Reversing Neurodevelopmental Disorders in Adults

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Abnormalities in brain development, thought to be irreversible in adults, have long been assumed to underlie the neurological and psychiatric symptoms associated with neurodevelopmental disorders. Surprisingly, a number of recent animal model studies of neurodevelopmental disorders demonstrate that reversing the underlying molecular deficits can result in substantial improvements in function even if treatments are started in adulthood. These findings mark a paradigmatic change in the way we understand and envision treating neurodevelopmental disorders.

The term "neurodevelopmental disorders" encompasses a large group of disorders that share the fact that disease onset is during periods of ongoing maturation and development. These disorders are often associated with complex neuropsychiatric features including intellectual disability, specific learning disabilities, ADHD, autism, and epilepsy, among others. Neurodevelopmental disorders are caused by a wide range of genetic mutations and environmental factors (e.g., infections, immune dysfunction, intoxication, endocrine and metabolic dysfunction, nutritional factors, trauma, etc.). Heritability estimates indicate that genetic factors play an important role in these disorders. Although our review is focused on single-gene disorders, the basic implications discussed may be more broadly relevant and therefore applicable to neurodevelopmental disorders in general.

The Traditional View

Neurodevelopmental disorders are thought to be caused by changes in development, potentially involving alterations in neurogenesis, cell migration, and neuronal connectivity that are responsible for cognitive deficits in adults. Accordingly, abnormalities in brain structure, resulting from perturbed development, are often associated with neurodevelopmental disorders. Additionally, development is an especially vulnerable period: insults with a minor impact in adults can result in significant pathologies when occurring during development. For example, absence of serotonin$_{1A}$ receptor function in the forebrain during postnatal development, but not in adulthood, results in anxiety-related behavioral phenotypes in mice (Gross et al., 2002). Similarly, maternal care during early postnatal periods has been shown to influence hippocampal glucocorticoid receptor expression, stress responsiveness, and behavior in the offspring via epigenetic modulations that last into adulthood (Caldji et al., 1998; Francis et al., 1999; Liu et al., 1997; Weaver et al., 2004). A recent study with an animal model of schizophrenia (Li et al., 2007) showed that a brief induction of a DISC1 mutant allele during postnatal development, but not in adults, is sufficient to trigger many of the phenotypes associated with this neurodevelopmen-

tal disorder (Weinberger, 1987). Clinical experience with endocrine and metabolic disorders also stresses the importance of insults during vulnerable periods of development: hypothyroidism and phenylketonuria, for example, can lead to profound and irreversible cognitive disability when left uncorrected during developmental periods, while they appear to have milder effects in adults (Davis and Tremont, 2007; Dugbartey, 1998; Hanley, 2004; Rovet and Daneman, 2003; Zoeller and Rovet, 2004). Nevertheless, there are many other examples of pathologies where the opposite is true: for example, trauma, infection, and ischemia may have much of the same or even more dire effects in adults than in developing organisms (Kolb et al., 2000; Vannucci and Hagberg, 2004).

Many of the mutations that cause developmental disorders disrupt gene(s) that are also expressed in the adult brain. Thus, in addition to developmental effects on brain structure and function, it is possible that altered gene function in adulthood may contribute to associated cognitive phenotypes. Accordingly, a number of recent studies of animal models of neurodevelopmental disorders strongly suggest that adult disruption of gene function makes a significant contribution to cognitive disability and neurological dysfunction associated with these disorders. These studies demonstrate that treating the disrupted molecular and cellular mechanisms specifically in adults can result in dramatic improvements in cognitive function. It is conceivable that biochemical amelioration of the underlying genetic deficits may allow robust molecular, cellular, structural, and behavioral plasticity mechanisms in the adult brain to compensate for or even correct specific developmental pathologies.

