591]
- Francavilla R, Villette V, Luo X, Chamberland S, Muñoz-Pino E, Camiré O, ... Topolnik L (2018). Connectivity and network state-dependent recruitment of long-range VIP-GABAergic neurons in the mouse hippocampus. *Nature Communications*, 9(1), 1–17. 10.1038/s41467-018-07162-5
- Fukuda T, Itoh M, Ichikawa T, Washiyama K, & Goto Y (2005). Delayed maturation of neuronal architecture and synaptogenesis in cerebral cortex of Mecp2-deficient mice. *Journal of Neuropathology and Experimental Neurology*, 64(6), 537–544. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/15977646> [PubMed: 15977646]
- Gao X, Castro-Gomez S, Grendel J, Graf S, Süsens U, Binkle L, ... Ohana O (2018). Arc / Arg3.1 mediates a critical period for spatial learning and hippocampal networks. *PNAS*, 115(49), 12531–12536. 10.1073/pnas.1810125115 [PubMed: 30442670]
- Garaschuk O, Linn J, Eilers J, & Konnerth A (2000). Large-scale oscillatory calcium waves in the immature cortex. *Nature Neuroscience*, 3(5), 452–459. 10.1038/74823 [PubMed: 10769384]
- Gdalyahu A, Lazaro M, Penagarikano O, Golshani P, Trachtenberg JT, & Geschwind DH (2015). The Autism Related Protein Contactin- Stabilizes New Spines : An In Vivo Mouse Study. *PloS One*, 10(5), 1–7. 10.1371/journal.pone.0125633
- Gibson JR, Beierlein M, & Connors BW (1999). Two networks of electrically coupled inhibitory neurons in neocortex. *Nature*, 402(6757), 75–79. [PubMed: 10573419]
- Gogolla N, Leblanc JJ, Quast KB, Südhof TC, Fagiolini M, & Hensch TK (2009). Common circuit defect of excitatory-inhibitory balance in mouse models of autism. *J Neurodevelop Disord*, 1(2), 172–181. 10.1007/s11689-009-9023-x
- Gonçalves J, Violante IR, Sereno J, Leitão RA, Cai Y, Abrunhosa A, ... Castelo-Branco M (2017). Testing the excitation/inhibition imbalance hypothesis in a mouse model of the autism spectrum disorder: In vivo neurospectroscopy and molecular evidence for regional phenotypes. *Molecular Autism*, 8(1), 1–8. 10.1186/s13229-017-0166-4 [PubMed: 28070266]
- Hensch TK (2005). Critical period plasticity in local cortical circuits. *Nature Reviews*, 6(11), 877–888. 10.1038/nrn1787
- Hernández-González S, Ballestín R, López-Hidalgo R, Gilabert-Juan J, Blasco-Ibáñez JM, Crespo C, ... Varea E (2015). Altered Distribution of Hippocampal Interneurons in the Murine Down Syndrome Model Ts65Dn. *Neurochemical Research*, 40(1), 151–164. 10.1007/s11064-014-1479-8 [PubMed: 25399236]
- Hernández S, Gilabert-Juan J, Blasco-Ibáñez JM, Crespo C, Nacher J, & Varea E (2012). Altered expression of neuropeptides in the primary somatosensory cortex of the Down syndrome model Ts65Dn. *Neuropeptides*, 46(1), 29–37. 10.1016/j.npep.2011.10.002 [PubMed: 22078870]
- Howard MA, & Baraban SC (2016). Synaptic integration of transplanted interneuron progenitor cells into native cortical networks. *Journal of Neurophysiology*, 116(2), 472–478. 10.1152/jn.00321.2016 [PubMed: 27226453]
- Hsieh J-Y, & Baraban SC (2017). Medial Ganglionic Eminence Progenitors Transplanted into Hippocampus Integrate in a Functional and Subtype-Appropriate Manner. *Eneuro*, 4(2), 1–17.
- Hu H, Gan J, & Jonas P (2014). Fast-spiking, parvalbumin+ GABAergic interneurons: From cellular design to microcircuit function. *Science*, 345(6196), 1255263. 10.1126/science.1255263

