Behavioral/Cognitive

Mind-wandering in people with hippocampal amnesia

Cornelia McCormick[1], Clive R. Rosenthal[2], Thomas D. Miller[2], Eleanor A. Maguire[1]

Affiliations:
[1]Wellcome Trust Centre for Neuroimaging, Institute of Neurology, University College London, London, WC1N 3BG, UK; [2]Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, OX3 9DU, UK

Abbreviated title: **Mind-wandering following hippocampal damage**

Corresponding authors: **Cornelia McCormick, Eleanor Maguire**
Wellcome Trust Centre for Neuroimaging, Institute of Neurology, University College London, 12 Queen Square, London, WC1N 3BG, UK**;** c.mccormick@ucl.ac.uk; e.maguire@ucl.ac.uk.

Number of pages: 31
Number of figures: 4
Number of tables: 3
Number of words for Abstract: 232
Number of words for Introduction: 649
Number of words for Discussion: 1324

Acknowledgments: We thank all the participants, particularly the patients and their relatives, for the time and effort they contributed to this study. We also thank the consultant neurologists: Drs. M.J. Johnson, S.R. Irani, S. Jacobs and P. Maddison. We are grateful to Martina F. Callaghan for help with MRI sequence design, Trevor Chong for second scoring the Autobiographical Interview, Alice Liefgreen for second scoring of the mind-wandering thoughts, and Elaine Williams for advice on hippocampal segmentation. E.A.M. and C.M. are supported by a Wellcome Trust Principal Research Fellowship to E.A.M. (101759/Z/13/Z) and the Centre by a Strategic Award from the Wellcome Trust (203147/Z/16/Z). C.R.R. was supported by the National Institute for Health Research and John Fell OUP Fund. T.D.M. was supported by the Guarantors of Brain, the Patrick Berthould Charitable Trust and the Encephalitis Society.

The authors declare no competing financial interests and no conflicts of interest.

Abstract

Subjective inner experiences, such as mind-wandering, represent the fundaments of human cognition. While the precise function of mind-wandering is still debated, it is increasingly acknowledged to have influence across cognition on processes such as future planning, creative thinking and problem-solving, and even on depressive rumination and other mental health disorders. Recently, there has been important progress in characterizing mind-wandering and identifying the neural networks associated with it. Two prominent features of mind-wandering are mental time travel and visuo-spatial imagery, which are often associated with the hippocampus. People with amnesia arising from selective bilateral hippocampal damage ('hippocampal amnesia') cannot vividly recall events from their past, envision their future or imagine fictitious scenes. This raises the question of whether the hippocampus plays a causal role in mind-wandering and if so, in what way. Leveraging a unique opportunity to shadow people with hippocampal amnesia for several days, we examined, for the first time, what they thought about spontaneously, without direct task demands. We found that they engaged in as much mind-wandering as control participants. However, whereas controls thought flexibly and creatively about the past, present and future, imagining vivid visual scenes, hippocampal amnesia resulted in thoughts primarily about the present comprising verbally-mediated semantic knowledge. These findings expose the hippocampus as a key pillar in the neural architecture of mind-wandering and also reveal its impact beyond memory, placing it at the heart of human mental life.

Significance statement

Humans tend to mind-wander about 30-50% of their waking time. Two prominent features of this pervasive form of thought are mental time travel and visuo-spatial imagery, which are often associated with the hippocampus. To examine whether the hippocampus plays a causal role in mind-wandering, we examined the frequency and phenomenology of mind-wandering in patients with selective bilateral hippocampal damage. We found that they engaged in as much mind-wandering as controls. However, hippocampal damage changed the form and content of mind-wandering from flexible, episodic, and scene-based to abstract, semanticized, and verbal. These findings expose the hippocampus as a key pillar in the neural architecture of mind-wandering and reveal its impact beyond memory, placing it at the heart of our mental life.

Introduction

Even when in the same place and involved in the same activity, at any given moment people can experience the world in different ways. Recently, there have been advances in delineating the various forms of spontaneous inner experiences and their neural correlates (Andrews-Hanna et al., 2014a; Christoff et al., 2016). Self-generated thinking typically refers to the ability to mentally decouple from current perceptual surroundings and generate independent internal thoughts (Smallwood and Schooler, 2015). These thoughts can either be intentional and task-related, such as actively thinking about how this manuscript should be structured, or unintentional and task-unrelated, where there is a spontaneous inner focus, such as thinking about what a nice time I had yesterday with my friends. The latter phenomenon is variously described as task-unrelated self-generated thought, daydreaming or mind-wandering (Smallwood and Schooler, 2015).

It has been shown that humans tend to mind-wander about 30-50% of waking time, irrespective of the current activity (Kane et al., 2007; Killingsworth and Gilbert, 2010). Nevertheless, mind-wandering frequency is particularly pronounced during restful periods and low-demanding tasks (Smallwood and Schooler, 2015), the latter of which is often exploited by experimentalists examining mind-wandering. While the precise function of mind-wandering is still debated, it is increasingly acknowledged to have influence across cognition on processes such as future planning, creative thinking and problem-solving (Baird et al., 2011; Baird et al., 2012), and even on depressive rumination and other mental health disorders (Ehlers et al., 2004; Andrews-Hanna et al., 2014a). Furthermore, the content of mind-wandering seems wide-ranging, including episodic memory recall (i.e., rich in detail and specific in time and place), future planning, mentalizing, simulation of hypothetical scenarios, and involves a variety of emotions and different sensory modalities (Andrews-Hanna et al., 2013; Smallwood et al., 2016). Interestingly, two of the most prominent features of mind-wandering are mentally travelling forwards and backwards in time and visual imagery, which are functions usually associated with the hippocampus (Tulving, 1985, 2002; Hassabis et al., 2007).

The Default Mode Network (DMN), within which the hippocampus is a node, has been associated with self-generated thoughts such as mind-wandering (Buckner et al., 2008; Andrews-Hanna et al., 2014b). Of particular relevance here, stronger hippocampal connectivity with other regions of the DMN was observed in individuals who experienced more episodic details and greater flexibility in mental time travel during mind-wandering episodes (Karapanagiotidis et al., 2016; Smallwood et al., 2016). Unfortunately, causal evidence for hippocampal involvement in mind-wandering is lacking (Fox et al., 2016). Behavioral studies of patients with lesions are crucial because they are one way to examine the causal effects of regional brain damage on the networks established by neuroimaging work. People with damage to the hippocampus cannot vividly recall events from their past (Rosenbaum et al., 2008) envision their future (Kurczek et al., 2015) or imagine fictitious scenes (Hassabis et al., 2007). Therefore, whether they experience mind-wandering, and if they do, what form does it take, are important and timely questions which we addressed by examining mind-wandering in patients with amnesia arising from selective bilateral hippocampal damage ('hippocampal amnesia').

