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Chapter 5

Dentate Gyrus Variation along Its Septo-Temporal Axis: Structure and Function in Health and Disease

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Abstract

A bulk of evidence currently suggests that hippocampal formation is a heterogeneous brain structure. Most recent studies recognize a hippocampal pole (dorsal/septal or posterior in humans) which is primarily related with memory and learning processes, and another one (ventral/temporal or anterior in humans) which is linked with anxiety, affective or emotional processes. An intermediate region separating the two poles appears to have overlapping characteristics with its neighbors.

The present chapter summarizes previously reported differences between septal and temporal dentate gyrus, a key component of the hippocampal circuitry, and provides new information on the segmental variation of the dentate gyrus.

Data on the cellular (neuronal and glial) composition of the dentate gyrus are linked with the diverged embryonic origin and continuous cell generation capacity of the septal and temporal poles, septo-temporal molecular/genomic patterns are correlated with trends reported by connectivity (tracing) studies, and distinct characteristics of the two poles in the healthy and the diseased brain are examined together with their peculiar neurochemical and vascularization patterns in order to i. provide an explanatory framework for the understanding of the segmental hippocampal functional and behavioral specialization, and ii. highlight the need for thorough and detailed knowledge of all possible parameters which may allow unlocking of the hippocampal dysfunction.

Introduction

Hippocampal formation, a complex brain structure with a long-established role in certain forms of memory, has been proved to be among the most extensively studied neural structures, especially in the rat brain. However, most of the studies have been and still are conducted on the septal/dorsal portion of this structure. Contemporary knowledge calls for careful re-examination of this practice.

Early neuroanatomical and electrophysiological data (Andersen et al., 1971) suggested that the major excitatory pathways of the hippocampus are oriented perpendicular to its long axis and exhibit limited septo-temporal spread. Therefore, hippocampal formation was largely conceived as a structure containing a series of repeated lamellae i.e., independent processing chips. Valid or not (see Andersen et al., 2000; Witter and Amaral, 2004), this view was progressively enriched with information documenting a number of differences in neuronal constitution, connectivity, gene expression, vascularization, function and dysfunction susceptibility across the longitudinal and transverse hippocampal planes. Since these differences appear to be evolutionary conserved (Colombo et al., 1998; Moser and Moser, 1998a; Small et al., 2001; Bannerman et al., 2002), it is now widely accepted that the hippocampal formation may exhibit graded or discontinuous differentiation and the dorsal/septal hippocampal pole (posterior in humans) is currently primarily related with memory and learning processes, while the ventral/temporal (anterior in humans) is linked with anxiety, affective or emotional processes. An intermediate region separating the two poles is considered to have overlapping characteristics with its neighbors.

Dentate gyrus is situated in a strategic position and is physiologically predisposed to shape and influence the spectrum of hippocampal functions. Receiving its afferent inputs from only one cortical area, the entorhinal cortex, and a limited number of subcortical regions (septal nuclei, supramammillary region of the posterior hypothalamus and monoaminergic nuclei of the brainstem), and giving rise to no extrinsic projections other than the mossy fiber projection to the CA3 hippocampal field, has been proposed to function as a gate or filter at the entrance of the hippocampus (Andersen et al.,1966; Hsu, 2007). Therefore, structural and functional segregation of the dentate gyrus along its septo-temporal or the transverse axis may be crucial factors contributing to hippocampal heterogeneity in health and disease.

The present chapter presents previously reported data as well new unpublished information on the structural and functional segmental variation of the rodent dentate gyrus. Knowledge on the varied cellular composition, embryonic origin and persisting neurogenesis, genomic and chemical anatomy, connectivity, vascularization, electrophysiology, function and dysfunction of the septal and temporal part of the developing and adult dentate gyrus is presented in order to facilitate thorough understanding of the functioning healthy hippocampus and stimulate insightful handling of the malfunctioning hippocampus.

Morphology and Cellular Composition

The dentate gyrus (DG) consists of three cell layers, molecular (ML), granule (GCL) and polymorphic (PL) or hilus, and exhibits three regions: the suprapyramidal blade (dorsal or lateral portion), the infrapyramidal blade (ventral or medial portion) and the crest, the

connecting portion between the suprapyramidal and the infrapyramidal blade. The shape of the DG is varied along its septo-temporal axis. The septal two thirds of the gyrus appear as a V- shaped structure and the crest is prominent. Moving gradually to the temporal third, it becomes progressively U-shaped. At the temporal pole, it is almost semicircular and the crest becomes indistinguishable.

Morphological and structural variations of the GCL and the mossy fibers along the septo-temporal axis have been described in details by Gaarskjaer (1978 a, b). He showed that the length of the GCL is greatest septally, while the length of the mossy fibers is greatest temporally. Variations were also described in the length of the two blades, with the infrapyramidal blade to be almost unchanged along the septal part, but to be largely decreased in the temporal part and reach a zero value at the temporal end. The length of the suprapyramidal blade progressively increases and reaches a maximal value at the halfway of the septal part, but moving further temporally, it reduces moderately. In the intermediate part of the DG, the two blades show roughly the same length. Our unpublished observations on the thickness of the two blades along the longitudinal axis show that, in the septal part, the suprapyramidal blade is significantly (P= 0.020) thicker (61.234±1.396 μm) than the infrapyramidal one (56.43±1.445 μm), in contrast to what happens in the temporal part, where, the infrapyramidal blade tends to be thicker, although not statistically significant, compared to the suprapyramidal blade. Measurements of the thickness of the GCL show that it remains the same (P=0.124) along the longitudinal axis (mean granule layer diameter in septal part: 58.832±1.048 μm; temporal part: 56.262±1.284 μm).

Measurements of the length of the mossy fibers (they travel throughout most of the transverse extent of the CA3 field), showed that it increases continuously from the septal end up to the levels of the intermediate part, where, it obtains its peak value, and it reduces thereafter (Gaarskjaer, 1978a,b). The ratio between the length of the mossy fibers and the GCL is low at the septal end, but gradually increases moving to the temporal end, where it becomes about two times greater compared to that at the septal end. Variations along the septo-temporal axis have also been described for the direction of the mossy fibers of granule cells. Granule cells located at septal levels give rise to mossy fibers which remain at approximately the same septo-temporal level as the cells of origin (Gaarskjaer 1978 a,b; Swanson et al., 1978; Claiborne et al., 1986; Acsady et al., 1998). At CA3/CA2 border, however, the mossy fibers make an abrupt turn temporally and extend for about 1mm or more towards the temporal pole. In actual fact, the extent of this longitudinal component depends on locations of the cells of origin along the septo-temporal dentate axis (Amaral and Witter, 1989) and/or the location of cells in the different regions of the DG. Thus, at septal levels, the larger extension of the mossy fibers was measured in granule cells situated in the crest of the DG, whereas, mossy fibers originating in the tip of the suprapyramidal blade had the shortest septal route and they terminated most caudally (Acsady et al., 1998). Gaarskjaer (1978b) showed that axons coming from the suprapyramidal blade have a longer course, as they deviate more temporally, than those originating in the infrapyramidal blade. Mossy fibers originating in the middle levels of the temporal part exhibit only a slight inclination at their distal extremity and those originating from cells located at the temporalmost part barely extend to CA3/CA2 border and they have little or no longitudinal component (Amaral et al., 2007).

Granule Cells

Granule cells, together with the hillar mossy cells, are the principal cells of the DG. They have an elliptical cell body (short axis: 7-10 μm, long axis: 10-18 μm,) and a characteristic cone-shaped tree of spiny apical dendrites (Claiborne et al., 1990; Amaral and Witter, 1995). According to our unpublished findings the granule cells retain the same elliptical shape throughout the DG, as the ratio of long to short axis of the cell does not show differences either between the blades or between the septal and the temporal parts. The mean cell area of the granule cells (Figure 1) is larger (although not significantly, P=0.053) in the temporal part (39.116±1.354 μm^2) than in the septal one (36.013±0.91 μm^2).

Statistically significant differences (P<0.0001) in the mean cell area also exist between the two blades of the temporal DG, with the suprapyramidal blade to contain larger cells (45.663±1.792 μm^2) than the infrapyramidal one (34.994±1.417 μm^2). In contrast, there are no statistical differences in the mean cell area between the two blades of the septal DG part (suprapyramidal blade: 36.947±1.021 μm^2; infrapyramidal blade: 35.08±1.51 μm^2).

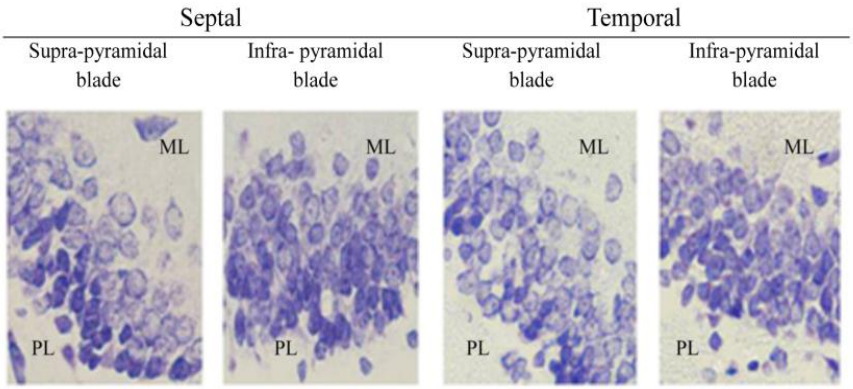
The granule cell bodies are closely spaced together, and very often there is no glial sheath between them. Our unpublished results (Figure 1) show that the mean distance between the granule cells (also referred to as margination) is significantly (P=0.037) greater (0.352±0.001 μm) in the temporal part than that in the septal one (0.349±0.000864 μm). Additionally, comparison of this parameter in the two blades of the septal and the temporal part showed statistically significant differences (P=0.038) only in the temporal part: mean distance in the infrapyramidal blade show greater value (0.354±0.002 μm) than in the suprapyramidal blade (0.350±0.001 μm).

The total number of the dentate granule cells in the rat has been reported to be 635000±33000 (West et al., 1991; Rapp and Gallagher, 1996), with their packing density to vary along the septo-temporal axis, and to be higher septally than temporally (Gaarskjaer, 1978b; Seress and Pokorny, 1981).

According to our unpublished quantifications (Figure 1), the total granule cells number is significantly higher (P<0.001) in the septal part (436313.33±14712.97) than in the temporal one (125826.67±20353.73). Additional measurements of the absolute numbers of the granule cell populations in the supra- and the infra-pyramidal blade, at both the septal and temporal parts of the DG, did not show significant differences between the two blades (septal suprapyramidal blade: 237740±12224.25 cells; septal infrapyramidal blade: 198573±5276.39 cells; temporal suprapyramidal blade: 93500±4278.23 cells; temporal infrapyramidal blade: 72020±3532.16 cells). Statistical analysis of the mean areal density did not show differences (P=0.829) between the septal (112.322±1.196 μm^2) and the temporal part (113.017±3.006 μm^2), but revealed statistically significant differences between the two blades in both the septal part (P=0.007; suprapyramidal blade: 115.483±1.832 μm^2; infrapyramidal blade 109.16±1.305 μm^2) and the temporal part (P=0.010; suprapyramidal blade: 120.513±4.180 μm^2; infrapyramidal blade 105.233±3.834 μm^2).

The number of the dendritic branches of the granule cells is highly variable along the longitudinal axis. Moreover, granule cells located in the suprapyramidal blade have larger dendritic trees (greater total dendritic length: 3500 μm, more dendritic segments, greater transverse spread) than those of cells in the infrapyramidal blade (total dendritic length: 2800 μm) (Desmond and Levy, 1982, 1985; Claiborne et al., 1986). The dendrites of the granule cells are heavily studded with spines. The spine density (number spines/μm) increases

gradually in more distal dendrites and there are slightly more spines in the suprapyramidal blade than in the infrapyramidal one (suprapyramidal blade: 1.6 spines/μm; infrapyramidal blade: 1.3 spines/μm) (Desmond and Levy, 1982, 1985; Hama et al., 1989) in both the septal and temporal part.



Total granule cell number (N^{o} of cells)	237,740±12,224.25*	198,573±5,276.39**	93,500±4,278.23*	72,020±3,532.16**	*'**P<0.001
Mean cell area (μm^{2})	36.947±1.021	35.08±1.51	45.663±1.792*	34.994±1.417*	*P<0.0001
Mean margination (μm)	0.34 ±0.001	0.349±0.000971	0.350±0.001*	0.354±0.002*	*P<0.05
Mean areal density (μm^{2})	109.16±1.305*	115.483±1.832*	105.233±3.834**	120.513±4.180**	*P<0.01 **P<0.05

Figure 1. Granule cells of the supra- and infra-pyramidal blade of the septal and temporal DG.

Mossy Cells

The hilar mossy cells receive excitatory synapses from mossy fiber collaterals (Ribak et al., 1985; Amaral and Witter, 1995; Scharfman, 1995; Buckmaster et al., 1996) and they form with the granule cells a recurrent excitatory circuit (Buckmaster et al., 1996). The number of the hilar mossy cells increases significantly from the septal part to the middle levels of the temporal part, where it reaches its peak value, and it declines towards the temporal end, to about half of the maximal value (Gaarskjaer,1978a,b). Similarly, the numerical density of the mouse hilar mossy cells was found significantly ($P < 0.05$) higher in the temporal levels than at the septal ones (Fujise and Kosaka, 1999). The cells of the hilus in the temporal part appear smallerand more circular than those of the septal part, with the nuclear-cytoplasmic ratio to be increased (Gaarskjaer, 1978a,b).

