

Phylogeny of neocortical-hippocampal projections provides insight in the nature of human memory

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Throughout mammalian evolution, the hippocampal region, unlike the neocortex, largely preserved its cytoarchitectural organization and its role in mnemonic functions. This contrast raises the possibility that the hippocampal region receives different types of cortical input across species, which may be reflected in species-specific memory-related differences. To test this hypothesis, we examined differences in unimodal and transmodal cortical input to the hippocampal region in the rat, marmoset, macaque and human. Our results demonstrate that unlike unimodal cortical input, transmodal cortical input to the hippocampal region was selectively preserved during mammalian evolution. These findings suggest that memory-related processes in different species likely operate on different types of sensory information. Our observations provide a comparative anatomical framework elucidating the process of dimensionality reduction underlying the formation of human memory.

The mammalian hippocampal region appeared more than 200 million years ago and can be broadly divided into the hippocampal formation and the adjacent parahippocampal region, that comprises the perirhinal cortex, entorhinal cortex and parahippocampal cortex (postrhinal cortex in the rodent)¹. Despite many opportunities for phylogenetical divergence, the gross anatomical, cytoarchitectural and functional properties of the hippocampal region remained largely conserved across species. This notion is particularly striking given the dramatic changes that occurred to the neocortex through evolution. This includes changes in cortical size, structural differentiation and functional specialization into increasingly larger number of cortical areas which have been hypothesised to enable an increase in the mammalian behavioral range². Comparative research into the structural features of mammalian cortex demonstrated that cortical areas involved in unimodal sensory processing and their relative anatomical locations are preserved across mammals. On the other hand, the relative size of cortical areas involved in transmodal processing increased through evolution, especially in humans, playing a major role supporting human high-order cognitive functions³.

The notion of preserved unimodal sensory areas across mammals is particularly important, since together with the phylogenetically preserved hippocampal region, it provides a second anchor in the neocortical divergence of the mammalian lineage. As the hippocampal region is typically positioned at the pinnacle of cortical hierarchy⁴, it implies that both the start and end points of cortical hierarchy – primary sensory regions and the hippocampal region, respectively - are present *in all mammals*. What might differ across species are the paths that the sensory input “travels” through, from being perceived to being funnelled into the memory system, thus potentially underpinning the differences in species-specific mnemonic functions⁵.

To examine whether the type of information funnelled into the memory system changed through evolution, we leveraged the contrast between the preserved hippocampal region and diverse neocortex and examined the differences in the cortical input to the hippocampal region across species⁶. To this end, we analyzed animal anatomical tract-tracing data and human functional magnetic resonance imaging (fMRI) connectivity data (as a proxy of anatomical connectivity⁷⁻⁹) and mapped the projections from unimodal and transmodal cortical areas to the parahippocampal region, a main recipient of diverse cortical inputs, in four species - the rat, marmoset, macaque and human. The species were considered relative to the time of having a last common ancestor with the human.

First, in each species, we calculated the proportion of the cortical mantle dedicated to unimodal and to transmodal processing. Next, we mapped the cortical input to the entorhinal, perirhinal and parahippocampal/postrhinal cortices, and calculated the proportion of unimodal

and transmodal input to these parahippocampal areas. Importantly, while in the rat and macaque the anatomical projections to the parahippocampal region were estimated directly by examining labelled cells following tracer injections into the parahippocampal region or the broader neocortex, in the marmoset and human, cortical projections to the parahippocampal region were estimated indirectly. In the marmoset, since only projections *from* the parahippocampal region are available, projections *to* the parahippocampal region were estimated based on the reciprocity of the anatomical connections between the parahippocampal region and the broader neocortex in the macaque¹⁰. A similar approach was applied while interpreting the associations of the human parahippocampal region with the broader neocortex estimated with fMRI connectivity (see Methods for more details).

