



## Manual

### Introduction

The interactive hippocampal parahippocampal diagram offers a customizable display of all known connections of the rat parahippocampal-hippocampal region. The diagram, together with the references, provide a fully searchable and interactive knowledgebase of hippocampal-parahippocampal connections in the rat.

#### Features of the diagram:

- The diagram incorporates in a single display all known anatomical literature to date of one species (i.e. the rat). In many previous anatomical reviews, data from different species were combined into "an average" description. This diagram offers an objective description of current anatomical data of the rat parahippocampal-hippocampal region; all connections reported in the literature are included whereas in most reviews only the prominent connections are reported. In this diagram 1600 connections are present.
- The diagram is interactive; users can switch on and off connections between cortical layers in the network. This will allow users to better comprehend the impact of a lesion, make anatomically correct theoretical models of this region, or help to interpret electrophysiological data of this common laboratory animal.
- The diagram is split out gaps in anatomical knowledge. In the diagram, several levels of detail are available in order to be able to draw all reported anatomical connections. This enables users to quickly spot which connections are described in the literature with or without much detail.

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### 2 Working with the diagram

#### 2.1 System requirements

In order to open the pdf-file, you need to have Adobe Acrobat Reader installed on your system. Adobe Acrobat Reader is available for most operating systems. You can download Adobe Acrobat Reader free of charge from the following url:

<http://www.adobe.com/products/acrobat/readstep2.html>.

It is recommended that you update your Acrobat Reader to the latest version. As of Acrobat Reader version 8, hardware accelerated drawing is introduced in the software which will speed up rendering of the diagram. Acrobat Reader prior to version 6 does not support layers, therefore it cannot display the diagram properly. See the also the **Troubleshooting** section (Appendix 2), if any problem occurs.

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#### 2.2 Opening the diagram

The diagram file is called supplement1.pdf, which can be opened by Adobe Acrobat Reader. Please refer to the "System requirements" for obtaining a copy of Adobe Acrobat.

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#### 2.3 The diagram interface

After opening the file supplement1.pdf a view similar to that in Figure 1 should be visible on your computer screen. On the left hand side, the layers navigation pane should be visible. If no layers are visible, please check your version of Acrobat Reader (see 2.1 System Requirements). The layers are alphabetically organized. At the top of the list a checkbox "options" is available to select or deselect the grey background and the diagram info.

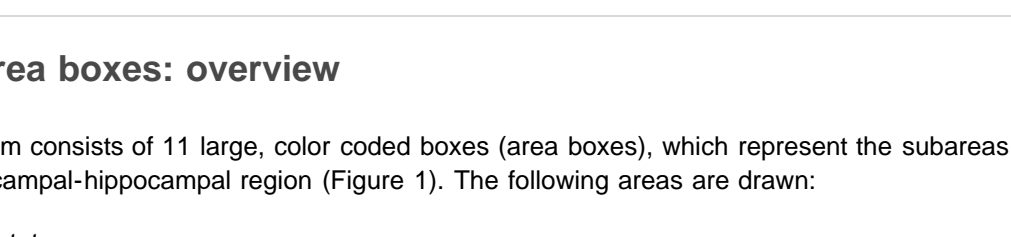


Figure 1: The diagram interface

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#### 2.4 The diagram area

##### 2.4.1 Area boxes: overview

The diagram consists of 11 large, color coded boxes (area boxes), which represent the subareas of the parahippocampal-hippocampal region (Figure 1). The following areas are drawn:

- Dentate gyrus
- CA3
- CA1
- Subiculum
- Presubiculum
- Parasubiculum
- Lateral Entorhinal Area
- Medial Entorhinal Area
- Perirhinal cortex Area 35
- Perirhinal cortex Area 36
- Postirhinal cortex

The area names are abbreviated in the diagram. Please refer to **Appendix 1** for a complete list of abbreviations.

