

Research report

Hippocampus activation related to ‘real-time’ processing of visuospatial change

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ABSTRACT

The delay associated with cerebral processing time implies a lack of real-time representation of changes in the observed environment. To bridge this gap for motor actions in a dynamical environment, the brain uses predictions of the most plausible future reality based on previously provided information. To optimise these predictions, adjustments to actual experiences are necessary. This requires a perceptual memory buffer. In our study we gained more insight how the brain treats (real-time) information by comparing cerebral activations related to judging past-, present- and future locations of a moving ball, respectively. Eighteen healthy subjects made these estimations while fMRI data was obtained. All three conditions evoked bilateral dorsal-parietal and premotor activations, while judgment of the location of the ball at the moment of judgment showed increased bilateral posterior hippocampus activation relative to making both future and past judgments at the one-second time-scale. Since the condition of such ‘real-time’ judgments implied undistracted observation of the ball’s actual movements, the associated hippocampal activation is consistent with the concept that the hippocampus participates in a top-down exerted sensory gating mechanism. In this way, it may play a role in novelty (saliency) detection.

1. Introduction

The relative slowness of cerebral processing time implies that commands for goal directed movements in a dynamic environment are not based on real-time representations of environmental changes. To overcome this processing slowness, the brain uses predictions about future states in which information about the past and the perceived present is used to predict following, most probable, outcomes (Buzsaki, 2006). The lag between real-time events and their perception, as well as the compensatory perceptual consequences are illustrated by e.g. the flash-lag illusion, a paradigm in which the concurrent appearance of a stationary flash and a moving object, at the same location, generates the illusion of displacement in such a way that the moving object is perceived ahead on its trajectory (Eagleman and Sejnowski, 2000; Nijhawan, 1994; Roulston et al., 2006; Wojtach et al., 2008). By using predictions, the brain, e.g. prepares the hand to be at the right time in the right position for catching a ball (Lacquaniti and Maioli, 1989).

In a previous fMRI study, we were able to distinguish cerebral representations of space and time concerning visually presented ball movements by contrasting spatial- and temporal predictions on such movements. In the experiment, subjects had to predict either where or

when a moving ball would touch the bottom edge of a screen after its disappearance. In addition, momentary place estimations and assessments of speed were made at the moment of the ball’s disappearance (Beudel et al., 2009). Both the momentary- and the anticipated future spatial condition showed increased dorsal parietal-premotor activations, while this parietal-premotor circuitry was even stronger activated in spatial prediction. In this previous study, a condition in which subjects had to indicate the ball’s start position after its trajectory had ended was not further analysed. In the present paper, we extended the analysis on spatial processing in dynamic conditions by including the task that required memorising the start locations. The design also provided the opportunity to further explore the presence of network foci specifically involved in assessing the *momentary* location of a moving object by contrasting this momentary place assessment to both the memorised- and predicted spatial conditions. In this respect, we were particularly interested in condition-related responses of the hippocampus. While a distinction was made between conditions concerning past, present, and predicted future locations, judgments were only in the 1-s range. This implies that, from a psychological perspective, all judgments may be regarded to be within the ‘specious present’.

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The effectiveness of predictions is based on continuously combining existing (spatial) knowledge with current sensory input. The delay of the latter indeed emphasises that real-time perception is based on extrapolations of past predictions (Eagleman and Sejnowski, 2000). Since the outcome of predictions is uncertain, the actual unwinding of predicted events needs to be temporarily kept *on-line*. The hippocampus region may play an important role in the ongoing comparison between predicted- and actual recordings of the observed events, as can be inferred from its involvement in novelty detection, i.e. the occurrence of unpredicted events (Knight, 1996; Kumaran and Maguire, 2007a, 2007b; Lisman and Grace, 2005), and “incidental” memory formation (Martin, 1999; Stark and Okado, 2003).

Aside from its on-line comparator function, the hippocampus classically plays a role in (episodic) memory formation (Squire et al., 2004). Both the intrinsic network characteristics and the interconnections with distant cortical circuitry reflect its functional equipment for this role (Bast, 2007; Bird and Burgess, 2008; Burgess et al., 2002; Rolls and Kesner, 2006). The time domain in which the hippocampus crucially contributes to the encoding of new information, however, has not been fully elucidated yet. It is clear that bilateral hippocampus lesions in humans result in paramount deficits in maintaining new information for longer than around 10 s, while working memory within such timeframe seems relatively unaffected (Squire et al., 2004). On the other hand, spatial location matching with 2 s intervals as well as working memory for object-location conjunctions are disturbed in hippocampus lesions (Hartley et al., 2007; Olson et al., 2006), while the maintenance of object-location-associations in short-term memory can be detected by increased activation in the intact right hippocampus between 2 and 20 s (Piekema et al., 2006). In this respect, the (right) hippocampus region appears to be involved in both long- and short-term spatial memory processes, as well as in non-memory spatial functions (Burgess et al., 2002). One may even speculate that the on-line ‘comparator function’ (Gaussier et al., 2007) and the late consolidation role of the hippocampus are based on similar re-entry mechanisms (Banquet et al., 2005), as the retrieval of stored information consequently results in renewed encoding for long-term memory (Bird and Burgess, 2008).

The main question we aimed to answer in the present study was whether hippocampus activation is particularly associated with real-time spatial assessment, which would support the dominance of the on-line comparator function, or whether increased hippocampus activation is related to the condition with memorised locations. The latter would favour the dominance of a memory buffer function (Schon et al., 2016). With regard to the latter, visuospatial working memory might also induce activation increases in the right prefrontal cortex (PFC), either with or without parietal-premotor increases (LaBar et al., 1999; Passingham and Sakai, 2004; Smith and Jonides, 1999).

2. Results

In the visuomotor fMRI paradigm, three experimental conditions were compared (Fig. 1). In condition 1 (‘place at start’) subjects had to indicate at which side of the screen a ball started moving. In condition 2 (‘place at stop’), subjects had to determine the side of the screen where this ball stopped moving. In condition 3 (‘place ahead’) they had to extrapolate the ball’s trajectory after its disappearance until it virtually touched the bottom edge of the screen and indicate the side of the screen where this would happen (Fig. 1).

