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INVITED REVIEW

Functional implications of hippocampal adult neurogenesis in intellectual disabilities

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Abstract The development of strategies capable to promote nervous system plasticity in adulthood is nowadays an important aim in neuroscience to improve not only cognitive abilities but also to ameliorate pathological dysfunctions. Several studies have demonstrated that adult neurogenesis is regulated by many physiological and pathological stimuli at almost every stage, from proliferation of neuronal precursors until integration and activation of newly formed neurons in the preexisting network. We review the process of generating functional neurons from precursors in the adult brain and its implications in intellectual disability disorders.

Neurogenesis in the adult brain

Neurogenesis, the process of generating functional neurons from precursors, was traditionally believed to occur only during embryonic and perinatal stages in mammals. However, several decades ago Altman and Das provided the first anatomical evidence of newly generated dentate granule cells in the postnatal rat hippocampus (Altman and Das 1965). The functional integration of the newly formed neurons in the adult central nervous system (CNS) was first shown some years later in songbirds (Paton and Nottebohm 1984). We now know that adult neurogenesis occurs throughout life in almost all mammals examined, including humans (Eriksson et al. 1998). Although some authors postulate that adult neurogenesis can take place in the neocortex (Gould et al. 1999), substantia nigra (Zhao et al. 2003), striatum (Luzzati et al. 2007) or amygdala (Bernier et al. 2002), the process is very rare and their functional consequences have not yet been established. By contrast, there are two well-defined main regions involved in adult neurogenesis: the subventricular zone (SVZ) of the lateral ventricles and the subgranular zone (SGZ) of the hippocampal dentate gyrus (DG). New neurons generated in SVZ migrate through the rostral migratory stream to the olfactory bulb to become interneurons (Kempermann and Gage 2000). The functional significance of newborn neurons in the olfactory bulb involves maternal behavior (Bridges and Grattan 2003), pheromone-related behavior, such as mating and social recognition (Feierstein et al. 2010) and odor discrimination (Gheusi et al. 2000; Schellinck et al. 2004), but its role in olfactory associated memories is not yet determined since most of the experiments with manipulated adult bulbar neurogenesis failed to demonstrate a direct role of adult neurogenesis and odor-related memories [reviewed in (Lazarini and Lledo 2011)]. Since cognitive dysfunction is considered one of the main hallmarks of intellectual disabilities, we will focus from now on hippocampal neurogenesis which has been widely involved in learning and memory (see below).

Newly formed neurons in the SGZ migrate shortly into granule cell layer (GCL) of the DG to mature into granule cells and be integrated in the preexisting network (Cheng et al. 2011). In the hippocampus, stem cells (also known as radial precursors) divide asymmetrically to produce one new stem cell and one neuronal precursor cell (also known

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as transient amplifying stem cells), returning to a quiescent state which supports a continuous self-renewal (Lugert et al. 2010). Indeed, this quiescent state of stem cells has been proposed as a way to maintain the size of the pool to prevent mutations (Rossi et al. 2007). Radial precursors, even though expressing glial fibrillary acidic protein (GFAP), differ from astrocytes by their morphology, expression phenotype (nestin and Sox2 proteins) and their ability to generate neurons. The transient amplifying stem cells are highly proliferative cells that have lost their glial characteristics and start to express more neuronal traits. Neuroblasts, characterized by expressing doublecortine, NeuroD and Prox1 proteins, represent the last stage of proliferating progenitor cells showing a more limited proliferative rate. After exiting cell cycle, postmitotic neurons considered as immature neurons, migrate into GCL and differentiate into dentate granule cells (Cheng et al. 2011). Within the first week of maturation, newborn neurons rapidly extend their axons toward the CA3 region and these projections become stable around the fourth week of birth (Gu et al. 2012). At around 10 days of maturation, the apical dendrites reach the inner molecular layer and grow to the middle and edge parts of the layer at around days 14 and 21, respectively. After 16 days of maturation, newborn neurons begin to develop dendritic spines (Toni et al. 2008; Zhao et al. 2006). Recently, it has been shown that newborn neurons assemble a primary cilium precisely at the time when dendritic synaptogenesis begins, being a critical regulatory event in the dendritic refinement and synaptic integration of adult-born neurons (Kumamoto et al. 2012). Interestingly, although 1 month old-newly generated neurons have acquired a more mature phenotype as indicated by morphological studies (Zhao et al. 2010), they are functionally immature both in their firing properties and excitatory synapses composition (Laplagne et al. 2007; Spampanato et al. 2012). Indeed, dendrites continue to mature along the molecular layer and the afferent spines develop until they become functionally integrated by about 8 weeks (Zhao et al. 2006).

One critical aspect is that while large numbers of new neurons are born in the DG, only a fraction of these cells survive. Concretely, within the first 2 weeks of birth half of the newborn neurons die. Indeed, there are two critical periods of neuronal survival: one between the transient amplifying stem cells and neuroblast stage (Sierra et al. 2010) and a second one at the immature neuron integration stage (Tashiro et al. 2006).

Adult neural stem cells (NSC) in the SGZ have the potential to give rise to both neurons and astrocytes (Suh et al. 2007). However, the majority of 1-month-old surviving cells differentiate toward a neuron fate at expenses of glial fate (Steiner et al. 2004). Newly formed astrocytes promote proliferation, neuronal differentiation and integration of newly formed neurons in the DG (Barkho et al. 2006; Song et al. 2002). Recent evidences pointed that some hippocampal adult NSC once are activated, leave the pool of stem cells and differentiate directly to mature hippocampal astrocytes (Encinas et al. 2011), contributing to the neuronal differentiation of other neighbor adult NSCs.

As we have shown here, hippocampal adult neurogenesis is a very dynamic complex cellular process with multiple steps finely tuned by epigenetic and molecular mechanisms. However, the plasticity of the system leads to positive activity-dependent changes in almost every stage from proliferation of neuronal precursors (Bonaguidi et al. 2011; Kronenberg et al. 2003; Lugert et al. 2010) until integration (Kitamura et al. 2010; Stone et al. 2011) and activation of newly formed neurons in the preexisting network (Zhao et al. 2008). Thus, the development of environmental strategies capable to interfere in those steps impaired in intellectual disorders could not only improve the cognitive abilities but also ameliorate pathological dysfunctions. An interesting field, not fully investigate yet, is open in the improvement of intellectual disabilities.

The role of adult hippocampal neurogenesis in cognitive functions

Several evidences support the idea that both young and mature newly born cells might contribute to adult brain function. Newly born neurons are distinct from the preexisting DG neurons and must undergo a considerable maturation process before becoming completely indistinguishable (van Praag et al. 2002) and integrated in the synaptic network (Carlen et al. 2002). Young granule cells in the adult DG show increased synaptic plasticity and influence the oscillations and synchrony of neuronal hippocampal activity (Ge et al. 2007). In spite of this increased plasticity in young newly formed cells diminishes upon maturation, it has been described that mature newly born neurons (4–6 postnatal weeks-old) are more likely than existing granule cells to be recruited into circuits supporting spatial memory (Kee et al. 2007). Although, many studies pointed the role of hippocampal adult neurogenesis in hippocampus-dependent spatial learning and memory and long-term spatial memory retention [reviewed in (Aimone et al. 2011; Deng et al. 2010)], many studies have also led to a number of controversies and intense debates. The apparent discrepancies in the literature probably derive from differences in many parameters, such as the timing, duration and cell types of ablation, paradigms of training and behavioral tests, and animals used (age, sex, and genetic background).

