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Research Report

The functional organisation of the hippocampus along its long axis is gradual and predicts recollection

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ABSTRACT

Understanding the functional organisation of the hippocampus is crucial for understanding its role in cognition and disorders in which it is implicated. Different views have been proposed of how function is distributed along its long axis: one view suggests segregation, whereas the alternative view postulates a more gradual organisation. Here, we applied a novel 'connectopic mapping' data-analysis approach to the resting-state fMRI data of participants of the Human Connectome Project, and demonstrate that the functional organisation of the hippocampal longitudinal axis is gradual rather than segregated into parcels. In addition, we show that inter-individual variations in this gradual organisation predict variations in recollection memory better than a characterisation based on functional parcellation. These results present an important step forward in understanding the functional organisation of the human hippocampus and have important implications for translating between rodent and human research.

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1. Introduction

The hippocampus is involved in multiple cognitive functions including episodic memory (Scoville & Milner, 1957; Squire, 1992), spatial navigation (Maguire et al., 1998; Morris, Garrud, Rawlins, & O'Keefe, 1982), and emotion-related processing (Bannerman et al., 2004; Gray & McNaughton, 2000). Despite decades of research, it is still unclear how its macroscopic organisation subserves these multiple cognitive functions. Although there is consensus that the hippocampus is functionally organised along its longitudinal axis, different views have been proposed of how function is distributed: one view suggests that the neural circuits associated with different functions are segregated into discrete hippocampal subdivisions with sharply demarcated borders, whereas the alternative view postulates a gradual organisation of function along the long axis (Strange, Witter, Lein, & Moser, 2014). Distinguishing between these alternative views is important, because these two alternative characterisations of the underlying neurobiology may lead to very different approaches when analysing signals recorded from the hippocampus and will certainly lead to different interpretations of hippocampal function, as we will demonstrate in this paper.

Early anatomical (Swanson & Cowan, 1977), electrophysiological (Elul, 1964; Racine, Rose, & Burnham, 1977) and lesion studies in rodents (Henke, 1990; Moser, Moser, & Andersen, 1993) found differences in cortical and subcortical projections from the dorsal and ventral hippocampus, lending support to the idea that the hippocampus can be parcellated into functionally-distinct subdivisions (for an extensive review, see Strange et al., 2014). Consequently, multiple proposals attempting to allocate alternative functions to the ventral and dorsal portions—which correspond to anterior and posterior sections of the hippocampus in humans—have been introduced (for a review, see e.g., Poppenk, Evensmoen, Moscovitch, & Nadel, 2013), suggesting that the ventral (anterior) portion is primarily involved in emotion-related processing and the dorsal (posterior) in memory and spatial processing (Strange et al., 2014). However, anatomical tracer studies in experimental animals have shown that the hippocampus receives projections from the entorhinal cortex that are organised in a smooth gradient without abrupt transitions along the long-axis (Witter, Wouterlood, Naber, & Van Haeften, 2000). In addition, hippocampal place cells can be found along the entire extent of the longitudinal axis of the hippocampus, with their field size increasing gradually from the dorsal to ventral sub-regions, demonstrating a scale-related gradient of functional change within the hippocampus (Brunec et al., 2018; Kjelstrup et al., 2008).

It is important to note that the parcellated- and gradient views are not necessarily mutually exclusive: it is possible that multiple functional gradients are superimposed on discrete hippocampal functional domains (Strange et al., 2014). Studies that could shed light on this are markedly lacking in the field, in particular in human neuroscience. One of the main reasons why the gradient-like organisation of the hippocampus has been under-explored in humans is a lack of appropriate methods: the invasive nature of tracing studies that have first suggested a gradient render them unsuitable for human participants. Studies into the functional organisation of the human hippocampus have therefore predominantly been based on parcellation-based approaches that rely on non-invasive brain imaging techniques (e.g., Chase et al., 2015; DeMaster, Pathman, Lee, & Ghetti, 2013; Poppenk & Moscovitch, 2011). However, by using parcellation methods, one forces the characterisation of functional organisation to be in terms of strictly segregated parcels, even if the true functional organisation is smooth without sharp borders. If the organisation is best characterised as a gradient, then a parcellation into anterior and posterior portions is unlikely to capture the full extent of variability in the individual-level functional organisation of the hippocampus and its relationship with behaviour.

Therefore, we here set out to investigate the functional organisation of the human hippocampus using 'connectopic mapping', an emergent approach to characterising functional organisation non-invasively in individual human participants without imposing a parcellation scheme (Haak, Marquand, & Beckmann, 2017). Connectopic mapping specifically aims at characterising changes in the location-dependent pattern of associated functional connectivity, which means that it can capture both sharp boundaries (i.e., sharp increase in connectivity change) and gradients (i.e., gradual connectivity change). Here, we test if the functional organisation of the human hippocampus in terms of the location-dependent pattern of functional connectivity might be more meaningfully described as a gradient than in terms of functional parcels. We do that by testing whether inter-individual variations in the gradient predict inter-individual variations in hippocampus-related behaviour better than a functional parcellation-based approach.

2. Materials and methods

2.1. *Resting-state fMRI data and pre-processing*

A data-set comprising participants of the WU-Minn Human Connectome Project (S-500 release) (HCP; Van Essen et al., 2013; see https://db.humanconnectome.org) was used in this study. In the connectopic mapping analysis we included only those participants ($N = 475$) who completed all four resting-state functional magnetic resonance imaging (fMRI) sessions (multi-band, TR = .72 sec). The within-run resting-state data were pre-processed as detailed in Smith et al., 2013 including spatial distortions and head motion correction, T1w registration, resampling to 2 mm MNI space, global intensity normalisation, high-pass filtering with a cut-off at 2000 sec, and the ICA-based artefact removal procedure (FSL-FIX, Griffanti et al., 2014; Salimi-Khorshidi et al., 2014). In addition, before applying connectopic mapping we smoothed the data with a 6 mm FWHM Gaussian kernel, regressed the mean ventricular as well as white-matter signal from the time-series, and Z-score normalised the time series to zero mean and unit standard deviation (pre-processing pipeline based on Marquand, Haak, & Beckmann, 2017). Finally, for each participant, we concatenated the data from their four resting-state scans into one one-hour session. These pre-processed data were then used to estimate connectopic maps for each individual.