Interneurons

While there is an ever growing literature on morphological, physiological and biochemical characteristics of the interneurons of the DG, there is limited knowledge concerning possible numerical or structural variations of interneurons along the septo-temporal axis. Seress and Pokorny (1981) quantitative estimates of the granule cells and the pyramidal basket cells (they are located especially along the interface between the granule cell layer and the hilus) revealed great regional differences in both the longitudinal and the transverse axis of the gyrus. More specifically, at septal levels, the ratio of basket cells to granule cells is 1:100 in the suprapyramidal blade and 1:180 in the infrapyramidal blade. At temporal levels, the number is 1:150 for the suprapyramidal blade and 1:300 for the infrapyramidal blade.

Astrocytes

In the DG, astrocytes are of protoplasmic type and they are traditionally classified into six subtypes, with particular structural features and position of their cell bodies (Kosaka and Hama, 1986). Ogata and Kosaka (2002) and Jinno (2011) reported a temporo-septal gradient of astrocytes in the mouse DG. On the other hand, Grivas (2006) reported a septo-temporal gradient of GFAPimmunoreactive elements in the rat DG, though not statistically significant. In more detail, Ogata and Kosaka (2002) reported statistically significant higher astrocyte numerical densities in the temporal part of all DG subfields, compared to the septal part, and Jinno (2011) reported statistically significant higher astrocyte numerical densities in temporal GCL and ML and slightly decreased in PL, compared to the septal part. Finally, Grivas (2006) reported statistically significant higher density of GFAPimmunoreactive elements in septal GCL and PL and temporal ML, compared to the opposed hippocampal pole. In addition, Ogata and Kosaka (2002) reported wider astrocytic projection areas in septal ML and temporal PL, compared to the opposed hippocampal pole.

The discrepancies emerging from the three studies may be attributed to species differences and to methodological particularities i.e., Grivas (2006) counted GFAP immunoreactive cellular elements, not cells, Ogata and Kosaka (2002) counted numerical densities of S100 immunoreactive astrocytes, and Jinno (2011) counted astrocytes expressing immunoreactivity for one or both GFAP and S100, but excluded from analysis cells in the subgranular zone (SGZ), because there GFAP is expressed in stem cells as well.

Higher density of astrocytic processes in the rat septal GCL and PL correlates with higher capillary density, confirming the close relationship and perhaps parallel development of astrocytes and capillaries and possibly reflecting increased neuronal activity (Piatti et al., 2011) and adult neurogenesis (Jinno, 2010; Snyder et al., 2009a;b; Bekiari et al., unpublished data).

Microglial cells in the DG, comprising a heterogeneous population, received particular interest, especially because of their involvement in the process of "microglia-associated granule cell death" (Kempermann et al., 2003; Zhao et al., 2006; Jinno et al., 2007; Shapiro et al., 2007, 2008; Toni et al., 2007, 2008). They are randomly arranged in the PL and the ML, but are clearly concentrated in the ML and the PL borders of the GCL (Dalmau et al., 1998; Wirenfeldt et al., 2003; Moga et al., 2005; Jinno et al., 2007; Shapiro et al., 2009), throughout

the DG. It has been emphasized that microglial cells adjacent and within the granule cell layer have various morphologies, probably because they represent different stages in the death sequence of associated/targeted granule cells (Ribak et al., 2009). While there are several studies on the morphology and the distribution of microglial cells in the dentate gyrus, studies examining possible septo-temporal variations of these characteristics are limited to that of Jinno et al. (2007) which shows no significant differences between the numerical densities of microglial cells in the septal and the temporal dentate part.

Perineuronal Net

The perineuronal net (specialized aggregate of the extracellular matrix) is considered to be implicated in the regulation of structural plasticity of neuronal circuits (Wang and Fawcett, 2012). A study on the perineuronal net expression in the developing and adult mouse hippocampus, revealed that while the intensity of Wisteria floribunda agglutinin-labeled perineuronal net in the young mice is low and there are no significant septo-temporal differences, there is a continuous increase in intensity, throughout development and aging mainly in the septal DG (Yamada and Jinno, 2013). This differential expression in the septal and temporal dentate circuits during development and aging may be indicative of a variable role in the cognition and emotion control.

Developmental and Adult Cytogenesis

Cytogenesis in the DG is an extremely complex and long lasting process, occurring from the late embryonic days (E16), when proliferation of the neural stem cells (NSCs) of the primary dentate neuroepithelium is triggered, to the first postnatal weeks (Schlessinger et al., 1975; Bayer, 1980; Altman and Bayer, 1990). Early autoradiographic studies have revealed the pattern and time plan embryonic NSCs follow in order to form the DG and the hippocampal formation as a whole (Schlessinger et al., 1975; Altman and Bayer, 1990). Ammon's horn, DG and fimbria originate from three areas of the hippocampal neuroepithelial lining of the lateral ventricle, called, respectively, Ammonic and primary dentate neuroepithelium, and fimbrial glioepithelium (Altman and Bayer, 1990).

During DG neurogenesis, significant differences in migration time and distribution pattern between each layer's (PL, GCL, ML) neural stem and progenitor cells are observed. The PL is the first to be formed, mainly during E15-E17, followed by the development of the ML, whose cells in their majority are added prenatally, during E15-E19 (Bayer, 1980), but continue to proliferate during the first postnatal week (Schlessinger et al., 1975). The GCL is the last to be generated, with the greater portion of its granule cell population (almost 80%) being produced postnatally (Bayer, 1980).

Morphogenesis of the GCL follows a mode different from that seen during development of the other DG layers. Whereas cells migrating to the PL and ML are added in a "deep to superficial" mode, a pattern seen during formation of almost all cerebral structures including the Ammon's horn pyramidal layer (Altman and Bayer, 1990), cytogenesis in the GCL follows the reversed pattern. The outer parts of the GCL, close to the ML, are formed prior to

the inner part that outline the PL (Altman and Das, 1965; Schlessinger et al., 1975; Bayer, 1980).

During the late gestational days, embryonic NSCs of the dentate neuroepithelium start to proliferate, and by E18, subventricular aggregations of newly formed progenitor cells have been created. Newborn cells start to migrate through the developing fimbria to the area of the dentate primordium, forming the dentate migratory stream (Altman and Bayer, 1990). Interestingly, on E22, only a small amount of proliferative cells is still found in the subventricular dentate zone and the migrating stream, and from this time point and on, dentate granule cell genesis occurs mainly within the PL, in a proliferative zone persisting at the tip of the migrating stream, progressively extending beneath the expanding GCL, forming a new germinal zone, the SGZ (Schlessinger et al., 1975; Altman and Bayer, 1990). Newly formed granule cells migrate radially from the proliferative SGZ to the GCL in order to form the GCL in its full extent (Bayer, 1980).

Existing literature provides evidence for two populations of migrating granule cell progenitors of common origin, distinguished however by their distinct date birth, migration pattern and distribution in the dentate primordium (Schlessinger et al., 1975; Altman and Bayer, 1990). Proliferating cells of the first dentate migration, born during the last embryonic days, move to the crest of the DG, and are progressively added in the primordium of the GCL in a "superficial to deep" way, as from the outer to the inner layers (Schlessinger et al., 1975; Bayer, 1980; Altman and Bayer, 1990). Proliferative cells of the second dentate migration on the other hand, are evident during the first postnatal days, moving in a stream beneath the Ammon's horn pyramidal layer and above the developing infrapyramidal blade, colonizing the PL's proliferative zone (Schlessinger et al., 1975; Bayer, 1980; Altman and Bayer, 1990). Although proliferative cells of the first dentate migration originate from neuroepithelial embryonic NSCs of the equivalent longitudinal level, recent evidence suggests that NSCs giving rise to the second migration stream are located mostly in the temporal level of the subventricular dentate zone, spreading in the temporo-septal direction (Li et al., 2013).

Granule cells, originating from the first dentate migration, are added primarily in the suprapyramidal blade, whereas progenies of the second migration are distributed in the infrapyramidal blade (Schlessinger et al., 1975; Bayer, 1980; Altman and Bayer, 1990; Sugiyama et al., 2013). At the end of the first postnatal week, however, no differences are seen in maturity of granule cells and extent of the two DG blades (Bayer, 1980).

In addition to the observed developmental differentiations along DG transverse axis, autoradiography reveals that inconsistencies are evident along the septo-temporal axis as well. An "edge to center" gradient is evident during formation of the DG along its septo-temporal axis, and granule cells destined for the septal and temporal extremities appear to be added earlier than cells of the middle DG part (Bayer, 1980). More interestingly, granule cells of the temporal DG are shown to originate from progenitor cells of the first dentate migration, in contrast to residents of the septal DG which are added at later time points (Schlessinger et al., 1975; Bayer, 1980).

Transcription factor analyses further support autoradiographic findings and provide new insight for the identity of the proliferating cells found in the sequential stages of the DG cell genesis process. Proliferating cells of the dentate neuroepithelium and of the dentate migration stream were shown to be positive for the transcription factor Sox2, whereas Prox1 expression was restricted in the proliferative PL's zone and the subsequent SGZ (Sugiyama et al., 2013; Seki et al., 2014). Considering that Sox2 is a reliable marker of embryonic NSCs,

essential for maintenance of their self-renewal and neurogenic ability (Thiel, 2013), and Prox1 is a postmitotic factor, required for granule cells maturation and cell fate determination (Lavado et al., 2010; Iwano et al., 2012), it can be concluded that differentiation and maturation of newborn granule cells occur strictly within the proliferative PL's zone, the SGZ and the extending GCL, and that proliferative cells migrating there are purely embryonic NSCs.

The SGZ preserves the characteristics of a germinative niche (rich vasculature, increased astrocytic and microglial content, close contact with the basal membrane) all through adulthood, creating a microenvironment permissive for the ongoing activity of the residing NSCs (Kempermann, 2011).

Neural stem cells of the adult SGZ exhibit the characteristic morphology of radial glia and have astrocytic properties (Kempermann et al., 2004; Seri et al., 2004). They retain their ability for self-renewal and multipotency, thus being able for continuous generation of new neurons and astrocytes, through intermediate precursor cells of the neurogenic or astrogliogenic lineage, and at the same time replenish their initial population (Bonaguidi et al., 2011). Newly formed astrocytes reside in the upper GCL next to the molecular layer and in the border between the SGZ and the polymorphic layer (Encinas et al., 2011), further promoting local microenvironment's permissiveness for the parallel neurogenesis process (Seri et al., 2004; Morrens et al., 2012). Gliogenesis is progressing all along DG septo-temporal axis, although at significantly lower levels than neurogenesis (Encinas et al., 2011).

Neuronal precursor cells (NPCs), after a complex proliferation and differentiation process, give rise to new immature neurons, that migrate radially from the neurogenic SGZ to the inner parts of the GCL, further maturing to functional granule cells that are undistinguished from older granule cells, being fully integrated into the local neuronal circuits (Kempermann, 2011). Stage-specific marker expression and distinct morphological characteristics of newborn neurons during their genesis and subsequent maturation process allow precise examination of their time-course and fate (Kempermann et al., 2004; Duan et al., 2008; von Bohlen und Halbach, 2011).

Nowadays, accumulating evidence suggests that known heterogeneities along the DG septo-temporal axis may be accompanied by an uneven granular cell genesis. A higher number of newborn granule cells found in the septal DG was interpreated as a clear sign for heterogeneous distribution along DG septo-temporal axis (Snyder et al., 2009a,b; Jinno, 2010). However, a parallel stereological analysis of the newborn and total granule cell populations of the two dentate parts, revealed equal ratios of newborn to pre-existing granule cells, suggesting that the septal and temporal DG parts possess an equivalent neurogenic ability (Bekiari et al., unpublished data).

Despite their similar neurogenic potential, the two dentate parts appear to differentially orchestrate the ongoing process. Continuous need of the septal DG for new functional granule cells, contributing to the spatial pattern separation process (Aimone et al., 2010), appears to urge the local proliferative cells for comparatively higher division rates (Bekiari et al., unpublished data). Additionally, septal's DG high network activity, seems to enhance maturation and functional integration rates of newly formed neurons, as assessed by immunoreactivity to mature neuronal markers (Snyder et al., 2012), glutamate synaptogenesis (Bekiari et al., unpublished data), intrinsic electrical activity recordings (Piatti et al., 2011) and activity-dependent immediate early genes expression (Piatti et al., 2011; Snyder et al., 2012). Temporal DG, on the other hand, is shown to preserve a disciplined division rate of the

local radial glia-like NSCs, highly maintaining their initial population, and achieving a balance between the number of newly generated granule cells and their gradual accession into the local circuits (Bekiari et al., unpublished data).

Apart from the above described effect of septo-temporal position on progression of the multi-staged neurogenesis process, recent findings point to an additional region-specific effect on distinct functional role of the adult born granule cells. Whereas new neurons of the septal DG appear to contribute in certain aspects of the spatial learning process, immature neurons of the temporal DG were involved in anxiolytic-related effect of chronic antidepressant treatment (Wu and Hen, 2014), consistent with the functional dissociation of the two hippocampal parts (Bannerman et al., 2004). However, both septal and temporal newborn neurons were found to be capable for synergistic action in more demanding situations (Wu and Hen, 2014).

Septo-temporal variations were also evident between neurogenesis in the supra- and infra-pyramidal blade. Although the two DG blades display equal ability for new cells genesis all along the septal and temporal DG axis (Snyder et al., 2012), supra-pyramidal blade accomplished higher newborn neurons survival rates, as mainly seen in the temporal DG (Bekiari et al., unpublished data).

Genomic/Molecular Anatomy

Recently developed molecular approaches reveal a variety of genes that are differentially expressed in the two DG parts, distinguishing each part's cellular and functional properties. A total of 229 genes appear to be selectively enriched in either the septal or the temporal DG (Christensen et al., 2010). Histidine decarboxylase (HDC), which catalyzes the synthesis of histamine from histidine, and cocaine and amphetamine regulated transcript (Cart) were shown to be enriched in the septal DG (Christensen et al., 2010). Both genes seem to contribute to septal DG's distinct functionality: histamine is crucial for the formation and integration of the reference, working and spatial memory (Dere et al., 2003; Xu et al., 2009), whereas Cart is involved in the reward process (Christensen et al., 2010).