Adult hippocampal neurogenesis involvement in learning and memory

The first evidence showing a possible contribution of adult neurogenesis in cognitive function came from correlation studies which associated proliferation and/or survival rates of newly generated cells with the behavioral performance in hippocampal-dependent learning tasks. For example, improved performance in a hippocampal-dependent associative learning test, the trace eyeblink conditioning, has been correlated with increased proliferation (Lemaire et al. 1999) and survival of newly formed cells in the DG of mice (Leuner et al. 2004). By contrast, similar cellular experiments after Morris Water Maze (MWM), a extensive used hippocampal-dependent task, have shown high controversial results. For example, some authors have found a good association between spatial learning and the number of newly generated neurons in the hippocampus in different mouse strains (Kempermann and Gage 2002) and old rats (Drapeau et al. 2003), while other authors did not find any correlation (Merrill et al. 2003). In view of the discrepancy observed in those correlation studies, some authors have used direct approach to abolish adult neurogenesis and determine their function on cognition. In this line, using the antimitotic drug MAM Shors and colleagues found a significant impairment in the trace eyeblink conditioning although no significant effects were observed in the MWM (Shors et al. 2001). However, this strategy caused potentially severe side effects due to inhibition of cell proliferation in the whole animal, complicating the interpretation of the results. Other neurogenesis ablation technique commonly used is the X-ray irradiation of the hippocampus. In 2-month old X-ray irradiated rats, Raber and colleagues showed significant spatial learning impairments in the Barnes maze (a non aversive hippocampal-dependent spatial learning paradigm) without affecting the MWM performance (Raber et al. 2004), whereas in young rats, irradiation produced a significant impaired spatial learning in the MWM (Rola et al. 2004). However, since irradiation might not be restricted to DG, could also affect postmitotic neurons and cause a substantial inflammatory response, the meaning of the data has been questioned. Thus, the disparities regarding the involvement of adult hippocampal neurogenesis on spatial learning could be due to the lack of specificity that neurogenesis ablation methods have on DG. One possible strategy to overcome this problem might be the generation of transgenic mice that selectively target neuronal precursors that could help to identify the function of specific cell populations on hippocampal-dependent learning and memory. Although nowadays there are few studies to address this idea, conditional and inducible transgenic mice targeting nestin precursor cells have shown impaired long-term retention and extinction of memory not only in the contextual fear conditioning test, an associative learning paradigm (Deng et al. 2009; Pan et al. 2012), but also in complex spatial learning and long-term memory retention in the Barnes maze and MWM when the starting position of the mice was changed at each daily trial phase (Arruda-Carvalho et al. 2011; Dupret et al. 2008; Imayoshi et al. 2008; Jessberger et al. 2009). Similarly, ablation of GFAP progenitor cells impaired acquisition of contextual fear (Saxe et al. 2006). Conversely, simple forms of spatial learning remain unchanged (Dupret et al. 2008). These results suggested that adult-born granule neurons could influence hippocampal-dependent spatial memory depending on the cognitive demand [for review see (Aimone et al. 2011)].

In view of these results, the correct election of the behavior paradigm appears crucial. For example, water maze is sensitive to conventional hippocampal lesions and even conventional lesions targeting the DG (Xavier et al. 1999), although yielded only a modest impairment when neurogenesis was blocked. Newborn neurons represent only a small cell population within the adult DG, thus their contribution on learning and memory could be complex to detect using common protocols. Moreover, the complexity of the water maze performance separated in different learning phases and the specific maturation characteristics of newly born cells could underlie the inconsistency between the studies. Thus, the development of new behavioral paradigms exclusively sensitive to neurogenesis changes is a present challenge.

Contribution of adult hippocampal neurogenesis to retrieval

The continuous integration of new neurons in the preexisting granule cells network of the DG is probably changing the structural organization where the preexisting information is stored and could, thus, provide new networks for new memories [for review see (Lledo et al. 2006)]. However, the role of adult neurogenesis may be far more complex. For example, (Kitamura et al. 2009) found that neurogenesis-arrested mice performed fear conditioning normally, but showed a significant impairment in the fear memory recall 1 month after training. These results are in contradiction to previous reports suggesting that although the retrieval of acquired memories initially depends on the hippocampus, this is followed by a progressive dependence on other brain structures such as cortex (Squire and Bayley 2007). However, (Kitamura et al. 2009) proposed that memory still resides in the hippocampus and reinforced the idea that newly generated adult neurons contribute to memory consolidation to other extra-hippocampal brain regions. In support of this assumption, it has been shown that newly generated

neurons up to 3–4 weeks of age are required not only to acquire new spatial information but also to use previously consolidated spatial memories in the MWM (Farioli–Vecchioli et al. 2008). Finally, specific blocking of neurogenesis in the DG of adult male rats by inhibiting Wnt signaling, which is critically involved in the generation of newborn neurons, impaired the long-term retention of spatial memory in the water maze task (Jessberger et al. 2009).

Regulation of adult hippocampal neurogenesis by learning

The regulation of neurogenesis by neural circuits' activity indicates that the activation of new neurons by learning paradigms would likewise enhance specifically the survival and integration of newly born neurons in the preexisting networks. Hippocampal-dependent learning tasks such as trace eyeblink conditioning and MWM have been shown to increase the number of surviving neurons in the DG, but not, hippocampal-independent learning tasks such as delayed eyeblink conditioning, cue maze training or active shock avoidance [for review see (Leuner et al. 2006)]. Even in the hippocampal-dependent tasks, the effects are different depending on the learning phase. For example, while the early learning phase in the MWM does not modify cell proliferation, it increases neuronal survival and dendritic complexity of neurons, born before the task (Dobrossy et al. 2003; Dupret et al. 2007; Tronel et al. 2010). Conversely, reaching asymptotic levels of performance in late learning phase increased the survival of cells generated before learning but induced apoptosis of those cells born during the early phase of learning. This may explain the decreased levels of surviving neurons upon hippocampal learning found in some studies (Ambrogini et al. 2004; Dobrossy et al. 2003). In these last phases of the learning, there is also an enhanced cell proliferation that provides the hippocampus with a new pool of young neurons (Anderson et al. 2011; Dupret et al. 2007). These results suggest that there is a critical window of time between one and two-weeks after cell birth where spatial and associative learning can influence newborn neurons. This time frame is consistent with the period of time that these newborn cells began to differentiate to neurons, receiving inputs from other parts of the brain and sending signals to the CA3 region.

Taken together, these evidences suggest a two-way relationship between the generation of new neurons in the adult hippocampus and cognitive processes. On one hand, changes in adult neurogenesis influence hippocampal-dependent learning and memory process, but cognitive tasks are also able to affect survival and integration of young newly formed neurons.