Adult Recovery of Cognition in Animal Models of Neurodevelopmental Disorders

Recent studies using animal models of several single-gene developmental disorders provide compelling evidence that cognitive deficits and neurological impairments associated with neurodevelopmental disorders can be reversed, even if treatment is initiated in adults (Table 1). For example, neurofibromatosis I (NF1) is a complex developmental genetic disorder caused by mutations

in the *NF1* gene. Specific learning disabilities, including difficulties with visuospatial skills, memory, and attentional-executive function, are commonly associated with NF1. Mice with a heterozygous deletion of the Nf1 gene (*Nf1*$^{+/-}$ mice) displayed spatial learning deficits (Silva et al., 1997) and impairments in attentional-executive function (Li et al., 2005), akin to neuropsychological impairments observed in NF1 patients. The *NF1* gene encodes neurofibromin, a GTPase-activating protein that accelerates the inactivation of Ras, thereby inhibiting Ras-MAPK signaling. Accordingly, loss-of-function mutations in the *NF1* gene lead to disinhibited Ras-MAPK signaling, a pathway with a known role in neurodevelopment. *Nf1*$^{+/-}$ mice show defects in long-term potentiation (LTP) due to increased inhibitory neurotransmission in the hippocampus (Costa et al., 2002).

Two pharmacological strategies that reduce the isoprenylation of Ras, and thereby decrease active (membrane-bound) Ras, have been used to rescue the signaling, physiology, and behavioral deficits of these mice: farnesyl-transferase inhibition with BMS 191563 (Costa et al., 2002) and HMG-CoA reductase inhibition with lovastatin (Li et al., 2005). HMG-CoA reductase is the rate-limiting enzyme in the mevalonate pathway in which isoprenyl groups (and then cholesterol) are synthesized. Notably, a short pharmacological treatment of adult mice was sufficient to decrease Ras-MAPK signaling, restore LTP, and reverse cognitive deficits in *Nf1*$^{+/-}$ mice. Drug doses sufficient to rescue the phenotypes of the mutants did not have a measurable effect on controls (Costa et al., 2002; Li et al., 2005), a result that indicates that the drugs used targeted the mechanisms disrupted in these mutants. Importantly, a recent clinical study reported that although a brief 12 week simvastatin treatment did not have a significant overall effect on the cognition of patients, it did rescue deficits in an object assembly test (Krab et al., 2008). Moreover, the treatment had the biggest impact on patients with the poorest performances, while not affecting the performances of patients with scores within the normal range. Although promising, longer treatments with larger sample sizes are needed to confirm that statins have a beneficial impact on the cognition of NF1 patients.

Remarkably, similar to the *Nf1*$^{+/-}$ mice (Costa et al., 2002), the hippocampal learning and memory deficits of an animal model of Down's syndrome (the Ts65Dn mice) appear to be due to deficits in hippocampal LTP caused by enhanced GABAergic inhibition (Kleschevnikov et al., 2004). Down's syndrome, caused by trisomy 21, is the most common genetic disorder associated with intellectual disability. The Ts65Dn mouse model of the disorder (Reeves et al., 1995) is based on the partial triplication of chromosome 16, the mouse homolog to human chromosome 21. Until recently, nearly all of the mechanistic studies of this disorder focused on the impact of genetic changes on development. A recent ground-breaking study, aimed at testing the hypothesis that abnormally high levels of inhibition in adult mice play a role in the pathogenesis of Down's syndrome-related cognitive dysfunction (Fernandez et al., 2007), showed that although acute treatment (1 day) with a GABA$_A$ receptor antagonist (picrotoxin) had no effect, a 2 week treatment with several GABA$_A$ receptor antagonists (picrotoxin, pentylenetetrazole, or bilobalide) rescued cognitive deficits (object recognition, spontaneous alternation) in adult Ts65Dn mice. The same treatment did not affect learning in controls, a result consistent with the idea

that increased inhibition accounts for the learning and memory deficits in Ts65Dn mice.

Surprisingly, an ~2 week treatment with GABA$_A$ antagonists (Fernandez et al., 2007) led to a persistent (for at least up to 2 months) behavioral recovery even though the treatment was not extended beyond the initial ~2 week period. Similarly, this treatment also resulted in the (partial) rescue of LTP, even when LTP was tested 3 months after the completion of the ~2 week treatment. These findings have been recently confirmed and extended in a study that showed that a 7 week treatment with the GABA$_A$ receptor antagonist pentylenetetrazole also rescues spatial learning deficits in adult Ts65Dn mice (Rueda et al., 2008). The results reviewed above show that reversing the increased inhibition in the Ts65Dn mutants triggered lasting adaptive changes that result in improvements in cognition. The unexpected (and unexplained) delayed therapeutic action of this treatment is reminiscent of other psychopharmacological effects, such as the well-known delayed effect of antidepressants. Could treatment with GABA receptor inhibitors, and the resulting lowering of inhibitory tone, lead to the reactivation of developmental plasticity processes (see discussion below) that contributed to the restored LTP and learning of the Ts65Dn mice? Could similar treatments reverse the cognitive deficits associated with Down's syndrome?

