Comparative contemplations on the hippocampus.

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Abstract

The hippocampus in mammals is a morphologically well-defined structure, and so are its main subdivisions. To define the homologous structure in other vertebrate clades, using these morphological criteria has been difficult, if not impossible, since the typical mammalian morphology is absent. Although there seems consensus that the most medial part of the pallium represents the hippocampus in all vertebrates, there is no consensus on whether all mammalian hippocampal subdivisions are present in the derivatives of the medial pallium in all vertebrate groups. The aim of this paper is to explore the potential relevance of connections to define the hippocampus across vertebrates, with a focus on mammals, reptiles, and birds.

Introduction

What can we learn from comparative studies of the hippocampus? An answer to this question is not straightforward since it depends, among others, on what one aims for. In this paper, we intend to define some basic requirements that need to be met before the question as such becomes tangible. For example, in order to compare, we need to define what to compare, and at which level of biological classification. Regarding the first, we will start with a definition of what to consider as hippocampus in the context of this paper, its divisions and the possible relevant levels of circuitry. As will become clear, decisions about definitions as well as about the level of biological classification, species, family, order, are strongly dependent on the available data. We will therefore use a pragmatic approach, restricting ourselves to available data relevant to the narrative of this paper. In this paper, we also aim to complement an accompanying paper {Butler, 2017 #12400} by emphasizing connectivity patterns as a tool to propose potential homology in the hippocampus.

Definition of hippocampus and its subdivisions

The first mentioning of the hippocampus in the mammalian brain can likely be found in the work of a pupil of the 16^{th} century anatomist Vesalius, named Arantius {Lewis, 1923 #9738}. The first part of the term refers to part of the formation in mammals resembling a horse's head and the second part refers to the caterpillar, or "silk-worm" appearance of the tail (for further details see {Butler, 2017 #12400}). One of the first detailed and comparative studies on the structure and connectivity of the hippocampus is by Ramon Y Cajal, published around the turn of the 19^{th} century {Ramón y Cajal, 1893 #8500;Ramón y Cajal, 1911 #10061}, followed by influential descriptions of the anatomy and connectivity of the main subdivisions of the hippocampus by his student Lorente de Nó {Lorente de N¢, 1933 #44;Lorente de N¢, 1934 #45} and subsequent detailed studies from the 1960s and 1970s (for details see {Witter, 1989 #10554}. The typical hippocampus in mammals includes the dentate gyrus, the Cornu Ammonis (CA) fields CA1, CA2 and CA3, or hippocampus proper, and the subiculum. Although several authors have described an area CA4, we will not use this in the present paper and consider this part of area CA3. The hippocampus is a three-layered cortex, consisting of the molecular layer, directly deep to the pia, a cellular layer, and deep to the latter, a polymorph layer. The superficial layer contains very few, mainly inhibitory neurons, and the polymorph layer has on average a larger number of neurons than the molecular layer. The neurons in the polymorph layer are either excitatory or inhibitory {van Strien, 2009 #12266}.

Depending on the definition used, the entorhinal cortex is part of the hippocampus or part of the parahippocampal region. Here we will take the perforant pathway, originating as the main cortical input from the entorhinal cortex to the hippocampus as belonging to the defining features of the main circuitry of the hippocampus (see also the next section). This is in line with the emphasis on the entorhinal-hippocampal connections, as mentioned by Cajal already, based on his own work and referring to previously published data. In his seminal paper on the entorhinal cortex {Ramon Y Cajal, 1902 #38} he stated twice that the connections between the entorhinal cortex and the hippocampal formation are so conspicuous that they necessarily imply the functional solidarity of both centers. We will however not deal extensively with the comparative aspects of the entorhinal cortex in this paper (for more details see {Medina, 2017 #12417}).

