

Gabaergic circuit dysfunctions in neurodevelopmental disorders

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Cortical neural networks consist of broadly two classes of neurons: excitatory projection neurons, primarily using glutamate as neurotransmitter, and inhibitory local-circuit interneurons, comprising of about 20% of all cortical neurons, and primarily using gamma-amino butyric acid (GABA) as a neurotransmitter. The last few years have seen a steep increase in our knowledge of the function of GABAergic interneurons. Cortical interneurons have been shown to play a vital role in modulating neuronal excitability ([Swadlow, 2003](#)), integration ([Pouille and Scanziani, 2001](#)), and in the generation of temporal synchrony and oscillation among networks of glutamatergic neurons ([Klausberger and Somogyi, 2008](#)). In addition, GABAergic interneurons contribute to almost all fundamental processes of cortical development; from neuronal proliferation, migration, and differentiation to experience-dependent refinement of local cortical circuits ([Owens and Kriegstein, 2002](#) ; [Hensch, 2005](#) ; [Sernagor et al., 2010](#)).

These findings have prompted a change in the way we view the role of GABAergic cells in cortical development and processing. Traditionally, GABAergic interneuron function has been described simply as “inhibition” of neuronal activity, similar to a traffic officer who signals simply to let cars stop or go; however it is now clear that the picture is much more complex. We may instead compare GABAergic interneuron function to that of a conductor of a symphony orchestra, whose role is to structure and coordinate the overall musical performance and interpretation of the individual players. Without proper direction, the orchestra cannot produce the right melody.

Considering the multifaceted role played by GABAergic cells in the development, function, and plasticity of cortical networks, it is straightforward to assume that any disturbance in the development of GABAergic interneurons, due to either genetic or epigenetic factors, will strongly affect brain function. Indeed, disruption of GABAergic circuit function has been implicated in various neurodevelopmental and psychiatric disorders including schizophrenia ([Gonzalez-Burgos et al., 2011](#)), autism ([LeBlanc and Fagiolini, 2011](#)), mental retardation ([Cramer et al., 2010](#)), and epilepsy ([Rossignol, 2011](#)). Our understanding of the mechanisms underlying development of GABAergic interneurons have started to reveal specific molecular and cellular substrates potentially affected in neurodevelopmental disorders. Further, selective modulation of inhibitory networks is being currently investigated as a tool to re-introduce plasticity and therefore facilitate the restoration of normal function to the diseased brain.

This review will summarize some of the compelling evidence on the role of alterations in GABAergic neuron function in the etiology of two neurodevelopmental disorders, schizophrenia, and autism. An exhaustive review of the genetic causes of schizophrenia and autism is beyond the scope of this paper, and several excellent reviews have already been published on these topics. We will further focus on and discuss recent efforts to modify GABAergic transmission as a targeted therapeutic approach to re-introduce plasticity in the brain.

Cortical Interneuron Diversity – A Continuous Challenge

Before describing evidence linking GABAergic dysfunction to neurodevelopmental diseases, we would like to stress that our understanding of GABAergic interneuron function in normal and pathological conditions is challenged by their startling heterogeneity. Indeed different interneuron subtypes display distinctly different morphology, physiological properties, connectivity patterns, and vary in their biochemical composition ([Markram et al., 2004](#)). Such complexity makes it difficult to establish a broad consensus regarding a generalized classification scheme of interneuron subtypes. In parallel however, several studies have singled out multiple criteria to distinguish between major interneuron groups. One criterion for instance is the expression of calcium binding proteins such as parvalbumin (PV), calbindin (CB), or calretinin (CR) and/or neuropeptides such as somatostatin (SST), vasoactive intestinal peptide (VIP), neuropeptide Y (NPY), or cholecystokinin (CCK). Such analysis has shown that the cortex has three largely independent populations of interneurons: (1) PV, (2) SST/CB, and (3) CR/VIP expressing interneurons ([Somogyi et al., 1998](#)).