Results and Discussion

Our results demonstrate that mammalian evolution has been associated with a general reduction in the percentage of the total cortical area projecting to the parahippocampal region (Figure 1a; Spearman's $r=1$, $p<0.001$). Importantly, this reduction disproportionately targeted the input from unimodal cortical areas, while the input from transmodal areas was relatively preserved across species (Figure 1b). Finally, we find that in the primate lineage, cortical input from the broader neocortex to the entorhinal cortex was dominated by transmodal areas compared with the cortical input to the perirhinal/parahippocampal cortices (Figure 2; z-test for proportion differences, all $p<0.001$); in the rat, the proportion of transmodal input was more equally distributed across the entorhinal and the perirhinal/postrhinal cortices.

Our results show an increasingly dominating role of transmodal compared with unimodal cortical input to the parahippocampal region across species. Importantly, these changes in connectivity cannot be explained merely by changes in the relative size of transmodal areas in different species³. In particular, while long-range projections tend to retract with increase in brain size across species¹¹, we observed a selective and almost absolute retraction of unimodal projections to the parahippocampal region from the rat to the human, even though about 27% of the human brain consists of unimodal areas. Specifically, our results show that the changes in cortical input to the parahippocampal region reflect a continuous transition - from all unimodal areas that project to the parahippocampal region in the rat¹² (motor, somatosensory, auditory, olfactory, and visual input) to minimal sensory associations with the parahippocampal region in the human¹³ (potential exceptions being olfactory and insular somatosensory input). This trend is dramatic, indicating that parahippocampal processing in different species operates on fundamentally different types of information. Since many of the anatomical connections between

the parahippocampal region and neocortex observed in the human exist already in the rat (e.g., connections with the parietal, retrosplenial, and limbic cortices⁶), we suggest that the gradual retraction of unimodal input through evolution reflects selective preservation, favouring input from transmodal areas.

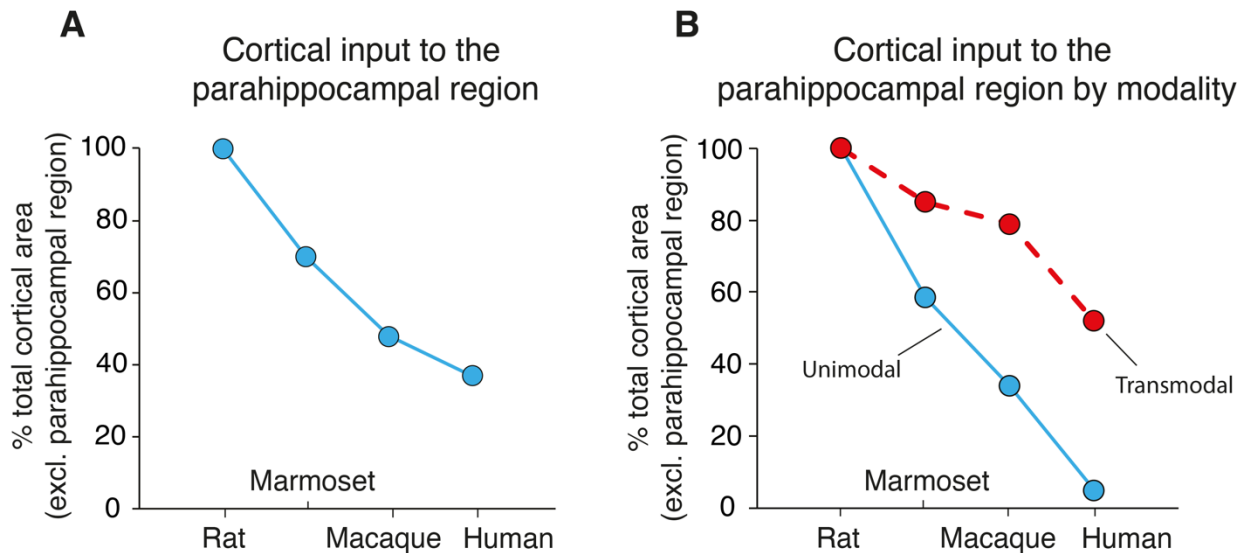


Figure 1. Cortical input to the parahippocampal region. (A) We find that the percentage of total cortical area (collapsed across unimodal and transmodal cortices) that projects to the parahippocampal region decreases across species (Spearman's $r=1$, $p<0.001$). (B) Percentage of cortical input to the parahippocampal region calculated separately from the total unimodal and transmodal areas in each species. This analysis demonstrates that even though there is a general decrease in total cortical areas projecting to the parahippocampal region, this decrease disproportionately targets unimodal input.

