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Pre-clinical models of neurodevelopmental disorders: focus on the cerebellum

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Abstract

Recent studies have advanced our understanding of the role of the cerebellum in non-motor behaviors. Abnormalities in the cerebellar structure have been demonstrated to produce changes in emotional, cognitive and social behaviors resembling clinical manifestations observed in patients with autism spectrum disorders (ASD) and schizophrenia. Several animal models have evaluated the effects of relevant environmental and genetic risk factors on the cerebellum development and function. However, very few models of ASD and schizophrenia selectively target the cerebellum and/or specific cell types within this structure. In this review, we critically evaluate the strength and weaknesses of these models. We will propose that the future progress in this field will require time- and cell type-specific manipulations of disease-relevant genes not only selectively in the cerebellum but also in frontal brain areas connected with the cerebellum to advance our knowledge of the cerebellar contribution to non-motor behaviors in mental health and disease.

Keywords

schizophrenia; autism; animal model; cerebellum; Purkinje cells

Introduction

The cerebellum is traditionally considered as the brain area that is involved in the coordination and motor activity (Evarts and Thach, 1969). It has recently become evident that the cerebellum also has extensive connections with the brain areas (e.g., prefrontal and posterior parietal cortex) that deal with non-motor tasks (Clower et al., 2001, 2005). Thus, altered cerebellar structure and function could lead to several abnormalities in the emotional,

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cognitive and social domains often observed in patients with such neurodevelopmental disorders as autism spectrum disorders (ASD) and schizophrenia (Leiner et al., 1986; Schmahmann, 1991; Leiner, 2010). Thus, our view of the complex neurobiology of ASD and schizophrenia will remain incomplete without a better understanding of the role of the cerebellum in the non-motor functions (Andreasen and Pierson, 2008).

Here, we provide a brief summary of the neuropathology and pathophysiology of the cerebellum in ASD and schizophrenia referring the readers to the comprehensive reviews of these topics. Among symptoms that suggest the cerebellum involvement in schizophrenia are abnormalities in coordination and posture, impaired eyeblink conditioning, deficits in procedural learning (Snider, 1982; Kinney et al, 1999; Konarski et al, 2005). The structural alterations in the cerebellum and related networks have been proposed to contribute to these neurological signs (Andreasen and Pierson, 2008; Yeganeh-Doost P et al, 2011).

Postmortem studies have found decreased gyrification, smaller granular and molecular layers of the vermis and loss of Purkinje cells (PC) (Martin and Albers, 1995; Supprian et al, 2000; Andreasen and Pierson, 2008). Neuroimaging studies have corroborated postmortem findings demonstrating reduced vermis volume, and the altered anatomical and functional connectivity of the cerebellum with the thalamus and cerebral cortex (Villanueva, 2012; Lungu et al, 2013). The neuropathological findings were further supported by gene and protein expression data to demonstrate down-regulation of synaptophysin, SNAP-25 (synaptosome-associated protein of 25 kDa) and complexin and up-regulation of an axonal chemorepellant semaphorin 3A (Eastwood et al., 2001, 2003; Mukaetova-Ladinska et al., 2002). Interestingly, activity and levels of D amino acid oxidase (DAO), the enzyme that metabolizes D-serine, a co-agonist of (N-methyl- D-aspartate) NMDA receptor, were also found upregulated (Burnet et al., 2008). Taking into account the extensive connections between the cerebellum and forebrain areas, cerebellar abnormalities have been suggested to produce “cognitive dysmetria” to explain the “poor mental coordination” observed in patients with schizophrenia (Andreasen et al., 1996; 1998).

Unlike research in schizophrenia, the cerebellum has been always a major focus of neuropathological evaluation in ASD (Fatemi et al, 2012). Several studies have indicated a decrease in the number of PC, although there are negative findings as well (Kemper and Bauman, 1998; Kern, 2003). In addition to PC, abnormal sizes and shapes of neurons of the deep cerebellar nuclei were also observed (Palmen et al, 2004; Amaral, 2008). The findings appear in line with the hypothesis that ASD has a prenatal origin, with some pathogenic processes continuing after birth (Fatemi et al, 2012). Structural magnetic resonance imaging (MRI) studies have produced conflicting data, possibly related to considerable heterogeneity of ASD, with the majority of individuals with ASD exhibiting vermal hypoplasia and a subset having vermal hyperplasia. Functional MRI studies have further indicated that the cerebellum is functionally abnormal in ASD patients (Courchesne, 1991; Verhoven et al, 2010; Fatemi et al, 2012). Similar to schizophrenia, the glutamatergic and GABA systems of the cerebellum are affected in ASD patients (Blatt, 2005). Thus, the available findings seem to point to common (e.g., decreased volume of the vermis) and somewhat disease-specific (e.g., reduced number and ectopic PC in ASD) pathology of the cerebellum in ADS and schizophrenia.

Human genetic and epidemiological studies have identified genetic risk factors (Sullivan et al., 2012) and environmental adversities (Chaste and Leboyer, 2012; Michel et al., 2012; Goines and Ashwood, 2013) associated with autism and schizophrenia. The known genetic and environmental risk factors seem to predominantly impact prenatal brain maturation, with behavioral abnormalities manifesting during postnatal period (Rapoport et al., 2012; Rodriguez-Murillo et al., 2012). Based on the human data, numerous genetic and environmental animal models have been generated to elucidate the mechanisms of abnormal neurodevelopment. The majority of animal preparations have focused on the frontal cortex, hippocampus and striatum (Pratt et al., 2012; Arguello and Gogos, 2012). Much fewer studies have attempted to evaluate the effects of genetic mutations or environment adversities on the cerebellum and resultant behaviors that would mimic clinical aspects of such neurodevelopmental disorders as autism spectrum disorder (ASD) and schizophrenia (Rogers et al., 2013). In this review, we will critically evaluate the animal models of cerebellar abnormalities pertinent to ASD and schizophrenia and provide the recommendations for the future research in the field.

Animal models of cerebellum dysfunction

Environmental models

Borna virus disease model—Borna disease virus (BDV) is a neurotropic RNA virus that was linked to schizophrenia, bipolar disorders and depression in several studies (Rott et al., 1985; Sierra-Honigmann et al., 1995; Waltrip et al., 1995; Taieb et al., 2001; Arias et al., 2012). However, BDV's involvement in human illnesses has always remained a controversial topic, and one recent report seemed to have conclusively demonstrated the lack of BDV presence in the samples from patients with autism and other psychiatric conditions (Lipkin et al., 2011). Nonetheless, neonatal BDV rat model of neurodevelopmental damage was instrumental in illuminating the pathways whereby neurotropic viruses impact brain maturation, resulting in behavioral abnormalities resembling ASD and schizophrenia (Pletnikov et al., 2002). Among others, the outcomes of neonatal BDV infection in rats include: (1) a gradual loss of Purkinje cells (PC) and the ensuing reduced size of the cerebellum; (2) hyperactivity, social-play deficits, cognitive deficits, and chronic anxiety; and (3) altered brain regional monoamine levels (Pletnikov et al., 2002). It has been demonstrated that both direct effects of the virus on PC (one of the main targets of BDV in the brain) and chronic inflammation resembling human postmortem data are responsible for the brain and behavior abnormalities in BDV-infected rats (Pletnikov et al., 2003; Dietz et al., 2004; Lancaster et al., 2007). Although BDV model no longer has relevance to human psychiatric disease, the neuroimmunological and neurobehavioral studies with this model were ones of the earliest systematic investigations of how a neurotropic virus infection affects neurodevelopment to produce behavioral alterations consistent with aspects of ASD and psychotic disorders.

Valproic acid—Valproic acid (VPA) is an anticonvulsant and mood-stabilizer used to treat certain types of epilepsy, mania in bipolar disorder, and migraines (Rouillet et al., 2013). VPA is a histone deacetylase inhibitor, preventing chromatin from transcriptional silencing. *In utero* exposure to VPA during the first trimester is associated with the elevated risk of

ASD (Boyadjieva and Varadinova, 2012; Chomiak and Hu, 2013), stimulating the development of rodent models to identify the mechanisms of action of VPA on neurodevelopment and behavior. These studies have been recently reviewed elsewhere (Roullet et al., 2013). In brief, the published data consistently indicate that prenatally VPA exposed animals demonstrate abnormalities resembling both the core symptoms of ADS and so-called “additional behaviors” related to the human behavioral pathology, supporting face validity of the model (Roullet et al., 2013). We will overview here only the studies that directly evaluated the effects of VPA on the cerebellum.

Rats exposed to VPA on embryonic (E) day 12.5 had aberrations in the cerebellum similar to those found in patients with ASD, including a reduction of Purkinje cells (PC) and the resultant decrease in the cerebellar volume (Ingram et al., 2000). Multiple studies have demonstrated that VPA-treated rats exhibit exacerbated sensitivity to non-painful stimuli, impaired prepulse inhibition (PPI) of the acoustic startle, hyperactivity, and altered social behaviors. All behavioral changes were found to be present before puberty, consistent with the time of appearance of the clinical symptoms of ASD in humans and different from other animal models of neurodevelopmental disorders, especially rodent models of schizophrenia (Schneider et al., 2006; Schneider et al., 2008; Markram et al., 2008; Dufour-Rainfray et al., 2010).

Stanton et al evaluated autism-relevant alterations in acquisition of classical eyeblink conditioning and in reversal of instrumental discrimination learning in offspring of female Long-Evans rats exposed to VPA at E12. Acquisition of discriminative eyeblink conditioning depends on the brainstem-cerebellar circuitry whereas reversal learning involves long-range interactions between the cerebellum and the hippocampus and prefrontal cortex. VPA exposed rats exhibited faster eyeblink conditioning, in line with the findings in autistic children (Stanton et al., 2007). In a series of cognitive tests, prenatally VPA-treated rats had changes in the delayed non-match-to-sample task, novel object recognition, activity box, and Whishaw tray reaching task. These behavioral alterations were associated with the reduced brain weight and cortical thickness, decreased dendritic branching in the orbitofrontal cortex (OFC) and medial prefrontal cortex (mPFC), and decreased spine density in the mPFC, OFC, and cerebellum (Mychasiuk, 2012). Thus, VPA-produced neuroanatomical abnormalities include a reduced number of PC in the posterior lobes of the cerebellum similar to changes observed in the human brain (Ingram et al., 2000). These neuropathological changes could be, at least in part, responsible for some autism-related behavioral alterations (Rodier et al., 1997).

Importantly, VPA-induced behavioral changes can be reversed by environmental factors. For example, environmental enrichment that included extensive training and handling developing pups and housing rats in large cages, has been shown to reverse almost all behavioral abnormalities produced by a single intraperitoneal injection of 600 mg/kg sodium valproate on day 12.5 after conception (Schneider et al., 2006). Similarly, it was found that VPA-induced behavioral alterations could be ameliorated by treadmill exercise. VPA treatment (400 mg/kg) of rats on P14 led to decreased motor coordination and balance in the rotarod test and vertical pole test. Both behaviors were significantly improved after forced daily 30-min treadmill exercise for 4 weeks, starting on P28. The therapeutic effect of

treadmill exercise on motor deficits was associated with the reelin-mediated anti-apoptotic effect of treadmill on PC (Kim et al., 2013). There is also an intriguing report on ameliorating VPA-produced abnormalities with *Bacopa monniera* (*B. monniera*), a creeping herb of wetlands of India where it is used in traditional ayurvedic medicine. Pregnant rats were exposed to VPA (600 mg/kg, ip) on E12.5 and the offspring was treated with saline or *B. monniera* (300 mg/kg/p.o.) from postnatal day (P) 21-35. Treatment with *B. monniera* significantly improved the behavioral alterations, decreased oxidative stress markers and restored histoarchitecture of the cerebellum (Sandhya et al. 2012).