Recent computational models have noted that adult neurogenesis may specifically contribute to pattern separation and the ability to discriminate between two similar events (Deng et al. 2010). Chronic ablation of neurogenesis by either irradiation or lentivirus-mediated overexpression of dominant-negative *Wnt* in mice impaired performance in spatial discrimination tasks when two stimuli were presented with limited spatial separation but not when the stimuli were widely separated in space (Clelland et al. 2009). Similar results were obtained in mice with ablation of adult hippocampal neurogenesis in the contextual fear discrimination learning task where mice had to discriminate between two similar contexts (Tronel et al. 2012). In addition, (Sahay et al. 2011) showed that transgenic mice lacking *Bax* in nestin positive precursor cells enhanced neurogenesis and were more efficient in differentiating between similar contextual representations, thus suggesting enhanced pattern separation. Similarly, running increased levels of adult neurogenesis enhanced the ability of adult mice to discriminate between two adjacent stimuli (Creer et al. 2010). Finally, recently Nakashiba and collaborators have demonstrated that pattern separation requires adult-born young granule cells but not old ones, and older granule cells contribute to the rapid recall by pattern completion. Therefore, their data suggest that as adult-born granule cells age, their function switches from pattern separation to rapid pattern completion (Nakashiba et al. 2012).

Hippocampal adult neurogenesis in cognitive disabilities

Intellectual disability is a developmental disorder characterized by significant impairment of cognitive functioning and altered adaptive skills. Neural mechanisms underlying intellectual disability may include defects in the formation of neuronal networks and/or defects in properties of brain plasticity that are believed to be important for information processing. One of the established features in intellectual disabilities refers to dendritic abnormalities, but in view of the relationship between adult neurogenesis and cognition, impairment in this cellular process should also be taken into consideration. We discuss the contribution of adult neurogenesis to the most frequent intellectual disabilities, such as Rett, Fragile X and Down syndrome (Fig. 1).

Rett syndrome

Rett syndrome (RTT; OMIM 312750) is a major cause of inherited intellectual disability in females affecting 1/10,000 girls (Amir et al. 1999). Most of the causes of RTT have been associated with a mutation in the gene

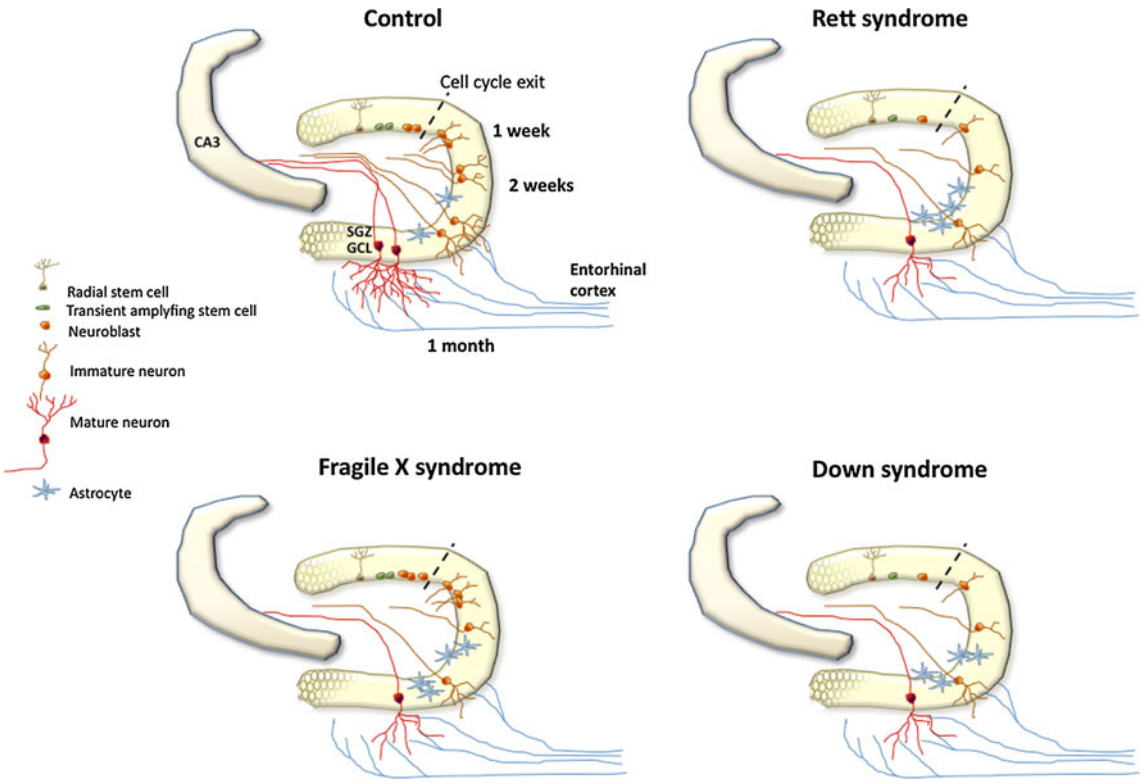

Fig. 1 Abnormal adult neurogenesis in the subgranular zone of Rett syndrome, Fragile X and Down syndrome. The image depicts the main findings summarized in this review

encoding for methyl-CpG-binding protein-2 (MECP2), which functions as transcriptional repressors by binding to methylated DNA (Chahrour and Zoghbi 2007). MECP2 mutant mice exhibit impaired spatial and emotional cognitive tasks (Pelka et al. 2006). MECP2 expression begins during embryogenesis and increases as cells acquire a more differentiated neural phenotype (Shahbazian et al. 2002), so that the protein levels of MECP2 correlate with neural maturation and synapse formation.

MECP2 has been widely involved in embryonic neurogenesis (see Table 1). The specific deletion of MECP2 in nestin positive progenitor cells reduced significantly neuronal size (Chen et al. 2001) similar to its deletion in postnatal CNS postmitotic neurons produced similar neuronal size alterations with later onset (Chen et al. 2001). Cell fate decisions during embryonic neurogenesis might also be modulated by MECP2, which regulates the expression of a neuronal repressor, the *xHairy2a* gene, at least in *Xenopus* (Stancheva et al. 2003). In this same line, MECP2 suppressed astrocytic differentiation and promoted neuronal differentiation of neural progenitor cells (NPCs) from E14.5 mice, without affecting proliferation or apoptosis (Setoguchi et al. 2006; Tsujimura et al. 2009).

In the context of this review, it is important to highlight the involvement of MECP2 in adult neurogenesis, since epigenetic regulation, including DNA methylation and histone modification, is known to play significant roles in the modulation of stem cell proliferation and differentiation (Abel and Zukin 2008) (see Table 1). As occurs during embryogenesis, in the absence of MECP2 function, newly formed hippocampal neurons cannot advance to their fully mature state showing delayed neuronal differentiation, altered neuronal gene expression and reduced dendritic spine density (Smrt et al. 2007). Indeed, MECP2 is expressed predominantly in differentiated neurons of the adult mammalian CNS rather than in less differentiated neuroblasts, reinforcing that MECP2 might be involved in the maturation and maintenance of neurons, including dendritic arborization (Kishi and Macklis 2004). On the other hand, previous studies using NPCs isolated from hippocampus of adult rats have demonstrated that MECP2 plays a critical role in astrocytic differentiation by preventing the conversion of neurons to astrocytes through its binding to DNA-methylated regions (Kohyama et al. 2008).