Rubinstein-Taybi syndrome (RTS) is another genetic disorder characterized by intellectual disability and characteristic physical features that include broad thumbs and toes as well as facial abnormalities (Rubinstein and Taybi, 1963). Although there are multiple genes implicated in RTS, mutations in the CREB-binding protein (CBP) are known to cause this syndrome (Petrij et al., 1995). CBP is a transcriptional coactivator, has histone acetyltransferase activity, and is involved in transcriptional control downstream of cAMP signaling, linking experience-dependent neuronal activation to gene expression and long-term memory formation (Hallam and Bourtchouladze, 2006; Lonze and Ginty, 2002). A mouse model of RTS (*Cbp*$^{+/-}$ mice) shows normal short-term memory but impaired long-term memory in context fear conditioning and object recognition (Alarcon et al., 2004; Bourtchouladze et al., 2003). Memory deficits in *Cbp*$^{+/-}$ mice could be restored in adult mice using pharmacological strategies that enhance CREB-dependent gene expression: the HDAC inhibitor SAHA is known to promote histone acetylation, and it was shown to improve context fear memory in *Cbp*$^{+/-}$ mice (Alarcon et al., 2004). Second, phospodiesterase-4 (PDE-4) inhibitors (inhibit breakdown of cAMP) also improve long-term memory in adult *Cbp*$^{+/-}$ mice (Bourtchouladze et al., 2003), perhaps because they enhance PKA-dependent CREB activation. HDAC inhibitors and PDE-4 antagonists therefore hold therapeutic promise for cognitive deficits associated with RTS. However, it is important to note that these drugs also improved long-term memory in wild-type mice. Importantly, these studies in *Cbp*$^{+/-}$ mice illustrate the potential power of targeting transcriptional regulatory processes to induce lasting therapeutic changes in the adult brain. In line with this, the work from Meaney and colleagues mentioned above also showed that transcriptional derepression (with the HDAC inhibitor trichostatin A) in adult animals reverses functional consequences (increased stress responsiveness) of early life experiences (maternal care

Table 1.

Syndrome	Neuropsychiatric Phenotypes	Genetic Cause	Animal Model	Drug	Treatment Details	Rescued Phenotype(s)	Reference
Neurofibromatosis I	learning disabilities	heterozygous *NF1* mutations	$Nf1^{+/-}$ mice	BMS 191563 (farnesyl-transferase inhibitor)	adult mice, treatment concomitantly with behavior	spatial learning deficits (Morris water maze)	Costa et al., 2002
				lovastatin (HMG CoA reductase inhibitor)	adult mice; treatment was initiated 3 days prior to behavior (Morris water maze)	spatial learning (Morris water maze) and attention deficits (lateralized reaction time test), prepulse inhibition deficits, deficits in long-term potentiation	Li et al., 2005
Down's Syndrome	intellectual disability, learning disabilities, behavior disorders, epilepsy	trisomy 21	Ts65Dn mice	picrotoxin, pentylene-tetrazole, bilobalide ($GABA_A$ receptor antagonists)	3- to 4-month-old mice; minimum effective treatment duration: 2 weeks; therapeutic effect lasted for months even if treatment was discontinued	learning and memory deficits in object recognition task, spontaneous alternation, deficient long-term potentiation	Fernandez et al., 2007
				pentylene-tetrazole ($GABA_A$ receptor antagonist)	7 week treatment started at 4 months	spatial learning deficits (Morris water maze)	Rueda et al., 2008
Rubinstein-Taybi Syndrome	intellectual disability	heterozygous mutations in *CBP* (but genetic heterogeneity)	$Cbp^{+/-}$ mice	HT0712, rolipram (PDE-4 inhibitors)	single treatment prior to behavior	long-term memory deficit in object recognition task	Bourtchouladze et al., 2003
				SAHA (HDAC inhibitor)	single treatment prior to behavior	long-term memory deficit in context fear conditioning, deficient long-term potentiation	Alarcon et al., 2004

