

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800

Open access books available

122,000

International authors and editors

135M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

**WEB OF SCIENCE™**Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Deficiency of Adult Neurogenesis in the Ts65Dn Mouse Model of Down Syndrome

Pavel V. Belichenko and Alexander M. Kleschevnikov
*University of California, San Diego, School of Medicine, La Jolla, California
USA*

1. Introduction

Neurogenesis in the mammalian adult brain is a well established phenomenon (for the recent reviews see Carpentier & Palmer, 2009; Kaneko & Sawamoto, 2009; Rodriguez & Verkhratsky, 2011) that is important in both young and aging brain (Galvan & Jin, 2007; Rao et al., 2006). The subventricular zone, subgranular layer of the dentate gyrus (DG), and cortex are the main sites of adult neurogenesis (Gould et al., 1999; Luskin & Boone, 1994; Palmer et al., 2000; Seki et al., 2007; Yoneyama et al., 2011). Newly-born neurons during adult neurogenesis have the ability to integrate into previously established neuronal networks (Kee et al., 2007; Markakis & Gage, 1999; Sandoval et al., 2011). Alteration of neurogenesis under different experimental and pathological conditions has been described to a great extent (Rodriguez & Verkhratsky, 2011; Sandoval et al., 2011; Winner et al., 2011; Yoneyama et al., 2011; Yu et al., 2009). Significant decreases of neurogenesis have been found in neurodevelopmental (Contestabile et al., 2007; Guidi et al., 2008, 2010) and in neurodegenerative diseases (Rodriguez & Verkhratsky, 2011). Numerous studies provide evidence that a lack of neurogenesis significantly diminishes plasticity in the adult brain and interferes with learning and memory (reviewed in Koehl & Abrous, 2011; Mongiat & Schinder, 2011). Different mechanisms have been proposed to regulate neurogenesis in the adult brain, including brain injury (Kernie & Parent, 2010; Moriyama et al., 2011), ischemia (Kernie & Parent, 2010; Kreuzberg et al., 2010), and inflammation (Voloboueva et al., 2010). One of the least studied factors that affects neurogenesis are chromosomal aberrations. Down syndrome (DS) results from the extra copy of chromosome 21 occurring with a prevalence of 1 in 733 live births (Canfield et al., 2006). Subjects with DS show developmental regression, diminished cognitive ability, and autonomic dysfunction (Antonarakis & Epstein, 2006; Chapman & Hesketh, 2000). The DS brain is severely affected showing a reduction in both overall size and of particular areas (frontal cortex, hippocampus, cerebellum, and brainstem) due to a reduced number of neurons (Aylward et al., 1997, 1999; Kesslak et al., 1994; Pinter et al., 2001; Raz et al., 1995; Wisniewski et al., 1984).

1.1 Neurogenesis in subjects with DS

Very little data is available describing neurogenesis in subjects with DS. In hippocampal DG and neocortex of fetuses with DS the number of proliferating cells was found to be significantly reduced (Contestabile et al., 2007). These reductions were mainly due to a

reduced number of cycling cells in S phase (Contestabile et al., 2007). Both a reduction in neurogenesis and significantly higher incidence of apoptotic cell death in the hippocampal region of fetuses with DS has been noted (Guidi et al., 2008). Also, trisomy 21 significantly modify cell phenotypes producing higher numbers of cycling cells going to a glial phenotype and less cells expressing neuronal markers (Guidi et al., 2008). Detailed analysis of the consequences of both reduced neurogenesis and increased apoptosis in fetuses with DS, revealed a severe reduction in the volume and cell number of investigated brain areas (Guidi et al., 2008). More recently, significant neurogenesis impairments were also revealed in the cerebellum of fetuses with DS (Guidi et al., 2010). However, apoptotic cell death was similar in the cerebellum in fetuses with DS vs. controls (Guidi et al., 2010). The differences between the levels of apoptosis in hippocampus vs. cerebellum in fetuses with DS points to different mechanisms for the reduced cell number in hippocampus and cerebellum in DS. For the hippocampus, a reduction of neurogenesis, increased apoptosis and changing cell phenotypes in favor of glia may underlie reduced cell number in fetuses with DS. As for the cerebellum, only a reduction in neurogenesis may be the main factor in decreased cerebellar volume in fetuses with DS.

1.2 Neurogenesis in mouse models of DS

Taking to account that this subject is very important for the neurobiology of DS, only a few papers addressed neurogenesis in mouse models of DS (Bianchi et al., 2010; Chakrabarti et al., 2007; Clark et al., 2006; Contestabile et al., 2007; Lorenzi & Reeves, 2006; Rueda et al., 2005). It was noted that in prenatal and newborn Ts65Dn mice neurogenesis was significantly reduced (Chakrabarti et al., 2007; Contestabile et al., 2007; Lorenzi & Reeves, 2006). At postnatal day 2 cell proliferation in Ts65Dn mice, assessed 2 hours after single injection of bromodeoxyuridine (BrdU) was significantly reduced (Contestabile et al., 2007); similar results were revealed at postnatal day 15 (Bianchi et al., 2010). However in young adult Ts65Dn mice the results are conflicting (Clark et al., 2006; Rueda et al., 2005). Similar procedures in young (3-5 months) Ts65Dn mice shows no difference in hippocampal cell proliferation and survival (Rueda et al., 2005). However, in aged (13-15 months) Ts65Dn mice, cell proliferation in the hippocampus (Rueda et al., 2005) and in the subventricular zone (Bianchi et al., 2010) were significantly reduced. Finally, Clark et al. (2006) found a difference in DG neurogenesis in young (2-5 months) Ts65Dn mice.

It seems that genetic dissections of mouse partial trisomy 16 (Ts65Dn model) did not restore reduced neurogenesis. Indeed, Ts1Cje and Ts2Cje mouse models of DS showed a similar degree of impairment in adult neurogenesis (Hewitt et al., 2010; Ishihara et al., 2010).

To solve these conflicting results in DS mouse models a recent study was initiated to examine young adult neurogenesis, and we also expanded this study to include DG, cortex and corpus callosum (CC) at three different levels. We chose to investigate whether or not trisomy has any affect on neurogenesis in Ts65Dn mice. To carry out this work we injected BrdU in 2N and Ts65Dn mice. Combining BrdU immunoreactivity and high resolution confocal microscopy, we examined the number of BrdU-positive (BrdU+) neurons in DG, cortex and CC at three different levels: rostral, middle and caudal. Comparing 2N and Ts65Dn mice, we discovered significant decreases in the density of BrdU+ cells in trisomic mice in the cortex and DG. We found that the number of cells per cluster was significantly reduced in both the rostral and the caudal parts of DG in the Ts65Dn vs. 2N. This change resulted in reduced cell density in the caudal DG, while the density of clusters was not

altered. Our findings are evidence for decreased neurogenesis in young adult cortex and DG of Ts65Dn mice and indicate neurogenesis as a potential target for pharmacological intervention to avert neuronal plasticity in individuals with DS.

2. Materials and methods

All experiments were conducted in accordance with the National Institutes of Health guidelines for the care and use of animals and with an approved animal protocol from the Stanford University Institutional Animal Care and Use Committee. All efforts were made to minimize animal stress and discomfort.