Granule cells of the septal DG are capable for inducing higher magnitudes of LTP (Maggio and Segal, 2007), compatible with the increased encoding of the 5-nucleotidase (Nt5) gene, which is proposed to be an accurate indicator of plastic synapses in the adult brain (Lie et al., 1999). On the contrary, enrichment of the somatostatin receptor 1 (Sstr1) gene in the temporal DG granule cells (Christensen et al., 2010), is suggested to be responsible for their reduced ability for LTP induction, since somatostatin reduces Ca(2+) levels in their dendritic terminals, inhibiting LTP onset (Baratta et al., 2002).

Apart from the enhanced ability for LTP induction, septal DG microenvironment appears to display higher levels of basal local network electrical activity, as compared to the temporal DG (Piatti et al., 2011), leading to high level expression of genes related to cellular biosynthesis and metabolism (Christensen et al., 2010). The essential components of the extracellular matrix Timp2 and decorin transcripts, also shown to be involved in cell cycle regulation (Kishioka et al., 2008; Benet et al., 2012), were found to be highly expressed in the temporal DG (Leonardo et al., 2006; Christensen et al., 2010). They possibly enhance

neurotrophin signaling through inhibition of the transforming growth factor-β (TGF-β) superfamily cytokines action (Sometani et al., 2001).

However, regional expression of another gene, the thyrotropin releasing hormone (Trhr) encoding gene, implicated in cognitive and spatial memory function (Horita et al., 1989; Horita, 1998), is not so clearly defined. Thompson et al. (2008) and Fanselow and Dong (2010) showed that Trhr expression preferentially persists in the temporal DG, whereas Christensen et al. (2010) revealed increased levels of Trhr in the septal DG. In another study, Trhr is shown to be increased during water maze performance both in the septal and temporal DG (Aguilar-Valles et al., 2007), implying that the temporal hippocampal part is also involved in the spatial memory formation process, possibly explaining the observed Trhr expression all along DG's septo-temporal axis.

Occurrence of a certain gene expression pattern all along DG's septo-temporal axis, engages DG with ability for neuroproliferation, and indicates that neurogenesis persisting in the DG during adulthood is strongly gene- regulated. Expression of the Prominin-1 and CD24 encoding genes, considered to be markers of the nestin-positive precursor cells (Walker et al., 2013) and of the differentiating newborn neurons (Belvindrah et al., 2002) respectively, although persisting all along DG's septo-temporal axis, is found to be greater in the temporal part (Christensen et al., 2010). An identical expression pattern is also evident for genes involved in different aspects of the cell differentiation and signal transduction process and for the serine/threonine kinase 23 gene (Christensen et al., 2010), whereas expression of the tyrosine kinase receptor EphA7 and the transforming growth factor-a (TGF-α) is preferentially greater in the septal DG (Leonardo et al., 2006; Christensen et al., 2010). Serine threonine kinase 23 is suggested to mediate actions of the TGF-β superfamily cytokines (Soderstrom et al., 1996), which are signaling molecules known to control neural stem/ progenitor cell proliferation in the adult brain (Wachs et al., 2006).

Eph's, on the other hand, are thought to guide dendritic extension and enhance their synaptic function during development (Clifford et al., 2014), and to play a role in the continuing remodeling of particular adult brain regions (Yamaguchi and Pasquale, 2004), helping the migration of the newborn cells (Rodger et al., 2012). Finally, TGF-α infusion is shown to increase nestin expression in the neuroproliferative zones, although its effect is mainly studied under pathological conditions (Alipanahzadeh et al., 2013).

More interestingly, many of the above described genes, apart from their distinct role in hippocampal plasticity and function, appear to be crucial determinants of the onset and outcome of severe CNS disorders. Research in septo-temporal involvement of the hippocampus in disease, point to a region-specific vulnerability, which, at least in part, appears to be gene-dependent. The posterior hippocampus is primarily affected in the Alzheimer's disease (Ball, 1978), and a decrease in HDC expression, shown to be essential for functionality of this part of the DG, was evident in affected brains (Shan et al., 2012). On the other hand, alterations in serotoninergic system's profile are involved in the biological basis of depression, temporal lobe epilepsy and efficacy of antidepressant drugs (Rahola, 2001; Martinez et al., 2013) and are known to severely impair temporal DG (Banasr et al., 2006; Tanti and Belzung, 2013b). In compliance with this, the serotonin receptor 3A (5-HT3AR) gene is preferentially expressed in the temporal DG. The temporal DG, also, shows a propensity for epileptic activity (Racine et al., 1977), and somatostatin, whose type 1 receptor gene is expressed in higher rates in the temporal DG (Christensen et al., 2010), is crucially involved in the pathophysiology of epilepsy. A reduction in the number of

somatostatin-positive interneurons in the PL leads to abnormal potentiation of granule cells contributing to epileptiform activity (Baratta et al., 2002). Finally, mutations in the Cyp7b encoding gene, shown to be selectively expressed in the septal DG (Thompson et al., 2008), cause a progressive neuropathy, called spastic paraplegia type 5 (Stiles et al., 2009).

Connectivity

The dentate gyrus is the gate through which the entorhinal cortex activates the hippocampal formation. Pyramidal cells of the entorhinal cortex project to granule cells (and to some extent, to CA3 pyramidal cells) via the perforant pathway. Granule cells, via their mossy fiber projection, organized in a lamellar fashion, terminate on CA3 pyramidal neurons, which send their Schaffer collaterals to the CA1 pyramidal cells. CA1 pyramidal neurons, in turn, project back to the entorhinal cortex, via the subiculum.

In addition to the entorhinal afferents, which are predominant, a number of other dentate afferents, such as those originating from the septum (Lewis and Shute, 1967; Segal and Landis, 1974a,b; Meibach and Siegel, 1977; Lynch et al., 1978; Alonso and Köhler, 1982; McKinney et al., 1983; Nyakas et al., 1987; Freund and Antal, 1988; Ohara et al., 2013), the supramammillary nucleus (Vertes, 1992; Ohara et al., 2013), the locus coeruleus (Loy et al., 1980) and the raphe nuclei (Moore and Halaris, 1975) have also been described.

Entorhinal, septal and supramammillary afferents are not homogeneously distributed along the longitudinal axis and show a topographical organization which is in line with physiological and behavioral septo-temporal differences (Gottlieb and Cowan, 1973; Steward, 1976; Hjorth-Simonsen and Laurberg, 1977; O'Leary et al., 1979; Wyss et al., 1979; Nyakas et al., 1987; Gaykema et al., 1990; Vertes et al., 1999).

Fibers of the entorhinal excitatory pathway terminate in the outer two-thirds of the ML, whereas commissural and associational excitatory projections terminate more proximal to the granule cell bodies in the inner third of the ML (Steward, 1976a,b). Additionally, granule cells also receive inputs from axons of several types of dentate local circuit neurons (Halasy and Somogyi, 1993; Han et al., 1993).

Entorhinal Afferents

Perforant path input to the DG has traditionally been regarded as the major pathway by which information is transferred. The entorhinal cortex, particularly in the rodents, is classically subdivided into the medial entorhinal area (MEA) and the lateral entorhinal area (LEA) according to cytoarchitectonic criteria (Krieg, 1946; Blackstad, 1956) and on the basis of the patterns of efferent projection (Hjorth-Simonsen and Jeune, 1972). Steward (1976) described the transition zone between the MEA and the LEA and defined it as the intermediate entorhinal area (IEA). The perforant fibers arise mainly from cells located in the layer II of the entorhinal cortex, although a minor component of the projection also comes from layers V and VI (Steward and Scoville, 1976; Deller et al., 1996). These fibers form the angular bundle, travel dorsally, perforate the pyramidal layer of the subiculum, along its long axis, and finally enter the DG and hippocampus. In addition to the entorhinal projections, the

DG receives minor projections originating in presubiculum and parasubiculum cortices (Köhler, 1985). The perforant path of the rat is composed of two distinct fiber systems (medial and lateral paths), originated from the MEA and the LEA respectively, as well as, an intermediate-transition path interposed between them (Hjorth-Simonsen and Jeune, 1972; Steward, 1976; Amaral et al., 2007). Fibers originating from the LEA terminate in the most superficial part of the ML, fibers from the MEA project to the middle third of the ML and the IEA fibers terminate between them. Fibers originating from the presubiculum and the parasubiculum also terminate in the ML between the lateral and the medial paths projections (Köhler, 1985). Afferents originating from neurons located in MEA terminate proximal to the granule cell soma, while, those originating from cells located in LEA terminate on more distal dendritic segments (Steward, 1976a,b).

Entorhinal projections to the dentate gyrus exhibit a striking organization pattern along the septo-temporal axis of the gyrus. In summary, the essential features of this pattern are as follows: the lateral and posterior parts of the entorhinal cortex project preferentially to the septal part of the DG, whereas, more medial and anterior parts of the entorhinal cortex project preferentially to more temporal parts of the DG (Steward, 1976a,b; Wyss 1981; Ruth et al., 1982,1988; Witter et al., 1989a,b; van Groen et al., 2003; Witter and Amaral, 2004; Ohara et al., 2013). Detailed studies, based on retrograde tracing experiments, with disctrete HRP injections in the septal, the intermediate and the temporal DG parts, lesions experiments (Ruth et al., 1982,1988) and/or the use of viral tracer (Ohara et al., 2013) examined the whole extent of the entorhinal cortex, including both the lateral and medial defined subdivisions along their antero-posterior extent, and demonstrated that: a. the septal part of the DG receives projections mainly from the dorsolateral and the ventrolateral parts of LEA and from the posteromedial, the extreme posterior and the posterolateral parts of both MEA and IEA; b. the temporal dentate part receives projections mostly from the posteromedial portion of the ventrolateral part of LEA, the posterior portion of the ventromedial part of LEA and from the anteromedial parts of both, MEA and IEA; c. in the intermediate dentate part there is a convergence of entorhinal afferents mainly from cells located in the ventral portion of the lateral part of LEA and the ventral and the anteromedial parts of IEA and, to a lesser extent, from MEA. It could be said that the dorsolateral-to-ventromedial axis of both lateral and medial subdivisions of the entorhinal cortex are mapped onto the septo-temporal axis of the D. Findings for widespread projections of the lateral entorhinal area along the dentate longitudinal axis (Segal and Landis, 1974; Wyss, 1981; Pohle and Ott, 1984) were attributed (Ruth et al., 1988) to methodological deficiencies of the studies. In addition, although it has been assumed that the majority of fibers originating from cells located in the layer II of entorhinal cortex branch off and project simultaneously to the suprapyramidal and the infrapyramidal blades (Tamamaki and Nojyo, 1993), it has been described a striking organization of these projections in the transverse axis of the gyrus, with the MEA to project preferentially to the infrapyramidal blade and the LEA to project mainly at the suprapyramidal blade, in both the septal and temporal dentate parts (Squire, 1992; Tamamaki, 1997). Evidence for septo-temporal differentiation of the sparse crossed/commissural entorhinal-DG fibers was given by Gottlieb and Cowan (1973), Goldowitz et al. (1975), Zimmer and Hjorth-Simonsen (1975), Steward and Scoville (1976), Wyss (1981), van Groen et al. (2003). The above authors showed that this contralateral projection is more prominent in the septal part of the DG and rapidly diminishes at more temporal levels. No crossed entorhinal projections to the DG have been observed in the mouse (van Groen et al., 2003).

Septal Afferents

Septal afferents originate mainly from the nuclei of the medial septum and the vertical diagonal band of Broca (Lewis and Shute, 1967; Meibach and Siegel, 1977; Lynch et al., 1978; McKinney et al., 1983; Nyakas et al., 1987)]. These fibers are largely cholinergic (type II fibers), but also GABAergic (type I fibers) (Leranth and Frotscher, 1987; Nyakas et al., 1987; Freund, 1989). GABAergic innervation is very dense in the PL and the subgranular layer, but it is considerably less in the supragranular region and the ML (Lynch et al., 1978; Chandler and Crutcher, 1983; Freund and Antal, 1988; Gulyas et al., 1991).

A dense plexus of choline acetyltransferase (ChAT) immunoreactive fibers, innervating granule cells and interneurons, is appeared in the interface between the GCL and the ML and in the PL, where they innervate mossy cells. An apparent topographical organization of the medial septum projections along the dentate longitudinal axis was revealed by using retrograde viral or WGA-HRP tracers (Ohara et al., 2013; Amaral and Kurz, 1985, respectively). More specifically, the septal part of the DG was found to receive fibers originating from neurons located in the medial non-cholinergic half of the medial septal nucleus, whereas the lateral half, in which the dorsal ChAT immunoreactive cell group is located, projects heavily to more temporal levels. It is recalled here that ChAT-positive cells of the septal complex are divided into dorsal, intermediate and ventral subdivisions (Amaral and Kurz, 1985).

Different findings were described by Nyakas and his colleagues (1987), who, employing the anterograde tracer phaseolus vulgaris leuco-agglutinin, showed that the septal part receives afferents almost exclusively from the vertical limb of the diagonal band of Broca, where the ventral ChAT cell group is its major component, whereas the temporal dentate part receives projections from both the vertical limb of the diagonal band of Broca and the medial septum nucleus.

Supramammillary Afferents

Supramammillary afferents terminate most heavily in the GCL and the immediately adjacent ML (Vertes, 1992; Ohara et al., 2013). The supramamillo-dentate projections show a clear topographical organization, with fibers originating from neurons located in the lateral part of the nucleus to project in the septal DG, and those arising from neurons positioned in the medial part to project in the temporal part. The supramamillo-dentate projections appear to be considerably denser in the septal part than the temporal one, with the suprapyramidal blade to receive twice as many projections than the infrapyramidal one, throughout the longitudinal axis (Wyss et al., 1979).