Tuberous Sclerosis	intellectual disability, learning disabilities, epilepsy, autism, behavior disorders	heterozygous mutations in *TSC1* or *TSC2*	*Tsc2*$^{+/-}$ mice	rapamycin (mTOR inhibitor)	3- to 6-month-old mice; treatment started concomitantly with behavior (Morris water maze) or 5 days prior to behavior (context discrimination)	spatial learning deficits (Morris water maze), context discrimination, long-term potentiation phenotype	Ehninger et al., 2008
			neuronal homozygous *Tsc1* mutant mice	rapamycin (mTOR inhibitor)	treatment started at postnatal day 1 and was continued to adulthood	neurological findings (hindlimb clasping, hypoactivity), brain enlargement and lethality	Ehninger et al., 2008
			neuronal homozygous *Tsc1* mutant mice	rapamycin, RAD001 (mTOR inhibitors)	treatment started at postnatal day 7–9 and was continued to adulthood	neurological findings (clasping, tremor, kyphosis, abberant tail position), elevated brain/ body weight ratio, impaired myelination	Meikle et al., 2008
			astroglial homozygous *Tsc1* mutant mice	rapamycin (mTOR inhibitor)	treatment initiated at 2 weeks (before seizure onset) or at 6 weeks of age (after seizure onset)	rescue of seizures and lethality (in both treatment groups); prevention of astrogliosis and abnormal neuronal organization	Zeng et al., 2008
Lhermitte-Duclos Disease; Cowden Disease; Autism	Lhermitte-Duclos disease: intellectual disability, ataxia epilepsy	*PTEN* mutations	mice with neuronal homozygous deletion of *Pten*	CCI-779 (mTOR inhibitor)	for analysis of adult mice, treatment started when mutant mice were clearly symptomatic (ranging from 6 to 16 weeks of age); treatment for 4–8 weeks	reversal of phenotypic features in symptomatic adult mice (seizures, dentate gyrus granule cell hypertrophy; lethality)	Kwon et al., 2003

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Table 1. *Continued*

Syndrome	Neuropsychiatric Phenotypes	Genetic Cause	Animal Model	Drug	Treatment Details	Rescued Phenotype(s)	Reference
Fragile X Syndrome	intellectual disability, autism, learning disabilities, behavior disorders, epilepsy	triplet repeat expansion that leads to transcriptional silencing of *FMR1* gene	fragile X drosophila model (homozygous *dfmr1* mutants with a transgene containing a frameshift mutation in the *dfmr1* open reading frame)	MPEP, LY341495, MPPG, MTPG (mGluR antagonists), lithium	4 days treatment started in adulthood (after eclosion)	naive courtship behavior (partial restoration in adult FXS flies by MPEP, LY341495, lithium, MPPG, MTPG; all drugs decreased courtship behavior in control flies), immediate recall memory (rescue in adult FXS flies by MPEP), short-term memory (rescue in adult FXS flies by MPEP, lithium, LY341495)	McBride et al., 2005
					treatment only during development (before eclosion)	naive courtship behavior, immediate recall memory, short-term memory (rescue in FXS flies by MPEP)	
			Fmr1 mutant mice	genetic rescue: *Fmr1* mutant mice were crossed to heterozygous *mGluR5* mutant mice	germline mutation in *mGluR5*: gene function reduced during development and in adulthood	inhibitory avoidance extinction, audiogenic seizures, accelerated body growth, dendritic spine density, ocular dominance plasticity	Dolen et al., 2007

Angelman Syndrome	intellectual disability, learning disabilities, movement disorders, language impairments, epilepsy, behavioral features (hyperactivity, frequent laughter, etc.)	loss-of-function of imprinted genes on chromosome 15q11-13; *UBE3A* mutations	heterozygous mice with a maternally inherited *Ube3a* mutation (*Ube3a*$^{p+/m-}$ mice)	genetic rescue: *Ube3a*$^{p+/m-}$ mice were crossed to heterozygous αCaMKII-T305V/T306A mutant mice	rescue of *Ube3a*$^{p+/m-}$ phenotypes by αCaMKII-T305V/T306A mutation suggests that *Ube3a*$^{p+/m-}$ phenotypes emerge as a consequence of postnatal pathology	audiogenic seizures, motor coordination deficits (accelerating rotarod), spatial learning deficits (Morris water maze), context fear conditioning deficits, increased body weight, deficient long-term potentiation	van Woerden et al., 2007
Rett Syndrome	intellectual disability, autistic features, epilepsy, motor symptoms (delay or absence of walking, ataxia, hypotonia, dystonia, chorea, spasticity)	*MECP2* mutations	*Mecp2* gene silenced by insertion of lox-STOP cassette	genetic rescue: activation of *Mecp2* expression by Cre-mediated deletion of STOP cassette (Cre translocation into nucleus only in presence of tamoxifen)	a series of experiments with different temporal activation of *Mecp2* was performed; activation of *Mecp2* after establishment of neurological symptoms reversed neurological disease	neurological compound score (hindlimb clasping, inertia, irregular breathing, gait, tremor, poor general condition)	Guy et al., 2007

behavior) that are mediated by epigenetic alterations (methylation within the glucocorticoid receptor promoter) (Weaver et al., 2004).

