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What does the developing brain tell us about neural diseases?

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Abstract

In a recently published report, the European Brain Council estimated that the annual cost of brain disorders is larger than the cost of all other disease areas combined, including cardiovascular diseases, cancer, and diabetes. The World Health Organization concluded that approximately one-third of the total burden of disease in Europe is attributable to brain disorders. Therefore, drug development for neural diseases should flourish and attract large pharmaceutical companies and smaller enterprises alike. However, this is far from being the case: industry is cutting down on research and investment in brain disorders in Europe. Political reasons may be contributing to this, but they do not constitute the only explanation. An important reason for the decreasing interest and investment is the lack of drug targets in neural diseases. In order to change this, greater efforts at understanding the etiologies and pathogenetic mechanisms of disorders of both the developing and the adult brain are required. We need to strengthen basic research to understand the brain in health and disease. A shift from translational to basic research is required to meet the need for drugs and therapies in the future. In support of this, I summarize some recent studies indicating that the developing brain has much to offer in this respect. The processes and genes involved in brain development are linked to the etiologies not only of neurodevelopmental but also of neurodegenerative diseases.

Introduction

According to a study of the European Brain Council, brain disorders caused costs of almost €800 billion in Europe in 2010 (Gustavsson *et al.*, 2011). Sixty per cent of these costs were healthcare costs, and 40% were indirect costs resulting from reduced or lost productivity of patients. These costs will rise as the population grows older, as age is the major risk factor for neurodegenerative diseases, which are the most expensive brain disorders when only direct costs are compared. In Europe, the prevalence of dementia was, on average, 14.8% for the ≥ 80-year group and 23.7% for the ≥ 85-year group when studies between 1989 and 2003 were taken as the basis. However, brain disorders are also expensive with regard to diseases that affect young individuals. Neurodevelopmental disorders, such as autism spectrum disorders (ASDs) and intellectual disability or mental retardation, are chronic diseases that require lifelong treatment and medical care. Mental retardation is the third most expensive disease when direct costs are compared. The European Brain Council estimates direct costs associated with intellectual disability to be more than €43 billion annually.

After many decades of searching for a cure for neural diseases, we find ourselves unable to cure any one of them. The currently available drugs can mostly delay disease onset or alleviate symptoms. Big pharmaceutical companies are dropping or shrinking research for neural diseases, because they see no quick fix for the problems (Abbott, 2011; Muglia, 2011). Their current strategy is influenced by shareholder value and success in the stock market. Therefore, companies shy away from long-term investment in basic research. However, this is very problematic, as there are no low-hanging fruits to pick. In many areas of drug development for neural diseases, not much progress has been made for decades. For instance, drugs for the treatment of schizophrenia are still largely based on the substances that were identified in the 1950s (Brandon & Sawa, 2011). One of the major problems is the absence of identified drug targets, as the molecular and cellular mechanisms underlying schizophrenia are not understood. This is not different for most other neural diseases. We do not understand the etiology and the pathogenesis of intellectual disability, autism, or depression. They have in common the fact that neural circuits do not function properly, but the underlying causes of the malfunction seem to be quite different. Whereas aberrant formation of neural circuits is linked to neurodevelopmental diseases, neurodegenerative diseases are associated with a problem in the maintenance of neural circuits. However, knowing this does not really help us much to understand the specific features of these diseases.

In this article, which is not intended to be a comprehensive review on neural diseases, I point out the link with neurodevelopmental genes and processes that is common to many neural diseases, including autism, schizophrenia, and intellectual disability. Interestingly, genome-wide association studies even point to a link between genes known to affect neural circuit formation and neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease

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(Lin *et al.*, 2009). Therefore, I consider a better understanding of brain development to be of the utmost importance in learning more about the etiology not only of neurodevelopmental diseases but also of neural diseases of the adult nervous system as the basis for drug development in the future.

