The influence of neurogenesis in hippocampal function

Lysanne Jorna
Biomedical sciences bachelor
Supervised by E.A. van der Zee

Summary

After the research community accepted the fact that neurogenesis takes place in the subventricular zone, after which the cells migrate to the olfactory bulb, and the dentate gyrus of the hippocampal formation, questions raised about the function of such mechanism. For many years, these functions were studied in a behavioral context, by ablating neurogenesis in for instance the dentate gyrus and the subsequent search for impairments in brain function. Other research focused on the cellular aspects of the birth and maturation of neurons.

The hippocampal formation has been found to have a function in spatial navigation and the formation of memories. It consists out of several connected regions, forming a signaling loop. The signal from various sensory regions of the brain first arrive in the entorhinal cortex. Subsequently, the signal is sent to the dentate gyrus. This region signals to the CA3. From there, the signal travels to the CA1, which sends to the subiculum. The subiculum closes the loop by sending the input back to the entorhinal cortex. There are many other signaling routes within this structure, which makes it hard to pinpoint the exact function of each of those areas, and how neurogenesis influences this function. Behavioral studies shed light on the more general features.

Neurogenesis in the hippocampus has been found to influence the capability of the organism to distinguish between two different events. The rate of neurogenesis does also correlate with the separating ability. However, the precise cellular mechanism of this process is unknown and highly disputed in the neuroscience field. Two opposing views, the one of Aimone *et al*, which supports the memory resolution theory, and the one of Sahay *et al*, which embraces the more accepted pattern separation view, both explain the behavioural findings of the recent years but differ highly in the mechanism in which this is controlled.

Unraveling this mechanism might be crucial for the proper treatment of conditions in which this separating function is disturbed, like autism, post traumatic stress disorder (PTSD) and anxiety.

Index

Introduction

In 1965 a scientist named Altman proposed that neurogenesis was possible in certain regions of the rat's brain.(Altman and Das 1965, 953-956) Unfortunately, this finding was not enough to break the general dogma that the brain has a constant number of cells. The science community thought there was not enough proof Altman's [^{3}H]thymidine-labelled cells were truly neurons. To prove those cells were of a neuronal nature, Kaplan used electron microscopy to determine the morphology.(Kaplan and Hinds 1977, 1092-1094) Unfortunately, a specific neuronal marker did not exist at that time thus the experiment was not enough to convince other scientists. For years Altman and Kaplan's findings were ignored, until Goldman and Nottebohm observed neurogenesis in the vocal control nucleus of the canary brain.(Goldman and Nottebohm 1983, 2390-2394) Since that discovery evidence piled up supporting the occurrence of adult neurogenesis. (Gould et al. 1992, 3642-3650; Cameron et al. 1993, 337-344) Now it is widely accepted that neurogenesis occurs in the Subventricular Zone (afterwhich the neurons migrate to the Olfactory Bulb) and the Dentate gyrus (DG) of the hippocampal formation (HF).

After the occurrence of neurogenesis was accepted by the scientific world, questions raised about the regulators, and more importantly, the function of such mechanism. Due to poor scientific techniques and research material this question was hard to answer. Now, a few decades later, the techniques have significantly improved. We now have markers that are neuron specific, which are used to support neurogenesis. (Gould et al. 1992, 3642-3650; Cameron et al. 1993, 337-344) Also, lineage tracing is made possible by the BrdU staining technique combined with immunohistochemistry (Kempermann, Kuhn, and Gage 1997, 493-495), to get more insight in the proliferation process, and the maturation and migration of the newly formed neurons. With the discovery of this method, studying neurogenesis in the rat brain became easier and attracted many interested scientists.

Since then, many intrinsic and extrinsic factors have been found to influence the rate of neurogenesis in rats and other mammals. Examples of intrinsic factors are factors that regulate the cell cycle, and those who control cell fate. Also a lot of extrinsic regulators have been found, each affecting neurogenesis in a positive or negative way. E.g. numerous hormones and steroids, neurotransmitters and –regulators, trophic factors (like VEGF), morphogenic factors, and neighboring glial cells. (for a review see (Abrous, Koehl, and Le Moal 2005, 523-569)) Also, changes in life environment and behavior seem to influence neurogenesis. When rats are placed a running wheel in their cage, and choose to use that (voluntary running), neurogenesis seems to be upregulated. (Wu et al. 2008, 1585-1594; Van Der Borght et al. 2006, 36-41; Van der Borght et al. 2007; Van Praag et al. 1999, 13427-13431) Environmental enrichment, the addition of toys and other rats to the environment, also enhances neurogenesis and the performance of those rats in hippocampus-specific learning tests.(Paizanis et al. 2007, 1762-1771; Bruel-Jungerman, Laroche, and Rampon 2005, 513-521)

An upregulation of neurogenesis is often associated with a possible cure for numerous brain-associated diseases. (Abrous, Koehl, and Le Moal 2005, 523-569; Perez-Gonzalez et al. 2011; Winner, Kohl, and Gage 2011, 1139-1151; Ang et al. 2010, 25; Taupin 2010, 16-21; Elder, De Gasperi, and Gama Sosa 2006, 931-940; Limke and Rao 2003, 615-623) But without extensive knowledge of the function and survival of those neurons, thus the function of the DG and the structures influencing it, the relevance of upregulating neurogenesis can be questioned. This essay focuses on the question whether or not changes in neurogenesis have an effect in hippocampal function. To find an answer to this question, the 'normal' function of the hippocampus and HF is described, along with the function of the different regions within this structure. Next we zoom in at one of such regions, namely the DG, and the specific role it plays in the storage and formation of memory. Since the DG is one of the regions that generate new neurons, the possible role of those new neurons in DG function is discussed, thereby describing different theories concerning the function of the new neurons in the DG. Subsequently the survival of the newly created neurons is discussed, along with a recent finding by Sahay et al. in this field of study.

1.0 Hippocampus, the place where new neurons are formed

In this chapter the HF and other important structures are introduced.
We zoom in from the greater brain structures like the limbic system, to the HF within that structure. Next, the components of this formation are discussed, to learn more about their location, anatomy and function. Several of those structures are further highlighted in this paper because of their significance in memory formation.