Tuberous sclerosis complex (TSC) is a single-gene disorder associated with intellectual disability and autism and involves signaling changes that affect translational control; TSC is caused by heterozygous mutations in either the *TSC1* or the *TSC2* gene (Consortium, 1993; van Slegtenhorst et al., 1997), and besides intellectual disability and autism, affected subjects frequently exhibit epilepsy, ADHD, and specific learning disabilities (de Vries et al., 2005; Joinson et al., 2003). Developmental brain abnormalities (cortical tubers) and early-onset seizures (infantile spasms) have long been proposed to cause the cognitive disability associated with TSC (O'Callaghan et al., 2004; Raznahan et al., 2007). Tubers and infantile spasms, however, only partially account for the variability in IQ in TSC subjects (O'Callaghan et al., 2004). Recent work with mouse models of TSC showed that cognitive deficits can emerge in the absence of tubers and spontaneous seizures (Ehninger et al., 2008; Goorden et al., 2007). Studies with a $Tsc2^{+/-}$ mouse model of tuberous sclerosis demonstrated that TSC-related increases in mTOR signaling lead to an abnormally low threshold for the late phase of LTP: conditions that induced only the unstable early phase of LTP in controls induced instead an abnormally stable potentiation in the mutants (Ehninger et al., 2008). Supposedly, this abnormal stabilization of LTP results in the inappropriate consolidation of error-prone information that interferes with normal learning and memory processes in TSC.

Strikingly, suppressing mTOR signaling with the FDA-approved drug rapamycin restored impaired spatial learning and context discrimination in adult $Tsc2^{+/-}$ mice and reversed abnormalities in LTP thresholds (Ehninger et al., 2008). Behavioral rescue in adult $Tsc2^{+/-}$ mice occurred after a brief 5 day treatment with rapamycin, suggesting that the pharmacological rescue of cognitive deficits was mediated directly through the inhibition of key biochemical changes in TSC mutant mice. Biochemical analysis of the mice suggested that these changes may involve mTOR-dependent increases in neuronal protein synthesis (Ehninger et al., 2008), which appear to also occur in other neurogenetic disorders associated with intellectual disability and autism (Bear et al., 2008; Vanderklish and Edelman, 2005). Unlike patients, mice with heterozygous mutations in the TSC genes do not exhibit either spontaneous seizures or cortical tubers (Ehninger et al., 2008; Goorden et al., 2007). Homozygous astrocyte-specific (Uhlmann et al., 2002) or neuronal-specific (Ehninger et al., 2008; Meikle et al., 2007) deletions of *Tsc1* in mice, however, result in seizures, neurological impairments, and high lethality. Remarkably, postnatal treatment with mTOR inhibitors dramatically reduced seizures, neurological impairments, and lethality in homozygous TSC mutants (Ehninger et al., 2008; Meikle et al., 2008; Zeng et al., 2008). Despite improving neurological findings in a homozygous neuronal model of TSC, mTOR inhibitors did not reverse abnormal neuronal morphology (orientation of apical dendrites in layer V of the somatosensory cortex) (Meikle et al., 2008); rapamycin treatment restored deficient myelination in a homozygous neuronal model of TSC which may significantly contribute to the improvement of neurological impairments in these mutant mice (Meikle et al.,

2008). Initiation of rapamycin treatment after seizure onset, in adolescence, also substantially improved seizures and increased survival in mice with an astrocyte-specific deletion of the *Tsc1* gene (Zeng et al., 2008).