Further, different subtypes of interneurons have different spatial and temporal origins. The neocortical interneuron population, as such, is derived from transient ventral telencephalic structures referred to as the ganglionic eminences as well as from the preoptic area ([Batista-Brito and Fishell, 2009](#) ; [Gelman and Marín, 2010](#)). The medial ganglionic eminence (MGE) produces ~70% of neocortical interneurons, including the PV-expressing and SST-positive interneurons. Meanwhile, the caudal ganglionic eminence (CGE) gives rise to a more heterogeneous group of cortical interneurons that share

the expression of 5HT3A ionotropic serotonergic receptors and are thus highly responsive to the neuromodulatory effects of serotonin ([Batista-Brito and Fishell, 2009](#) ; [Gelman and Marín, 2010](#) ; [Lee et al., 2010](#)).

Another striking characteristic of GABAergic interneurons is that different subtypes innervate distinct domains of the postsynaptic glutamatergic cells. For example, SST/CB expressing interneurons selectively innervate distal dendrites of target neurons, while PV-expressing, fast-spiking interneurons can be divided in two major classes, basket cells which selectively innervate the soma and proximal dendrites and chandelier cells, which selectively innervate the axon initial segment of pyramidal cells ([Huang et al., 2007](#)).

The spatial organization of GABAergic synapses along glutamatergic neurons has provided important clues as to the specific functions of various interneuron subtypes ([Huang et al., 2007](#) ; [Rossignol, 2011](#)).

To truly understand how GABAergic circuits develop and function, it is essential to differentiate between distinct GABAergic interneuron subtypes. It is indeed likely that specific interneuron types differentially contribute to network processing that underlies cortical functions ranging from perception to cognition. Consequently, we can hypothesize that deficits in specific interneuron classes may account, at least in part, for different neuropathological conditions.

Recent technical advances have significantly accelerated progress in the interneuron field. In particular, the development of genetic strategies based on interneuron cell type-specific promoters in combination with inducible Cre-loxP knockin driver lines and fluorescent protein reporter lines has

allowed efficient high-resolution labeling and manipulation of specific GABAergic interneuron classes in intact or “ semi-intact” tissues (such as organotypic brain cultures; [Chattopadhyaya et al., 2004](#), [2007](#); [Taniguchi et al., 2011](#)). Due to the availability of these new tools, it is now possible to study specific GABAergic interneuron types, from cell fate specification, migration, and connectivity, to their function in network dynamics and behavior. Combining insights obtained from basic biological research on GABAergic interneuron development, plasticity, and function with genetic and clinical findings will provide us a detailed picture of the molecular events that result in diseases characterized by GABAergic dysfunction, and will suggest putative useful methods for targeted corrective intervention.

GABAergic Alterations in Neurodevelopmental Diseases

Schizophrenia

Schizophrenia is a severe brain disorder that afflicts 0.5–1% of the world’s population and is usually first diagnosed in late adolescence or early adulthood. The illness manifests with three classes of symptoms: positive or psychotic symptoms (i. e., delusions, hallucinations, and disorganization of thought), negative symptoms (i. e., flat affect, avolition, and alogia), and cognitive impairments such as abnormalities in working memory, inferential thinking, selective attention, as well as defects in executive functions, linguistic fluency, and social-emotional processing.

Although positive symptoms presents the most prominent clinical feature of schizophrenia, disturbances in cognition appear to be the core feature of the illness as they are present before the onset of psychosis and are the best

predictor of long-term functional outcome for schizophrenia patients. Therefore, understanding neural mechanisms underlying cognitive and dysfunctions is critical to develop new therapeutic strategies particularly given that currently approved pharmacological treatments for schizophrenia are largely ineffective at improving cognition.