2.1. Behavioural data

The analysis of reaction times revealed that the fastest responses were made in the ‘place at start’ condition (282 ms) successively followed by the ‘place at stop’ (455 ms) and ‘place ahead’ (548 ms) condition (Fig. 2A). These differences were significant between each condition: ‘place at stop’ vs ‘place at start’ [$F(1,17) = 11.56; p = 0.004$],

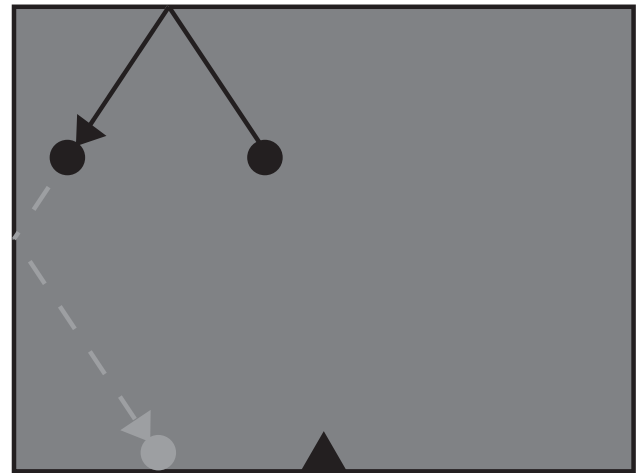


Fig. 1. Display of the Stimulus Presentation. The solid line indicates one possible trajectory of the moving ball. The three balls points at the successive locations of respectively un-cued appearance, stop and disappearance and virtually touching the bottom of the screen. The dotted line indicates the extrapolated trajectory enabling the subjects to make a prediction. The solid arrowhead (triangle) demarcates the middle of the screen. Subjects indicated whether the ball started (condition 1) or stopped (condition 2) moving on the left or on the right side of the screen after the ball had stopped moving. In condition 3, subjects predicted whether the ball would touch the bottom of the screen on the left or on the right side of the bottom edge. Responses were made by pressing the left or right button of a response box.

‘place at stop’ vs ‘place ahead’ [$F(1,17) = 10.85; p = 0.005$], and ‘place at start’ vs ‘place ahead’ [$F(1,17) = 41.55; p < 0.001$]. The visuomotor control, (‘press at stop’) condition had a reaction time of 352 ms. Accuracy results indicated the best performance was in the ‘place at start’ condition (94% correct) that was significantly better than in the ‘place at stop’ [81%, $F(1,17) = 120.62; p < 0.001$] and ‘place ahead’ [84%, $F(1,17) = 40.56; p < 0.001$] condition (Fig. 2B). Accuracy of the ‘place at stop’ and that of ‘place ahead’ condition were less different from each other than from the ‘place at start’. However, this difference between the two was still significant, in which the ‘place ahead’ condition was performed better [$F(1,17) = 10.73; p = 0.005$] (Fig. 2B). The visuomotor control condition (‘press at stop’) had an accuracy of 99%. The subjective difficulty ratings confirmed that the tasks were easily performed. Mean ratings were below 4 on a scale rating from 1 to 10 (Fig. 2C). The ‘place ahead’ condition was nevertheless judged significantly more difficult (4/10) than the ‘place at stop’ [1/10, $p < 0.001$] and ‘place at start’ [1/10, $p < 0.001$] conditions. The latter were judged as equally difficult [$p = 0.92$]. The visuomotor control condition was rated as 1/10.

2.2. Functional imaging data

The comparison of each of the experimental conditions with the visuomotor control condition ‘press at stop’ resulted in patterns of increased activation that included the bilateral posterior parietal and dorsal premotor cortex (Table 1A,B,C). A conjunction analysis confirmed this overlap (Fig. 3, Table 1D). Besides the parietal-premotor activation present in all three conditions, additional activation of the extrastriate cortex was present bilaterally in the ‘place at stop’ and ‘place ahead’ condition.

Activations that were exclusively present in the ‘place at stop’ condition were identified by contrasting this condition to the ‘place at start’ as well as the ‘place ahead’ conditions. The resulting increases of activation were found in the posterior hippocampal region of both hemispheres (Fig. 4C,D,H, Table 1F). Further anatomical characterisation revealed that the largest fractions of the activation clusters were located in the subiculum. The results of each of the two individual contrasts showed that the comparison of ‘place at stop’ with ‘place at start’ was located more posterior in the hippocampus (Fig. 4C), while

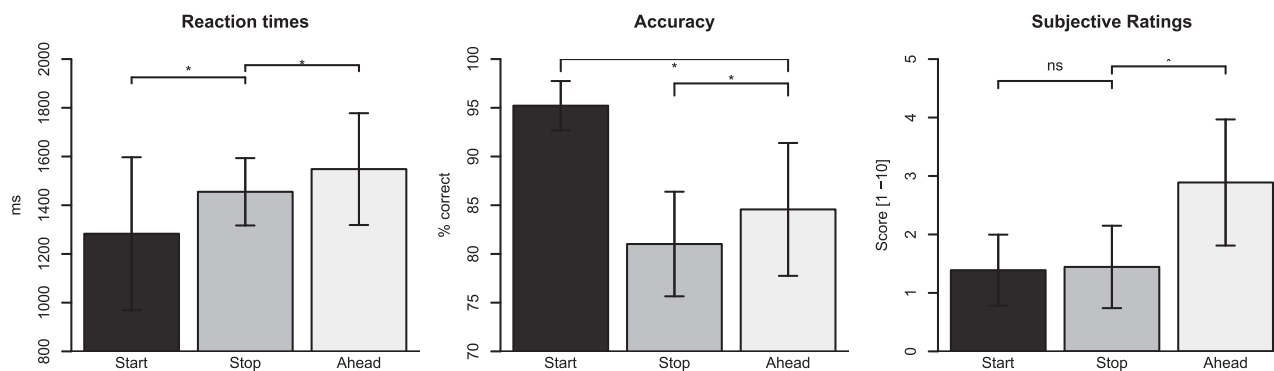


Fig. 2. Behavioural Data. Reaction times (A) and accuracy of responses (B) obtained in the conditions during scanning. For each condition, the mean (\pm SD) of 18 subjects is presented, while each subject's value is based on the mean of all measurements in a given condition. In addition, the subjective difficulty rating for each of the three conditions (C) is shown by the mean score (\pm SD) of the 18 subjects. After the scanning procedure, they rated this difficulty with a range between 1 (easy) and 10 (difficult). Statistical analysis of differences between conditions was performed with a one-way ANOVA, of which the results were given in the text.

anterior hippocampus activation resulted from the comparison with the 'place ahead' condition (Fig. 4D).

When contrasted to each of the other experimental conditions, the 'place ahead' condition showed bilateral increases of activation in the posterior parietal- and dorsal premotor cortex (Fig. 4E,F,I, Table 1G). This pattern of increases highly resembled the distribution of increased activations after contrasting each of the three experimental conditions with the visuomotor control condition (Fig. 3). The additional activation increase that was specific for the 'place at start' condition, revealed by contrasting it to the other two experimental conditions, was located in the frontal pole but did not reach statistical significance (Fig. 4H, Table 1E). By relaxing the threshold to $p < 0.05$ (voxel level, uncorrected), the increased activation exclusively extended around the frontal pole. Contrasting 'place at start' to only the 'place ahead' condition (Fig. 4B) resulted in similar frontal pole activation, together with activations in the posterior cingulate and the left angular gyrus. On the contrary, increased activation was virtually absent when contrasting the 'place at start' with the 'place at stop' condition (Fig. 4A).