Interestingly, the involvement of MECP2 on neuronal differentiation has been also proven in humans. Induced pluripotent stem cells (iPSCs) from RTT patients' fibroblasts generate fewer neurons with reduced number of spines and synapses and poor neurite arborization (Kim et al. 2011; Marchetto et al. 2010). One of the mechanisms recently proposed to explain the impaired neuronal

Table 1 Representative embryonic and adult neurogenesis studies related to Rett syndrome

Model	Species	Age	Type of study	Type of neurogenesis alteration	References
Embryonic neurogenesis					
XMeCP2-KO	Xenopus	Stage 15	In vivo	Reduced number of differentiated neurons	(Stancheva et al. 2003)
MECP2-KO	Mouse	E12	In vivo	Reduced neuronal size from nestin progenitors and postnatal postmitotic MECP2 deleted cells	(Chen et al. 2001)
Ectopic MECP2	Mouse	E14.5	In vitro	Inhibited astrocytic differentiation from NPC	(Setoguchi et al. 2006)
MECP2-KO	Mouse	E13.5	In vitro	No differences in cell proliferation or cell fate of NPCs in neocortex	(Kishi and Macklis 2004)
Ectopic MECP2	Mouse	E14.5	In vitro	No effect on proliferation or apoptosis of NPCs Increased neuronal differentiation and reduced astrocytic differentiation from NPC and NSC	(Tsujimura et al. 2009)
Adult neurogenesis					
MECP2-KO	Mouse	8 w	In vivo	Reduced neuronal dendritic arborization complexity and neuronal size	(Kishi and Macklis 2004)
MECP2-KO	Mouse	6 w	In vitro	No differences in proliferating rate or neuronal and astrocytic differentiation of adult NSC	(Smrt et al. 2007)
MECP2-KO	Mouse	4–8 w	In vivo	No differences in cell proliferation, survival and differentiation, but altered presynaptic protein expression and reduced number of spines in newly formed cells in the DG Increased percentage of transitioning neurons (DCX+/NeuN+) in the DG of 8 weeks-old mice	
Ectopic MECP2	Mouse	Adult	In vivo	Increased neuronal differentiation and reduced astrocytic from NPC in striatum	(Tsujimura et al. 2009)
MECP2-KO	Mouse	7 w	In vitro	Increased proliferation and reduced neuronal differentiation of adult NSC through miR-137 expression regulation	(Szulwach et al. 2010)
Ectopic MECP2	Rat	Adult	In vitro	Reduced astrocytic differentiation of adult NPC in the hippocampus	(Kohyama et al. 2008)
RTT	Human	Adult	In vitro	Reduced spine density, number of synapses, soma size, altered calcium signaling and electrophysiological defects of neurons from iPSC	Marchetto (2010)
RTT	Human	Adult	In vitro	Reduced neuronal differentiation with reduced neurite arborization and electrophysiological defects of iPSC	(Kim et al. 2011)
RTT	Human	Adult	In vitro	Reduced neuronal differentiation through increased senescence from MSC	(Squillaro et al. 2012)
Silenced *Mecp2*	Human neuroblastoma cell line		In vitro	Reduced cell proliferation, neuronal differentiation and number of neurons Increased senescence of progenitor cells and neurons	
Embryonic neurogenesis					
Slp1/2-KO	*Drosophila*	E9–15	In vivo	Increased number of glia cells	(Mondal et al. 2007)

Table 1 continued

Model	Species	Age	Type of study	Type of neurogenesis alteration	References
FOXG1-KO	Mouse	E9.5–12.5	In vivo	No differences in apoptosis Reduced cell proliferation in the telencephalic neuroepithelium and premature neuronal differentiation	(Xuan et al. 1995)
FOXG1-KO	Mouse	E11.5–17.5	In vivo	Increased cell cycle length of neocortical neuronal progenitors and premature neuronal differentiation	(Hanashima et al. 2004)
FOXG1-KO	Mouse	E9.5–14.5	In vivo	Increased cell cycle length in the telencephalon and reduced apoptosis Increased differentiating rate	(Martynoga et al. 2005)
FOXG1 overexpression	Mouse	E11.5	In vitro	Reduced glial differentiation and enhanced neurogenesis with increased neurite outgrowth in cortical neural precursors	(Brancaccio et al. 2010)
FOXG1-HET	Mouse	E12.5	In vitro	Reduced NSC and increased glial differentiation	
Adult neurogenesis					
FOXG1-HET	Mouse	P15–42	In vivo	No alteration in cell proliferation Reduced survival and neuronal differentiation of newly formed cells in the DG	(Shen et al. 2006)
FOXG1-HET	Mouse	P100	In vivo	Reduced cell proliferation and survival and neuronal differentiation of newly formed cells in the DG	
FOXG1-KO	Mouse	P5–14	In vivo	Reduced cell proliferation of NSC and intermediate progenitor cells Increased neurogenesis and gliogenesis Increased apoptosis and reduced survival of newly formed cells Immature neurons were occasionally ectopically located in the GCL and had abnormal dendritic projections	(Tian et al. 2012)

The first two tables describe data related to MECP2 function and the lasts ones related to FOXG1 function. For each study we represented the model and the species used, the age of the sample, the type of study and a brief description of the neurogenesis alterations observed

NPC neuronal progenitor cell, *NSC* neural stem cells, *DG* dentate gyrus, *iPSC* induced pluripotent stem cell, *MSC* mesenchymal stem cell, *GCL* granular cell layer, *E* embryonic day, *P* postnatal day, *w* weeks, *m* months

differentiation is that reduced expression of MECP2 triggers senescence as it has been shown in a neuroblastoma cell line with MEPC2 silenced where neural cell fate and neural maintenance were perturbed by senescence activation (Squillaro et al. 2012).

Interestingly, recent publications support a role of MECP2 in regulating the expression of specific miRNAs (miR137) modulating adult neurogenesis in adult mouse NPCs. Concretely, the inhibition of miR137 expression by MECP2-mediated epigenetic regulation reduces proliferation and induces adult NSC differentiation (Szulwach et al. 2010).

In around 10 % of Rett syndrome cases, a congenital variant of the disease caused by mutations in *Foxg1* gene has been described (Ariani et al. 2008; Mencarelli et al. 2010). *Foxg1* encodes a forkhead box protein G1 (FOXG1) that belongs to a family of transcription factors that regulates neurogenesis (Xuan et al. 1995). FOXG1 generally promotes self-renewal of neural precursors and antagonizes their neuronal differentiation. Concretely, in the cerebral cortex, the loss of *Foxg1* results in premature cell cycle exit and neuronal differentiation of neocortical progenitors (Hanashima et al. 2004; Martynoga et al. 2005). In fact, the role of FOXG1 on cellular differentiation has been also shown in *Drosophila,* where the orthologs genes of *Foxg1*, Sloppy paired-1 (*Slp1*) and Sloppy paired-2 (*Slp2*) promote neurogenesis at the expenses of gliogenesis (Mondal et al. 2007). In the same line, in cortical neural precursors, FOXG1 inhibits gliogenesis and promotes neurogenesis (Brancaccio et al. 2010). However, this effect is not only restricted to embryonic neurogenesis but also in postnatal hippocampus. Using a conditional knockout mouse of *Foxg1*, Tian and collaborators were able to demonstrate that FOXG1 is involved in the development of the postnatal DG affecting different processes of adult neurogenesis from proliferation to differentiation and neuronal survival. They suggest that FOXG1 is important in maintaining a balance between progenitor proliferation and differentiation (Tian et al. 2012). In addition, FOXG1 has also been involved in promoting postmitotic neuronal survival in the hippocampus (Shen et al. 2006).