Furthermore, we find that in the primate lineage, cortical input to the entorhinal cortex is consistently dominated by transmodal input. For example, in the macaque, other than the input from the piriform cortex, the entorhinal cortex receives no cortical feedforward projections from any primary sensory or unimodal association cortices¹⁴. This finding is particularly interesting in light of the historical context of memory research and can potentially explain why the widespread anatomical connections of the entorhinal cortex with the broader cortex were often overlooked and the main functional role assigned to the entorhinal cortex was a relay point between the perirhinal/parahippocampal cortices and the hippocampus. Though the cortical input to the primate entorhinal cortex is mostly transmodal, the total input to the parahippocampal region across species became increasingly transmodal as well. Since it was suggested that changes in anatomical connectivity would develop if proven advantageous to the survival and propagation

of the species¹⁵, we will next discuss potential benefits and functional implications of mnemonic cognition driven by transmodal inputs.

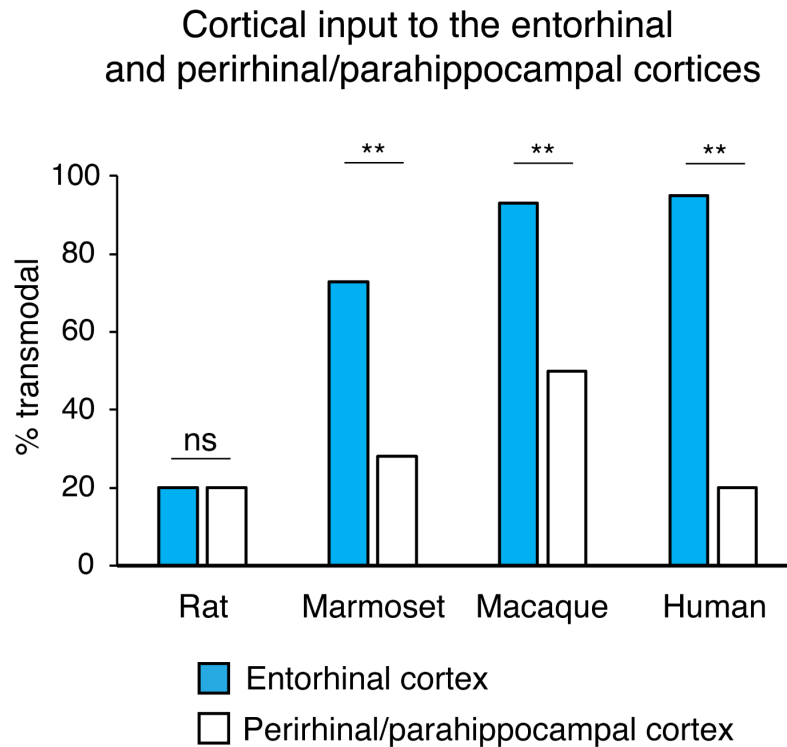


Figure 2. Cortical input to the entorhinal cortex and to the perirhinal/parahippocampal cortex. In each species, we calculated the proportion of unimodal and transmodal input separately for the entorhinal cortex and the perirhinal/parahippocampal cortices (postrhinal in the rodent). Our results show that in the primate lineage, cortical input to the entorhinal cortex is consistently more transmodal than to the perirhinal/parahippocampal cortices (z-test for proportion difference, ** $p < 0.001$). In the rat, the proportion of unimodal vs transmodal input is more equally distributed across the entorhinal cortex and perirhinal/postrhinal cortex; ns – not significant.