- Hunt RF, Girskis KM, Rubenstein JL, Alvarez-Buylla a, & Baraban SC. (2013). GABA progenitors grafted into the adult epileptic brain control seizures and abnormal behavior. *Nat Neurosci*, 16(6), 692–697. 10.1038/nn.3392 [PubMed: 23644485]
- Ito-Ishida A, Ure K, Chen H, Swann JW, & Zoghbi HY (2015). Loss of MeCP2 in Parvalbumin-and Somatostatin-Expressing Neurons in Mice Leads to Distinct Rett Syndrome-like Phenotypes. *Neuron*, 88(4), 651–658. 10.1016/j.neuron.2015.10.029 [PubMed: 26590342]
- Jurgensen S, & Castillo PE (2015). Selective Dysregulation of Hippocampal Inhibition in the Mouse Lacking Autism Candidate Gene CNTNAP2. *Journal of Neuroscience*, 35(43), 14681–14687. 10.1523/jneurosci.1666-15.2015 [PubMed: 26511255]
- Kaleueff A, & Nutt DJ (1997). Role of GABA in Memory and Anxiety: a theoretical review article. *Depression and Anxiety*, 4(3), 100–110.
- Kawaguchi Y, & Kubota Y (1997). GABAergic Cell Subtypes and their Synaptic Connections in Rat Frontal Cortex. *Cerebral Cortex*, 7(6), 476–486. [PubMed: 9276173]
- Kee SE, Mou X, Zoghbi HY, & Ji D (2018). Impaired spatial memory codes in a mouse model of Rett syndrome. *ELife*, 7, 1–21.
- Kelsom C, & Lu W (2013). Development and specification of GABAergic cortical interneurons. *Cell & Bioscience*, 3(1), 1–19. [PubMed: 23286669]
- Kleijer KTE, Schmeisser MJ, Krueger D, Boeckers T, Scheiffele P, Bourgeron T, ... Burbach JPH (2014). Neurobiology of autism gene products : towards pathogenesis and drug targets. *Psychopharmacology*, 231(6), 1037–1062. 10.1007/s00213013-3403-3 [PubMed: 24419271]
- Kleschevnikov AM, Belichenko PV, Faizi M, Jacobs LF, Htun K, Shamloo M, & Mobley WC (2012). Deficits in Cognition and Synaptic Plasticity in a Mouse Model of Down Syndrome Ameliorated by GABAB Receptor Antagonists. *Journal of Neuroscience*, 32(27), 9217–9227. 10.1523/jneurosci.1673-12.2012 [PubMed: 22764230]
- Kleschevnikov AM., Belichenko PV., Villar AJ., Epstein CJ., Malenka RC., & Mobley WC. (2004). Hippocampal Long-Term Potentiation Suppressed by Increased Inhibition in the Ts65Dn Mouse, a Genetic Model of Down Syndrome. *Journal of Neuroscience*, 24(37), 8153–8160. 10.1523/jneurosci.1766-04.2004 [PubMed: 15371516]
- Knopp A, Frahm C, Fidzinski P, Witte OW, & Behr J (2008). Loss of GABAergic neurons in the subiculum and its functional implications in temporal lobe epilepsy. *Brain*, 131(6), 1516–1527. 10.1093/brain/awn095 [PubMed: 18504292]
- Larimer P, Spatazza J, Espinosa S, Tang Y, Kaneko M, Hasenstaub A, ... Alvarez-Buylla A (2016). Caudal Ganglionic Eminence Precursor Transplants Disperse and Integrate as Lineage-Specific Interneurons but Do Not Induce Cortical Plasticity Article Caudal Ganglionic Eminence Precursor Transplants Disperse and Integrate as Lineage-Specific Interneurons. *Cell Reports*, 16(5), 1391–1404. 10.1016/j.celrep.2016.06.071 [PubMed: 27425623]
- Lauber E, Filice F, & Schwaller B (2018). Dysregulation of Parvalbumin Expression in the Cntnap2^{-/-} Mouse Model of Autism Spectrum Disorder. *Frontiers in Molecular Neuroscience*, 11, 1–15. 10.3389/fnmol.2018.00262 [PubMed: 29403353]
- Lazaro MT, Taxis J, Shuman T, Bachmutsky I, Ikrar T, Santos R, ... Golshani P (2019). Reduced Prefrontal Synaptic Connectivity and Disturbed Oscillatory Population Dynamics in the CNTNAP2 Model of Autism. *Cell Report*, 27(9), 2567–2578. 10.1016/j.celrep.2019.05.006
- Levine TM, Materek A, Abel J, O'Donnell M, & Cutting LE (2006). Cognitive Profile of Neurofibromatosis Type 1. *Seminars in Pediatric Neurology*, 13(1), 8–20. 10.1016/j.spen.2006.01.006 [PubMed: 16818171]
- Lim L, Mi D, Llorca A, & Marin O (2018). Development and Functional Diversification of Cortical Interneurons. *Neuron Review*, 100(2), 294–313. 10.1016/j.neuron.2018.10.009
- Lott IT, & Dierssen M (2010). Cognitive deficits and associated neurological complications in individuals with Down's syndrome. *The Lancet Neurology*, 9(6), 623–633. 10.1016/S1474-4422(10)70112-5 [PubMed: 20494326]
- Lu H, Ash RT, He L, Kee SE, Wang W, Yu D, ... Zoghbi HY (2016). Loss and Gain of MeCP2 Cause Similar Hippocampal Circuit Dysfunction that Is Rescued by Deep Brain Stimulation in a Rett Syndrome Mouse Model. *Neuron*, 91(4), 739–747. 10.1016/j.neuron.2016.07.018 [PubMed: 27499081]