2.2. Connectopic mapping

Connectopic mapping (Haak et al., 2017) is a data-driven approach for mapping the connectopic organisation of brain areas based on resting-state fMRI data. Previous work has shown that this method accurately traces known functional gradients in brain regions such as retinotopic and somatotopic cortex, as well as striatum and entorhinal cortex (Haak et al., 2017; Marquand et al., 2017; Navarro Schröder, Haak, Jimenez, Beckmann, & Doeller, 2015). Furthermore, inter-individual differences in these gradients can be linked to individual-level behaviour, as for instance demonstrated by recent work that has shown that differences in cortico-striatal connectopic organisation are meaningfully related to variations in goal-directed behaviour (Marquand et al., 2017).

Details of the connectopic mapping procedure are described in Haak et al., 2017. Briefly, for every voxel in the region of interest (ROI; here, the left or right hippocampus), we obtained a "connectivity fingerprint" by computing the correlation between the voxel-wise time-series and the rest of the cortex (based on a loss-less singular value decomposed matrix of time-series of all grey-matter voxels outside the ROI). We then computed the within-ROI similarity of functional connectivity, and applied non-linear manifold learning (Laplacian Eigenmaps) to the graph representation of this similarity matrix to obtain the connectopic maps, indicating how hippocampal-neocortical connections vary topographically across the ROI.

Connectopic mapping was applied to the resting-state fMRI data of 475 participants. Hippocampal ROIs (one for each cerebral hemisphere) were based on the Harvard–Oxford atlas. As a result, we obtained the connectopic maps describing each participant's hippocampal-neocortical functional connectivity patterns for left and right hippocampus separately. The connectopic maps of interest were captured by the eigenmaps associated with smallest non-zero eigenvalue, which were then used in all subsequent analyses. To ascertain the replicability of these connectopic maps, we estimated the overlap between individual-level gradients across resting-state sessions, and found that they are highly replicable within subjects (R^2 = .994 and .992 for the left- and right hemisphere, respectively).

2.3. Trend surface modelling

In order to enable statistical inference over the connectopic maps we used trend surface modelling (Haak et al., 2017). This approach involves fitting series of polynomial basis functions along canonical axes to the connectopic maps to capture their overall spatial pattern in a small number of coefficients. A spatial model of the dominant connectopic map was estimated for each participant and hemisphere independently.

We started the estimation with fitting a polynomial of degree 1 (a straight line with a slope) and investigated progressively more refined approximations, by combining the lower order models up to the fifth model order. Because hippocampi are three-dimensional structures, this entails estimation along the x, y and z direction (in MNI space), resulting in three trend surface model parameters (TSM parameters) capturing the gradient's overall spatial pattern in the first model order estimation. The second model order entails estimation in the same directions but fitting the polynomial of degree 2 (a parabola per direction). After combining this with the estimates of lower polynomial basis functions, it results in six parameters that refer to x, y, z, x^2, y^2, z^2. Accordingly, the number of parameters increases as we move to the higher order of the trend surface models.

We fitted these models using Bayesian linear regression, which also yielded estimates of the likelihood of the model given the data. From these likelihoods, we computed the Bayesian Information Criterion (BIC) and Akaike Information Criterion (AIC) scores, which we used for model order selection purposes (also see section 3.2).

2.4. Behavioural data

To test associations between inter-individual differences in connectivity gradients and subject-dependent behaviour, we derived a surrogate measure of hippocampal-dependent recollection performance. HCP participants performed a series of tasks during separate fMRI scanning sessions, including an *N*-back task in which four different stimulus types (pictures of faces, places, tools and body parts) were shown in separate blocks. After completing the *N*-back task in the scanning session, each participant's memory was tested using a Remember-Know paradigm (Tulving, 1983; 1985). Participants were presented with the images of faces and places earlier presented in the *N*-back task, mixed with an equal number of foil items (48 old items, 48 foils). The body parts and tools were not included in the testing set, as there were not enough new items to create foil stimuli for those categories (see Barch et al., 2013 for additional details). Items were presented for 2 sec each, followed by a 2 sec inter-stimulus interval. For each item, participants reported whether they had seen it before (old-new discrimination), and for each item that was reported as old, they were asked to indicate whether they could recollect the encoding context of the item ("Remember"-response) or not ("Know"-response). The "Remember" and "Know" responses are thought to reflect different, independent processes as evidenced by neuroimaging research that has shown that "Remember" responses are hippocampus-dependent, whereas "Know" responses rely on higher-order visual processing areas (Eldridge, Knowlton, Furmanski, Bookheimer, & Engel, 2000).

We computed *d*-prime (*d'*) measures of old-new discrimination (recognition), and excluded participants whose *d'* was at or below zero (i.e., participants with below chance performance in either the face or place condition or both) from further analysis (16 subjects were excluded based on below-chance performance in the face condition, four for below-chance performance in the place condition). Three additional participants with missing behavioural data were also excluded from further analysis. This resulted in $N = 448$ (265 females; 22–36 years, mean age = 29.21, $SD = 3.50$) subjects for analyses of the face items, and $N = 460$ (271 females; age, 22–36 years, mean age = 29.16 years; $SD = 3.51$ years) subjects for analyses of the place items. To isolate hippocampus-mediated recollection from more generic recognition (as measured by *d'*), we computed the inverse of the independence remember/know equation (Jacoby, Yonelinas, &

Jennings, 1997): Recollection = proportion of "Remember" responses/1-proportion of "Know" responses. In its original form, this formula quantifies the contribution of familiarity-based recognition (i.e., recognising an item but not recollecting its encoding context) to overall memory performance. The inverse represents the proportion of recollection over and above recognition, and therefore specifically taps into the hippocampal mechanisms that underlie retrieval of episodic detail. This measure was used as the dependent variable in subsequent analyses.