1.1 The location and anatomy of the hippocampal formation.
The HF lies in the medial temporal lobe of the human brain, and is part of the limbic system. This system consists out of many other highly conserved and closely connected regions. Those regions do not only play a role in memory formation, but also in emotional and sexual behavior, motivation and the integration of homeostatic responses. (Afifi and Bergman, 2005) Because of the numerous connections between the different regions it has been found that the HF, normally known for regulating memory formation and spatial navigation, could also help to fight emotional diseases like depression by reacting to antidepressants.(Veena et al. 2011; Surget et al. 2011) Another example of interconnection of the limbic system components is the activation of the HF by fear. (Kirby et al. 2011) The amygdala, a limbic structure, sends activating signals to the HF when a human or other animal is startled or anxious. This activation leads to a powerful memory formation of the event, warning you when you find yourself in a similar situation. This interconnection of regions makes it hard to study the specific function of separate brain structures.

The HF is a collection of several highly connected brain regions. It consists out of the entorhinal cortex, DG, hippocampus proper and the subiculum (presubiculum, parasubiculum). (Andersen, 2007) The DG is a C-shaped structure, which lies adjacent to the hippocampus proper. The hippocampus proper lies within the inner part of the C, and curls upwards around the C making the complete structure somewhat S-shaped. Out of the hippocampus proper follows the subiculum, making the C of the DG almost entirely enclosed by tissue. The pre- and parasubiculum again curl backwards, positioning the adjacent entorhinal cortex almost parallel to the subiculum.

The hippocampus proper is often divided in several regions called CA3, CA2 and CA1. (CA stands for Cornu Ammonis, or Ammon's horn because of the horn-like shape of the hippocampus) The CA3 region is located closest to the DG. It consists out of a group of densely packed neurons and can be easily identified in humans and other species. (Andersen, 2007) The CA1 region is the largest hippocampal CA region in humans and is located at the end of the hippocampus proper, close to the subiculum. Next to the CA-division of the hippocampus, there is a 'horizontal' division, which separates the hippocampus into three layers. These are the molecular layer, the pyramidal cell layer and the stratum radiatum. These layers extend from (the end of) the DG all the way to the subiculum. The pyramidal cell layer is a place where the most pyramidal cells are found. These cells are the ones that generate hippocampal output, with dendrites in the molecular layer and the stratum radiatum, and axons towards the fornix. The stratum

radiatum houses some polymorphic or ‘basket’ cells. These cells inhibit the function of the pyramidal cells and establish connections with hundreds of pyramidal cells.

Like the hippocampus, the DG also consists out of three layers. These are the same as the hippocampus, but the stratum radiatum is now called the polymorphic layer. This is because of the slightly different composition of the layer. The molecular layer of the DG is continuous with that of the hippocampus proper. The cellular layer of the DG is called the granule cell layer, or granular layer. This is also the place where new neurons are formed. Granule cells within this layer also extend their dendrites to the molecular layer and project their axons to the CA3 region. This feature is further discussed below. Within the polymorphic layer of the DG various cells reside, including basket cells and pyramidal cells. (Afifi and Bergman, 2005)

The entorhinal cortex (EC) is a structure that signals to the hippocampus, thus providing the input. The EC consists out of two or more distinct cellular layers, depending on the species (Witter 2007, 43-61). Rats have five different layers, out of which I and VI are acellular and II, III, IV, V consist out of cells. Layer II and III are the most important here, because the cells in those layers extend their axons to the HF. All layers differ in composition, for instance layer II consists mainly out of stellate cells, and layer III out of various cells of all shapes and sizes, but mainly pyramidal cells.

1.2 Connections

Like described before, the HF is densely interconnected. The EC is responsible for most of the input the structure receives. Important to know is that this input travels through several regions of the HF, where it is processed, and then travels back to the EC. Also, in contrast to other regions of the brain, the signal is often not transferred backwards (no reciprocal innervation) and is always excitatory, exept for basket cells. (Afifi and Bergman, 2005) The different connections of the loop will be discussed below.

It starts when the EC receives diverse sensory information from the frontal, parietal, occipital and temporal lobe of the brain. This incoming signal is transferred to the rest of the HF using the perforant pathway (Witter 2007, 43-61). This pathway is called the perforant path because in order to reach the HF it has to perforate the subiculum. Axons originating from layer II of the EC project their signal to the DG and the CA3 region of the hippocampus. Those originating from layer III innervate the CA1 region of the hippocampus and the subiculum. The main route the signal takes however is to the DG. The DG extends its axons to the CA3 region of the hippocampus. These axons are called the mossy fibers. Subsequently, the CA3 region sends the signal via axons called Shaffer collaterals, through the CA2 area to the CA1. From here the signal can be projected back to the EC or to the subiculum, which then projects to the EC. (*fig.1*)

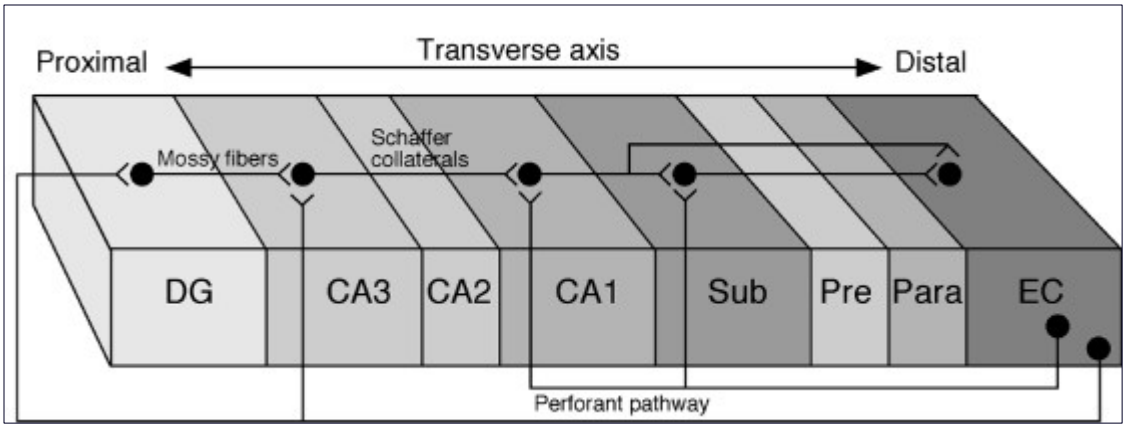

Figure 1. **The connections of the hippocampal formation.** The cells from EC layer II project via the perforant pathway to the CA3 and the DG. EC layer III connects to the CA1 and the subiculum. From the DG the signal is sent to the CA3 through Mossy fibers. From there, the Shaffer collaterals signal to the CA1 region. The CA1 region sends his input to both the subiculum and the EC. The subiculum sends his signals to the EC. This image is adapted from The Hippocampus Book by Andersen and coworkers.