A central cognitive deficit in schizophrenia is the dysfunction of working memory, i. e., the ability to store information and use it while performing complex tasks ([Baddeley, 2010](#)). Gamma oscillations (30–80 Hz) are thought to play an important role in normal working memory because gamma band synchrony increases with increasing working memory load ([Howard et al., 2003](#)). In patients with schizophrenia, working memory deficits are accompanied by altered patterns of cortical oscillatory activity. In particular, gamma activity does not augment with increasing working memory load in schizophrenia patients ([Basar-Eroglu et al., 2007](#) ; [Barr et al., 2010](#) ; [Haenschel and Linden, 2011](#)). Working memory related gamma activity, but not theta activity, is reduced in the frontal cortex of first-episode schizophrenia patients independent of medication status, suggesting a deficit related to the disease process as opposed to medication side effects or as a consequence of being chronically ill ([Minzenberg et al., 2010](#)). Moreover, subjects with schizophrenia have decreased oscillations in various frequency bands during specific phases of the working memory process including encoding, maintenance, and retrieval ([Haenschel et al., 2009](#)).

Among the several mechanisms proposed to play a role in the generation of synchronized oscillations in neocortical circuits, computational modeling

studies, and numerous experimental evidence support a leading role of GABA-mediated inhibition. In particular, convergent evidence indicates that synchronous activity in PV-expressing, fast-spiking basket interneurons is key to the emergence of gamma oscillations ([Bartos et al., 2007](#)). *In vitro* studies in rodent hippocampus and cortex show that blocking GABA suppresses gamma oscillations, and that driving fast-spiking interneurons by activating metabotropic glutamate receptors generates gamma oscillations ([Whittington et al., 1995](#) ; [Bartos et al., 2002](#)). Correlative *in vivo* studies similarly show that fast-spiking cells fire action potentials in phase with the gamma oscillations in the neocortex ([Hasenstaub et al., 2005](#) ; [Sirota et al., 2008](#)). Causal evidence for this hypothesis *in vivo* has been recorded in the neocortex using optogenetics, which allow the bidirectional modulation of neuronal activity of selective cell populations that have been made sensitive to light by genetic manipulation. Optogenetic-mediated activation of PV-expressing interneurons selectively amplifies gamma oscillations and modulates sensory responses in rat somatosensory cortex ([Cardin et al., 2009](#)). Conversely, suppressing PV-expressing interneuron activity with optogenetic methods significantly reduced or abolished gamma oscillations ([Sohal et al., 2009](#)). Finally, mice lacking NMDAR-mediated neurotransmission only in PV-expressing interneurons show altered cortical gamma rhythms with largely normal behavior except for selective cognitive impairments, including deficits in habituation, working memory, and associative learning ([Carlén et al., 2011](#)). Therefore, GABA_A R-mediated currents from PV-expressing basket cells appear to be the main source of GABA-mediated synchronization underlying cortical gamma oscillations.

In parallel, evidence from post-mortem studies of brains of subjects with schizophrenia supports the notion that specific alterations in GABAergic interneurons are associated with this disease ([Lewis et al., 2005](#)). In particular, one of the most reliable findings in schizophrenia research is the decrease in mRNA for GABA-synthesizing enzyme GAD67, which appears to be markedly deficient in PV-positive interneurons in schizophrenic brains ([Hashimoto et al., 2003](#) ; [Lewis et al., 2005](#)). In addition, several GABA-related transcripts including those for GAD67, PV, the GABA transporter GAT1, SST, and the GABA_A R subunits $\alpha 1$ and δ , are decreased in dorsolateral PFC as well as in the anterior cingulate, primary motor, and primary visual cortices ([Hashimoto et al., 2008](#)). Overall these data suggest that disturbances in GABAergic neurotransmission in specific cell types could represent a common pathological mechanism for different domains of cortical dysfunction in schizophrenia. It is therefore possible that pharmacological agents with the appropriate specificity for certain GABAergic synapses might be effective for a range of clinical features in the illness. While direct demonstration of a decrease in GABA-mediated synaptic transmission, in particular from basket cells, in the cortex of subjects with schizophrenia is challenging and still missing, the evidence available at the moment strongly points toward a direct link between PV-positive basket cell dysfunction, gamma oscillation alterations, and working memory deficits in schizophrenia patients.

Understanding PV-positive basket cell development in normal conditions should indicate the natural events occurring during this process and point out potential pathogenic mechanisms that can cause GABAergic dysfunction

and schizophrenia. GABAergic interneuron development is a prolonged process, which starts in the embryo, progresses through childhood, and is completed by adolescence in all mammalian species studied including rodents and humans. During this prolonged period, the interplay between genetic, epigenetic, and environmental factors can produce subtle developmental alterations in GABAergic circuits that may contribute to the pathophysiology of schizophrenia.