3. Discussion

The applied paradigm, with experimental conditions containing a visual display of similar ball movements, enabled the distinction of cerebral activations related to the judgment of its past, its present or its predicted future location. Our major finding was the bilateral increase of activation in the caudal segment of the hippocampal formation when the present-spatial condition ('place at stop') was compared to each of the other two assessments. This increased activation was not associated with a perception of increased task difficulty. The relation between increased hippocampus activation and momentary spatial assessments provided support for the model that the hippocampus acts as a 'comparator' that deals with predicted and actually recorded spatial locations (Vinogradova, 2001) see also Introduction).

3.1. Behavioural data

In our behavioural data we found significantly different reaction times in the three experimental conditions. The fact that the 'place ahead' condition showed a significant longer reaction time than the other two conditions might reflect the time required for the forward spatial estimation mentioned in paragraph 3.4. On the other hand, the shortest reaction time in the 'place at start' condition supports the idea that subjects already knew which response they needed to give and just waited for the ball to disappear to give the required response (see also paragraph 3.3). Apart from the shortest reaction time, the 'place at start' condition also showed the highest accuracy rate (approximately 95%). This might be explained by the facts that more time was available

to make the decision and that no extra spatial (potentially imperfect) extrapolations needed to be made. The fact that the 'place at stop' showed the lowest accuracy, while difficulty rating was as low as in 'place at start', may seem contra-intuitive at first sight. On the other hand, consistent with the flash-lag phenomenon, which we treated in the introduction to explain how the brain makes predictions to overcome its shortcoming in momentary dealing with actual information, one might speculate that particularly in the condition of estimating the ball's location at the moment it disappears, suboptimal perceptual information introduces inaccuracy (Roulston et al., 2006). In the other two conditions, inferences on the estimated locations are less dependent on the single moment of unpredicted disappearance of the ball.

3.2. 'Real-time' visuospatial processing in the hippocampus

Within the hippocampus, the focus of maximum activation we found was located at a relative caudal (and ventral) position, which supported the explicit reference we made to it as putative (posterior) subiculum (O'Mara, 2005). Previous results of functional imaging studies that addressed navigation (Maguire et al., 2000), spatial memory (Burgess et al., 2001) or sequence learning (Kumaran and Maguire, 2005) have pointed at contributions of more rostral hippocampus divisions. The latter comprise the dentate gyrus and CA3, CA2 and CA1 fields of the cornu ammonis. These regions constitute the core elements for intrinsic hippocampus processing, which includes the establishment of 'classic' activity-induced synaptic plasticity (Neves et al., 2008). The output of the hippocampus CA pyramidal cells to distant neuronal circuitry is partly by direct connections, but the major output is indirect via the subiculum (O'Mara, 2005; Witter and Groenewegen, 1990; Young et al., 1997). Interestingly, CA pyramidal cells can fire as a function of both the present and future trajectory of the moving rat (Johnson and Redish, 2007; Catanese et al., 2012, 2014, de Hoz and Wood, 2006).

In our paradigm, 'real-time' visuospatial processing optimally occurred in the condition that required judging the location at which the ball disappeared because in each trial of this condition, attention was strongly focussed on the ball's movements, while only momentary information was needed for giving the right response at the time of its disappearance. It is important to notice that this activation is not the result of a single spatial estimation but from the ongoing perception and processing of visuospatial change. In contrast, although using the same visual display, the explicit assessment of the ball's start position was already made at the beginning of the trial and had to be kept in memory to make the appropriate response after disappearance, while the prediction of a future location required additional computation at the moment of disappearance. The selective increase of hippocampus activation related to more attentively observing the actual ball movements, without additional task-load, may therefore reflect a condition

Table 1
Condition Related Cerebral Activations.

Brain Region, Brodmann's Area (BA)	Stereotactic coordinates/ T value							
	left				right			
	x	y	z	T	x	y	z	T
A. Place at Start vs. Press at Stop (1 vs. 4)								
Dorsolateral extrastriate visual cortex, V3A (BA 19)	-38	-70	14	6.7				
Superior parietal cortex (BA 7)	-24	-68	40	5.2	16	-64	54	5.3
Dorsal premotor cortex (BA 6)	-18	-2	48	6.1	22	-6	48	4.8*
Postcentral gyrus (BA 3)	-50	-26	58	4.8				
B. Place at Stop vs. Press at Stop (2 vs. 4)								
Dorsolateral extrastriate visual cortex, V3A (BA 19)	-26	-74	18	8.6	34	-70	22	6.6
Superior parietal cortex (BA 7)	-26	-62	48	8.6	14	-62	52	7.2
Putative ventral V5 (BA 19)	-48	-66	-12	7.0				
Dorsal premotor cortex (BA 6)	-20	0	52	9.2	20	8	48	6.2
Thalamus	-16	-28	14	5.6	22	-32	12	6.9
Cerebellum (anterior)	-12	-68	-26	4.9	24	-62	-34	4.5
Cerebellum (posterior)					12	-76	-48	5.1
C. Place Ahead vs. Press at Stop (3 vs. 4)								
Dorsolateral extrastriate visual cortex, V3A (BA 19)	-34	-86	28	9.3	40	-84	22	10.2
Superior parietal cortex (BA 7)	-18	-60	52	9.9	32	-52	44	10.0
Putative ventral V5 (BA 19)	-46	-66	-12	8.1				
Dorsal premotor cortex (BA 6)	-26	-8	60	8.8	28	0	60	6.8
Cerebellum (vermis)					4	-76	-28	5.2
D. Conjunction (1vs. 4 & 2vs. 4 & 3vs. 4)								
Dorsolateral extrastriate visual cortex, V3A (BA 19)	-26	-74	18	8.2				
Superior parietal cortex (BA 7)	-26	-62	48	8.6	14	-62	52	7.2
Putative ventral V5 (BA 19)	-48	-66	-12	7.0	50	-54	-14	5.2
Dorsal premotor cortex (BA 6)	-20	0	52	9.2	20	-4	48	6.2
Inferior parietal cortex (BA 2)	-44	-38	44	7.1				
E. Place at Start vs. Place at Stop & Place Ahead (1 vs. 2 & 1 vs. 3)								
Non significant	-26	-74	18	8.2				
F. Place at Stop vs. Place at Start & Place Ahead (2 vs. 1 & 2 vs. 3)								
Hippocampus (subiculum)	-22	-54	-2	5.3*	22	-44	-4	5.2*
G. Place Ahead vs. Place at Start & Place at Stop (3 vs. 1 & 3 vs. 2)								
Dorsolateral extrastriate visual cortex, V3A (BA 19)	-32	-90	28	5.5	44	-82	26	8.0
Superior parietal cortex (BA 7)	-22	-64	64	6.2	12	-70	56	6.0
Putative ventral V5 (BA 19)	-54	-70	-6	4.2				
Dorsal premotor cortex (BA 6)	-54	-70	-6	4.2*				
Dorsal premotor cortex (BA 6)	-28	-2	60	5.8	28	-4	58	6.3