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##### 2.4.2 Three-dimensional axes

The parahippocampal-hippocampal region is a complexly organized three-dimensional region. In order to display the three-dimensional connectivity patterns in a two-dimensional diagram, several anatomical axes were introduced to draw each subarea. The vertical axis in the diagram (indicated with the grey vertical banners at the outer left and right hand sides of the diagram; Figure 2) represents the septo-temporal axis of DG, CA3, CA1, Sub, PrS and PaS, the dorso-lateral-ventromedial axis of MEA, LEA, and the dorso-ventral axis of A35, A36 and POR. The horizontal axis within the area boxes represents the proximo-distal axis in CA3, CA1, Sub, PrS and PaS and the rostro-caudal axis in A35, A36 and POR. The DG is subdivided into the inner/or outer blades and crest region. Within the boxes the deep to superficial axis is given for each layer in the specific subarea (layer boxes). In the center of the diagram (Figure 2, highlighted in red) the axis is titled "unspecified", indicating that no information about the dorso-lateral or septo-temporal topography of these connections is known.



Figure 2: Three dimensional axes

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##### 2.4.3 Area boxes: details

In this paragraph, we will introduce the elements within the area boxes and their three-dimensional axes. The Sub and A35 will serve as examples.



Figure 3: Subiculum area box - top part

Let us first take a look at the top part of the Subiculum area box (Figure 3). At the very top the word "Sub" is written, which is the abbreviation for Subiculum (See Appendix 1). In the next row, the words "prox", "int", "dist" and "unsp" are written. These labels specify the proximo-distal axis of the Sub, with "prox" meaning proximal, "int" meaning intermediate and "dist" meaning distal with respect to the DG. The label "unsp" (unspecified) indicates that no information is available on the proximo-distal distribution of these connections. Below the proximo-distal axis three rows of smaller boxes are displayed. These columns of smaller boxes represent the cortical layers that are defined in the Sub at the three levels of the proximo-distal axis or at the unspecified proximo-distal level. The layers in the Sub are the stratum moleculare and the stratum pyramidale. In the Sub the stratum moleculare is subdivided into a superficial (sup) and deep part of the layer.