The findings in mice generally paralleled those in rats. BALB/c mice injected on P14 with 400 mg/kg VPA engaged in fewer social interactions, reduced motor activity in a social context. At 12 and 24 h following VPA, treated mice had up to a 30-fold increase in the number of TUNEL-positive cells in the external granule cell layer of the cerebellum and a 10-fold increase in TUNEL-positive cells in the dentate gyrus of the hippocampus. These observations may provide a histopathological correlate for the social deficits observed following postnatal VPA exposure (Yochum et al., 2008). These authors also tested the hypothesis that genetically altered mice might be more sensitive to toxicants early in life. They used mice with deletion of glutathione-S-transferase M1 (GSTM1), a gene that was associated with increased risk of autism (Buyske et al., 2006) and that encodes for an enzyme involved in the management of toxicant-induced oxidative stress (Wu et al., 2012). GSTM1 knockout (KO) mice treated with VPA on P14 performed significantly fewer crawl-under behaviors compared to saline-treated KO or wild-type (WT) mice given either treatment. It was hypothesized that the *GSTM1* gene may be protective against VPA-induced neuronal injury (Yochum et al., 2010).

Taken together, VPA models are important experimental preparations to recreate cerebellar pathology and neurobehavioral alterations observed in patients with ASD. The main caveat of the VPA models is limited regional specificity of the effects, complicating interpretation of the contribution of cerebellar pathology to behavioral alterations.

Influenza models—Prenatal influenza viral infection has been associated with the development of schizophrenia and ASD (Brown and Derkits, 2010). Fatemi laboratory has pioneered a mouse model of prenatal influenza infection following intranasal administration of live virus to pregnant mice at different time points across pregnancy (Meyer et al., 2009; Kneeland and Fatemi, 2013). In addition to a number of brain and behavioral abnormalities observed in offspring exposed *in utero* to influenza infection, Fatemi's group found maldevelopment of the cerebellum and significantly altered expression of several genes associated with schizophrenia or ASD (Sema3a, Trfr2 and Vldlr) and involved in abnormal glial-neuronal communication and neuron migration (connexin 43 and aquaporin 4) and myelination (Fatemi et al., 2008a,b; Fatemi et al., 2009).

A Swedish group reported that neonatal olfactory bulb injection of the neuroadapted influenza A virus strain, WSN/33, in C57BL/6 mice produced decreased anxiety and impaired spatial learning in the Morris water maze test. Early postnatal infection also elevated transcriptional activity of two genes encoding for synaptic regulatory proteins, regulator of G-protein signaling 4 and calcium/calmodulin-dependent protein kinase II

alpha, in the amygdala, hypothalamus and cerebellum. Pronounced alteration in expression of the *RGS4* gene, which has been associated with schizophrenia, is intriguing (Beraki et al., 2005).

Although influenza models have convincingly demonstrated the pathogenic properties of live viral infection, one needs to be cautious in generalization of the data to human conditions. First, live influenza infection is usually sub-lethal in mice, suggesting that a number of factors unrelated to direct virus infection (e.g., hypoxia or general sickness of pregnant dams) may be also responsible for the observed phenotypes. Second, there are appreciable differences in the biology of influenza infection between human and mouse, including the brain distribution of the viral receptors (Kim et al., 2013). One of the approaches to overcome the limitations of live infection models includes use of the synthetic compounds that produce immune activation similar to the live virus. It has been argued that these immune stimulators are helpful in evaluating the generic processes of immune activation common to animals and humans (Meyer and Feldon, 2012).

Immune activation—There is a growing appreciation of neurodevelopmental rodent models that mimic prenatal immune activation as one of the major environmental risk factors for ASD and schizophrenia (Meyer et al., 2009; Boksa, 2010; Piontkewitz et al., 2012). Two most popular models are based on maternal exposure to the bacterial endotoxin, lipopolysaccharide (LPS), and the synthetic analogue of double-stranded RNA, polyriboinosinic:polyribocytidilic acid (PolyI:C). LPS is a ligand of toll-like receptor 4 (TLR4), whereas PolyI:C is recognized by TLR3 (Alexopoulou et al., 2001; Triantafilou and Triantafilou, 2002). TLRs are pathogen recognition receptors, which detect invariant structural patterns present on pathogens. LPS and PolyI:C stimulate the production and release of pro-inflammatory cytokines (Kimura et al., 1994; Fortier et al., 2004). LPS exposure leads to a cytokine-associated innate immune response that is typically seen after infection with gram-negative bacteria (Triantafilou and Triantafilou, 2002), administration of poly I:C induces immune activation similar to that due to viral infection (Alexopoulou et al., 2001). Several excellent reviews have been recently published on these models (Meyer, 2009; Meyer and Feldon, 2012; Harvey and Boksa, 2012). We will review a few studies that specifically examined the effects of maternal immune activation on the cerebellum.

Patterson lab assessed the effects of poly I:C (E12.5) on the cerebellum in the offspring. The linear density of PCs in the cerebellum of adult or P11-offspring was studied. To study granule cell migration, BrdU was injected to offspring on P11. Adult offspring of poly (I:C)-exposed mice displayed a localized deficit in PCs in lobule VII of the cerebellum, as do P11 offspring. In addition, heterotopic PCs, as well as delayed migration of granule cells in lobules VI and VII were noted. Importantly, cerebellar abnormalities were observed in both male and female mice. The data suggest that cerebellar abnormalities occur during embryonic development, and may be an early deficit in ASD and schizophrenia (Shi et al., 2009).

Maternal LPS exposure rat model was used to examine the potential link between ASD-like alterations and maternal infection, and expression of neurotrophin-3 (NT-3) and brain-derived neurotrophic factor (BDNF) in the cerebellum. Cerebellar NT-3 levels were elevated

in LPS-exposed pups on P21. LPS exposure was also found to impact the developing cerebellum in strain- and sex-dependent manner via complex mechanisms of oxidative stress (Xu et al., 2013,a,b).

Thyroid models—Thyroid hormone is essential for brain development and maintenance of basal metabolic rates, and hypothyroidism during brain development induces considerable damage to the central nervous system, including cerebellar abnormalities as abnormal migration of granule cells and fewer synapses in cerebellar cortex as well as malformed dendrites on PC (Sadamatsu et al., 2006). A popular model of early postnatal hypothyroidism is based on exposure to 0.02% propylthiouracil (PTU) lactating rats and their pups to induce a temporary mild hypothyroidism in developing animals (Van Middlesworth and Norris, 1980). Kato and his colleagues conducted a series of experiments to systematically investigate the effects of temporary neonatal PTU-induced hypothyroidism on the behavior of rats treated with 0.02% PTU from P0–19 (Kato et al., 1982). The treatment decreased serum T4 level below the limit of detection at 2 weeks of age followed by a recovery by 4 weeks of age (Akaike et al., 1991). Behavioral testing demonstrated hyperactivity and attenuated habituation in the open field test in PTU rats (Akaike et al., 1991; Akaike and Kato, 1997). PTU rats also showed deficient learning and memory in water maze and radial maze tests. Compared to control rats, PTU rats also were inferior in reversal learning in the modified T maze test, suggesting the inability to adapt to changes in the environment (Akaike et al. 1991; Akaike and Kato, 1997). Furthermore, PTU rats were susceptible to audiogenic seizures (Yasuda et al., 2000). These behavioral alterations were associated with delayed granular cell migration in the external granular layer (Sadamatsu and Watanabe, 2005). Taken together, these results suggest that mild hypothyroidism in PTU exposed mice mimic aspects of pathology and behavioral changes in ASD (Sadamatsu et al., 2005).

Table 1 summarizes the main features of the environmental models described. Although these models have shed light on how environmental adversities associated with human psychiatric disease can impact the cerebellum development and function, the main caveats of these models include their limited specificity, significantly impeding our ability to discriminate the primary and secondary cerebellar effects. The recent progress in mouse genetics allows for more accurately linking specific cerebellar defects to resultant behavioral alterations.

Genetic models

Human genetic studies have identified genetic risk factors for ASD or schizophrenia (Gejman et al., 2011; Sullivan et al., 2012). Many of those mutations have been recreated in animals, and we refer the readers to recent reviews of this field (Pletnikov, 2009; Jaaro-Peled et al., 2010; Ey et al., 2011). Here, we will focus on the studies of mutations that impact the cerebellum and have been implicated in ASD and/or schizophrenia in humans. We will not review multiple spontaneous cerebellar mutations in mice that have been extensively reviewed elsewhere (Harkins and Fox, 2002; Dusart, 2006; Vogel, 2007).

Models for autism

Staggerer mice—The staggerer mouse has a mutation of the retinoic acid receptor-related orphan receptor alpha (ROR α) gene that has been implicated in ASD (Hamilton et al., 1996; Nguyen et al., 2010). Studies of staggerer mice have illuminated the functions of ROR α in peripheral tissues and in the brain. This gene is critically involved in maturation and survival of PCs (Boukhtouche et al., 2006) as deletion of this gene leads to a marked loss (up to 80%) of PCs (Herrup et al., 1979, 1996; Doulazmi et al., 2001) and a nearly complete disappearance of granule cells (Landis and Sidman, 1978; Roffler-Tarlov and Herrup, 1981), resulting in profound hypoplasia of the cerebellum. Although ensuing ataxia significantly confounds evaluation of non-motor phenotypes in this mutant model, there are reports about impaired spatial and reversal learning and memory deficits, perseverative behavior, and abnormal responses to novel environments (Goldowitz and Koch, 1986; Misslin et al., 1986; Lalonde et al., 1996). Besides the cerebellum, ROR α is expressed in other brain regions although its role there remains less studied. In addition to neurons, glial cells, particularly astrocytes, have been found to express ROR α , possibly to regulate inflammatory and oxidative pathways (Jolly et al., 2012). New animal models with time-, cell type and region-dependent manipulations of ROR α are needed to better appreciate the possible multiple roles of the gene.

SHANK3—The *SHANK3* gene is localized at chromosome 22q13 and encodes for a postsynaptic protein (Boeckers et al., 2002; Durand et al., 2007). Shank 3 mutation has been found in 2% of autism cases and has been associated with cognitive deficits (Bonaglia et al., 2006; Bozdagi et al., 2010). Although the existing Shank3 models have not yet directly studied the effects on the cerebellum, Shank3 is expressed by granule cells of the cerebellum, suggesting that this gene might be important for cerebellar maturation and synaptic functioning (Beri et al., 2007; Peça et al., 2011; Jiang and Ehlers, 2013). Deletions of the human *SHANK3* gene also span another gene, *IB2*, which is widely expressed in the brain within postsynaptic densities. Ib2 KO mice have altered glutamatergic transmission in the cerebellum, abnormal dendritic arborization of PC and motor and cognitive deficits, consistent with ASD and supporting the role of the human *IB2* mutation in cognitive dysfunction (Giza et al., 2010).

ENGRAILED 2 (En2)—ENGRAILED 2 (En2) is a transcription factor involved in the development of the hindbrain and cerebellum (Kuemerle et al., 1997, 2007; Sillitoe et al., 2008). The gene has been associated with autism in genetic linkage studies (Petit et al., 1995; Sen et al., 2010). EN2 KO mice have decreased number of PC and foliation defects (Millen et al., 1994; Kuemerle et al., 1997, 2007), and demonstrate decreased play, social behavior, and enhanced aggressive behavior (Cheh et al., 2006). En2 null mutants also exhibit robust deficits in reciprocal social interactions as juveniles and adults, and absence of sociability in adults. In addition, impairment in fear conditioning and water maze learning, high immobility in the forced swim test, reduced pre-pulse inhibition, mild motor coordination impairments and reduced grip strength were also reported in En2 null mice. Curiously, other autism-related behavioral measures such as ultrasonic vocalizations, stereotypy or anxiety were found to be unaltered in these KO mice. These findings implicate En2 signaling in social and cognitive behaviors (Brielmaier et al., 2012).