While the molecular mechanisms regulating postnatal development of basket cells are not yet fully understood, recent papers have started to address this issue. In particular, it has been shown that the maturation of perisomatic innervation from GABAergic basket cells is modulated by neuronal activity and sensory experience during a critical postnatal period ([Chattopadhyaya et al., 2004](#) ; [Chattopadhyaya, 2011](#)). A crucial factor regulating the development of innervation patterns by basket cells is GABA release itself, which regulates both the number of postsynaptic targets, as well as the number of synapses made onto each target by a single basket cell, in an age-dependent manner ([Chattopadhyaya et al., 2007](#) ; [Baho and Di Cristo, 2012](#) ; [Wu et al., 2012](#)). In particular, GAD67 knockdown in single basket cells dramatically decreases the formation of terminal axon branches and perisomatic synapses, as well as the number of postsynaptic neurons innervated by each basket cell ([Chattopadhyaya et al., 2007](#)). This finding is particularly interesting since polymorphisms in the 5' region of the *Gad1* gene (coding for GAD67) have been associated with decreased GAD67 and schizophrenia ([Addington et al., 2005](#) ; [Straub et al., 2007](#)). One possibility, therefore, is that altered inhibitory transmission caused by the genetic

impairment of GAD67 gene early in development might alter the developmental trajectory of GABAergic neural circuit maturation, thus causing global network alterations predisposing to schizophrenia.

Another remarkable study showed that the trophic factor Neuregulin-1 and its receptor ErbB4, which are both schizophrenia susceptibility genes, regulate the development of PV-positive basket cell synapses ([Fazzari et al., 2010](#)). Further, Neuregulin signaling facilitates activity-dependent GABA release from mature basket cells and selective loss of ErbB4 in these cells causes a disinhibition of prefrontal pyramidal cells and results in schizophrenia-relevant phenotypes in mice ([Wen et al., 2010](#)).

In another study, the polysialylated form of the neural cell adhesion molecule NCAM has been shown to regulate the timing of perisomatic GABAergic synapse maturation in mouse cortex ([Di Cristo et al., 2007](#)). NCAM is polysialylated by two polysialyltransferases ST8SialII and ST8SialIV. SNPs in ST8SialII have been implicated in schizophrenia ([Arai et al., 2006](#) ; [Tao et al., 2007](#) ; [Isomura et al., 2011](#)), providing a mechanism by which genetic interference with the complex coordination of NCAM polysialylation and GABAergic synapse maturation may lead to a neurodevelopmental predisposition to psychiatric disease.

In summary, multiple lines of evidence both in humans and animals suggests that the development and function of PV-expressing interneuron are particularly affected in schizophrenia. How can we use this knowledge to design novel targeted therapeutic approaches? Understanding the mechanisms underlying PV-expressing basket cell synapse development and

plasticity may give us tools to modulate their function. Further, it has been proposed that combining pharmacological tools to enhance neural synchrony mediated by PV-positive basket cells along with behavioral therapies involving learning paradigms to reduce or reverse the consequences of altered neuronal circuit development could be an effective means of improving cognitive control in individuals with schizophrenia ([Gonzalez-Burgos et al., 2011](#) ; [Lewis, 2011](#)). It is however important to underline that basket neurons are not the only ones affected in schizophrenia and future efforts are needed to understand how alterations in specific circuits give rise to associated cognitive impairments.

Autism

Autism is a complex neurodevelopmental disorder characterized by abnormal socialization, deficits in verbal and non-verbal communication, and a limited interest in the surrounding environment associated with stereotyped and repetitive behaviors. The incidence of this disorder, which varies between 10 and 20 per 10000 children, has risen dramatically over the past two decades mainly because of the use of broader diagnostic criteria and the increased attention of the medical community ([Levy et al., 2009](#)). Clinical signs are usually present at the age of 3 years, but prospective studies of infants at risk have demonstrated that deficits in social responsiveness and communication could already be present as early as 6–12 months.