Defective synaptogenesis in schizophrenia

Schizophrenia affects ~1% of the population worldwide. Schizophrenia, first described approximately 100 years ago by Eugen Bleuler and Emil Kraepelin, manifests with so-called positive and negative symptoms, as well as cognitive deficits. Positive symptoms include thought disorders, delusions, hallucinations, and paranoia (Lewis & Lieberman, 2000). Social withdrawal, anhedonia, apathy and paucity of speech are summarized as negative symptoms. Cognitive impairments have gained increasing recognition as a central feature of schizophrenia (Ross *et al.*, 2006). They consist of deficits in perception, attention, learning, short-term and long-term memory, and executive functions. Currently available antipsychotics effectively treat the positive symptoms, but have little or no effect on the negative symptoms, and do not improve cognitive impairment. Some patients are not responsive to antipsychotic drugs, which have severe side effects (Field *et al.*, 2011).

Until recently, the dominant hypothesis suggested excessive dopaminergic transmission in the forebrain as a key factor in the pathogenesis of schizophrenia. This hypothesis was based on the observation that antagonists of dopamine D2 receptors were clinically effective antipsychotic drugs. Indirectly, this hypothesis was supported by the psychomimetic properties of dopamine agonists and alterations in striatal dopamine release observed in schizophrenic patients (Conn *et al.*, 2009). Alternatively, dysfunction of glutamatergic neurotransmission was suggested as an explanation for the symptoms of schizophrenia (Gaspar *et al.*, 2009).

More recently, a imbalance between inhibition and excitation in neural circuits was postulated as the basis of schizophrenia. An excellent recent review summarizes the evidence for a link between interneuron dysfunction and cognitive impairment in neural diseases (Marin, 2012). A particular paravalbumin-positive subtype of GABAergic interneurons has been identified as a promising candidate for a central role in the pathogenesis of schizophrenia.

In addition to physiological disturbances, structural changes in the brains of schizophrenic patients have been identified with modern imaging methods (summarized by Ross *et al.*, 2006). Furthermore, functional magnetic resonance imaging studies suggest that the communication between different brain areas is more affected than the function of individual brain areas, consistent with the idea that schizophrenia is caused by defective neural circuits (Schmitt *et al.*, 2011). So far, the deficits have been largely attributed to the late stages of neural development, in particular pruning of excessive synapses, and aberrant synaptic plasticity (Lewis & Levitt, 2002).

This view is, in part, corroborated by genetic studies. The heritability of schizophrenia is high (Lewis & Levitt, 2002). Many of the genes that have been linked to schizophrenia are involved in synaptic structure and function (Xu *et al.*, 2008; 2011; Gejman *et al.*, 2011; Rodriguez-Murillo *et al.*, 2012). However, genes involved in the earlier stages of development have been linked to schizophrenia in several studies. One study searching for genes disrupted in schizophrenia patients as compared with their unaffected relatives found an overrepresentation of genes known to affect neural circuit formation (Walsh *et al.*, 2008). Among the pathways and processes that were significantly overrepresented were axon guidance, integrin signaling, ephrin receptor signaling, and Shh signaling. Preliminary evidence from a small cohort of patients with schizophrenia also identified a number of polymorphisms in genes linked to early neural development and axon guidance, such as those involved in the Notch pathway, the Wnt pathway, and semaphorin and neuropilin signaling (Gregório *et al.*, 2009).

Another example of a gene linked to schizophrenia with a known role in early neural development is *DISC1*, suggesting that neuronal migration is affected in patients suffering from schizophrenia (Brandon & Sawa, 2011). Disc1 is a scaffold protein that interacts with proteins known to be required for neuronal migration, both in animal models and in humans. In animal studies with mice and worms, Disc1 was shown to interact with Fez1 during neurite outgrowth (Miyoshi *et al.*, 2003; Kang *et al.*, 2011). A direct interaction of Disc1 with Trio and the Rac–Pak pathway was linked to axon guidance defects (Chen *et al.*, 2011).

Similarly, *NRG1* and *ERBB4*, which have been linked to schizophrenia, affect the early stages of neural development (Rico & Marin, 2011). The number of parvalbumin-expressing GABAergic interneurons depends on Nrg1–ErbB4 interaction, as the migration of interneuron precursors from the medial ganglionic eminence to their final destination in the cortex fails in its absence. Furthermore, the absence of ErbB4 appears to correlate with a decrease in synaptic contacts between parvalbumin-positive interneurons and pyramidal neurons. These findings are consistent with the hypothesis that schizophrenia is the result of an imbalance between excitation and inhibition (see above), but they also point to contributions of early developmental events to the pathogenesis of the disease. Synaptogenesis and synaptic pruning are not the only processes that are affected in schizophrenia, at least not in all patients.