FMR1—The *FMR1* gene encodes for the fragile X mental retardation protein. Mutations of the *FMR1* gene are responsible for fragile X syndrome (Verkerk et al., 1991; Goodrich-Hunsaker et al., 2011) that is characterized by cognitive impairment and other autism-resembling phenotypes (Rogers et al., 2001; Tsiouris and Brown, 2004). *Fmr1* KO mice are hyperactive, exhibit perseverative behavior, and poor learning and memory, including eye blink conditioning and fear conditioning (Koekkoek et al., 2005; Olmos-Serrano et al., 2011). Cerebellar abnormalities in this mouse model include altered (elongated) spines on PCs and a smaller volume of cerebellar nuclei (Koekkoek et al., 2005; Ellegood et al., 2010). Given an emerging role for glia and neuroimmune dysfunction in neurodevelopmental disorders (Schwarz and Bilbo, 2012; Bartzokis, 2012), it is intriguing that *Fmr1* KO mice have cerebellar astroglial activation that could be attenuated with lithium (Yuskaitis et al., 2010). Future studies with this model could address a putative link between neuroimmune activation and behavioral alterations.

Tuberous sclerosis complex (TSC)—TSC is a neurogenetic disorder that is characterized by epilepsy, developmental delay, and autism. TSC is caused by inactivating mutations in either of two genes encoding for the proteins hamartin (TSC1) and tuberlin (TSC2). These proteins form a heterodimer that inhibits the mammalian target of rapamycin complex 1 (mTORC1) pathway, controlling translation and cell growth. Loss of either protein results in altered mTORC1 activation. About 30% of TSC patients have cerebellar pathology (Ertan et al., 2010). To investigate the effects of TSC on the cerebellum, a mouse model with selective deletion of the *Tsc2* gene in PC starting at PND 6 was generated. *Tsc2* conditional knockout mice have a progressive PC loss and ensuing motor deficits amenable to treatment with rapamycin, mTORC1 inhibitor. In a follow-up study, the same group reports that that *Tsc2*^{f/-};Cre mice display increased repetitive behavior in marble burying test and no preference for a live mouse or a novel partner. Intriguingly, these behavioral alterations can be also ameliorated with rapamycin, suggesting that the PC pathology could in part explain ASD-like abnormalities (Reith et al., 2011, 2013). Another group reports that both heterozygous and homozygous loss of *Tsc1* selectively in PC produces abnormal social interaction, repetitive behavior and vocalizations. Treatment of these mutants with rapamycin also prevents the pathological and behavioral deficits (Tsai et al., 2012).

Foxp2—Forkhead box protein P2 (a.k.a. FOXP2) is encoded by the *FOXP2* gene on chromosome 7q31. The protein contains a forkhead-box DNA-binding domain, making it a member of the FOX group of transcription factors (Fisher and Scharff, 2009). Human mutations of *FOXP2* cause severe speech and language disorders (Kang and Drayna, 2011; Bacon and Rappold, 2012). FOXP2 directly regulates a large number of downstream target genes, including a member of the neurexin family, the CNTNAP2 gene associated with language impairment (Penagarikano and Geschwind, 2012).

As the 7q31 region was implicated in ASD, where language impairment is a core component, FOXP2 has also been considered as a potential susceptibility locus for the language deficits in ASD (Newbury and Monaco, 2010). Homozygous *Foxp2* KO mice demonstrate motor impairment, premature death, and absence of maternal separation-induced ultrasonic vocalization. Heterozygous *Foxp2* mice also have altered ultrasonic

vocalization, with learning and memory remaining unaffected. The cerebellum pathology includes misaligned and ectopic PCs with underdeveloped dendritic arbors, thinning of the molecular layer and clumped fibers of radial glia were observed in mice with disruptions in *Foxp2*, supporting a role for *Foxp2* in cerebellar development and social communication (Shu et al., 2005).

Foxp2 (R552H) knock-in (KI) mice carrying the mutation associated with human speech-language disorder have impaired ultrasonic vocalization and abnormal development of PC. mRNA levels of *Cntnap2*, a gene regulated by *Foxp2*, were significantly increased in the cerebellum of KI pups. Although CNTPNAP2 expression is not decreased in poorly developed PC, synaptophysin immunofluorescence is diminished. Interestingly, CNTPNAP2 and CtBP were ubiquitously expressed, while *Foxp2* co-localized with CtBP only in PC. The findings implicate *Foxp2* in ultrasonic vocalization by associating with CtBP in PC, with *Cntnap2* being a putative target of CtBP (Fujita et al., 2012a,b).

The same group also evaluated a possible interplay between *Foxp2* and the mouse orthologue of the gene, *CADMI*, encoding the synaptic adhesion molecule CADM1 (RA175/Nec12/SynCAM1/Cadm1) and associated with autism and language impairment. Similar to *Foxp2* (R552H) KI mouse pups, *Cadm1* KO pups exhibit impaired ultrasonic vocalization (USV) and smaller cerebella. *Cadm1* is predominantly expressed in the apical-distal portion of the dendritic arbor of PC in the molecular layer. VGluT1 levels are decreased in the cerebellum of *Cadm1* KO mice. Reduced immunoreactivity of CADM1 and VGluT1 is found on stunned dendrites of PC in *Foxp2* (R552H) KI pups, whereas *Cadm1* mRNA expression was not altered in *Foxp2*(R552H) KI pups, indicating that *Foxp2* does not seem to target *Cadm1* and loss of *Cadm1*-expressing synapses on the dendrites of PC may be associated with the USV impairment found in both mutant models (Fujita et al., 2012b,c).

GABA receptors—A role of cerebellar γ -aminobutyric acid (GABA) receptors in mediating altered USV in *Cadm1* KO mice was also examined as the C-terminal peptide of *Cadm1* associated with Mupp1 at PSD-95/Dlg/ZO-1(PDZ)(1-5), a scaffold protein containing 13 PDZ domains, which interacts with GABA type B receptor (GABBR)2 at PDZ13, but not with PSD-95. *Cadm1* was demonstrated to co-localize with Mupp1 and GABBR2 on the dendrites of PC in the molecular layers of the developing cerebellum. The amount of GABBR2 protein was increased in the cerebella of *Cadm1* KO mice, suggesting up-regulation of GABBR2 in the cerebellum in the absence of CADM1 may contribute to aspects of autism-related behavioral phenotype (Fujita et al., 2012c). A putative role for GABA receptors of the cerebellum in autism-related behavioral alterations was also evaluated with *Gabrb3* KO mice that displayed less sociability and nesting behavior as well as hypoplasia of the cerebellar vermis (DeLorey et al., 2008). Table 2 summarizes the autism models reviewed.

Models for schizophrenia

G72/G30—Compared to autism models, much fewer studies of cerebellar abnormalities have been conducted with genetic mouse models for schizophrenia. Human genetic studies

have implicated the primate-specific gene locus G72/G30 in schizophrenia, bipolar and panic disorders (Shi et al., 2008; Gomez et al., 2009; Drews et al., 2012). It encodes for a protein LG72 that regulates the peroxisomal enzyme, D-amino-acid-oxidase (DAO), or functions as a mitochondrial protein, which promotes robust mitochondrial fragmentation (Kvajo et al., 2008). Bacterial artificial chromosome (BAC) transgenic mice (G72Tg) expressing alternatively spliced G72 and G30 transcripts, and the LG72 protein, display impaired PPI reversible with haloperidol, increased sensitivity to PCP, motor-coordination deficits, increased compulsive behaviors and deficits in smell identification. G72 expression is prominent in granular cells of the cerebellum, the hippocampus, the cortex and the olfactory bulb. Compared to controls, G72Tg mice had altered expression of proteins involved in myelin-related processes, oxidative stress and mitochondrial function in the cerebellum, indicating the potential molecular correlates of schizophrenia-like behavior (Otte et al., 2009; Filiou et al., 2012; Cheng et al., 2013). Interestingly, an oral treatment with N-acetyl cysteine, a precursor of glutathione, increased the antioxidant capacity and rescued the spatial learning deficit in G72Tg mice (Otte et al., 2011).

Df(16)A KO model—A recent study conducted a high-resolution brain region volumetric MRI analysis of mutant mice, (Df(16)A+/-), that mimic the 22q11.2 deletion, which has been established as a strong genetic risk factor for the development of schizophrenia and cognitive dysfunction. Mutant mice have been shown to have disease-associated abnormalities on synaptic, cellular, neurocircuitry, and behavioral levels (Stark et al., 2008). The MRI analysis revealed a striking similarity in the specific volumetric changes of Df(16)A+/- mice compared to patients with the 22q11.2 deletion in the cortical, striatal and limbic brain areas. Intriguingly, the study also identified the cerebellar abnormalities within both the deep cerebellar nuclei and the cerebellar cortex in mutant mice. Although these findings support the potential role for the cerebellum in schizophrenia-related pathology, it remains unclear if these volumetric changes are primary or secondary with regard to the mutation (Ellegood et al., 2013).

Disrupted in Schizophrenia 1 (DISC1)—The *DISC1* gene has first been identified in a balanced chromosomal translocation [t(1;11)] in a Scottish pedigree with a history of major psychiatric disorders including schizophrenia, bipolar disease, and depression (St Clair et al., 1990). The existence of a clear identifiable mutation has put DISC1 in a unique position in the basic research on schizophrenia and related major mental illnesses (Millar et al., 2001; Chubb et al., 2008). Although, there are several negative findings with this gene, including lack of findings from recent GWA studies (Sullivan, 2013). DISC1 acts as a scaffold protein, with multiple motifs mediating binding to several proteins and facilitating formation of protein complexes (Camargo et al., 2007). Accordingly, DISC1 has been implicated various brain processes in neuronal proliferation, migration, synaptic formation and synaptic transmission (Brandon and Sawa, 2011; Kamiya et al., 2012; Thomson et al., 2013).

In the adult mouse brain, *Disc1* mRNA has a very restricted distribution. Highest expression is present in the dentate gyrus of the hippocampus, with lower expression levels in the CA1–CA3 subfields of the hippocampus, the PC layer in the cerebellum, the dorsal neocortex, the hypothalamus, and the olfactory bulbs. Curiously, in the cerebellum, although the *Disc1*

expression was restricted to the PC layer, PC themselves did not seem to express *Disc1*. Rather, the cells that expressed *Disc1* in the cerebellum were NeuN negative, small in size, and located at the periphery of PC, consistent with these cells being Bergmann glia (Ma et al., 2002). A follow-up report evaluated a developmental course of *Disc1* expression and demonstrated *Disc1* expression in the olfactory bulbs and cerebellum by P1. Curiously, cerebellar distributions were suggestive of interneuron and Bergmann glia identity, respectively, as seen previously in the adult. By P21, the mature pattern of *Disc1* expression was established (Austin et al., 2004).

The study of expression of mRNA for *Disc1* were further corroborated with immunohistochemical analysis of different regions of adult mouse brain show that DISC1 protein is broadly expressed within several areas of the brain, especially in the cortex, hippocampus, hypothalamus, cerebellum and brain stem. In the cerebellum, however, PC were predominantly DISC1+ cells (Schurov et al., 2004).

Regional expression of DISC1 in the primate brain was also evaluated with *in situ* hybridization. DISC1 expression was most prominent in the dentate gyrus of the hippocampus and lateral septum. Lower levels of expression were noted in the cerebral cortex, amygdala, paraventricular hypothalamus, cerebellum, interpeduncular nucleus, and subthalamic nucleus. Similar to the mouse study, DISC1+ cells were abundant in the cerebellum and were scattered throughout the molecular layer, consistent with glial cell identity (Austin et al., 2003). Another group confirmed the cerebellar expression of DISC1 in the primate brain by western blotting (Bord et al., 2006).