A high concordance rate between monozygotic twins (~70%) and a significant sibling risk suggests that autism has a strong genetic component ([Bailey et al., 1995](#)). Although there is a clear genetic basis to autism, the <https://assignbuster.com/gabaergic-circuit-dysfunctions-in-neurodevelopmental-disorders/>

majority of cases have unknown causes (non-syndromic autism). Similar to other complex brain diseases, it is likely that inherited risk factors, in combination with certain environmental or epigenetic triggers, ultimately causes autism. For many human diseases, the generation and characterization of animal models is an essential bridge between understanding the biological features of the disease and the development of targeted therapeutic approaches. The high genetic inheritance of autism has resulted in the generation of several animal models, however their validation has been controversial. Indeed, in the case of autism, modeling human symptoms requires rigorous behavioral tests to examine socialization, communication, and repetitive behavior, which are rather difficult to do in mice.

The majority of autism research has focused on the higher cognitive symptoms, however, its important to consider that the development and proper execution of higher cognitive processes depends on basic primary processing. The behaviors typically altered in autism arise from multiple sensory areas; for example, communication and socialization involve parallel auditory, visual, and somatosensory information processing. Recent studies suggest that altered low-level perceptual information processing is one of the main problems in autism, and this affects higher integrative areas of the brain ([Bertone et al., 2003](#); [Belmonte et al., 2004](#)). Systematic developmental studies in autistic, high-risk infant siblings and control subjects are necessary to better understand the role of sensory processing and perception in the pathogenesis of autism. Nevertheless, these studies suggest that testing sensory processing in mouse models of autism is a

promising approach that could allow for a better understanding of the biological features altered in the autistic brain.

Studies in autistic patients strongly suggest a correlation with dysfunction in the GABAergic system. For example, analysis of post-mortem tissues from autistic patients has shown that the GABA-synthesizing enzymes GAD65 and GAD67 are significantly reduced (~50%) in the parietal cortex and cerebellum ([Fatemi et al., 2002](#) ; [Yip et al., 2007](#)). Multiple studies have also found both GABA_A and GABA_B receptor alterations in autistic brains ([Collins et al., 2006](#) ; [Fatemi et al., 2009](#) , [2010](#) ; [Oblak et al., 2010](#)). Reduced benzodiazepine binding to hippocampal GABA_A receptors further suggests altered modulation of GABA_A receptors in the presence of GABA ([Guptill et al., 2007](#)). The cortex is organized in vertical mini columns of functionally related glutamatergic and GABAergic neurons that process thalamic inputs. Local GABAergic circuits contribute to control the functional integrity of minicolumns via lateral inhibition. Interestingly, the number of mini columns is increased while their width is decreased in autistic brains indicating abnormal cortical organization regulated by inhibitory circuitry ([Casanova et al., 2003](#)). Further, a meta-analysis study of PV expression across multiple autism mouse models found a consistent reduction of PV-positive cells in the neocortex of autism mouse models as compared to controls ([Gogolla et al., 2009](#)). Maybe one of the most convincing indications of altered GABAergic function in autism is the high co-morbidity of autism with epilepsy. Altered GABA function may reduce the threshold for developing seizures. Indeed, ~30% of autistic patients also have epilepsy, and inter-ictal epileptic activity

recorded on scalp EEG occurs in up to 85% of autistic children ([Gillberg and Billstedt, 2000](#) ; [Yasuhara, 2010](#)).

Non-idiopathic autism has been difficult to study because of the lack of suitable animal models. By comparing the molecular mechanisms underlying different single-gene disorders, it may be possible to discover commonalities and general principles that might hold true even for those cases in which no specific genetic cause has been identified. Dysfunction of GABAergic signaling has been shown to occur in the majority of animal models of autism obtained by experimentally manipulating candidate genes for autism susceptibility. Here, we summarize the GABAergic dysfunctions found in animal models carrying either rare mutations identified in autism patients or mutations known to cause diseases that are comorbid with autism. In fact, autism is comorbid with a number of other diseases, including Rett and Angelman Syndrome, which have known genetic causes and have been modeled in transgenic mice.