It is well established that in the early levels of cortical processing, primary and unimodal association cortices encode different features of sensory modalities originating in the extrapersonal environment. In contrast, at the later levels of cortical processing, transmodal areas converge these low-level, modality-specific signals and form cross-modal associative representations. For example, the ventral stream of visual processing, beginning in primary visual cortex, transforms low-level visual features into increasingly complex transmodal representations in anterior temporal cortex¹⁶. Therefore, transmodal areas that are associated with the parahippocampal region funnel to the memory system highly processed multisensory information which is not tuned to a single stimulus property, such as the size of the respective

representation on the retina or sound frequency. It is difficult to imagine mnemonic processing driven by unimodal sensory features (e.g., in the rat), nevertheless, animal studies show that marmosets perform better in visual memory tasks requiring object-centred perception compared with rats that are more prone to viewer-centred bias¹⁷. This finding is consistent with reduced visual-mnemonic hierarchy in the rat compared with the marmoset, suggesting that in rats mnemonic fidelity to low-level sensory features hinders object-centred generalization. Taken to the extreme, behaviour driven by unimodal sensory input can be suboptimal and barely adaptive - for example, brook stickleback fish that choose to prey based on the size of its retinal representation or turkey poults that kill their own progeny mistaking it for predators when deafened¹⁸. Even though currently speculative, we suggest that the selective increase in transmodal input provides increased capacity to extract generalized and abstract information from the organism's extrapersonal environment, thus contributing to mnemonic functions increasingly better described not in terms of concrete sensory experiences, but in terms of low-dimensional latent states¹⁹.

Our findings imply that hippocampus-dependent mnemonic cognition dramatically differs across species which can be manifested in different memory-related behaviours. In addition to episodic memory, which is studied mostly in humans, the mammalian hippocampal region is known to be involved in additional functions, such as associative learning and navigation²⁰⁻²². While these seemingly distinct functional properties of the hippocampus are typically considered separately and species-specific, they can also be seen in tandem, representing a functional continuum of a hierarchical increase in mnemonic complexity across species^{22,23}. For example, early memory theories suggested an existence of multiple memory systems that can be classified, for example, into “associative memory”, “representational memory” and “abstract memory”²⁴. Importantly, these systems were proposed to be phylogenetically dependent on each other, such that different systems have emerged at different evolutionary stages²⁵. More recent accounts on spatial navigation suggest a common framework that can account for the rich behavioral and experimental variability across different species²³. According to this framework, human memory can be studied as a form of navigation (albeit in abstract spaces²⁶), even though these two functions seem to be different and are typically tested by different experimental paradigms. Our current results suggest that the notion of memory may have changed through evolution from supporting functions, such as response inhibition²⁰ to supporting episodic construction and future thinking^{27,28} through increasingly dominating role of transmodal input to the parahippocampal region.

While, transmodal input to the parahippocampal region offers a substantial increase in the behavioural range, it comes with a drawback of losing the high-dimensional sensorial fidelity following cross-modal associative binding¹⁸. Without direct projections from unimodal sensory areas to the memory system, the high-dimensional sensorial fingerprint of external events is inevitably lost and transformed prior to its mnemonic encoding. Instead, mnemonic processing must operate on low-dimensional products of transmodal processing. This suggests that generalization and abstraction (i.e., “forgetting” the high-dimensional detail) are *inherent features* of memory, and increasingly so, of human memory²⁹. Therefore, when sensory information is declaratively generated (during either recall or imagery), this fundamentally cannot be a reinstatement of the exact sensory stimulus, but merely its reconstruction. The constructive nature of human memory is further supported by neuropsychological studies showing that individuals with damage to the hippocampal region struggle with describing their personal future³⁰ and, more generally, with constructing details-rich fictitious scenarios²⁷. Furthermore, we suggest that the dominating role of transmodal input in human mnemonic processing supports the ability to detach from the immediate sensory surroundings and to perform “mental time travel”, an ability that is believed to be uniquely human³⁰.