ASDs result from aberrant neural circuit formation

The importance of a balance between excitation and inhibition for normal cortical function is undisputed. Schizophrenia is not the only neuropsychiatric disease in which this balance is perturbed. Other developmental diseases, such as ASDs, are also associated with aberrant connectivity and a resulting imbalance between inhibition and excitation. This has been particularly well studied in mouse models of Rett syndrome.

Rett syndrome is a monogenetic form of autism

Rett syndrome is an X-linked developmental disease that belongs to the ASDs (Chahrour & Zoghbi, 2007). Mutations in the gene for methyl-CpG-binding protein 2 (*MECP2*) have been identified as underlying cause of the disease. Mecp2 binds to methylated DNA and represses the expression of many different target genes (Chahrour *et al.*, 2008). Females affected with the disease develop normally for the first 6–18 months life, but then start to lose previously achieved developmental milestones. In particular, they show a loss of acquired motor and language skills. The disease is accompanied by repetitive hand-wringing, abnormal breathing patterns, and autistic traits. Boys with *MECP2* mutations rarely survive the first year of life. Interestingly, duplication of *MECP2* was also found in patients with mental retardation, seizures, respiratory problems, and progressive spasticity, along with features of autism and Rett syndrome [summarized in Chahrour & Zoghbi (2007)].

Mouse models provide evidence for a shift in the balance between excitation and inhibition that leads to reduced cortical activity. Importantly, these changes were found in mice before the onset of

detectable symptoms at the age of 3–6 weeks. However, distinct brain areas are affected differently, as shown by the analyses of many different *Mecp2* mouse mutants [see Marin (2012) for a summary of available brain area-specific mouse mutants]. Mice with a deficiency in Mecp2 in GABAergic neurons showed a reduced level of GABA and, as a consequence, higher excitability of cortical neurons. In contrast, mice with a global deficiency of Mecp2 in all neurons show reduced cortical excitability. Nevertheless, both types of mouse show features of Rett syndrome [reviewed in Shepherd & Katz (2011)].

The phenotype of *Mecp2* null mice manifests with uncoordinated gait, tremor, hindlimb clasping, and breathing problems. Symptoms worsen until mice die as young adults. The brains of *Mecp2* knockout mice are smaller in size and weight than those of normal mice. The cells are smaller and more densely packed than in littermate controls. Similarly, reduced brain and neuron size are also found in postmortem analyses of patients with Rett syndrome.

ASDs are highly heritable but the genetics are still poorly understood

Most forms of autism are not caused by mutations in a single gene. First described by Leo Kanner, autism was characterized by a severe disturbance of social interactions. ASD, the term used today, reflects the fact that autism is a disorder that is found with variable degrees of severity, all including the core features: problems in social interactions and communication, as well as stereotypic, repetitive behaviors. In most types of autism, language deficits are found, and ~50% of patients are mildly to severely mentally retarded. In the USA, ASD is diagnosed in 1/150 to 1/200 live births, and classical autism in about 1/500 (Geschwind, 2009). Motor disturbances, such as gait abnormalities and incoordination of upper body movements, sleep disruption, and epilepsy, are common co-morbidities of autism (Maski *et al.*, 2011).

Largely triggered by support from organizations such as 'Autism Speaks' and 'Cure Autism Now', now merged into a single organization, autism research has experienced an enormous boost in the last few years. Genome-wide association studies (GWASs), linkage analyses and the genome-wide analysis of copy number variations have provided long lists of ASD susceptibility genes (Sebat *et al.*, 2007; Marshall *et al.*, 2008; Pinto *et al.*, 2010; Gilman *et al.*, 2011).