- Luscher B, Shen Q, & Sahir N (2011). The GABAergic deficit hypothesis of major depressive disorder. *Molecular Psychiatry*, 16(4), 383–406. 10.1038/mp.2010.120 [PubMed: 21079608]
- Mao W, Watanabe T, Cho S, Frost JL, Truong T, Zhao X, & Futai K (2015). Shank1 regulates excitatory synaptic transmission in mouse hippocampal parvalbumin-expressing inhibitory interneurons. 41(September 2014), 1025–1035. 10.1111/ejn.12877
- Miles R, Tóth K, Gulyás AI, Hájos N, & Freund TF (1996). Differences between somatic and dendritic inhibition in the hippocampus. *Neuron*, 16(4), 815–823. 10.1016/S0896-6273(00)80101-4 [PubMed: 8607999]
- Millichap JG (2012). Treatment of ADHD in Neurofibromatosis Type 1. *Pediatric Neurology Briefs*, 16(4). 10.15844/pedneurbriefs-16-4-11
- Minlebaev M, Colonnese M, Tsintsadze T, Sirota A, & Khazipov R (2011). Early Gamma Oscillations Synchronize Developing Thalamus and Cortex. *Science*, 334(6053), 226–230. [PubMed: 21998388]
- Miyoshi G., Hjerling-Leffler J., Karayannis T., Sousa VH., Butt SJB., Battiste J., ... Fishell G. (2010). Genetic fate mapping reveals that the caudal ganglionic eminence produces a large and diverse population of superficial cortical interneurons. *The Journal of Neuroscience*, 30(5), 1582–1594. 10.1523/JNEUROSCI.4515-09.2010 [PubMed: 20130169]
- Mohns EJ, & Blumberg MS (2008). Synchronous Bursts of Neuronal Activity in the Developing Hippocampus: Modulation by Active Sleep and Association with Emerging Gamma and Theta Rhythms. *Journal of Neuroscience*, 28(40), 10134–10144. 10.1523/jneurosci.1967-08.2008 [PubMed: 18829971]
- Morello N, Schina R, Pilotto F, Phillips M, Melani R, Pizzorusso T, ... Giustetto M (2018). Loss of Mecp2 Causes Atypical Synaptic and Molecular Plasticity of Parvalbumin-Expressing Interneurons Reflecting Rett Syndrome - Like Sensorimotor Defects. *ENeuro*, 5(5), 1–19.
- Nakazawa K, Zsiros V, Jiang Z, Nakao K, Kolata S, Zhang S, & Belforte JE (2012). GABAergic interneuron origin of schizophrenia pathophysiology. *Neuropharmacology*, 62(3), 1574–1583. 10.1016/j.neuropharm.2011.01.022 [PubMed: 21277876]
- Pelkey KA, Chittajallu R, Craig MT, Tricoire L, Wester JC, & McBain CJ (2017). Hippocampal GABAergic inhibitory interneurons. *Physiol Rev*, 97(4), 1619–1747. 10.1152/physrev.00007.2017 [PubMed: 28954853]
- Penagarikano O, Abrahams BS, Herman EI, Winden KD, Gdalyahu A, Dong H, ... Geschwind DH (2011). Absence of CNTNAP2 leads to epilepsy, neuronal migration abnormalities, and core autism-related deficits. *Cell*, 147(1), 235–246. 10.1016/j.cell.2011.08.040 [PubMed: 21962519]
- Pérez-Cremades D, Hernández S, Blasco-Ibáñez JM, Crespo C, Nacher J, & Varea E (2010). Alteration of inhibitory circuits in the somatosensory cortex of Ts65Dn mice, a model for Down's syndrome. *Journal of Neural Transmission*, 117(4), 445–455. 10.1007/s00702-010-0376-9 [PubMed: 20157742]
- Pfeffer CK, Xue M, He M, Huang ZJ, & Scanziani M (2013). Inhibition of inhibition in visual cortex: The logic of connections between molecularly distinct interneurons. *Nature Neuroscience*, 16(8), 1068–1076. 10.1038/nn.3446 [PubMed: 23817549]
- Pleasure SJ, Anderson S, Hevner R, Bagri A, Marin O, Lowenstein DH, & Rubenstein JLR (2000). Cell Migration from the Ganglionic Eminences Is Required for the Development of Hippocampal GABAergic Interneurons. *Neuron*, 28(3), 727–740. [PubMed: 11163262]
- Poliak S, Gollan L, Martinez R, Custer A, Einheber S, Salzer JL, ... Peles E (1999). Caspr2, a New Member of the Neurexin Superfamily, Is Localized at the Juxtaparanodes of Myelinated Axons and Associates with K⁺ Channels. *Neuron*, 24(4), 1037–1047. [PubMed: 10624965]
- Poliak S, Salomon D, Elhanany H, Sabanay H, Kiernan B, Pevny L, ... Peles E (2003). Juxtaparanodal clustering of Shaker-like K⁺ channels in myelinated axons depends on Caspr2 and TAG-1. *The Journal of Cell Biology*, 162(6), 1149–1160. 10.1083/jcb.200305018 [PubMed: 12963709]
- Ramamoorthi K, & Lin Y (2011). The contribution of GABAergic dysfunction to neurodevelopmental disorders. *Trends in Molecular Medicine*, 17(8), 452–462. 10.1016/j.molmed.2011.03.003 [PubMed: 21514225]