1.3 The function of the hippocampal formation

Now we know the structure and connections of the HF, the function of this formation can be explored. It is generally accepted that the HF plays a role in contextual and spatial memory, thus the storage and retrieval of facts and events and finding your way in an environment respectively. This aspect has been found in as early as 1971 by a scientist called D. Marr. (Squire, Stark, and Clark 2004, 279-306; Eichenbaum, Yonelinas, and Ranganath 2007, 123-152) Many other functions are thought to be connected to the hippocampus as well. These are for example short-term memory (Marr 1971, 23-81), decision making (Ranganath and D'Esposito 2001, 865-873), and others (Kumaran et al. 2009, 889-901).

The mechanisms underlying the storage and retrieval of facts and spatial navigation have been studied extensively, although the contribution of each subregion of the hippocampus is still a subject of debate. An already accepted view is that the HF first creates a complete picture of the event. To do that, it connects specific bits of sensory and spatial information provided by the cortex and the EC. It also compares the event with previous ones, and tries to distinguish subtle differences between them, eventually making associations and play a role in the storage or encoding of the event.

To eventually explore the role of neurogenesis in this process, it is important to have an impression of the specific function of each hippocampal region. The least controversial viewpoints are described below.

The Entorhinal Cortex

The enthorhinal cortex collects information from various regions of the brain. This information is often sensory (e.a. visual, occipital). The EC is said to provide a context to the memories that are formed by the hippocampus. This context can be divided in the ‘spatial’ aspects of the event, and the ‘nonspatial’ aspects.(Bonnici et al. 2011) The lateral

EC mainly activates context specific neurons and the medial EC to the 'place neurons' to provide spatial information.
The spatial aspects of a particular event, like the direction you're heading, the location's relative position along a common type of route, the distance to the environment's walls, whether or not you are walking clockwise or counterclockwise (the direction of movement), and your location in a specific environment, are combined in the EC and give a general idea of the current location and heading. (Hargreaves et al. 2005, 1792-1794) Several different cell types, like place cells, border cells, path cells and grid cells are responsible for these spatial aspects. (Jacobs et al. 2010b, 6487-6492; Moser, Kropff, and Moser 2008, 69-89; Solstad et al. 2008, 1865-1868) These cells fire at different rates to give information about the organism's location and direction. For example, grid cells fire when an organism is moving freely around in a particular space. The grid cells will fire only when the organism is at certain locations. When these places of high grid cell activity are mapped in one figure, dots appear that form a triangle-shaped grid covering the entire space. (Moser, Kropff, and Moser 2008, 69-89; Solstad et al. 2008, 1865-1868; Jacobs et al. 2010a, 6487-6492) Path cells however fire continuous when the organism is moving and give information about the general heading. Some path cells fire more intensively when the organism is moving clockwise, others when moving counterclockwise. (Jacobs et al. 2010a, 6487-6492; Doeller, Barry, and Burgess 2010, 657-661)

The nonspatial aspects, like smell, taste and recognition of objects, are also collected in the EC. This makes that every cell within the EC contains a bit of the information of the event and its context, whether it is perceptual, spatial or cognitive. (Jacobs et al. 2010a, 6487-6492) This information is then sent to the DG.

The Dentate gyrus
There are many theories of the function of the DG. (Jacobs et al. 2010a, 6487-6492) The theory that states that the DG provides specific codes to the hippocampal network is one of the least controversial. (Aimone and Gage 2011, 1160-1169) The DG processes incoming information to separate a previous event from the current one. Also, the DG can recall a complete memory based on a particular cue, like remembering your beach vacation when spotting a palm tree. Thus, the DG is needed to make associations between events. These two processes are called pattern separation and pattern completion respectively. Also, new neurons are formed in the DG.

Pattern separation
The DG contains about five to ten times more neurons compared to the EC.(Bakker et al. 2008, 1640-1642; Leutgeb et al. 2007, 961-966) Due to this feature, the signal from the EC is spatially divided. The input from the EC is provided by the many neurons that signal, and can be seen as a specific pattern. Through the interplay of inhibitory neurons and the granule cells, the DG codes sparsely but powerful to the CA3 region, creating a memory trace of fewer cells. Due to this interplay the DG enlarges slight differences in the EC signal, thus a following event in a different context will create a different pattern of activated cells in the DG, and subsequently in the CA3. (Amaral, Scharfman, and Lavenex 2007, 3-22,788-790).(Deng, Aimone, and Gage 2010, 339-350)

Therefore pattern separation can be considered as a mechanism which separates highly similar yet different events and translates them to specific codes. (*fig.2*) Due to this mechanism an organism is able to store and recall these memories properly, thus be able to notice slight differences between events. This is considered the main function of the DG.

Pattern completion

There are two definitions of pattern completion. One states that the recall of a complete memory based on an associated cue is considered pattern completion. (Aimone, Wiles, and Gage 2006, 723-727) Another one states that when the overlap of the input signal to a reference memory is enhanced in the output signal you can speak of pattern completion. (Hopfield 1982, 2554-2558) Pattern completion is used to make associations with previously formed memories, recalling that when you see a pink rubber duck this is almost the same object compared to the yellow one, instantly knowing where and when to use this object, and maybe recalling a childhood memory of you playing in the bathtub.