2.1 Mice husbandry

Details of maintenance and using Ts65Dn mouse colony were described previously (Belichenko et al., 2004). The Ts65Dn mouse colony was maintained for more than 10 generations by crossing B6EiC3Sn-Ts(17¹⁶)65Dn females (Jackson Laboratory, Bar Harbor, ME) with B6EiC3Sn F1/J A/a males (Jackson Laboratory). This breeding scheme was used because trisomic mice breed very poorly or not at all when inbred; the B6C3 background has been the most successful. To distinguish 2N from Ts65Dn mice, genomic DNA was extracted from tail samples. A quantitative PCR protocol (provided by The Jackson laboratory) was used to measure Mx1 gene expression, which is present in three copies in Ts65Dn. Each mouse was genotyped twice. Male littermates mice were used in all studies at ages 2-3 months.

2.2 BrdU injections and immunofluorescent staining

In the beginning of experiment we weighed mice. Each animal was injected once a day for 6 consecutive days with 5-bromo-2'-deoxyuridine (BrdU, 10 mg/ml in saline, i.p.) (Cat. # B9285, Sigma-Aldrich Corp., St. Louis, MO, USA) to a final dose of 50 mg/kg body weight. Twenty four hours after the last injection, animals were deeply anesthetized with sodium pentobarbital (200 mg/kg i.p.) (Abbott Laboratories, North Chicago, IL, USA), again weighed, and transcardially perfused for 1 minute with 0.9% sodium chloride (10 ml) and then for 20 minutes with 4% paraformaldehyde in 0.1 M phosphate-buffered saline (PBS), pH 7.4 (200 ml). After perfusion, the brain was immediately removed and postfixed for another 24 hours. The weight of the entire brain (including the olfactory bulbs, cerebellum, and brainstem along with the cervical spinal cord through C1-C2) was recorded. The brain was then sectioned coronally at 100- μ m with a Vibratome (series 1000, TPI Inc., St. Louis, MO, USA), and sections were placed in 0.9% NaCl solution. Immunofluorescence method with anti-BrdU antibody was used to reveal BrdU⁺ cells as follows. Free-floating sections were rinsed twice in saline (0.9 % NaCl) for 10 min at RT, and then pretreated with 1M HCl for 30 minutes at 37°C. Sections were neutralized by rinsing 3 times in PBS and then pre-incubated in a solution of 0.1 M PBS containing 5% non-fat milk and 0.3% Triton-X 100 (PBS+), for 1 hour at room temperature. Then sections were incubated overnight at 4°C with primary rat anti-BrdU antibody (Cat. #MCA2060, Serotec, Raleigh, NC, USA) at a dilution 1:100 in PBS+. Sections were rinsed in PBS (20 minutes, three changes) and incubated for 1 hour at room temperature with biotinylated donkey anti-rat IgG (1:200; Jackson ImmunoResearch Labs, West Grove, PA). After being rinsed with PBS (20 minutes, three changes), sections were incubated with FITC-conjugated streptavidin (1:500; Jackson

ImmunoResearch Labs, West Grove, PA) for 1 hour at room temperature. Following further careful rinsing, the sections were mounted on microscope glass slides and coverslipped with 90% glycerol in PB.

2.3 Confocal microscopy imaging, cell quantification, cluster and statistical analyses

To study cell proliferation and clustering in 2N and Ts65Dn mice we used confocal microscopy imaging of BrdU+ cells in the cortex, hippocampus and CC. Confocal imaging of brain slices labeled with one fluorophore was performed as previously described (Belichenko et al., 2004). In brief, slices with BrdU+ cells were examined and scanned in a Radiance 2000 confocal microscope (BioRad, Hertfordshire, United Kingdom) attached to a Nikon Eclipse E800 fluorescence microscope. LaserSharp software (Bio Rad) was used to establish optimal conditions for collecting images. The laser was an argon/krypton mixed gas laser with exciting wavelengths for FITC (488 λ). The emission was registered with HQ515/30 "green" filter. Sections with FITC staining of BrdU immunoreactivity were studied under the following optimal conditions: the lens was a x10 objective (Nikon; Plan Fluor x10/0.30); laser power was 10%; the zoom factor was 1; scan speed was 500 lines per second; each optical section was the result of 3 scans followed by Kalman filtering; the size of the image was 512 x 512 pixels (i.e., 1208 x 1208 μm).

LazerPix software (Bio Rad) analysis of confocal images was used to measure the area or length of investigated brain structures, and for quantitative analysis of BrdU+ cells. Three slices per mouse (500 μm apart) were used. The location of each coronal section was designated based on its relative position to bregma in mm (Hof et al., 2000). Rostral section was corresponded to bregma -1.60 mm level, middle section - to bregma -2.10 mm level, and caudal section to bregma -2.60 mm level. Entire DG at these three different locations was imaged. CC was imaged from midline and then for 1200 μm to the left or right extension at the same three different locations. Based on mouse brain atlas (Hof et al., 2000), cortex were correspondent to motor cortex at rostral and middle sections and to visual cortex at caudal section). Images from the both the left and right side for each mouse brain were analyzed. To count number of BrdU+ cells, we first outlined the area of interest and measure area or length (in a case of DG). Next, for each image, the intensity thresholds were estimated by analyzing the distribution of pixel intensities in the image areas that did not contain immunoreactivity. This value, the background threshold, was then subtracted and number of BrdU+ cells was counted. In addition each BrdU+ cells were traced manually and their XY coordinates were exported to Excel. The number of BrdU+ cell in each hemisphere was expressed for DG as per 100- μm length of neurogenic subgranule zone, and for cortex and CC as per 1 mm^2 . We also counted the occurrence of BrdU+ cell clusters. To quantify the number of clusters we used previously established criteria (Palmer et al., 2000), where cluster was defined as a contiguous group of cells separated by less than 25 μm . Special macro was design in Excel program for cluster counting. For every section, X and Y coordinates of individual BrdU+ cell were recorded using LazerPix software (BioRad). Distance between all pairs of the BrdU+ cells within one section were calculated using an Excel Microsoft macro, and the cells with distances < 25 μm were regarded as belonging to a cluster. All analyses were performed by the same investigator blinded to mice genotype.

Digital images were imported, enhanced for brightness and contrast, assembled and labeled in Adobe Photoshop CS2 9.0.2, and archived. Figures were printed with a Phaser 7300 color printer (Tektronix by Xerox, Norwalk, CT).

The data for body and brain weights, total number of BrdU+ cells, their coordinates and cluster evaluations were exported to Excel (Microsoft, Redmond, WA) and statistical comparisons were performed using two-way analysis of variance (ANOVA) and for two samples using two-tailed Student's *t*-tests. All results are expressed as mean \pm SEM, and *P* values < 0.05 were considered to be significant.

3. Results

3.1 Body and brain weights

The body weight of 2N and Ts65Dn mice at 2-3 months was similar (2N: 31.1 ± 1.6 g, *n* = 6; Ts65Dn = 26.7 ± 2.3 g, *n* = 5; *P* = 0.14). The brain weight was also unchanged (2N: 0.43 ± 0.01 g, *n* = 6; Ts65Dn = 0.43 ± 0.01 g, *n* = 5; *P* = 0.60). Of note, there was no effect of the BrdU injection on changes in body weight during 6 day injections since no significant differences were found between 2N and Ts65Dn mice (2N: -0.60 ± 0.29 g, *n* = 6; Ts65Dn = -0.20 ± 0.51 g, *n* = 5; *P* = 0.49). These mice also showed no aversive or any other neurological symptoms during injection.