In accordance with the classical reactivation theory³¹, we believe that mnemonic reconstruction of high-dimensional sensory stimulus can be potentially supported by feedback projections connecting multiple transmodal areas (including the parahippocampal region) with ‘early’ sensory regions⁴. Even though one of the proposed functional roles of these projections is to allow top-down modulation of early sensory processing by high-level regions (e.g., modulating visual perception by organisms’ attention, goals or intentions), these connections can also potentially support reinstatement of concrete sensory experiences during mnemonic recollection or imagery. Supporting this notion, it has been shown that vivid recall in humans is associated with activity in sensory areas that are involved in sensory encoding³². However, these mnemonic reconstructions cannot be other than approximations, affected by other experiences, modalities, and arbitrary associations. Furthermore, in line with our results indicating minimal direct sensory input to the human memory system, recent accounts of the reactivation theory suggest that mnemonic representations are fundamentally different from the original sensory stimulation both in terms of neuroanatomical localization and the level of conceptual representation³².

It is important to consider two main limitations pertaining to the current study. The first limitation is the indirect estimation of anatomical connectivity in humans using fMRI connectivity methods. Even though these methods were proved to be valid tools for non-

invasively studying neuroanatomical connectivity⁷, unlike tract-tracing methods in the rat, marmoset and macaque, they are *a proxy* for measuring neuroanatomical connections. The second limitation of our study is the definition of unimodal and transmodal cortical areas, which is particularly challenging given recent evidence pointing to multisensory properties of early sensory cortices³³ (see extended Materials and Methods for more details).

To conclude, our study provides evidence for a continuous trend towards an increased role of transmodal input in mnemonic processing during mammalian evolution culminating in humans. This finding suggests that memory-related processes in different species operate on different types of sensory information, which is reflected in cross-species differences in mnemonic cognition. Our biologically driven observations provide a comparative anatomical framework potentially elucidating the process of dimensionality reduction underlying the formation of human memory and supporting its fundamentally constructive, rather than reproductive, nature.

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Methods

Cortical specialization across species

We mapped cortical areas dedicated to unimodal and transmodal processing in four species – the rat, marmoset, macaque, and human. In each species, unimodal areas included motor, visual, auditory, and somatosensory cortices. Unimodal cortical areas were defined as areas that are known to selectively respond only to one type of modality; note that in this study, motor system was defined as a separate modality. Transmodal areas included cortical areas that do not show specificity to any single modality, which included polymodal, heteromodal and limbic cortices. The unimodal and transmodal cortical areas used for the analysis are presented in Tables S1-S4.

Table S1. Unimodal and transmodal cortical areas in the rat.

Unimodal	Transmodal
Motor cortex (primary, secondary)	Orbital cortex (lateral, ventrolateral, medial)
Somatosensory cortex (primary, secondary)	Retrosplenial cortex (dorsal, ventral)
Visual cortex (primary, lateral, medial)	Limbic cortex
Auditory cortex (primary, posterior, ventral)	Ventral temporal association cortex
Visceral cortex	Posterior parietal association cortex
Gustatory cortex	Agranular insular cortex
Piriform cortex	
Periamygdaloid cortex	

Table S2. Unimodal and transmodal cortical areas in the marmoset.

Unimodal	Transmodal
Visual occipital areas (V1, V2, V3, V3A, V4, V4t, MT, prostriate cortex)	Prefrontal cortex (areas 8, 9, 10, 11, 12, 13, 14, 45, 46, OPro, OPAI, FEF)
Visual parietal areas (MST, V6, V6A, A19DI, A19M)	Parietal cortex (LIP, VIP, MIP, PGM, PG, PEC, Opt)
Visual temporal areas (FST, IT)	STP, TPpro, PGa/IPa
Somatosensory cortex (areas 1, 2, 3, PE, SII, granular insular cortex)	PF, PFG
Motor cortex (SMA, area 4, dorsal area 6)	Ventral area 6
Auditory (A1, caudal STG)	Auditory belt areas, STR
Pyriform cortex	Limbic cortex (23, 24, 25, 29, 30, 32)

Periamygdaloid cortex	Agranular and dysgranular insular cortex
Gustatory cortex	

Due to functional ambiguity, marmoset cortical areas TPro, TF and TFO remained unclassified.

Table S3. Unimodal and transmodal areas in the macaque.