Catecholaminergic Afferents

Noradrenergic afferents of the DG originate entirely from the locus coeruleus. Noradrenaline (NA) exerts multiple effects in the DG, at both cellular and behavioral levels. It promotes and permits long-term perforant path potentiation (Lacaille and Harley, 1985; Stanton and Sarvey, 1985; Harley and Milway, 1986; Ezrokhi et al., 1999; Munro et al.,

2001), it plays a selective role in long-term memory (Walling and Harley, 2004), and its modulation could be part of a coordinated system to enhance behavioral adaptation to new circumstances (Bouret and Sara, 2004). Noradrenaline is considered to inhibit granule cells and excite presumed inhibitory interneurons (Brown et al., 1985; Pang and Rose, 1989; Rose and Pang, 1989), although the study of Harley (2007) showed that release of noradrenaline after locus coeruleus burst transiently inhibits feedforward interneurons and, either excites or inhibits subpopulations of feedback interneurons. The noradrenergic projection to the DG is bilateral (Wyss et al., 1979; Loy et al., 1980). Noradrenaline concentration is higher in the temporal levels than in septal ones (Gaze et al., 1978; Loy et al., 1980). However, the innervation pattern is roughly similar in the transverse axis of the gyrus, at all septo-temporal levels, with densest noradrenergic plexuses in the infragranular hilus of the DG (Loy et al., 1980).

In contrast to the very dense noradrenergic innervation, the DG receives only a minor and diffusely distributed dopaminergic projection. Dopaminergic fibers arise from neurons located in the ventral tegmental area and the substantia nigra pars compacta. Dopamine (DA) exerts a strong control of transmission in the perforant path (Otmakhova and Lisman, 1998), strongly depresses cholinergic effects in the CA3 field (Weiss et al., 2003) and probably plays a role in the selective retention of memory events before reward (Otmakhova and Lisman, 1998). DA fibers innervate homogeneously the suprapyramidal and the infrapyramidal blades of the gyrus, including the SGZ (Swanson, 1982; Gasbarri, 1994; Höglinger et al., 2014). In the SGZ, dopaminergic nerve terminals were found to contact proliferating cells (Höglinger et al., 2004), implying that DA may control adult neurogenesis. Studies on the distribution pattern of the dopaminergic fibers in the DG revealed that there is a topographical relationship between the neurons of origin and the termination regions. More specifically, DA fibers originating from neurons located in the ventral tegmental area project in both the septal and temporal part of the DG, with a slight preference for the temporal part (10-12% or 15-18% of the total VTA cell numbers give rise to fibers terminating in the septal or the temporal part respectively), whereas, fibers arising from neurons in the substantia nigra (15-18% of the total SN cell number) project only to the temporal part (Gasbarri et al., 1994). Contralateral dopaminergic projection, to both the septal and temporal part, has been found to originate only from DA neurons (in a percentage of approximately 10%) located in the ventral tegmental area and not in the substantia nigra (Gasbarri et al., 1994). It is worth noting that although the temporal part appears to receive denser DA innervation than the septal one, Mansour et al., (1992) revealed that the granule cells of the DG express D1 mRNA in septal but not in temporal levels.

Serotoninergic Afferents

Serotoninergic effect on the dentate gyrus depends on what subset of the serotoninergic receptors has been activated, meaning that neurons of the DG may be either depolarized by serotonin or hyperpolarized and inhibited (Djavadian, 2004). Dentate gyrus exhibits a very dense plexus of serotoninergic fibers in the ML and in the PL, especially in the SGZ, where, the fibers form synapses preferentially with interneurons (Halasy and Smogyi, 1993). These afferents are classified into two types, according to the nuclei of their origin (median or dorsal raphe nucleus), with different morphological characteristics and mechanisms of action. More

specifically, serotoninergic fibers originating from the median raphe nucleus (they constitute the vast majority) have axons of variable diameter with large, spherical varicosities and project especially to the GCL and the SGZ. The less numerous fibers, arising from the dorsal raphe nucleus, are very fine with small, granular or fusiform in shape varicosities and project mainly to the ML (Kosofsky and Molliver, 1987; Törk, 1990; Bjarkam et al., 2003).

Polymorphic layer, in general, receives a marked serotoninergic innervation, with numerous intermingled fine and beaded fibers, which form a dense plexus. Both types of fiber projections preferentially innervate the infrapyramidal blade and become less pronounced towards the suprapyramidal one. The above innervation pattern is present throughout the entire DG, but there are considerable septo-temporal differences in the innervation density, with the temporal part to exhibit high fiber density in contrast to the septal one, which receives only a moderate to weak serotoninergic innervation (Bjarkam et al., 2003).

Mossy Fibers

The main mossy fibers exhibit septo-temporal variations in the way they project to the CA3 pyramidal cell layer, terminating on the apical and in some cases the basal dendrites of the CA3 pyramidal neurons (Claiborne et al., 1986). More specifically, mossy fiber terminals (impregnated with Timm's method) enter deep into the CA3 pyramidal layer at septal levels, where the pyramidal layer is broad and its cells are relatively widely spaced between them. On the contrary, at temporal levels, where the pyramidal layer is narrower and the cells are tightly packed, the mossy fibers terminals preferentially terminate supra-pyramidally (Gaarskjaer, 1978a,b). Claiborne and colleagues (1986), applying intracellular HRP injections, observed that mossy fibers terminating in the superficial part of the pyramidal cell layer originate from granule cells located in the suprapyramidal blade, whereas those found in the middle and deep portion of the layer originate from cells in the infrapyramidal blade, in both the septal and temporal dentate parts. The detailed study of Gaarskjaer (1978a,b) for the organization of mossy fibers revealed that the ratio of the terminal field area of the mossy fiber system to the number of CA3 pyramidal neurons is four to five times greater in the septal part than in the temporal one. This occurs because the greatest number of granule cells is observed in septal levels, whereas the reverse is the case for the CA3 pyramidal cells (Gaarskjaer, 1978a,b). Septo-temporal variation has also been described for the supragranular projections of the mossy fiber pathway in the DG of normal and kindled rats (Cavazos et al., 1992). In normal rats, the mossy fibers project into the SGZ of the DG mainly in the temporal part and there is only a sparse projection into the same region at more septal levels (Haug, 1973,1974; Zimmer 1973, 1974; Cavazos et al., 1992). It is worth noting here that the temporal pole of the DG is more susceptible to kindling. In addition, there is considerable evidence that the synaptic connections of the mossy fiber pathway are reorganized in response to repeated seizures induced by kindling or other methods (Represa et al., 1989; Sutula et al., 1989; Cavazos et al., 1991; Qiao et al., 1991). More specifically, there is distinct regional variation of this reorganization along the septo-temporal axis, which depends on the kindling stimulation location. For example, kindling of the perforant path induced mossy fiber synaptic reorganization that was relatively more prominent in the septal pole than in the temporal pole of the DG. In contrast, rats that received kindling stimulation of the amygdala had a more uniform distribution of synaptic reorganization along the septo-temporal axis

(Cavazos et al., 1992). Similarly, infragranular mossy fibers, often appearing as fibers perpendicular to the long axis of the GCL, are found especially in the temporal pole and only a small number of these fibers occur in the septal pole and throughout most of the septo-temporal extent of the DG (Ribak and Peterson, 1991). These fibers are observed, at periodic intervals, in both dentate blades, although they are more common in the suprapyramidal blade. The infragranular mossy fibers form asymmetric synapses with the somata and apical dendrites of GABAergic basket cells, which provide additional circuitry for feedback inhibition to granule cells (Ribak and Peterson, 1991).

Commissural and Associational Fibers

The commissural and the associational projections to the DG (they are often referred to as commissural/associational system of the DG) are considered to be anatomically homologous fiber systems (Gottlieb and Cowan, 1973; Deller et al., 1996). It is described that there is a "great deal of parallelism between the different commissural and associational fibers, suggesting a coordinated effect of the two systems in the two hippocampi" (Deller et al., 1996). Namely, the associational pathway projects to the same region of the ML as does the commissural pathway, which arises from the contralateral hilar neurons and travels through the ventral hippocampal commissure (Laatsch and Cowan, 1967; Swanson et al., 1981). The commissural/associational pathway originates from cells in the hilus and it has been reported that at least some of the hilar neurons have both associational and commissural branches (Swanson et al., 1980; Laurberg and Sorensen, 1981). Intracellularly-labeled rat hilar cells, which had thorny excrescences (mossy cells) gave rise to both an ipsilateral (associational fibers) and contralateral (commissural fibers) terminal plexus in the inner ML (Buckmaster et al., 1996). The commissural projections to the DG have their origin in the hilus of the opposite side and the majority of them terminate on a restricted segment of the granule cells dendrites in the inner third of the ML. It is noteworthy that all the axonal arborizations provide terminals to cells having their bodies in the same septo-temporal level (Han et al., 1993). Detailed autoradiographic studies of Gottlieb and Cowan (1973) showed that the commissural projection is widely distributed in both the suprapyramidal and infrapyramidal blades, exhibiting a clear septo-temporal decline. In details, the commissural projection to the DG is very dense septally; moving to the temporal end, it decreases slightly and remains constant until the first segment of the temporal part; it drops significantly at the most temporal levels of the gyrus (Raisman et al., 1965; Gottlieb and Cowan, 1973; West et al., 1979). Deller et al. (1996), described four different commissural fiber types with distinct laminar termination pattern, but their study was limited only to the septal part of the DG.

The associational fibers appear to arise nearly exclusively from polymorphic neurons of the DG. Axons from these neurons terminate on the dendrites of ipsilateral granule cells in the inner third of the ML (Zimmer, 1971; Segal and Landis, 1974a,b; Amaral, 1978; Swanson et al., 1978; Laurberg and Sorensen, 1981). Intra-dentate association projections are massively divergent and more or less equally extensive along the longitudinal axis, with a predominant termination in the suprapyramidal blade (Amaral and Witter, 1989; Bekenstein and Lothman 1991; Han et al., 1993). Associational projections originating from hilar mossy cells are not homogeneous along the longitudinal dentate axis (Buckmaster et al., 1996). More specifically, hilar mossy cells located in the temporal dentate part project primarily in the

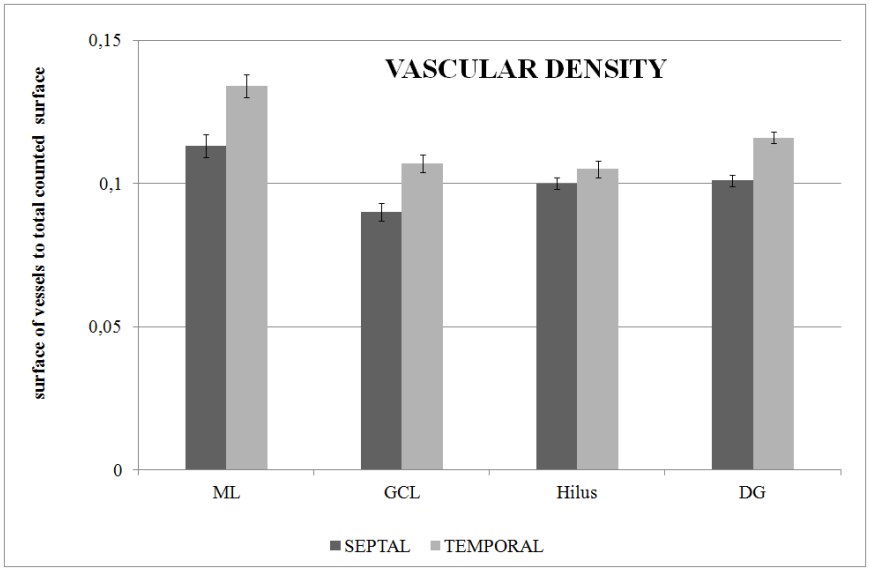
hilus and far away in distant septal levels, mainly on granule cells dendrites in the inner ML. In contrast, mossy cells located in the septal part have similar local (hilar) and distant projections (inner molecular layer) but their axons do not extend so far as those of the temporal mossy cells. These findings are consistent with data from mouse indicating that axons of temporal mossy cells diverge widely compared to those of the septal part (Blasco-Ibanez and Freund, 1997). Ishizuka (2008) described the existence of two distinct types (type I and type II) of longitudinal fiber systems innervating the ML of the DG. These systems originate from hilar cells and they are apparently involved in the propagation of information to the entire septo-temporal extent of the DG. Type I fiber system originating from entire hilus, but not its temporal most part, distributes its axonal collaterals in the inner ML and extends over almost the entire longitudinal axis of the gyrus. On the contrary, type II fiber system distributes its terminals in the outer ML, and its axons are very short and extend about 1.5 mm from the level of their origin at each septo-temporal direction.