3.2 Changes in BrdU+ cells number and in cell cluster density in Ts65Dn mice

We examined the density of BrdU+ cells in DG of hippocampus, cortex and CC in 2N and Ts65Dn male mice (Table 1, Figs. 1, 2). The BrdU+ cells were bright fluorescent, allowing for a detailed quantitative analysis by confocal microscopy (Figs. 1a, 2a). For this analysis, the number of BrdU+ cells per 100 μ m length of subgranule zone for DG or per 1 mm² area of cortex or CC was counted to define cell density (Table 1). In addition we measured the number of cell cluster, the number of BrdU+ cells per cluster and the frequency distribution of BrdU+ cells per cluster (Table 1; Figs. 1 d,e; 2 d,e).

Comparing BrdU+ cell densities in 2N and Ts65Dn mice, there was a statistically significant decrease in the caudal part of DG (by 27%) and in the rostral part of motor cortex (by 36%; *P* < 0.01 ; Table 1). Interestingly, BrdU+ neurons in the inferior blade were on average 30% fewer than in the superior blade for 2N, and 23% fewer for Ts65Dn mice (*P* < 0.01 ; Table 1). BrdU+ cell density were similar for CC in 2N and Ts65Dn mice, and 33% more in caudal than rostral CC for 2N mice (*P* < 0.01 ; Table 1).

Comparing BrdU+ cell cluster densities in 2N and Ts65Dn mice, there was a statistically significant decrease in the rostral part of motor cortex (by 29%; *P* < 0.01 ; Table 1). In the inferior blade there were on average 9% fewer than in superior blade for 2N, and 25% fewer for Ts65Dn mice (*P* < 0.05 ; Table 1). Interestingly, in the DG the BrdU+ cell cluster density was not different in 2N and Ts65Dn mice (Table 1).

We next quantified the number of cells per cluster (Table 1). As compared to 2N mice, significantly lower numbers of BrdU+ cells per cluster were present in rostral (mainly due to superior blade, *P* < 0.003 ; Table 1) and in the caudal part of DG in Ts65Dn mice (*P* = 0.03; Table 1), and in the rostral part of motor cortex in Ts65Dn mice (*P* < 0.01 ; Table 1). Comparing the superior and inferior blades in 2N mice, numbers of cells per cluster were ~1.5 times higher in the rostral and middle parts of the superior blade of the DG in 2N mice (*P* < 0.02 ; Table 1).

In conclusion, significant differences in the number of BrdU+ cells, cell cluster densities, and in number of BrdU+ cells per cluster were evident for Ts65Dn mice as compared to their 2N cohorts. These findings are evidence for reduced neurogenesis in both DG and cortex due to mouse chromosome 16 trisomy.

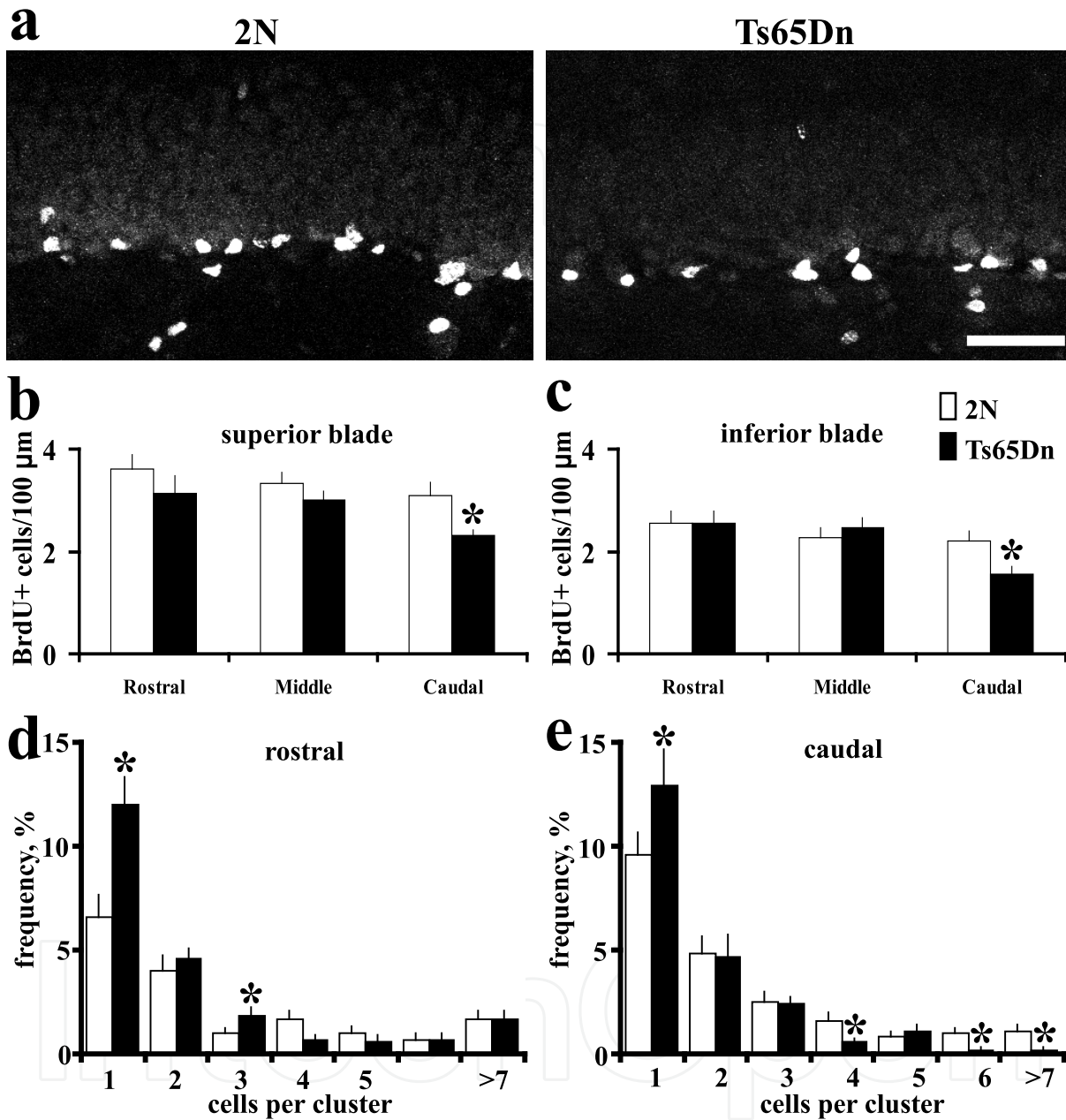


Fig. 1. Morphometry of BrdU+ cells in dentate gyrus in 2N and Ts65Dn mice. (a) Confocal image of BrdU+ cells in caudal part of dentate gyrus of 2N and Ts65Dn mice. BrdU+ cell density in superior (b) and inferior blades (c) of dentate gyrus. Note a significant reduction of BrdU+ cell in caudal DG in Ts65Dn mice. The number of cells per cluster in rostral (d) and caudal (e) part of DG. Scale bar = 50 μ m.