Unimodal	Transmodal
Visual occipital areas (V1, V2, VP, V3A, V4, VOT, V4t, MT, prostriate cortex)	Prefrontal cortex (areas 9, 10, 11, 12, 13, 14, 45, 46, Pro, Pall, FEF)
Visual parietal areas (MST, PO, PIP, DP)	Parietal cortex (AIP, LIP, VIP, MDP, 7a)
Visual temporal areas (FST, IT)	STP, temporal pole
Somatosensory cortex (areas 1, 2, 3, 5, SII, granular insular cortex)	Area 7b
Motor cortex (SMA, area 4, dorsal area 6)	Ventral area 6
Auditory (A1, caudal STG)	Auditory belt areas and rostral STG
Pyriform cortex	Limbic cortex (23, 24, 25, 29, 30, 32)
Periamygdaloid cortex	Agranular and dysgranular insular cortex
Gustatory cortex	

Table S4. Unimodal and transmodal areas in the human. Human data were based on the 17-networks parcellation presented in Yeo, Krienen et al.³⁴; note that the human auditory system, including primary and secondary auditory cortex, is included in somatosensory networks; human piriform cortex is believed to occupy the cortical area at the border of the temporal and frontal lobes, around the temporal pole³⁵, and is included in the limbic network. Assignment of the Dorsal Attention Network A and Dorsal Attention Network B to unimodal and transmodal processing was based on connectivity data presented in Reznik et al.¹³

Unimodal	Transmodal
Visual networks	Saliency networks
Somatomotor networks (including primary and secondary auditory cortex)	Frontoparietal networks
Dorsal Attention Network A	Default networks
Piriform cortex (part of the limbic network)	Limbic network
	Dorsal Attention Network B

Percentage of each cortical modality in the rat was calculated based on the data presented in Burwell & Amaral¹² and Burwell, Witter & Amaral⁵. Percentage of each cortical modality in the marmoset was calculated based on the data presented in Atapour et al³⁶. Percentage of each area in the macaque was calculated based on the data presented in Felleman & Van Essen³⁷. Percentage of each cortical modality in the human was calculated based on the 17-network parcellation presented in Yeo, Krienen et al.³⁴ converted to MNI space and on the homotopic parcellation of the cortex³⁸. In all species, the regions comprising the parahippocampal region (the entorhinal, perirhinal and parahippocampal/postrhinal in the rodent cortices) were excluded from the total percentage calculation.

Cortical projections to the parahippocampal region across species

To estimate the proportion of cortical areas involved in unimodal and transmodal processing from the total cortical input to the parahippocampal region in each species, we analyzed animal tract-tracing and human fMRI data examining connectivity of the entorhinal, perirhinal and parahippocampal (postrhinal in the rodent) cortices with the broader cortex (Table S5). Where possible, we considered projections from the unimodal and transmodal cortical areas to the parahippocampal region; in species without direct data about cortical input to the parahippocampal region, cortical projections were estimated indirectly (see below).

Table S5. Studies used for estimating the connectivity between the parahippocampal region and the broader neocortex in each species.

Species	Source
Rat	Burwell, Witter, Amaral ⁵ , Kerr et al. ³⁹ , Agster & Burwell ⁴⁰ , Burwell & Amaral ¹² , Burwell ⁴¹ .
Marmoset	Majka et al. ^{42,43} , unpublished tracing data that are to be released in the updated version of the online marmoset connectivity atlas (www.marmosetbrain.org/).
Macaque	Suzuki et al. ⁴⁴ , Lavenex et al. ⁴⁵ , Insausti et al. ⁴⁶ , Cavada & Goldman-Rakic ⁴⁷ , Seltzer & Pandya ⁴⁸ , Muñoz & Insausti ⁴⁹ , Mohedano-

	Moriano et al. ⁵⁰ ; Markov et al. ⁵¹ ; Rockland & Van Hoesen ⁵² ; Smiley et al. ⁵³ .
Human	Reznik et al. ⁵⁴ , Kahn et al. ⁵⁵ , Wang et al. ⁵⁶ , Libby et al. ⁵⁷

To account for methodological differences in quantification of animal tracing data, we included all anatomical connections, including weak cortical input to the parahippocampal region (e.g., 1-5% connectivity in the macaque). To account for weaker return projections from the parahippocampal region to the primate cortex⁴⁵, we used a connectivity threshold of $\log_{10}(\text{FLNe}) = -3$ (fraction of extrinsic labelled neurons; average value across all available experiments in the same cortical area) in the marmoset (see input vs output projections below). Only connections that showed up in more than half of the experiments were considered.