Previous studies with PTEN mutant mice had also documented surprising recovery of neurological impairment in adult animals after disease onset (Kwon et al., 2003). PTEN is an upstream regulator of TSC-mTOR signaling, and mutations in this gene are linked to Lhermitte-Duclos disease (associated with intellectual disability, ataxia, cerebellar ganglion cell hypertrophy, and seizures), Cowden syndrome (a multiple hamartoma syndrome), and autism (Butler et al., 2005; Goffin et al., 2001; Marsh et al., 1999). Inhibition of mTOR has been found to reverse seizures in neuronal-specific homozygous PTEN mutant mice, even when treatment was initiated in adult animals (Kwon et al., 2003). Altogether these studies suggest that disease-related alterations in TSC-mTOR signaling result in reversible brain dysfunction that is accessible to pharmacological correction.

Fragile X syndrome (FXS) is another neurodevelopmental genetic disorder highly associated with intellectual disability and autism; learning disabilities, ADHD and epilepsy are also common in this X-linked disorder (Hagerman and Hagerman, 2002). FXS is caused by mutations in the *FMR1* gene frequently involving CGG triplet repeat expansions in the 5′ untranslated region of the gene. This is thought to lead to hypermethylation and transcriptional silencing of the *FMR1* gene. *FMR1* encodes a protein (FMRP) that is thought to be involved in mRNA transport and translational regulation. According to the "mGluR theory" of FXS, increased group I mGluR signaling plays a central role in the pathophysiology of FXS, including associated cognitive dysfunction (Bear et al., 2004). Recent experimental work provided compelling support for the role of mGluR signaling in the pathogenesis of FXS (Dolen et al., 2007). Reducing mGluR signaling throughout development and adulthood with a heterozygous *mGluR5* germ-line mutation rescued a wide range of phenotypes in the *Fmr1* knockout mouse model of FXS, suggesting that mGluR signaling plays an important role in FXS.

To determine whether mGluR inhibition is critical in development and/or in adults, McBride et al. tested the effect of various mGluR antagonists on defective courtship behavior, impaired memory (in a conditioned courtship task), and CNS structural brain abnormalities in a *Drosophila* model of FXS (McBride et al., 2005). Treatment administered exclusively during development rescued abnormal courtship behavior, memory impairments, and CNS (mushroom body) neuroanatomical defects in adult FXS flies. In contrast, treatment of adult FXS flies with mGluR antagonists partially rescued the abnormal courtship behavior and the memory impairments *without* reversing the structural brain abnormalities. Interestingly, the same treatment led to impairments in wild-type control flies. These findings suggest that abnormal mGluR signaling during both development and in adulthood contribute to behavioral deficits in FXS flies. Moreover, rescue of either (developmental or adult) component was sufficient to (at least partially) reverse behavioral impairments in FXS flies. Therefore, it is possible that despite developmental deficits associated with Fragile X, treatment with mGluR antagonists in adulthood may significantly improve behavioral and cognitive function.

Angelman syndrome is caused by loss of function of imprinted genes on chromosome 15q11-13 or mutations in the *UBE3A* gene (Kishino et al., 1997; Knoll et al., 1989). Individuals affected by Angelman syndrome typically appear normal at birth but show clear developmental delays by 6–12 months. Associated neurological, behavioral, and cognitive symptoms frequently include intellectual disability, seizures, movement disorders, language impairments, hyperactivity, and learning disabilities (Williams et al., 2006). A mouse model of Angelman syndrome that carries a mutation in the maternally inherited *Ube3a* gene (*Ube3a*$^{p+/m-}$) recapitulates features of the human disorder, including motor impairments, learning deficits, and seizures (Jiang et al., 1998). *Ube3a*$^{p+/m-}$ mice show increased inhibitory autophosphorylation of αCaMKII and deficient hippocampal long-term potentiation (Weeber et al., 2003). To test whether increased inhibitory autophosphorylation of αCaMKII accounts for cognitive and neurological symptoms of *Ube3a*$^{p+/m-}$ mice, these mice were crossed to mutants heterozygous for a mutation that prevents inhibitory autophosphorylation of αCaMKII (αCaMKII-T305V/T306A) (van Woerden et al., 2007). Strikingly, a range of *Ube3a*$^{p+/m-}$ phenotypes (audiogenic seizures, motor coordination deficits, hippocampus-dependent learning deficits, deficient hippocampal long-term potentiation) was rescued by a heterozygous αCaMKII-T305V/T306A mutation. These findings suggest that Angelman syndrome-related neurological and cognitive phenotypes may result from decreased αCaMKII activity due to increased inhibitory autophosphorylation. αCaMKII expression is largely restricted to the postnatal brain (Colbran et al., 1989), implicating disturbed postnatal development and/or adult function in the pathophysiology of Angelman syndrome-related neurological and neurocognitive symptoms.