Fragile X syndrome

Fragile X syndrome (FXS; OMIM, 300624) is the most frequent single-gene mutation causing intellectual disability. In most cases, the disorder is produced by the unstable expansion of a trinucleotide (CGG) repeat greater than 200 repeats in the *Fmr1* gene (located in the long arm of the X chromosome), which results in suppression of *Fmr1* transcription and decreased Fragil X mental retardation protein (FMRP) levels in the brain (Bassell and Warren 2008). FMRP is a selective RNA-binding protein that regulates the transport and translation of several mRNAs (Dictenberg et al. 2008). Moreover, recent evidences suggested a role for FMRP in protein synthesis-dependent synaptic plasticity and in the regulation of neuronal architecture throughout development, which ultimately controls the function of neural networks in the brain (Scotto–Lomassese et al. 2011). Interestingly, FMRP mutant mice showed impaired associative hippocampal-dependent learning in several tasks such as the trace conditioning learning test (Zhao et al. 2005) or the MWM.

In *Drosophila*, the homologous FMRP protein (dFMRP) is involved in germline stem cell (GSC) specification (Costa et al. 2005) and in GSC maintenance by repressing differentiation through interaction with Argonaute protein 1 (AGO1) (Yang et al. 2007). More recently, Callan and colleagues found that dFMRP controls proliferative capacities of neuroblasts during the brain development of *Drosophila* larva so that the loss of dFMRP increased the number of neuroblasts in the S and G2/M phase of the cell cycle together with a reduced exit from the quiescent state (Callan et al. 2010).

The first study demonstrating a role for FMRP protein in embryonic mammalian neurogenesis was performed in cultured embryonic neural progenitor cells (NPCs) derived from FMRP knockout mice or from postmortem human fetuses deficient for *FMR1* (see Table 2). The loss of FMRP produced defects in the differentiation of the NSC as shown by a higher number of generated neurons with morphological alterations and reduced gliogenesis. This was accompanied by an accumulation of newborn cells in the SVZ and the increase in the numbers of immature cells of neuronal lineage (Castren et al. 2005). However, a more recent study performed by Bhattacharyya and colleagues did not find significant differences in proliferation and neuronal differentiation of human neuronal progenitors cells carrying the *Fmr1* mutation (Bhattacharyya et al. 2008). Since both studies relied on *Fmr1* human mutant NPCs derived from single embryos, differences in the genetic background or developmental stage (14 vs. 18 gestational weeks) may underlie the discrepancies regarding the role of FMRP. Embryonic neocortex from *Fmr1*-knockout mice showed higher number of intermediate NPCs in the cortical layers adjacent to the lateral ventricles (Tervonen et al. 2009). Moreover, the loss of FMRP promoted a shift from neocortical radial-glial progenitor cells (RGC) to the intermediate progenitor cells leading to reduced number of RGC in the embryonic period (Saffary and Xie 2011).

The involvement of FMRP in adult neurogenesis regulation has recently been described by Luo and colleagues (see Table 2), who showed that the loss of functional FMRP in NSC derived from the DG of adult *Fmr1*

Table 2 Representative embryonic and adult neurogenesis studies related to Fragile X syndrome

Model	Species	Age	Type of study	Type of neurogenesis alteration	References
Embryonic neurogenesis					
dfmr1-KO	*Drosophila*	Eggs	In vivo	Alteration in GSC maintenance	(Costa et al. 2005)
dfmr1-KO	*Drosophila*	2–14 d	In vivo	Defects in GSC maintenance and increased GSC differentiation	(Yang et al. 2007)
dfmr1-KO	*Drosophila*	Larvae	In vivo/ In vitro	Increased neuroblasts in S and G2-M phase and reduced exit from the quiescent state	(Callan et al. 2010)
				Increased neurons that survive until adulthood	
fmr1-KO	Mouse	E13	In vitro	Increased neurons with defects in differentiation and reduced glial cells from NPC	(Castren et al. 2005)
fmr1-KO	Mouse	E13	In vivo	Increased BrdU positive cells in SVZ	
fmr1-KO	Mouse	E13–17	In vivo	Increased number of intermediate NPC in the neocortex	(Tervonen et al. 2009)
fmr1-KO	Mouse	E11.5–17.5	In vivo	Promoted a shift from neocortical RGC to IPC	(Saffary and Xie 2011)
FXS	Human	fetuses (18 w)	In vitro	Increased neurons and reduced glia cells from hNSCs	(Castren et al. 2005)
FXS	Human	fetuses (14 w)	In vitro	No differences in proliferation and neuronal differentiation of hNSCs	(Bhattacharyya et al. 2008)
Adult neurogenesis					
fmr1-KO	Mouse	8–10 w	In vitro In vivo	Increased adult NSC proliferation, reduced neuronal and increased glial differentiation	(Luo et al. 2010)
				Increased proliferation of stem cells and progenitor cells, reduced neuronal and increased glial differentiation, reduced survival of newly formed cells	
fmr1-KO	Mouse	8–10 w	In vitro	Increased number of adult NSC,but reduced number of neuroblasts, immature neurons and mature neurons	(Guo et al. 2011)
fmr1-KO	Mouse	9–12 m	In vivo	Reduced *type 2* progenitor cells, surviving cells and mature neurons	(Lazarov et al. 2012)

For each study we represented the model and the species used, the age of the sample, the type of study and a brief description of the neurogenesis alterations observed

GSC germline stem cells, *NPC* neuronal progenitor cell, *SVZ* subventricular zone, *RGC* radial glia cell, *IPC* intermediate progenitor cell, *hNSC* human neural stem cell, *E* embryonic day, *d* days, *w* weeks, *m* months

knockout mice increased adult NSC proliferation and decreased neuronal differentiation together with increased glial differentiation. Similarly, *Fmr1* knockout mice had increased BrdU positive cells, suggesting higher proliferation levels, and a significant reduced neuronal survival that was accompanied with increased differentiated astrocytes. The observation of a deficit in the Wnt signaling pathway and reduced expression of Neurogenin (Neurog1), an early initiator of neuronal differentiation and an inhibitor of glial differentiation, could underlie these adult neurogenesis alterations (Luo et al. 2010). In the same line, (Guo et al. 2011) using an inducible conditional FMRP knockout mouse, with confined Cre expression to adult NSC, described that the lack of FMRP in adult NSC increased proliferation, and their progenies' fate changed from neurons to astrocytes. From these results, it can be extracted that the loss of FMRP might produce opposite effects in the differentiation fate at embryonic and adult stages. Finally, recent evidence supports an age-dependent effect of FMRP in adult neurogenesis, where the number of fast proliferating progenitor cells was dramatically reduced and the surviving cells presented less maturation in aged FMRP knockout mice (Lazarov et al. 2012). Although the fact that FMRP is necessary for normal neural stem cell proliferation and differentiation is widely accepted, the impact of adult neurogenesis regulation by FMRP on learning has been demonstrated recently. Regarding the functional significance, selective deletion of FMRP from adult NSC leaded to altered performance on two hippocampus-dependent learning tasks, an impairment that was completely rescued using a FMRP conditional restoration mouse line (Guo et al. 2011).