Previous studies have examined the effects of hippocampal amnesia during demanding tasks, such as autobiographical memory retrieval (Rosenbaum et al., 2008), designed to challenge the patients' cognitive abilities. In contrast, the focus of the current study was to examine what patients with hippocampal amnesia do in their mentally "free" time, to establish what they think about spontaneously when there is no concurrent task. We initially sought to ascertain whether or not patients with hippocampal amnesia were able to mentally decouple from the current perceptual input. If yes, we then had a series of further questions. First, would they engage in mental time travel? Second, what form would their mind-wandering take – spontaneous episodic, detailed thoughts or semantic, abstract thoughts? Lastly, we asked whether they experienced spontaneous visual imagery similar to that typically reported by control participants during mind-wandering (Andrews-Hanna et al., 2013; Smallwood et al., 2016)?

Materials and Methods

Participants

Six patients (all right-handed males, mean age 57.0 years (SD 16.9), age range 27 to 70) with selective bilateral hippocampal lesions and selective episodic memory impairment took part (see Tables 1 and 2 for demographic information and neuropsychological profiles). Hippocampal damage (see example in Fig. 1a) resulted in all cases from voltage-gated potassium channel (VGKC)-complex antibody-mediated limbic encephalitis (LE). In line with previous reports of this patient population (Dalmau and Rosenfeld, 2014; Miller et al., 2017), manual (blinded) segmentation of the hippocampi from high-resolution structural MRI scans confirmed that our patients showed volume loss confined to the left (Patients – HC: 2506mm^3 (mean) +/-394 (standard deviation), control participants – CTL: 3173 mm^3 +/-339, $t(15)=3.7$, $p=0.002$, Cohen's d=1.8) and right (HC: 2678mm^3 +/-528, CTL: 3286mm^3 +/-301, $t(15)=3.1$, $p=0.008$, Cohen's d=1.4) hippocampus. To rule out pathological differences between patients and controls elsewhere in the brain, an automated voxel-based-morphometry (VBM; Ashburner, 2009) analysis was carried out on whole brain T1 weighted MRI images and, in line with previous reports on patients of this sort (Wagner et al., 2015; Finke et al., 2017; Miller et al., 2017), did not result in any significant group differences outside of the hippocampus even at a liberal uncorrected p-value of less than 0.001.

Table 1. Summary of demographic information.

Group	N	HD	Age	Chronicity	LHC vol*	RHC vol*
HC group	6 (M)	6 (R)	57.0	6.8	**2506**	**2678**
			16.9	2.1	394	528
CTL group	12 (M)	11 (R)	57.2	n.a.	**3173**	**3286**
			16.6		339	301
p-value			0.98	n.a.	**0.002**	**0.008**

For both groups, means are displayed with standard deviations below the corresponding mean. HC=hippocampal-damaged patients; CTL=healthy control participants; M=Male; HD=Handedness; n.a.=not applicable; R=Right; L=Left; vol=volume in mm^3. *One control participant could not be scanned, therefore hippocampal volumes are based on all six patients and 11 control participants. Age and chronicity are described in years. p-value=p-value of two-sample t-test with significant differences depicted in bold.

Neuropsychologically, the patients displayed an impairment in immediate and delayed recall, and they recollected significantly fewer episodic ('internal'), but not semantic ('external') details on the Autobiographical Interview (Levine et al., 2002), as detailed in Table 2. All other cognitive and emotional aspects of cognition were intact in these patients. Importantly, their working memory capacity did not differ from that of controls, suggesting that the differences in mind-wandering episodes we report here are not merely due to an inability to remember the thoughts.

Twelve healthy control participants also took part (all male, one left-handed, mean age 57.2 (16.6) years, age range from 25 to 77). In addition to comparing the two groups, we ensured that each patient was matched closely to two of the control subjects on sex, age, and general cognitive ability (measured by the Matrix Reasoning and Similarities subtests of the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999). There were no significant differences between patients and controls on age, general cognitive ability and a range of neuropsychological tests assessing semantic memory, language, perception, executive functions and mood (see Table 2). All participants gave informed written consent in accordance with the local research ethics committees.

Table 2. Summary of neuropsychological profile.

	WASI-M	WASI-S	AMint*	AMext*	IRM	DRM	RM	SEM	WM	Lang	EF	Perc	Mood
HC	13.2	12.8	**31.7**	6.1	**-0.7**	**-0.7**	-0.3	-0.3	-0.3	-0.3	-0.2	-0.4	0.0
	2.2	1.8	6.7	3.8	0.8	0.8	1.1	1.0	0.8	0.9	0.5	1.6	1.0
CTL	13.8	11.8	**51.3**	5.9	**0.3**	**0.4**	0.1	0.1	0.1	0.1	0.1	0.2	0.0
	1.5	2.6	13.6	2.2	0.3	0.6	0.6	0.8	1.1	0.9	0.6	0.3	0.8
p	0.46	0.41	**0.01**	0.92	**0.001**	**0.01**	0.29	0.39	0.42	0.37	0.39	0.22	0.94

For both groups, means are displayed with standard deviations underneath. HC=hippocampal-damaged patients; CTL=healthy control participants; p=p-value of two-sample t-test with significant differences (all memory-related) depicted in bold; WASI=Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999); M=Scaled scores of the WASI Matrix Reasoning subtest, S=Scaled scores of the WASI Similarities subtest. AI=autobiographical interview (Levine et al., 2002): int=average number of internal (episodic) details over five memories, ext=average external (semantic) details over five memories. *Of note, autobiographical memory performance of the patients was compared to a separate control group (5 males, 1 female, mean age 55.2+/-18 years, range 22-69, all right-handed). After the vertical line, test scores (where available, scaled scores) of individual tests have been transformed into z-scores and averaged across patients and controls within each neuropsychological domain. Therefore, a mean z-score of zero indicates that both groups had the same mean. Domains contained the following subtests: IRM=immediate recall memory: Wechsler Memory Scale (WMS-III; Wechsler, 1997), logical memory 1 units and thematic scores, wordlist 1 total recall, and Rey-Osterrieth complex figure immediate recall (Osterrieth, 1944). DRM=delayed recall memory: WMS-

III logical memory 2 units and thematic scores, and Rey-Osterrieth complex figure delayed recall. RM=recognition memory: Warrington Recognition Memory Test for words and faces (Warrington, 1984), WMS-III wordlist 2 recognition. SEM=semantic memory: Warrington Graded Naming Test (McKenna and Warrington, 1980; Warrington, 2010). WM=working memory: WMS-III digit span subtest. Lang=language abilities: Delis-Kaplan Executive Function System (D-KEFS) letter fluency and category fluency tests (Delis et al., 2001). EF=executive functions: D-KEFS category switch test, word-colour interference test, trails test (average of visual scanning, number sequencing, letter sequencing, number-letter switching, and motor speed tests), Hayling Sentence Completion Test (Burgess and Shallice, 1997). Perc=perception: Visual Object and Space Perception Battery (VOSP) dot counting, cube analysis, position discrimination subtests (Warrington and James, 1991; Gabrovska et al., 1996), and the Rey-Osterrieth Complex Figure copy. Mood=Hospital Anxiety and Depression Scale (HADS; Zigmond and Snaith, 1983).