The hippocampus is a key component of an ensemble of brain structures that became known as the limbic system. The term limbic is derived from an anatomical description by Thomas Willis {Willis, 1664 #8729}, who referred to the brain area that surrounds the brainstem as the limbus. Subsequently, Broca referred to the cortical fringe of the hemisphere, including the subcallosal, cingulate and parahippocampal gyri as well as the underlying hippocampal formation, as 'le grand lobe limbique' {Broca, 1878 #12415}. Although this designation was purely anatomical, Broca suggested that these limbic structures might constitute a functional entity. Much later, Papez {Papez, 1937 #12060} postulated the presence of a closed circuit that would play an important role in the elaboration and the expression of emotions. This 'Papez-circuit' comprises a sequence of interconnected structures, i.e. the hippocampus projects by way of the fornix to the mammillary bodies which connect by way of the mammillothalamic tract to the anterior nuclei of the thalamus; from here, the cingulate cortex is reached, which through the ventral continuation of the cingular bundle is connected with areas in the parahippocampal region, including the entorhinal cortex, projecting back into the hippocampus. In 1952, MacLean {Maclean, 1952 #12416} coined the term 'limbic system' suggesting that these structures, including the amygdaloid complex, represented the 'visceral brain'.

It was the seminal publication by Scoville and Milner {Scoville, 1957 #59} that made the scientific community aware of the potentially important role of the hippocampus in episodic memory. In that paper, it was reported that bilateral removal of structures in the medial temporal lobe, including substantial parts of the hippocampus, the parahippocampal domain and the amygdala, resulted in profound anterograde amnesia {Annese, 2014 #12389;Augustinack, 2014 #12390}. The implication of the hippocampus in memory processes boosted interest in its anatomical and functional organization. Major breakthrough findings, such as the discovery of long term potentiation {Bliss, 1973 #11459} as a potential synaptic mechanism for the formation and storage of memories, the discovery of place cells in the hippocampus {O'Keefe, 1971 #102} and the subsequent influential theoretical description of the hippocampus as a cognitive map {O'Keefe, 1978 #256} strongly led the field into a focal research effort to unravel the mysteries of hippocampal circuits and functions. Interestingly, the idea of the hippocampus as part of a more elaborate network of limbic structures has started to make its comeback in recent years {Aggleton, 2014 #12393;Aggleton, 2015 #12392}.

Standard Connectivity of the hippocampus

The connectivity of the hippocampus, known in that groundbreaking era was guided by two well-established conventions. First, the main fiber connection of the hippocampus was formed by the fornix, providing the output and input pathway of the hippocampus with subcortical structures like the septal complex and the mammillary bodies. Second, the entorhinal cortex provided the point of entry of cortical inputs to the hippocampus. This projection was initially referred to as the direct perforating spheno- or temporo-ammonic pathway by Cajal {Ramon Y Cajal, 1902 #38;Ramón y Cajal, 1893 #8500;Ramón y Cajal, 1911 #10061} as one of a tripartite connection system, collectively referred to as the temporo-ammonic pathway (for more details, see {Stephan, 1975 #8628}). The designation direct and perforating referred to the massive entorhinal fiber bundles perforating the subiculum on their direct course into the hippocampus. This pathway became later known as the perforant pathway {Lorente de N¢, 1934 #45}. An additional temporo-alvear tract was described as well, with fibers travelling from the entorhinal cortex through the alveus of the hippocampus into the CA fields. The third component referred to as the angular pathway, carries mainly but not exclusively commissural fibers. As indicated by the name, in this early description, emphasis was on the projections to the CA fields, although projections to the dentate gyrus were included as part of the direct perforating temporo-ammonic/perforant pathway. In a detailed anterograde tracing description of the entorhinal-hippocampal connectivity in the rat in the mid-seventies {Steward, 1976 #10329}, the projections to the dentate received more emphasis. The latter author referred to this projection as the temporo-dentate pathway, contrasting it with the temporo-ammonic pathway reaching the CA fields and the subiculum. Together with the knowledge about intrinsic hippocampal pathways, this led to the attractive concept of the so-called trisynaptic pathway as the blueprint circuit characterizing the hippocampus {Andersen, 1969 #8844; but see Amaral, 1989 #8840}. Over years, this also resulted in confusing changes in nomenclature such that the temporo-dentate pathway became erroneously referred to as the perforant pathway by many authors, since it perforated the hippocampal fissure on its way to the dentate gyrus, and the usage of temporo-ammonic pathway became restricted to the entorhinal projections to CA1. The trisynaptic circuit thus encompassed 1) the entorhinal, perforant pathway synapse on the dendrites of dentate granule cells, which in turn originate 2) the mossy fiber projection, synapsing onto the complex spines of the CA3 pyramidal cells. The latter originate not only the intrinsic auto-associative projections in CA3, but also 3) the Schaffer collateral projection, forming the third synapse on CA1 pyramidal neurons (Fig. 1A). In that concept, the projections from the entorhinal cortex to the CA-fields became essentially ignored and it was only in the late 80th/early 90th that they were 'rediscovered' {Yeckel, 1990 #1447;Amaral, 1989 #8840;Witter, 1988 #10552} while the projections to the subiculum, also already mentioned by Cajal, were introduced on the scene again {Witter, 1990 #10553;Witter, 1992 #10557}. Since then, the projection to CA1 is referred to as the temporo-ammonic pathway by some, and by others as the direct EC-to CA1 projection, forming one component of the perforant pathway. Within the context of the present comparative study this vague nomenclature becomes a problem, since searching for the perforant path in a non-mammalian animal might become as issue, depending on how this pathway is defined. It is therefore appropriate to redefine the entorhinal-hippocampal projections, also because we now know that neurons in layer II are the main source of the entorhinal projections to the dentate gyrus and fields CA2 and CA3, and neurons in layer III give rise to the entorhinal projections to CA1 and subiculum (note that a small number of neurons in deeper entorhinal layers contribute to both projections). For the present paper, we therefore propose to differentiate between the EC-layer II projection and the EC-layer III projection. It has been shown that single layer II cells project to the dentate gyrus and CA2/CA3 {Tamamaki, 1993 #1946}, but whether this is true for the layer III projection to CA1 and subiculum is as yet unclear.