Co-ordinates refer to the voxels of maximum activation within significant clusters ($P < 0.05$, whole brain corrected at cluster level). Clusters that reached significance only at uncorrected cluster level are marked with *. For the comparisons at first level (A–D) an initial voxel-level statistical threshold of $P < 0.001$ (uncorrected) was used. At second level (E–G) a statistical threshold of $P < 0.005$ (voxel-level, uncorrected) was used.

in which trains of presented stimuli are locally processed, including early-stage matching of such new information with re-entered available information. This may include the comparison between predicted- and actually observed steps in a sequence of events, and would imply that information is only conveyed by the hippocampus to distant neuronal circuitry if relevant for current cerebral operations (Boutros et al., 2008). The strategic role of the subiculum in mediating hippocampal output (O'Mara, 2006) provides a logical gating function in this respect. In other words, when potential salient information enters the hippocampus, the subiculum may provide a 'gating' signal for further sensory

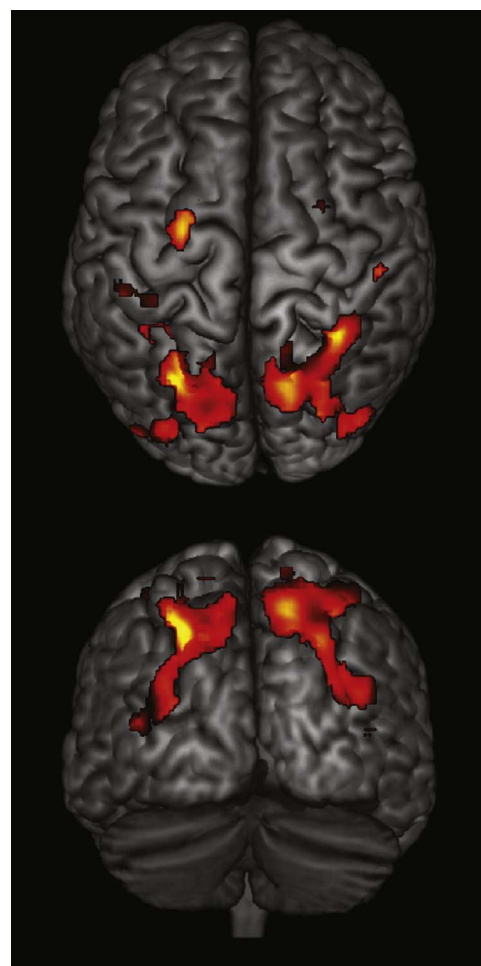
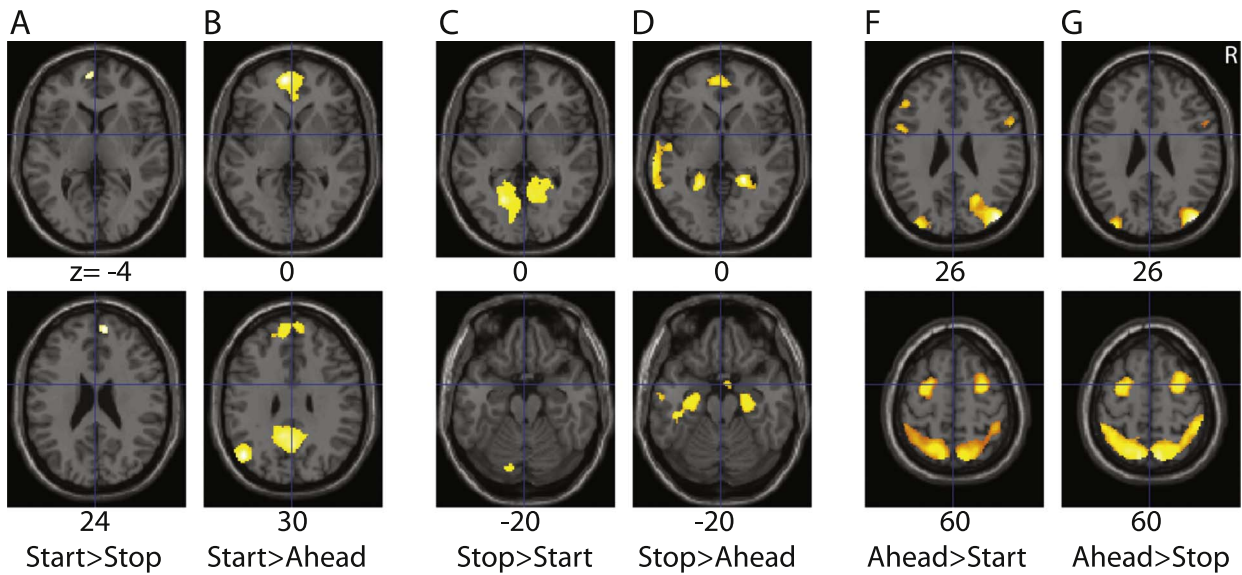


Fig. 3. Common Activation Related to the Experimental Conditions, when Compared to Visuomotor Control (surface-projected). Conjunction analysis with SPM $<Z>$ of activations that resulted from the comparisons of the three experimental conditions with the visuomotor control condition. Local activations are rendered onto the surface of a standard anatomical brain volume (Montreal Neurological Institute, MRIcron). The upper picture depicts the dorsal surface of the brain from a top view; the posterior surface is shown in the lower picture. All regional activations above initial significance threshold $P < 0.001$ (voxel level, uncorrected) are depicted. Coordinates and T values of clusters that reached statistical significance after whole-brain correction for multiple comparisons are reported in Table 1D.

transmission (Cooper et al., 2005; Gaussier et al., 2007). This is consistent with the concept that mismatch/novelty signals are generated when prior predictions are violated by sensory reality (Kumaran and Maguire, 2005). In this way, we regard the hippocampus activation optimally consistent with our interpretation of the neural basis of each of the three conditions. As all three conditions are in the 1-s time range of a 'specious present', seen from a psychological perspective, one might additionally speculate that the condition of ongoing comparisons between predicted and actually observed information provides optimal circumstances for hippocampus-based memory encoding.