- Reyes A, Lujan R, Rozov A, Burnashev N, Somogyi P, & Sakmann B (1998). Targetcell-specific facilitation and depression in neocortical circuits. *Nature Neuroscience*, 1(4), 279–285. [PubMed: 10195160]
- Rivera C, Voipio J, Payne JA, Ruusuvuori E, Lahtinen H, Lamsa K, ... Kaila K (1999). The K⁺/Cl⁻-co-transporter KCC2 renders GABA hyperpolarizing during neuronal maturation. *Nature*, 397(6716), 251–255. [PubMed: 9930699]
- Rodenas-Cuadrado P, Ho J, & Vernes SC (2014). Shining a light on CNTNAP2: complex functions to complex disorders. *European Journal of Human Genetics*, 22(2), 171–178. 10.1038/ejhg.2013.100 [PubMed: 23714751]
- Rosman NP, & Pearce J (1967). The brain in multiple neurofibromatosis (von Recklinghausen's disease): a suggested neuropathological basis for the associated mental defect. *Brain*, 90(4), 829–838. [PubMed: 4965489]
- Rubenstein J L R, & Merzenich MM. (2003). Model of autism: increased ratio of excitation/inhibition in key neural systems. *Genes Brain & Behavior*, 2(5), 255–267. 10.1046/j.1601-183X.2003.00037.x
- Rueda N, Flórez J, & Martínez-Cué C (2008). Chronic pentylentetrazole but not donepezil treatment rescues spatial cognition in Ts65Dn mice, a model for Down syndrome. *Neuroscience Letters*, 433(1), 22–27. 10.1016/j.neulet.2007.12.039 [PubMed: 18226451]
- Scott-McKean JJ, Roque AL, Surewicz K, Johnson MW, Surewicz WK, & Costa ACS (2018). Pharmacological Modulation of Three Modalities of CA1 Hippocampal Long-Term Potentiation in the Ts65Dn Mouse Model of Down Syndrome. *Neural Plasticity*. 10.1155/2018/9235796
- Scott R, Sánchez-Aguilera A, K. Van Elst, Lim L., Dehorter N, Bae SE., ... Marín O. (2019). Loss of Cntnap2 Causes Axonal Excitability Deficits, Developmental Delay in Cortical Myelination, and Abnormal Stereotyped Motor Behavior. *Cerebral Cortex*, 29(2), 586–597. 10.1093/cercor/bhx341 [PubMed: 29300891]
- Shilyansky C, Lee YS, & Silva AJ (2010). Molecular and Cellular Mechanisms of Learning Disabilities: A Focus on NF1. *Annual Review of Neuroscience*, 33(1), 221–243. 10.1146/annurev-neuro-060909-153215
- Shilyansky Carrie, Karlsgodt KH, Cummings DM., Sidiropoulou K, Hardt M, James AS., ... Silva AJ. (2010). Neurofibromin regulates corticostriatal inhibitory networks during working memory performance. *Proceedings of the National Academy of Sciences*, 107(29), 13141–13146. 10.1073/pnas.1004829107
- Sik A, Penttonen M, Ylinen A, & Buzsáki G (1995). Hippocampal CA1 interneurons: an in vivo intracellular labeling study. *The Journal of Neuroscience*, 15(10), 6651–6665. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/7472426> [PubMed: 7472426]
- Smeets EEJ, Pelc K, & Dan B (2011). Rett syndrome. *Molecular Syndromology*, 2(3–5), 113–127. 10.1922/ai2018.S117
- Sohal VS, & Rubenstein JLR (2019). Excitation-inhibition balance as a framework for investigating mechanisms in neuropsychiatric disorders. *Molecular Psychiatry*. 10.1038/s41380-019-0426-0
- Strauss K, Puffenberger E, Huentelman M, Gottlieb S, Dobrin SE, Parod JM, ... Morton DH (2006). Recessive Symptomatic Focal Epilepsy and Mutant Contactin-Associated Protein-like 2. *The New England Journal of Medicine*, 354(13), 1370–1377. [PubMed: 16571880]
- Thomas AM, Schwartz MD, Saxe MD, & Kilduff TS (2017). Cntnap2 Knockout Rats and Mice Exhibit Epileptiform Activity and Abnormal Sleep – Wake Physiology. *Sleep*, 40(1).
- Treiman DM (2001). GABAergic mechanisms in epilepsy. *Epilepsia*, 42(3), 8–12. [PubMed: 11520315]
- Tricoire L, Pelkey KA, Erkkila BE, Jeffries BW, Yuan X, & McBain CJ (2011). A blueprint for the spatiotemporal origins of mouse hippocampal interneuron diversity. *The Journal of Neuroscience*, 31(30), 10948–10970. 10.1523/JNEUROSCI.0323-11.2011 [PubMed: 21795545]
- Ullrich NJ, Ayr L, Leaffer E, Irons MB, & Rey-Casserly C (2010). Pilot study of a novel computerized task to assess spatial learning in children and adolescents with neurofibromatosis type i. *Journal of Child Neurology*, 25(10), 1195–1202. 10.1177/0883073809358454 [PubMed: 20139412]