Neurogenesis

In rats, a relatively great number of neurons is added to the DG each day. (Nolan et al. 2011, 647-660) However, the survival rate of newly born neurons is low(Altman and Das 1965, 953-956) (Altman and Das 1965, 953-956), stabilizing the total DG neuron population. In a few weeks, the newly born cells form connections with the DG network and extend axons to the CA3 region of the hippocampus. (Kempermann et al. 2003, 391-399)

Scientists haven't found the function of these neurons yet. The most common finding is that these neurons contribute to the pattern separation mechanism, explaining the great capacity of the DG to do this. (No other area in the HF involved in pattern separation shows neurogenic activity) The general idea is that without neurogenesis, the EC codes to the distinct subset of neurons within the DG. Consequently, a limited amount of 'codes', or combination of cells is possible. The addition of extra 'unwritten' neurons to the DG is said to increase the amount of available codes. This prevents the overlapping of memory traces, helping pattern separation. (Deng, Aimone, and Gage 2010, 339-350)

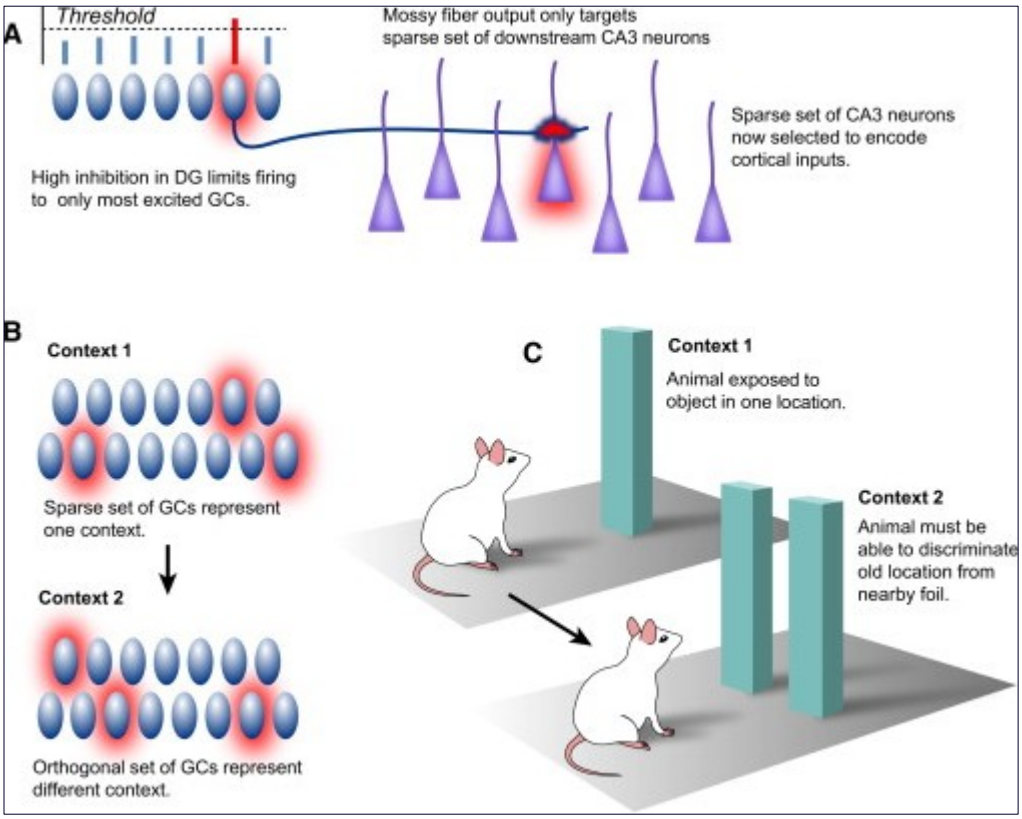

Figure 2. **Pattern separation in the Dentate gyrus.** A. The interplay of intrinsic inhibitory neurons limits the output of the DG, resulting in a limited amount of neurons coding to the CA3. B. Two (slightly) different contexts will activate different subsets of neurons. C. The different contexts are encoded differently making it easier to distinguish one contest from another, noticing slight differences in the environment. This figure is adapted from Resolving New Memories: A Critical Look at the Dentate Gyrus, Adult Neurogenesis, and Pattern Separation by Deng *et al.* (Deng, Aimone, and Gage 2010, 339-350)

The CA3 region

The CA3 region receives input from various brain regions, but the residing neurons are mostly connected to each other.(Aimone, Deng, and Gage 2011, 589-596) Only one-third of the neuronal signal is received from those other brain regions, in which the signal derived from the EC is the most prominent. Only a small part is received from the DG. Like described in section 1.1 of this essay, the CA3 and the DG receive the same information through the Perforant path. Input is used to make a neuronal network of activated neurons, mostly connecting the neurons activated by the DG. Within the CA3, the information obtained from the DG and the EC is used to separate known from unknown information. To do this it uses the pattern separation as well as a pattern completion method, contributing to the DG signal.

Like in the EC, the CA3 region contains place cells that give information about the location of the organism, heading, and context of the event. In order to separate known from unknown information, the input pattern is compared to a reference memory. When the amount of overlap reaches some kind of threshold, the CA3 region switches from pattern separation to pattern completion. (Amaral, Ishizuka, and Claiborne 1990, 1-11)If not, this information is considered ‘different’ or ‘unknown’. Upon storage, this will become a different memory trace. This makes the CA3 well suited for registering subtle differences in the environment. (Nolan et al. 2011, 647-660)

The CA1 region

The neurons of the CA1 are highly similar to those of the CA3 in terms of their firing properties. (Leutgeb et al. 2004, 1295-1298)However, the CA1 pyramidal cells are not as interconnected compared to the CA3. Another difference is that the CA1 receives information from a different cellular layer of the EC, layer III. It also receives information from the thalamus directly. An interesting fact is that the Shaffer collaterals descending from the CA3 region connect to the same CA1 cells innervated by the EC. (Leutgeb et al. 2004, 1295-1298)

The function of the CA1 seems to be different compared to CA3. The CA1 contains a high number of place cells, giving information about the context of the event. This might be completed by the EC signal. Leutgeb et al stated that, because of the strongly separated codes of the CA3 in overlapping contexts, the CA1 therefore measures the amount of overlap between events. (Kajiwara et al. 2008, 266-280)

The output of the CA1 is sent back to the EC, but also to the subiculum. The subiculum is the end stage of the pathway. It combines the information obtained from the CA1 and the EC into the final image, and sends this information back to the EC and along the other output routes of the hippocampus.