On the basis of studies of patients diagnosed with ASD, as well as animal models, the concept of ASD as a 'developmental disconnection syndrome' or as an 'underconnectivity disorder' has been put forth (Geschwind & Levitt, 2007). Other than in schizophrenia, the involvement of factors affecting the early stages of neural development in the pathogenesis of the disease is more obvious and has been widely accepted. Processes such as cell migration, axon pathfinding, and synapse formation, that is, the initial wiring of brain, are affected, although late developmental events such as synaptic pruning may also be involved. Disturbances in the regulation of these processes are in line with the ASD features seen in patients. In addition to the functional disturbances, transient macrocephaly is seen in a subpopulation of ASD patients. Interestingly, this 'overgrowth' of the brain appears to be mainly a postnatal event, as head circumference was not above average in 90–95% of the neonates who were diagnosed with ASD later (Courchesne *et al.*, 2007). Adult patients no longer have larger brains than controls, with few exceptions.

Some of the recurrent findings in postmortem analyses of ASD brains or analyses of patient brains with modern imaging techniques show aberrant positions of Purkinje cells and decreased connectivity of the two hemispheres, as concluded from the smaller size of the corpus callosum [summarized by Courchesne *et al.* (2007)]. Thus, aberrant axon guidance during development is widely accepted as a contributor to the disease in some patients with ASD, and particularly in Joubert syndrome (Juric-Sekhar *et al.*, 2012). Joubert syndrome is a rare autosomal recessive disorder (Doherty, 2009). Patients suffer from hypotonia, ataxia, abnormal breathing patterns, mental retardation, and autism. Aberrant axonal connectivity and underdevelopment of the cerebellar vermis, together with aberrant development of the cerebellar peduncles, summarized as the 'molar tooth sign' on the basis of their appearance in magnetic resonance images, are hallmark findings in Joubert syndrome. In some patients with Joubert syndrome, axon tracts differ so strongly from those in normal brains that their aberrant formation is detectable at the resolution provided by imaging techniques, such as magnetic resonance imaging and diffusion tensor imaging (Poretti *et al.*, 2007; Engle, 2010; Juric-Sekhar *et al.*, 2012). Despite the distinct genetic mutations found in patients with Joubert syndrome, the observed brain abnormalities are similar, consistent with the idea that these genes affect a common developmental process. In the case of Joubert syndrome, the common denominator appears to be the cilium. Primary cilia are signaling centers of cells during development (Goetz & Anderson, 2010; Louvi & Grove, 2011). In particular, cilia have been linked to Wnt and Shh signaling during patterning and differentiation. So far, cilia have not been implicated directly in axon guidance and synaptogenesis. However, as both Wnt and Shh signaling have been linked to these processes (see below), a role for cilia in these later developmental steps cannot be ruled out.

A role for cilia-based Shh signaling in cerebellar development is well supported by experimental evidence for regulation of granule cell proliferation by Purkinje cell-derived Shh. Reduced proliferation rates, in turn, result in hypoplasia, failure of foliation, and reduced size of the cerebellar lobes (Wallace, 1999; Juric-Sekhar *et al.*, 2012).

Among the first genes linked to autism were *NLGN3* (encoding neuroligin-3) and *NLGN4* (encoding neuroligin-4), genes that are involved in synapse formation (Jamain *et al.*, 2003; Varoqueaux *et al.*, 2006). Interestingly, the genes encoding the presynaptic binding partners of neuroligin-3 and neuroligin-4, neurexin-1 and neurexin-3, were also identified as ASD susceptibility genes (Betancur *et al.*, 2009). Neurexins (Dean *et al.*, 2003) and neuroligins (Scheiffele *et al.*, 2000) are trans-synaptic adhesion molecules that organize inhibitory and excitatory synapses (Budreck & Scheiffele, 2007; Craig & Kang, 2007).