Down syndrome

Down syndrome (DS; OMIM 190685) is considered the most frequent genetic cause of intellectual disability affecting 1 each 1,000 newborn children in European countries [reviewed in (Dierssen 2012)]. DS is the most common autosomal aneuploidy determined by a chromosomal aberration that involves the total or partial trisomy of chromosome 21 (HSA21). Neuropsychological tests have revealed specific deficits in learning and memory, language and movement in DS individuals that lead to mild to profound impairment in intellectual functioning (Lott and Dierssen 2010). Even though gross abnormalities are not obvious in DS brain at birth, the early occurrence of neuroanatomical abnormalities in DS points to neurodevelopmental impairment, such as embryonic neurogenesis, as the major determinant of intellectual disability. Since DS is caused by a trisomy, and aberrant copies of single chromosomes could alter the timing of cell cycle and the proliferating rate of neuronal precursors (Mittwoch and Wilkie 1971), several studies in DS fetuses have identified alterations in embryonic hippocampal neurogenesis (see Table 3). Indeed, in DS fetuses (17–21 weeks of gestation), neurogenic cell proliferation is significantly impaired, as demonstrated by reduced numbers of dividing cells in the dentate gyrus (−65 %), probably due to a prolonged cell cycle G2 phase in progenitor cells (Contestabile et al. 2007). In addition to reduced proliferation, Guidi and colleagues found impaired neuronal differentiation together with increased number of cycling cells going to glial phenotype and increased levels of apoptosis in DS developing brain (Guidi et al. 2008). Alterations in cellular differentiation have also been described in in vitro studies showing that NPCs isolated from DS fetal brains give rise to reduced numbers of neurons (Bahn et al. 2002; Esposito et al. 2008) and defects in their ability to give rise to GABAergic interneurons (Bhattacharyya et al. 2009).

The alterations of adult neurogenesis cannot be studied in human DS individuals, but the conserved synteny between genomic segments on HSA21 and mouse chromosome (MMU) 16, 10 and 17 has led to the generation of many valuable mouse models that have helped to understand the impact of gene dosage imbalance on neurogenesis in DS.

In some cases, as for example the Ts16 mouse model carrying a complete extra copy of the MM16, no studies regarding postnatal neurogenesis have been described since these mice die in utero (Cheng et al. 2004; Haydar et al. 1996, 2000), but this model showed a delay in embryonic neocortical development.

However, a mouse models bearing a segmental trisomy of MMU16, Ts1Cje, even though bearing less triplicated genes than Ts16, also have smaller brains and show decreased cortical neurogenesis in the embryos, along with alterations in cell cycle exit (Ishihara et al. 2010). Moreover, Ts1Cje NPCs from the developing neocortex cultured as neurospheres, showed a decrease in proliferation rate due to longer cell cycle duration, an increase in glial differentiated positive cells and cellular death. As a possible mechanism, the expression of genes involved in cell cycle regulation (*Cdk1*, *cyclin D1* and *D2*, *Cdk6*) and cellular differentiation (*Mt1*, *Pfkfb3*, *Aqp4*) was altered (Moldrich et al. 2009).

Similar reductions in neurogenesis have also been described during embryogenesis and postnatal development of Ts65Dn, a mouse model that bears a partial trisomy of the MMU16 (Contestabile et al. 2007; Chakrabarti et al. 2007; Lorenzi and Reeves 2006) and shows most of the sign and symptoms of DS. Concretely, postnatal day 2 (P2) Ts65Dn mice showed reduced survival of newly formed cells and cell proliferation partially due to a higher number of proliferating cells in the G2 phase of the cell cycle at expenses of the M phase, suggesting alterations in cell cycle progression. Interestingly, while no significant differences concerning the percentage of surviving cells with neuronal phenotype have been described, Ts65Dn mice showed a higher percentage of surviving cells with astrocytic phenotype similar to DS individuals (Contestabile et al. 2007).

Regarding adult neurogenesis (see Table 3), Ts1Cje mice showed decrease number of BrdU proliferating cells and doublecortin positive neuroblasts in the DG (Ishihara et al. 2010), along with deregulated expression of genes involved in cell proliferation and cell cycle progression (Hewitt et al. 2010). Similarly, juvenile and adult Ts65Dn mice showed reduced proliferation and survival of newly born cells as well as decreased neurogenesis and gliogenesis (Bianchi et al. 2010; Clark et al. 2006; Chakrabarti et al. 2011; Lorenzi and Reeves 2006; Rueda et al. 2005; Belichenko et al. 2011). Although the impaired adult neurogenesis should possibly underlie part of the cognitive deficits described in these DS murine models, no experiments to specifically address this question have been performed yet (Table 4).

The trisomic condition in DS suggests that expression deregulation of some specific genes in the brain may contribute more importantly to the intellectual dysfunction and adult neurogenesis impairment. One of these genes is *Dyrk1A* (Dual specificity Yak1-Related Kinase 1A), located in the 21q22.13 within the Down Syndrome Critical Region (Hattori et al. 2000). *Dyrk1A* encodes a dual specificity protein kinase that autophosphotylates on tyrosin (Tyr) residues but phosphorylates substrates on serine and threonine residues (Becker et al. 1998; Kentrup et al. 1996). DYRK1A is overexpressed in fetal and adult DS brain (Guimera et al. 1996, 1999) and plays important roles during brain development. The fact that Dyrk1A is expressed in adult brain regions involved in cognition such as the hippocampus and cortex (Marti et al. 2003)

Table 3 Representative embryonic and adult neurogenesis studies related to Down syndrome

