Abstract The hippocampal formation is a part of the limbic system located in the medial temporal lobe and consists of the three layered archicortex, mostly pyramidal cells. Hippocampal formation encompasses dentate gyrus, hippocampus proper and subiculum, and possibly presubiculum, parasubiculum and entorhinal cortex. It receives inputs from primary and secondary cortical sensory areas and multimodal associative areas. The main input comes through entorhinal cortex and output through fornix and other paths. It has been associated with declarative and procedural learning and memory, spatial orientation and memory, modulation of aggressive behavior, attention, and some endocrine and autonomic functions via hypothalamus. The complex functions of the hippocampal formation can be explained by the unifying hypothesis that the main hippocampal role is the generation and utilization of complex high-resolution bindings unifying the individual characteristics of an event. The main pathology of hippocampus has been described in depression, Alzheimer’s disease, Parkinson’s disease, schizophrenia, addiction, stroke, autoimmune encephalitis and epilepsy but it is susceptible to injury to various noxes. It has been documented that physical and mental exercise can improve the hippocampal function. It can improve the neurogenesis in adult dentate gyrus and improve mental health.

Key words: Hippocampus; Dentate Gyrus; Memory; Alzheimer’s disease; Depression;

Sažetak: Hipokamalna formacija je deo limbičkog sistema u medijalnom delu temporalnog režnja i sastoji se od troslojnog arhikorteksa, uglavnom piramidnih čelija. Hipokampalna formacija obuhvata gyrus dentatus, hipokampus u užom smislu reči i subikulum, a prema nekim i presubikulum, parasubikulum i entorinalnu koru. Informacije prima iz primarne i sekundarne senzorne kore i multimodalnih asocijativnih area. Glavni ulaz u hipokampus je preko entorinalne kore, izlaz preko fornix i drugih puteva. Hipokampus je doveden u vezu sa deklarativnim i proceduralnim učenjem i pamćenjem, prostornom orientacijom i pamćenjem, modulacijom agresivog ponašanja, pažnjom i nekim endokrinim i autonomnim funkcijama preko hipotalamusa. Kompleksna funkcija hipokampalne formacije može da se objasni objedinjujućem hipotezom da je glavna uloga hipokampusa stvaranje i korišćenje kompleksnih veza visoke rezolucije koje daju individualnu karakteristiku događajima. Glavna patologija hipokampusa je opisana u depresiji, Alzhajmerovoj bolesti, parkinsonovoj bolesti, shizofreniji, adikcijama, moždanom udaru, autoimunom encefalitisu i epilepsiji, ali je hipokampus osetljiv i na razne noške. Pokazano je da fizička i mentalna vežba mogu da poprave funkciju hipokampusa, odn. da poboljšaju neurogenezu u adultnom girusu dentatusu i unaprede mentalno zdravlje.

Ključne reči: hipokampus, gyrus dentatus, pamćenje, Alzhajmerova bolest, depresija

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Received: August 16, 2014
Accepted: October 1, 2014

Financial disclosure: This article is partially financed by the Ministry of Science, Republic of Serbia, Project No 175033 and 175022
INTRODUCTION

The hippocampal formation is located in the medial temporal lobe and is part of the limbic system. Hippocampus is classified as archicortex and has only three layers. It receives inputs from primary cortical sensory areas, secondary unimodal areas and multimodal associative areas. The main input comes through entorhinal cortex. Hippocampus sends back fibers to primary cortices where information is stored in the long term memory. For information to be preserved it has to be processed by the limbic system with additional influence of other, predominantly prefrontal areas (1). Hippocampal formation is a part of the limbic system along with the amygdala, parts of the thalamus, hypothalamus, ventral striatum, cingular gyrus, orbital and medial prefrontal cortex. It has been associated with declarative learning and memory, spatial orientation and memory, modulation of aggressive behavior, and some endocrine and autonomic functions via hypothalamus.

The most consistent findings confirm the role of hippocampus in memory processes, as a crucial part of broader system (2). Long-term memory is mediated by anterior temporal lobe, less frequently posterior temporal lobe (convergence zones) and other neocortical areas. It has role as well in recollection of semantic and episodic memories. Prefrontal cortex activation is of utmost importance in these processes. Hippocampus has practically no role in olfaction, but is involved in perception and organization of other sensory information.