The 'place at start' and 'place at stop' conditions were not maximally balanced with regard to attentional demand: the 'place at stop' condition required a more accurate observation of the trajectory of the stimulus, 'waiting' for the ball's unpredictable disappearance. This difference in attentional demand might reflect an intrinsic prerequisite for novelty detection since an association between memory functions of the hippocampus and modulation of attention networks has been described (Nyberg, 2005; Summerfield et al., 2006). On the other hand, in our study no increased activation in parieto-prefrontal attentional networks was present in the 'place at stop' task, while

I. Individual Contrasts (p=0.001, k=20)



II. Conjunction Analyses (p=0.005, k=20)

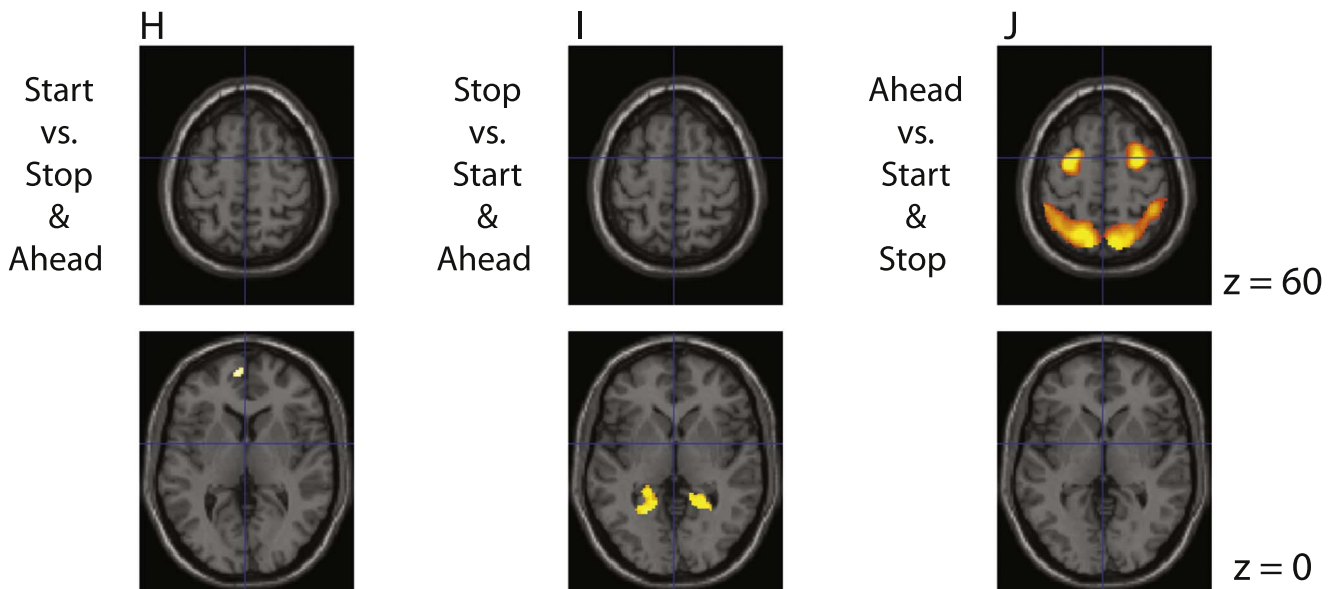


Fig. 4. SPM $<Z>$ of Activations Derived from the Mutual Comparisons of the Experimental Conditions. The foci of activation are projected on transversal sections of a standard anatomical brain. The upper two rows depict the increased activations that resulted from contrasting each of the three experimental conditions to one of the two others (A-F). The conjunction maps (G-I) were subsequently obtained from these initial comparisons. The distance to the plane traversing the anterior- and posterior commissures (ac–pc) is indicated by z coordinates (in mm). The statistical threshold was $P < 0.001$ (voxel-level, uncorrected) for the individual contrasts (A-F) and $P < 0.005$ (voxel-level, uncorrected) for the conjunction analyses (G-I). Coordinates and T values of clusters that reached statistical significance after whole-brain correction for multiple comparisons are reported in Table 1 (E,F,G).

hippocampus activation has not been described in general spatial attention tasks either (Gitelman et al., 1999). These two observations underscore our interpretation that the presently identified hippocampus activation reflected a specific role in momentary visuospatial perception.

3.3. Working memory?

No increase of hippocampus activation was found in the ‘place at start’ condition relative to ‘place at stop’ and ‘place ahead’, which is in line with the view that the hippocampus involvement in relational-memory starts after longer delays, i.e. longer than 1 s (Olson et al.,

2006). However, it could also be the case that once the side of the screen was estimated, subjects only remembered the button they had to press. Neither did we find support either for our hypothesis concerning ‘place at start’ activation that an increased demand on visuospatial working memory, known to operate over time periods from a few tens of seconds to approximately 12 s (Baddeley, 1983), would result in an increase of (right) lateral PFC activation (Geier et al., 2007). We did, however, find medial PFC involvement in assessing the ball’s start position. In this respect it is important to conceive that the estimation of this start position implies that the subsequent response has to be delayed until the moment the ball disappears, which implies that the increased medial PFC activation might reflect response preparation

and -inhibition (de Jong and Paans, 2007). The fact that the reaction times in ‘place at start’ were even shorter than in the control condition of just pressing the same button at the moment of the ball’s disappearance supports this explanation.

It is thus plausible to conclude that response preparation in this condition already started at the onset of the ball’s movement. This early response preparation might imply that attention on events is less-focussed in the outside world during the course of the stimulus. The latter would be in line with the view that the association of medial PFC- and posterior cingulate activations suggests ‘default network’ activation (Damoiseaux et al., 2006; Raichle et al., 2001). Such a network is particularly active when an individual is not focussed on the outside world (Buckner et al., 2008). A link between this concept of a default network and early stages of response preparation is indeed not unlikely as the involved medial cortical regions are optimally positioned to play a role in the transition of non-directed wakefulness to specified external responses.

3.4. Forward spatial estimation

When compared to the conditions addressing present- and past spatial assessments, predicting the ball’s future locations showed increased activation in parietal-premotor circuitry, highly resembling the distribution implicated in all three tasks. In our previous paper we extensively described the embedding of this prediction-related processing in the basic spatial network (Beudel et al., 2009). Although other task-related activities have been observed in similar circuitry (eg Niendam et al., 2012; Radua et al., 2014), the present study adds further support for the parietal-premotor co-involvement in spatial prediction by the comparison of prediction with judging the ball’s start position, which is consistent with a forward estimation function described for the posterior parietal cortex (Mulliken et al., 2008). Furthermore, these forward spatial estimations might be goal-driven in such a way that premotor areas guide hippocampal circuitry in detecting salient locations (Hok et al., 2005, 2007 and, 2013). Future studies examining the interactions between these premotor and hippocampal regions may further reveal this dynamic relation between intention and saliency processing in humans.