Vascularization

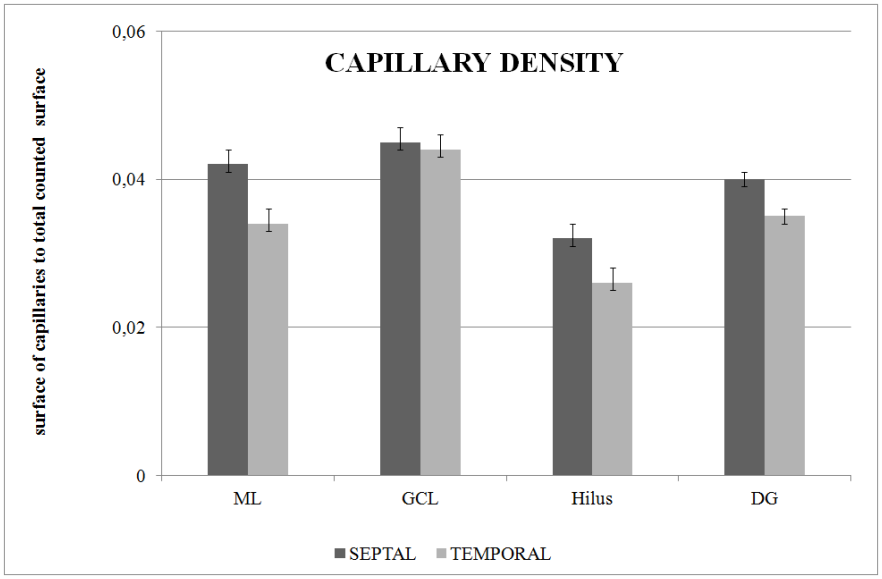
Sufficient, incessant blood flow is of paramount importance for CNS function. Increased angiosis and higher capillary density resulting in increased local blood flow meet increased metabolic demands reflecting structural and functional differentiation in the developing brain (Craigie, 1925; Rowan and Maxwell, 1981; Black et al., 1991; Carmeliet, 2005; Moore and Cao, 2008; Karbowski, 2011). Topographic differences in vascular supply are not limited between synaptically active gray matter and fiber tracts, but they are also present across gray matter (Cavaglia et al., 2001). Selective vulnerability to ischemia and regional differences in reperfusion and post-ischemic response suggest correlation between amplitude of hypoxic-ischemic damage and quantitative characteristics of the vascular bed (Spielmeyer, 1925; Ito et al., 1975; Pulsinelli et al., 1982; Smith et al., 1984a,b; Pulsinelli, 1985; Imdahl and Hossmann, 1986; Ashton et al., 1989a; Schmidt-Kastner and Freund, 1991; Akai and Yanagihara, 1993; Leker and Shohami, 2002).

Following Coyle's (1978) suggestion for segmental hippocampal vascularization, Grivas and colleagues (Grivas et al., 2003, Grivas, 2006) documented differentiation of specific vascular parameters along the septo-temporal axis of DG (see Figures 2 and 3). Septal DG was found to exhibit lower values for vascular density and vessels diameter, but higher values for capillary (≤8μm diameter) density compared to temporal DG (Figure 2). Septal PL exhibits lower values for large vessels (>20μm diameter) density, but higher values for capillary density and capillary diameter compared to temporal PL. Septal GCL exhibits lower values for vascular density, vascular diameter, capillary diameter and medium vessels density compared to temporal GCL. Septal ML exhibits lower values for vascular density, vascular diameter and large vessels density, but higher values for capillary density compared to temporal ML. These data reveal an antithesis, increased vascularization in temporal DG with reduced capillary contribution, due to capillaries of minor diameter in PL and lower number of capillaries in GCL and ML. As Coyle (1976) described, the longitudinal hippocampal artery, a branch of the posterior cerebral artery, courses approximately parallel to the longitudinal axis of the hippocampus, ascending in a rostrodorsal direction, and close to the porta of the hippocampal fissure branch to transverse hippocampal arteries, which supply

small, short branches to the adjacent DG and CA fields. Transverse hippocampal arteries are mainly categorized to internal arteries (large, long vessels of nearly equal diameter located in the hippocampal fissure), and external arteries (more variable in number and course, and mainly present in the midpolar and the temporal hippocampal part). Veins follow a spatial distribution approximately parallel to the corresponding arteries. The lack of external transverse hippocampal arteries and veins in the septal DG may partially explain the observed discrepancy of higher capillary and lower vascular density in the septal part.



(a)



(b)

Figure 2. Histograms of vascular (a) and capillary (b) density in the rat DG.

Septo-temporal heterogeneity of angiosis in the hippocampal DG may reflect phylogenetic and/or functional differences under normal and pathological conditions. Phylogenetically younger cortical areas exhibit higher capillary density compared to older ones (Klein et al., 1986; Cavaglia et al., 2001; Michaloudi et al., 2006) and septal DG appears phylogenetically later than the temporal DG (Schlessinger et al., 1975; Bayer, 1980). In addition, enriched capillary bed of the septal DG could be attributed to its elevated levels of neuronal activity (Piatti et al., 2011) and/or adult neurogenesis (Snyder et al., 2009a,b;Jinno, 2010; Bekiari et al., unpublished data).

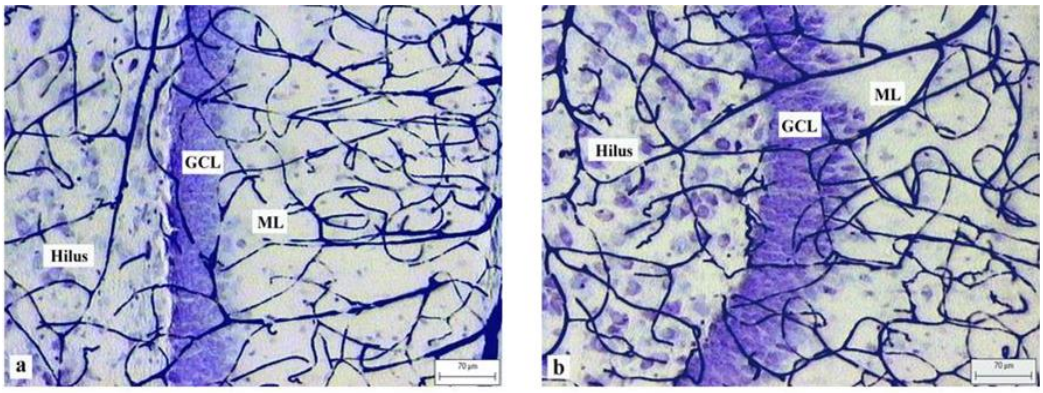


Figure 3. Photomicrographs of India ink-labeled, 100 μm thick, transverse rat septal (a) and temporal (b) DG section, counterstained with Cresyl Violet.

Hypoxia-Ischemia Vulnerability

Hippocampal formation has been known from quite early to be among the most sensitive to hypoxia-ischemia brain structures (Bratz, 1899; Brierley et al., 1971; Brown and Brierley, 1972; Ito et al., 1975; Klatzo, 1975; Pulsinelli et al., 1982; Brierley and Graham, 1984; Kirino and Sano, 1984; Smith et al., 1984b; Akai and Yanagihara, 1993). Moreover, different hippocampal parts and regions i.e., CA1, CA3 and DG, exhibit selective sensitivity to hypoxia-ischemia. Septal hippocampus exhibits high vulnerability, whereas temporal hippocampus is less vulnerable and shows the first signs of neuronal damage only after relatively prolonged ischemic insults (Pulsinelli et. al., 1982; Kirino and Sano, 1984; Smith et al., 1984a,b; Ashton et al., 1989a; Auer et al., R.N. 1989; Akai and Yanagihara, 1993; Rami et al., 1997). Regarding selective regional vulnerability, longstanding differences in the hippocampal anatomical nomenclature used by various authors pose some difficulties in interpreting previously published results. Pyramidal cell layer (PyL) of CA1 (often called h1 or regio superior) is indisputably the most vulnerable hippocampal region to ischemia (Sommer, 1880; Spielmeyer, 1927; Kirino, 1982; Pulsinelli et. al., 1982; Smith et al., 1984b; Kadar et al., 1998; Lalonde and Mielke, 2014) and hypoxia (Aitken and Schiff, 1986;Kass and Lipton, 1986; Ashton et al., 1989b). Sommer had noticed this already in 1880, hence CA1 is often called Sommer's sector. Pyramidal neurons in CA2 (widely but not universally accepted as part of the CA1) are almost equally sensitive, whereas PyL of CA3 (often called h2-3 or regio inferior) is relatively resistant (Pulsinelli and Brierley, 1979; Kirino, 1982; Kirino and Sano, 1984; Smith et al., 1984a; Schmidt-Kastner and Freund, 1991), excluding the most septal part (Schmidt-Kastner and Hossmann, 1988). A confusion arises when DG is

examined. Part of the literature describes DG as the most resistant hippocampal region to hypoxia-ischemia (Schmidt-Kastner and Freund, 1991; Lalonde and Mielke, 2014), but it appears that PL is not considered as a part of the DG. Polymorphic layer (often defined as hilus, or CA4, or endfolium, or h4-5), or at least some of the hilar neurons (e.g., neurons containing the neuropeptide somatostatin), exhibit equal or even higher sensitivity to ischemia compared to CA1 neurons (Bratz, 1899; Kirino, 1982; Pulsinelli et. al., 1982; Schmidt-Kastner and Freund, 1991). In fact, the regional hippocampal susceptibility to ischemia follows a decreasing rank order: PL> PyL CA1 > PyL CA3 >GCL (Kirino, 1982; Kirino and Sano, 1984; Smith et al., 1984a; Schmidt-Kastner and Hossmann, 1988; Schmidt-Kastner and Freund, 1991). Another feature of PL cells is the rapidity of their damage, appearing only few hours after the ischemic insult, corresponding to the 'ischemic cell change' (ICC) type of neuronal damage (Brown and Brierley, 1972). In contrast, damage of CA1 pyramidal neurons at the border of CA3 appears at least 24 hours after the ischemic insult, corresponding to the 'reactive change' (RC) type (Ito et al., 1975; Bubis et al., 1976) and 'matures' further, till almost complete destruction of CA1 PyL, corresponding to the 'delayed neuronal death' (DND) type (Ito et al., 1975; Kirino, 1982; Pulcinelli et. al., 1982; Kirino et al., 1984; Kirino and Sano, 1984; Johansen et al., 1987; Schmidt-Kastner and Hossmann, 1988). The vulnerability of PL neurons to ischemia is relatively similar along the septo-temporal hippocampal axis, though subtly higher in the septal hippocampus (Smith et al., 1984a). Dentate granule cells, albeit notably resistant to ischemia, do not completely elude the ubiquitous septo-temporal variation. Schmidt-Kastner and Hossmann (1988), have shown that 8 hours after a 30 min global brain ischemia, severe neuronal damage is confined in the septal edge.

Neurochemistry

The heterogeneity of the principal and non principal neurons can be revealed by the differential expression of neurotransmitters, neuropeptides, calcium binding proteins, receptors and neurotrophic factors, reflecting basic functional characteristics. In the past decades, a number of studies focused on the septo-temporal chemical diversification of identified subpopulations of hippocampal neurons. Loy et al. (1980) examined the DA and the NA contents of the DG and found those of the temporal part significantly higher, compared to the septal ones. Springer et al. (1987) found the muscarinic receptor binding in aged animals higher in the temporal, compared to the septal DG, ascribing the difference in possible age related cholinergic denervation. Hörtnagl et al. (1991) performed a detailed analysis of most relevant neurotransmitter systems in the rat hippocampus and found significantly higher ChAT and acetylcholinesterase (AChE) activities, and higher DA, 5-hydroxytryptamine (5-HT), 5-hydroxyindoleacetic acid (5-HIAA), glutamate and somatostatin (SS) content in the temporal, compared to the septal DG. On the contrary, taurine content and 5-HT/5-HIAA ratio exhibited statistically significant lower values in the temporal, compared to the septal DG. A trend, albeit not statistically significant, for septo-temporal increase in NA and 3-methoxy-4-hydroxyphenylglycol (MHPG) content and a septo-temporal decrease in molar MHPG/NA and NA/DA ratios, was also noticed. No septo-temporal difference was found for GABA, aspartate, glycine and neuropeptide Y (NPY)

levels, and glutamic acid decarboxylase (GAD) activity. Grivas (2006) found that neuronal nitric oxide synthase (nNOS)-immunoreactive (IR) neurons show a septo-temporal decrease, albeit not statistically significant, in the rat DG.

A detailed analysis of the non-principal GABAergic subpopulations along the septo-temporal axis of the rat and mouse hippocampus was published in a series of related articles by a Japanese group in Kyushu University (Liu et al., 1996; Nomura et al.,1997a,b; Fujise et al., 1998; Jinno et al., 1998, 1999, 2001; Jinno and Kosaka, 2002; 2003a,b, 2004, 2006). According to the published information, the numerical densities (NDs) of calretinin (CR)-, SS- and NOS-IR cells exhibit significantly higher values in the temporal, compared to the septal part of DG, whereas no differences exist for parvalvumin (PV)-, vasoactive intestinal polypeptide (VIP)- and cholecystokinin (CCK)-IR cells. Similar quantitative characteristics exhibited CR-, SS-, NOS- and PV- immunoreactivity in the rat hilus, though the difference was statistically significant only for CR. In the mouse DG, GAD67-IR cells were most frequently seen in the GCL. NDs of GABAergic and nNOS-IR neurons were found significantly higher in the temporal part of DG and its layers, whereas the sizes of the respective cells were significantly larger in the septal part, with two exceptions, the difference of GAD67-IR cell sizes is not statistically significant in PL and negligible in ML. The percentage of GABAergic neurons expressing nNOS-IR did not differ septo-temporally in DG, exhibit a septo-temporal increase in GL and a septo-temporal decrease in PL and ML, but with statistical significance only in ML. NDs of PV-IR interneurons were found significantly higher in the temporal, compared to the septal DG, PL, GCL and ML. NDs of CB-IR interneurons were found significantly higher in the temporal, compared to the septal DG and PL and with a non statistically significant septo-temporal increase in GL and decrease in ML. NDs of CR-IR GABAergic neurons were found significantly higher in the temporal, compared to the septal GCL and with a non statistically significant septo-temporal increase in DG and ML and decrease in PL. NDs of SS- and VIP-IR GABAergic neurons were found higher in DG and all its layers in the temporal, compared to the septal part, but differences were statistically significant only in DG and hilus. CCK-IR in DG was more intense in the temporal part of DG, PL and GCL and in the septal part of ML, but differences were without statistical significance. ND's of NPY-IR cells were found higher in DG and PL in the temporal, compared to the septal part and with reverse gradient in GCL and ML, though there was no statistical significance for GCL. The co-expression percentage of CB- and nNOS-IR was reported significantly higher in the temporal, compared to the septal PL. The co-localization of CR- and nNOS-IR was significantly higher in the temporal, compared to the septal DG, PL and GCL. The co-localization of PV- and nNOS-IR was reported significantly higher in the septal, compared to the temporal DG and GCL. The co-localization of SS- and nNOS-IR was significantly higher in the septal, compared to the temporal DG and PL.