2.0 The effect of neurogenesis in the dentate gyrus

Like described before, the formation of neurons in the DG of the HF is a generally accepted event. Lots of theories explaining the function of the DG in the memory encoding and recall process have been proposed. (Leutgeb et al. 2004, 1295-1298)When neurogenesis was accepted by the scientific world, these theories had to somehow incorporate neurogenesis. Most theories stated that the addition of fresh neurons is a way to expand the amount of specific codes the DG can produce. This will prevent overlap between different memories.(Aimone and Gage 2011, 1160-1169) (see also section 1.2.2) Two different recently published theories will be compared.

2.1 The theory by Aimone *et al.*

One theory explaining the function of neurogenesis in the DG, the one of Aimone and coworkers, (Deng, Aimone, and Gage 2010, 339-350) is a model with a high focus on neurogenesis because it addresses some key functions to the newly formed neurons, due to their maturation and corresponding changes in connectivity and physiological properties. They see the new neurons as individual encoding units, but found in their computational studies that the new neurons negatively influenced the pattern separating function of the DG. (Aimone, Wiles, and Gage 2009, 187-202)In short;

Immature neurons integrate into the DG network very early in their maturation process. However, their electrophysiological properties remain different from mature neurons for a few months. Within this time their excitability is enhanced, and they show more neuronal plasticity compared to their mature counterparts. (Aimone, Wiles, and Gage 2009, 187-202)(Deng, Aimone, and Gage 2010, 339-350) Aimone et al found that neurogenesis partly inhibits pattern separation. They used a computational model to make a complex neuronal network with the same topography and properties as the DG. The rate of neurogenesis could be varied. They found that when the events were highly similar in both inputs the pattern separation was comparable to the no-neurogenesis model. However, when the inputs are completely different, thus have changes in context and spatial location, the rate of neurogenesis influenced the output signal. When there was no neurogenesis, the two nonoverlapping patterns became the most distinct. The higher the degree of neurogenesis, the more the output signals seem to overlap and blur together. They call this phenomenon pattern integration. This is not to be confused by pattern completion, because pattern completion is a process that happens downstream of the DG and aims to connect and associate overlapping events. According to Aimone et al this blurring happens due to the incorporation of time in memories by new neurons. This also explains the finding that pattern separation increases when there is more time between the two events.

The results of this computational study seem to be the complete opposite of most behavioral studies, including the one of Sahay *et al* (described below). Most of those studies found that neurogenesis enhanced pattern separation in the DG. But pattern separation happens in more brain areas involved in memory and learning, and there is a lack of a clear role for young neurons that makes them advantageous in the 'classic' pattern separation mechanism. But the fact that neurogenesis happens in the DG, and therefore is biologically conserved, supports the generally accepted view that this process is important. This made Aimone et al question the concept pattern separation as a role for the DG. Therefore they developed a theory that attributes an autonomous role to the newly formed neuron. This theory is called the 'memory resolution theory'.

Memory resolution theory

By memory resolution they mean the extent of information encoded by the DG during memory formation. Because the DG signals to the rest of the HF, this also influences the extent of information the rest of the HF receives. Suppose you retrieve previously learnt information to make some kind of decision. When the coding of the DG is low on information, or resolution, the image retrieved is low-detailed which makes it hard to make the decision. When the retrieved image is of high resolution, the high amount of details within makes it more easy to separate two different contexts, thus decision making. (*fig.3)*

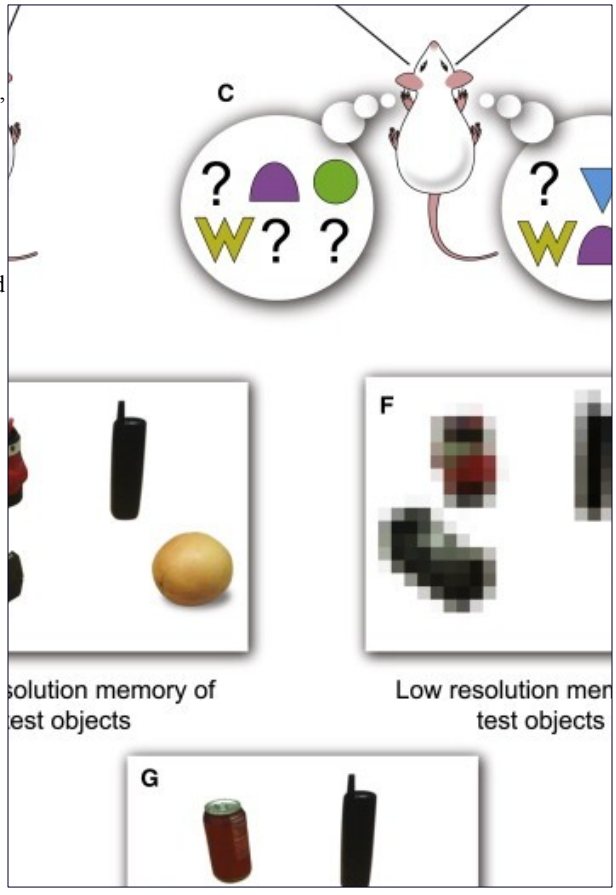

Figure 3. **The memory resolution theory.** A. a reference context is learned. This contains several different objects arranged in a specific way. B. Upon encountering a context where you have to choose the previous learned memory (A), the low resolution memory impairs discrimination (C) and the high resolution memory enables discrimination. (D) E. A high resolution memory. F. a low resolution memory. G. novel objects are better discriminated by a high resolution memory.
This figure is adapted from Resolving New Memories: A Critical Look at the Dentate Gyrus, Adult Neurogenesis, and Pattern Separation by Aimone *et al.* (Ge et al. 2007, 559-566)

But how does neurogenesis fit into this picture? According to Aimone *et al* the mature neurons provide a highly specific but sparse representation of the event, by reacting to features that are already known. The immature neurons provide a broad, unspecific representation by reacting to all signals (also new ones) arriving in the DG. (*fig. 4*) Combining these neuronal signaling pathways optimizes the information coded by the DG, thus further increasing the resolution. New neurons react during their maturation to numerous new events, allowing them to form a neuron that codes specifically to the new event. On a population level, these events can be already known, maintaining the information, or new, incorporating new information. This completes the memory and enhances the resolution. A high resolution also helps to separate the formed memories and minimizes the interference in downstream networks, a feature that is consistent with the generally accepted function of the DG and the pattern separation theory.