Characterization of hippocampal damage

High resolution T2-weighted structural MRI scans of the medial temporal lobes

Five of the patients and 10 of the control participants underwent structural MR imaging limited to a partial volume focused on the temporal lobes using a 3.0-T whole body MR scanner (Magnetom TIM Trio, Siemens Healthcare, Erlangen, Germany) operated with a radiofrequency (RF) transmit body coil and 32-channel head RF receive coil. These structural images were collected using a single-slab 3D T2-weighted turbo spin echo sequence with variable flip angles (SPACE; Mugler et al., 2000) in combination with parallel imaging, to simultaneously achieve a high image resolution of ~500µm, high sampling efficiency and short scan time while maintaining a sufficient signal-to-noise ratio (SNR). After excitation of a single axial slab the image was read out with the following parameters: resolution=0.52 x 0.52 x 0.5 mm, matrix=384 x 328, partitions=104, partition thickness=0.5 mm, partition oversampling=15.4%, field of view=200 x 171 mm 2, TE=353 ms, TR=3200 ms, GRAPPA x 2 in phase-encoding (PE) direction, bandwidth=434 Hz/pixel, echo spacing=4.98 ms, turbo factor in PE direction=177, echo train duration=881, averages=1.9. For reduction of signal bias due to, for example, spatial variation in coil sensitivity profiles, the images were normalized using a prescan, and a weak intensity filter was applied as implemented by the scanner's manufacturer. It took 12 minutes to obtain a scan.

High resolution T1-weighted structural MRI scans of the whole brain at 3.0 Tesla

In addition, five of the patients and 11 of the control participants underwent a whole brain structural T1weighted sequence at an isotropic resolution of 800µm (Callaghan et al., 2015) which was used for the automated VBM analysis (one control participant could not be scanned). These images had a FoV of 256mm head-foot, 224mm anterior-posterior (AP), and 166mm right-left (RL). This sequence was a spoiled multi-echo 3D fast low angle shot (FLASH) acquisition with a flip angle of 21^0 and a repetition time (TR) of 25ms. To accelerate the data acquisition, partially parallel imaging using the GRAPPA algorithm was employed in each phase-encoded direction (AP and RL) with forty reference lines and a speed up factor of two. Gradient echoes were acquired with alternating readout polarity at eight equidistant echo times ranging from 2.34 to 18.44ms in steps of 2.30ms using a readout bandwidth of 488Hz/pixel (Helms and Dechent, 2009). The first six echoes were averaged to increase SNR (Helms and Dechent, 2009) producing a T1-weighted image with an effective echo time of 8.3 ms.

High resolution T1-weighted MRI scans of the whole brain at 7.0 Tesla

One patient could not be scanned at our Centre due to recent dental implants. We therefore used a whole brain T1-weighted image acquired previously on a 7.0 Tesla MRI scanner - a three-dimensional whole-brain T1- weighted phase sensitive inversion recovery sequence (Mougin et al., 2015) with 0.6 × 0.6 × 0.6 mm resolution with a tailored inversion pulse for magnetization inversion at ultrahigh field (Hurley et al., 2010), which provided inherent bias field correction.

Hippocampal segmentation

To improve the SNR of the anatomical images, two or three T2-weighted high resolution scans were acquired for a participant. Images from each participant were co-registered and denoised following the Rician noise estimation (Coupe et al., 2010). The denoised images were averaged and smoothed with a full-width at half maximum kernel of 2x2x2mm. In each case, left and right hippocampi were manually (blindly) segmented and volumes extracted using the ITK Snap software version 3.4.0 (Yushkevich et al., 2006).

VBM analysis

An automated VBM analysis was performed using SPM12 (Statistical Parametric Mapping, Wellcome Trust Centre for Neuroimaging, London, UK). The averaged T1-weighted images were segmented into grey and white matter probability maps using the unified segmentation approach (Ashburner and Friston, 2005). Inter-subject registration of the tissue classes was performed using Dartel, a nonlinear diffeomorphic algorithm (Ashburner, 2007). The resulting Dartel template and deformations were used to normalize the tissue probability maps to the stereotactic space defined by the Montreal Neurological Institute (MNI) template. For VBM analysis, the normalization procedure included modulating the grey matter tissue probability maps by the Jacobian determinants of the deformation field and smoothing with an isotropic Gaussian smoothing kernel of 8 mm full width at half maximum (FWHM). The normalized grey matter from controls and the patients with hippocampal damage were contrasted using a two sample t-test and thresholded at $p<0.001$ uncorrected and a cluster extend of 50 voxels.

Experimental design and procedure

We had the opportunity to shadow the patients with selective bilateral hippocampal damage over two days during day-time hours, and so we adapted for use a well-established method, descriptive experience sampling (DES), in which participants are asked frequently over an extended period of time to describe what was on their minds just before they were aware of being asked (Hurlburt, 1979; Hurlburt and Heavey, 2001; Hurlburt and Akhter, 2006). DES has the advantage that thought probes can extend over a long period of time and the sampling interval can be more extensive than alternative approaches in which a few thought samples are taken while participants perform low-demanding distractor tasks (Smallwood et al., 2002; Smallwood and Schooler, 2015). Furthermore, using DES, participants are encouraged to describe freely what was on their minds, rather than categorizing thoughts into pre-specified classes.

Due to the hippocampal-damaged patients' inability to remember task instructions over longer time-scales, the exact DES approach was not feasible. We therefore made a number of adaptations to the original protocol. For example, we changed the type of reminder. The reminder is an important tool as it identifies the precise moment of sampling and happens externally to the participant, meaning that the participant does not have to remember to track their own thoughts (Hurlburt and Stuart, 2014). Usually, DES participants carry a beeper and receive frequent sampling reminders while going about their everyday life (Hurlburt and Akhter, 2006). However, we adapted this sampling method to suit an extended experimental setting over two days in which patients and controls experienced the same structured days (three MRI scans, various cognitive tasks, breaks, lunches, etc). In our case, the experimenter provided the external cue for the participant. Equally important as the reminder is the exact time point of the sample. While previous studies have used a random sampling schedule

(Hurlburt, 1979; Smallwood and Schooler, 2015), our main goal was to examine the general ability to perceptually decouple and the content of spontaneous thoughts of these rare patients. We therefore tried to maximize our chances of catching perceptually decoupled thoughts. Hence, we probed 20 times over the course of two structured research days at pre-specified times in restful moments. To keep the experimental context of the sampling time points as closely matched across participants as possible, thoughts for all participants were probed in the same rooms of our Centre, around the same times of day, and in approximately the same experimental situations. In addition, in order to ascertain that all participants, especially the patients, could remember time spans long enough to report their thoughts, we asked them to describe shortly after completion two experiments unrelated to the current study. All participants were able to provide detailed accounts of those experiments.