2.5. Statistical analysis

2.5.1. General linear model (GLM)

A GLM approach was used to investigate whether the TSM parameters, which quantitatively describe the hippocampal connectivity gradients derived from resting-state fMRI at an individual level, predict recollection memory. The recollection scores for faces and places were used as dependent variables in two separate models. Age, head movement during the scan (mean frame-wise displacement), and the reconstruction algorithm version that was used for reconstruction the resting-state fMRI data from k-space were added as covariates (the latter changed during HCP data collection and has a substantial influence on resting-state fMRI connectivity estimates). As we were interested in the variance explained by the TSM parameters *over and above* the variance explained by the covariate variables, we computed the partial R^2 as ($RSS_{reduced} - RSS_{full}$)/$RSS_{reduced}$. Accordingly, in the full model we included the TSM parameters, age, motion, and the reconstruction method, whereas the reduced model included only age, motion, and the reconstruction method. The same approach was used to test if the TSM models predict *d'* measures of old-new discrimination. A permutation testing procedure implemented in FSL-PALM (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/PALM; sign flipping) that accounts for the family structure of the HCP sample was used to assess the statistical significance of the ensuing partial R^2 values (with 5K permutations; Winkler, Webster, Vidaurre, Nichols, & Smith, 2015).

2.5.2. K-means clustering

Hard parcellation approaches have suggested a positive relationship between recollection and posterior hippocampus volume, in particular when expressed as a ratio to anterior hippocampus volume (e.g., Poppenk & Moscovitch, 2011 based on structural information). We therefore tested whether the gradient-organisation of hippocampus explains individual differences in recollection over and above a functional parcellation. We used k-means clustering to obtain anterior and posterior parcels, and computed the ratio between them to approximate previous parcellation studies. K-means clustering is widely used in the context of connectivity-based parcellation (see for instance Yeo et al., 2011), and can be used to partition data points into a pre-defined number of clusters. This clustering method identifies k cluster centroids in the data, and assigns each data point to the closest centroid. In the context of this study, this means that each voxel is assigned to one of two clusters—either an anterior or posterior cluster. We then computed the ratio between posterior and anterior voxels for each participant. In line with the analyses presented in Poppenk & Moscovitch, 2011, we used this ratio as a predictor in the GLM analysis to test whether the ratio on its own (over and above the covariates age, motion and reconstruction version) can predict recollection memory. We then tested whether the TSM parameters explain variance over and above this model. Lastly, we tested whether both the ratios and TSM estimates of the gradients, can explain substantially more variance in the recollection score than the TSM estimates alone.

2.6. Data, materials, and code availability

All data and materials are openly available via the Human Connectome Project Database (https://db.humanconnectome.org). All information about how sample size and data exclusion was determined, which inclusion criteria were used (established prior to data analysis), and all derived measures used in this study are described in the Methods and Results sections. No part of the analysis was pre-registered prior to the research being conducted. The pre-processing pipeline that was used is described extensively in Smith et al., 2013. Connectopic mapping is extensively described in Haak et al., 2017, and code for the procedure can be found here: https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/OtherSoftware. All reported statistical analyses account for the family structure in the HCP data, the public sharing of which is not permitted by the HCP data-usage agreements in order to assure the confidentiality and privacy of the participants. Additional code for performing the statistical analyses while accounting for family structure is therefore available from the authors after confirming compliance with data-usage agreements for the HCP restricted data (https://www.humanconnectome.org/study/hcp-young-adult/document/restricted-data-usage).

3. Results

3.1. Gradual functional connectivity patterns within the human hippocampus

Connectopic mapping was applied to the resting-state fMRI data to estimate the hippocampal-neocortical functional connectivity patterns in the hippocampus at the individual level. At the group-level, the dominant connectopic map, which represents the first dominant mode of the connectivity change, followed the expected anterior-to-posterior trajectory (Fig. 1). To visualise the average change in connectivity (i.e., the connectivity 'fingerprints' that entered into the similarity analysis of the connectopic mapping procedure), we conducted a group-level analysis in which we estimated the seed-based connectivity (Pearson correlations) of various points along the longitudinal axis with neocortex. Seeds were defined by performing k-means clustering with $k = 5$ on the group-level gradient for each hemisphere (Fig. A.1). Fig. 2 shows the projections of these seeds (percentage of individuals showing co-activation at $Z > 1.96$). The anterior-to-posterior gradient appears to map onto gradual changes in connectivity with neocortex, moving from connectivity with regions that are associated with higher-order conceptual representations (middle temporal lobe, angular gyrus, precuneus), and cognitive control (ventromedial prefrontal

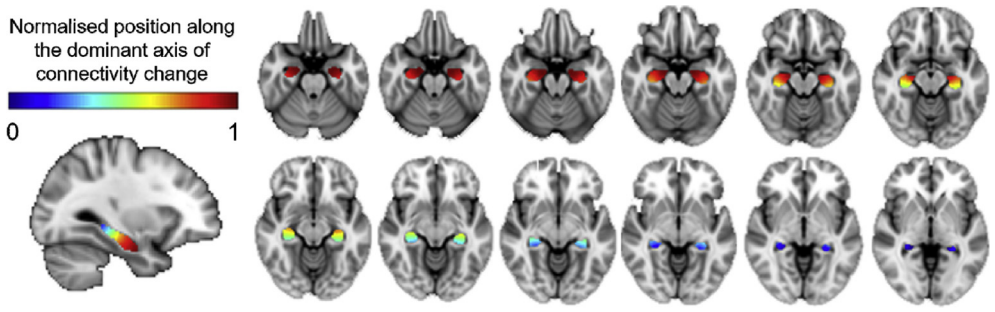

Fig. 1 – The hippocampal-neocortical connectivity gradient at the group level ($N = 475$) stretches along the hippocampal long-axis. The colour bar indicates the position along the dominant mode of connectivity change, and so similar colours represent similar connectivity patterns. Changes in colour represent changes in topographically organised functional connectivity (values are on an arbitrary scale).