Mutations in neuroligin-neurexin adhesion complex

A small percentage of autistic patients carry single mutations in genes encoding for synaptic cell adhesion molecules of the neurexin (NRXN)-neuroligin (NLG) families. These include mutations in genes encoding for NRXN1 ([Szatmari et al., 2007](#) ; [Kim et al., 2008](#)), NLG3, and NLG4 ([Jamain et al., 2003](#) ; [Laumonier et al., 2004](#)). Neuroligins are postsynaptic transmembrane molecules localized at both excitatory and inhibitory synapses, where they bind with presynaptic neurexins. Neuroligin-neurexin complex has been shown to regulate the formation of both excitatory and

inhibitory synapse (for a review see [Craig and Kang, 2007](#); [Huang and Scheiffele, 2008](#); [Südhof, 2008](#)). In particular, a point mutation (R451C) that replaces an arginine with a cysteine in the extracellular portion of neuroligin-3 was identified in two brothers, one with severe autism and the other with Asperger syndrome ([Jamain et al., 2003](#)). In addition, a mutation in neuroligin-4 has been discovered in another set of autistic brothers ([Jamain et al., 2003](#)). Interestingly, mice carrying the mutation R451C show an upregulation of inhibitory markers, including the vesicular GABA transporter (VGAT) and the postsynaptic scaffolding protein gephyrin. Further, inhibitory transmission in the somatosensory cortex is functionally augmented as shown by increased frequency of miniature IPSCs, increased amplitude of evoked IPSCs, and increased IPSC amplitude in response to GABA application. Mutant mice show behaviors relevant to autism, including altered socialization and enhanced spatial learning ([Tabuchi et al., 2007](#); but see also [Chadman et al., 2008](#)). However, none of these molecular, physiological, and behavioral phenotypes were found in neuroligin-3 knockout mice, suggesting that this particular mutation results in a gain-of-function though the mechanism is still not well understood. In addition, mice lacking neuroligin-4 show lack of reciprocal social interaction and reduced ultrasonic vocalization, providing further evidence that mutant neuroligin mouse models may be useful to study neuronal circuit alterations in autism ([Jamain et al., 2008](#)).

Rett syndrome

Mutations in the X-linked MeCP2 gene, which encodes the transcriptional regulator methyl-CpG-binding protein 2 (MeCP2), causes the majority of Rett <https://assignbuster.com/gabaergic-circuit-dysfunctions-in-neurodevelopmental-disorders/>

syndrome the majority of Rett syndrome cases. Rett syndrome is characterized by an apparently normal early development followed by developmental regression, including loss of language skills, motor abnormalities, cognitive deficits, stereotyped behavior, respiratory dysrhythmias, and seizures sometimes leading to premature death.

To uncover the molecular changes that underlie Rett syndrome, mouse models with different MeCP2 mutations have been generated. The analysis of synaptic circuit structure and function in these mouse lines showed several defects in the formation/maturation of neuronal GABAergic connectivity, which seem to be specific to selected brain regions, including the ventro-lateral medulla, the ventral basal complex, the reticular thalamic nucleus, and the cerebellum (reviewed in [Boggio et al., 2010](#)). Interestingly, wildtype GABAergic neurons express 50% more MeCP2 than wildtype non-GABAergic cells. Based on this observation, a conditional mutant mouse was generated where MeCP2 was exclusively disrupted in GABAergic cells using a VGAT-Cre mouse line. These mice develop nearly all of the symptoms that arise in germline MeCP2 knockout mice, including limb clasping, self-injury from excessive grooming, motor deficiencies, increased prepulse inhibition, altered socialization, and decreased lifespan. Further, GABAergic neurons, in these mice, exhibit reduced inhibitory quantal size, reduced GAD65 and GAD67 levels, and reduced GABA immunoreactivity. In addition, specific knockout of MeCP2 in forebrain GABAergic neurons recapitulates many of the symptoms observed in germline MeCP2 knockout mice ([Chao et al., 2010](#)), therefore suggesting that disruption of MeCP2 exclusively in inhibitory neurons is sufficient to cause Rett syndrome in mice.