3.5. Conclusion

The applied paradigm provided arguments for a functional relation between the caudal segments of the hippocampal formation and (approximate) real-time assessments of spatial locations in a dynamic visual scenery. The previously described concept of the hippocampus as a signal comparator may explain this relation. Such comparator function is the basis of saliency (novelty) detection, and points at a top-down sensory gating mechanism. In this experiment, we did not obtain arguments for a contribution of the hippocampus to working memory at the 1 s time scale.

4. Experimental procedure

Eighteen healthy right-handed subjects, mean age 27y (SD \pm 8.4), 9 females, participated in this study. None of the subjects had neurological, ophthalmologic or upper extremity disorders. They signed an informed consent to a protocol approved by the Medical Ethics Committee of the University Medical Centre Groningen. The data that were used for the new analysis in the present study were collected and described in our previous publication (Beudel et al., 2009). Procedures and task instructions were practiced shortly until the tasks were clearly understood. The practice sessions were performed on two occasions: the first one or two days before the experiment and the second immediately prior to the experiment.

4.1. Experimental task equipment

During the acquisition of fMRI images, subjects watched a visual display of a black ball moving on a grey screen. After judging specific spatiotemporal characteristics of the ball’s behaviour (see description of the experimental conditions), responses were made by pressing a button on a MR compatible response-box (fORP, Current designs, Inc. U.S.A.). A projector (resolution 1024 \times 768 pixels, Barco, Belgium) projected the computer-generated videos of the moving ball on the screen (display dimensions 44 \times 34 cm). Subjects viewed the screen via a mirror placed at a distance of 11 cm from the face. The distance between mirror and screen was 64 cm. An arrowhead marked the middle of the bottom edge of the screen. With blank intervals, the ball appeared at an uncued location and moved until it disappeared. It moved along a straight line, which was continued in a new direction after rebound from either the upper edge or one of the side-edges of the screen (Fig. 1). Stimuli were presented using the ‘Presentation’ program (Neuro Behavioural Systems, Inc. CA, USA).

4.2. Experimental paradigm

The experimental paradigm was constituted by six stimulus-response conditions and one passive visual viewing task. In the latter, the ball remained at a fixed position in the centre of the screen. In condition 1 (‘place at start’) subjects had to indicate at which side of the screen, either left or right, the ball started moving. This judgment was made at the moment that ball stopped moving and disappeared, by pressing one of two buttons with either the index- or middle finger of the right hand. In condition 2 (‘place at stop’), subjects had to determine the side of the screen where the ball actually stopped moving, while in condition 3 (‘place ahead’) they had to extrapolate the ball’s trajectory after its disappearance until it virtually touched the bottom edge of the screen and indicate the side of the screen where this would happen (Fig. 1). In all three conditions, subjects had to respond at the moment the ball stopped moving and disappeared. In a visuomotor control condition 4 (‘press at stop’), subjects had to press always the same button at the moment the ball stopped, no additional choices needed to be made. Left and right starting, stopping and predicted locations were equally probable in each condition and had no relation with the place the previous trial left off. Conditions 5 and 6 (‘time ahead’ and ‘speed’) addressed temporal aspects of the task, and were described in our previous paper (Beudel et al., 2009). These conditions were not treated in the present analyses.

A total of 72 stimuli were designed that varied with regard to ball directions and trajectory lengths. The stimulus presentation time of 1000 ms was kept constant. The experiment consisted of a practice block (3 min) followed by two 15 min runs of task performance during functional imaging. In between these two runs, an anatomical T1 weighted scan (7 min) was made. The two runs contained 6 blocks each. Each block contained the 6 stimulus-response conditions, while the passive viewing task was placed in between blocks. The order of the conditions was randomized and balanced. In each block-segment, containing a single condition, the task was preceded by respectively a blank screen (500–3000 ms, jittering compatible), a visually presented task instruction (2000 ms) and another blank screen (1000 ms). The subsequent task consisted of stimulus observation (1000 ms) and a 2000 ms interval in which a response had to be given. These stimulus-response trials were repeated six times in each 21 s segment. This amounted to a total of 72 trials per condition.

4.3. MRI characteristics

Data acquisition was performed using a 3 T Philips MR system (Best, The Netherlands) with a standard 6 channel SENSE head coil. A T1 weighted 3D anatomical scan was acquired to obtain high-resolution anatomical information, matrix size =256 \times 256 in axial orienta-

tion. Functional images were acquired with a gradient-echo T2* Blood Oxygen Dependent Level (BOLD) contrast technique using the following scanning parameters: TR =3000 ms, TE =35 ms, 41 slices, isotropic voxels 3.5×3.5×3.5 mm, axial orientation, 218 volumes per run.

4.4. Data analysis

Image processing and statistical analysis were conducted with Statistical Parametric Mapping (SPM, Friston et al., 1995) version 5 (2005, Wellcome Department of Cognitive Neurology, London, UK; <http://www.fil.ion.ucl.ac.uk/spm>). Pre-processing with SPM included realignment and spatial normalization (template of the Montreal Neurological Institute, MNI). Images were smoothed using a Gaussian filter of 8 mm FWHM. Cortical activations were rendered onto the surface of a standard MNI brain. For the projection on brain slices, the same template was used. For the statistical analysis of regional differences in cerebral activation, all conditions (including 5 and 6) were modelled in a blocked design at subject level. To identify the distribution of activations related to cerebral processing beyond primary visuomotor control in the experimental conditions 1–3, each of these three conditions was contrasted to the visuomotor control condition (4) at subject level, after which each contrast was separately analysed at group level using one sample *t*-tests. To look at the activations that were commonly present in all three conditions, a conjunction analysis was conducted of the three SPM $<Z>$ maps obtained from the *t*-tests. For the contrasts of the experimental conditions with the visuomotor control condition, an initial threshold of $p < 0.001$ was used (response height at voxel-level, uncorrected; extent *kE* of 20 voxels). Differences between conditions 1, 2 and 3 were made by making comparisons at second level using a one-way ANOVA for repeated measures (random effect analysis). The contrasts of the conditions 1,2,3 with the baseline task of passive viewing a stationary ball in the centre of the screen were used in the ANOVA. Conditions were assumed to be dependent and equally variant, whereas subjects were assumed to be independent and equally variant. For the differences that resulted from these comparisons, an initial threshold of $p < 0.001$ (response height at voxel-level) was used with extend (*kE*) of 20 voxels. Resulting clusters were considered statistically significant at $p < 0.05$ (cluster-level, corrected for the entire brain volume). To look at cerebral activations that were exclusively present in one of the three experimental conditions, the individual contrasts of each experimental condition with the other two experimental conditions were combined using exclusive masking in SPM5. For these conjunction analyses a relaxed statistical threshold of $p < 0.005$ (voxel-level) was used. The anatomical characterisation of the obtained activation patterns was further specified by the SPM anatomy toolbox for selected regions (Eickhoff et al., 2005).