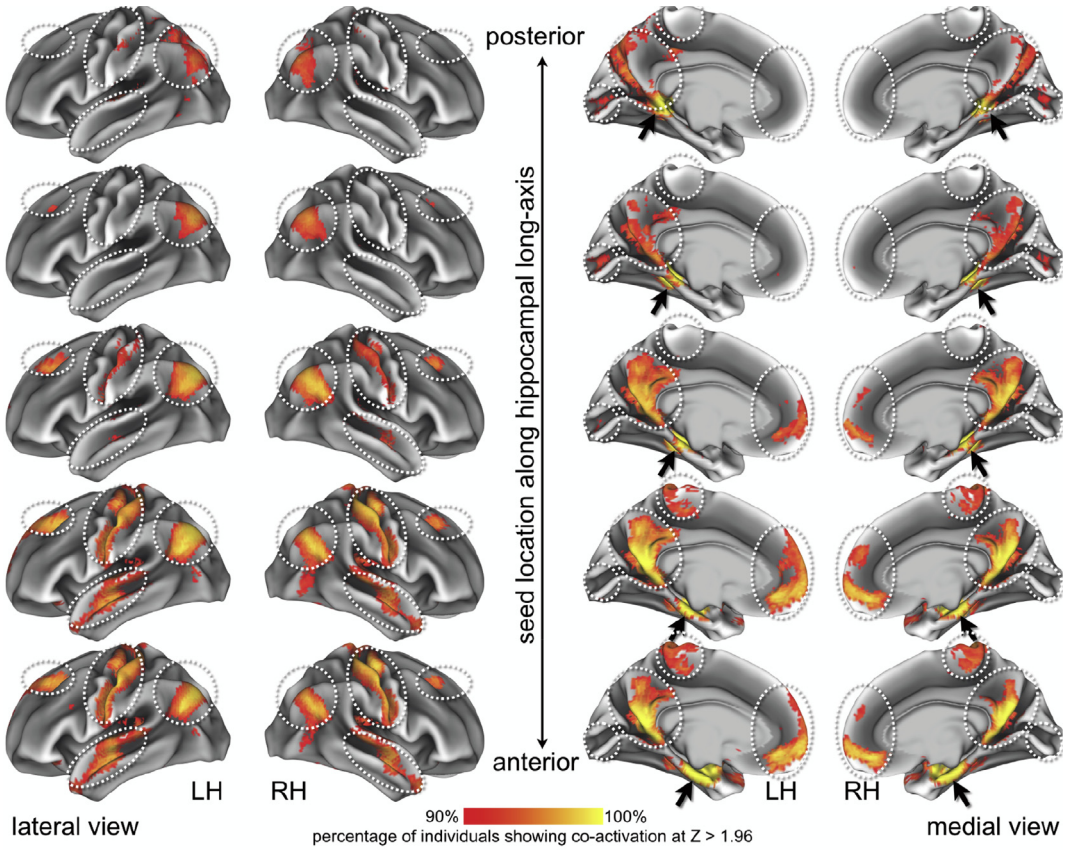

Fig. 2 – Summary of the connectivity fingerprints that entered into the similarity analysis of the connectopic mapping procedure based on seed-based connectivity estimates along the hippocampal long-axis (Pearson correlations). The black arrows represent the approximate location of the seeds along the hippocampal long-axis (see Fig. A.1 for exact seed definitions). Maps show the percentage of individuals showing co-activation at $Z > 1.96$.

cortex) to connectivity with areas that subserve visual and sensory processing (visual cortex, superior parietal lobule). Individual differences along the longitudinal axis thus represent subtle differences in the organisation of functional connectivity with these sub-systems.

Importantly, connectivity change along the longitudinal axis varied across participants. The coloured lines in Fig. 3 shows each individual's dominant connectopic map (i.e., the amount of connectivity change along the longitudinal axis) as a function of the Euclidian cortical distance from the hippocampus' most posterior voxel (for the left and right hippocampus separately). This figure illustrates that while the overall patterns across participants look similar, patterns are not identical between participants. We therefore estimated

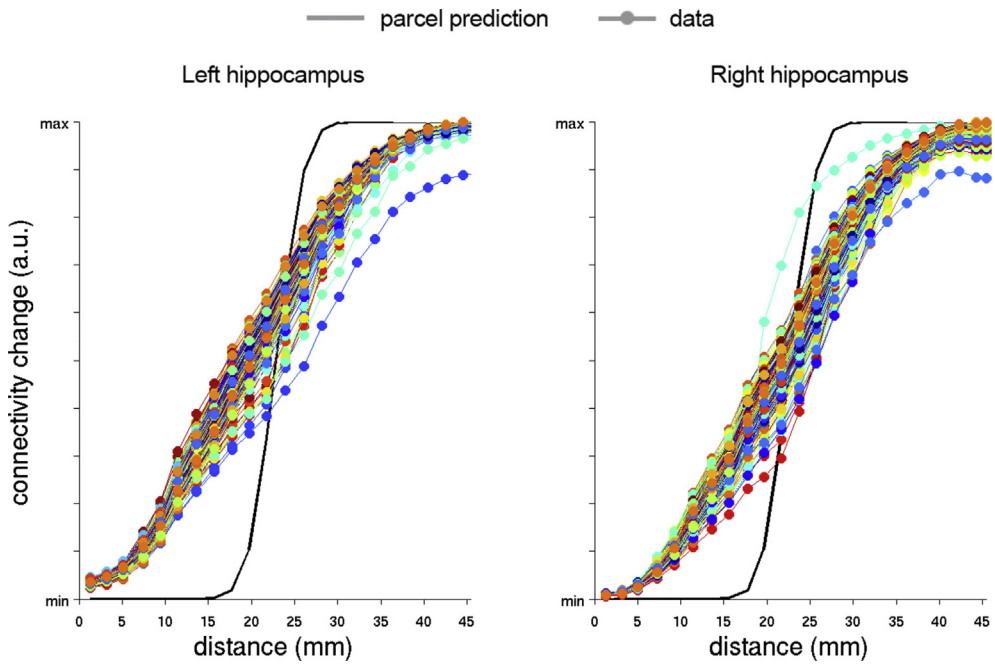

Fig. 3 – Left and right hippocampal-neocortical functional connectivity patterns plotted against the distance from the most posterior voxel in the hippocampus. Data were binned in terms of distance (23 bins of ~2 mm). Each coloured line represents one participant. The black line represents a non-gradient (parcellation) where the transition is fully induced by smoothing discrete parcels using a 6 mm FWHM Gaussian kernel (same smoothing as used in pre-processing the resting-state fMRI data).

the spatial properties of these single-level gradients with trend surface modelling, and established their functional relationship with individual-level recollection.