During sampling moments, such as after obtaining consent, and at the beginning of the tea break, the experimenter would allow for a moment of quiet to evolve. That is, the experimenter would fill out some forms or naturally disengage from any conversation. When there was an appropriate time of silence, the experimenter would provide the prompt "What were you thinking about just before I asked you?". On a prepared note sheet, the participant's response was written down verbatim. In a follow-up question, the experimenter established whether the thought had been a visual image (if yes, scene or object) or a verbal thought. Then, the experimenter clarified whether that thought had concerned the past, present day or future (and if it had been past or present, how far into the past or future). The sampling procedure lasted no longer than approximately one minute. Lastly, divergent from other DES reports, we opted not to train our participants before the start of the study. While the training may have provided useful guidance in tracking one's own thoughts in a natural environment, we felt that patients might forget parts of the training and would be at a disadvantage.

However, as the experimenter was present for all samples, all follow-up questions were identical for patients and controls.

Whereas previous research has examined the frequency and content of mind-wandering episodes in healthy participants for features such as goal-orientation and emotional valence (Andrews-Hanna et al., 2013; Andrews-Hanna et al., 2014a; Christoff et al., 2016), we focused here on examining the effect of hippocampal damage on the frequency, time range, representational content and form of mind-wandering, which are key to understanding hippocampal function. In a few instances, patients and control participants reported thinking about nothing (i.e., blank thoughts) which we excluded from further analysis.

In summary, our adapted sampling protocol permitted us to leverage the naturalistic approach of the typical DES reports that sample over an extended period of time, and allowed participants to report their thoughts freely, while equating the daily activities and the sampling moments of patients and controls participants to maximize our chances of catching perceptually decoupled thoughts in an experimentally rigorous manner.

Scoring

Perceptually coupled or decoupled thoughts

An episode was considered mind-wandering when the response indicated that the mind was disengaged from the external world (perceptually decoupled; Smallwood and Schooler, 2015). For example, the thought “I see your watch” was considered perceptually coupled, whereas the thought “Time is sometimes slow and sometimes fast” was considered perceptually decoupled.

Temporal range

After each sample, we clarified directly with participants whether that thought had concerned the past, present day or future, and if past or future, how distant from the present moment. For statistical analysis, thoughts were binned into three main time categories, namely past (any thought related to yesterday and earlier), present day (including right now, earlier and later today), and future (any thought related to tomorrow and later). Of note, we further sorted participants' responses from the "now"-category, based on the observation that patients and controls reported very different types of thoughts. Hence, we classified each mind-wandering episode that was labelled by participants as concerning the present moment (i.e., now) as either an atemporal scenario or not (Jackson et al., 2013). A mind-wandering episode was considered an atemporal scenario if the participant reported a mental event that had no temporal direction. For example, a typical control participant's description was "I noticed this apparatus [EEG box] and I just imagined a picture in my mind in which that box was being used in a horror setting." By contrast, a patient reported while noticing the same EEG box "I wonder what this box with all these cables does. But I have no idea."

Representation type

Thoughts were classified as either semantic or episodic (in line with established methods; Levine et al., 2002; Andrews-Hanna et al., 2014b) and in addition, whether they contained self-referential thinking (Andrews-Hanna et al., 2014b; Andrews-Hanna et al., 2014a). A thought was classified as semantic if it contained mentalization, or general knowledge about the world or the participant. For example, a semantic, self-referential thought of a patient was: "I am self-pondering. Am I a creative person?" A thought was classified as episodic if it contained specificity of time and place. For example, an episodic, self-referential thought of a control participant was: "I am remembering a discussion I had with my friend at King's Cross concourse a few weeks ago. I can see the scene clearly in front of me." Of note, we also classified thoughts as episodic that had reference to a specific place and time, even if one or both were fictitious (time was more often fictitious). For example, an atemporal, episodic, non self-referential thought of a control was: "I'm thinking about my friend. He's travelling around giving lectures. I imagine an auditorium and see my friend speaking."

Form of thoughts

We asked participants after each sample whether the thought had been verbal or visual, and if visual, whether it had been a scene or an object. Each thought was sorted into only one of these categories. Some participants reported that some of the visual scenes also contained verbal aspects, however, they regarded the visual scene as being more dominant. Therefore, these thoughts were classified as scenes. This classification was accomplished in agreement with each participant.

Interrater reliability

In order to avoid potential rater biases, a second rater, who was blind to group membership, scored all thoughts from the patients and the control participants (except for one control dataset which was used as a training set). Interrater reliability was calculated as the direct correspondence between the two raters. That is, thoughts that were scored identically in a category were given a '1' otherwise they were given a '0'. The reliability was then established as the sum divided by the total amount of rated thoughts. Therefore a value of 0.99 indicates that in 99% of samples the raters categorized them identically. The overall agreement between raters ranged between 84 and 99% across the thought categories (i.e., atemporal: 88%, coupled/decoupled 99%, semantic: 84%, episodic: 85%, and self-referential: 87%).

Statistical analyses

Statistical significance levels of the frequency of mind-wandering, temporal range, representation type and form of thoughts were assessed using separate two-way repeated measures analysis of variance (2way-RM-ANOVA) with participant group (patients, controls) as a factor with two levels and mind-wandering characteristics as a repeated measurement factor (i.e., two levels for coupled and decoupled samples; three levels for temporal extent, representation type, and form). Main effects and interaction effects were evaluated first and a two-sided p-value of less than 0.05 was used as a threshold to reject the null hypotheses in each case. Where 2way-RM-ANOVAs yielded significant main or interaction effects, we conducted post-hoc comparisons using Sidak's multiple comparison tests, again considering p-values less than 0.05 as statistical significant. Independent pairwise comparisons between the two groups (e.g., hippocampal volumes, neuropsychological test scores) were assessed using the Student's two sample t-test. Again, a two-sided p-value of less than 0.05 was used as the threshold to reject the null hypotheses in each case. We also report the effect sizes (using Cohen's d) and, where appropriate, show the data of every participant.

Results

Frequency of mind-wandering

We first examined whether or not patients with hippocampal amnesia were able to mentally decouple from the current perceptual input (Fig. 1b, c). We found that the percentage of perceptually decoupled thoughts was greater than perceptually coupled thoughts in the patient and the control groups ($F(1,16)=292.7$, $p<0.0001$; Table 3). Notably, we found no difference between the patient and the control groups (F(1,16)=2.1, p=0.16) in the percentage of mind-wandering thoughts.