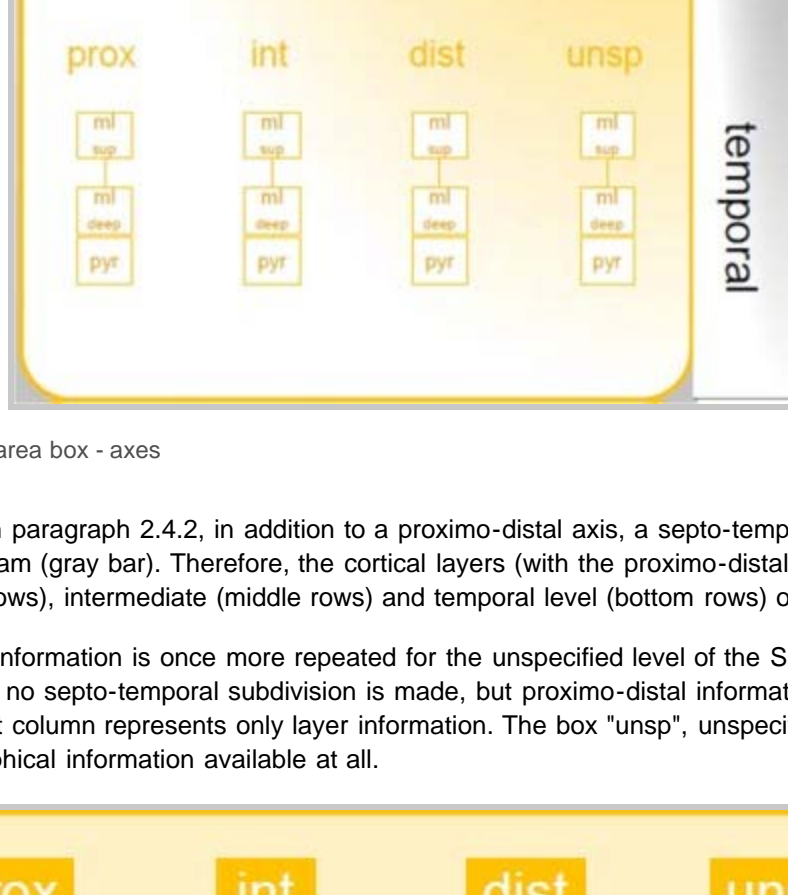


Figure 4: Subiculum area box - axes

As was explained in paragraph 2.4.2, in addition to a proximo-distal axis, a septo-temporal axis is also present in the diagram (gray bar). Therefore, the cortical layers (with the proximo-distal axis) are repeated for the septal (top rows), intermediate (middle rows) and temporal level (bottom rows) of the Sub (Figure 4).

The proximo-distal information is once more repeated for the unspecified level of the Sub. In the three columns on the left, no septo-temporal subdivision is made, but proximo-distal information is available (Figure 5). The right column represents only layer information. The box "unsp", unspecified, is used when there is no topographical information available at all.

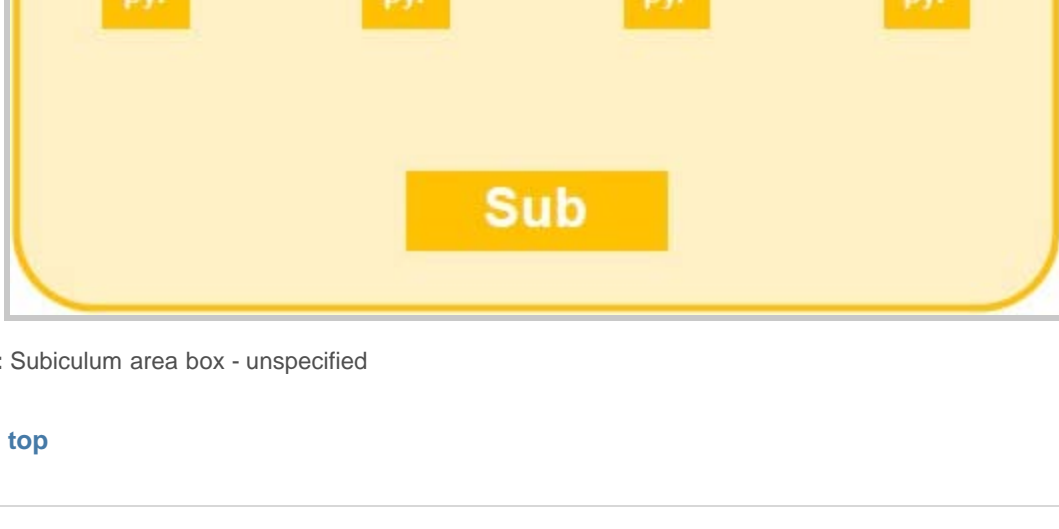


Figure 5: Subiculum area box - unspecified

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##### 2.4.4 Connections

In order to show or hide connections between areas, you need to use the layers navigation pane on the left side of the screen (Figure 1). By checking a box, you can switch on or off all the projections from a specific sub-area to another (Figure 6). The "eye"-icon appears when the connection is displayed in the diagram area. Layers that are marked with a "lock"-sign are inactive (for instance "areas" in Figure 6) and cannot be selected or excluded ("deselected").