Rett syndrome (Rett, 1966) is another X-linked developmental genetic disorder associated with intellectual disability, autistic features (impaired reciprocal social interaction, language and communication deficits, stereotyped behaviors) and motor symptoms (delay or absence of walking, ataxia, respiratory dysfunction, hypotonia, dystonia, chorea, spasticity). Affected girls are initially asymptomatic and neurological abnormalities start to emerge by the age of 6–18 months. Rett syndrome is caused by mutations in the X-chromosomal gene *MECP2* (Amir et al., 1999), which encodes the transcriptional regulator MeCP2. Mecp2 expression in the brain is restricted to cells of the neuronal lineage and increases with neuronal maturation (Kishi and Macklis, 2004). Several mouse models of Rett syndrome have been engineered by deleting murine *Mecp2* (Chen et al., 2001; Guy et al., 2001; Shahbazian et al., 2002). *Mecp2* null male mice show progressive neurological disease (gait abnormalities, hindlimb clasping, respiratory dysfunction) and high mortality. Female mutant mice also display progressive neurological impairments, which eventually stabilize and by-and-large do not interfere with survival. *Mecp2* mutant mice have lower brain volumes, accompanied by normal neuron numbers but decreased neuronal arborization.

Recently, a loxP genetic strategy was used to restore Mecp2 levels in *Mecp2* mutant mice at various ages (Guy et al., 2007): the authors first silenced *Mecp2* by insertion of a lox-STOP cassette. Later, at specific time points, *Mecp2* expression was restored by inducible activation of Cre recombinase; the recom-

binase excised the lox-STOP cassette, thereby allowing expression of the *Mecp2* gene. Gradually restoring Mecp2 expression after the onset of neurological symptoms—that include hindlimb clasping, inertia, irregular breathing, gait, and tremor—reversed these impairments and improved survival in male *Mecp2* mutant mice. Accordingly, restoring Mecp2 expression in mature female mutant mice, after onset of neurological disease, reversed function to wild-type levels and restored proper levels of neuronal plasticity. These remarkable results demonstrate that deficits caused by Mecp2 loss in development do not result in irreversible deficits. Instead, these data demonstrate that restoring function in adults can reverse at least some of the deficits caused by loss of gene function during development.

Interestingly, a lower excitation-to-inhibition ratio was found in the neocortex of *Mecp2* mutant mice (Dani et al., 2005). Fragile X mice showed reduced excitatory drive of inhibitory neurons and thus an increased excitation to inhibition ratio (Gibson et al., 2008). As reviewed above, both NF1 and Down's syndrome mouse models were found to have higher levels of inhibition but normal excitation (see above) (Costa et al., 2002; Kleschevnikov et al., 2004). The analyses of these four models suggest that a change in the ratio of excitation to inhibition is an important feature of neurodevelopmental disorders (Rubenstein and Merzenich, 2003).

Taken together, the studies summarized above suggest that cognitive disability in classic "neurodevelopmental" disorders may be reversible in adults, even when developmental neuroanatomical abnormalities are not reversed. Thus, these studies demonstrate that, for at least some of these disorders, loss of gene function specifically in adults makes a sizeable contribution to the resulting pathology and that treating this facet of the disorder, in animal models, can result in dramatic improvements. A cautionary note is however in order: we do not know whether the rescues described in this review will be the norm for neurodevelopmental disorders or whether these results in mice will be mirrored by similar findings in humans. Indeed, we mentioned examples where normal gene function in adults does not reverse developmental deficits (Gross et al., 2002; Li et al., 2007).

Plasticity of the Adult Brain and the Treatment of Neurodevelopmental Disorders

An interesting possibility is that adult rescue of genetic defects, such as those mentioned above, alleviate or correct developmental phenotypes by tapping into adult mechanisms of cellular, structural, and behavioral plasticity. A large number of studies have shown that the developing brain is endowed with high levels of plasticity that are vital for shaping its structure and function. The classical view has been that plasticity is restricted to a defined window in time known as the critical period (Hubel and Wiesel, 1970). For example, the critical period for ocular dominance plasticity occurs from 19 to 32 days of age in the mouse (Gordon and Stryker, 1996). Critical periods are usually defined as times in development when changes in sensory input can alter the structure and function of the brain, but they may also exist outside of primary sensory areas. For example, the acquisition of specific cognitive skills, such as language, also appears to be constrained by specific ontological windows in humans (Lenneberg, 1967).