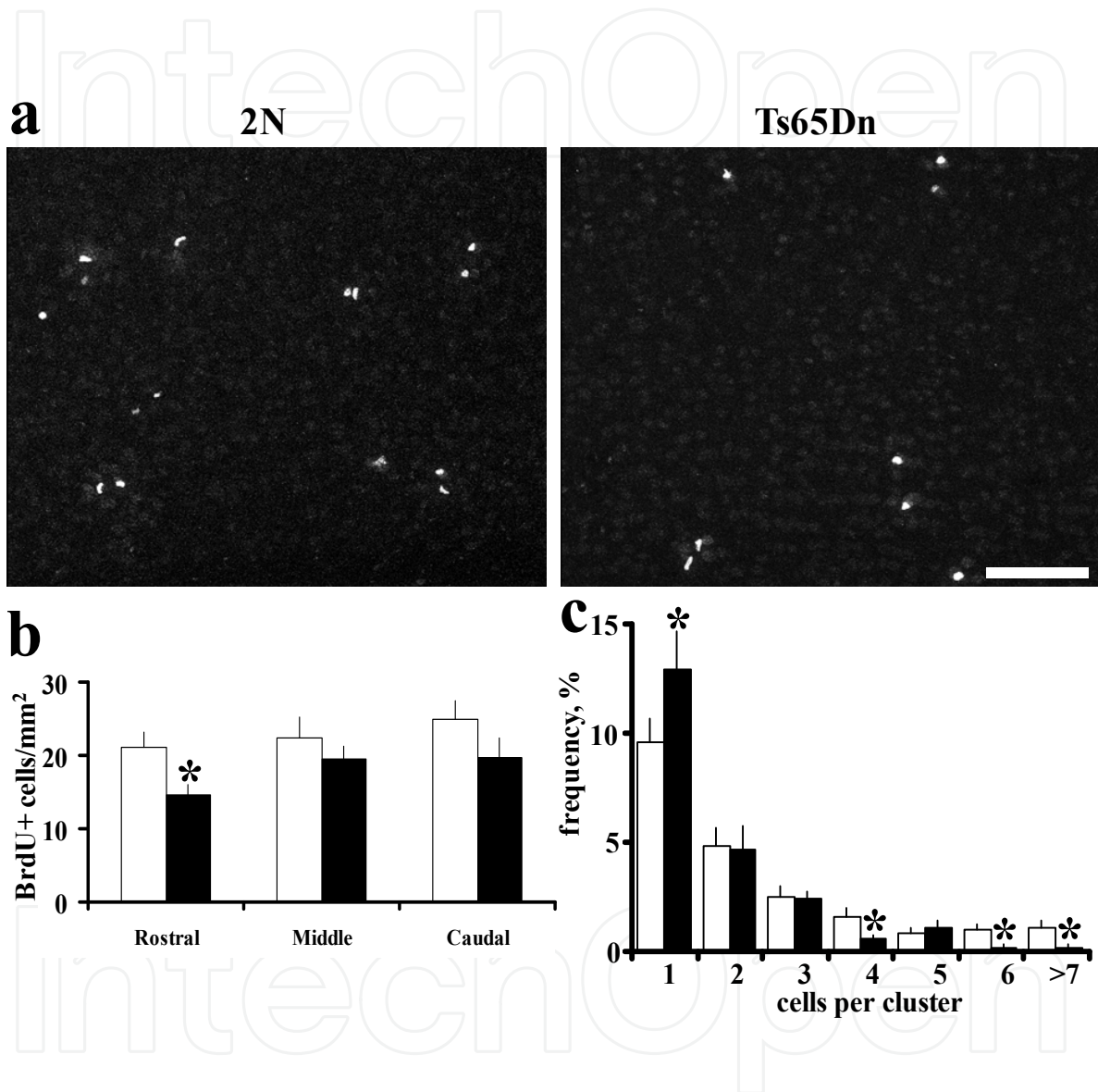


Fig. 2. Neurogenesis in cortex in 2N and Ts65Dn mice. (a) Confocal image of BrdU+ cells in the rostral part of cortex of 2N and Ts65Dn mice. (b) BrdU+ cell density in cortex. Note significant reduction of BrdU+ cell in rostral cortex in Ts65Dn mice. (c) The number of cells per cluster in rostral part of cortex. Scale bar = 100 μ m.

	cell density		cluster density		# cells per cluster	
	2N	Ts65Dn	2N	Ts65Dn	2N	Ts65Dn
Dentate gyrus						
Rostral						
Total	3.06 ± 0.27	2.87 ± 0.25	1.01 ± 0.08	1.22 ± 0.09	3.05 ± 0.22	2.39 ± 0.16a
Superior blade	3.61 ± 0.29	3.13 ± 0.36	1.02 ± 0.11	1.25 ± 0.09	3.69 ± 0.29	2.47 ± 0.21a
Inferior blade	2.55 ± 0.25b	2.55 ± 0.25	0.99 ± 0.08	1.19 ± 0.13	2.65 ± 0.29b	2.42 ± 0.37
Middle						
Total	2.88 ± 0.17	2.77 ± 0.15	1.21 ± 0.05	1.17 ± 0.08	2.56 ± 0.20	2.52 ± 0.12
Superior blade	3.33 ± 0.21	3.01 ± 0.17	1.23 ± 0.05	1.24 ± 0.09	3.01 ± 0.26	2.66 ± 0.12
Inferior blade	2.28 ± 0.18b	2.46 ± 0.20c	1.19 ± 0.08	1.08 ± 0.14	1.96 ± 0.17b	2.51 ± 0.34
Caudal						
Total	2.73 ± 0.19	2.00 ± 0.08a	1.13 ± 0.04	1.10 ± 0.08	2.59 ± 0.31	2.01 ± 0.12a
Superior blade	3.09 ± 0.27	2.31 ± 0.12a	1.21 ± 0.07	1.22 ± 0.10	2.84 ± 0.27	1.69 ± 0.16a
Inferior blade	2.20 ± 0.19b	1.55 ± 0.15a,c	1.10 ± 0.06b	0.92 ± 0.07c	2.21 ± 0.22	1.69 ± 0.16a
Cortex						
Rostral	21.1 ± 2.2	14.6 ± 1.4a	14.4 ± 1.4	10.2 ± 1.2a	1.46 ± 0.04	1.24 ± 0.05a
Middle	22.3 ± 2.9	19.5 ± 1.8	15.9 ± 1.5	14.9 ± 1.7	1.25 ± 0.03	1.22 ± 0.02
Caudal	25.0 ± 2.5	19.7 ± 2.7	14.9 ± 1.7	13.9 ± 1.7	1.30 ± 0.03	1.26 ± 0.04
Corpus callosum						
Rostral	74.7 ± 11.3	87.2 ± 12.6	56.7 ± 3.1	53.0 ± 5.6	1.15 ± 0.05	1.16 ± 0.03
Middle	96.1 ± 15.8	77.3 ± 13.4	64.1 ± 7.2	62.6 ± 7.6	1.28 ± 0.07	1.22 ± 0.03
Caudal	111.2 ± 11.8b	105.1 ± 16.1	73.8 ± 7.3	73.2 ± 9.4	1.36 ± 0.06	1.32 ± 0.04

The number of mice used was as follows: 2N/Ts65Dn = 6/5.

Each value represents the mean ± SEM.

BrdU+ cells and clusters densities are expressed as: for FD per 100 µm length of subgranule zone, for cortex and CC per 1 mm².

a, $P < 0.05$, significantly different from 2N mice.

b, $P < 0.05$, significantly different between 2N mice.

c, $P < 0.05$, significantly different between Ts65Dn mice.