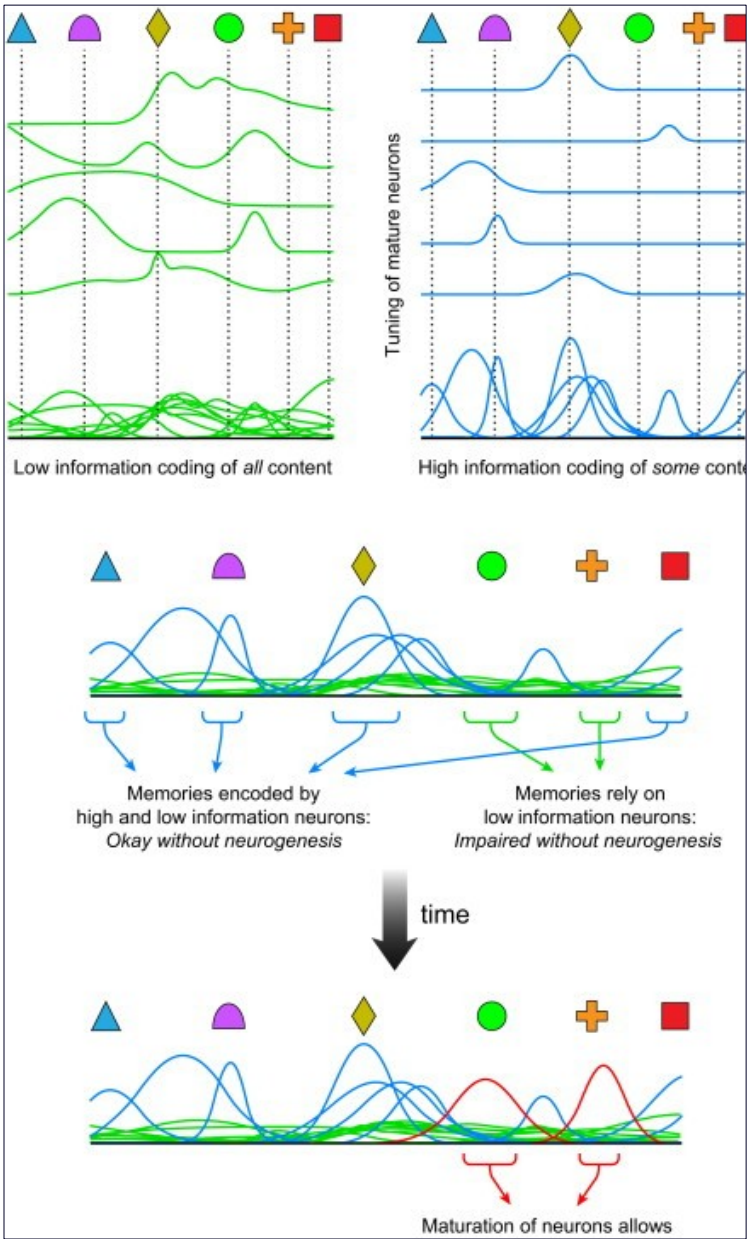

Figure 4. **Resolution of mature and immature neurons.**
A. immature neurons fire unspecifically to all input received from the EC. This creates a general, low-informative image of all objects. B. Mature neurons fire to specific bits of EC input, giving a high resolution image. C. These two inputs combined, with only the unspecific, low-informative picture from the immature neurons for new objects. D. Over time, the young neurons mature and specify to input met during maturation. This leads to a specific, high-information signal to that input, enhancing the overall resolution to that memory.

2.2 The theory of Sahay *et al.*

The opposing view of Sahay et al states that new neurons do play a role in pattern separation. (Sahay et al. 2011) This view is based on biological findings in mice. By DG X-ray irradiation of mice, thus inhibiting new neurons to be formed, they were able to show that the mice had problems in discriminating two highly similar contexts. Moreover, the genetic upregulation of the survival of neurons (described below) showed an enhanced pattern separation of two similar contexts. (Aimone, Deng, and Gage 2011, 589-596)

The proposed mechanism behind these findings is that young neurons, due to their different properties like lower activation threshold and higher plasticity, respond earlier to subtle changes in contexts (weak signal). They signal to the interneurons of the DG, thereby regulating the firing properties of the mature cell population by feedback inhibition. This will regulate the sparseness of the code to the CA3. Enhanced sparseness will result in an enhanced pattern separation. A finding in favor of this proposed mechanism is that of Singer *et al* (Singer, B.H. 2009 567-582; Singer B.H. 20115 437-5442). They found that the ablation of neurogenesis in the DG diminishes the inhibitory stimuli of the interneurons.

Just like Aimone et al, Sahay et al do not believe this is the only thing new neurons do in the DG. Sahay et al speculate the new neurons could have a role in the transforming of memories to the neocortex, 'clearing' the DG to make room for new memories. Also, due to the competition of new neurons versus mature ones for EC input and postsynaptic targets they might play a role in the redistribution of synaptic strengths.

What makes neurogenesis unique in the pattern separating function of the DG according to Sahay et al? Neurogenesis acts as a highly sensitive regulator, detecting the subtle changes in the environment. By reacting to small changes and subsequently signaling to the interneurons of the DG, they play a role in enhancing pattern separation in the DG. This makes the DG a sensitive pattern separator, minimizing the interference or overlapping of memories in the downstream areas of the hippocampus.

Also, when combining the findings that enhanced neurogenesis promotes pattern separation and an ablation of neurogenesis does not (thus promotes pattern completion), you can say that the rate of neurogenesis influences whether or not the balance shifts to pattern completion or separation. (*fig*.*5*) This could indicate a functional role in the effect of the environment on neurogenesis. Like stated before, exercise and environmental enrichment, as well as learning and diverse compounds like antidepressants enhance neurogenesis. If the survival of neurons is also enhanced, the balance shifts to pattern separation, inducing enhanced discrimination between events and cognitive flexibility. Stress, ageing, and sensory deprivation decrease neurogenesis which shifts the balance to

pattern completion. This induces a generalization of events. A maladaptive response could be the mechanism of several pattern separation associated diseases.