A recent study reports a novel interaction between DISC1 and Tensin2, an intracellular actin-binding protein that bridges the intracellular portion of transmembrane receptors to the cytoskeleton, thereby regulating signaling for cell shape and motility. Intriguingly, DISC1-Tensin2 co-localization was strongest in PC. DISC1 specifically interacts with the C-terminal PTB domain of Tensin2 in a phosphorylation-independent manner. This new knowledge on the DISC1-Tensin2 interaction, as part of the wider DISC1 interactome, should further elucidate the signaling pathways that are perturbed in schizophrenia and other mental disorders (Goudarzi et al., 2013).

In order to address the role of DISC1 in the development and function of the cerebellum *in vivo*, we have generated a model of inducible expression of dominant-negative mutant DISC1 in the cerebellum. In this model, single transgenic mutant DISC1 mice are mated with single transgenic mice that express tetracycline trans-activator (tTA) under the control of the modified Parvalbumin-2A promoter (Zariwala et al., 2011). Our preliminary experiments demonstrated that expression of mutant DISC1 was present in the cerebellum but not in the cortex or hippocampus as detected by RTPCR and western blotting. Cell-specific activity of the promoter was predominantly observed in PC and a few cerebellar interneurons as confirmed with a reporter TRE-tdTomato line. Mutant mice showed significantly elevated horizontal and vertical activities in open field, deficits in object recognition and recognition of a new social partner. In addition, decreased cue- and context-dependent fear conditioning was observed in male and female mice with PC-selective expression of mutant DISC1. Further evaluation of this mouse model is under way. We

think that this mouse model may be helpful in elucidating the role of DISC1 in normal and abnormal cerebellar development and may shed more light on psychiatric disorders with cerebellar dysfunction. Table 3 summarizes the schizophrenia models reviewed above.

Conclusions and future directions

The cerebellum is reclaiming its important role in the regulation of emotional and cognitive spheres of human mind. Our understanding of the complex picture of mental illness will remain incomplete without considering the contributions of abnormal development of the cerebellum. Although recent progress in psychiatric genetics and epidemiological studies has facilitated the development of animal models, very few models have specifically studied the effects of a mutation or an environmental factor on the cerebellum. Even fewer models were able to address the cerebellar effects without confounding influences of changes elsewhere in the brain. Future studies should use technologies to manipulate with a gene in a circuitry- or cell-specific manner. Similarly, we increasingly need models that would be able to target the cerebellar cells in a time-dependent fashion given a time-specific course of maturation of different cell type of the cerebellum. We also need models that allow for gradually regulating levels of expression of risk factors in PC to minimize confounding effects of loss of PC and motor dysfunction on non-motor behaviors.

Another potentially fruitful direction is to generate models with simultaneous manipulations of genetic risk factors in the cerebellum and frontal cortex and/or striatum to decipher the role of distant brain connections in the brain-wide neuronal networks that control behaviors. This direction arguably presents a research avenue of enormous promise.

Most studies have focused on neuronal functions of susceptibility genes. However, these genes are also expressed by glial cells (Prevot et al., 2003; Iijima et al., 2009). For example, a recent study has provided the first evidence for interaction between DISC1 and serine racemase in astrocytes, connecting DISC1 and D-serine/NMDA receptor hypofunction (Ma et al., 2013). In the cerebellum, Bergmann glia, which express Disc1, are essential for cerebellar development and function (Buffo and Rossi, 2013). Given, growing interest in the role for glia cells in the pathogenesis and pathophysiology of autism and schizophrenia, one can anticipate more models in which selective glial manipulation of risk factors will be incorporated.

Exploring the role for protective factors to counteract adverse effects of mutations and environment has been thus far very minimal (Mihali et al., 2012). New approaches using resilience factors can advance this exiting direction (Takuma et al., 2011; Burrows et al., 2011). Combining this type of treatments with current models will demonstrate if and how environmental enrichment can compensate for deleterious effects caused by aversive environment to suggest novel treatments (Laviola et al., 2008; Pratt et al., 2012).

In conclusion, the role of the cerebellum in non-motor function has been increasingly appreciated. There is a need in advancing our knowledge of the mechanisms whereby the cerebellum influences emotional, cognitive and social aspects of the human mind. This will undoubtedly stimulate our better understanding of how pathology of the cerebellum contributes to non-motor symptoms of major psychiatric disorders. Genetic animal models

are valuable experimental preparation to address molecular and cellular mechanisms of abnormal cerebellar development and associated behavioral changes relevant to human mental conditions. Unfortunately, the role for the genes involved in cerebellar development remain poorly characterized as there is a scarcity of models to selectively perturb expression of the genes implicated in autism, schizophrenia and associated psychotic disorders. More sophisticated and advanced genetic manipulations are needed to refine the present models in order to increase their relevance and utility to studies of the cerebellum and its role in mental health and disease.

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References

- Akaike M, Kato N, Ohno H, Kobayashi T. Hyperactivity and spatial maze learning impairment of adult rats with temporary neonatal hypothyroidism. *Neurotoxicol Teratol*. 1991; 13:317–322. [PubMed: 1886541]
- Akaike, M.; Kato, N. Abnormal behavior, spatial learning impairment and neuropeptides caused by temporary neonatal hypothyroidism.. In: Hendrich, CE., editor. *Recent Research Development in Neuroendocrinology – Thyroid Hormone and Brain Maturation*. Research Signpost; Trivandrum: 1997. p. 39-48.
- Alexopoulou L, Holt AC, Medzhitov R, Flavell RA. Recognition of double-stranded RNA and activation of NF-kappaB by Toll-like receptor 3. *Nature*. 2001; 413:732–738. [PubMed: 11607032]
- Amaral DG, Schumann CM, Nordahl CW. Neuroanatomy of autism. *Trends Neurosci*. 2008; 31:137–45. [PubMed: 18258309]
- Andreasen NC, Paradiso S, O'Leary DS. Cognitive dysmetria" as an integrative theory of schizophrenia: a dysfunction in cortical-subcortical-cerebellar circuitry? *Schizophr Bull*. 1998; 24:203–18. [PubMed: 9613621]
- Andreasen NC, O'Leary DS, Cizadlo T, Arndt S, Rezai K, Ponto LL, Watkins GL, Hichwa RD. Schizophrenia and cognitive dysmetria: a positron-emission tomography study of dysfunctional prefrontal-thalamic-cerebellar circuitry. *Proc Natl Acad Sci U S A*. 1996; 93:9985–90. [PubMed: 8790444]
- Andreasen NC, Pierson R. The role of the cerebellum in schizophrenia. *Biol Psychiatry*. 2008; 64:81–88. [PubMed: 18395701]
- Arias I, Sorlozano A, Villegas E, de Dios Luna J, McKenney K, Cervilla J, Gutierrez B, Gutierrez J. Infectious agents associated with schizophrenia: a meta-analysis. *Schizophr Res*. 2012; 136:128–136. [PubMed: 22104141]
- Arguello PA, Gogos JA. Genetic and cognitive windows into circuit mechanisms of psychiatric disease. *Trends Neurosci*. 2012; 35:3–13. [PubMed: 22177981]
- Austin CP, Ky B, Ma L, Morris JA, Shughrue PJ. DISC1 (Disrupted in Schizophrenia-1) is expressed in limbic regions of the primate brain. *Neuroreport*. 2003; 14:951–954. [PubMed: 12802181]
- Austin CP, Ky B, Ma L, Morris JA, Shughrue PJ. Expression of Disrupted-In-Schizophrenia-1, a schizophrenia-associated gene, is prominent in the mouse hippocampus throughout brain development. *Neuroscience*. 2004; 124:3–10. [PubMed: 14960334]
- Bacon C, Rappold GA. The distinct and overlapping phenotypic spectra of FOXP1 and FOXP2 in cognitive disorders. *Hum Genet*. 2012; 131:1687–1698. [PubMed: 22736078]
- Bartzokis G. Neuroglialpharmacology: myelination as a shared mechanism of action of psychotropic treatments. *Neuropharmacology*. 2012; 62:2137–2153. [PubMed: 22306524]
- Bauman ML, Kemper TL. Neuroanatomic observations of the brain in autism: a review and future directions. *Int J Dev Neurosci*. 2005; 23:183–187. [PubMed: 15749244]

- Beraki S, Aronsson F, Karlsson H, Ogren SO, Kristensson K. Influenza A virus infection causes alterations in expression of synaptic regulatory genes combined with changes in cognitive and emotional behaviors in mice. *Mol Psychiatry*. 2005; 10:299–308. [PubMed: 15241434]
- Beri S, Tonna N, Menozzi G, Bonaglia MC, Sala C, Giorda R. DNA methylation regulates tissue-specific expression of Shank3. *J. Neurochem*. 2007; 101:1380–1391. [PubMed: 17419801]
- Blatt GJ. GABAergic cerebellar system in autism: a neuropathological and developmental perspective. *Int Rev Neurobiol*. 2005; 71:167–78. [PubMed: 16512350]
- Boeckers TM, Bockmann J, Kreutz MR, Gundelfinger ED. ProSAP/Shank proteins – a family of higher order organizing molecules of the postsynaptic density with an emerging role in human neurological disease. *J. Neurochem*. 2002; 81:903–910. [PubMed: 12065602]
- Boksa P. Effects of prenatal infection on brain development and behavior: a review of findings from animal models. *Brain Behav Immun*. 2010; 24:881–897. [PubMed: 20230889]
- Bonaglia MC, Giorda R, Mani E, Aceti G, Anderlid BM, Baroncini A, Pramparo T, Zuffardi O. Identification of a recurrent break point within the Shank3 gene in the 22p13.3 deletion syndrome. *J. Med. Genet*. 2006; 43:822–828. [PubMed: 16284256]
- Bord L, Wheeler J, Paek M, Saleh M, Lyons-Warren A, Ross CA, Sawamura N, Sawa A. Primate disrupted-in-schizophrenia-1 (DISC1): high divergence of a gene for major mental illnesses in recent evolutionary history. *Neurosci Res*. 2006; 56:286–293. [PubMed: 16965828]
- Boukhtouche F, Janmaat S, Vodjdani G, Gautheron V, Mallet J, Dusart I, Mariani J. Retinoid-related orphan receptor alpha controls the early steps of purkinje cell dendritic differentiation. *J. Neurosci*. 2006; 26:1531–1538. [PubMed: 16452676]
- Boydjjeva N, Varadinova M. Epigenetics of psychoactive drugs. *J Pharm Pharmacol*. 2012; 64:1349–1358. [PubMed: 22943166]
- Bozdagi O, Sakurai T, Papapetrou D, Wang X, Dickstein DL, Takahashi N, Kajiwaraya Y, Yang M, Katz AM, Scattoni ML, Harris MJ, Saxena R, Silverman JL, Crawley JN, Zhou Q, Hof PR, Buxbaum JD. Haploinsufficiency of the autism-associated Shank3 gene leads to deficits in synaptic function, social interaction, and social communication. *Mol. Autism*. 2010; 1:15. [PubMed: 21167025]
- Brandon NJ, Sawa A. Linking neurodevelopmental and synaptic theories of mental illness through DISC1. *Nat Rev Neurosci*. 2011; 12:707–722. [PubMed: 22095064]
- Brielmaier J, Matteson PG, Silverman JL, Senerth JM, Kelly S, Genestine M, Millonig JH, DiCicco-Bloom E, Crawley JN. Autism-relevant social abnormalities and cognitive deficits in engrailed-2 knockout mice. *PLoS One*. 2012; 7:e40914. [PubMed: 22829897]
- Brown AS, Derkits EJ. Prenatal infection and schizophrenia: a review of epidemiologic and translational studies. *Am J Psychiatry*. 2010; 167:261–280. [PubMed: 20123911]
- Buffo A, Rossi F. Origin, lineage and function of cerebellar glia. *Prog Neurobiol*. 2013; 109:42–63. [PubMed: 23981535]
- Burnet PW, Eastwood SL, Bristow GC, Godlewska BR, Sikka P, Walker M, Harrison PJ. D-amino acid oxidase activity and expression are increased in schizophrenia. *Mol Psychiatry*. 2008; 13:658–60. [PubMed: 18560437]
- Burrows EL, McOmish CE, Hannan AJ. Gene-environment interactions and construct validity in preclinical models of psychiatric disorders. *Prog. Neuropsychopharmacol Biol Psychiatry*. 2011; 35:1376–1382. [PubMed: 21168465]
- Buyske S, Williams TA, Mars AE, Stenroos ES, Ming SX, Wang R, Sreenath M, Factura MF, Reddy C, Lambert GH, Johnson WG. Analysis of case-parent trios at a locus with a deletion allele: association of GSTM1 with autism. *BMC Genet*. 2006; 7:8. [PubMed: 16472391]
- Camargo LM, Collura V, Rain JC, Mizuguchi K, Hermijakob H, Kerrien S, Bonnert TP, Whiting PJ, Brandon NJ. Disrupted in Schizophrenia 1 Interactome: evidence for the close connectivity of risk genes and a potential synaptic basis for schizophrenia. *Mol Psychiatry*. 2007; 12:74–86. [PubMed: 17043677]
- Chaste P, Leboyer M. Autism risk factors: genes, environment, and gene-environment interactions. *Dialogues Clin Neurosci*. 2012; 14:281–292. [PubMed: 23226953]