Considering the fornix as the main if not sole hippocampal output pathway triggered a wave of experimental studies in which fornix lesions were considered as a convenient experimental model for the more complex hippocampal lesions. Although attractive, results from these studies rapidly pointed to a serious conceptual problem in that fornix lesions did not reliably mimic the profound amnesic syndrome seen after complete hippocampal lesions. In addition, the amnesic syndrome seen in patient HM was characterized as an anterograde amnesia, since memories from before the surgery seemed more or less intact, indicating that the actual memory storage had to be somewhere else in the brain, most likely in the cortex {Squire, 2011 #12394}. Since the fornix does not provide an output pathway to the cortex, an emerging challenge was to find the potential pathway mediating memory storage in the cortex. This challenge was resolved by an insightful study in the rhesus monkey, published in a series of three papers showing that the subiculum projected to deep layers of the entorhinal cortex, which in turn contain neurons that are the origin of direct or indirect widespread projections to higher order cortical areas {Rosene, 1977 #204;Van Hoesen, 1975 #10459;Van Hoesen, 1975 #10460;Van Hoesen, 1975 #10462}. These findings were shortly after corroborated and extended in an extensive series of publications in cat {Witter, 1986 #832}, guinea pig {Sorensen, 1985 #10291}, and rat {Swanson, 1986 #10363;Insausti, 1997 #9510;Kosel, 1982 #9661}. These and subsequent studies painted the current more complex connectional diagram of the cortico-hippocampal system (Fig 1B; {van Strien, 2009 #12266}).

In our quest to find defining connections as arguments to establish homologies, we should however not ignore the massive fornix projection targeting a variety of basal forebrain and hypothalamic structures, including the lateral septum and to a lesser extent the medial septum, the nucleus accumbens, and several hypothalamic domains, with the mammillary bodies likely receiving the densest innervation {Witter, 2006 #10547;Kishi, 2000 #9595}. It is now well established that these pathways and the interconnected structures all play roles in higher order cognitive functions {Aggleton, 2000 #2363}, but manipulations result in dysfunctions dissimilar to those seen after damage to the cortico-hippocampal system. Clinically, the human syndrome of diencephalic amnesia is the closest to medial temporal lobe amnesia, and there is general agreement that all patients share damage to the mammillo-thalamic tract {Van der Werf, 2003 #2528;Van der Werf, 2003 #2529;Aggleton, 2010 #8794}. A complete understanding of these complexities await further details about the connectivity and functional interactions of all structures involved.