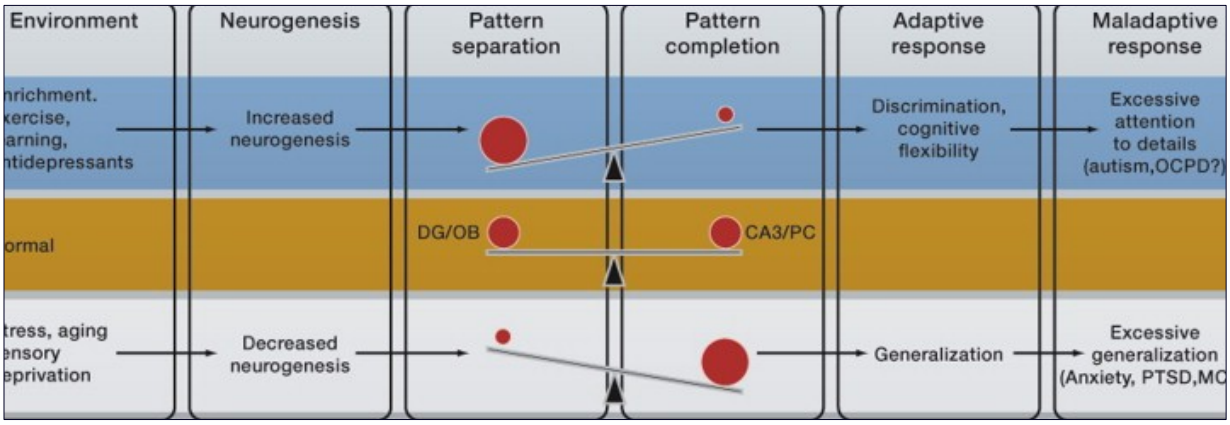

Figure 5. **The influence of neurogenesis on the balance between pattern separation and pattern completion.** Environmental factors determine the increase or decrease of neurogenesis. The theory proposed by Sahay et al states that an increase in neurogenesis shifts the balance to pattern separation. The decrease in neurogenesis has the opposing effect, by shifting the balance to pattern completion. This balance opens ways for an adaptive response to changes in the environment, by either enhancing discrimination and cognitive flexibility (pattern separation), or generalization (pattern completion). Numerous diseases have been associated with an exaggeration of the adaptive response. Autism and obsessive compulsive personality disorder (OCPD) are associated with an overactive pattern completion mechanism, and anxiety, post traumatic stress disorder (PTSD) and mild cognitive impairment (MCI) with extensive pattern completion. This picture is adapted from Pattern separation: A common function for the DG and the olfactory bulb' by Sahay *et al*.

2.3 Comparison

The purely computational study of Aimone *et al* speculates that the newborn neurons have an autonomous function in memory encoding. They enhance the resolution of memories by encoding the new features. Sahay *et al* state that the new neurons are purely regulatory and code to the inhibitory interneurons of the DG, which in turn regulate the sparse coding of the DG to the CA3. If you relate the theory of Aimone *et al* to the behavioral findings of Sahay *et al*, it also perfectly correlates, because it can be stated that alterations in neurogenesis would affect the quality of memories. This can only be measured when the behavioral task needs high memory precision, like discriminating between two highly similar events. In Sahay et al, mice performed a task like this, while their neurogenesis was ablated. This test revealed that these mice performed poor in separating the two events, supporting both visions because this could be caused by impaired regulation as well as a low resolution memory. Also, enhanced neurogenesis results in a better performance because of a better regulation of a better resolution due to a higher chance that a new neuron fires to a new stimulus. In summary, both theories yield the same results, yet the mechanisms by which they do that are different.

However, the function of the CA3 region in separating known from unknown information gets easier when the theory of Aimone *et al* is followed. Because the downstream CA3 region gets signals from both the DG and the EC, the function of separating known from unknown information gets easier, and a more defined task. When the CA3 is somehow able to recognize the axons descended from newborn neurons, which is plausible because of their altered physiology and firing rate, they know which information is new.

Overlaying this information with the one of the EC or a reference memory, new features are easily spotted. Only, this does not rule out the theory of Sahay *et al*. More research has to be done to be able to fully exclude the wrong theories.

2.4 Integration

Van der Borght and coworkers found that exercise improved the acquisition and retrieval of memory in mice, and also the performance in reversal learning. (Van der Borght et al. 2007) Neurognesis was enhanced due to voluntary running, and memory retrieval induced a reduction in the number of maturing neurons. They concluded that the acquired results suggest that learning, memory and neurogenesis are related to each other, however they were not able to elucidate the exact mechanism of this interaction because of the complex and highly dynamic nature.

The memory resolution theory states that new memories, thus learning, and recall in the DG is dependent of the resolution of the memory. The enhanced performance in the voluntary running group is due to the increase in neurognesis. The mice were habituated to the Y-maze, making the memory to the Y-maze structure (without reward) a high resolution memory using the mature neurons. Upon training, the mice received a food reward (which was important to the mice due to the restricted diet) when they choose the correct side. This is a new event, and thus learned by the new/immature neurons. These neurons react to all input, in an unspecific way. The more immature neurons an organism has, the higher the chance a neuron reacts to the new event, creating a slightly higher resolution of the event compared to mice with normal neurogenesis rates. *(fig. 4)*
The reduction in the number of maturing neurons induced by memory retrieval could be due to the memory trace itself, because only high resolution mature neurons and the few new neurons coding for the 'new' part of the memory are needed. The rest of the maturing neurons might not have a function in this and could only cause memory interference. Like they speculate in Van der Borght et al. the decrease in maturing neurons could be to prevent memory interference.

The pattern separation theory as stated by Sahay and coworkers has another explanation considering the findings of Van der Borght et al. New neurons detect small changes in the environment due to their enhanced sensitivity. These neurons code to the interneurons which in turn regulate the sparseness of the coding to the CA3. The sparser the code, the less interference or 'noise' is transferred. The more neurons, the more pure and separate the signal becomes. Thus, more neurons due to voluntary wheel running contributes to the 'pureness' of the signal, making it easier to learn new tasks. Sahay and coworkers do not mention the process of memory retrieval in detail, but according to their statement that new neurons react to small changes in the environment you can state that they are not involved in the retrieval process of already formed memories. This is also in agreement with the finding of Van der Borght et al., stating that the amount of maturing neurons decreases in memory retrieval. The new neurons do not benefit the retrieval process, because they react to new features in the environment which could influence and interfere with the recalled memory.