- Cheh MA, Millonig JH, Roselli LM, Ming X, Jacobsen E, Kamdar S, Wagner GC. En2 knockout mice display neurobehavioral and neurochemical alterations relevant to autism spectrum disorder. *Brain Res.* 2006; 1116:166–176. [PubMed: 16935268]
- Cheng L, Hattori E, Nakajima A, Woehrle NS, Opal MD, Zhang C, Grennan K, Dulawa SC, Tang YP, Gershon ES, Liu C. Expression of the G72/G30 gene in transgenic mice induces behavioral changes. *Mol Psychiatry.* 2013 doi: 10.1038/mp.2012.185. [Epub ahead of print] PubMed PMID: 23337943; PubMed Central PMCID: PMC3636154.
- Chomiak T, Hu B. Alterations of neocortical development and maturation in autism: insight from valproic acid exposure and animal models of autism. *Neurotoxicol Teratol.* 2013; 36:57–66. [PubMed: 22967743]
- Chubb JE, Bradshaw NJ, Soares DC, Porteous DJ, Millar JK. The DISC locus in psychiatric illness. *Mol Psychiatry.* 2008; 13:36–64. [PubMed: 17912248]
- Clower DM, West RA, Lynch JC, Strick PL. The inferior parietal lobule is the target of output from the superior colliculus, hippocampus, and cerebellum. *J Neurosci.* 2001; 21:6283–6291. [PubMed: 11487651]
- Clower DM, Dum RP, Strick PL. Basal ganglia and cerebellar inputs to 'AIP'. *Cereb Cortex.* 2005; 7:913–920. [PubMed: 15459083]
- Courchesne E. Neuroanatomic imaging in autism. *Pediatrics.* 1991; 87(5 Pt 2):781–90. [PubMed: 2020537]
- DeLorey TM, Sahbaie P, Hashemi E, Homanics GE, Clark JD. Gabrb3 gene deficient mice exhibit impaired social and exploratory behaviors, deficits in non-selective attention and hypoplasia of cerebellar vermal lobules: a potential model of autism spectrum disorder. *Behav Brain Res.* 2008; 5:207–220. [PubMed: 17983671]
- Dietz D, Vogel M, Rubin S, Moran T, Carbone K, Pletnikov M. Developmental alterations in serotonergic neurotransmission in Borna disease virus (BDV)-infected rats: a multidisciplinary analysis. *J Neurovirol.* 2004; 10:267–277. [PubMed: 15385249]
- Doulazmi M, Frédéric F, Capone F, Becher-André M, Delhay-Bouchaud N, Mariani J. A comparative study of Purkinje cells in two ROR alpha gene mutant mice: stagger and ROR alpha(–/–). *Dev. BrainRes.* 2001; 127:165–174.
- Drews E, Otte DM, Zimmer A. Involvement of the primate specific gene G72 in schizophrenia: From genetic studies to pathomechanisms. *Neurosci Biobehav Rev.* 2012; 37:2410–2417. [PubMed: 23092656]
- Dufour-Rainfray D, Vourc'h P, Le Guisquet AM, Garreau L, Ternant D, Bodard S, et al. Behavior and serotonergic disorders in rats exposed prenatally to valproate: a model for autism. *Neurosci Lett.* 2010; 470:55–59. [PubMed: 20036713]
- Durand CM, Betancur C, Boeckers TM, Bockmann J, Chaste P, Fauchereau F, Nygren G, Rastam M, Gillberg IC, Anckarsater H, Sponheim E, Goubran-Botros, Delorme R, Chabane N, Mouren-Simeoni M, de Mas P, Bieth E, Roge B, Heron D, Burglen L, Gillberg C, Leboyer M, Bourgeron T. Mutations in the gene encoding the synaptic scaffolding protein Shank3 are associated autism spectrum disorders. *Nat Genet.* 2007; 39:25–27. [PubMed: 17173049]
- Dusart I, Guenet JL, Sotelo C. Purkinje cell death: differences between developmental cell death and neurodegenerative death in mutant mice. *Cerebellum.* 2006; 5:163–173. [PubMed: 16818391]
- Eastwood SL, Cotter D, Harrison PJ. Cerebellar synaptic protein expression in schizophrenia. *Neuroscience.* 2001; 105:219–29. [PubMed: 11483314]
- Eastwood SL, Law AJ, Everall IP, Harrison PJ. The axonal chemorepellant semaphorin 3A is increased in the cerebellum in schizophrenia and may contribute to its synaptic pathology. *Mol Psychiatry.* 2003; 8:148–55. [PubMed: 12610647]
- Ellegood J, Pacey LK, Hampson DR, Lerch JP, Henkelman RM. Anatomical phenotyping in a mouse model of fragile X syndrome with magnetic resonance imaging. *Neuroimage.* 2010; 53:1023–1029. [PubMed: 20304074]
- Ellegood J, Markx S, Lerch JP, Steadman PE, Genç C, Provenzano F, Kushner SA, Henkelman RM, Karayiorgou M, Gogos JA. Neuroanatomical phenotypes in a mouse model of the 22q11.2 microdeletion. *Mol Psychiatry.* 2013; 19:99–107. [PubMed: 23999526]

- Ertan G, Arulrajah S, Tekes A, Jordan L, Huisman TA. Cerebellar abnormality in children and young adults with tuberous sclerosis complex: MR and diffusion weighted imaging findings. *J Neuroradiol.* 2010; 37:231–238. [PubMed: 20381146]
- Evarts EV, Thach WT. Motor mechanism of the CNS: cerebrotocerebellar interrelations. *Annu. Rev. Physiol.* 1969; 31:451–498. [PubMed: 4885774]
- Ey E, Leblond CS, Bourgeron T, Pletnikov MV. Behavioral profiles of mouse models for autism spectrum disorders. *Autism Res.* 2011; 4:5–16. [PubMed: 21328568]
- Fatemi SH, Folsom TD, Reutiman TJ, Sidwell RW. Viral regulation of aquaporin 4, connexin 43, microcephalin and nucleolin. *Schizophr Res.* 2008a; 98:163–177. [PubMed: 17997079]
- Fatemi SH, Reutiman TJ, Folsom TD, Huang H, Oishi K, Mori S, Smee DF, Pearce DA, Winter C, Sohr R, Juckel G. Maternal infection leads to abnormal gene regulation and brain atrophy in mouse offspring: implications for genesis of neurodevelopmental disorders. *Schizophr Res.* 2008b; 99:56–70. [PubMed: 18248790]
- Fatemi SH, Folsom TD, Reutiman TJ, Abu-Odeh D, Mori S, Huang H, Oishi K. Abnormal expression of myelination genes and alterations in white matter fractional anisotropy following prenatal viral influenza infection at E16 in mice. *Schizophr Res.* 2009; 112:46–53. [PubMed: 19487109]
- Fatemi SH, Aldinger KA, Ashwood P, Bauman ML, Blaha CD, Blatt GJ, Chauhan A, Chauhan V, Dager SR, Dickson PE, Estes AM, Goldowitz D, Heck DH, Kemper TL, King BH, Martin LA, Millen KJ, Mittelman G, Mosconi MW, Persico AM, Sweeney JA, Webb SJ, Welsh JP. Consensus paper: pathological role of the cerebellum in autism. *Cerebellum.* 2012; 11:777–807. [PubMed: 22370873]
- Filiou MD, Teplytska L, Otte DM, Zimmer A, Turck CW. Myelination and oxidative stress alterations in the cerebellum of the G72/G30 transgenic schizophrenia mouse model. *J Psychiatr Res.* 2012; 46:1359–1365. [PubMed: 22884423]
- Fisher SE, Scharff C. FOXP2 as a molecular window into speech and language. *Trends Genet.* 2009; 25:166–177. [PubMed: 19304338]
- Fortier ME, Kent S, Ashdown H, Poole S, Boksa P, Luheshi GN. The viral mimic, polyinosinic:polycytidylic acid, induces fever in rats via an interleukin-1-dependent mechanism. *Am J Physiol Regul Integr Comp Physiol.* 2004; 287:759–766.
- Fujita E, Tanabe Y, Imhof BA, Momoi MY, Momoi T. Cadm1-expressing synapses on Purkinje cell dendrites are involved in mouse ultrasonic vocalization activity. *PLoS One.* 2012a; 7:e30151. [PubMed: 22272290]
- Fujita E, Tanabe Y, Momoi MY, Momoi T. Cntnap2 expression in the cerebellum of Foxp2(R552H) mice, with a mutation related to speech-language disorder. *Neurosci Lett.* 2012b; 506:277–280. [PubMed: 22133810]
- Fujita E, Tanabe Y, Imhof BA, Momoi MY, Momoi T. A complex of synaptic adhesion molecule CADM1, a molecule related to autism spectrum disorder, with MUPP1 in the cerebellum. *J Neurochem.* 2012c; 123:886–894. [PubMed: 22994563]
- Gejman PV, Sanders AR, Kendler KS. Genetics of schizophrenia: new findings and challenges. *Annu Rev Genomics Hum Genet.* 2011; 12:121–144. [PubMed: 21639796]
- Giza J, Urbanski MJ, Prestori F, Bandyopadhyay B, Yam A, Friedrich V, Kelley K, D'Angelo E, Goldfarb M. Behavioral and cerebellar transmission deficits in mice lacking the autism-linked gene islet brain-2. *J Neurosci.* 2010; 30:14805–14816. [PubMed: 21048139]
- Goines PE, Ashwood P. Cytokine dysregulation in autism spectrum disorders (ASD): possible role of the environment. *Neurotoxicol Teratol.* 2013; 36:67–81. [PubMed: 22918031]
- Goldowitz D, Koch J. Performance of normal and neurological mutant mice on radial arm maze and active avoidance tasks. *Behav. Neural Biol.* 1986; 46:216–226. [PubMed: 3767833]
- Gomez L, Wigg K, Feng Y, Kiss E, Kapornai K, Tamás Z, Mayer L, Baji I, Daróczi G, Benák I, Kothencné VO, Dombóvári E, Kacsvinsz E, Besnyó M, Gáboros J, King N, Székely J, Kovacs M, Vetró A, Kennedy JL, Barr CL. G72/G30 (DAOA) and juvenile-onset mood disorders. *Am J Med Genet B Neuropsychiatr Genet.* 2009; 150:1007–10012. [PubMed: 19089835]
- Goodrich-Hunsaker NJ, Wong LM, McLennan Y, Tassone F, Harvey D, Rivera SM, Simon TJ. Adult female fragile X permutation carriers exhibit age- and CGG repeat length-related impairments on an attentionally based enumeration task. *Front. Hum. Neurosci.* 2011; 5:63. [PubMed: 21808616]