Is the characteristic hippocampal circuit really trisynaptic?

Aiming for solid features to embark on a comparative analysis, it is important to agree on what we are looking for to argue what in the non-mammalian brain might be the hippocampus. We could look for morphology, chemical or genetic identity of neurons, developmental origin, or aspects of circuitry. Focussing on the latter, in view of the above section on connectivity, is it the trisynaptic circuit that we should be looking for in non-mammalian species? In recent years, an alternative view has been proposed, which puts emphasis on the entorhinal layer III projection and the marked reciprocating projections from CA1 and the subiculum. Reciprocity is a common feature of cortical connectivity and the EC layer II projection is a clear exception to that common pattern in that neither the dentate gyrus nor CA3 seem to originate reciprocating projections to EC {van Strien, 2009 #12266}. So, it could be argued that searching for a canonical trisynaptic pathway might not be the best comparative approach. This line of thinking is supported by the suggestion that the dentate gyrus is unique to mammals {Striedter, 2016 #12395}. In this view the medial cortex in reptiles and amphibians represents the pyramidal hippocampal layer, i.e the CA fields, and no dentate granular cells are present. Per this scenario, the evolutionary preserved circuit thus includes the pyramidal cells of the hippocampus, receiving cortical inputs from more lateral parts of the cortex, in turn sending output to the lateral cortex and, via the fornix, to septum and hypothalamus.

The morphological definition of dentate granule cells as globular cells without basal dendrites is however ambiguous. In some mammalian species, such as postnatal rats, but also in adult monkeys and humans, dentate granular cells come in different forms, some being less globular and occasionally having basal dendrites, such they have some resemblance to pyramidal neurons {Treves, 2008 #7166}. A better criterion might be that in the commonly studied mammals, the dentate granule cells give rise to a morphologically characteristic axon, the mossy fiber, showing complex, moss-like multi-synaptic terminal complexes with equally complex spine structures on the target pyramidal neurons {Treves, 2008 #7166}. The mossy fiber projection also expresses high levels of zinc, as traditionally stained in several species with the Timm-stain {Treves, 2008 #7166}.

If the dentate gyrus is a mammalian addition, this raises the question what to do with the two components of the entorhinal inputs, the layer II versus layer III system. Since the layer II system projects to CA2 and CA3 as well as the dentate gyrus, would we expect that a similar division is already present in non-mammals. Alternatively, is the layer II projection an addition like the dentate gyrus, that subsequently expanded to also innervate adjacent pyramidals of the CA fields? Assuming the latter, did this occur parallel to the dentate mossy fiber projection innervating CA3 and CA2 {Haussler, 2016 #12397;Kohara, 2014 #12398}?

Another recent hypothesis postulates that the dentate as such is not new but that the folding of dentate, resulting in the hippocampal fissure and the discontinuity between DG and CA-fields, is the characteristic feature of the mammalian brain {Hevner, 2016 #12396}. Attractive as this may seem, this concept seems to pass over the fact that in all mammals studied, there are parts of the hippocampus that do not show these particular features. A good example can be found in the brain of marsupials, such as the opossum (Fig.2). Whereas at more posterior levels (Fig. 2B,C), the hippocampus indeed comprises a folded dentate gyrus and a separated CA field emerging close to the hilar region of the dentate, at more anterior levels (Fig. 2A), the two structures become aligned such as to show a striking similarity to what is found in some reptilian species {Striedter, 2016 #12395;Butler, 2017 #12400}. A similar arrangement has been described in monotremes, such as Echidna {Hassiotis, 2004 #12399}. However, also in placental mammals, such a non-differentiated hippocampal-like structure is present, called the taenia tecta (Fig. 2D) and the supracallosal indusium griseum {Stephan, 1975 #8628;Treves, 2008 #7166}.

Subdivisions and standard connectivity compared.