Model	Species	Age	Type of study	Type of neurogenesis alteration	References
Embryonic neurogenesis					
Ts16	Mouse	E16	In vivo	Delay in neocortical neuronal development	(Haydar et al. 1996)
Ts16	Mouse	E14	In vivo	Reduced neocortical precursors and increased apoptosis Increased S phase duration and reduced cell cycle exit in neocortical VZ	(Haydar et al. 2000)
Ts16	Mouse	E12.5–14.5	In vivo	Delay in neocortical neuronal development	(Cheng et al. 2004)
Ts1Cje	Mouse	E14.5	In vitro	Reduced proliferating rate and increased cell cycle duration, glia differentiation and apoptosis of NPC	(Moldrich et al. 2009)
Ts1Cje	Mouse	E14.5	In vivo	Reduced cell cycle exit and cortical neurogenesis	(Ishihara et al. 2010)
Ts65Dn	Mouse	E14.5–18.5	In vivo	Increased S phase and reduced cell cycle progression, cell cycle exit and number of generated neurons	(Chakrabarti et al. 2007)
Ts65Dn	Mouse	P2	In vivo	Reduced cell proliferation and survival and increased differentiation of glia cells Higher number of proliferating cells in the G2 phase at expenses of the M phase	(Contestabile et al. 2007)
DS	Human	fetuses (8–18 w)	In vitro	NPC give rise to reduced number of neurons	(Bahn et al. 2002)
DS	Human	fetuses (17–21 w)	In vivo	Reduced number of dividing cells with reduced cells in S phase and increased proliferating cells in the G2 phase at expenses of the M phase	(Contestabile et al. 2007)
DS	Human	fetuses (17–21 w)	In vivo	Reduced cell proliferation and number of differentiated neurons Increased differentiation of glia cells and apoptosis	(Guidi et al. 2008)
DS	Human	fetuses (19–21 w)	In vitro	NPC give rise to reduced number of neurons and increased a more glial-predominant progenitor phenotype	(Esposito et al. 2008)
DS	Human	fetuses (13–18 w)	In vitro	NPC give rise to reduced GABAergic interneurons in the cortex	(Bhattacharyya et al. 2009)
mnb-KO	*Drosophila*	larvae	In vivo	Abnormal spacing of neuroblasts leading to reduced neuronal progeny	(Tejedor et al. 1995)
Mnb/Dyrk1A overexpression	Chick	Stage 12	In vivo	Reduced cell proliferation, increased cell cycle exit and increased neuronal differentiation	(Hammerle et al. 2011)
	Mouse	E14.5	Electroporation ex vivo		
Dyrk1A inhibition	Chick	Stage 12	In vivo	Increased cell proliferation and apoptosis	
	Mouse	E14.5	Electroporation ex vivo		
Dyrk1A-KO	Mouse	E9.5–11.5	In vivo	Reduced postmitotic neurons	(Fotaki et al. 2002)
BACTgDyrk1A	Mouse	E14.5	In vivo	Reduced cell proliferation through increased p53 phosphorylation and p21 ^{CIP1}	(Park et al. 2010)

Table 3 continued

Model	Species	Age	Type of study	Type of neurogenesis alteration	References
Dyrk1A overexpression	Mouse	E14.5	In utero electroporation	Reduced cell proliferation and cell cycle progression by promoting the nuclear export and degradation of cyclin D1 in the neocortex	(Yabut et al. 2010)
				Premature neuronal differentiation	
Dyrk1A overexpression	Human ES		In vitro	Impaired G0/G1-S phase transition	(Park et al. 2010)
Kinase-inactive DYRK1A	Human cell line		In vitro	Reduced ability of cells to enter quiescence by disrupting DREAM assembly	(Litovchick et al. 2011)
Adult neurogenesis					
Ts1Cje	Mouse	3 m	In vivo	Reduced cell proliferation and number of neuroblasts	(Ishihara et al. 2010)
Ts1Cje	Mouse	3 m	In vivo	No differences in the number of NSC in SVZ	(Hewitt et al. 2010)
Ts1Cje	Mouse	3 m	In vitro	Reduced numbers of neural progenitors, neuroblasts and differentiated neurons	
				Increased number of astrocytes	
Ts65Dn	Mouse	13–15 m	In vivo	Reduced cell proliferation	Rueda et al. (2005)
Ts65Dn	Mouse	2.5 m	In vivo	Reduced cell proliferation and survival	(Clark et al. 2006)
Ts65Dn	Mouse	P6 and P30	In vivo	Reduced mitotic cells	(Lorenzi and Reeves 2006)
Ts65Dn	Mouse	P15	In vivo	Reduced cell proliferation survival, neurogenesis and gliogenesis	(Bianchi et al. 2010)
				No differences in apoptosis	
Ts65Dn	Mouse	12 m	In vivo	Reduced cell proliferation in SVZ	(Bianchi et al. 2010)
Ts65Dn	Mouse	P18	In vivo	Reduced cell proliferation survival, neurogenesis and gliogenesis	(Chakrabarti et al. 2011)
Ts65Dn	Mouse	2–3 m	In vivo	Reduced cell proliferation	(Belichenko et al. 2011)
				Increased levels of cyclin B1	
Dyrk1A-HET	Mouse	3 m	In vivo	Reduced number of stem cells, progenitor cells (not neuroblasts) and life-long maintenance of adult progenitors	(Ferron et al. 2010)
				Defects in self-renewal of adult neural stem cells in SEZ	

For each study we represented the model and the species used, the age of the sample, the type of study and a brief description of the neurogenesis alterations observed

VZ ventricular zone, *NPC* neuronal progenitor cell, *NSC* neural stem cells, *SVZ* subventricular zone, *DG* dentate gyrus, *SEZ* subependimal zone, *E* embryonic day, *P* postnatal day, *w* weeks, *m* months

suggested that this protein could be involved in cognition as has been demonstrated in several mouse models with changes in Dyrk1A dosage (Ahn et al. 2006; Altafaj et al. 2001; Arque et al. 2008, 2009).

At the moment, Dyrk1A is the best-characterized genes in DS participating in neurogenesis. It has been suggested to be critical for the sequential events required for proper neuronal development during embryogenesis (Aranda et al. 2011; Tejedor and Hammerle 2011) affecting both proliferation and differentiation processes (Dierssen and de Lagran 2006). In this line, the *Drosophila* ortholog, the minibrain (*mnb*) gene is required for normal postembryonic neurogenesis and mutant *Drosophila* flies display a size reduction in specific brain areas such as optical lobes due to the abnormal spacing of neuroblasts in the outer proliferation center of larval brain that leads to reduced neuronal progeny (Tejedor et al. 1995). The homozygous Dyrk1A mice are lethal, supporting the idea that Dyrk1A has an important function during the development. They present a large reduction in the embryo size due to a developmental structural delay and a decrease in the number of postmitotic neurons (Fotaki et al. 2002). The heterozygous Dyrk1A mice have a general delay in the development and present reduced brain size (Fotaki et al. 2002).

Dyrk1A is expressed in four sequential phases during the development of CNS: transient expression in preneurogenic progenitors; cell cycle-regulated expression in neurogenic progenitors; transient expression in recently born neurons; and persistent expression in late differentiating neurons (Hammerle et al. 2008). Several authors have implicated Dyrk1A in cell cycle regulation of NPCs mainly over G1-S phase transition. Concretely, Dyrk1A has been shown to induce p53 phosphorylation at Ser-15 leading to a robust induction of p53 target genes such as $p21^{CIP1}$ and impaired G0/G1-S phase transition, resulting in attenuated cell proliferation in human embryonic stem cells (Park et al. 2010). In the same line, the transient overexpression of Dyrk1A by in utero electroporation has been shown to inhibit cell cycle progression in the developing mouse neocortex due to a nuclear export and degradation of cyclin D1 (Yabut et al. 2010). Recently, another mechanism for Dyrk1A-induced cell cycle arrest has been published where Dyrk1A is able to upregulate at the transcriptional level, the expression of cyclin-dependent kinase inhibitor $p27^{KIP1}$ in the embryonic chick spinal cord and mouse telencephalon (Hammerle et al. 2011). Interestingly, Dyrk1A has also been reported to regulate DREAM activity in order to induce cells into quiescence (Litovchick et al. 2011). Finally, one of the proposed mechanisms by which Dyrk1A could regulate neuronal differentiation refers to the inhibition of NOTCH signaling in cells (Hammerle et al. 2011). In addition, Dyrk1A dosage imbalance perturbs NRSF/REST levels, deregulating pluripotency and embryonic stem cell fate (Canzonetta et al. 2008). Recently, Dyrk1A has been shown to positively and selectively modulate p120-catenin protein levels, affecting the expression of certain Wnt target genes involved in development (Hong et al. 2012).