In this article we review the basic anatomical and functional characteristics of the hippocampal formation and the essential neurological and psychiatric conditions where hippocampal pathology is important.

Anatomical considerations

Hippocampal formation is located in the medial temporal lobe encompassing (but with no consensus among scientists) (3): dentate gyrus, hippocampus proper and subiculum, while other authors add presubiculum, parasubiculum and entorhinal cortex (4). It extends along the floor of the inferior horn of the lateral ventricle and continues with the fornix below the splenium of the corpus callosum. Hippocampus is also a part of the inner limbic gyrus of the limbic lobe and can be subdivided to head, body and tail (5).

Hippocampus belongs to the three-layered archicortex. The main type of cells are pyramidal cells. There are also several classes of spatial cells in the hippocampal formation involved in various space functions (place cells, head direction cells, grid cells and boundary cells) (6).

The hippocampus is formed by two joined layers of cortex with a very defined laminar structure. The main pyramidal cell layers of the hippocampus are the Cornu Ammonis (CA)1-4 regions and the dentate gyrus, which lies on the upper plane of the parahippocampal gyrus. The dentate gyrus, consisting mainly of granule cells, receives inputs from the entorhinal cortex and sends its axons (mossy fibers) to the other parts of the hippocampal formation (7). The hippocampus and the dentate gyrus are interlocked as two C-shaped structures on coronal section of mid body. Recurrent (Schaffer) collaterals project from CA3 pyramidal cells back to the CA1. CA1 field or Sommer’s sector is the cortical area most susceptible to various noxious stimuli as anoxia, intoxication, injury etc. The alveus is the superficial white matter layer of the hippocampus adjacent to the inferior horn of the lateral ventricle. Subiculum is a transitional area between entorhinal cortex and hippocampus, rich in pyramidal cells.

The connections within the hippocampus are uni-directional and form closed loops that originate mostly in the entorhinal cortex and finally ends in it (the so called hippocampal network). The main input to the hippocampus comes from the entorhinal cortex (EC) (Table 1.). The fornix is a major output from the hippocampal formation. Hippocampal formation is irrigated by the posterior cerebral artery (PCA) with three main hippocampal branches that can be derived either directly or indirectly from PCA: the anterior, middle and the posterior hippocampal arteries (5). The vascular supply of the head may come, to various extent, from the anterior chorioidal artery.
Table 1. Input and output connections of hippocampal formation

<table>
<thead>
<tr>
<th>Connection</th>
<th>Input</th>
<th>Output</th>
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</thead>
<tbody>
<tr>
<td>Entorhinal cortex (EC)</td>
<td>perforant path</td>
<td>Dentate gyrus (DG)</td>
</tr>
<tr>
<td>Dentate gyrus (DG)</td>
<td>lateral EC</td>
<td>medial EC</td>
</tr>
<tr>
<td>CA3</td>
<td>lateral EC</td>
<td>medial EC</td>
</tr>
<tr>
<td>CA1</td>
<td>lateral EC</td>
<td>medial EC</td>
</tr>
<tr>
<td>Subiculum</td>
<td>lateral EC</td>
<td>medial EC</td>
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</tbody>
</table>

Distal CA1/proximal Sb receives input from the lateral EC while proximal CA1/distal Sb receives input from medial EC and output follow the same pattern, therefore two closed loop networks are present within the hippocampal network. These loops are additionally extended to perirhinal and post-rhinal cortices. The Perirhinal Cortex projects to the lateral EC and receives returning projections while the post-rhinal cortex projects to and receives inputs from the medial EC.

Perirhinal cortex and postrhinal cortex are much less structured than hippocampus and surround the hippocampal formation. These areas receive visual, olfactory and somato-sensory inputs thus mediating interpretation of novelty and familiarity. There are two main loops:

1. perirhinal - lateral entorhinal cortex-hippocampus and
2. postrhinal- medial entorhinal cortex -hippocampus.

Probably there are also direct paths from perirhinal and postrinal cortices to the hippocampus.
Entorhinal cortex. The entorhinal cortex (EC) (BA 28, 34) is located in the rostral end of the temporal lobe dorsolaterally and characteristically lacks layer IV. It is a part of the network for declarative memory and navigation and is connecting hippocampus with the neocortex (7). It has an important role in memory formation, consolidation and optimization in sleep, and gives us the sense of familiarity.