Table 1. Morphometry of BrdU+ cells in 2N and Ts65Dn mice

4. Discussion

Numerous studies have shown that adult neurogenesis is affected by various neurodegenerative diseases such as Alzheimer's, Parkinson's, and Huntington's diseases (reviewed in Curtis et al., 2011; Kaneko & Sawamoto, 2009; Rodriguez & Verkhatsky, 2011; Winner et al., 2011). Alteration of neurogenesis in neurodevelopmental disorders were studied to a lesser extent in DS (Contestabile et al., 2007; Guidi et al., 2008, 2010), autism spectrum disorders (Greco et al., 2011; Wegiel et al., 2010), including Rett syndrome (Ronnett et al., 2003). Studies to understand the neurobiology of DS have benefited from the ability to examine mouse models of the disorder (Belichenko et al., 2004; 2007; 2009; Kleschevnikov et al., 2004; Popov et al., 2011). Previous studies demonstrated that trisomy in Ts65Dn mouse model of DS resulted in alteration of hippocampal long-term potentiation (LTP) (Kleschevnikov et al., 2004; Siarey et al., 1997). Significant alteration of neurogenesis could be one of the contributing factors to diminished plasticity in DS. Interestingly, studies involving mice to different enrichments or pharmacotherapies enhanced both neurogenesis and learning (Deng et al., 2010; Mongiat & Schinder, 2011; Saxe et al., 2006; Shors et al., 2002; Singer et al., 2011), including Ts65Dn mice (Bianchi et al., 2010). Moreover, manipulations that stimulate adult neurogenesis in mice also increase LTP (van Praag et al., 1999).

Our study in the Ts65Dn mouse model of DS presents novel evidence of altered neurogenesis in adult young mice (2-3 months of age). Significant increases in the number of clusters containing single BrdU+ cells in Ts65Dn mice point to severely affected cell proliferation. Our present data are in agreement with previous data (Clark et al., 2006) and conflicting with Rueda et al. (2005) data on young adult Ts65Dn mice. The discrepancy with the Rueda et al. (2005) results likely result from several factors including the different gender of mice (we used only male mice and no gender of studied mice were mentioned in Rueda et al., 2005), the different brain areas investigated (we studied rostral, middle, and caudal parts of hippocampus, cortex and CC separately, while in Rueda et al. (2005) the entire hippocampus was studied). The BrdU injection protocol was also different. We used standard a procedure with BrdU injection during 6 days, while Rueda et al., (2005) used a 12 days injection approach.

The majority of BrdU+ cells in adult brain during the proliferation phase formed clusters (Palmer et al., 2000; Seki et al., 2007). Data on neurogenesis in adult rat hippocampus suggests that newly-born cells appeared to stay in clusters for a few days and then migrate from clusters (Seki et al., 2007). Currently, little is known about the molecular mechanisms of cluster formation. Previous reports suggested that cell clustering supports intercellular contacts and/or signals that encourage neurogenesis (Seki et al., 2007). It is possible that the initial formation of a cluster is triggered by a certain factor, which is not affected in Ts65Dn mice. Thus, we have similar cluster density in Ts65Dn vs. 2N mice. The 'just-divided' cells could be divided further, thus resulting in a cluster (Seki et al., 2007). However, this could be only accomplished when the cell is going through all cycles. Indeed, as was shown previously (Contestabile et al., 2008) that the dividing in Ts65Dn cells are 'stuck' in S phase, thus decreasing the probability of cell cycle re-entry. This delay could suspend the second and the following divisions, thus resulting in a reduced number of the newly-born cells per cluster. Interestingly, we observed that the number of cells per cluster was reduced only in the rostral and caudal, but not in the middle part of the Ts65Dn hippocampus. The exact nature of this phenomenon is not clear yet, but may result from differences in the structure and function of hippocampus along the rostral-caudal axis. Indeed, neuronal network architecture is different in hippocampus (Witter et al., 2000).

Reduction in the number of cells per cluster leads to a reduction of total number of newly-born neurons in the Ts65Dn hippocampus. It was shown previously that LTP in the DG depends strongly on neurogenesis, and that a blockade of neurogenesis results in reduced synaptic plasticity (Snyder et al., 2001). Because we observed that LTP in the DG of Ts65Dn mice is significantly diminished (Kleschevnikov et al., 2004), it is tempting to assume that reduced neurogenesis is one of the factors contributing to this abnormality. It is clear that alteration in prenatal growth of the cortex and hippocampus in trisomic mice is due to a longer cell cycle and reduced neurogenesis (Chakrabarti et al., 2007; Contestabile et al., 2007).

We further propose that alteration of neurogenesis may also affect the balance between excitation and inhibition. Indeed, the putative young neurons are completely unaffected by GABA(A) inhibition (Wang et al., 2000). Reduced number of such disinhibited neurons in DG of Ts65Dn mice could thus result in elevation of the overall efficiency of the inhibitory system (Belichenko et al., 2009; Kleschevnikov et al., 2004). The excitatory/inhibitory neuron ratio could be affected also in other brain regions. The new granule cells of the DG, olfactory bulb, and cerebellum and the new cells in cortex are constantly produced during adult neurogenesis. However, there are many differences between these cells. For example, in the olfactory bulb and neocortex the newly-born cells are mainly inhibitory (GABAergic) (reviewed in Cameron & Dayer, 2008). Reduced neurogenesis in these regions could result in relative disinhibition and, thus, could be regarded as a factor contributing to epilepsy in DS (Goldberg-Stern et al., 2001; Menendez, 2005; Pueschel et al., 1991). In contrast, DG and cerebellar granule cells are excitatory (glutamatergic). However, this question needs to be studied in greater detail. The influence of chromosomal aberration on the transition from proliferating stage to differentiated stage into either glutamatergic or GABA-ergic neurons should be also studied.

Numerous factors can be implicated in the control of adult neurogenesis, including chromosomal aberrations. Although the exact mechanism(s) of influence of partial or complete trisomy on neurogenesis is not known, we can extract some data from the scattered information. Impaired neurogenesis has been described not only in Ts65Dn (Rueda et al., 2005; Clark et al., 2006; Lorenzi and Reeves, 2006; Contestabile et al., 2007; Chakrabarti et al., 2007; Bianchi et al., 2010) and Ts2Cje (Ishihara et al., 2010) mouse models of DS, but also in TsCje1 mice (Hewitt et al., 2010; Ishihara et al., 2010) with smaller triplicated chromosomal region. Genetic dissection approaches (Ts65Dn vs. Ts1Cje) point out to the same genes in smaller triplicated region, i.e. *Itsn1*, *Dyrk1A*, *Olig2* may involve in neurogenesis (Hewitt et al., 2010; Ishihara et al., 2010). It has been proposed that overexpressions of *Dyrk1A* in trisomic segment may be responsible for impaired neurogenesis in Ts65Dn, Ts2Cje, and Ts1Cje mouse models of DS (Canzonetta et al., 2008; Ishihara et al., 2010). These authors also suggest that altered neurogenesis in the Ts1Cje mouse is due to a reduction in neuronal progenitors and neuroblasts rather than neural stem cells (Hewitt et al., 2010). The further identification and characterization of triplicated genes in altered neurogenesis may significantly contribute to understanding the neurobiology of DS and may lead to the development of pharmacotherapy for DS.