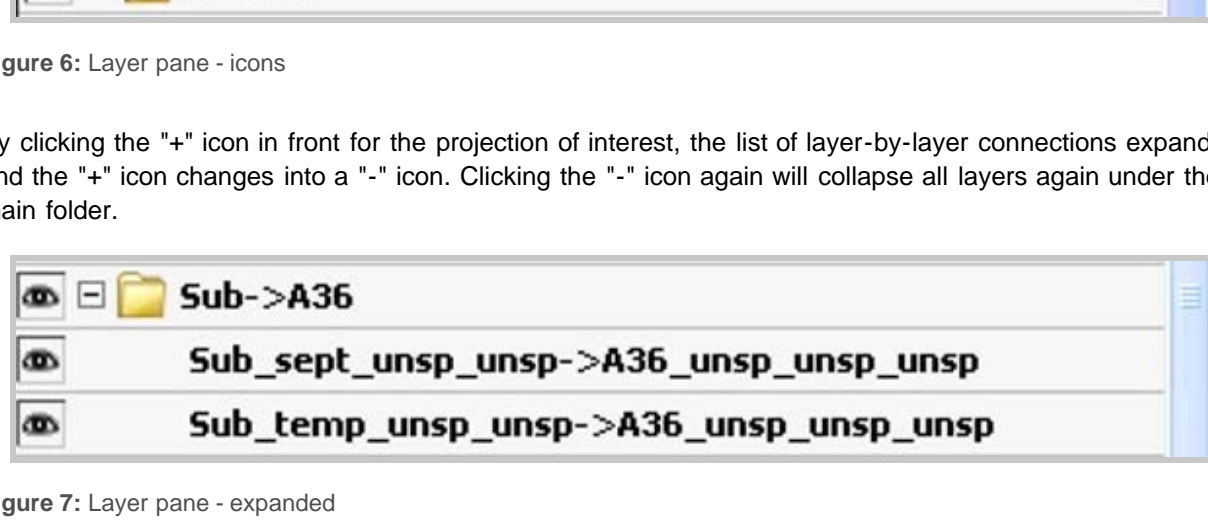


Figure 6: Layer pane - icons

By clicking the "+" icon in front of the projection of interest, the list of layer-by-layer connections expands and the "+" icon changes into a "-" icon. Clicking the "-" icon again will collapse all layers again under their main folder.

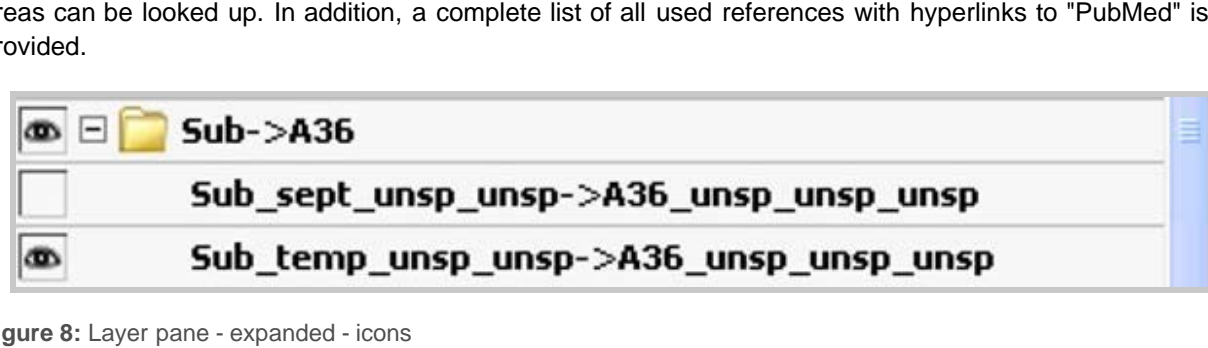


Figure 7: Layer pane - expanded

When the layer-by-layer connections are expanded (Figure 7), a list allows you to individually switch on and off connections. In order for Adobe to draw individual connections, the top checkbox (Figure 8), which in this example is Sub->A35, needs to be selected. This may mean that you need to deselect many individual layers when you wish to view only a specific layer in a "From->To" connection.

Supplement 2 (see [References](#)) provides a reference table in which the references between two specific areas can be looked up. In addition, a complete list of all used references with hyperlinks to "PubMed" is provided.