Contactin-associated protein-like 2 (*CNTNAP2*), which encodes a protein that is structurally related to neurexins, has also been characterized as an ASD susceptibility gene. In the peripheral nervous system, Cntnap2 binds to contactin 2 (Cntn2) at the nodes of Ranvier. This interaction is essential for the molecular organization of the nodes. In particular, the accumulation of potassium channels was perturbed in the absence of Cntnap2/Caspr2 (Poliak *et al.*, 2003; Traka *et al.*, 2003). In the mouse central nervous system, cell migration and the number of GABAergic interneurons were affected in the absence of Cntnap2 (Penagarikano *et al.*, 2011). Interestingly, behavioral anomalies in these mice reflect autistic traits in patients. In one study, a link between *CNTNAP2* and language disorders was described, based on the fact that *CNTNAP2* is a target of FoxP2 (Vernes *et al.*, 2008). So far, molecular interaction partners of Cntnap2 in the central nervous system have not been described.

Axon guidance molecules as candidate disease genes

Axon guidance molecules have been identified as candidate disease genes in both neurodevelopmental and neurodegenerative disorders (Lesnick *et al.*, 2007; Engle, 2010; Mitchell, 2011). Prominent among those are L1CAM (mutations in which were shown to cause CRASH

or MASA syndrome, characterized by mental retardation, hydrocephalus, and gait disturbances) (Wong *et al.*, 1995; Kenwrick *et al.*, 1996), Robo1 (linked to dyslexia in humans; Hannula-Jouppi *et al.*, 2005), semaphorins, plexins, and neuropilins. All of these genes have been found in GWASs for ASD, schizophrenia, and mental retardation.

A link to autism has been found for *CNTN4* (Roohi *et al.*, 2009). The contactin family (*CNTN1–6*) has been identified in several screens for disease susceptibility genes. Deletions and chromosomal abnormalities affecting *CNTN3* and *CNTN4* have been linked to ASD and intellectual disability (Roohi *et al.*, 2009; Pinto *et al.*, 2010). *CNTN5* has been linked to schizophrenia (Glessner *et al.*, 2010) and Alzheimer's disease (Hardy & Williams, 2010).

Contactins are involved in cerebellar development (Stoeckli, 2010) both as axon guidance molecules and in synapse formation. Cntn2/axonin-1 was one of the first molecules characterized as an axon guidance cue required for axonal midline crossing in the spinal cord (Stoeckli & Landmesser, 1995), for proper orientation of granule cell axons in the cerebellum (Baeriswyl & Stoeckli, 2008), and for the appropriate navigation of sensory afferents to their target layers in the spinal cord gray matter (Perrin *et al.*, 2001). Contactin 1 and Cntn2 were shown to interact directly with L1CAM, a gene product linked to intellectual disability (Wong *et al.*, 1995; Kenwrick *et al.*, 1996), schizophrenia (Kurumaji *et al.*, 2001), and depression (Laifenfeld *et al.*, 2005). Furthermore, a direct interaction between Cntn2 and NrCAM, another ASD candidate, was shown to be required for axon guidance (Stoeckli & Landmesser, 1995; Fitzli *et al.*, 2000; Pekarik *et al.*, 2003).

The list of axon guidance molecules as disease candidate genes does not only contain cell adhesion molecules of the immunoglobulin superfamily, but also Slits, Ephs, ephrins, and semaphorins (Lin *et al.*, 2009). Furthermore, it should be kept in mind that some molecules that are labeled as synaptic cell adhesion molecules, owing to their role in synapse formation or synaptic plasticity, have also been shown to affect axon guidance. For example, Cadm1 and Cadm2, better known as SynCAM1/nectin-like molecule 2 or SynCAM2/nectin-like molecule 3, respectively, are required for axon guidance at the midline of the spinal cord (Biederer *et al.*, 2002; Niederkofler *et al.*, 2010).

Wnt signaling affects neurodevelopment and neurodegeneration

A recurrent finding in the lists of genes found in disease susceptibility screens or genome-wide association studies are members of the Wnt signaling pathway. Ten years ago, Wnts were largely thought to act very early in development as morphogens, that is, as molecules that are required for cell differentiation and patterning. However, this has changed completely. In recent years, an involvement of Wnt signaling in axon guidance and synapse formation has been clearly demonstrated (see below). Thus, Wnts constitute an excellent example with which to illustrate my point that understanding the contribution of genes to brain development will teach us about the brain in health and disease.