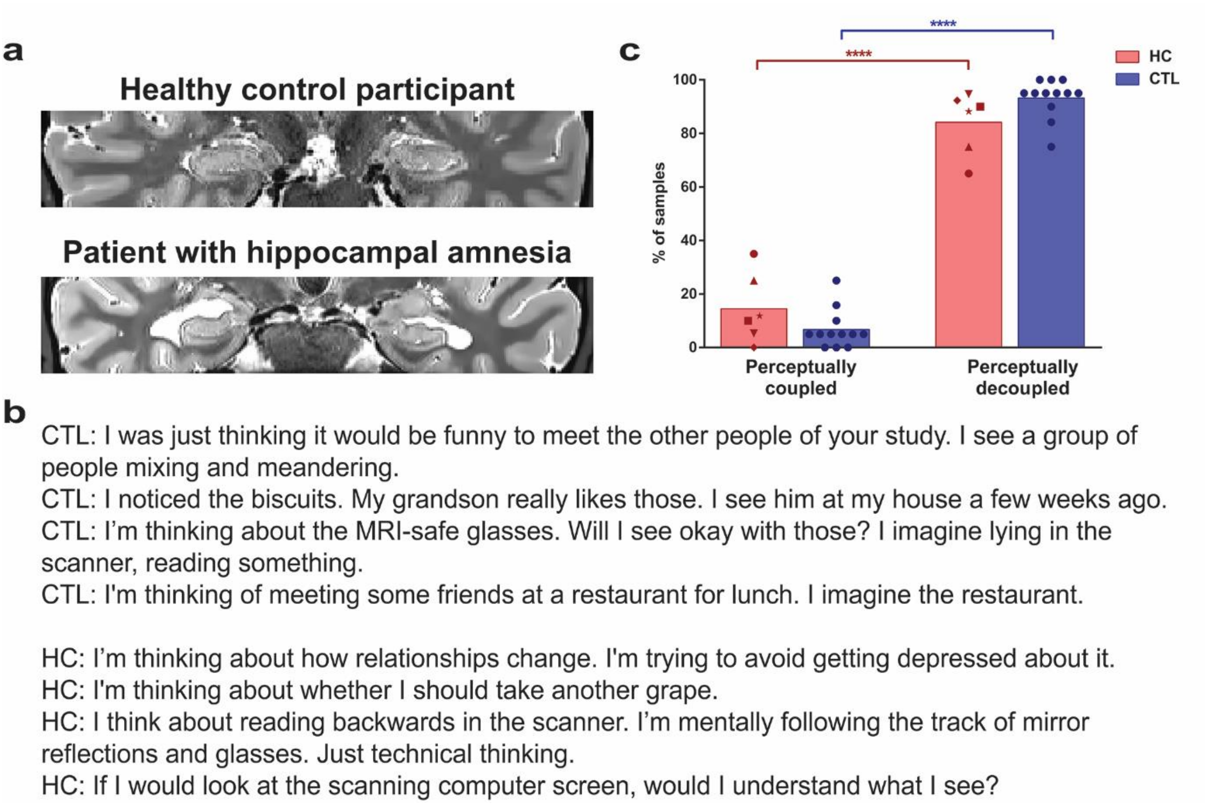

Figure 1. Hippocampal damage and the frequency of mind-wandering. **(a)** A T2-weighted structural MR image of an example patient with selective bilateral hippocampal damage and an age, gender and IQ-matched healthy control participant. Images are displayed in native space corresponding approximately to the position of y=-10 in the MNI coordinate system. **(b)** Examples of mind-wandering experiences from controls (CTL) and patients with hippocampal damage (HC). **(c)** The average percentage of perceptually coupled and decoupled spontaneous thoughts during quiet restful moments for individual patients with hippocampal damage (red symbols) and healthy control participants (blue circles); ****=p<0.0001. Both groups reported a high level of mind-wandering experiences, with no differences between patients and control participants.

Table 3. Summary of mind-wandering data

	CTL		HC		p
Frequency					
Perceptually coupled	6.7	(7.3)	14.5	(13.1)	n.s.
Perceptually decoupled	93.3	(7.3)	84.2	(11.6)	n.s.
Temporal range					
Past	28.0	(10.1)	7.5	(5.5)	****
Present	66.1	(11.1)	87.7	(8.1)	****
Future	5.8	(5.1)	4.8	(4.2)	n.s.
Atemporal scenarios	64.3	(8.7)	24.1	(8.8)	****
Representation type					
Episodic	72.6	(12.4)	24.8	(14.3)	****
Semantic	27.4	(12.4)	75.2	(14.3)	****
Self-referential	75.2	(10.1)	75.6	(8.4)	n.s.
Form of thoughts					
Scenes	63.5	(5.4)	12.3	(11.7)	****
Objects	9.8	(6.9)	9.1	(9.9)	n.s.
Words	26.8	(8.4)	78.7	(16.2)	****

For both groups, means (percentages) are displayed with standard deviations next to them in parentheses. CTL=healthy control participants; HC=hippocampal-damaged patients; p=p-value for between group posthoc t-tests following 2-way-repeated measures ANOVAs. ****=p<0.001; n.s.=not significantly different.

Temporal range of mind-wandering

Since mental time travel seems to occur frequently during mind-wandering (Smallwood and Schooler, 2015), we next examined whether patient and control groups spontaneously thought about the past, present day or future. After each thought sample, we asked participants whether the thought concerned the present day, past or future, and if the latter two, how distant was it from the present moment (Fig. 2). We observed significant main effects of time period ($F(2,32)=222.7$, $p<0.0001$; Table 3) and participant group ($F(1,16)=7.5$, $p=0.014$), and an interaction effect ($F(2,32)=16.89$, $p<0.0001$), indicating that the temporal range of mind-wandering was not balanced across the three time bins, and was significantly different between groups.