- Goudarzi S, Smith LJ, Schütz S, Hafizi S. Interaction of DISC1 with the PTB domain of Tensin2. *Cell Mol Life Sci.* 2013; 70:1663–1672. [PubMed: 23233134]
- Hamilton BA, Frankel WN, Kerrebrock AW, Hawkins TL, Fitzhugh W, Kusumi K., I. Russell L,B, Mueller K, L. van Berkel V, Birren BW, Kruglyak L, Lander ES. Disruption of the nuclear hormone receptor ROR alpha in staggerer mice. *Nature.* 1996; 379:736–739. [PubMed: 8602221]
- Harkins AB, Fox AP. Cell death in weaver mouse cerebellum. *Cerebellum.* 2002; 1:201–206. [PubMed: 12879981]
- Harvey L, Boksa P. Prenatal and postnatal animal models of immune activation: relevance to a range of neurodevelopmental disorders. *Dev Neurobiol.* 2012; 72:1335–1348. [PubMed: 22730147]
- Herrup K, Mullen RJ. Staggerer chimeras: intrinsic nature of Purkinje cell defects and implications for normal cerebellar development. *Brain Res.* 1979; 178:443–457. [PubMed: 509213]
- Herrup K, Shojaeian-Zanjani H, Panzini L, Sunter K, Mariani J. The numerical matching of source and target populations in the CNS: the inferior olive to Purkinje cell projection. *Dev Brain Res.* 1996; 96:28–35. [PubMed: 8922665]
- Iijima S, Masaki H, Wakayama Y, Inoue M, Jimi T, Hara H, Unaki A, Oniki H, Nakano K, Hirayama Y, Kishimoto K. Immunohistochemical detection of dysbindin at the astroglial endfeet around the capillaries of mouse brain. *J Mol Histol.* 2009; 40:117–121. [PubMed: 19495999]
- Ingram JL, Peckham SM, Tisdale B, Rodier PM. Prenatal exposure of rats to valproic acid reproduces the cerebellar anomalies associated with autism. *Neurotoxicol Teratol.* 2000; 22:319–324. [PubMed: 10840175]
- Jaaro-Peled H, Ayhan Y, Pletnikov MV, Sawa A. Review of pathological hallmarks of schizophrenia: comparison of genetic models with patients and nongenetic models. *Schizophr Bull.* 2010; 36:301–313. [PubMed: 19903746]
- Jiang YH, Ehlers MD. Modeling autism by SHANK gene mutations in mice. *Neuron.* 2013; 78:8–27. [PubMed: 23583105]
- Jolly S, Journiac N, Vernet-der Garabedian B, Mariani J. RORalpha, a key to the development and functioning of the brain. *Cerebellum.* 2012; 11:451–452. [PubMed: 22223133]
- Kamiya A, Sedlak TW, Pletnikov MV. DISC1 Pathway in Brain Development: Exploring Therapeutic Targets for Major Psychiatric Disorders. *Front Psychiatry.* 2012; 3:25. [PubMed: 22461775]
- Kang C, Drayna D. Genetics of speech and language disorders. *Annu Rev Genomics Hum Genet.* 2011; 12:145–164. [PubMed: 21663442]
- Kato N, Sundmark VC, Van Middlesworth L, Havlicek V, Friesen HG. Immunoreactive somatostatin and beta-endorphin content in the brain of mature rats after neonatal exposure to propylthiouracil. *Endocrinology.* 1982; 110:1851–1855. [PubMed: 6122558]
- Kemper TL, Bauman M. Neuropathology of infantile autism. *J Neuropathol Exp Neurol.* 1998; 57:645–52. [PubMed: 9690668]
- Kern JK. Purkinje cell vulnerability and autism: a possible etiological connection. *Brain Dev.* 2003; 25:377–82. [PubMed: 12907269]
- Kim JE, Shin MS, Seo TB, Ji ES, Baek SS, Lee SJ, Park JK, Kim CJ. Treadmill exercise ameliorates motor disturbance through inhibition of apoptosis in the cerebellum of valproic acid-induced autistic rat pups. *Mol Med Rep.* 2013; 8:327–334. [PubMed: 23760019]
- Kim M, Yu JE, Lee JH, Chang BJ, Song CS, Lee B, Paik DJ, Nahm SS. Comparative analyses of influenza virus receptor distribution in the human and mouse brains. *J Chem Neuroanat.* 2013; 52:49–57. [PubMed: 23726946]
- Kimura M, Toth LA, Agostini H, Cady AB, Majde JA, Krueger JM. Comparison of acute phase responses induced in rabbits by lipopolysaccharide and double-stranded RNA. *Am J Physiol.* 1994; 267:1596–1605.
- Kinney DK, Yurgelun-Todd DA, Woods BT. Neurologic signs of cerebellar and cortical sensory dysfunction in schizophrenics and their relatives. *Schizophr Res.* 1999; 35:99–104. [PubMed: 9988846]
- Kneeland R,E, Fatemi SH. Viral infection, inflammation and schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry.* 2013; 42:35–48. [PubMed: 22349576]
- Koekkoek SK, Yamaguchi K, Milojkovic BA, Dortland BR, Ruigrok TJ, Maex R, De Graff W, Smit AE, VanderWerf F, Backker CE, Willemsen R, Ikeda T, Kakizawa S, Onodera K, Nelson DL,

- Mienties E, Joosten M, De Schutter E, Oostra BA, Ito M, De Zeeuw CI. Deletion of FMR1 in Purkinje cells enhances parallel fiber LTD, enlarges spines, and attenuates cerebellar eyelid conditioning in Fragile X syndrome. *Neuron*. 2005; 47:339–352. [PubMed: 16055059]
- Konarski JZ, McIntyre RS, Grupp LA, Kennedy SH. Is the cerebellum relevant in the circuitry of neuropsychiatric disorder? *J Psychiatry Neurosci*. 2006; 30:178–186. [PubMed: 15944742]
- Kuemerle B, Zanjani H, Joyner A, Herrup K. Pattern deformities and cell loss in Engrailed-2 mutant mice suggest two separate patterning events during cerebellar development. *J. Neurosci*. 1997; 17:7881–7889. [PubMed: 9315908]
- Kuemerle B, Gulden F, Cherosky N, Williams E, Herrup K. The mouse engrailed genes: a window into autism. *Brain Res*. 2007; 176:121–132.
- Kvajo M, Dhillia A, Swor DE, Karayiorgou M, Gogos JA. Evidence implicating the candidate schizophrenia/bipolar disorder susceptibility gene G72 in mitochondrial function. *Mol Psychiatry*. 2008; 13:685–696. [PubMed: 17684499]
- Lalonde R, Filali M, Bensoula AN, Lestienne F. Sensorimotor learning in three cerebellar mutant mice. *Neurobiol Learn Mem*. 1996; 65:113–120. [PubMed: 8833100]
- Landis DM, Sidman RL. Electron microscopic analysis of postnatal histogenesis in the cerebellar cortex of staggerer mutant mice. *J. Comp.Neurol*. 1978; 179:831–863. [PubMed: 641237]
- Lancaster K, Dietz DM, Moran TH, Pletnikov MV. Abnormal social behaviors in young and adult rats neonatally infected with Borna disease virus. *Behav Brain Res*. 2007; 176:141–148. [PubMed: 16860408]
- Laviola G, Hannan AJ, Macrì S, Solinas M, Jaber M. Effects of enriched environment on animal models of neurodegenerative diseases and psychiatric disorders. *Neurobiol Dis*. 2008; 31:159–168. [PubMed: 18585920]
- Leiner HC, Leiner AL, Dow RS. Does the cerebellum contribute to mental skills? *Behav Neurosci*. 1986; 100:443–454. [PubMed: 3741598]
- Leiner HC. Solving the mystery of the human cerebellum. *Neuropsychol Rev*. 2010; 20:229–235. [PubMed: 20809199]
- Lipkin WI, Briese T, Hornig M. Borna disease virus - fact and fantasy. *Virus Res*. 2011; 162:162–172. [PubMed: 21968299]
- Lungu O, Barakat M, Laventure S, Debas K, Proulx S, Luck D, Stip E. The incidence and nature of cerebellar findings in schizophrenia: a quantitative review of fMRI literature. *Schizophr Bull*. 2013; 39:797–806. [PubMed: 22267533]
- Ma L, Liu Y, Ky B, Shughrue PJ, Austin CP, Morris JA. Cloning and characterization of Disc1, the mouse ortholog of DISC1 (Disrupted-in-Schizophrenia 1). *Genomics*. 2002; 80:662–672. [PubMed: 12504857]
- Ma TM, Abazyan S, Abazyan B, Nomura J, Yang C, Seshadri S, Sawa A, Snyder SH, Pletnikov MV. Pathogenic disruption of DISC1-serine racemase binding elicits schizophrenia-like behavior via D-serine depletion. *Mol Psychiatry*. 2013; 18:557–567. [PubMed: 22801410]
- Markram K, Rinaldi T, La Mendola D, Sandi C, Markram H. Abnormal fear conditioning and amygdala processing in an animal model of autism. *Neuropsychopharmacology*. 2008; 33:901–912. [PubMed: 17507914]
- Martin P, Albers M. Cerebellum and schizophrenia: a selective review. *Schizophr Bull*. 1995; 21:241–50. [PubMed: 7631171]
- Meyer U, Feldon J, Fatemi SH. In-vivo rodent models for the experimental investigation of prenatal immune activation effects in neurodevelopmental brain disorders. *Neurosci Biobehav Rev*. 2009; 33:1061–1079. [PubMed: 19442688]
- Meyer U, Feldon J. To poly(I:C) or not to poly(I:C): advancing preclinical schizophrenia research through the use of prenatal immune activation models. *Neuropharmacology*. 2012; 62:1308–1321. [PubMed: 21238465]
- Michel M, Schmidt MJ, Mirnics K. Immune system gene dysregulation in autism and schizophrenia. *Dev Neurobiol*. 2012; 72:1277–1287. [PubMed: 22753382]
- Mihali A, Subramani S, Kaunitz G. Modeling resilience to schizophrenia in genetically modified mice: a novel approach to drug discovery. *Expert Rev Neurother*. 2012; 12:785–799. [PubMed: 22853787]