5. Conclusion

Down syndrome (DS) is a neurodevelopmental disorder caused by the triplication of chromosome 21. Few studies have explored neurogenesis in mouse models of DS and these have produced conflicting results on the alteration of neurogenesis. Using confocal

microscopy analysis we have examined adult neurogenesis in the hippocampus (dentate gyrus, DG), motor cortex and corpus callosum (CC) of male wild-type (2N) and Ts65Dn mice at age 2-3 months. In Ts65Dn we found significant decreases in the BrdU+ cells density in DG and motor cortex. BrdU+ cell cluster density were higher in rostral motor cortex in Ts65Dn. Number of BrdU+ cells per cluster were significantly lower in DG and motor cortex of Ts65Dn mice, mainly due to the presence of single cell clusters. Density of BrdU+ cells was significantly lower in the inferior than in the superior blade of DG. Thus, we show for the first time a lower density of BrdU+ cells in Ts65Dn mice. Our findings are evidence on a deficiency of adult neurogenesis in Ts65Dn mouse model of DS. Moreover, we propose a correlation of the present data with our previously published data on alteration of LTP due to excessive inhibition in Ts65Dn mouse model of DS. The new findings can shed light on possible mechanisms underlying the changes in the Ts65Dn neurogenesis, synaptic structure and function that were described previously. Based on our data and recent studies we reasonable suggested that new complex therapies should improve neurogenesis, and as consequence also learning and memory.

6. Acknowledgments

We thank Dr. Theo D. Palmer and Dr. William C. Mobley for their critical inputs in the beginning of this work. We also thank Michael Maloney for critically reading the article. This work was supported by the Larry L Hillblom Foundation and by the Down Syndrome Research and Treatment Foundation.

7. References

- Antonarakis, S.E. & Epstein, C.J. (2006). The challenge of Down syndrome. *Trends Mol Med*, Vol. 12, No. 10, pp. 473-479.
- Aylward, E.H., Li, Q., Habbak, Q.R., Warren, A., Pulsifer, M.B., Barta, P.E., Jerram, M. & Pearlson, G. (1997). Basal ganglia volume in adults with Down syndrome. *Psychiatry Res*, Vol. 74, No. 2, pp. 73-82.
- Aylward, E.H., Li, Q., Honeycutt, N.A., Warren, A.C., Pulsifer, M.B., Barta, P.E., Chan, M.D., Smith, P.D., Jerram, M. & Pearlson, G.D. (1999). MRI volumes of the hippocampus and amygdala in adults with Down's syndrome with and without dementia. *Am J Psychiatry*, Vol. 156, No. 4, pp. 564-568.
- Belichenko, P.V., Kleschevnikov, A.M., Masliah, E., Wu, C., Takimoto-Kimura, R., Salehi, A. & Mobley, W.C. (2009). Excitatory-inhibitory relationship in the fascia dentata in the Ts65Dn mouse model of Down syndrome. *J Comp Neurol*, Vol. 512, No. 4, pp. 453-466.
- Belichenko, P.V., Kleschevnikov, A.M., Salehi, A., Epstein, C.J. & Mobley, W.C. (2007). Synaptic and cognitive abnormalities in mouse models of Down syndrome: exploring genotype-phenotype relationships. *J Comp Neurol*, Vol. 504, No. 4, pp. 329-345.
- Belichenko, P.V., Masliah, E., Kleschevnikov, A.M., Villar, A.J., Epstein, C.J., Salehi, A. & Mobley, W.C. (2004). Synaptic structural abnormalities in the Ts65Dn mouse model of Down Syndrome. *J Comp Neurol*, Vol. 480, No. 3, pp. 281-298.

- Bianchi, P., Ciani, E., Guidi, S., Trazzi, S., Felice, D., Grossi, G., Fernandez, M., Giuliani, A., Calza, L. & Bartesaghi, R. (2010). Early pharmacotherapy restores neurogenesis and cognitive performance in the Ts65Dn mouse model for Down syndrome. *J Neurosci*, Vol. 30, No. 26, pp. 8769-8779.
- Cameron, H.A. & Dayer, A.G. (2008). New interneurons in the adult neocortex: small, sparse, but significant? *Biol Psychiatry*, Vol. 63, No. 7, pp. 650-655.
- Canfield, M.A., Honein, M.A., Yuskiv, N., Xing, J., Mai, C.T., Collins, J.S., Devine, O., Petrini, J., Ramadhani, T.A., Hobbs, C.A. & Kirby, R.S. (2006). National estimates and race/ethnic-specific variation of selected birth defects in the United States, 1999-2001. *Birth Defects Res A Clin Mol Teratol*, Vol. 76, No. 11, pp. 747-756.
- Canzonetta, C., Mulligan, C., Deutsch, S., Ruf, S., O'Doherty, A., Lyle, R., Borel, C., Lin-Marq, N., Delom, F., Groet, J., Schnappauf, F., De Vita, S., Averill, S., Priestley, J.V., Martin, J.E., Shipley, J., Denyer, G., Epstein, C.J., Fillat, C., Estivill, X., Tybulewicz, V.L., Fisher, E.M., Antonarakis, S.E. & Nizetic, D. (2008). DYRK1A-dosage imbalance perturbs NRSF/REST levels, deregulating pluripotency and embryonic stem cell fate in Down syndrome. *Am J Hum Genet*, Vol. 83, No. 3, pp. 388-400.
- Carpentier, P.A. & Palmer, T.D. (2009). Immune influence on adult neural stem cell regulation and function. *Neuron*, Vol. 64, No. 1, pp. 79-92.
- Chakrabarti, L., Galdzicki, Z. & Haydar, T.F. (2007). Defects in embryonic neurogenesis and initial synapse formation in the forebrain of the Ts65Dn mouse model of Down syndrome. *J Neurosci*, Vol. 27, No. 43, pp. 11483-11495.
- Chapman, R.S. & Hesketh, L.J. (2000). Behavioral phenotype of individuals with Down syndrome. *Ment Retard Dev Disabil Res Rev*, Vol. 6, No. 2, pp. 84-95.
- Clark, S., Schwalbe, J., Stasko, M.R., Yarowsky, P.J. & Costa, A.C. (2006). Fluoxetine rescues deficient neurogenesis in hippocampus of the Ts65Dn mouse model for Down syndrome. *Exp Neurol*, Vol. 200, No. 1, pp. 256-261.
- Contestabile, A., Fila, T., Ceccarelli, C., Bonasoni, P., Bonapace, L., Santini, D., Bartesaghi, R. & Ciani, E. (2007). Cell cycle alteration and decreased cell proliferation in the hippocampal dentate gyrus and in the neocortical germinal matrix of fetuses with Down syndrome and in Ts65Dn mice. *Hippocampus*, Vol. 17, No. 8, pp. 665-678.
- Curtis, M.A., Kam, M. & Faull, R.L. (2011). Neurogenesis in humans. *Eur J Neurosci*, Vol. 33, No. 6, pp. 1170-1174.
- Deng, W., Aimone, J.B. & Gage, F.H. (2010). New neurons and new memories: how does adult hippocampal neurogenesis affect learning and memory? *Nat Rev Neurosci*, Vol. 11, No. 5, pp. 339-350.
- Galvan, V. & Jin, K. (2007). Neurogenesis in the aging brain. *Clin Interv Aging*, Vol. 2, No. 4, pp. 605-610.
- Goldberg-Stern, H., Strawsburg, R.H., Patterson, B., Hickey, F., Bare, M., Gadoth, N. & Degrauw, T.J. (2001). Seizure frequency and characteristics in children with Down syndrome. *Brain Dev*, Vol. 23, No. 6, pp. 375-378.
- Gould, E., Reeves, A.J., Graziano, M.S. & Gross, C.G. (1999). Neurogenesis in the neocortex of adult primates. *Science*, Vol. 286, No. 5439, pp. 548-552.