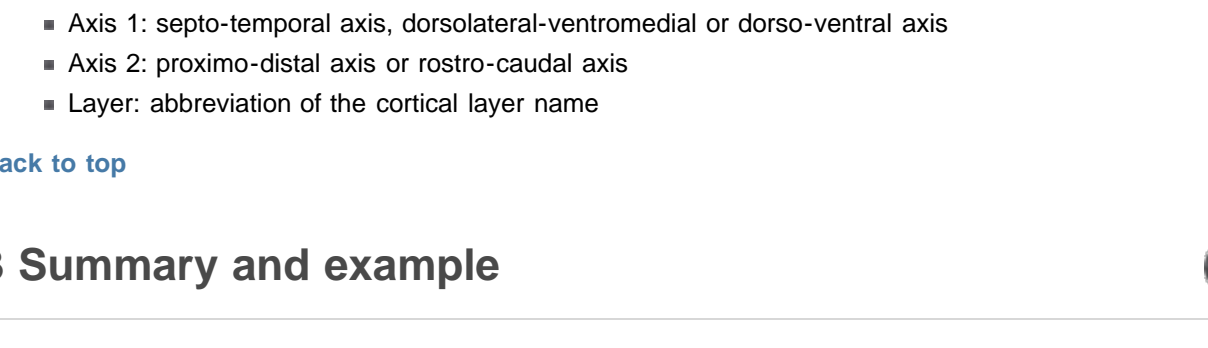


Figure 8: Layer pane - expanded - icons

If you deselect the top checkbox, all individual layers underneath the deselected connection will be hidden from the diagram.

The layer names in the layer panel follow a regular syntax which explains what is meant:

From -> To

Area\_axis1\_axis2\_layer -> Area\_axis1\_axis2\_layer

Area\_axis1\_layer -> Area\_axis1\_layer (only for LEA and MEA)

- Area: abbreviation of the area name
- Axis 1: septo-temporal axis, dorso-lateral-ventromedial or dorso-ventral axis
- Axis 2: proximo-distal axis or rostro-caudal axis
- Layer: abbreviation of the cortical layer name

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### 3 Summary and example

Figure 9 provides a summary of all the information that was presented step-by-step in Section 2. As an example the connections between Sub and A35 are shown and here we will give a short interpretation.

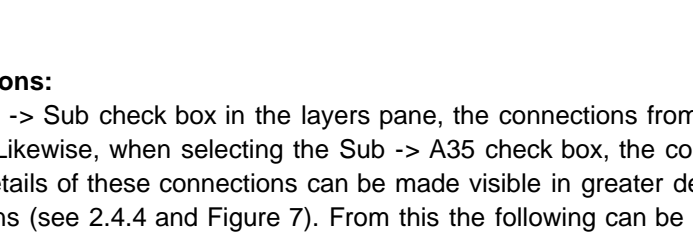


Figure 9: Example

#### Selecting the connections:

When selecting the A35 -> Sub check box in the layers pane, the connections from Area 35 to the Subiculum will appear. Likewise, when selecting the Sub -> A35 check box, the connections from Sub to A35 will appear. The details of these connections can be made visible in greater detail by looking at the layer-to-layer connections (see 2.4.4 and Figure 7). From this the following can be learned:

**Sub->A35:** from the diagram it follows that both septal and temporal levels of the Sub project to A35. However, not much detail of this connection is provided in the literature. Therefore, the origin of the connection in the Sub is drawn at the "unsp"-box at both septal and temporal levels. The connection arrives in the unspecified level of A35 because nothing has been reported about the dorso-ventral and rostro-caudal level of the termination. In fact, so little is known that the connection arrives in "unsp", which means that no information has been reported about the cortical layer in which this connection terminates. From Supplement 2 (see section 4: Quality assurance) it can be learned that this connection was reported in two references 2-3.

**A35->Sub:** From the layer-to-layer details it follows that the dorsal part of A35 projects to the deep part of the stratum moleculare of the proximal Sub, whereas the ventral part of A35 projects to the deep part of the stratum moleculare or the distal Sub. Furthermore, it has also been reported that rostral and caudal parts of A35 both project to septal and temporal levels of the Sub. Supplement 2 shows that this information is based on two references 1-2.