Martens et al. (1998) evaluated, in the rat hippocampus, the septo-temporal distribution of the major ionotropic glutamate receptor subtypes i.e N-methyl-D-aspartate (NMDA), quisqalic acid or amino-3-hydroxy-5-methyl-4-isoxazoleproprionate (AMPA) and kainic acid (Kainate), using autoradiography for NMDA receptor antagonist [^{3}H]MK-801, AMPA receptor agonist [^{3}H]AMPA and [^{3}H]kainate binding sites respectively. They reported values for [^{3}H]MK-801 binding sites significantly increased in the PL and decreased in the ML, from septal to temporal levels. Significantly increased values for [^{3}H]AMPA and [^{3}H]kainate binding sites, from septal to temporal levels, were restricted in PL. Fujise and Kosaka (1999)

found significantly increased AMPA type receptor subunits 2 and 3 (GluR2/3)-IR cells in the temporal, compared to the septal PL. Pandis et al. (2006) reported increased levels of gene expression in the septal, compared to the temporal DG, for GluRA, GluRB and GluRC subunits of AMPA receptors and NR1, NR2A, NR2B subunits of NMDA receptors, all with statistical significance, except NR1 and NR2B. Furthermore, they determined by quantitative autoradiography higher specific [^{3}H]AMPA and [^{3}H]MK-801 binding in the septal, compared to the temporal ML. Sotiriou et al. (2005) examined possible differences regarding the $GABA_A$ receptors along the septo-temporal axis of rat hippocampus. Relative optical density units evaluation from 'in situ' hybridization autoradiograms revealed lower values only for alpha2 (a2) subunit of $GABA_A$ receptors and higher values for a1, a4, beta1 (b1), b2, b3, gamma2 (γ2) and delta (δ) subunits of $GABA_A$ receptors in the septal, compared to the temporal DG, the difference for a4, b3, γ and δ being statistically significant. Furthermore, they found higher values for the $GABA_A$ receptor agonist [^{3}H]muscimol binding in the septal, compared to the temporal DG.

Function

In the entire hippocampus, the DG is part of a largely repeated trisynaptic circuit transverse to its longitudinal axis ("on beam" module, Sloviter and Lomo, 2012). Granule cells of the DG receive excitatory input from the entorhinal cortex and send excitatory output to the hippocampal CA3 region via the mossy fibers. Differential entorhinal cortex input to the DG, depending on the septo-temporal level, lead to a functional dissociation of the septal and temporal part (see 'entorhinal afferents'). The septal DG, via the lateral entorhinal cortex, receives inputs from the associative, visual and auditory cortex (Dolorfo and Amaral, 1998), suggesting that the septal hippocampal part is preferentially involved in the cognitive process of learning and memory and mainly in spatial memory formation and acquisition. Temporal DG on the other hand, receives inputs from the medial part of the entorhinal cortex and is tightly connected to the prefrontal cortex, amygdala and other subcortical areas associated with the hypothalamus-pituitary-adrenal axis, proposing a role in regulation of emotional behavior (Dolorfo and Amaral, 1998; Kerr et al., 2007).

The DG is the "gateway" to the hippocampus and is believed to serve, on the one hand as a barrier for extraneous or irrelevant information (Lemon et al., 2009) and on the other hand as a pattern separator (Hunsaker and Kesner, 2008). By employing pattern separation and converting relatively similar inputs into substantially different outputs (Aimone et al., 2010), the DG may act as a preprocessor of incoming information, preparing it for efficient storage in the hippocampal CA3 region (Efstratova and Toth., 2014). The high-pass filter nature of the DG–CA3 circuit allows the conversion of multiple place fields of DG place cells into a single receptive field observed in CA3 place cells (Efstratova and Toth, 2014).

Indicative of a crucial role of DG synapses learning about novel information is that granule cells sustain the highest activity during acquisition of novel information (Montag-Sallaz et al., 1999). This encoding function of DG differs in septal as compared to temporal sites not only with regards to the sensory modality encoded but also in the mechanism employed. Place cells recorded at septal sites tend to have smaller fields, and higher spatial resolution ability, while those recorded at temporal sites are more broadly tuned (Jung et al.,

1994; Kjelstrup et al., 2008; Hartley et al., 2013), possibly due to the higher contact probability of granule cells to CA3 pyramidal cells temporally than septally (septal ratio is about of 12:1, whereas at the temporal pole the ratio drops to 2:3) (Andersen et al., 2007).

Experimental lesions, mechanical or cytotoxic, restricted to the septal or temporal pole, provided additional information for each part's functional outcome. Animals with septal hippocampal lesions presented impaired navigation, locomotion and exploratory performance in a variety of spatial tasks (Moser and Moser, 1998a,b; Bannerman et al., 1999; Zhang et al., 2004) and both the reference and working spatial memory were disrupted (Pothuizen et al., 2004). Reduced spatial performance in tasks involving different sensorimotor and motivational requirements, clearly shows that the septal part is the dominant region when it comes to spatial memory formation and acquisition (Bannerman et al., 2004). Temporal hippocampal lesions, on the other hand, had no effect on spatial learning process (Bannerman et al., 2003), but had a significant impact in anxiety-related behavior, as examined under various behavioral assessments. Performance in unconditioned tests of anxiety, including the light/dark exploration, open field, contextual fear conditioning, hyponeophagia and social interaction test, suggests that temporal hippocampal lesions possess a strong anxiolytic effect (Bannerman et al., 2003).

Lesion studies, moreover, highlight the functional role of the intermediate hippocampal part. Considering that ability for accurate place encoding decreases when moving from the septal to the temporal pole (Jung et al., 1994), and that behavioral control of performance takes place mainly in the temporal pole, data from lesion studies suggest that the intermediate zone translates place learning and cognitive knowledge, in general, into behavioral performance (Bast et al., 2009; Fanselow and Dong, 2010).

In contrast to established heterogeneity of entorhinal and cerebral cortex inputs along DG septo-temporal axis, inputs from the olfactory bulb are equally distributed all along the longitudinal extend of the hippocampus (Kosel et al., 1981). However, lesion studies suggest that the temporal hippocampus is the region that supports working memory related to odor information (Kesner et al., 2011). Temporal DG also, is found to play a pivotal role in olfactory pattern separation for highly similar odors (Weeden et al., 2014), further establishing temporal hippocampal key role in olfactory learning and memory.

More recently used techniques, as the study of immediate-early genes (IEGs) expression and the oxygen constant potential amperometry (CPA) technique, further support findings of the lesion studies, and provide new knowledge on functional segregation along the septo-temporal axis. Expression of IEGs is considered as a reliable marker of neuronal activity in the DG (Chawla et al., 2005; Satvat et al., 2011). Behavioral challenging on spatial memory tasks increased c-Fos, Arc and zif268 activation selectively in the septal part (Vann et al., 2000; Guzowski et al., 2001), whereas challenging in anxiety-related tasks, as the hyponeophagia and social defeat task, caused an increased c-Fos expression in the temporal part (Calfa et al., 2007; Smith et al., 2007). Expression of IEGs suggests that neuronal activation differences are evident along the transverse axis of the DG as well. Expression of Arc and zif268 was found to be increased in the suprapyramidal blade, revealing the increased overall cell activity of the suprapyramidal granule cells (Schmidt et al., 2012). Moreover, oxygen CPA, an *in vivo* technique that measures at high temporal resolution the region-specific cerebral flow changes in response to increased excitatory synaptic activity at freely-moving animals, showed that blood flow in the septal hippocampal part is not only increased during spatial navigation tasks, but also during physical movement and REM sleep

(McHugh et al., 2011). This is in accordance with electrophysiological findings evincing that theta activity, found to be high during both REM sleep and physical movement (McHugh et al., 2011), shows significantly decreasing coherence across the septo-temporal axis of the DG (Sabolek et al., 2009).

While external connectivity differences and lesion-behavior correlates point to a segregation of differing functions in the septal and temporal parts of hippocampus, there is evidence suggesting that hippocampal networks involved in spatial learning and contextual fear do not extend strictly within the boundaries of the septal or temporal hippocampus, respectively, but, are more widely distributed. Septal hippocampal lesions, for instance, appear to attenuate contextual freezing during contextual fear conditioning task (McNish et al., 1997). Temporal hippocampal lesions, on the other hand, delayed early learning during goal-oriented searching, suggesting a temporal hippocampal role in spatial learning (Ruediger et al., 2012). More interestingly, following lesions of a hippocampal part preferentially supporting a certain function, the remainder hippocampus seems to be able to contribute in some aspects, although less effectively. Thus, the temporal hippocampus, seems to mediate new learning memory formation after septal lesions (de Hoz and Martin, 2014). Similarly, following temporal hippocampal lesions, neurons of the septal part possess a critical time-limited role in context fear expression (Maren et al., 1997) and appear to contribute in the acquisition and consolidation of contextual representations (Anagnostaras et al., 2001).

Following recent advances in electrophysiological methods allowing multisite recordings, a change in focus is emerging: from the septo-temporal segregation of properties and functions to the integrative role of networks spanning the long axis of hippocampus as revealed by the bidirectional spread and interaction of functionally important rhythms like theta and gamma during distinct behaviors (Gloveli et al., 2005; Patel et al., 2012; Penley et al., 2013; Long et al., 2014). The DG, with its mossy cells passing information between lamellae, appears to have a critical role in this, both in enabling information encoding and neuronal plasticity and in keeping the latter within homeostasis limits (see its role in epileptogenesis).

Dysfunction

Neuroinflammatory Diseases

As it is described above (see ‘DEVELOPMENTAL AND ADULT CYTOGENESIS’), adult neurogenesis has been reported to be predominant in the septal DG compared to the temporal DG (Snyder et al., 2009a,b;Jinno, 2010). Conditions stimulating cell proliferation enhance the number of early postmitotic cells in the DG (Brandt et al., 2003), affecting mainly the septal part. Innate neuroinflammation due to experimental allergic encephalomyelitis (EAE) or lipopolysaccharide (LPS)-induced, enhance the proliferation of NPCs in DG (Ekdahl et al., 2003,2009; Das and Basu, 2008; Pluchino et al., 2008; Huehnchen et al., 2011; Volobouéva and Giffard, 2011; Belarbi et al., 2012; Giannakopoulou et al., 2013), being more intense in the septal DG. Although the exact molecular mechanisms that regulate NPCs proliferation and differentiation are largely unknown, several factors have been shown to affect DG neurogenesis. Under CNS pathological conditions associated with

neuroinflammation, inflammatory mediators such as cytokines and chemokines can affect the proliferative capacity of NPCs and alter neurogenesis (Russo et al., 2011). However, despite the general agreement about an inflammation-induced transient increase in subventricular zone precursor proliferation (Calza et al., 1998; Picard-Riera et al., 2002; Nait-Oumesmar et al., 2007), the role of inflammation in hippocampal neurogenesis is still unclear, and the experimental evidence appears to be controversial (Ekdahl et al., 2003,2009; Gerber et al., 2003;).

In inflammatory and demyelinating diseases of the CNS of human adults, such as multiple sclerosis (MS), apart from motor and sensory deficits, cognitive decline is also reported (Rao et al., 1991). Decline in information processing, impaired working memory performance and deficits in spatial memory are commonly found (Rovaris et al., 2000), indicating that the septal hippocampus is primarily affected. Evidence of hippocampal dysfunction and atrophy in MS has been reported from recent histopathologic studies (Geurts et al., 2007; Papadopoulos et al., 2009), however, the manner in which hippocampal damage affects hippocampal function and memory performance is not well established (Roosendaal et al., 2010). Although previous observations have revealed that neuroinflammation influences the proliferation of progenitor cells resident in SGZ (Aharoni et al., 2005; Aharoni and Arnon, 2009; Guo et al., 2010; Huehnchen et al., 2011), it remains unknown whether and how it affects their differentiation process and survival.

By using the EAE model of MS in order to investigate the effects of CNS inflammation on hippocampal NPCs and neurogenesis, we confirmed that the inflammatory environment prevailing in the brain of EAE mice enhances the proliferation of NPCs. We also proved that neuroinflammation intervenes in NPC differentiation by increasing the symmetrical divisions and modify the proportions of their subpopulations (Giannakopoulou et al., 2013). It is interesting to note that increased microglial activation in EAE hippocampus was found, but with a relative paucity of inflammatory infiltrates in this structure. This finding indicates that indirectly activated brain cells with immune functions (microglia and astrocytes) are responsible for NPC proliferation, rather than local cell-to-cell contact interactions between inflammatory cells and NPCs of DG. Thus, in this animal model the activated T cells may constitute indirectly the major promoter of the increased neuroproliferation.

The enhanced neuroproliferation during the acute phase of an inflammatory CNS disease may seem contradictory to the widely held opinion supporting the detrimental effect of inflammation (Ekdahl et al., 2003,2009; Guo et al., 2010 ;Saino et al., 2010; Volobоueva and Giffard, 2011). In contrary, Huehnchen and colleagues (2011) reported a total increase in the number of BrdU-positive cells in the septal DG not only in the acute but also in the chronic phase of the disease.

Acute inflammation appears to enhance the proliferation of NPCs, but the long-term effects of inflammation are more complex. It should be taken into account that the proliferation of NPCs is a perquisite of neurogenesis, but it is not the only stage ensuring the efficiency of the neurogenic process. Adult neurogenesis is a complex and multistage process, and impaired neurogenesis should not be considered synonymous with decreased proliferation of NPCs of the DG, because their overproduction or differentiation delay may have the same declining result. Furthermore, proliferation can fluctuate during the course of a neuroinflammatory disease. Increased neuronal proliferation has been observed in both brain proliferative zones (SVZ & SGZ) shortly after disease appearance (Magavi et al., 2000;

Picard-Riera et al., 2002) but subsequently declines at chronic phase, below that of naive mice (Aharoni et al., 2005).