- Greco, C.M., Navarro, C.S., Hunsaker, M.R., Maezawa, I., Shuler, J.F., Tassone, F., Delany, M., Au, J.W., Berman, R.F., Jin, L.W., Schumann, C., Hagerman, P.J. & Hagerman, R.J. (2011). Neuropathologic features in the hippocampus and cerebellum of three older men with fragile X syndrome. *Mol Autism*, Vol. 2, No. 1, pp. 2.
- Guidi, S., Bonasoni, P., Ceccarelli, C., Santini, D., Gualtieri, F., Ciani, E. & Bartesaghi, R. (2008). Neurogenesis impairment and increased cell death reduce total neuron number in the hippocampal region of fetuses with Down syndrome. *Brain Pathol*, Vol. 18, No. 2, pp. 180-197.
- Guidi, S., Ciani, E., Bonasoni, P., Santini, D. & Bartesaghi, R. (2010). Widespread Proliferation Impairment and Hypocellularity in the Cerebellum of Fetuses with Down Syndrome. *Brain Pathol*, Vol. No., pp. 1-13.
- Hewitt, C.A., Ling, K.H., Merson, T.D., Simpson, K.M., Ritchie, M.E., King, S.L., Pritchard, M.A., Smyth, G.K., Thomas, T., Scott, H.S. & Voss, A.K. (2010). Gene network disruptions and neurogenesis defects in the adult Ts1Cje mouse model of Down syndrome. *PLoS One*, Vol. 5, No. 7, pp. e11561.
- Hof, P.R., Young, W.G., Bloom, F.E., Belichenko, P.V. & Celio M.R. (2000) *Comparative Cytoarchitectonic Atlas of the C57Bl/6 and 129/Sv Mouse Brains*. Elsevier, Amsterdam.
- Ishihara, K., Amano, K., Takaki, E., Shimohata, A., Sago, H., Epstein, C.J. & Yamakawa, K. (2010). Enlarged brain ventricles and impaired neurogenesis in the Ts1Cje and Ts2Cje mouse models of Down syndrome. *Cereb Cortex*, Vol. 20, No. 5, pp. 1131-1143.
- Kaneko, N. & Sawamoto, K. (2009). Adult neurogenesis and its alteration under pathological conditions. *Neurosci Res*, Vol. 63, No. 3, pp. 155-164.
- Kee, N., Teixeira, C.M., Wang, A.H. & Frankland, P.W. (2007). Preferential incorporation of adult-generated granule cells into spatial memory networks in the dentate gyrus. *Nat Neurosci*, Vol. 10, No. 3, pp. 355-362.
- Kernie, S.G. & Parent, J.M. (2010). Forebrain neurogenesis after focal Ischemic and traumatic brain injury. *Neurobiol Dis*, Vol. 37, No. 2, pp. 267-274.
- Kesslak, J.P., Nagata, S.F., Lott, I. & Nalcioglu, O. (1994). Magnetic resonance imaging analysis of age-related changes in the brains of individuals with Down's syndrome. *Neurology*, Vol. 44, No. 6, pp. 1039-1045.
- Kleschevnikov, A.M., Belichenko, P.V., Villar, A.J., Epstein, C.J., Malenka, R.C. & Mobley, W.C. (2004). Hippocampal long-term potentiation suppressed by increased inhibition in the Ts65Dn mouse, a genetic model of Down syndrome. *J Neurosci*, Vol. 24, No. 37, pp. 8153-8160.
- Koehl, M. & Abrous, D.N. (2011). A new chapter in the field of memory: adult hippocampal neurogenesis. *Eur J Neurosci*, Vol. 33, No. 6, pp. 1101-1114.
- Kreuzberg, M., Kanov, E., Timofeev, O., Schwaninger, M., Monyer, H. & Khodosevich, K. (2010). Increased subventricular zone-derived cortical neurogenesis after ischemic lesion. *Exp Neurol*, Vol. 226, No. 1, pp. 90-99.
- Lorenzi, H.A. & Reeves, R.H. (2006). Hippocampal hypocellularity in the Ts65Dn mouse originates early in development. *Brain Res*, Vol. 1104, No. 1, pp. 153-159.

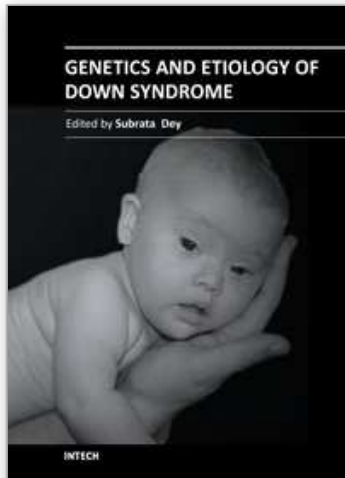
- Luskin, M.B. & Boone, M.S. (1994). Rate and pattern of migration of lineally-related olfactory bulb interneurons generated postnatally in the subventricular zone of the rat. *Chem Senses*, Vol. 19, No. 6, pp. 695-714.
- Markakis, E.A. & Gage, F.H. (1999). Adult-generated neurons in the dentate gyrus send axonal projections to field CA3 and are surrounded by synaptic vesicles. *J Comp Neurol*, Vol. 406, No. 4, pp. 449-460.
- Menendez, M. (2005). Down syndrome, Alzheimer's disease and seizures. *Brain Dev*, Vol. 27, No. 4, pp. 246-252.
- Mongiati, L.A. & Schinder, A.F. (2011). Adult neurogenesis and the plasticity of the dentate gyrus network. *Eur J Neurosci*, Vol. 33, No. 6, pp. 1055-1061.
- Moriyama, M., Fukuhara, T., Britschgi, M., He, Y., Narasimhan, R., Villeda, S., Molina, H., Huber, B.T., Holers, M. & Wyss-Coray, T. (2011). Complement Receptor 2 Is Expressed in Neural Progenitor Cells and Regulates Adult Hippocampal Neurogenesis. *J Neurosci*, Vol. 31, No. 11, pp. 3981-3989.
- Palmer, T.D., Willhoite, A.R. & Gage, F.H. (2000). Vascular niche for adult hippocampal neurogenesis. *J Comp Neurol*, Vol. 425, No. 4, pp. 479-494.
- Pinter, J.D., Eliez, S., Schmitt, J.E., Capone, G.T. & Reiss, A.L. (2001). Neuroanatomy of Down's syndrome: a high-resolution MRI study. *Am J Psychiatry*, Vol. 158, No. 10, pp. 1659-1665.
- Popov, V.I., Kleschevnikov, A.M., Klimenko, O.A., Stewart, M.G. & Belichenko, P.V. (2011). Three-dimensional synaptic ultrastructure in the dentate gyrus and hippocampal area CA3 in the Ts65Dn mouse model of down syndrome. *J Comp Neurol*, Vol. 519, No. 7, pp. 1338-1354.
- Pueschel, S.M., Louis, S. & McKnight, P. (1991). Seizure disorders in Down syndrome. *Arch Neurol*, Vol. 48, No. 3, pp. 318-320.
- Rao, M.S., Hattiangady, B. & Shetty, A.K. (2006). The window and mechanisms of major age-related decline in the production of new neurons within the dentate gyrus of the hippocampus. *Aging Cell*, Vol. 5, No. 6, pp. 545-558.
- Raz, N., Torres, I.J., Briggs, S.D., Spencer, W.D., Thornton, A.E., Loken, W.J., Gunning, F.M., McQuain, J.D., Driesen, N.R. & Acker, J.D. (1995). Selective neuroanatomic abnormalities in Down's syndrome and their cognitive correlates: evidence from MRI morphometry. *Neurology*, Vol. 45, No. 2, pp. 356-366.
- Rodriguez, J.J. & Verkhratsky, A. (2011). Neurogenesis in Alzheimer's disease. *J Anat*, Vol. No., pp. 1-12.
- Ronnett, G.V., Leopold, D., Cai, X., Hoffbuhr, K.C., Moses, L., Hoffman, E.P. & Naidu, S. (2003). Olfactory biopsies demonstrate a defect in neuronal development in Rett's syndrome. *Ann Neurol*, Vol. 54, No. 2, pp. 206-218.
- Rueda, N., Mostany, R., Pazos, A., Florez, J. & Martinez-Cue, C. (2005). Cell proliferation is reduced in the dentate gyrus of aged but not young Ts65Dn mice, a model of Down syndrome. *Neurosci Lett*, Vol. 380, No. 1-2, pp. 197-201.
- Sandoval, C.J., Martinez-Claros, M., Bello-Medina, P.C., Perez, O. & Ramirez-Amaya, V. (2011). When are new hippocampal neurons, born in the adult brain, integrated into the network that processes spatial information? *PLoS One*, Vol. 6, No. 3, pp. e17689.