In spite of the clear role of Dyrk1A in embryonic neurogenesis, very few data have been published regarding adult neurogenesis. DYRK1A is expressed during adult neural stem cell divisions and modulates the self-renewal of those derived from the subependimal zone (Ferron et al. 2010). Moreover, recent studies have shown that Dyrk1A could be involved in adult neurogenesis in the DG of the hippocampus affecting different stages of adult neurogenesis from cell cycle progression to newly formed neuronal survival and integration in the preexisting dentate granule cells network (Pons-Espinal et al. unpublished results).

Cognitive therapies targeting adult neurogenesis

The development of strategies capable to promote nervous system plasticity in adulthood is nowadays an important aim in neuroscience to improve not only cognitive abilities but also to ameliorate pathological dysfunctions. Several studies have demonstrated that adult neurogenesis is regulated by many physiological and pathological stimuli at almost every stage, from proliferation of neuronal precursors until integration and activation of newly formed neurons in the preexisting network (Zhao et al. 2008).

Table 4 Schematic summary of the main results concerning embryonic and adult neurogenesis studies related to Rett, Fragile X and Down syndrome murine models

Embryonic neurogenesis in mammals				
	RTT		FXS	DS
	MECP2	FOXG1		
Proliferation	No differences	−	+	−
Survival	?	?	+	−
Neuronal differentiation	No differences	+ Premature	+	−
Glial differentiation	?	+	−	+
Adult neurogenesis in mammals				
	RTT		FXS	DS
	MECP2	FOXG1		
Proliferation	+/−	−	+	−
Survival	No differences	−	−	−
Neuronal differentiation	−	+/−	−	−
Glial differentiation	?	+	+	+/−

Interpretation of symbols: + increase, − reduction, +/− contradictory results depending on the model and type of study used

Activity-dependent regulation of adult neurogenesis

One of the strategies to promote in vivo neuroplasticity in rodents is the environmental enrichment (EE) that provides animals an increased physical exercise, learning experiences and social interaction (Rosenzweig and Bennett 1996). Many studies have shown that EE enhances learning and memory (Nithianantharajah and Hannan 2006) through the induction of biochemical, morphological and functional changes in the adult brain due to changes in the expression of genes involved in neuronal structure, synaptic signaling and plasticity (Rampon et al. 2000). However, although EE increases adult hippocampal neurogenesis and improves hippocampal-dependent learning in rodents, the causal link between these observations has been questioned (Meshi et al. 2006).

EE modulates hippocampal adult neurogenesis mainly by increasing the number of surviving newly formed cells (Kempermann et al. 1997; van Praag et al. 2000) by reducing spontaneous apoptotic cell death by 45 % (Young et al. 1999). However, it is important to highlight that the impact of EE in neurogenesis is different depending on the age that is applied. Some studies showed that in contrast to post-weaning enrichment, preweaning enrichment had no lasting measurable effect on adult hippocampal neurogenesis in four-months-old mice (Kohl et al. 2002). The effect of EE in neurogenesis has also been observed in aged subjects and in some diseases that are accompanied by hippocampal neuronal loss and abnormal neurogenesis like Alzheimer's disease (AD) (Berardi et al. 2007). However, another study using 10–12 months old Ts65Dn mice, that share the basal prosencephalon cholinergic cell loss and hippocampal dysfunction, reported that although physical exercise was able to rescue hippocampal-dependent learning deficits in these mice, they did not find any effect on hippocampal neurogenesis (Llorens-Martin et al. 2010), suggesting a relevant loss of plasticity with aging in this model.

Conversely, postweaning EE was able to rescue specifically adult neurogenesis impairments in the hippocampal DG of Ts65Dn mice (Chakrabarti et al. 2011). On the other hand, although EE has been shown to improve learning and memory and to rescue cognitive deficits and neuronal morphological abnormalities in different MECP2 and FMRP mutant mice (Lonetti et al. 2010; Restivo et al. 2005), no data regarding EE effects on adult neurogenesis have been yet described.

Pharmacological regulation of adult neurogenesis

In the last years, several studies have identified drugs that affect proliferation of neuronal populations. However, their application in murine models of intellectual disability has been very limited until now. We here review a few pharmacological approaches in this line.

Impaired neurogenesis may contribute not only to intellectual disability, as discussed above, but also to certain psychiatric diseases, particularly mood disorders, and enhancement of neurogenesis may be partly responsible for the therapeutic effects of mood stabilizers, antidepressants, and antipsychotics. However, it is not evident what mechanisms can impair neurogenesis in these disorders that can be reversed by therapeutic agents. One candidate mechanism is hyperactive glycogen synthase kinase 3β (GSK3-β), because accumulating evidence suggests that dysregulated GSK3 may contribute to mood disorders and GSK3 is inhibited by mood stabilizers, antidepressants, and antipsychotics. SB216763, a specific and competitive inhibitor of GSK3-β kinase activity, has been shown to improve hippocampal-dependent learning and to rescue hippocampal neurogenesis in adult *Fmr1* knockout mice (Guo et al. 2012). Fluoxetine, a serotonin (5-HT) reuptake inhibitor, and lithium, a non-specific GSK3 inhibitor, has been shown to increase neurogenesis in the DG and improves on learning and memory in DS mouse models (Bianchi et al. 2010; Clark et al. 2006). In fact, both may act through convergent mechanisms since activation of 5-HT1A receptors enhances neurogenesis and also causes inactivation of GSK3. GSK3-β is a negative regulator of β-catenin and the canonical Wnt signaling pathway which modulates hippocampal neurogenesis (Hur and Zhou 2010). Interestingly, the levels of GSK3-β are increased in FXS, and the reduction of GSK3-β has been proposed as a therapeutical approach for this disease. Several studies have also shown that epigallocatechin-3-gallate (EGCG) which is a natural component from the green tea extract improved hippocampal-dependent learning and memory in different mouse models with cognitive impairments, such as Dyrk1A overexpressing mice (Guedj et al. 2009). Moreover, Wang and colleagues described that EGCG affected adult neurogenesis in the hippocampus by increasing proliferation of adult hippocampal NPC cultures and in the DG of adult mice through a molecular mechanism involving the Shh signaling pathway (Wang et al. 2012), so that EGCG might be taken in consideration to future experiments as a therapeutic tool for cognitive disabilities.

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