- Mukaetova-Ladinska E, Hurt J, Honer WG, Harrington CR, Wischik CM. Loss of synaptic but not cytoskeletal proteins in the cerebellum of chronic schizophrenics. *Neurosci Lett*. 2002; 317:161–5. [PubMed: 11755264]
- Millar JK, Christie S, Anderson S, Lawson D, Hsiao-Wei LD, Devon RS, Arveiler B, Muir WJ, Blackwood DH, Porteous DJ. Genomic structure and localisation within a linkage hotspot of Disrupted In Schizophrenia 1, a gene disrupted by a translocation segregating with schizophrenia. *Mol Psychiatry*. 2001; 6:173–178. [PubMed: 11317219]
- Millen KJ, Wurst W, Herrup K, Joyner AL. Abnormal embryonic cerebellar development and patterning of postnatal foliation in two mouse Engrailed- 2 mutants. *Development*. 1994; 120:695–706. [PubMed: 7909289]
- Misslin R, Cigrang M, Guastavino J. Responses to novelty in staggerer mutant mice. *Behav Process*. 1986; 12:51–56.
- Mychasiuk R, Richards S, Nakahashi A, Kolb B, Gibb R. Effects of rat prenatal exposure to valproic acid on behaviour and neuroanatomy. *Dev Neurosci*. 2012; 34:268–276. [PubMed: 22890088]
- Newbury DF, Monaco AP. Genetic advances in the study of speech and language disorders. *Neuron*. 2010; 68:309–320. [PubMed: 20955937]
- Nguyen A, Rauch TA, Pfeifer GP, Hu VW. Global methylation profiling of lymphoblastoid cell lines reveal epigenetic contributions to autism spectrum disorders and a novel autism candidate gene, RORA, whose protein product is reduced in autistic brain. *FASEB J*. 2010; 24:3036–3051. [PubMed: 20375269]
- Olmos-Serrano JL, Corbin JG, Burns MP. The GABA(A) Receptor Agonist THIP Ameliorates Specific Behavioral Deficits in the Mouse Model of Fragile X Syndrome. *Dev Neurosci*. 2011; 33:395–403. [PubMed: 22067669]
- Otte DM, Bilkei-Gorzó A, Filiou MD, Turck CW, Yilmaz O, Holst MI, Schilling K, Abou-Jamra R, Schumacher J, Benzel I, Kunz WS, Beck H, Zimmer A. Behavioral changes in G72/G30 transgenic mice. *Eur Neuropsychopharmacol*. 2009; 19:339–348. [PubMed: 19189879]
- Otte DM, Sommersberg B, Kudin A, Guerrero C, Albayram O, Filiou MD, Frisch P, Yilmaz O, Drews E, Turck CW, Bilkei-Gorzó A, Kunz WS, Beck H, Zimmer A. N-acetyl cysteine treatment rescues cognitive deficits induced by mitochondrial dysfunction in G72/G30 transgenic mice. *Neuropsychopharmacology*. 2011; 36:2233–2243. [PubMed: 21716263]
- Palmen SJ, van Engeland H, Hof PR, Schmitz C. Neuropathological findings in autism. *Brain*. 2004; 127(Pt 12):2572–83.
- Peça J, Feliciano C, Ting JT, Wang W, Wells MF, Venkatraman TN, Lascola CD, Fu Z, Feng G. Shank3 mutant mice display autistic-like behaviors and striatal dysfunction. *Nature*. 2011; 472:437–442. [PubMed: 21423165]
- Penagarikano O, Geschwind DH. What does CNTNAP2 reveal about autism spectrum disorder? *Trends Mol Med*. 2012; 18:156–163. [PubMed: 22365836]
- Petit E, Héroult J, Martineau J, Perrot A, Barthélémy C, Hameury L, Sauvage D, Lelord G, Muh JP. Association study with two markers of a human homeogene in infantile autism. *J.Med.Genet*. 1995; 32:269–274. [PubMed: 7643354]
- Piontkewitz Y, Arad M, Weiner I. Tracing the development of psychosis and its prevention: what can be learned from animal models. *Neuropharmacology*. 2012; 62:1273–1289. [PubMed: 21703648]
- Pletnikov MV, Moran TH, Carbone KM. Borna disease virus infection of the neonatal rat: developmental brain injury model of autism spectrum disorders. *Front Biosci*. 2002; 7:593–607.
- Pletnikov MV, Rubin SA, Moran TH, Carbone KM. Exploring the cerebellum with a new tool: neonatal Borna disease virus (BDV) infection of the rat's brain. *Cerebellum*. 2003; 2:62–70. [PubMed: 12882236]
- Pletnikov MV. Inducible and conditional transgenic mouse models of schizophrenia. *Prog Brain Res*. 2009; 179:35–47. [PubMed: 20302816]
- Pratt J, Winchester C, Dawson N, Morris B. Advancing schizophrenia drug discovery: optimizing rodent models to bridge the translational gap. *Nat Rev Drug Discov*. 2012; 11:560–579. [PubMed: 22722532]

- Prevot V, Rio C, Cho GJ, Lomniczi A, Heger S, Neville CM, Rosenthal NA, Ojeda SR, Corfas G. Normal female sexual development requires neuregulin-erbB receptor signaling in hypothalamic astrocytes. *J Neurosci*. 2003; 23:230–239. [PubMed: 12514220]
- Rapoport JL, Giedd JN, Gogtay N. Neurodevelopmental model of schizophrenia: update 2012. *Mol Psychiatry*. 2012; 17:1228–1238. [PubMed: 22488257]
- Reith RM, Way S, McKenna J 3rd, Haines K, Gambello MJ. Loss of the tuberous sclerosis complex protein tuberin causes Purkinje cell degeneration. *Neurobiol Dis*. 2011; 43:113–122. [PubMed: 21419848]
- Reith RM, McKenna J, Wu H, Hashmi SS, Cho SH, Dash PK, Gambello MJ. Loss of Tsc2 in Purkinje cells is associated with autistic-like behavior in a mouse model of tuberous sclerosis complex. *Neurobiol Dis*. 2013; 51:93–103. [PubMed: 23123587]
- Rodier PM, Ingram JL, Tisdale B, Croog VJ. Linking etiologies in humans and animal models: studies of autism. *Reprod Toxicol*. 1997; 11:417–422. [PubMed: 9100317]
- Rodriguez-Murillo L, Gogos JA, Karayiorgou M. The genetic architecture of schizophrenia: new mutations and emerging paradigms. *Annu Rev Med*. 2012; 63:63–80. [PubMed: 22034867]
- Roffler-Tarlov S, Herrup K. Quantitative examination of the deep cerebellar nuclei in the staggerer mutant mouse. *BrainRes*. 1981; 215:49–59.
- Rogers SJ, Wehner DE, Hagerman R. The behavioral phenotype in fragile X: symptoms of autism in very young children with fragile X syndrome, idiopathic autism, and other developmental disorders. *J. Dev Behav Pediatr*. 2001; 22:409–417. [PubMed: 11773805]
- Rogers TD, McKimm E, Dickson PE, Goldowitz D, Blaha CD, Mittleman G. Is autism a disease of the cerebellum? An integration of clinical and pre-clinical research. *Front Syst Neurosci*. 2013; 7:15. [PubMed: 23717269]
- Rott R, Herzog S, Fleischer B, Winokur A, Amsterdam J, Dyson W, Koprowski H. Detection of serum antibodies to Borna disease virus in patients with psychiatric disorders. *Science*. 1985; 228:755–756. [PubMed: 3922055]
- Roulet FI, Lai JK, Foster JA. In utero exposure to valproic acid and autism--a current review of clinical and animal studies. *Neurotoxicol Teratol*. 2013; 36:47–56. [PubMed: 23395807]
- Sadamatsu M, Watanabe K. Is a neonatal hypothyroid rat useful as an animal model of autism? *Neurosci Res*. 2005; 52:28.
- Sadamatsu M, Kanai H, Xu X, Liu Y, Kato N. Review of animal models for autism: implication of thyroid hormone. *Congenit Anom*. 2006; 46:1–9.
- Sandhya T, Sowjanya J, Veeresh B. Bacopa monniera (L.) Wettst ameliorates behavioral alterations and oxidative markers in sodium valproate induced autism in rats. *Neurochem Res*. 2012; 37:1121–1131. [PubMed: 22322665]
- Schmahmann JD. An emerging concept. The cerebellar contribution to higher function. *Arch Neurol*. 1991; 48:1178–1187. [PubMed: 1953406]
- Schneider T, Przewlocki R. Behavioral alterations in rats prenatally exposed to valproic acid: animal model of autism. *Neuropsychopharmacology*. 2005; 30:80–89. [PubMed: 15238991]
- Schneider T, Turczak J, Przewlocki R. Environmental enrichment reverses behavioral alterations in rats prenatally exposed to valproic acid: issues for a therapeutic approach in autism. *Neuropsychopharmacology*. 2006; 31:36–46. [PubMed: 15920505]
- Schneider T, Roman A, Basta-Kaim A, Kubera M, Budziszewska B, Schneider K, Przewlocki R. Gender-specific behavioral and immunological alterations in an animal model of autism induced by prenatal exposure to valproic acid. *Psychoneuroendocrinology*. 2008; 33:728–740. [PubMed: 18396377]
- Schurov IL, Handford EJ, Brandon NJ, Whiting PJ. Expression of disrupted in schizophrenia 1 (DISC1) protein in the adult and developing mouse brain indicates its role in neurodevelopment. *Mol Psychiatry*. 2004; 9:100–110.
- Schwarz JM, Bilbo SD. Sex, glia, and development: interactions in health and disease. *Horm Behav*. 2012; 62:243–253. [PubMed: 22387107]
- Sen B, Singh AS, Sinha S, Chatterjee A, Ahmed S, Ghosh S, Usha R. Family-based studies indicate association of Engrailed 2 gene with autism in an Indian population. *Genes Brain Behav*. 2010; 9:248–255. [PubMed: 20050924]

- Shi J, Badner JA, Gershon ES, Liu C. Allelic association of G72/G30 with schizophrenia and bipolar disorder: a comprehensive meta-analysis. *Schizophr Res.* 2008; 98:89–97. [PubMed: 18023149]
- Shi L, Smith SE, Malkova N, Tse D, Su Y, Patterson PH. Activation of the maternal immune system alters cerebellar development in the offspring. *Brain Behav Immun.* 2009; 23:116–123. [PubMed: 18755264]
- Shu W, Cho JY, Jiang Y, Zhang M, Weisz D, Elder GA, Schmeidler J, De Gasperi R, Sosa MA, Ravidou D, Santucci AC, Perl D, Morrissey E, Buxbaum JD. Altered ultrasonic vocalization in mice with a disruption in the *Foxp2* gene. *Proc Natl Acad Sci U S A.* 2005; 102:9643–9648. [PubMed: 15983371]
- Sierra-Honigsmann AM, Carbone KM, Yolken R, H. Polymerase chain reaction (PCR) search for viral nucleic acid sequences in schizophrenia. *Br J Psychiatry.* 1995; 166:55–60. [PubMed: 7894877]
- Sillitoe RV, Stephen D, Lao Z, Joyner AL. Engrailed homeobox genes determine the organization of Purkinje cell sagittal stripe gene expression in the adult cerebellum. *J Neurosci.* 2008; 28:12150–12162. [PubMed: 19020009]
- Snider SR. Cerebellar pathology in schizophrenia--cause or consequence? *Neurosci Biobehav Rev.* 1982; 6:47–53. [PubMed: 7041016]
- Stanton ME, Peloso E, Brown KL, Rodier P. Discrimination learning and reversal of the conditioned eyeblink reflex in a rodent model of autism. *Behav Brain Res.* 2007; 176:133–140. [PubMed: 17137645]
- Stark KL, Xu B, Bagchi A, Lai WS, Liu H, Hsu R, Wan X, Pavlidis P, Mills AA, Karayiorgou M, Gogos JA. Altered brain microRNA biogenesis contributes to phenotypic deficits in a 22q11-deletion mouse model. *Nat Genet.* 2008; 40:751–760. [PubMed: 18469815]
- St Clair D, Blackwood D, Muir W, Carothers A, Walker M, Spowart G, Gosden C, Evans HJ. Association within a family of a balanced autosomal translocation with major mental illness. *Lancet.* 1990; 336:13–16. [PubMed: 1973210]
- Sullivan PF, Daly MJ, O'Donovan M. Genetic architectures of psychiatric disorders: the emerging picture and its implications. *Nat Rev Genet.* 2012; 13:537–551. [PubMed: 22777127]
- Sullivan PF. Questions about DISC1 as a genetic risk factor for schizophrenia. *Mol Psychiatry.* 2013; 18(10):1050–1052. [PubMed: 24056909]
- Supprian T, Ulmar G, Bauer M, Schüler M, Püschel K, Retz-Junginger P, Schmitt HP, Heinsen H. Cerebellar vermis area in schizophrenic patients - a postmortem study. *Schizophr Res.* 2000; 16:19–28. [PubMed: 10706982]
- Taieb O, Baleyte JM, Mazet P, Fillet AM. Borna disease virus and psychiatry. *Eur Psychiatry.* 2001; 16:3–10. [PubMed: 11246286]
- Takuma K, Ago Y, Matsuda T. Preventive effects of an enriched environment on rodent psychiatric disorder models. *J Pharmacol Sci.* 2011; 117:71–76. [PubMed: 21881295]
- Thomson PA, Malavasi EL, Grünwald E, Soares DC, Borkowska M, Millar JK. DISC1 genetics, biology and psychiatric illness. *Front Biol (Beijing).* 2013; 8:1–31. [PubMed: 23550053]
- Triantafilou M, Triantafilou K. Lipopolysaccharide recognition: CD14, TLRs and the LPS-activation cluster. *Trends Immunol.* 2002; 23:301–304. [PubMed: 12072369]
- Tsai PT, Hull C, Chu Y, Greene-Colozzi E, Sadowski AR, Leech JM, Steinberg J, Crawley JN, Regehr WG, Sahin M. Autistic-like behaviour and cerebellar dysfunction in Purkinje cell *Tsc1* mutant mice. *Nature.* 2012; 488:647–651. [PubMed: 22763451]
- Tsiouris JA, Brown WT. Neuropsychiatric symptoms of fragile X syndrome: pathophysiology and pharmacotherapy. *CNS Drugs.* 2004; 18:687–703. [PubMed: 15330685]
- Van Middlesworth L, Norris CH. Audiogenic seizures and cochlear damage in rats after perinatal antithyroid treatment. *Endocrinology.* 1980; 106:1686–1690. [PubMed: 6154569]
- Verhoeven JS, De Cock P, Lagae L, Snaert S. Neuroimaging of autism. *Neuroradiology.* 2010; 52:3–14. [PubMed: 20033797]
- Verkerk AJ, Pieretti M, Sutcliffe JS, Fu YH, Kuhl DP, Pizzuti A, Reiner O, Richards S, Victoria MF, Zhang F, Eussen BE, van Ommen GB, Blonden LAJ, Riggins GJ, Chastain J, Kunst C, Galjaard H, Caskey CT, Nelson DL, Oostra BA, Warren ST. Identification of a gene (*FMR-1*) containing a CGG repeat coincident with a break point cluster region exhibiting length variation in fragile X syndrome. *Cell.* 1991; 65:905–914. [PubMed: 1710175]