Behavioural differences between the 3 stimulus-response conditions regarding response times and error rates obtained during scanning were analysed by a one-way ANOVA for repeated measures using the means of single subjects for each condition and post-hoc comparisons. The reaction times concerned the interval between disappearance of the stimulus and the recorded response. In addition, subjects rated the difficulty of the conditions after performance in the scanner. The scale of this rating was from 1 to 10 in which 10 was most difficult. Differences in perceived difficulty were analysed using Friedman's test for repeated measures (non-parametric) and post-hoc comparisons.

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References

- Baddeley, A.D., 1983. Working Memory. *Philos Trans. R. Soc. Lond., B, Biol. Sci.* B302, 311–324.
- Banquet, J.P., Gaussier, P., Quoy, M., Revel, A., Burnod, Y., 2005. A hierarchy of associations in hippocampo-cortical systems: cognitive maps and navigation strategie. *Neural Comput.* 17, 1339–1384. <http://dx.doi.org/10.1162/0899766053630369>.
- Bast, T., 2007. Toward an integrative perspective on hippocampal function: from the rapid encoding of experience to adaptive behavior. *Rev. Neurosci.* 18 (3–4), 253–281.
- Beudel, M., Renken, R., Leenders, K.L., de Jong, B.M., 2009. Cerebral representations of space and time. *NeuroImage* 44 (3), 1032–1040.
- Bird, C.M., Burgess, N., 2008. The hippocampus and memory: insights from spatial processing. *Nat. Rev. Neurosci.* 9 (3), 182–194.
- Boutros, N.N., Mears, R., Pflieger, M.E., Moxon, K.A., Ludowig, E., Rosburg, T., 2008. Sensory gating in the human hippocampal and rhinal regions: regional differences. *Hippocampus* 18 (3), 310–316.
- Buckner, R.L., Andrews-Hanna, J.R., Schacter, D.L., 2008. The brain's default network: anatomy, function, and relevance to disease. *Ann. N. Y. Acad. Sci.* 1124, 1–38.
- Burgess, N., Maguire, E.A., O'Keefe, J., 2002. The human hippocampus and spatial and episodic memory. *Neuron* 35 (4), 625–641.
- Burgess, N., Maguire, E.A., Spiers, H.J., O'Keefe, J., 2001. A temporoparietal and prefrontal network for retrieving the spatial context of lifelike event. *NeuroImage* 14 (2), 439–453.
- Buzsaki G., 2006. *Rhythms of the Brain*. Oxf Univ Press, Oxford.
- Catanesi, J., Cerasti, E., Zugaro, M., Viggiano, A., Wiener, S.I., 2012. Dynamics of decision-related activity in hippocampus. *Hippocampus* 22, 1901–1911. <http://dx.doi.org/10.1002/hipo.22025>.
- Catanesi, J., Viggiano, A., Cerasti, E., Zugaro, M.B., Wiener, S.I., 2014. Retrospectively and prospectively modulated hippocampal place responses are differentially distributed along a common path in a continuous T-maze. *J. Neurosci.* 34, 13163–13169. <http://dx.doi.org/10.1523/JNEUROSCI.0819-14.2014>.
- Cooper, D.C., Chung, S., Spruston, N., 2005. Output-mode transitions are controlled by prolonged inactivation of sodium channels in pyramidal neurons of subiculum. *PLoS Biol.* 3 (6), e175.
- Damoiseaux, J.S., Rombouts, S.A., Barkhof, F., Scheltens, P., Stam, C.J., Smith, S.M., Beckmann, C.F., 2006. Consistent resting-state networks across healthy subject. *Proc. Natl. Acad. Sci. USA* 103 (37), 13848–13853.
- de Jong, B.M., Paans, A.M., 2007. Medial versus lateral prefrontal dissociation in movement selection and inhibitory control. *Brain Res.* 1132 (1), 139–147.
- Eagleman, D.M., Sejnowski, T.J., 2000. Motion integration and postdiction in visual awareness. *Science* 287 (5460), 2036–2038.
- Eickhoff, S.B., Stephan, K.E., Mohlberg, H., Grefkes, C., Fink, G., Amunts, K., Zilles, K., 2005. A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. *NeuroImage* 25 (4), 1325–1335.
- Friston, K.J., Holmes, A.P., Worsley, K.J., Poline, J., Frith, C.D., Frackowiak, R.S.J., 1995. Statistical parametric maps in functional imaging: a general linear approach. *Hum. Brain Map* 2 (4), 189–210.
- Geier, C.F., Garver, K.E., Luna, B., 2007. Circuitry underlying temporally extended spatial working memory. *NeuroImage* 35 (2), 904–915.
- Gaussier, P., Banquet, J.P., Sargolini, F., Giovannangeli, C., Save, E., Poucet, B., 2007. A model of grid cells involving extra hippocampal path integration, and the hippocampal loop. *J. Integr. Neurosci.* 6, 447–476.
- Gitelman, D.R., Nobre, A.C., Parrish, T.B., LaBar, K.S., Kim, Y.H., Meyer, J.R., Mesulam, M., 1999. A large-scale distributed network for covert spatial attention: further anatomical delineation based on stringent behavioural and cognitive control. *Brain* 122, 1093–1106.
- Hartley, T., Bird, C.M., Chan, D., Cipolotti, L., Husain, M., Vargha-Khadem, F., Burgess, N., 2007. The hippocampus is required for short-term topographical memory in human. *Hippocampus* 17 (1), 34–48.
- Hok, V., Chah, E., Save, E., Poucet, B., 2013. Prefrontal cortex focally modulates hippocampal place cell firing pattern. *J. Neurosci.* 33, 3443–3451. <http://dx.doi.org/10.1523/JNEUROSCI.3427-12.2013>.
- Hok, V., Lenck-Santini, P.-P., Roux, S., Save, E., Muller, R.U., Poucet, B., 2007. Goal-related activity in hippocampal place cell. *J. Neurosci.* 27, 472–482. <http://dx.doi.org/10.1523/JNEUROSCI.2864-06.2007>.
- Hok, V., Save, E., Lenck-Santini, P.P., Poucet, B., 2005. Coding for spatial goals in the prelimbic/infralimbic area of the rat frontal cortex. *Proc. Natl. Acad. Sci. USA* 102, 4602–4607. <http://dx.doi.org/10.1073/pnas.0407332102>.
- de Hoz, L., Wood, E.R., 2006. Dissociating the past from the present in the activity of place cells. *Hippocampus* 16, 704–715. <http://dx.doi.org/10.1002/hipo.20207>.
- Johnson, A., Redish, A.D., 2007. Neural ensembles in CA3 transiently encode paths forward of the animal at a decision point. *J. Neurosci.* 27, 12176–12189. <http://dx.doi.org/10.1523/JNEUROSCI.3761-07.2007>.
- Knight, R., 1996. Contribution of human hippocampal region to novelty detection. *Nature* 383 (6597), 256–259.
- Kumaran, D., Maguire, E., 2005. The human hippocampus: cognitive maps or relational memory. *J. Neurosci.* 25 (31), 7254–7259.
- Kumaran, D., Maguire, E.A., 2007a. Match mismatch processes underlie human hippocampal responses to associative novelty. *J. Neurosci.* 27 (32), 8517–8524.
- Kumaran, D., Maguire, E.A., 2007b. Which computational mechanisms operate in the hippocampus during novelty detection. *Hippocampus* 17 (9), 735–748.
- LaBar, K.S., Gitelman, D.R., Parrish, T.B., Mesulam, M., 1999. Neuroanatomical overlap of working memory and spatial attention networks: a functional MRI comparison