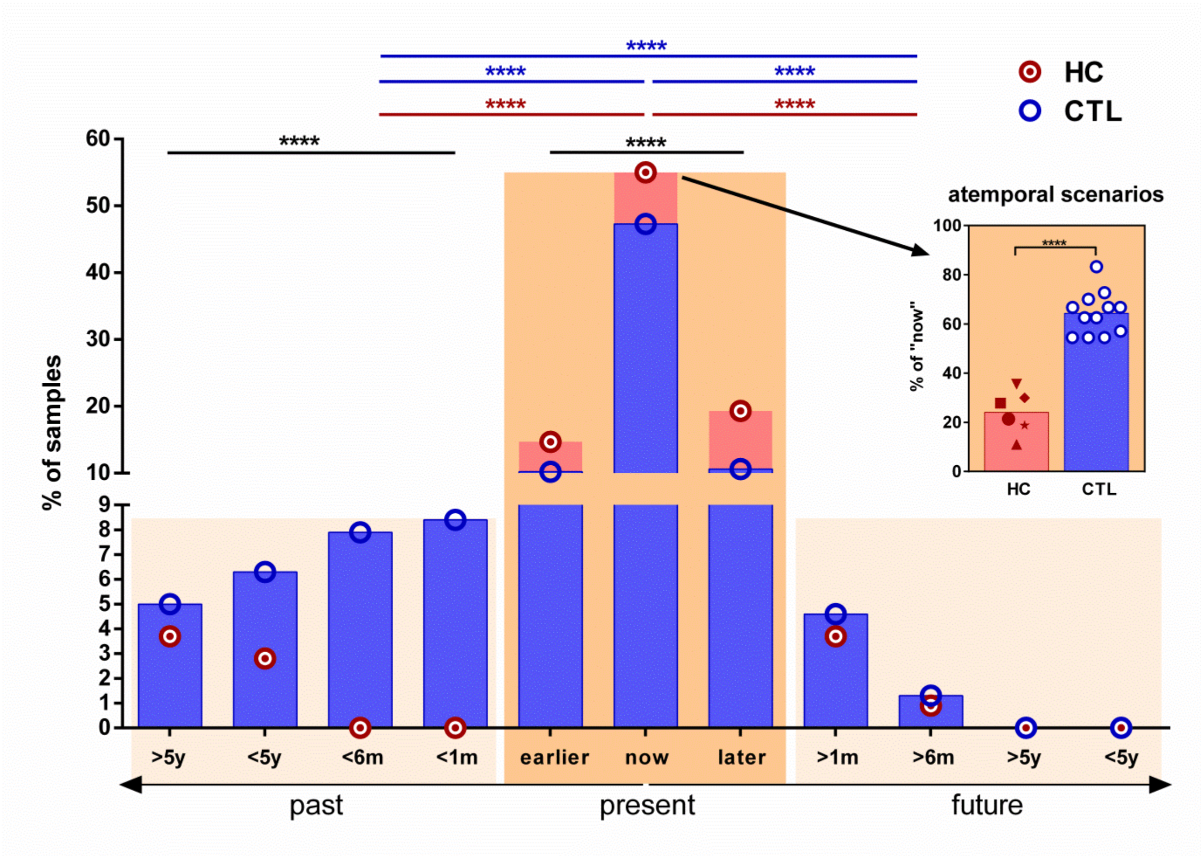

Figure 2. The temporal range of mind-wandering. Mean percentages of mind-wandering thoughts of patients with hippocampal damage (HC, red circles with a dot) and controls (CTL, blue circles) for the past, present and future. For display purposes, thoughts are classified into time bins according to today (now, earlier and later today), past months (m) and years (y) and future months and years. Of note, statistics are based on the three main categories (past, present, future) only. Between-group effects are displayed in black, within-patient effects in red and within-control effects in blue. Control participants reported more thoughts related to the past than patients. In contrast, patients reported more thoughts related to the present than controls; ****=p<0.0001. Both groups reported a large amount of thoughts related to "now". However, the content of these thoughts differed considerably. The inset shows the percentage of thoughts related to "now" during which patients (red symbols) and controls (blue circles) engaged in the imagining of atemporal scenarios; ****=p<0.0001.

Examining these results for control participants in the first instance, we found that controls spent a significant amount of their mind-wandering time thinking about the present day (including right now, earlier and later today) rather than the past ($t(32)=9.1$, $p<0.0001$, Cohen's d=3.6) or future ($t(32)=14.4$, $p<0.0001$, Cohen's d=6.9). They also spent more time thinking about the past than the future ($t(32)=5.31$, $p<0.0001$, Cohen's d=2.8). In contrast, patients thought almost exclusively about the present day, rather than the past ($t(32)=13.5$, $p<0.0001$, Cohen's d=11.6) or future ($t(32)=14.1$, $p<0.0001$, Cohen's d=12.8).

There was no difference between past and future-thinking in the patients since both categories hardly featured (t(32)=0.46, p=0.96, Cohen's d=0.6).

Directly comparing the two groups, we found that the patients thought significantly less often than controls about past events (t(48)=4.9, p<0.0001, Cohen's d=2.5). By contrast, the patients thought significantly more often about the present day than control participants (t(48)=5.2, p<0.0001, Cohen's d=2.2). There was no difference between the groups in the percentage of future-thinking, which was generally low for both groups (t(48)=0.2, p=0.99, Cohen's d=0.2).

Both groups had a significant percentage of mind-wandering episodes related to the present moment (see Fig. 2 "now"-category). However, on closer inspection, the content of these thoughts differed dramatically. We found that, in comparison to the patients, controls' present thoughts mostly involved imagining atemporal events and hypothetical scenarios that concerned a fictitious reality, which was not attached to any temporal dimension (see the inset of Fig. 2, t(16)=9.2, p<0.0001, Cohen's d=4.6).

Representation type

We next investigated what the patients mind-wandered about. We found a main effect of representation type (episodic/semantic/self; F(2,32)=17.3, p<0.0001; Fig. 3; Table 3) and an interaction effect between representation type and participant group (F(2,32)=45.7, p<0.0001).

Focusing first on the control participants, we found that they reported significantly more episodic than semantic thoughts (t(32)=7.8, p<0.0001, Cohen's d=3.6). The patients with hippocampal amnesia, on the other hand, experienced significantly more semantic than episodic thoughts (t(32)=6.2, p<0.0001, Cohen's d=3.5).

These effects were further confirmed by post-hoc analyses directly comparing the participant groups. Whereas controls reported more episodic thoughts than patients (t(48)=8.0, p<0.0001, Cohen's d=3.6), patients reported more semantic thoughts than control participants (t(48)=8.0, p<0.0001, Cohen's d=3.6). As expected, there was no significant difference in the percentage of self-referential thinking between the groups (t(48)=0.1, p>0.99, Cohen's d=0.1). Together, these results show striking differences in the representational nature of spontaneous inner experiences between control participants and hippocampal-damaged patients.