- Villanueva R. The cerebellum and neuropsychiatric disorders. *Psychiatry Res.* 2012; 198:527–32. [PubMed: 22436353]
- Vogel MW, Caston J, Yuzaki M, Mariani J. The Lurcher mouse: fresh insights from an old mutant. *Brain Res.* 2007; 1140:4–18. [PubMed: 16412991]
- Waltrip RW 2nd, Buchanan RW, Summerfelt A, Breier A, Carpenter WT Jr, Bryant NL, Rubin SA, Carbone KM. Borna disease virus and schizophrenia. *Psychiatry Res.* 1995; 56:33–44. [PubMed: 7792340]
- Wu W, Peden D, Diaz-Sanchez D. Role of GSTM1 in resistance to lung inflammation. *Free Radic Biol Med.* 2012; 53:721–729. [PubMed: 22683820]
- Xu M, Sajdel-Sulkowska EM, Iwasaki T, Koibuchi N. Aberrant cerebellar neurotrophin-3 expression induced by lipopolysaccharide exposure during brain development. *Cerebellum.* 2013a; 12:316–318. [PubMed: 23319369]
- Xu M, Sulkowski ZL, Parekh P, Khan A, Chen T, Midha S, Iwasaki T, Shimokawa N, Koibuchi N, Zavacki AM, Sajdel-Sulkowska EM. Effects of perinatal lipopolysaccharide (LPS) exposure on the developing rat brain; modeling the effect of maternal infection on the developing human CNS. *Cerebellum.* 2013b; 12:572–586. [PubMed: 23475384]
- Yasuda S, Ishida N, Higashiyama A, Morinobu S, Kato N. Characterization of audiogenic-like seizures in naive rats evoked by activation of AMPA and NMDA receptors in the inferior colliculus. *Exp Neurol.* 2000; 164:396–406. [PubMed: 10915578]
- Yeganeh-Doost P, Gruber O, Falkai P, Schmitt A. The role of the cerebellum in schizophrenia: from cognition to molecular pathways. *Clinics (Sao Paulo).* 2011; 66(Suppl 1):71–7. [PubMed: 21779725]
- Yochum CL, Dowling P, Reuhl KR, Wagner GC, Ming X. VPA-induced apoptosis and behavioral deficits in neonatal mice. *Brain Res.* 2008; 1203:126–132. [PubMed: 18316065]
- Yochum CL, Bhattacharya P, Patti L, Mirochnitchenko O, Wagner GC. Animal model of autism using GSTM1 knockout mice and early postnatal sodium valproate treatment. *Behav Brain Res.* 2010; 210:202–210. [PubMed: 20178820]
- Yuskaitis CJ, Beurel E, Jope RS. Evidence of reactive astrocytes but not peripheral immune system activation in a mouse model of Fragile X syndrome. *Biochim Biophys Acta.* 2010; 1802:1006–1012. [PubMed: 20600866]
- Zariwala HA, Madisen L, Ahrens KF, Bernard A, Lein ES, Jones AR, Zeng H. Visual tuning properties of genetically identified layer 2/3 neuronal types in the primary visual cortex of cre-transgenic mice. *Front Syst Neurosci.* 2011; 4:162. [PubMed: 21283555]

Table 1

Environmental models of autism and schizophrenia

Environmental factors	Animal models	Behavioral alterations	Cerebellar pathology	Strengths	Caveats	Refs
Borna virus	Neonatal brain infection in rats	Hyper-reactivity Elevated anxiety Deficient learning Abnormal social behaviors	Hypoplasia Gradual loss of PC	Comprehensive face validity Neurotropic virus	No human infection Intracerebral inoculation Widespread effects	Plenikov et al., 2002; 2003; Dietz, 2004; Lancaster, 2007
Valproic acid (VPA)	Prenatal exposure in rodents	Impaired PPI Eye blink conditioning Stereotypy and hyperactivity Decreased social behaviors	Reduction of PC Decreased cerebellar volume	Relevance to human conditions Abnormalities start during development	Responsible for limited numbers of cases Widespread effects on the brain and whole body	Ingram et al., 2000; Schneider, 2006, 2008; Dufour-Rainfray et al., 2009; Markram, 2007, 2008 ; Stanton et al., 2007; Mychasiuk, 2012; Yochum et al., 2008
Influenza virus	Prenatal and early postnatal exposure in mice	Altered anxiety Deficit in Morris water maze	Not reported	Relation to human	Specificity of flu in mice vs. humans Confounding effects of sickness and stress	Fatemi et al., 2008a,b, 2009; Beraki et al., 2005
Immune activation	Prenatal exposure to poly IC or LPS	Elevated anxiety Decreased social behaviors Deficits in learning and memory	A localized deficit in PC in lobule VII of the cerebellum Heterotopic PC Delayed migration of granule cells in lobules VI and VII	Relevance to human conditions Amenable to dosing, timing and routes of exposure	Artificial immune activation Wide-spread effects	Shi et al., 2009 Xu et al., 2013
Altered thyroid production	Early postnatal hypothyroidism in rats	Hyperactivity Decreased habituation Deficient learning and memory	Retarded granular cell migration in the external granular layer	Relevance to human conditions	Responsible for limited numbers of cases Widespread effects on the brain and whole body	Sadamatsu and Watanabe, 2005; Sadamatsu et al., 2006 Akaike et al., 1991; Akaike and Kato, 1997

Table 2

Genetic models of autism

Gene/ Protein/ Function	Animal models	Behavioral alterations	Cerebellar pathology	Strengths	Caveats	Refs
<i>RORα</i>	Staggerer mice	Ataxia Impaired reversal learning Perseverative behavior Abnormal responses to novelty	Loss of PC A disappearance of granule cells Severe hypoplasia	Face validity	Limited relation to human cases Widespread effects	Herrup and Mullen, 1979; Herrup et al., 1996; Doulazmi et al., 2001; Goldowitz and Koch, 1986; Misslin et al., 1986; Lalonde et al., 1996
<i>SHANK3</i> Postsynaptic protein <i>IB2</i>	KO mice	Social abnormalities Stereotypy Poor learning and memory	Altered glutamatergic transmission Abnormal dendritic arborization of PC	Gene implicated in humans Face validity	No cell type- regional- or time- dependent manipulation	Beri et al., 2007; Peça et al., 2011; Jiang and Ehlers, 2013
<i>ENGRAILED 2</i> a transcription factor	KO mice	Attenuated play Reduced aggressive and non-aggressive social behaviors Impaired learning	Hypoplasia Decreased number of PC Foliation abnormalities	Gene implicated in humans Face validity	No cell type- regional- or time- dependent manipulation	Millen et al., 1994; Kuemerle et al., 1997, 2007; Cheh et al., 2006; Brielmayer et al., 2012
<i>FMR1</i> the fragile X mental retardation protein	KO mice	Hyperactivity Perseverative behavior Poor learning and memory	Elongated spines on PC Reduced volume of the cerebellar nuclei	Gene implicated in humans Face validity	No cell type- regional- or time- dependent manipulation	Koekkoek et al., 2005; Olmos-Serrano et al., 2011; Ellegood et al., 2010; Yuskaitis et al., 2010
<i>TSC1</i> and <i>2</i> hamartin (<i>TSC1</i>) and tuberin (<i>TSC2</i>)	Conditional PC KO mice	<i>TSC1</i> KO mice Abnormal social interaction Repetitive behavior and altered ultrasonic vocalizations <i>TSC2</i> KO mice Repetitive behavior Decreased sociability	A progressive PC loss	Gene implicated in humans PC- and time-specific Amenable to treatment Face validity	Later effects of PC loss confound the phenotypes	Reith et al., 2011, 2013; Tsai et al., 2012
<i>FOXP2</i> Transcriptional factor	<i>Foxp2</i> KO mice <i>Foxp2</i> (R552H) knock-in	Motor impairment Altered ultrasonic vocalization	Thick EGL at P15-17 Thinning of the molecular layer Ectopic PC Underdeveloped dendrites Misaligned Bergman glia	Gene and mutation implicated in humans Face validity	No cell type- regional- or time- dependent manipulation	Shu et al., 2005; Fujita et al., 2012a-c
GABA receptors	<i>Gabrb3</i> KO mice	Deficient sociability and nesting behavior	Hypoplasia of the vermis	Face validity	Limited relation to human cases Widespread effects	DeLorey et al., 2008

Table 3

Genetic models of schizophrenia

Gene/ Protein/ Function	Animal models	Behavioral alterations	Cerebellar pathology	Strengths	Caveats	Refs
G72/G30 Chr. 13q LG72 protein DAO regulator mitochondrial protein	G72Tg mice	Impaired PPI reversible with haloperidol Increased sensitivity to PCP Motor-coordination deficits Increased compulsive behaviors Deficits in smell identification	Not reported	Expression of primate-specific mutation with high expression in the cerebellum	Constitutive over-expression	Otte et al., 2009, 2011; Filiou et al., 2012
22q11.2 deletion encompasses 27 genes	Df(16)A ^{+/-} mice	Hyperactive and anxiety Impaired contextual fear- conditioning	Abnormalities within the deep nuclei and the cortex	Deletion of the segment syntenic to the human chromosome segment	No region- or time-dependent expression	Stark et al., 2008; Ellegood et al., 2013
DISC1 Scaffold protein with extended interactome	Inducible expression of mutant DISC1	Elevated ambulatory and rearing activity; Deficits in object recognition and social recognition Decreased fear conditioning	Decreased volumes of the cerebellum and PC	Region-specific and time-dependent expression DOX-regulated	Over-expression of heterologous protein	Shevelkin et al., Manuscript in preparation