The cortex of reptiles comes in different flavors, one main group, including lizards and snakes, presenting a markedly three-layered cortex, while the others come with variable changes in that pattern from a less laminated version, generally seen in turtles to the one in crocodiles, that comes closer to the totally non-laminated version seen in birds {Striedter, 2016 #12395}. In lizards, the medial part of the cortical sheet is commonly divided into three domains, a small-celled medial domain, a large-celled medio-dorsal domain, continuing into the dorsal cortex, which is bordered in turn by the lateral cortex. The small-celled medial domain contains several morphologically different cell types, some of which give rise to a zinc-positive mossy fiber-like projection to the adjacent large-celled mediodorsal and dorsal domains, indicative for a dentate homologue. Zinc-positive terminals have also been reported on neurons in the polymorph layer of the small-celled portion. The targets are large neurons looking similar to hilar mossy cells described in the mammalian hippocampus {Treves, 2008 #7166}. These observations seem to indicate that, at least in some reptiles a dentate-like structure is present, not well differentiated from the adjacent cortex which could be considered to represent an as yet not differentiated representation of the CA component described in mammals. From a morphological point of view, the resemblance between the small- and large-celled parts of the lizard cortex to what has been described for the taenia tecta and indusium griseum in rodents is striking, including a zinc-positive projection system that has been described in mice {Adamek, 1984 #531;Laplante, 2013 #12418}. These authors conclude that the indusium griseum and potentially also the taenia tecta might be phylogenetically old representations of the hippocampus. However, studies in the Madagascan hedgehog tenrec, led to the conclusion that the indusium griseum, again showing a zinc-positive projection, might be correlated with lizard medial cortex, , but that it is incorrectly considered a hippocampal homologue {Kunzle, 2004 #2722}. One would hope that more detailed functional studies on the lizard brain as well as on the taenia tecta and indusium griseum in mammals might support the validity of these assumptions.

Alternative subdivisions of the hippocampus

Alternative ways to divide the hippocampus have been proposed, contrasting to the trisynaptic and entorhinal layer II versus layer III partitions. Among the most prominent ones are a functional differentiation along the longitudinal axis, and a functional differentiation represented by two parallel cortical input/output systems, mediated by different components of the entorhinal cortex.

The hippocampal long axis. Based on a large body of connectional and functional data in rodents, carnivores and primates, a dominant view has been that the dorsal (or posterior) hippocampus is implicated in memory and spatial navigation and the ventral (or anterior) hippocampus mediates anxiety-related behaviors. The border between the two domains in the hippocampus has not been well established and some authors have suggested dividing the hippocampus into three components, inserting an intermediate domain. Gene expression studies demonstrate multiple domains along the hippocampal long axis, which often exhibit sharply demarcated borders. Together these data suggest a model in which long-axis gradients are superimposed on discrete connectionally and genetically defined domains, resulting in at least three functionally different domains {Strange, 2014 #12401;Navarro Schroder, 2015 #12403;Maass, 2015 #12402}. Among these functional differences is the notion that dorsal (posterior) parts are specifically involved in cognitive processes and the more ventral (anterior) domains might be more involved in emotional and stress responses. Interestingly, such a functional differentiation might exist in the avian hippocampus as well {Smulders, 2017 #12419}.

Another striking example of functional differences along the long axis has been reported with respect to the representation of space through the firing properties of place cells, found in all three of the CA divisions {O'Keefe, 1976 #185;O'Keefe, 1971 #102;Lu, 2015 #12404}, but also to a lesser extent in dentate gyrus and the subiculum. The most detailed analysis has been carried out in CA1 and CA3, showing that the size of a place field is related to the position of the place cells along the long axis. Place cells in the dorsal hippocampus have the smallest place fields, and at more ventral levels the sizes increase gradually {Kjelstrup, 2008 #5523}. Place field size can be interpreted as a measure of spatial scale, indicating that environments might be represented at different spatial resolutions along the long axis of the HF. Recent fMRI findings in humans support such a difference in representational resolution along the hippocampal long axis {Evensmoen, 2015 #12406;Evensmoen, 2013 #12405}. These findings, when combined with the comparative data summarized above, lead to a clear prediction about a possible spatial code in for example the medial and dorsal cortex of the lizard. In case place cells were to be found in this cortical domain, they will show a gradient such that spatial representation anteriorly is more fine-grained than at more posterior levels. This might result in functional differences in the medial cortex, as suggested previously {Hoogland, 1994 #12412}. This prediction will hold irrespective of whether the lizard medial cortex comprise a dentate gyrus and an entorhinal layer II input system or not, since place fields in rodents, are independent of the entorhinal layer II-dentate-CA3 system {Brun, 2002 #8970}, instead depending on the entorhinal layer III system, more in particular the component that arises from the more posteromedial part of the entorhinal cortex {Brun, 2008 #5172}. Moreover this input plays a role in long-term spatial memory {Remondes, 2004 #2820}.