The adult cortex retains the potential for several features of developmental plasticity, including structural changes in spines (Trachtenberg et al., 2002), axons (Florence et al., 1998), and dendrites (Tailby et al., 2005). Plasticity can occur at high levels in the somatosensory cortex into adulthood (Clark et al., 1988; Fox, 1992; Merzenich et al., 1984; reviewed in Buonomano and Merzenich, 1998) and plasticity in the visual cortex can also occur beyond the classical critical period (Daw et al., 1992; Sawtell et al., 2003). One possibility for therapies therefore lies in using the inherent natural plasticity of adult brain for restoration of function.

Another possibility is to tap into the plasticity mechanisms present during developmental critical periods. Even though plasticity is present in adult animals, it does not appear to have the same set of mechanisms that are present in developing animals. For example, spine motility decreases beyond the critical period (Holtmaat et al., 2005), thalamocortical axon plasticity and thalamocortical LTP are reduced or eliminated, respectively (Crair and Malenka, 1995; Hubel and Wiesel, 1977), silent synapses are eliminated (Isaac et al., 1997; Rumpel et al., 2004), and presynaptic NMDA receptors, which are important for a developmental form of synaptic depression, are lost (Corlew et al., 2007). The loss or reduction of these factors (and most likely others yet to be discovered) means that adult plasticity is slower to take effect and lacks some of the features of developmental plasticity.

It was therefore a source of great interest and excitement when it was discovered that the critical period could be delayed and manipulated by altering levels of cortical inhibition (Hensch et al., 1998), and plasticity resembling that in the critical period could be reinstated in adult animals by degradation of components of the extracellular matrix surrounding the inhibitory cells with the enzyme chondroitinase (Pizzorusso et al., 2002). Since that report, other treatments, such as administering the antidepressant fluoxetin (a serotonine/norepinephrine reuptake inhibitor; Maya Vetencourt et al., 2008) and exposure to an enriched environment, have also been found to increase sensory plasticity in adult animals (Sale et al., 2007). These findings suggest that the adult brain could retain the potential for some features of developmental plasticity.

Inhibition is a possible common link between factors that have so far been found to increase adult plasticity. The critical period can be delayed in the visual cortex if the function of the inhibitory system is attenuated and reinstated by increasing inhibition (Hensch et al., 1998). Interestingly, the shift toward higher inhibition observed in several models of neurodevelopmental disorders reviewed here raises the possibility for premature closure of critical periods in these mutant mice, a mechanism that could contribute to their deficits. It is possible that high levels of plasticity, characteristic of critical periods, are actively suppressed in adults by mechanisms such as increased levels of inhibition (Spolidoro et al., 2008). Accordingly, strategies that decrease inhibition may reactivate "developmental" levels of plasticity and reopen developmental windows in the adult brain.

Conclusions

Altogether the findings reviewed here mark a paradigmatic change in the way we understand and envision treating neurodevelopmental disorders. They show that reversing the underlying molecular deficits of these disorders can result in dramatic improvements in cognitive function even if treatments are started in adulthood. These findings also highlight the surprising potential for plasticity in the adult brain, and they raise the possibility that adult rescue of phenotypes associated with neurodevelopmental disorders may take advantage of these mechanisms.

Additionally, these results may also have implications for treating other disorders, such as brain injury, stroke, addiction, etc. For example, prolonged substance abuse leads to stable molecular, cellular, structural, and behavioral changes that present a formidable problem for recovering patients (Volkow and Li, 2005). The results reviewed here suggest that correcting the maladaptive biochemical states brought about by these disorders (e.g, addiction, brain injury, etc.) may allow the brain to recover, even when key neuroanatomical changes associated with pathology are not reversed. In addition to correcting disrupted molecular processes, it is possible that manipulations that reopen highly plastic developmental states may facilitate recovery from neurodevelopmental disorders, addiction, or any other disorder that disrupts the structure and function of the brain. Altogether the findings reviewed here raise the possibility that adult treatments could one day help the many millions of people affected with neurodevelopmental disorders. They also highlight the importance and urgency of understanding the absolutely fascinating ability of the adult brain to reinvent itself.

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