EC projects to the dentate gyrus and hippocampus (layers II and III) and transmits information from prefrontal cortex of ongoing cognitive processes, all sensory associational cortices, perirhinal and parahippocampal cortices. Especially layer V receives one of the three main outputs of the hippocampus.

Neurons of the medial entorhinal cortex, exhibit multiple “place fields” that mediate directional activity irrespective of the location, in contrast to place cells in the hippocampus, which are activated by specific locations (8). In such manner EC gives general properties about current contexts allowing hippocampus to create representations. The lateral entorhinal cortex is the first area of the brain to be affected in Alzheimer’s Disease (9).

Perirhinal cortex. The perirhinal cortex (Brodmann areas 35 and 36) receives highly-processed sensory information from all sensory cortices, and is important for memory. Posteriorly it borders with postrhinal cortex and ventrally and medially with entorhinal cortex. It lacks layer IV. The important functions of the perirhinal cortex are visual perception, memory, recognition and identification of environmental stimuli (10). It is part of the larger semantic system.

Parahippocampal gyrus - Post-rhinal cortex. The parahippocampal cortex surrounds the hippocampus and seems to have attentional function in the service of episodic memory encoding and retrieval. The anterior part of the parahippocampal gyrus includes the entorhinal and perirhinal cortices. Posteriorly the parahippocampal gyrus comprise parahippocampal cortex i.e. post-rhinal cortex.

The parahippocampal place area is a sub-region of the medial parahippocampal cortex in the inferior temporo-occipital area and is involved in the encoding and recognition of environmental (topographical) scenes of landscapes, cityscapes or rooms (11). The lesion in this area manifests clinically as inability of visual recognition of scenes but preserved recognition of individual objects. Another function of parahippocampal place area is identification of the social context, including paralinguistic elements of verbal communication, including sarcasm (12). Place area is the complement of the fusiform face area important for face recognition.

Functions of the hippocampal formation

Hippocampus has an inner place-responsive cognitive map of the environment as well as the ability for forming episodic declarative memory of places and times where and when something happened (13). Hippocampal place cells enable successful spatial navigation but also information retrieval. Experimental and clinical studies indicate that the hippocampal formation plays an important role in the control of aggression and rage. The dorsal hippocampus is more involved in learning and memory, as well as in spatial navigation and the ventral part has the role in emotional behavior and neuroendocrine stress axis regulation (14). Classical antidepressants act on both areas, while new putative antidepressant compounds act selectively on the ventral part. Physical exercise influence positively both subdivisions. There is also specialization along the long axis, with global representations in anterior hippocampus and local representations in posterior hippocampus (15). Newer studies found hippocampal involvement in semantic and procedural memory.

Recognition/familiarity/novelty. Delayed recall is a complex function depending on attention, executive functions, anterograde memory and nomination (7). Frontal lobes are crucial as they formulate strategy for information retrieval, execute and monitor the outcome making necessary corrections if needed.

Recognition consists of recollection and sense of familiarity (16). Recollection requires specific contextual details while the sense of familiarity is independent of contextual details.
Recollection critically depends on the caudal half of the hippocampus, with additional processing in higher order cortices: left parieto-temporal cortex, retrosplenial/ventral posterior cingulate cortex and ventrolateral prefrontal cortex. Para-hippocampal gyrus receives input from sensory regions and formation of the percept can trigger the sense of familiarity through its posterior region. Higher cortical areas involved in this function are: parieto-occipital cortex, occipital association cortex, dorsal posterior cingulate cortex and pre-cuneus. Anterior hippocampus and rhinal cortex (anterior medial temporal lobe) are discovering novelty with higher areas in the right dorsolateral prefrontal cortex (17).

These are three independent processes and functional systems: recollection, sense of familiarity and the sense of novelty. The coordination is dependent on supramodal convergention zones located in association areas and limbic cortex (para-hippocampal and entorhinal cortex) that carry the code of connection or schemes of synaptic activity for access to informations in sensory and motor cortices. The connection code enables linkage of information stored in unimodal cortical regions in the same temporal and spatial order as during the original event. This is the path of recall. Various pathological processes can disrupt the critical areas or their connections (disconnection syndromes). The most frequently stricken area in long-term memory dysfunction is the anterior temporal lobe, less frequently posterior temporal lobe (convergence zones) but are also seen in parieto-occipital lesions (disconnection of unimodal and amodal cortex) (18).