Parallel cortical pathways. The second differentiation is strongly based on observations that the more posteromedial part of the entorhinal cortex, generally referred to as the medial entorhinal cortex has been shown to be functionally and connectionally different from the anterolateral part, the so-called lateral entorhinal cortex. Firing of neurons in the medial entorhinal cortex represents spatial, directional and speed information {Kropff, 2015 #12407;Sargolini, 2006 #10145;Solstad, 2008 #7310;Fyhn, 2004 #9261}. In contrast, recordings in LEC have not indicated the presence of pure spatially modulated neurons; rather the firing of neurons in LEC seems to reflect the presence of objects in context {Tsao, 2013 #12409;Knierim, 2014 #12383}. Although the causes for these striking functional differences are as yet not fully understood, it is likely that different connectional streams into MEC and LEC, strongly involving different connectivity patterns from adjacent parts of the parahippocampal regions such as the postrhinal/parahippocampal cortex and perirhinal cortex are key determinants of this difference {Ranganath, 2012 #7740;Eichenbaum, 2012 #7742;Witter, 2000 #10559}. Interestingly, the projections of the two entorhinal domains to area CA1 and the subiculum in all mammalian species studied, including non-primates and primates are topographically organized along the transverse axis of both fields {Witter, 1991 #10550;Witter, 2000 #10559;van Strien, 2009 #12266}. Recent connectional MRI studies in humans have pointed to a similar connectional bipartite system separating anterolateral from posteromedial entorhinal cortex, showing clear differences with respect to connectivity measures in the hippocampus, resembling those reported in rodents {Maass, 2015 #12402}. This thus indicates that functionally different types of input may be mapped onto different hippocampal domains along the transverse axis, a prediction that was shown to be correct in CA1 in rats with respect to spatial information carried by firing properties of neurons {Henriksen, 2010 #8138}. It remains to be established whether comparable functional differences exist in other clades, but recent gene expression patterns during embryological development indicate that in birds and lizards, a lateral and medial entorhinal cortex might be identifiable {Abellan, 2014 #12410;Medina, 2017 #12417}. It remains to be established whether these different entorhinal domains in birds and lizards show connectional differences, comparable to those seen in mammals, but it is of interest that in the lizard Gekko gecko, two connectional pathways have been described originating from lateral and medial portions, though only the lateral portion seem to project to the small- celled and large-celled medial cortex {Hoogland, 1995 #12411}.

Concluding remarks

For all mammalian species where we have connectional and functional data, it is apparent that the hippocampus receives its main cortical inputs from the entorhinal cortex, organized in a two X two matrix of origin, consisting of the EC-layer II and EC-layer III projections on one axis, and the lateral and medial entorhinal cortex on the other. This matrix of connections seems well conserved. With respect to reptiles, most data on the potential homologous areas in the medial and lateral cortex are restricted to a few species of lizards and although genetically defined lateral and medial entorhinal cortex might exist, data on the connectivity of these recently identified areas are sparse if not missing. In birds, the situation is even less clear although at least in the chicken, comparable entorhinal areas have been identified.