One major advantage of the marmoset tracing data is that it allowed us to examine the connections between the parahippocampal region and almost all sensory systems – somatosensory, motor, visual, and auditory. Nevertheless, almost half of the marmoset cortical mantle was not covered by tracer injections. For example, there were no available injections into the piriform cortex and the orbital frontal cortex (except for area A11). To account for these cross-species differences in anatomical coverage, we inferred anatomical connectivity between the marmoset parahippocampal region and the cortical areas *that were not injected with a tracer* if these regions were found to be anatomically connected in the macaque. These inferred connections included the piriform cortex, insular cortex, gustatory cortex, middle inferior temporal cortex (TE2 and TE3), fundus of superior temporal sulcus, A13, A14, A25, A30, A31, A45, A47 (medial and orbital parts), orbital priso- and periallo-cortex, and temporopolar cortex.

Since no tract-tracing is feasible in humans, we used correlations in spontaneous brain activity patterns as a proxy to indirectly measure in vivo mono- and polysynaptic neuroanatomical connectivity. This method was proved to be a powerful tool in elucidating the anatomical organization of the brain both at the level of local circuitry⁵⁸ and at the level of macro-scale network architecture⁷. Specifically, correlations in blood oxygenation level-dependent (BOLD) signal measured with functional magnetic resonance imaging (fMRI) during spontaneous brain activity (fixation task data, also known as “resting state”) were found to mirror cortical pathways estimated using tract-tracing both in the macaque and marmoset. However, even though fMRI connectivity methods allow to indirectly measure anatomical organization at the whole-brain level, the unimodal connectivity of the human olfactory modality with the parahippocampal

region still remains unresolved. Since direct connections exist between the piriform cortex and the entorhinal cortex both in the rat and the macaque, we assume this connectivity to be present also in the human. Another potentially unimodal sensory region that remains unresolved in humans is the insular cortex. In our previous study we found consistent connectivity between the human perirhinal cortex and the insular cortex. It is difficult to determine whether the part of the insular cortex we find to be associated with the human perirhinal cortex is unimodal somatosensory (typically positioned caudally) or transmodal (typically positioned rostrally) without functional task targeting these functional properties, nevertheless, we adopted a conservative approach and treated this connection as another sensory connection with the human parahippocampal region.

Input versus output projections

In the current study we could directly examine projections from the broader neocortex to the parahippocampal region only in the rat and in the macaque. In two other species, the marmoset and the human, such projections were estimated indirectly. In the marmoset, anatomical tracing data included only retrograde injections covering about half of the cortical mantle, excluding the parahippocampal region. Therefore, in this species we could examine only projections from the entorhinal, perirhinal and parahippocampal cortices to the broader neocortex. Tracing data from the macaque suggest that most of cortical projections to the parahippocampal region are reciprocal with some of the reciprocating projections being weaker⁴⁵. Therefore, we inferred cortical projections to the marmoset parahippocampal region based on the return projections from this region to the broader cortex. Importantly, even though almost all of macaque cortical-to-parahippocampal projections are reciprocal, many of the return projections are not. For example, while there are no known projections directly connecting the macaque primary visual cortex to the parahippocampal region, projections from the parahippocampal areas TH/TF to the primary visual cortex do exist^{51,52}. Another example comes from the auditory modality. While retrograde injections in the auditory caudomedial belt area resulted in labelled cells along the macaque entorhinal cortex⁵³, retrograde injections directly into the entorhinal cortex resulted in no labelled cells in auditory areas⁴⁶. These examples suggest that using output projections as an estimate of input projections might result in overestimation, but not underestimation, of total projections from the cortex to the parahippocampal region. Importantly, if we remove the estimated cortical projections to the parahippocampal region in the marmoset that do not exist in the macaque (visual cortices V1, V2, primary somatosensory cortex 3a, secondary somatosensory cortex,

primary auditory cortex), the percentage of transmodal input in the marmoset will be similar to that of the macaque. Therefore, as a final estimate of marmoset projections from the broader cortex to the parahippocampal region, we averaged the percentage of input projections estimated solely on output projections and the percentage of input projections estimated using macaque anatomical priors. It is still an open question whether projections from early visual, somatosensory, and/or auditory cortices to the parahippocampal region exist in the marmoset.