- Saxe, M.D., Battaglia, F., Wang, J.W., Malleret, G., David, D.J., Monckton, J.E., Garcia, A.D., Sofroniew, M.V., Kandel, E.R., Santarelli, L., Hen, R. & Drew, M.R. (2006). Ablation of hippocampal neurogenesis impairs contextual fear conditioning and synaptic plasticity in the dentate gyrus. *Proc Natl Acad Sci U S A*, Vol. 103, No. 46, pp. 17501-17506.
- Seki, T., Namba, T., Mochizuki, H. & Onodera, M. (2007). Clustering, migration, and neurite formation of neural precursor cells in the adult rat hippocampus. *J Comp Neurol*, Vol. 502, No. 2, pp. 275-290.
- Shors, T.J., Townsend, D.A., Zhao, M., Kozorovitskiy, Y. & Gould, E. (2002). Neurogenesis may relate to some but not all types of hippocampal-dependent learning. *Hippocampus*, Vol. 12, No. 5, pp. 578-584.
- Siarey, R.J., Stoll, J., Rapoport, S.I. & Galdzicki, Z. (1997). Altered long-term potentiation in the young and old Ts65Dn mouse, a model for Down Syndrome. *Neuropharmacology*, Vol. 36, No. 11-12, pp. 1549-1554.
- Singer, B.H., Gamelli, A.E., Fuller, C.L., Temme, S.J., Parent, J.M. & Murphy, G.G. (2011). Compensatory network changes in the dentate gyrus restore long-term potentiation following ablation of neurogenesis in young-adult mice. *Proc Natl Acad Sci U S A*, Vol. 108, No. 13, pp. 5437-5442.
- Snyder, J.S., Kee, N. & Wojtowicz, J.M. (2001). Effects of adult neurogenesis on synaptic plasticity in the rat dentate gyrus. *J Neurophysiol*, Vol. 85, No. 6, pp. 2423-2431.
- van Praag, H., Christie, B.R., Sejnowski, T.J. & Gage, F.H. (1999). Running enhances neurogenesis, learning, and long-term potentiation in mice. *Proc Natl Acad Sci U S A*, Vol. 96, No. 23, pp. 13427-13431.
- Voloboueva, L.A., Lee, S.W., Emery, J.F., Palmer, T.D. & Giffard, R.G. (2010). Mitochondrial protection attenuates inflammation-induced impairment of neurogenesis in vitro and in vivo. *J Neurosci*, Vol. 30, No. 37, pp. 12242-12251.
- Wang, S., Scott, B.W. & Wojtowicz, J.M. (2000). Heterogenous properties of dentate granule neurons in the adult rat. *J Neurobiol*, Vol. 42, No. 2, pp. 248-257.
- Wegiel, J., Kuchna, I., Nowicki, K., Imaki, H., Marchi, E., Ma, S.Y., Chauhan, A., Chauhan, V., Bobrowicz, T.W., de Leon, M., Louis, L.A., Cohen, I.L., London, E., Brown, W.T. & Wisniewski, T. (2010). The neuropathology of autism: defects of neurogenesis and neuronal migration, and dysplastic changes. *Acta Neuropathol*, Vol. 119, No. 6, pp. 755-770.
- Winner, B., Kohl, Z. & Gage, F.H. (2011). Neurodegenerative disease and adult neurogenesis. *Eur J Neurosci*, Vol. 33, No. 6, pp. 1139-1151.
- Wisniewski, K.E., Laure-Kamionowska, M. & Wisniewski, H.M. (1984). Evidence of arrest of neurogenesis and synaptogenesis in brains of patients with Down's syndrome. *N Engl J Med*, Vol. 311, No. 18, pp. 1187-1188.
- Witter, M.P., Wouterlood, F.G., Naber, P.A. & Van Haeften, T. (2000). Anatomical organization of the parahippocampal-hippocampal network. *Ann N Y Acad Sci*, Vol. 911, No., pp. 1-24.
- Yoneyama, M., Shiba, T., Hasebe, S. & Ogita, K. (2011). Adult Neurogenesis Is Regulated by Endogenous Factors Produced During Neurodegeneration. *J Pharmacol Sci*, Vol. No., pp. 1-8.

Yu, Y., He, J., Zhang, Y., Luo, H., Zhu, S., Yang, Y., Zhao, T., Wu, J., Huang, Y., Kong, J., Tan, Q. & Li, X.M. (2009). Increased hippocampal neurogenesis in the progressive stage of Alzheimer's disease phenotype in an APP/PS1 double transgenic mouse model. *Hippocampus*, Vol. 19, No. 12, pp. 1247-1253.

IntechOpen

IntechOpen



Genetics and Etiology of Down Syndrome

Edited by Prof. Subrata Dey

ISBN 978-953-307-631-7

Hard cover, 328 pages

Publisher InTech

Published online 29, August, 2011

Published in print edition August, 2011

This book provides a concise yet comprehensive source of current information on Down syndrome. Research workers, scientists, medical graduates and paediatricians will find it an excellent source for reference and review. This book has been divided into four sections, beginning with the Genetics and Etiology and ending with Prenatal Diagnosis and Screening. Inside, you will find state-of-the-art information on: 1. Genetics and Etiology 2. Down syndrome Model 3. Neurologic, Urologic, Dental & Allergic disorders 4. Prenatal Diagnosis and Screening Whilst aimed primarily at research workers on Down syndrome, we hope that the appeal of this book will extend beyond the narrow confines of academic interest and be of interest to a wider audience, especially parents and relatives of Down syndrome patients.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Pavel V. Belichenko and Alexander M. Kleschevnikov (2011). Deficiency of Adult Neurogenesis in the Ts65Dn Mouse Model of Down Syndrome, *Genetics and Etiology of Down Syndrome*, Prof. Subrata Dey (Ed.), ISBN: 978-953-307-631-7, InTech, Available from: <http://www.intechopen.com/books/genetics-and-etiology-of-down-syndrome/deficiency-of-adult-neurogenesis-in-the-ts65dn-mouse-model-of-down-syndrome>

INTECH
open science | open minds

InTech Europe

University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2011 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the [Creative Commons Attribution-NonCommercial-ShareAlike-3.0 License](#), which permits use, distribution and reproduction for non-commercial purposes, provided the original is properly cited and derivative works building on this content are distributed under the same license.

IntechOpen

IntechOpen