For coding and recollection of semantic and episodic memories activation of prefrontal cortex is necessary (19). Controversial is involvement of parietal activation during recall as lesions of these areas do not lead to disturbances of episodic memory (20). In the double attentional processes hypothesis, dorsal parietal area (BA 7) is involved in top-down attentional processes led by targets of recollection while ventral parietal cortex (BA 40 and 39) mediates bottom-up attentional processes in recall. The inferior parietal cortex is being activated by sensory stimuli but also with memory traces. The role of medial parietal cortex in memory is not studied in sufficient detail. According to this theory, goals determine the importance of information input, while events can change the goals of behavior. Right parietal lesions can cause memory neglect in which there is no spontaneous recall but is possible as an answer to a question (preservation of upper parietal region).

Procedural memory. Although classically associated with declarative memory, newer studies revealed the role of hippocampus also in procedural memory, especially in motor sequencing (21). Hippocampus is in functional interaction with striatum and prefrontal cortex in the acquisition of motor skills, and is involved in sleep-related memory consolidation processes.

Temporal organization of memories is one of the hippocampal functions (22). There are not only well known “place” cells that map location in space by also “time” cells registering the time marks. With the passing of time, exact moments are not so accurate as in the first few thousand seconds after experience. These two characteristic enable hippocampus to put events in a specific spatiotemporal frame.
Along with anterior cingulate cortex hippocampus is involved in the control of attention (23). It is also a system for making predictions of future events and planning novel actions (24). The diversity of hippocampal functions is a challenge for an all-encompassing hypothesis (25). Yonelinas (25) proposed that the main hippocampal role is the generation and utilization of complex high-resolution bindings unifying the individual characteristics of an event. These bindings are necessary for the recollection.

Clinical expressions of hippocampal dysfunction

Depression It has been found in several cross-section studies that patients with major depressive disorder have smaller hippocampal volume than control subjects (26). But longitudinal follow up shows the specific regional changes in hippocampal head and tail, CA1 and subiculum, bilaterally (26). The more days without antidepressant therapy the patients had, the more pronounced the atrophy was, evidencing the impact of the depression per se on the hippocampus, and not the other way around.

Depression and anxiety can occur as the result of chronic stress, via the increased glucocorticoid release that interferes with glutamatergic transmission in the hippocampus (27). This action can be neutralized by oral ingestion of omega-3 polyunsaturated fatty acids.
Adult neurogenesis in the dentate gyrus is very important in information encoding and in emotional control (14). Depression is linked to the decreased neoneurogenesis and antidepressants’ action to the restoration of this function. Neurogenesis, along with axon branching, dendritogenesis and synaptogenesis is the core of synaptic plasticity that is impaired in depression (28). Depression lowers the level of the brain-derived neurotrophic factor (BDNF) the crucial trophic factor in neuroplasticity.

Hipocampus is the brain area rich in almost all serotonergic receptors (29). Serotonin is important in the patogenesis and treatment of depression and is involved in the signaling in neurons, glia and immune cells.

Alzheimer’s disease. Hippocampal lesions lead to memory problems and amnesia, as typically occurs in Alzheimer’s disease (AD) (30). Alzheimer’s disease is also characterised by behavioral problems that positively correlate with cognitive decline (31). This means that both ventral and dorsal hippocampal subregions are involved in the pathological process. Current therapies hardly influence hippocampal damage initiated with upstream risk factors, such as aging, genetic mutations and polymorphisms, depression, methabolic factors etc., and laeding to downstream factors such as inflammation, oxidative stress, hypoxia, amyloid beta, excitotoxicity etc. (32) (33).

One of the most important processes that are impaired early in the course of AD is the neurogenesis in the subgranular zone of the dentate gyrus (34). New granule cells are the main excitatory neurons in the dentate gyrus and are important for the memory processes. Among other molecules, bone morphogenetic protein-4 (BMP4) and its antagonist Noggin regulate neurogenesis and thus the functioning of the hippocampus.

Parkinson’s disease. Hippocampus has been recently connected to Parkinson disease’s cognitive loss through dopamine-involved mechanisms of synaptic plasticity, adaptive memory and motivated behaviour and behavioral signs of impulse control disorder, anosmia, and fatigue (35). Hippocampus is a structure where various neurotransmiters’ networks interact. More so there is an influence of various neurotrophic factors.