Fig. 3 also demonstrates that across participants, the amount of connectivity change along the long-axis is best understood in terms of gradual changes. To facilitate comparison, the black line represents a parcellation of the hippocampus into anterior and posterior portions—i.e., a sharp increase in connectivity change between voxels—smoothed with a 6 mm FWHM Gaussian kernel to match the blurring induced by the smoothing of our data during pre-processing. The comparison between the coloured lines and the black line illustrates that connectopic changes are substantially more smooth and gradual, without any sharp transitions. This lack of sharp boundaries indicates a gradual change along the long hippocampus axis that follows an anterior-to-posterior trajectory, resembling previously reported findings from animal studies that showed a ventral-dorsal gradient-like organisation in rodent hippocampi.

3.2. *Trend surface modelling analysis of the connectopic maps*

In order to investigate whether individual differences in the obtained connectivity gradients are functionally meaningful, we first reduced the number of estimates characterising the connectopic maps by employing trend surface modelling (TSM), which summarises the overall voxel-wise spatial pattern of the individual connectopic maps in a small number of spatial model parameters. From the series of trend surface models that were fitted, the Bayesian Information Criterion (BIC) indicated that the third and fourth TSM model orders were most favourable, with only very little difference between them in terms of variance explained (average across hemispheres 98.65% and 98.75%, respectively; see Fig. 4; the Akaike Information Criterion (AIC) showed similar results). We therefore report the results for both model orders.

3.3. *Behavioural results*

The average of *d'* scores ($N = 464$, including scores of those participants that had *d'* scores equal or less than zero) collapsed across both stimulus types was 1.37 ($SD = 1.24$), indicating that on average the participants performed the task well. The average *d'* for faces was 1.06 ($SD = .980$) and the average *d'* for places was 1.70 ($SD = 1.49$). The difference between *d'* faces and *d'* places was statistically significant (average difference = .637, $p < .001$), where statistical significance was assessed using FSL-PALM (5K sign-flipping). The hippocampus-mediated recollection scores were calculated based on the inverse of the independence remember/know equation (see Methods), which ranges between 0 and 1. The average recollection score for faces was .609 ($SD = .224$), whereas the average recollection score for places was .468 ($SD = .215$). This difference was statistically significant (average difference = .141, $p < .001$; significance tested using FSL-PALM 5K sign-flipping), indicating that faces were recollected more often than places. Face and place recollection were moderately correlated ($r = .299$), which indicates that participants who were good at one task were not necessarily

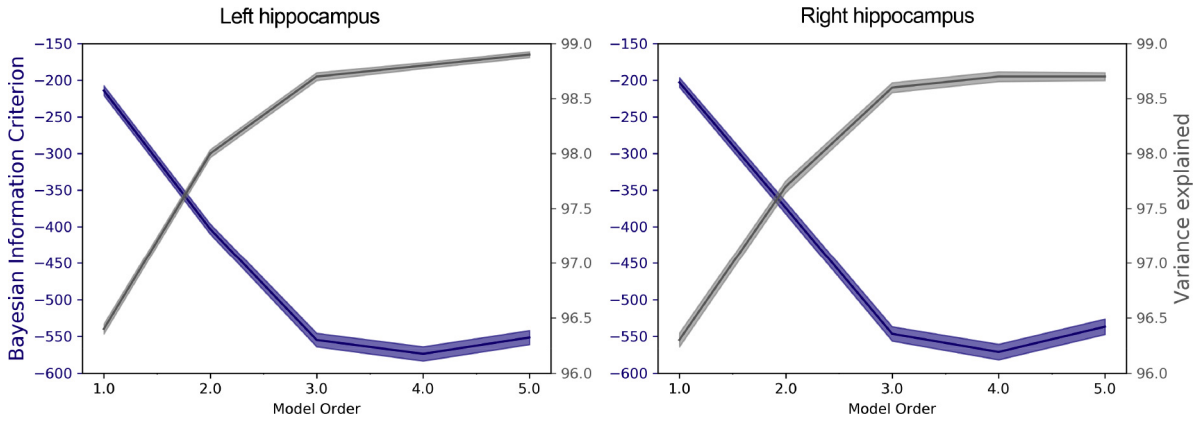

Fig. 4 – Trend surface model order selection. The average values of the Bayesian Information Criterion (BIC) (left vertical axes) and the proportion of the variance of the overall spatial pattern explained (right vertical axes) by the respective trend surface model orders. The shaded area around the lines represents the 95% confidence interval.

also good at the other task. Since there are differences between these behavioural measures in terms of old-new discrimination and recollection, we treat them separately in subsequent analyses.