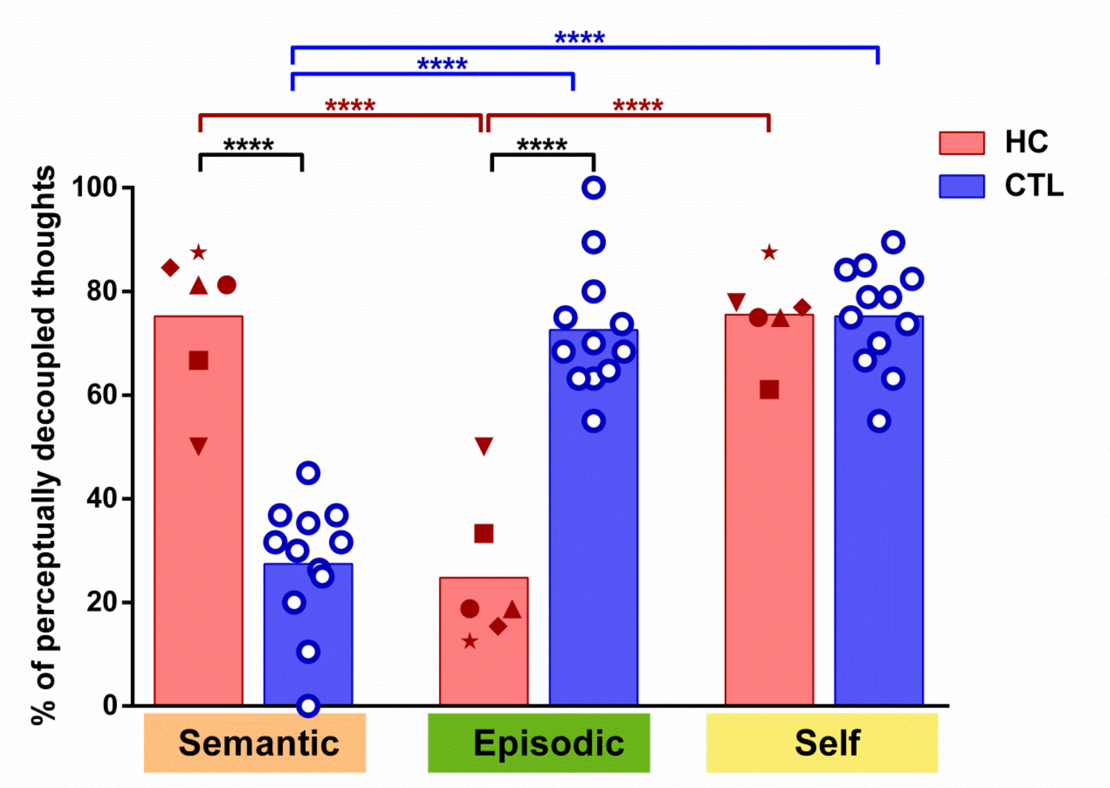

Figure 3. Semantic and episodic thinking during mind-wandering. Percentages of mind-wandering samples classified as semantic, episodic and self-referential for patients with hippocampal damage (HC, red symbols) and controls (CTL, blue circles). Of note, whereas a thought could only be classified as semantic or episodic, each thought could also be self-referential; ****=p<0.0001. The patients had predominantly semantic thoughts, whereas the thoughts of the control participants were mainly episodic.

Form of thoughts

Finally, after each sample we asked participants whether the thought had been verbal or visual, and if visual, whether it had been a scene or an object. We found a significant main effect of the form of thought ($F(2,32)=60.3$, $p<0.0001$; Table 3) and an interaction effect between the form of thought and participant group ($F(2,32)=82.9$, $p<0.0001$; Fig. 4).

Control participants reported that a striking majority of their thoughts involved visual scenes, more so than visual objects ($t(32)=11.6$, $p<0.0001$, Cohen's $d=8.6$) or verbal thoughts ($t(32)=7.9$, $p<0.0001$, Cohen's $d=5.2$), but more verbal thoughts than visual objects ($t(32)=3.7$, $p=0.003$, Cohen's $d=2.2$). This was in stark contrast to the patients, who thought almost entirely verbally. They reported more verbal thoughts than visual scenes ($t(32)=10.2$, $p<0.0001$, Cohen's $d=4.7$) and visual objects ($t(32)=10.6$, $p<0.0001$, Cohen's $d=5.2$) with no difference between visual scenes and objects ($t(32)=0.5$, $p=0.95$, Cohen's $d=0.3$).

These clear differences in the experiential form of mind-wandering were corroborated by directly comparing the participant groups. Whereas controls reported more visual scenes than patients ($t(48)=11.1$, $p<0.0001$, Cohen's $d=5.6$), patients reported more verbal thoughts than controls ($t(48)=11.2$, $p<0.0001$, Cohen's $d=4.0$), with no difference between participant groups for visual objects ($t(48)=0.2$, $p=0.99$, Cohen's $d=0.1$).

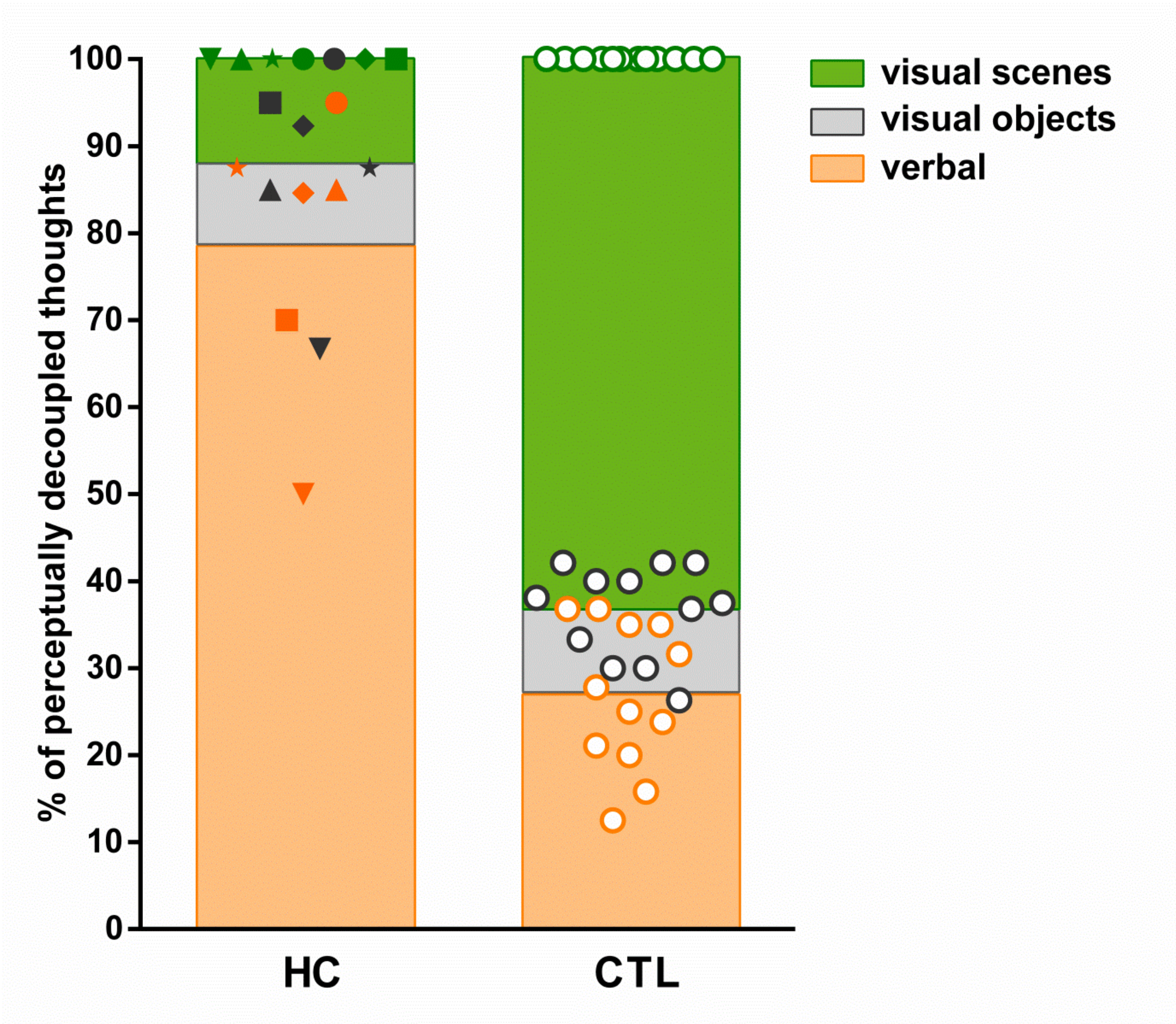

Figure 4. Cumulative percentages of visual and verbal mind-wandering thoughts. The average percentage of verbal thoughts is depicted per group (HC=hippocampal-damaged patients, CTL=controls) as an orange bar; the individual data points are illustrated with orange symbols. The average cumulative percentage of thoughts containing visual objects is depicted as a grey bar above the average percentage of the verbal thoughts. The individual data points of thoughts containing visual objects (grey symbols) are illustrated as cumulative percentages above the orange data points (i.e., the patient represented as a square symbol reported around 70% verbal and around 25% visual object thoughts). Lastly, the average cumulative percentage of thoughts containing visual scenes is depicted as a green bar on top of the grey bar (green symbols all adding up to 100%). Whereas patients with hippocampal damage reported thinking in words for the majority of samples, healthy control participants' thoughts were predominantly in the form of visual scenes.