3.0 Behavioral studies

The viewpoints of both Aimone and Sahay and corresponding coworkers are just two out of many viewpoints. Numerous views concerning the mechanism of adult neurogenesis, including the ones described above, are based on the findings of behavioral studies. These studies significantly contribute to the understanding of neuronal mechanisms, and might play an important role in unraveling the cellular mechanisms of learning and memory. In order to determine the right viewpoint, more of these studies have to be done. However, there are some hurdles to overcome. An important technical difficulty and recent progress in overcoming this difficulty is discussed in this chapter.

3.1 Proliferation versus the survival of neurons

In order to study the function of the new neurons, it is necessary to be able to alter the number of neurons (thus neurogenesis) in the DG. The ablation of neurogenesis was established easily by e.a. X-ray irradiation of the DG, and furthermore a lot of compounds have been found to increase neurogenesis, along with changes in the environment and voluntary exercise. (Veena et al. 2011; Lagace et al. 2010, 4436-4441; Leuner, Glasper, and Gould 2010; Van der Borght et al. 2007) However, the upregulation of neurogenesis was disputed because of the technical difficulties to proof that the increased proliferation was not accomplished with an equally enhanced rate of cell death.

The neuronal progenitor cells that give rise to the new neurons have a relatively high turnover rate. (Schoenfeld and Gould 2011; Wojcik-Stanaszek, Gregor, and Zalewska 2011, 103-112; Balu and Lucki 2009, 232-252) If all those neurons are maintained throughout life, the hippocampus would be increasing in size. This is not the case, and therefore it is safe to state that neurons die at the same rate in which they are created. Now you encounter some problems, because an increase in neuronal turnover does not have to give more neurons, because the survival of the neurons is evenly decreased. Therefore an increase in neuronal proliferation does not have to give an increase in hippocampal function, thus memory retrieval and spatial navigation. Also, investigating the survival of the neurons is technically very difficult. Knockdown of neurogenesis in the animal was subsequently used to test the potentially beneficial effects of neurogenesis.(Amaral, Scharfman, and Lavenex 2007, 3-22,788-790; Amaral, Ishizuka, and Claiborne 1990, 1-11). Some studies did investigate the increase of proliferation rate of adult neurons on hippocampal function, and many studies found that an increase in ‘neurogenesis’ did enhance spatial navigation and memory performance (Jessberger et al. 2009, 147-154; Goodman et al. 2010, 769-778; Dupret et al. 2008), but this has been disputed because they found an increase in neuronal proliferation but could not investigate the survival of the neurons.

3.2 Upregulating the survival of newborn neurons

Sahay *et al* have found a way to enhance the survival of the new neurons in mice. (Sahay et al. 2011) They did this by ablating the *Bax* gene, a gene involved in neuronal

apoptosis. This selectively inhibited the apoptosis of the neuronal progenitor cells in the adult brain.

In order to check whether the genetically modified neurons really had the wanted features, they checked the amount of neurons, survival, brain architecture and integration of the cells. They found that the neuronal expansion of the cells was equal to, if not greater than the increase in neurogenesis found by DG stimulation by different compounds, environmental enrichment or exercise. The survivability was also increased. The body weight and brain architecture of the modified and control mice were similar, as well as the expression of DG markers such as calbindin. Interestingly, the volume of the granule cell layer of the DG was the same in both groups, suggesting that the cells are more densely packed in the *Bax*-modified mice. The modified adult born neurons were functionally integrated in the existing neuronal network, just like the 'normal' adult-born neurons.

Using this *Bax*-modification on mice, they were able to test the specific function of adult neurogenesis. In order to do so, the mice underwent several tests to investigate the effect on hippocampus-dependent learning and memory. An increase in neurgenesis did not influence the spatial learning and memory in the reference version of the Morris water maze, during reversal learning or in the active place avoidance test in *Bax*-modified mice and the control group. The exploration of a novel or a similar object was also comparable, as well as the ability to distinguish between two very different contexts.

However, the ability to distinguish between two highly similar contexts seemed to depend on the DG neurogenesis. Mice lacking adult-born neurons (by X-ray radiation) were impaired in their ability to distinguish highly similar events. The upregulation of neurogenesis enhanced the ability of the *Bax*-modified mice to discriminate between the two events, compared to the control mice. These results were found in three different fear-discriminating tests.

These findings tell us that enhancing the survival of the new neurons give the same results compared to the previous studies in which the neuronal turnover (proliferation) was upregulated, indicating that the survival of the neurons in these studies was also enhanced. This increases the reliability of those studies.

These findings also point out that the need to unravel the exact mechanism in which neurogenesis influences hippocampal function is important, because many diseases have been associated with an increase or decrease in neurogenesis. Finding the function of new neurons might help in the search for a proper treatment. For example, autism has been associated with an increase in neurogenesis (Sahay et al. 2011), which might explain their extensive attention to details. (with the so-called savants as an extreme example) Anxiety and PTSD have been found to have a decreased neurogenesis, associated with overgeneralization of events. For example, a soldier who accidentally shot a child might go through the whole memory again when seeing a child with the same haircut.

4.0 Conclusion

To determine the effect of adult neurogenesis in hippocampal function, research has to be done to pinpoint the exact function of the area in which neurogenesis takes place, namely the DG, and the effect of neurogenesis in DG function.

There are many theories concerning the function of the DG. The one of Aimone *et al* states that the DG plays a role in the resolution of the memory, thus determining the amount of information a memory contains. The higher the amount of information, the easier it gets to separate new memory traces from old ones. Most other theories, like the one of Sahay *et al*, state that the DG is involved in the 'classic' mechanism of pattern separation. Behavioral studies found that neurogenesis influences this function of the DG. Adding neurons enhances the capability to distinguish two events, whereas depletion of neurons lowers this capability thus induces pattern completion. Both Sahay et al and Aimone et al have a theory of the mechanism of this neuronal regulation, but more research has to be done to determine who is right.

There is some progress in this field, because Sahay et al found that increasing the survival of newborn neurons had the same effect compared to previous studies in which it was unclear whether or not the survival of neurons was also upregulated when increasing neurogenesis. This enhances the reliability of the findings in previous behavioral studies.The need for unraveling the exact mechanism in which neurogenesis influences hippocampal function is evident, because many diseases have been associated with an increase or decrease in neurogenesis. This could help to find a proper treatment for those diseases.

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