Epilepsy

Pathological stimuli, such as seizures, induce abnormalities in hippocampal neurogenesis, though the overall effect depends on the type of seizures: acute seizures or status epilepticus (SE) vs spontaneous recurrent motor seizures that occur in chronic temporal lobe epilepsy (TLE).

Studies on neurogenesis in animal models of TLE evidence a dramatic increase in the production of new cells/neurons in the SGZ-GCL of the DG following pilocarpine-induced SE (Parent et al., 1997) or kindling stimulations (Bengzon et al., 1997). However, by 3–4 weeks after SE, neurogenesis returned to baseline levels. A subsequent study showed that administration of chemoconvulsant kainic acid under anesthesia also increases neurogenesis in the hippocampus (Gray and Sundstrom, 1998). Investigations in a variety of epilepsy models have confirmed the above plasticity of hippocampal neurogenesis to acute seizures (Covolan et al. 2000; Nakagawa et al. 2000; Sankar et al., 2000; Ekdahl et al. 2001; Radley and Jacobs 2003; Hattiangady et al. 2004; Jessberger et al. 2005; Kralic et al. 2005; Shapiro et al. 2005b; Kuruba et al., 2009). The precise mechanisms underlying the seizure-induced increase in hippocampal neurogenesis are unclear.

The increased DG neurogenesis after acute seizures is associated with anomalous migration of a fraction of newly born granule cells into the PL and/or the ML (Houser, 1990; Parent et al., 1997,2006a; Parent and Lowenstein, 2002; Scharfman et al., 2002, 2003; McCloskey et al., 2006; Gong et al., 2007; Parent, 2007; Scharfman and Gray, 2007; Scharfman and Hen, 2007; Shetty and Hattiangady, 2007a; Hattiangady and Shetty, 2008). Further investigations demonstrate that aberrantly migrated newly born granule cells exhibit deviant integration with the CA3 network, and respond to perforant path stimulation with a longer latency to onset of evoked responses (Scharfman et al., 2003). Additional studies imply that displaced granule cells in the PL establish afferent connectivity with mossy fiber terminals (Pierce et al., 2005), exhibit spontaneous bursts of action potentials (Scharfman et al., 2000), and contribute to spontaneous seizures in chronically epileptic animals (Jung et al., 2004; McCloskey et al., 2006). Thus, it appears that acute-seizure-induced abnormal DG neurogenesis promotes aberrant circuitry development, which likely contributes to the evolution of initial-seizure-induced hippocampal injury into chronic epilepsy.

The precise reasons for anomalous migration of newly born granule cells are still being examined. A study by Jessberger et al. (2005) demonstrates that acute seizures do not significantly influence the proliferation of nestin-expressing NSCs (type 1 cells) but rather stimulate the division of doublecortin (DCX)-expressing cells (transit-amplifying cells/type 2 cells) and immature neurons (type 3 cells). Based on this, it is presumed that this delayed proliferation interferes with migration, leading to a significant dispersion of DCX-positive early postmitotic neurons away from the GCL into the PL and the ML. However, Gong et al. (2007) suggest that loss of reelin (a secreted migration guidance cue) expression after acute seizures largely contributes to the chain migration and aberrant integration of newly born granule cells into ectopic locations. A significant fraction of new granule cells that are born after acute seizures exhibit abnormal morphological features in the form of basal dendrites (Shapiro et al., 2005a). These basal dendrites persist for prolonged periods and exhibit

immature synapses (Shapiro and Ribak, 2006), suggesting their involvement in the formation of epileptogenic circuitry. Furthermore, seizures seem to accelerate the morphological development of newly born granule cells, causing their dendrites to extend swiftly through the molecular layer, leading to a rapid functional integration of adult-generated granule cells (Overstreet-Wadiche et al., 2006). Thus, the overall dendritic properties of newly born neurons that are born shortly after SE are predisposed for epileptogenesis.

Increased neurogenesis observed shortly after acute seizures returns to baseline by about 2 months after the initial seizure episode in rats (Jessberger et al., 2007) and the extent of neurogenesis declines radically in the chronic phase of epilepsy, when significant numbers of spontaneous seizures manifest (Hattiangady et al., 2004; Hattiangady and Shetty, 2008). By employing DCX as a marker of newborn neurons in two distinct rat models of TLE, Hattiangady and colleagues reported 64–81% decrease in neurogenesis. Additional evaluation using pulsed injections of Brdu at 5 months post-SE demonstrated that the overall addition of new cells to the SGZ-GCL and the extent of long-term survival in chronic epilepsy are analogous to those observed in the age-matched intact hippocampus. However, phenotypical characterization revealed that only 4% of newly generated cells differentiated into mature neurons in chronic epileptic conditions, in contrast to 80% of newly born cells exhibiting neuronal differentiation in the age-matched intact hippocampus. A study using a mouse model of TLE also reported similar changes in neuronal differentiation of newly born cells in chronic epilepsy in which reduced neurogenesis was associated with increased production of new astrocytes (Kralic et al., 2005). Another study reported a gradual fall in neurogenesis at 1 week and virtual loss of all neurogenesis by 4–6 weeks after the initial seizure episode, which, interestingly, paralleled granule cell dispersion and widening of the GCL (Heinrich et al., 2006). However, the decreased levels of hippocampal neurogenesis in chronic epilepsy depend on the model and the age of the animal at the time of the initial seizure episode. Adult animals seem to be vulnerable to an almost complete loss of neurogenesis in the chronic phase after the initial seizure episode.

While the precise mechanisms underlying decreased neurogenesis in chronic TLE are unknown, several potential reasons have been proposed. Although a role for chronic inflammation in this decline is an attractive hypothesis, a study on activated microglial cells has almost ruled out this possibility, as only minimal density of such cells was found in the hippocampus during chronic epilepsy (Hattiangady et al., 2004). Another possible reason underlying decreased neurogenesis includes the presence of an adverse hippocampal milieu for neurogenesis from NSCs and decreased numbers of NSCs. While an unfavorable NSC milieu can be gleaned from decreased levels of NSC mitogenic factors such as FGF-2, IGF-1 and BDNF in chronic epilepsy (Shetty et al., 2003; Shetty and Hattiangady, 2007b), numbers of NSCs do not appear to change drastically in chronic epilepsy. In fact, a study on humans suggests an increased number of putative NSCs positive for Musashi-1 in chronic TLE (Crespel et al., 2005). Thus, significant numbers of NSCs persist during chronic epilepsy.

The intriguing finding that epileptic seizures influence stem cell proliferation within the rodent hippocampus (Parent et al., 1997) has not been confirmed in human brain. Major obstacles include the restricted experimental approach to human brain tissue, lack of appropriate controls, impact of age and developmental maturation as well as individual genetic background, seizure histories and antiepileptic drug treatment. Thus, only a few studies have so far examined neurogenesis in hippocampal tissues of TLE patients.

While evaluation of hippocampal neurogenesis shortly after acute seizures is yet to be performed in humans, examination of the hippocampus from young TLE patients (<2 years of age) suggested increased cell proliferation. Furthermore, epileptic hippocampus from young children (<4 years of age) also exhibited significant numbers of NPCs (Blumcke et al., 2001). Thus, there is some evidence for increased hippocampal neurogenesis in the early phase of TLE in pediatric patients, which is consistent with studies in animal models of TLE described above.

Findings in humans are also in consistence with the declined hippocampal neurogenesis observed in animal models of chronic epilepsy. It has been demonstrated a decreased density of cells positive for PSA–NCAM (a putative marker of newly born neurons) in the DG of children exhibiting frequent spontaneous seizures compared to the DG from age-matched autopsy samples, implying that severe seizures during early childhood are associated with decreased hippocampal neurogenesis (Mathern et al., 2002). Examination of hippocampal tissues from adult patients with chronic TLE also revealed reduced density of $PSA–NCAM^+$ cells (Pirttila et al., 2005). Another study by Crespel et al. (2005) also found minimal numbers of DCX^+ cells in the SGZ of hippocampal tissues from patients with mesial TLE, despite evidence for increased proliferation of cells immunopositive for Musashi-1 (a putative marker of NSCs) in these samples. Furthermore, a study by Fahrner et al. (2007) demonstrated both decreased synthesis of mRNA for DCX and absence of cells positive for Ki-67 (an endogenous marker of proliferative cells) in hippocampal tissues from chronic TLE patients.

Diminished hippocampal neurogenesis might contribute to the persistence of spontaneous seizures, learning and memory impairments, and depression prevalent in chronic TLE. First, it is plausible that decreased addition of new neurons to the GCL interferes with the possible spontaneous repair of hyperexcitability in the DG (Jakubs et al., 2006). Second, decreased addition of new functional granule cells into the GCL in chronic epilepsy is likely to contribute to impairments in hippocampal-dependent learning and memory functions observed in TLE. This notion is also supported by the finding that overall granule cell density is the most significant predictor accounting for the total memory capacity in an individual TLE patient (Pauli et al., 2006; Siebzehnrubl and Blumcke, 2008). Third, from the perspective of findings that increased production of new neurons in the hippocampus is essential for the effective action of antidepressants (Santarelli et al., 2003; Drew and Hen, 2007; Sahay and Hen, 2007; Perera et al., 2008;), diminished addition of new granule cells into the GCL perhaps plays a role in depressive-like behaviour prevalent in chronic epilepsy. Thus, available evidence is supportive of the perception that diminished hippocampal neurogenesis plays a role in maintaining spontaneous seizures, learning and memory impairments, and depression in chronic TLE.

Studies addressing the molecular pathomechanism of granule cell dispersion (GCD) found in mesial temporal sclerosis (MTS) rather point to a compromised reelin signaling pathway to be involved (Haas et al., 2002). Altered reelin profile was shown to guide aberrant migration of newborn granule cells after acute seizures as well (Gong et al., 2007). Decreased reelin RNA and protein levels have been identified in patients with MTS and severe granule cell dispersion (Haas et al., 2002). Intriguingly, semiquantitative assessments of Cajal-Retzius cells showed no differences between hippocampal specimens obtained from epileptic or nonepilepsy patients. The obvious association between MTS and GCD lead to the hypothesis that newly formed neurons/granule cells aberrantly integrate into the DG and disturb the

trisynaptic hippocampal pathway, thereby increasing seizure susceptibility. Newborn granule cells not only anatomically and functionally integrate into the GCL (as destined) or ectopically into the ML but also ectopically into the PL (Parent et al., 2006a,b). Ectopic granule cells at the PL/CA3 boundary have been first identified and functionally characterized in animal models for TLE (Scharfman et al., 2000). However, these complex findings are compatible with the notion that aberrant anatomical organization of the epileptic hippocampus contributes to increased seizure susceptibility and that neurogenesis is critically involved in this process. The majority of findings points to a predominately young age of seizure-induced neurogenesis, which contributes to aberrant network integration and seizure progression. The decreased propensity of neurogenesis in chronic TLE stages, whether reflecting a depletion or exhaustion of the precursor cell pool (Blumcke et al., 2001) would rather result in the well-recognized cell loss patterns and severe cognitive deterioration (Pauli et al., 2006).

Limited studies have examined the impact of seizures or TLE on hippocampal DG along its septo-temporal axis. Toyoda et al. (2013) evidenced that after spontaneous seizures, temporal hippocampus and subiculum displayed the earliest seizure activity in a pilocarpine (PC)-treated rat model of TLE, as opposed to the septal hippocampus and other brain regions involved. These data were also confirmed in the mouse kainate (KA) model of TLE, where a stronger intensity of intrahippocampal in vivo recordings and c-fos immunoreactivity was observed in the temporal hippocampus (Hausler et al., 2012). Earliest and stronger activation of the temporal hippocampal part may, in part, be responsible for the more severe neuronal damage observed in granule cells and PL' s neurons of the temporal DG, as compared to the septal ones, seen after a 40 minute-lasting seizure in the PC-induced status epilepticus rat model (Fujikawa, 1996). In the same study, PL's neurons appeared to be damaged prior to the granule cells in both the septal and the temporal part. However, the degree of neuronal damage in the GCL and PL of the temporal DG was shown to be stable regardless of the length of the recovery time following seizure, whereas neuronal damage in the septal GCL and PL tend to worsen with increasing recovery time (Fujikawa, 1996).

Apart from the differential response of septal and temporal principal neurons to epileptic seizures, a differential vulnerability of local interneurons was observed as well. In the KA mouse model of TLE, at 2 days after KA injection, expression of GAD67 mRNA was significantly reduced in interneurons of the ipsilateral septal and middle PL, whereas interneurons of the temporal PL were rather unaffected (Marx et al., 2013). Region-selective loss of GAD 67-expressing interneurons was accompanied by an upregulation of GAD67 mRNA expression in the septal and middle DG's granule cells, possibly reflecting a compensatory mechanism. Loss of septal PL's NPY-positive interneurons was also present, followed by a NPY upregulation in septal granule cells and an increased NPY staining in septal mossy fibers. Considering that NPY upregulation is shown to decrease seizure susceptibility (Vezzani et al., 2002), the more severe damage seen in the temporal granule cells could be partially explained. Synchronously, increased granule cell GAD67 expression is thought to strengthen local GABAergic transmission (Marx et al., 2013), creating a shift towards inhibitory mechanisms, resulting, in part, to the delayed seizure onset in the septal DG.