In the human genome, 19 *WNT* genes are found. Wnts bind to one or several of the 10 frizzled receptors. Signaling can be further modulated by co-receptors that form a receptor complex together with frizzled. Historically, Wnt signaling was segregated into three distinct pathways, the canonical or β-catenin-dependent pathway, the planar cell polarity pathway, and the calcium pathway. The latter two are β-catenin-independent (Logan & Nusse, 2004; Angers & Moon, 2009). However, the segregation into three pathways may only be valid for classical Wnt functions during morphogenesis. Wnt signaling during the later stages of development may even be more complex, and appears to recruit additional components, both as co-receptors at the cell surface and for intracellular signal transduction (Davis *et al.*, 2008).

Wnts were first known for their role in morphogenesis, hence the name morphogens. Morphogens are active very early in embryonic development by controlling the proliferation and differentiation of precursor cells. Morphogens are released by organizers, form gradients, and affect receiving cells in a concentration-dependent manner.

Because of their function in the very early stages of embryonic development, later functions could only be detected after the establishment of more sophisticated gene knockout strategies or by alternative approaches for gene silencing, such as RNA interference. These studies revealed roles of morphogens in the later stages of development. Wnts and other morphogens have been implicated in axon guidance (Lyuksyutova *et al.*, 2003; Liu *et al.*, 2005; Schmitt *et al.*, 2006; Domanitskaya *et al.*, 2010; Fenstermaker *et al.*, 2010) and synapse formation (Hall *et al.*, 2000; Krylova *et al.*, 2002; Salinas, 2005). In addition, Wnt signaling has been shown to contribute to synaptic plasticity (Ataman *et al.*, 2008; Gogolla *et al.*, 2009; Avila *et al.*, 2010; reviewed in Budnik & Salinas, 2011). In axon guidance, Wnt signaling requires planar cell polarity components (Shafer *et al.*, 2011), but it may also act directly on microtubule dynamics via the 'canonical' pathway component glycogen synthase kinase 3β, as suggested for synapse formation (Lucas & Salinas, 1997).

Given these many roles in neural development, it might not be surprising if aberrant Wnt signaling contributed to a variety of neural diseases. Components of the Wnt signaling pathway, that is, Wnts themselves, their receptors, the frizzleds, or intracellular components of the signal transduction cascade downstream of Wnts have been linked to intellectual disability, autism, schizophrenia, depression, and Alzheimer's disease [for reviews, see De Ferrari & Moon (2006) and Inestrosa & Arenas (2010)].

Interestingly, a recent study demonstrated a link between *DISC1*, a gene linked to schizophrenia and depression (see above), and Wnt signaling (Wray *et al.*, 2012). Singh *et al.*, (2011) demonstrated that different Disc1 variants had distinct effects on Wnt-dependent proliferation of precursor cells, most likely via interaction with glycogen synthase kinase 3β, a crucial component of Wnt signaling.

A call for more basic research addressing the development and function of the brain

From the findings of GWASs, linkage analyses, and genome sequencing data, it is clear that the genes involved in neural development are causally linked to a large number of neural diseases. Most importantly, mutations or specific alleles not only predispose individuals to neurodevelopmental diseases, such as intellectual disability, ASDs, and schizophrenia, but also contribute to diseases of the adult brain, such as depression, and even neurodegenerative diseases, such as Parkinson's disease and Alzheimer's disease. Given that the common denominator of all neural diseases is the malfunction of neural circuits, a contribution of aberrant neural circuit formation may be expected not only for neurodevelopmental diseases. Suboptimal connectivity may have been sufficient for apparently normal functioning of the brain during adolescence and young adulthood, but changes in myelin structure and function (Hinman & Abraham, 2007), and the normal loss of synaptic connections associated with aging, may not be tolerated, and may result in symptoms typical of neurodegenerative diseases (Dickstein *et al.*, 2007).