Schizophrenia. There are many structural and functional changes found in hippocampal formation of schizophrenic patients such as parahippocampal asymmetry (36). Hippocampal function is altered in schizophrenia with increase in baseline blood perfusion and decreased task-related activation along with postsynaptic protein changes (37). These and other alterations reduce the hippocampal pattern separation (due to partial dentate gyrus disfunction) leading to false associations as well as accelerated pattern completion (due to increased CA3 associational action) generating delusions and thought disorder. These false associations are remembered and then they perpetuate the psychotic impairment.

Another important characteristic of hippocampal function in schizophrenia is impairment attention, up to the extreme example of catatonia when the patient seems totally unresponsive and stops reacting and moving altogether, but with hyperactive electroencephalographic activity (38). Patients sometimes report the catatonic phenomena as the way to stop excessive “noise” from the environment and that they were hyperaware of their surroundings. The defective sensory gating function of the hippocampus in schizophrenia is a probable culprit for the sense of the increased environmental noise that they experience. Gating function is shown to be acethyl choline-dependent and mediated by the α-bungarotoxin-sensitive receptors.

Addiction The role of hippocampus in addiction is discovered as we began to see the bigger picture than just the involvement of the mesolimbic pathway and nucleus accumbens (39). Addictive substances impair neurogenesis influencing the memory, stress responsivness and emotional processes. Downstream, deficient neurogenesis influence the emergence and maintenance of addiction and its characteristic phenomena an behavioral patterns.

Stroke. Isolated hippocampal stroke occures rarely and expresses clinically as sudden onset of homonymous quadrantanopia, dyslexia, neglect, memory deficits, sensory loss, dysesthesias, or other signs often due to the involvement of adjacent structures pertaining to posterior circulation (5). There can be complete involvement, the lateral, the dosal and circumscribed (usually in the lateral hippocampus). Verbal episodic long-term memory deficits are found in the cases of involvement of the left hippocampus, and non-verbal in the right hippocampal lesions. Bilateral ischaemia causes profound amnesia but is extremly rare.
Transient Global Amnesia. Transient global amnesia (TGA) is a transient and fully reversible amnesia, both anterograde and retrograde (40). It typically lasts for several hours and the etiology is still unknown. Functional neuroimaging shows selective involvement of the CA1 region (41).

Epilepsy. Many patients with complex partial status epileptics have hyperintensities in the hippocampal formation. Most patients show the whole hippocampus involvement. Changes are considered to be the consequence of low energy metabolism and edema in prolonged seizures (5).

Inflammation. The most frequent infection involving hippocampal formation is limbic encephalitis, leading to altered attention, memory deficits, seizures and psychiatric symptomatology (5). It encompasses hippocampus, entorhinal cortex, uncus, amygdala and subiculum.

Prevention of hippocampal atrophy

The hippocampus is very susceptible to various noxious factors such as ischemia, brain trauma, anoxia, infective diseases, degenerative processes, hypertension, diabetes mellitus, depression, bipolar disorder, epilepsy, obesity etc. These conditions lead to smaller hippocampal volume and consequent cognitive decline, more than in persons with “normal” ageing process (42). In order to prevent or minimize the damage, or even reverse the pathological processes, all modifiable factors and diseases should be optimally treated and mental and physical activity put in place. These measures are the basis of the dynamic polygon hypothesis which sheds an optimistic light to the outcome of multimodal treatment. Some of these activities can even reverse the hippocampal atrophy.

Neurogenesis, the production of new neurons, is retained in adult brain in several areas, one of the most important being the dentate gyrus of the hippocampal formation (43). As reduction of neurogenesis is characteristic of many pathological states, for instance dementia, depression, addiction and others, the obvious question is how can we enhance this process? It has been shown that physical activity, mostly of aerobic type, increases the number of new cells while mental training such as skill learning increases the number of survive. This leads to the idea of combination of mental and physical training in enhancing the mental health.

Another protective factor in the hippocampus is estradiol which is necessary for for adequate synaptic plasticity and neuroprotection in both females and males (44). The higher biological effect has the hormone synthesized locally than from the gonades. Adenosine is an important neuromodulating factor in the hippocampus, possibly with some neuroprotective function.

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