Differential effects of seizures or TLE on the ongoing DG neurogenesis along the septo-temporal axis have also been reported. Ferland et al. (2002) proved that there is a significant increase in hippocampal DG mitotic activity in adult mice exposed to flurothyl seizures and

this increase was greater in the septal as compared to the temporal hippocampus. However, animals exposed to eight flurothyl-induced seizures had significant differences between septal and temporal hippocampus on day 0, 1, and 3 seizure-free interval, with temporal hippocampus always having higher proportional increase in BrdU-positive cell densities (350–400% increase) from control levels than the septal hippocampus (200–250% increase). This result suggests that progenitor cell mitotic activity is increased in the temporal hippocampus to a larger extent than that which is observed in the septal hippocampus and is consistent with previous reports (Scott et al. 1998). Selective increase of NPCs proliferation and number of immature neurons was also present in the temporal DG part of the KA seizure-induced model, and it was partly attributed to the increased numerical density of surviving NPY-positive interneurons in temporal PL (Haussler et al., 2012), as NPY is shown to promote DG neurogenesis (Howell et al., 2003, 2005). By contrast, no significant differences were found on day 7, 14, and 28 seizure-free interval in the septal and temporal hippocampus, suggesting that mitotic activity had returned to baseline levels at these time points. Following one seizure, there were no differences between the septal and temporal hippocampus in comparing their relative increases in hippocampal progenitor cell mitotic activity from control levels, suggesting that the septal and temporal hippocampus had equal proportional increases in mitotic activity following a single seizure (Ferland et al., 2002). Lastly, the majority of these mitotically active cells differentiate into neurons, a finding which is consistent with previous results (Bengzon et al., 1997; Parent et al., 1997; Gray and Sundstrom, 1998; Scott et al., 1998; Nakagawa et al., 2000).

Interestingly, electrical kindling studies have demonstrated significant differences in afterdischarge thresholds between the septal and temporal hippocampus in that the septal hippocampus has lower afterdischarge thresholds than the temporal hippocampus (Racine et al., 1977). Speculatively, this apparent regional difference in afterdischarge threshold might be linked to the differential amounts of mitotic activity observed in the septal and temporal hippocampus. Since septal hippocampus has a lower threshold for triggering an afterdischarge, then this propensity for the septal hippocampus to be more easily excitable might explain the overall higher amounts of mitotic activity in this area. Conversely, the temporal hippocampus has higher afterdischarge thresholds, indicating that it is less excitable, which could contribute to less mitotic activity. This interpretation suggests that the excitability state of the hippocampus is critically involved in the rate at which mitotic activity is occurring. In the epileptic hippocampus, however, selective loss of neuropeptide-secreting cell populations and re-arrangement of remaining neuronal populations alter the local excitation-inhibition balance, creating a septo-temporal neuroproliferative profile other than that seen in the intact hippocampal microenvironment. The functional role of the seizure-induced increases in mitotic activity in the septal and temporal hippocampus remains to be determined.

Depression

The smaller pool of radial glia-like progenitors in temporal hippocampal DG might be associated with the susceptibility to affective or mental disorders. By virtue of the asymmetry in hippocampal connectivity, neurogenesis in the temporal DG may have a role in the regulation of emotion, distinct from the role of neurogenesis in the septal DG (Sahay and

Hen, 2007). For instance, exposure to chronic mild stress results in decreased cell proliferation in the temporal but not in the septal hippocampus (Jayatissa et al., 2006). Possible involvement of temporal hippocampus in mental illness has been suggested by several analyses of anxiety-related behaviors (McEown and Treit, 2009). In line with these findings, chronic treatment with agomelatin, an antidepressant, increases neurogenesis only in the temporal DG (Banasr et al., 2004).

Animal models of depression are associated with impairments of adult neurogenesis, with a tendency for a preferential effect in the temporal hippocampus (Tanti and Belzung, 2013a). However, the septo-temporal specificity of the effects depends upon the stage assessed. Indeed, most studies show homogenous effects on proliferation along the axis, but when assessing survival or neurogenesis, most of the studies show a higher specificity of the temporal part. In summary, models of depression impact neurogenesis more frequently in the temporal hippocampus, than in both subdivisions of the hippocampus. Antidepressant therapy should therefore be expected to counteract the effects of models of depression, and thus to stimulate adult neurogenesis preferentially in the temporal part. Surprisingly, several studies tested the effects of selective serotonin reuptake inhibitors and found them to act in a more uniform way both on septal and temporal adult neurogenesis. The same results were found for the tricyclic antidepressant imipramine, which was recently found to stimulate the number of doublecortin cells in both septal and temporal hippocampus of rats exposed to the CORT model (Diniz et al., 2013). However, less classical treatments endowed with antidepressant-like action either in clinical or animal models of depression, including the new antidepressant agomelatine, and also lithium, a GABA-B receptor antagonist, and orexin antagonists have recently been found to specifically modulate different steps in the generation of new neurons in the temporal hippocampus, indicating that an action restricted to the temporal part of the hippocampus could be sufficient to achieve remission. Finally, non-pharmacological treatments that are also able to promote recovery, such as environmental enrichment or physical exercise, act on both subdivisions, even though some studies highlight specificity for adult septal neurogenesis (Tanti et al., 2012; Tanti and Belzung, 2013b). Both these behavioral manipulations are known to have mood-improving and anxiolytic properties which seem dependent upon their pro-neurogenic effects (Bruel-Jungerman et al., 2005; Schloesser et al., 2010; Lehmann et al., 2013).

Neurodegenerative Diseases

Neurodegenerative diseases, which present chronic and slowly progressive processes, have different impacts on stem cell maintenance, proliferation, survival and functional integration in hippocampal DG. When comparing studies of adult neurogenesis in animal models of neurodegenerative diseases, the results seem very diverse and variable. The transgenic animal models vary in promoters used, age of the animal and age of onset of the disease, transgene expression, neurotransmitter content and amount of overexpression/loss of the disease-causing protein. Thus, the interpretation of the obtained results in different studies is sometimes divergent.

Alzheimer's Disease

The pathology of Alzheimer's disease (AD), cause among others olfactory deficits, memory impairment, and cognitive decline. These symptoms can be partly related to regions and functions of adult neurogenesis. Loss of spatial memory acquisition and spatial performance is frequently seen in patients already from the onset of the disease, revealing the initial selective impairment of the posterior hippocampus. Morphometric studies showed a proportional increase of neurofibrillary tangles and granulovacuolar degeneration in the posterior hippocampal formation of AD patients (Ball, 1978).

In different transgenic models of the disease, adult neurogenesis is compromised and precedes neuronal loss. Dysfunctional neurogenesis has been reported for AD transgenic models in both regions of adult neurogenesis (reviewed in: Lazarov and Marr, 2010; Marlatt and Lucassen, 2010). Experimental conditions largely differ, depending on the use of PSEN1, PSEN2 or different APP single mutations, knock-ins or combinations. Adult neurogenesis is impaired in almost all of these transgenic AD models, specifically when a single mutation of PSEN1 (Wang et al., 2004; Wen et al., 2004; Choi et al., 2008) was studied. Although a single APP transgene mutation (Indiana mutation) has only negative effects on adult neurogenesis at an aged and symptomatic stage after amyloid deposition (Donovan et al., 2006), double and triple mutations of APP (APP Swedish and Indiana) under many circumstances result in increased proliferation and, in some cases, survival of new neurons (Haughey et al., 2002; Mirochnic et al., 2009).

An important study using a commonly used AD model, the triple transgenic mice (3× Tg-AD) harboring three mutant genes (APP, PSEN1 and tau), reported impaired adult neurogenesis (Rodriguez et al., 2008). The reduction in proliferation was directly associated with the presence of Aβ plaques and an increase in the number of Aβ-containing neurons in the hippocampus, which, in the case of 3× gTg females, was directly correlated. In an aged APP23 transgenic mouse model of cerebral amyloidosis with strong Aβ deposits, Ermini et al. (2008) reported a decrease of quiescent astrocyte type 1-like cells, in conjunction with strong attraction of granule cell layer-derived new neurons by Aβ deposits. Longer dendrites, increased spine density and functional responses in early-stage, newly generated neurons in APP transgenic mice (Sun et al., 2009), possibly represent compensatory mechanisms. During later maturation, the morphology and functionality of these newly generated neurons were impaired, suggesting that an imbalance in GABAergic and glutamatergic neurotransmission was present in APP models. How the slow neurodegenerative process may also induce NSC proliferation is still a matter of debate.

Studies of human AD have led to seemingly variable results; one study reported that hippocampal neurogenesis was increased in patients with AD, as shown by an increase in protein expression of DCX and PSA-NCAM, TOAD-64/Ulip/CRMP (TUC-4), and neurogenic differentiation (NeuroD) in Western blots from AD hippocampus (Jin et al., 2004). This increase was attributed to a compensatory mechanism in the neurodegenerative process. Another study indicated an increase in gliosis and vascular-associated changes in presenile AD human hippocampus (Boekhoorn et al., 2006). More detailed studies during different disease stages will be necessary to understand the effects of AD on hippocampal neurogenesis.

Parkinson Disease

Prominent clinical features of Parkinson disease (PD) are motor symptoms (bradykinesia, tremor, rigidity and postural instability), however, non-motor-related PD symptoms are observed early in the course of the disease. The latter include rapid eye movement (REM) sleep behavior disorder, subtle cognitive deficits, depression, olfactory dysfunction and constipation (for review see Tolosa and Poewe, 2009). A subset of these functions is connected to the stem and progenitor cell populations located in the hippocampal DG. Interestingly, several monogenetic forms of PD show a decreased gray matter volume in the hippocampal region (Reetz et al., 2010).

The overexpression of hWT α-synuclein in transgenic mice has a negative impact on adult neurogenesis (Winner et al., 2004; Crews et al., 2008; Nuber et al., 2008; Winner et al., 2008). Under the platelet-derived growth factor (PDGF) promoter, co-expression of hWT α-synuclein and neural progenitor cell markers in regions of neurogenesis is found as early as Sox2 expression, a marker of newborn cells. There is strong expression of α-synuclein in DCX-positive neuroblasts in hippocampal DG, but also in target regions of adult neurogenesis with transgene expression in the hippoacampal CA3 region (Winner et al., 2004). Therefore, impaired adult neurogenesis in mice may be due to cell-autonomous effects of the transgene (Marxreiter et al., 2013b). Although proliferation is not changed in hWT α-synuclein-over-expressing mice, a decrease in neuroblasts and newly generated neurons is present. This decrease is paralleled by an increase in cell death in regions of neurogenesis, indicative of reduced survival of newly generated neurons.

Anxiety and depression are common neuropsychological features in the premotor phase of PD in humans, implying that the temporal DG is initially affected. In general, these neuropsychiatric symptoms have been correlated with defective adult neurogenesis in non PD animal models. Lesion models characterized by the loss of dopaminergic and serotoninergic projections to the hippocampus show reduced proliferation of NSCs and it is known that specific ablation of hippocampal neurogenesis induces anxiety-related behaviour in mice. It seems likely that impaired adult neurogenesis contributes to the development of these neuropsychiatric symptoms during the premotor phase of PD (Braak stages II and III).

Upon disease progression, alpha-synuclein pathology progresses to meso- and allocortical regions reaching the hippocampus (Braak stages IV and V). In addition to motor symptoms resulting from progressive nigrostriatal degeneration, cognitive impairment correlates with allocortical alpha-synuclein pathology. At this later stage, excessive alpha-synuclein expression in target regions of adult neurogenesis like the CA3 region might hinder proper axonal integration of newly generated neurons (Braak stages IV and V). Of course, the question arises how anxiety, depression, and cognitive impairment as early PD symptoms may be related to or influenced by impaired hippocampal neurogenesis. First, distinct connections of the temporal and the septal hippocampus may contribute separately to these symptoms. Moreover, adult neurogenesis-dependent memory performance is highly variable depending crucially on the different maturation stages of the newly generated cells. Perturbations of post- and pre-synaptic integration might cause functional impairment of newborn neurons besides quantitative reduction by decreased proliferation resulting from deafferentation in SGZ. Thus, Marxreiter and colleagues hypothesize that de-afferentation accounts for alterations in emotional behaviour, whereas perturbed integration of adult-born neurons is involved in cognitive decline (Marxreiter et al., 2013a,b)

Huntington's Disease

DG adult neurogenesis has been studied mostly in R6/1 and R6/2 mice and the rat Huntington's disease (HD) model. The transgenic R6/1 and R6/2 mice are among the most widely used animal models for HD with the introduction of exon 1 of the human HD gene carrying highly expanded CAG repeats into the mouse germ line. They differ in their number of CAG repeats, age of onset and survival (Mangiarini et al., 1996), and they develop a progressive neurological phenotype that exhibits many of the features of HD, including involuntary stereotypic movements, tremor and epileptic seizures, as well as non-movement disorder components. Several studies have reported reduced progenitor proliferation rates in both mouse models of HD in the DG. In the DG, a decline in proliferation was documented in the R6/1 (Lazic et al., 2004, 2006) and R6/2 (Phillips et al., 2005; Kohl et al., 2007) HD mouse models, which resulted in a reduction in newly generated neurons, although in most reports neuronal differentiation was not compromised. Different stimuli known to increase adult neurogenesis were tested. Physical activity and environmental enrichment (van Dellen et al., 2000; Spires et al., 2004) had positive effects on survival, cognitive performance and striatal brain-derived neurotrophic factor levels (Pang et al., 2006), as well as the reduction of the neuronal intranuclear inclusion load (Benn et al., 2010).

The DG adult neurogenesis has also been studied extensively in the transgenic rat model of HD (von Horsten et al., 2003), which represents an interesting model for translational research, as 51 CAG repeats more closely reflect the human disease, and the longer survival of these animals allows age-related studies. Adult neurogenesis was analyzed in 8- and 12-month-old HD rats. The decrease in hippocampal progenitor cells was accompanied by an expansion of the quiescent stem cell pool (characterized by BrdU and Sox2 co-expression) and diminished cAMP-responsive element-binding protein signaling (Kandasamy et al., 2010). Phospho-Smad 2, which is involved in TGF-β signaling that is normally not present in subgranular stem cells, is increased in neural quiescent stem cells in these HD transgenic rats, indicating that TGF-b signaling is involved in modulating adult neurogenesis in HD (Kandasamy et al., 2010).

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