At the clinical level, fuzzy boundaries between different neuropsychiatric diseases and large patient-to-patient variability have been recognized. At the molecular level, the etiologies and pathogenetic

mechanisms of these diseases clearly overlap, as genes involved in cell migration, axon guidance, synapse formation and function are found in genetic screens for most of them. Given the complexity of neural development, it should not be surprising that genes found in one patient cohort are not necessarily confirmed in a second cohort. After all, the diagnoses of all neural diseases are based on symptoms that are variable and extremely difficult to specify qualitatively and quantitatively. Brain functions cannot be segregated into independent neural circuits, and malfunction of one brain area will trigger adaptive and maladaptive changes in other brain areas. The resulting phenotype and, thus, the characteristic features seen in a patient will be the summary of neural circuit function. Depending on the genetic background, not all neural circuits will be affected to the same extent. It is very likely that some circuits will not be affected at all, whereas others will be severely reduced in efficiency. Reduced efficiency of a particular circuit can be the result of a decreased number of cells, aberrant cell migration and therefore mislocalization of neurons in the mature nervous system, aberrant axonal connectivity caused by guidance defects or axonal degeneration, altered synapse formation, and reduced synaptic efficiency and plasticity. These steps are not independent of each other. For example, a decrease in cell number can be caused by a lack of cell proliferation or defects in cell differentiation. However, it can also be the consequence of aberrant cell migration, which, in turn, affects cell fate determination and cell survival.

Fewer neurons means fewer axons and fewer synapses with target cells. Mislocalized neurons may undergo apoptosis, fail to extend neurites, or fail to connect to the appropriate target cell, as axon navigation from an inappropriate location is less likely to be successful. Axon guidance depends on a tightly regulated set of guidance cues and receptors. These guidance cues are provided by intermediate targets and other axons. The precise temporal control of receptors and axon guidance molecules is key for the correct navigation of axons. Axons that fail to establish synapses with their target cells will not contribute to neural circuit function, or may even have detrimental consequences. Most likely, they will not persist and will degenerate. Aberrant synapse formation will cause disturbances in neural activity and prevent the establishment of the proper balance between excitation and inhibition in the brain.

Each of these developmental processes depends on a complex pattern of molecular interactions. In most cases, a slight disturbance of a particular interaction will be tolerated by the system, as each step is regulated by several different contributing molecules. However, multiple disturbances may exceed the safety measures of the system, and have similar consequences as the complete loss of a gene product. Depending on the nature of the faulty protein–protein interaction, different cell types or axons are affected differently. As a result, some neural circuits will be particularly affected, and determine the functional deficits and thus the diagnosis.

Furthermore, the requirement for precise temporal regulation of gene function during neural development explains findings that indicate the involvement of environmental factors in the etiology of neural diseases. Viral infections or substance abuse during pregnancy have distinct consequences for the fetus, depending on the time of gestation. So far, the impact of environmental factors on the molecular mechanisms of neural development has not been extensively analysed. Similarly, the reversibility of aberrant developmental processes resulting from intrinsic plasticity or interventions at later stages of development or in the mature nervous system has been largely unexplored. The remarkable finding that developmental deficits caused by the absence of Mecp2 in a mouse model of Rett syndrome was reversible in adult mice should provide hope that even structural deficits can be overcome, to some degree, at the functional level (Guy *et al.*, 2007). Improvement and reversal of symptoms were also found in a number of other animal models of neurodevelopmental disorders (Ehninger *et al.*, 2008).

As indicated by all of the above, the common basis of neural diseases and their distinctive features can only be understood if we learn more about brain development. We should take advantage of the long lists of candidate genes identified by GWASs and linkage analyses for different neural diseases, and try to assign them to different processes in brain development and function. We should also not be too concerned about failures to identify the same genes in different patients. Rather, we should start thinking in terms of pathways and gene networks underlying specific processes. The analysis of gene function cannot be performed with high-throughput approaches, and is not an aspect of translational or applied research. It will not make headlines in the evening news. It is basic research that enhances our understanding of the brain in health and disease. Therefore, I hope that funding agencies will resist the temptation to shift their focus more and more away from basic to applied research, because applied research is 'easier to sell' to politicians and taxpayers. We need a strong commitment to basic research, not only, but particularly, in neuroscience.

Abbreviations

ADS, autism spectrum disorder; Cntn2, contactin 2; Cntnap2, contactin-associated protein-like 2; GWAS, genome-wide association study; Mecp2, methyl-CpG-binding protein 2.

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