- within subject. *NeuroImage* 10 (6), 695–704.
- Lacquaniti, F., Maioli, C., 1989. The role of preparation in tuning anticipatory and reflex responses during catching. *J. Neurosci.: Off. J. Soc. Neurosci.* 9 (1), 134–148.
- Lisman, J.E., Grace, A.A., 2005. The hippocampal-VTA loop: controlling the entry of information into long-term memory. *Neuron* 46 (5), 703–713.
- Maguire, E.A., Gadian, D.G., Johnsrude, I.S., Good, C.D., Ashburner, J., Frackowiak, R.S., Frith, C.D., 2000. Navigation-related structural change in the hippocampi of taxi driver. *Proc. Natl. Acad. Sci. USA* 97 (8), 4398–4403.
- Martin, A., 1999. Automatic activation of the medial temporal lobe during encoding: lateralized influences of meaning and novelty. *Hippocampus* 9 (1), 62–70.
- Mulliken, G.H., Musallam, S., Andersen, R., 2008. Forward estimation of movement state in posterior parietal cortex. *Proc. Natl. Acad. Sci. USA* 105 (24), 8170–8177.
- Neves, G., Cooke, S.F., Bliss, T.V., 2008. Synaptic plasticity, memory and the hippocampus: a neural network approach to causality. *Nat. Rev. Neurosci.* 9 (1), 65–75.
- Niendam, T.A., Laird, A.R., Ray, K.L., Dean, Y.M., Glahn, D.C., Carter, C.S., 2012. Meta-analytic evidence for a superordinate cognitive control network subserving diverse executive function. *Cogn. Affect. Behav. Neurosci.* 12, 241–268.
- Nijhawan, R., 1994. Motion extrapolation in catching. *Nature* 370 (6487), 256–257.
- Nyberg, L., 2005. Any novelty in hippocampal formation and memory. *Curr. Opin. Neurol.* 18 (4), 424–428.
- O'Mara, S., 2005. The subiculum: what it does, what it might do, and what neuroanatomy has yet to tell us. *J. Anat.* 207 (3), 271–282.
- O'Mara, S., 2006. Controlling hippocampal output: the central role of subiculum in hippocampal information processing. *Behav. Brain Res* 174 (2), 304–312.
- Olson, I.R., Page, K., Moore, K.S., Chatterjee, A., Verfaellie, M., 2006. Working memory for conjunctions relies on the medial temporal lobe. *J. Neurosci.* 26 (17), 4596–4601.
- Passingham, D., Sakai, K., 2004. The prefrontal cortex and working memory: physiology and brain imaging. *Curr. Opin. Neurobiol.* 14 (2), 163–168.
- Piekema, C., Kessels, R.P., Mars, R.B., Petersson, K.M., Fernandez, G., 2006. The right hippocampus participates in short-term memory maintenance of object-location association. *NeuroImage* 33 (1), 374–382.
- Radua, J., Del Pozo, N.O., Gómez, J., Guillen-Grima, F., Ortuño, F., 2014. Meta-analysis of functional neuroimaging studies indicates that an increase of cognitive difficulty during executive tasks engages brain regions associated with time perception. *Neuropsychologia* 58, 14–22.
- Raichle, M.E., MacLeod, A.M., Snyder, A.Z., Powers, W.J., Gusnard, D.A., Shulman, G.L., 2001. A default mode of brain function. *Proc. Natl. Acad. Sci. USA* 98 (2), 676–682.
- Rolls, E.T., Kesner, R.P., 2006. A computational theory of hippocampal function, and empirical tests of the theory. *Prog. Neurobiol.* 79 (1), 1–48.
- Roulston, B.W., Self, M.W., Zeki, S., 2006. Perceptual compression of space through position integration. *Proc. R. Soc. Lond., B, Biol. Sci.* 273 (1600), 2507–2512.
- Schon, K., Newmark, R.E., Ross, R.S., Stern, C.E., 2016. A working memory buffer in parahippocampal regions: evidence from a load effect during the delay period. *Cereb. Cortex* 26, 1965–1974. <http://dx.doi.org/10.1093/cercor/bhv013>.
- Smith, E.E., Jonides, J., 1999. Storage and executive processes in the frontal lobes. *Science* 283 (5408), 1657–1661.
- Squire, L.R., Stark, C.E., Clark, R.E., 2004. The medial temporal lobe. *Annu. Rev. Neurosci.* 27, 279–306.
- Stark, C.E., Okado, Y., 2003. Making memories without trying: medial temporal lobe activity associated with incidental memory formation during recognition. *J. Neurosci.* 23 (17), 6748–6753.
- Summerfield, J.J., Lepsien, J., Gitelman, D.R., Mesulam, M.M., Nobre, A.C., 2006. Orienting attention based on long-term memory experience. *Neuron* 49 (6), 905–916.
- Vinogradova, O.S., 2001. Hippocampus as comparator: role of the two input and two output systems of the hippocampus in selection and registration of information. *Hippocampus* 11 (5), 578–598.
- Witter, M.P., Groenewegen, H.J., 1990. The subiculum: cytoarchitecturally a simple structure, but hodologically complex. *Prog. Brain Res* 83, 47–58.
- Wojtowicz, W.T., Sung, K., Truong, S., Purves, D., 2008. An empirical explanation of the flash-lag effect. *Proc. Natl. Acad. Sci. USA* 105 (42), 16338–16343.
- Young, B.J., Otto, T., Fox, G.D., Eichenbaum, H., 1997. Memory representation within the parahippocampal region. *J. Neurosci.* 17 (13), 5183–5195.