- Vogt D, Cho KKA, Shelton SM, Paul A, Huang ZJ, Sohal VS, & Rubenstein JLR (2017). Mouse *Cntnap2* and Human *CNTNAP2* ASD Alleles Cell Autonomously Regulate PV+ Cortical Interneurons. *Cerebral Cortex*, 28(11), 3868–3879. 10.1093/cercor/bhx248
- Wester JC, & McBain CJ (2016). Interneurons Differentially Contribute to Spontaneous Network Activity in the Developing Hippocampus Dependent on Their Embryonic Lineage. *The Journal of Neuroscience*, 36(9), 2646–2662. 10.1523/jneurosci.4000-15.2016 [PubMed: 26937006]
- Wonders CP, & Anderson SA (2006). The origin and specification of cortical interneurons. *Nature Reviews*, 7(9), 687–696. 10.1038/nrn1954
- Xu X, & Callaway EM (2009). Laminar Specificity of Functional Input to Distinct Types of Inhibitory Cortical Neurons. *The Journal of Neuroscience*, 29(1), 70–85. 10.1523/JNEUROSCI.4104-08.2009 [PubMed: 19129386]
- Zhang L, He J, Jugloff DGM, & Eubanks JH (2008). The MeCP2-Null Mouse Hippocampus Displays Altered Basal Inhibitory Rhythms and Is Prone to Hyperexcitability. *Hippocampus*, 18(3), 294–309. 10.1002/hipo.20389 [PubMed: 18058824]

Table 1:

Summary of circuit dysfunctions in Cntnap2 KO mouse model

	2–3 weeks	4–8 weeks	> 2 months
Hippocampus	Reduced density of PV+ INs (Lauber et al. 2018)	No difference in INs density (PV+, SOM+, CR+ (Scott et al. 2019)	Reduced density of PV+ INs (Penagarikano et al. 2011) Reduced immature DCX neurons in ventral hippocampus (Cope et al. 2016) No difference in astroglia (Cope et al. 2016) Decreased perisomatic inhibition (Jungersen et al. 2015)
mPFC		No difference in density of PV+ INs, (Lauber et al. 2018; Lazaro et al. 2019) Decreased inhibitory & excitatory Input into layer II/III (Lazaro et al. 2019) Decreased phase-locking excitatory units to delta and theta rhythm during locomotion (Scott et al. 2019)	No difference in astroglia (Cope et al. 2016)
Somatosensory cortex	Reduced density of PV+ INs (Penagarikano et al. 2011) Increased expression of CUX1 in deep layers (Penagarikano et al. 2011) Normal expression of Chat (Penagarikano et al. 2011)	No difference in INs density (PV+, SST+, CR+ (Scott et al. 2019) Reduced density of PV+ and Reelin+ INs and no difference in VIP+ and SST+ (Vogt et al. 2017) Increased sEPSC and no difference in sIPSC in layer II/III (Scott et al. 2019) Reduced mIPSC and Increased firing rate of PC in layer II/III (Antoine et al. 2019) Decreased whisker-evoked firing rate for FS units in layer II/III and RS units in layer IV (Antoine et al. 2019)	Reduced spine density in layer V (Gdalyahu et al. 2015) Increased expression of CUX1 in deep layers (Penagarikano et al. 2011) Normal expression of Foxp2 (Penagarikano et al. 2011) Asynchronous firing pattern in layer II/III (Penagarikano et al. 2011)
Striatum	Reduced density of PV+ INs (Penagarikano et al. 2011; Lauber et al. 2018) Normal expression of Chat (Penagarikano et al. 2011)	Reduced density of PV+ INs with no difference in WA+ cells (Lauber et al. 2018)	No difference in astroglia (Cope et al. 2016)
Visual cortex		Reduced phasic inhibition and no difference in tonic inhibition (Bridi et al. 2017)	
Other	Neural migration abnormalities (Penagarikano et al. 2011) Increased gray matter myelination (Scott et al. 2019)	Normal gray matter myelination (Scott et al. 2019) Altered clustering of Kv2.1 in cortical axons (Scott et al. 2019)	Reduced power (9–12 Hz) during wakefulness (Thomas et al. 2017) Absence of spontaneous seizures (Thomas et al. 2017) Spontaneous seizures in mice older than 6 months (Penagarikano et al. 2011) Neural migration abnormality (Penagarikano et al. 2011)

FR: firing rate; PC: principal cells

Table 2:

Summary of circuit dysfunctions in Rett syndrome mouse model

		Asymptomatic 2 weeks	Pre-symptomatic 4 –5 weeks	Symptomatic 8 weeks
Hippocampus	In vivo			Reduced theta frequency during locomotion (D'Cruz et al. 2010) CA1 hypersynchrony in vivo & in vitro (Lu et al. 2016) Impaired place field stability in familiar env at P90 (Kee et al. 2018)
	In vitro		Normal LTP and LTD (Asaka et al. 2006)	Increased hippocampal excitability (Zhang et al. 2008; Calfa et al. 2011) Reduced FR in PVBC+ in area CA3 due to decreased glutaminergic drive (Calfa et al. 2015) Decreased LTP and absent LTD (Asaka et al. 2006; Chao et al. 2010)
Sensory-motor cortex	Anatomy	Normal cortical thickness (Fukuda et al. 2005) Absence of PV cells (Fukuda et al. 2005)	No difference in PV+ density (Morello et al. 2018) Reduced cortical thickness (mostly in layer II/III) (Fukuda et al. 2005)	Increased PV+ expression in upper layers (Morello et al. 2018) Normal PV+ density (Fukuda et al. 2005) Increased excitatory input to PV+ INs (Morello et al. 2018) Reduced cortical thickness (mostly in layer II/III) (Fukuda et al. 2005) Reduced dendritic complexity in PC in layer II/III (Fukuda et al. 2005)
	In vitro	2-fold FR reduction in PC in layer V (Dani et al. 2005)	4-fold FR reduction in PC in layer V (Dani et al. 2005) Increased inhibitory & decreased excitatory drive into PC in layer V (Dani et al. 2005)	

FR: firing rate; env: environment; PC: principal cells