#### References:

- T. W. Deacon, et al., "Afferent connections of the perirhinal cortex in the rat," J. Comp Neurol. 220(2), 168 (1983).
- S. C. Furtak, et al., "Functional neuroanatomy of the parahippocampal region in the rat: The perirhinal and postirhinal cortices," Hippocampus (2007).
- K. C. Kosel, G. W. Van Hoesen, and D. L. Roseme, "A direct projection from the perirhinal cortex (area 35) to the subiculum in the rat," Brain Res. 269(2), 347 (1983).

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### 4 Quality assurance

References of all connections are provided in Supplement 2. However, for each connection that is drawn, we can provide the source, reference(s) and the page and/or figure number in which it was described. However, most questions regarding to literature can be answered by looking into the reference lookup table. In case you require more details about the references than is provided in Supplement 2, we kindly invite you to send your questions using the contact link at the top of this page. Unfortunately we cannot distribute original articles, since they are copyright protected. Should you feel that a connection is missing, please send the details of the reference in which the connection is mentioned. We will review the suggestion and if accurate, we will add it to our diagram. Although much care has been taken to make this diagram as accurate as possible, small inaccuracies may exist in the almost 1600 connections that were hand-drawn for this diagram. Should you find errors or have suggestions to improve the diagram, please send an e-mail. Thank you.

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### Appendix 1: Abbreviations

- A35: Area 35 of the perirhinal cortex
- A36: Area 36 of the perirhinal cortex
- CA1: Cornu Ammonis 1
- CA3: Cornu Ammonis 3
- caud: caudal
- crest: crest area of DG
- DG: Dentate Gyrus
- dist: distal part
- dl: dorso-lateral band of the entorhinal cortex
- enc: enclosed blade of DG
- exp: exposed blade of DG
- gran: granular cell layer
- hilus: polymorphic layer of DG
- l, ..., VI: first to sixth layer of the isocortex of the parahippocampal area
- int: intermediate band of the entorhinal cortex
- iml: inner 1/3th of the molecular layer
- int: intermediate part, i.e. in between the proximal and distal part
- LEA: Lateral entorhinal area
- luc: stratum lucidum
- MEA: Medial entorhinal area
- mi deep: deep part of the molecular layer
- mi sup: superficial part of the molecular layer
- mml middle: 1/3th of the molecular layer
- oml outer: 1/3th of the molecular layer
- or: stratum oriens
- PaS: Parasubiculum
- POR: Postirhinal cortex
- PROX: proximal part
- PrS: Presubiculum
- pyr: pyramidal cell layer
- rad: stratum radiatum
- rost: rostral
- slm: stratum lacunosum moleculare
- Sub: Subiculum
- unsp: unspecified
- vm: ventromedial band of the entorhinal cortex

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### Appendix 2: Problem solving

**Problem:** Sometimes Adobe 8 shows a "content preparation" dialog box, which indicates that the software is preparing the document in some way for reading. Unfortunately, this dialog returns every time you switch on/off a layer in the layer navigation pane. This slows down the interaction with the diagram to an undesirable speed.

**Cause:** The problem is caused by a screen reader plugin that is automatically loaded on Adobe 8 startup.

**Solution:** This plugin cannot be disabled from the Adobe 8 interface. Therefore one has to manually disable the plugin. To do so, follow these steps:

- Close Adobe Reader
- Open Windows Explorer and navigate to the plugins subdirectory of the Adobe Reader install directory (by default C:\Program Files\Adobe\Reader 8.0\Reader\plug\_ins)
- Find the following files in these folder: Accessibility.api, MakeAccessible.api, ReadOutLoud.api
- For safety, store them in a zip archive. This will allow you to undo the action.
- Delete these 3 files.
- Restart Adobe
- Select "OK" on any message dialog that complains about loss of functionality.

**Applic:** This fix has been tested only on Windows XP (SP3) with Adobe Acrobat Reader version 8. However, it is likely that this solution will also work for Acrobat Reader 9. Please feel free to provide us with feedback, so that other users may benefit from your experience.

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