3.4. *Associations between recollection memory and connectopic organisation*

We used a GLM to investigate whether the TSM parameters that summarise the gradients at the individual level predict hippocampal-dependent recollection. We found that indeed, recollection was significantly predicted by TSM parameters (3rd order, nine parameters) over and above the covariates, such that the left hippocampal connectivity gradient predicted recollection memory for faces (Partial $R^2 = .057$, $p = .002$, grey bar in Fig. 5A, below the exemplary image of the stimulus type: faces), and the right hippocampal connectivity gradient predicted recollection for places (Partial $R^2 = .041$, $p = .032$, grey bar in Fig. 5A, below the exemplary image of the stimulus type: places). A similar pattern was found when the gradient was approximated with a 4th model order and 12 parameters (these results are not presented in the figure): the left hippocampal connectivity gradient was significantly predictive of recollection for faces (Partial $R^2 = .063$, $p = .006$), whereas the right hippocampal connectivity gradient showed a relationship with recollection for places, albeit marginally significant (Partial $R^2 = .042$, $p = .092$). These results suggest that the gradient-like functional organisation of the

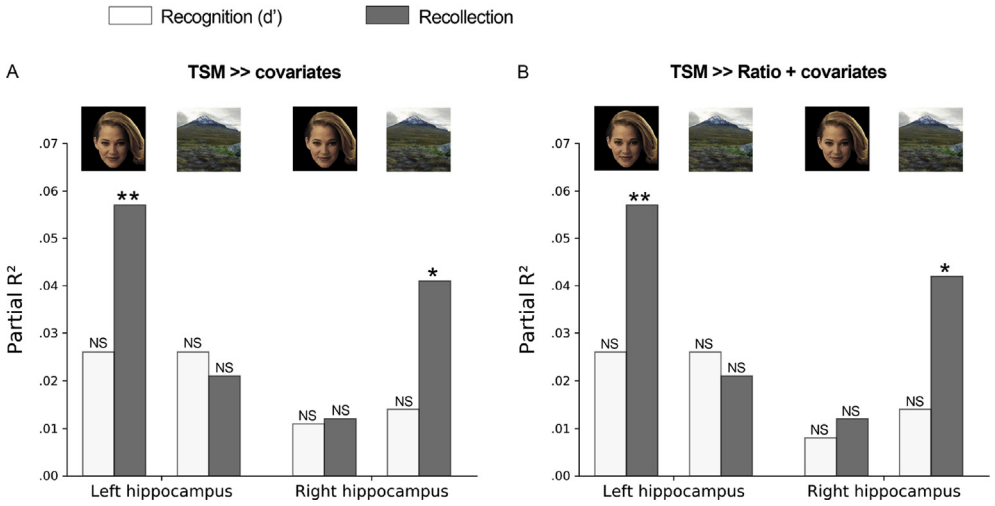

Fig. 5 – A. Proportion of the variance of the recognition (*d'*) and recollection scores explained by the spatial model coefficients (TSM parameters) over and above the variance explained by age, head motion and MR reconstruction algorithm version. B. Proportion of the variance of the recognition (*d'*) scores and recollection scores explained by the spatial model coefficients (TSM parameters) over and above the variance explained by age, head motion, MR reconstruction algorithm version and the parcel's ratio. Model order refers to the model order of the trend surface model that was fitted to each individual's hippocampal connectopic map. Here, the results are presented for the third model order. *$p < .05$, **$p < .01$. Correlations between recollection and each individual parameter can be found in Fig. A.2 in the Appendix.

hippocampus at the individual level is predictive of individual differences in recollection.

To establish the specificity of the relationship between individual variations in the TSM parameters and recollection, we also tested the relationship between these parameters and old-new discrimination (*d'* faces and *d'* places), which is thought to not critically rely on the hippocampus (e.g., Barker & Warburton, 2011; Yonelinas, Hopfinger, Buonocore, Kroll, & Baynes, 2001). As predicted, the GLM results for both third and fourth model order showed that the TSM parameters of the gradient in neither the left nor right hippocampus predicted recognition (discrimination between old-new items) for places and faces (all $p \geq .204$); white bars in Fig. 5A). Despite the fact that the *d'*s and recollection scores shared some variance ($R^2 = .154$ and $R^2 = .015$ for faces and places, respectively), the specificity of the relationships suggests that the organisation of the hippocampal gradient is associated with hippocampal-dependent recollection, and not with more generic recognition that does not (critically) rely on the hippocampus. We also quantified the amount of familiarity-based recognition using the independence remember/know equation (Jacoby et al., 1997; Familiarity = proportion of "Know" responses/1-proportion of "Remember" responses), and again found no significant associations with the hippocampal gradient for faces (all $p \geq .568$) or places (all $p \geq .143$).

To illustrate how inter-individual variations in the distribution of functional connectivity across the hippocampus underlie differences in behaviour, we visualised the reconstructed gradients for eight participants: four participants with the highest predicted recollection score (two for face items, two for place items), and four with the lowest predicted recollection score (two for faces, two for places) (Fig. 6). These gradients were reconstructed from the trend surface model parameters, and are visualised on a red-blue colour scale to facilitate interpretation (note that this does not indicate a parcellation). Specifically, these individual-level gradients show that the transition between red and blue (as indicated by the direction of the yellow arrows) is different between participants with the highest and lowest scores, as the transition zone rotates along the y- and z-axes.

3.5. *Functionally derived parcels versus a gradient along the long axis*

Previous studies showed a relationship between recollection and the ratio between anatomically defined posterior and anterior hippocampus (e.g., Poppenk & Moscovitch, 2011). It is possible that the gradients capture the same variance in recollection as these ratios. In that case, TSM parameters should not explain variance over and above the posterior versus anterior ratios. It is also possible that the TSM parameters and ratios each explain unique variance, which means that a model that contains both the ratios and TSM parameters explains most variance, suggesting a superposition of a gradient on top of a parcellation. However, if the TSM parameters — and critically, not the ratios — explain individual differences in recollection (i.e., a significant increase in variance explained when adding the TSM parameters to the ratio model but not vice versa), the findings would suggest that a description of the functional organisation of the hippocampus in terms of a gradient is more functionally meaningful than a description in terms of parcels.