Angelman syndrome

Linkage and association studies have revealed that the chromosomal region 15q11-q13 is strongly implicated in autism spectrum disorders ([Shao et al., 2003](#)). Maternal duplications of this region remains one of the most common cytogenetic abnormalities found in cases of idiopathic autism, which account for 1-2% of the total cases. Deletion of this region results in either Angelman or Prader-Willi syndrome, depending on which parent the deletion comes from. Within this chromosomal region, there is a gene cluster of GABA_A receptors: Gabrb3, Gabra5, and Gabrg3, encoding for β 3, α 5, and γ 3 subunits, respectively. Individuals with 15q11-13 deletions usually have more severe epilepsy than those with more specific mutations for example in the gene E3 ubiquitin ligase, which are sufficient to cause Angelman syndrome, but spares the GABA_A R gene clusters ([Minassian et al., 1998](#)). Among different GABA_A receptor genes, the targeted deletion of Gabrb3 gene, encoding for the β 3 subunit, leads to abnormalities in social behavior, cognitive deficits, motor stereotypes, and seizures, reminiscent of the autistic phenotype ([DeLorey et al., 1998](#)).

In summary, numerous studies both in human and animal research suggests that GABAergic interneuron development and function are affected in autism. It remains to be seen however, whether these alterations are brain region and/or circuit specific and most importantly, if they are a general feature of all autism cases. So far autism is defined as a “ spectrum disorder” due to the extraordinary heterogeneity of intellectual ability, associated symptoms, and possible etiology. Future studies, therefore, are critical to establish specific network alterations that are reliably and

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consistently associated with the autism phenotype. Moreover, the generation of animal models carrying human mutations will be invaluable in dissecting the network, cellular, and molecular changes underlying autism.

Modulation of GABAergic Transmission as a Tool to Restore Plasticity

Multiple lines of evidence critically implicate GABAergic dysfunction in neurodevelopmental diseases, including schizophrenia and autism. It is important to note that alterations in GABAergic functions are most likely not limited to these disorders. For example, a mouse model of neurofibromatosis Type 1, a neurodevelopmental disorder associated with cognitive impairments, including difficulties with visuospatial skills and executive function, as well as an increased incidence of autism, shows increased GABA release, which underlies LTP and learning deficits ([Cui et al., 2008](#)). These findings open the question as to whether rescuing specific GABAergic defects might ameliorate at least in part the cognitive deficits. Since the GABAergic network is truly heterogeneous with distinct GABAergic cell types, and multiple GABAergic receptor isoforms, further studies are essential to develop a targeted approach toward a specific class of GABAergic cells or/and its associated specific cognitive function(s).

Altered GABA function, caused either by genetic/epigenetic or environmental factors, or most likely by a combination of the above, affects the developmental trajectory of interneuron connectivity ([Chattopadhyaya et al., 2007](#) ; [Baho and Di Cristo, 2012](#) ; [Wu et al., 2012](#)). In turn, the formation of interneuron connectivity during early development is critical to the emergence of optimal network architecture that subserve different cognitive

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functions in the adult brain. Therefore it is likely that factors that cause the initial perturbation in GABAergic circuits would consequently affect the processing of incoming sensory stimuli and drive the developmental process along an abnormal trajectory. This leads to important, recurrent questions for the appropriate therapeutic strategies: What is the developmental window of opportunity for pharmacological treatment of neurodevelopmental diseases? Can existing symptoms be corrected or improved, or is it necessary to initiate treatment early in pre- or postnatal development prior to the onset of symptoms? In other words, is it possible to change abnormal neuronal circuits after their formation and consolidation? Recent studies aiming at reversing cognitive and neural circuit deficits using genetic, pharmacological, or environmental strategies in different mouse models of neurodevelopmental diseases have shown encouraging results. For example, in a mouse model of Rett syndrome, MeCP2 function was restored during or following onset of symptoms using a tamoxifen-inducible Cre-LoxP strategy, resulting in the robust reversal of several associated phenotypes ([Guy et al., 2007](#)). Further, early enriched environment starting before the second postnatal week dramatically improved several phenotypes of MeCP2 mutant mice ([Lonetti et al., 2010](#)). In addition, pharmacological treatments have been shown to improve memory impairments in mouse models of Tuberous Sclerosis ([Ehninger et al., 2008](#) ; [Auerbach et al., 2011](#)) or Fragile X Syndrome ([Krueger and Bear, 2011](#)). All together, these studies constitute an important proof of principle that the course of neurodevelopmental diseases could be arrested and even reversed with manipulations begun in late childhood and early adolescence, at least in animal models.