In the human, since anatomical tract-tracing is unfeasible, we used spontaneous intrinsic brain activity patterns as a proxy to indirectly measure *in vivo* mono- and polysynaptic neuroanatomical connectivity. Like we elaborated above, even though functional connectivity methods serve as a powerful means to noninvasively estimate large-scale anatomical connectivity, they cannot distinguish between the directionality of connections. Therefore, it is possible that the correlations between the human entorhinal cortex and the putative olfactory cortex in or around the temporal pole are output connections; a similar limitation applies to the perirhinal connections with the insular cortex. Moreover, unlike in the macaque and the marmoset, precision imaging implies that human parahippocampal areas TH/TF are not associated with early visual cortex¹³ (but see Bergmann et al.⁵⁹), potentially meaning that even projections from the parahippocampal region to the primary visual cortex, which are present in the macaque and the marmoset, are absent in humans.

Cortical projections to the entorhinal cortex

To estimate the differences in cortical input within the parahippocampal region, for each species in the primate lineage (the marmoset, macaque, and human) we calculated separately the proportion of input from unimodal/transmodal areas to the entorhinal cortex and to the rest of the parahippocampal region (the perirhinal cortex and parahippocampal cortex). Since almost all of the cortical connections with the human parahippocampal region are transmodal (except for the unresolved olfactory and insular cortices; see above), we followed the logic introduced by Paul Flechsig⁶⁰ and divided the human transmodal regions into areas that share a direct boundary with one of the unimodal areas and areas that share no boundary with any of the unimodal areas. For the sake of this analysis, connections of the human parahippocampal region with transmodal regions that share a direct boundary with one of the unimodal areas were treated as connections with unimodal cortical areas in the marmoset and macaque.

Since this analysis was performed within species, we used a z-test for proportion differences to estimate the significance level of the difference between the proportion of transmodal input; the sample size was defined as the total number of cortical brain areas connected with either

entorhinal cortex or with the perirhinal/parahippocampal cortices and their assigned functional property.

Limitations of the current study

Our study has two main limitations. The first limitation pertains to anatomical interpretability of fMRI connectivity methods. While the connectivity in the rat, marmoset, and macaque is based on tracing data, namely, data that provides the ground truth regarding anatomical connectivity between certain brain regions, the anatomical connectivity in the human was estimated based on MRI functional connectivity data. Even though correlations in intrinsic brain activity patterns were proved to be a powerful and valid means for studying anatomical connectivity (see above), we must keep in mind that this method is *a proxy* for measuring neuroanatomical architecture. Therefore, absence of functional connectivity between brain regions in humans cannot indicate lack of anatomical connectivity (see for example Reznik et al.⁵⁴, for direct testing of connections between early sensory regions and the human parahippocampal region). Nevertheless, a similar limitation holds also for the animal tracing experiments which often contain “hidden” data, either unpublished or not looked for. Therefore, no evidence for anatomical connectivity between certain regions in animal studies does not mean that this connectivity does not exist.

The second limitation of our study pertains to the definition of unimodal and transmodal cortical areas. Growing anatomical and functional evidence points to multisensory integration already at the level of early sensory processing^{33,61}, thus challenging the traditional notion of cortical unimodal encoding and cortical sensory hierarchy in general³⁷. Even though in the current study we classified many of the traditionally unimodal association areas as transmodal⁶² (e.g., LIP and ventral premotor cortex), since the functional properties of the low-level multisensory integration are not yet clarified and their anatomical and physiological profiles contrast with those in “classic” multisensory areas (e.g., VIP and STS)⁵³, in the current study we treated early sensory cortices as unimodal.

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