We therefore first tested whether the ratios, obtained by splitting the functional connectivity gradient into two parcels

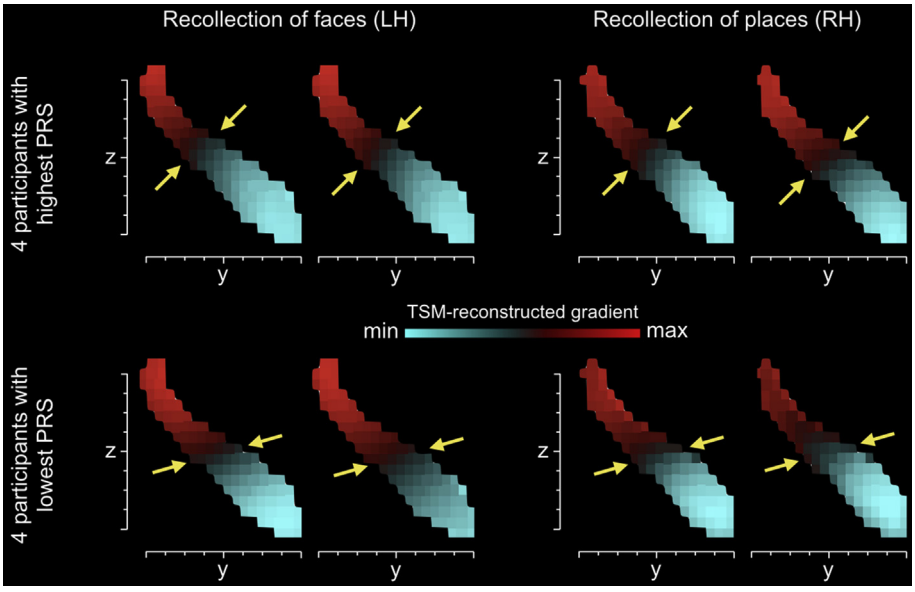

Fig. 6 – Visualisation of individual differences in gradient organisation related to behaviour. Gradients are reconstructed from the TSM parameters (see Fig. A.2), and visualised on the y- and z-axes. The blue-to-red colour scale (TSM-reconstructed gradient) represents each voxel's loading onto the dominant axis of connectivity change predicted based on the TSM parameter estimates for that participant. The arrows point towards the transition zone between red and blue, which differs between participants with highest and lowest predicted recollection scores (PRS) for faces (left) and places (right), respectively.

and computing the ratio of the posterior versus anterior part, predicted memory performance. The group level average parcellation is close to (but not exactly on) the boundary between anterior and posterior hippocampus as defined by previous work (Poppenk & Moscovitch, 2011) using the uncal apex as an anatomical landmark (see Fig. A.3 in the Appendix). We found no significant relationships between recognition (d'), familiarity, and recollection scores and the posterior versus anterior ratios (all $p \geq .190$).

Adding the TSM parameters to the ratio model explained a significant amount of variance in recollection performance over and above the ratios. The results are summarised in Fig. 5B. For the third model order, the left hippocampal connectivity gradient predicted recollection for faces (Partial $R^2 = .057$, $p = .003$; grey bar below the exemplary image of the stimulus type: faces), and the right hippocampal connectivity gradient predicted recollection for places (Partial $R^2 = .042$, $p = .027$, grey bar below the exemplary image of the stimulus type). We found similar results for the fourth model order (left hippocampal connectivity gradient and recollection for faces: Partial $R^2 = .063$, $p = .005$; right hippocampal connectivity gradient and recollection for places, Partial $R^2 = .042$, $p = .094$). Vice versa, adding the ratios to a model that predicts recollection from the TSM parameters did not significantly increase the explained variance (all $p \geq .180$), suggesting that inter-individual differences in the gradient, rather than inter-individual differences in the posterior-anterior ratio, are related to recollection.

4. Discussion

In the present study, we tested whether inter-individual differences in the gradual change of topographically organised, hippocampal-neocortical functional connectivity predict hippocampus-dependent recollection, over and above a functionally parcellated view. We used a novel data analysis approach, connectopic mapping, which revealed a smooth connectivity gradient that follows the anterior to posterior trajectory of the longitudinal hippocampus axis. After estimating these gradients in each individual participant of the HCP (S-500) dataset, we assessed their functional meaning by testing their functional relationship with recollection, a type of memory retrieval that the human hippocampus is known to be involved in. As predicted, we found that the TSM parameters summarising the overall spatial structure of the connectivity gradients predicted hippocampal-dependent recollection memory. Additionally, we tested whether the prediction of recollection memory required a gradient representation, or whether a characterisation in terms of functionally derived parcels is sufficient. Our findings indicate that the gradient representation is more meaningful than a representation in terms of parcels when it comes to the prediction of recollection from the organisation of functional connectivity.

A 2014 review by Strange and colleagues already suggested that the dichotomous parcellation view, which has dominated the field for years, needs to be revisited as animal studies suggested that differences in connectivity between the hippocampus and other cortical and subcortical regions seem to be more gradual than abrupt. Although the most anterior and posterior parts of the hippocampus may have different functional specialisations, as suggested by studies linking behaviour to anatomical divisions (e.g., Poppenk & Moscovitch, 2011), there might not to be such a clear functional segregation of these parts. It is nevertheless possible that structural information to some extent correlates with functional organisation: for instance, individual-level hippocampal morphology might put constraints on how its functional organisation is distributed. Our findings add weight to the idea that function varies gradually along the long axis of the hippocampus by showing that, at least in the context of functional connectivity, a characterisation in terms of a gradient is significantly more meaningfully related to recollection than a characterisation in terms of functionally derived parcels at the individual level.

Our study is not the first to coin the idea that a gradient-like organisation might underlie the observed functional specialisation of anterior and posterior hippocampus (see e.g., Strange, Fletcher, Henson, Friston, & Dolan, 1999). Recently, Persson, Stening, Nordin, and Söderlund (2018) reported that episodic memory performance could be predicted from anterior, but not posterior resting-state functional connectivity, whereas the posterior resting-state functional connectivity was predictive of spatial memory. Despite not embedding this idea explicitly in the analysis, the authors explained these discrepancies by potential issues with disentangling the spatial and episodic components in their tasks, but they also pointed out another explanation, which emphasises distribution of spatial representations along the entire long axis of the hippocampus, referring to a gradient of function. The evidence reported by Persson and colleages is based on the strength (not the organisation) of resting-state connectivity of a priori-defined seeds predicts hippocampal function, which is different from the question whether functional organisation within the hippocampus predicts hippocampal function. Nevertheless, both Persson and colleagues' and our study point toward the idea that the characterisation of the functional organisation of the hippocampus in terms of a gradient is more meaningful than its characterisation in terms of functionally derived parcels.