Although the human brain retains plasticity through life, continuously reorganizing its connections in the face of new experiences, the foremost period of heightened plasticity is during childhood when there exist “critical periods” during which experience can produce permanent, large-scale changes in neuronal circuits. Understanding the mechanisms that underlie activation and regulation of such critical periods in the central nervous system may help us develop rational pharmacological approaches to correct alterations in the brain of children with neurodevelopmental disorders involving altered synapse formation and/or plasticity.

The most widely studied model of experience-dependent plasticity is ocular dominance (OD) plasticity in the visual cortex. Electrophysiological recordings from neurons in the primary visual cortex show activation to different degrees by visual stimuli presented to one eye or the other, a property termed OD. Closing one eye during a specific postnatal time period causes synaptic reorganization of neural circuits in visual cortex, resulting in lifelong, irreversible reduction of the ability of the deprived eye to drive neuronal responses in the cortex, and an increase in the number of neurons responsive to stimuli presented to the open eye. This time period specific change in eye preference following manipulation of visual inputs is called OD plasticity ([Hubel and Wiesel, 1970](#)). In adults, however, such plasticity in OD, while not eliminated, is strongly restricted.

Convergent studies show that development of inhibitory circuitry in the cortex is critical for controlling the onset and time course of critical periods. For example, the onset of visual cortical plasticity is delayed by genetic

disruption of GABA synthesis ([Hensch et al., 1998](#)). In parallel, application of benzodiazepines or other treatments that accelerate GABA circuit function triggers premature plasticity ([Huang et al., 1999](#) ; [Fagiolini and Hensch, 2000](#) ; [Di Cristo et al., 2007](#)). Further, recent results implicate intracortical inhibition as a fundamental limiting factor for adult cortical plasticity. In adult animals, where inhibitory circuits are fully developed, a brief reduction of GABAergic inhibition is sufficient to reopen a window of plasticity in the visual cortex well after the normal closure of the critical period ([Harauzov et al., 2010](#)). In addition different pharmacological and environmental strategies shown to enhance plasticity in the adult visual cortex, act at least in part, through a reduction of GABAergic inhibition ([Sale et al., 2007](#) ; [Maya-Vetencourt et al., 2008](#)).

In an elegant study, [Southwell et al. \(2010\)](#) showed that transplanted MGE GABAergic precursors are sufficient to trigger a plasticity response in the host cortex of young mice. Interestingly, grafted interneurons promote plasticity only when they reach a cellular age comparable to that of the endogenous counterpart during the critical period, suggesting that plasticity is successfully initiated by a cell-autonomous program present in interneuron progenitors and is minimally influenced by the age of the host tissue. It is still unknown, however, whether transplantation of interneurons could induce visual plasticity in adults; nevertheless these findings suggest that cell transplantation might be effective in triggering plasticity processes.

In addition to GABAergic inhibition, several other factors have been implicated in limiting adult plasticity ([Pizzorusso et al., 2002](#) ; [McGee et al.,](#)

[2005](#) ; [Syken et al., 2006](#) ; [Bavelier et al., 2010](#) ; [Morishita et al., 2010](#)).

Therefore, targeting multiple pathways maybe key to successfully increase plasticity in the adult brain at a level sufficient enough to trigger long-lasting neural circuitry reorganization. Further along the road, coupling cognitive rehabilitation with pharmacological treatments that facilitate brain plasticity, could correct neuronal network connectivity and function and, ultimately, improve cognitive deficits.

Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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