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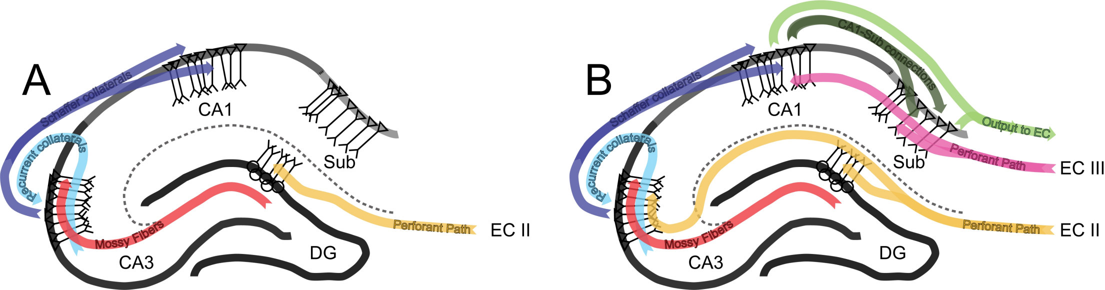
References

Figure **legends**

Figure 1. Schematic representation of main hippocampal connectivity. **A**. The traditional trisynaptic pathway comprising the entorhinal-dentate perforant path synapse, the DG-CA3 mossy fiber synapse and the CA3-CA1 Schaffer synapse. Also indicated are the strong intrinsic CA3 auto-associational connections. **B**. A more elaborate connectional diagram including the parallel entorhinal layer II and III projections, as well as incorporating the subiculum and CA1 and subicular projections to the entorhinal cortex.

Figure 2. The presence of an unfolded dentate gyrus in non-placental and placental species. **A**. Series of coronal sections from rostral (1) to caudal (3) through the brain of the marsupial opossum. At most anterior levels (1), the hippocampus/dentate gyrus does exhibit a non-folded appearance, comparable to the medial cortex in reptiles. B. In rodents, such as the rat, a comparable non-folded structure, called the taenia tecta, can be found at levels ventral to the genu of the corpus callosum.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Schaffer collaterals
Recurrent collaterals
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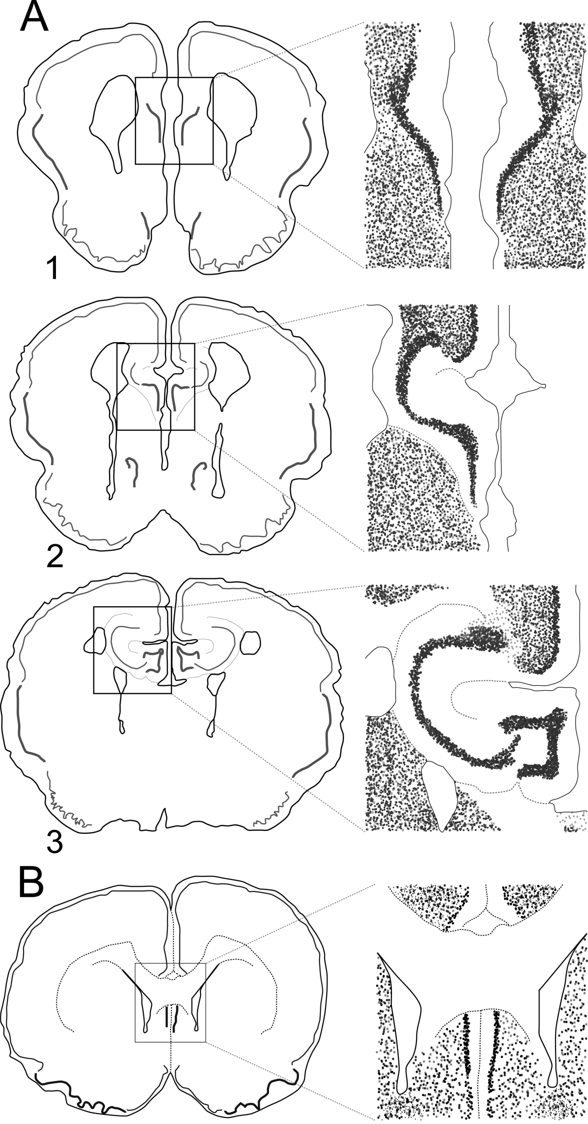
Sub
Mossy Fibers
Perforant Path
EC II
CA3
DG
B
CA1-Sub connections
Output to EC
Perforant Path
EC III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