The idea that the hippocampus is functionally organised in terms of gradients has also recently been corroborrated by work in humans that has shown that perpendicular to the long-axis, a medial-to-lateral gradient maps onto the cytoarchitectonic organisation of the hippocampus in terms of its subfields (Vos de Wael et al., 2018). This suggests that multiple, overlapping gradients are likely to co-exist in the hippocampus, which each represent hippocampal function at distinct levels: the long-axis gradient is thought to link to the macroscopic functional organisation of the hippocampus—i.e., its functional connectivity with neocortex—whereas the medial–lateral axis is thought to represent its local microstructure. An open question is whether and how these gradients are interrelated, how they develop, and how the topographical layout of each influences cognition and behaviour.

Another open question is what mechanistic explanation underlies the result that the spatial organisation of the gradient estimated by resting-state functional connectivity predicts recollection. One possibility is that differences in the gradient reflect differences in the amount of neuronal resources that are dedicated to the task. Hippocampal neurons

that are dedicated to the same task likely exhibit similar hippocampal-neocortical connectivity fingerprints, which is captured by similar colours in the connectivity gradient (e.g., in Fig. 1). Thus, if recollection is poor in a participant, this participant might have fewer hippocampal neurons with a particular connectivity fingerprint (i.e., connectivity with neocortex) than a participant with good recollection, yielding different gradient maps as suggested by Fig. 6. An alternative possibility is that the functional organisation at the individual level varies in "gradient-ness", i.e., whether the distribution of function is more parcellated or smooth along the hippocampal long axis. However, connectivity profiles appear to be gradual across the board (no sharp transitions in any of the coloured lines in Fig. 3 or in the transition zones in Fig. 6), suggesting that small variations in the spatial configuration of hippocampal-neocortical connectivity (as illustrated in Fig. 2) underpin differences in behaviour.

More specifically, previous research has shown that connections from the neocortex to the hippocampus have preserved topographic organisation. The entorhinal cortex plays an important part as a relay in this process. It receives information from prefrontal cortex via topographically organised connections (Jones and Witter, 2007). We have previously demonstrated that within entorhinal cortex there is a topographic organisation that can be estimated using connectopic mapping (Navarro Schröder et al., 2015). This information in turn constitutes input to the hippocampus, which again exhibits topographic preservation. The implication is that differences in topographic organisation, as measured here, are indicative of differences in functional connectivity with the rest of cortex, potentially via topographic connections with entorhinal cortex. Although the present approach is limited to hippocampal-neocortical connectivity, it is likely that hippocampus displays similar gradients of connectivity with subcortical structures such as lateral septum (Risold and Swanson, 1996), amygdala (Kishi, Tsumori, Yokota, & Yasui, 2006), and nucleus accumbens (Groenewegen, Vermeulen-Van der Zee, Te Kortschot, & Witter, 1987). Future studies could elucidate whether individual differences in subcortical-hippocampal gradients predict motivated (e.g., reward-related) behaviours (Sheehan, Chambers, & Russell, 2004).

Unexpectedly, our results appear to suggest hemispheric differences, as the TSM parameters capturing the spatial organisation of the left connectivity gradient predicted face recollection, whereas the estimates of the right connectivity gradient (marginally) predicted recollection of places. The fact that our results did not show that recollection for faces can be predicted from the right hippocampus, and recollection for places by the left hippocampus does not necessary mean that these effects are not there, as our analyses might have been underpowered. However, it is also possible that our analysis is reflecting a true differentiation in hemispheric lateralisation. Previous studies have shown that damage to the right medial temporal regions, including the hippocampus, causes spatial memory impairments (Bohbot et al., 1998; Piggot & Milner, 1993), whereas similar damage in the left hemisphere affects primarily verbal memory (Bohbot et al., 1998; Milner, 1965). Though possible, these findings remain controversial, as other studies have shown that resections of either left or right temporal cortex produce impairments in spatial memory (Maguire et al., 1996). The observation that the topographic organisation subserving face recollection might be left lateralised resonates with the idea that face recollection might depend on concept forming, which in the broader context of face processing has been shown to be left-lateralised (Rangarajan et al., 2014). However, until these potential lateralisation effects are further scrutinised, these post-hoc accounts remain merely speculative.

In conclusion, we have shown that the macroscopic functional organisation along the long-axis of the hippocampus is more appropriately described in terms of a functional gradient than in terms of functionally segregated parcels. We found that inter-individual differences in this gradient are behaviourally relevant: the spatial organisation of the gradient along the anterior–posterior axis at an individual level predicted recollection, over and above the ratio of posterior-anterior hippocampus obtained by functional parcellation. In addition, we have demonstrated that connectopic mapping approach is capable of mapping these gradients in individual subjects (albeit requiring high quality data; see Haak et al., 2017), opening up the possibility to study how (aberrant) connectopic organisation of the hippocampus may underlie cognitive function in health and disease.

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Conflict of interest

The authors declare no competing financial interests. CFB is Director and shareholder of SBGneuro Ltd.

CRediT authorship contribution statement

Izabela Przeździk: Conceptualization, Formal analysis, Visualization, Writing - original draft, Writing - review & editing. **Myrthe Faber:** Conceptualization, Formal analysis, Methodology, Supervision, Visualization, Writing - original draft, Writing - review & editing. **Guillén Fernández:** Conceptualization, Funding acquisition, Supervision, Writing - review & editing. **Christian F. Beckmann:** Conceptualization, Funding acquisition, Methodology, Supervision, Writing - review & editing. **Koen V. Haak:** Conceptualization, Data curation, Formal analysis, Methodology, Software, Supervision, Validation, Visualization, Writing - review & editing.

Open practices

The study in this article earned an Open Data (Protected Access) badge for transparent practices. Materials and data for the study are available at https://db.humanconnectome.org.

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Supplementary data

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