Discussion

Mind-wandering is pervasive in humans and likely has an important role to play across cognition, influencing processes such as future planning, creative thinking and problem-solving (Baird et al., 2011; Baird et al., 2012; Andrews-Hanna et al., 2013). Here we showed that patients with hippocampal amnesia were able to perceptually decouple from the external world and experience spontaneous thoughts. Nevertheless, the small, selective lesions of their hippocampi dramatically affected the nature of their mind-wandering. Whereas healthy participants thought flexibly about the past, present and future, primarily in terms of episodic, detail-rich visual scenes, the patients mainly experienced verbally-mediated semantic thoughts anchored in the present. Previous studies have examined episodic thought processes in patients with hippocampal amnesia using explicit tasks, such as the autobiographical interview (Levine et al., 2002) or the scene construction task (Hassabis et al., 2007), that were designed to challenge the patients' ability. In contrast, our findings show that even when there is no direct cognitive demand, the thought structure of people with hippocampal amnesia is strikingly different from healthy controls.

The first point to consider is whether our results can be explained simply by a short-term memory deficit in the patients which caused them to rapidly forget their mind-wandering thoughts before they could be accurately reported. The patients' intact performance on a working memory digit span test (Table 2) suggests this was not the case. In addition, we also asked participants to describe two experiments unrelated to the current study shortly after completion, thus mirroring the timescale of reporting their mind-wandering experiences. All participants, including the patients, were able to provide detailed accounts of those experiments. Moreover, it was not that the patients were devoid of endogenously generated thoughts, but rather, what they experienced was not typical of control participants.

Previous reports have estimated that humans tend to mind-wander about 30-50% of waking time (Kane et al., 2007; Killingsworth and Gilbert, 2010). In the current study, we report percentages nearer 80-90%. However, we specifically aimed to catch restful periods and so our higher percentage of mind-wandering thoughts suggests that we were successful at probing time points when mind-wandering levels were very high.

Numerous studies have focused on delineating different aspects of inner experiences. For example, self-generated thinking typically refers to the ability to mentally decouple from the current perceptual surroundings and generate independent internal thoughts (Smallwood and Schooler, 2015), a dichotomous definition that we employed in the current study. In reality, these self-generated thoughts align on a continuum ranging from closely task-related to totally task-unrelated (Smallwood and Schooler, 2015). What was most important for our research question was whether patients were able to decouple perceptually from their immediate surroundings in a completely task-free context. We found that they were able to do so and that the frequency of their mind-wandering did not differ from that of the control group. This result is especially noteworthy, given a recent study that found reduced frequency of mind-wandering in patients with ventromedial prefrontal cortex (vmPFC) lesions (Bertossi and Ciaramelli, 2016), a brain region with dense functional and anatomical connections with the hippocampus (Andrews-Hanna et al., 2010; Catani et al., 2012; Catani et al., 2013). Whilst acknowledging the differences in the experimental setup between our study and that involving the vmPFC patients, the difference in mind-wandering frequency observed in these two studies might indicate that the vmPFC is critical for the initiation of endogenous spontaneous thought and the hippocampus for its form and content.

At first glance, our finding of group differences in the temporal extent of mind-wandering is not surprising given the difficulty patients with hippocampal amnesia are known to have with recalling recent and remote episodic memories and imagining the future (Rosenbaum et al., 2008; Kurczek et al., 2015). However, these previous results were based on active and cognitively demanding tasks. To the best of our knowledge, this is the first indication that hippocampal-damaged patients experience reduced mental time travel even in their spontaneous thoughts. Of note, we did not replicate previous reports suggesting a near future-thinking bias in the mind-wandering of healthy participants (Stawarczyk et al., 2011; Song and Wang, 2012; Bertossi and Ciaramelli, 2016). The current experimental procedure and the older age of our participants may have influenced these results (Maillet and Schacter, 2016). For example, instead of sampling during low-demanding computer tasks or in natural environments that may encourage thoughts about the near future (e.g., "What will I do after this boring task is finished?", or "Where am I going after I'm finished here?"), we sampled thoughts during a structured day of stimulating research activities. This may have provided more opportunities to think about the recently-completed cognitive tasks or MRI scans. In addition, many previous studies have not included an atemporal category of thoughts, and it has been argued that thoughts labelled as future-oriented might in some instances be more accurately characterized as atemporal (Jackson et al., 2013). Indeed, in line with our results, it has been reported that healthy older adults experience more atemporal than future-oriented mind-wandering episodes (Jackson et al., 2013).

Recently, there have been increased efforts to map the complex cognitive processes that support mind-wandering to specific brain regions. While it is has been established that the DMN is associated with mind-wandering (Buckner et al., 2008; Andrews-Hanna et al., 2014a; Smallwood and Schooler, 2015), the contributions of specific brain areas within the DMN to mind-wandering remain unclear. Our results provide novel evidence that the hippocampus plays a causal role in flexible, episodic mind-wandering that is rich in detail and mental time travel. These findings align with recent neuroimaging work that focused on a subsystem of the DMN, of which the hippocampus (and vmPFC) are nodes (Andrews-Hanna et al., 2010), and illustrated that functional and structural connectivity is stronger in individuals who report many detail-rich mental time travel experiences during mind-wandering (Karapanagiotidis et al., 2016; Smallwood et al., 2016). Our results further accord with network analyses in patients with hippocampal damage that showed altered hippocampal-neocortical connectivity patterns (Hayes et al., 2012; McCormick et al., 2014; Henson et al., 2016), that were associated with worse episodic memory capacity (McCormick et al., 2014). Of note, to the best of our knowledge, ours is the first report of a concomitant increase in spontaneous semantic thoughts associated with hippocampal damage. This may help to explain previous findings of increased connectivity between brain areas involved in semantic processing in resting state fMRI studies involving similar patients (Hayes et al., 2012; McCormick et al., 2014).

In line with previous studies, our results demonstrate that mind-wandering episodes of control participants typically comprise visual imagery (Andrews-Hanna et al., 2013). We expand on existing studies by showing that visual imagery in task-unrelated mind-wandering of healthy controls primarily consists of spatially coherent visual scenes. In striking contrast, the patients with bilateral hippocampal damage no longer visualized mental scenes, relying instead on a verbal thought structure. A scene construction deficit has been implicated in the impaired autobiographical memory and future thinking of patients with hippocampal amnesia (Hassabis and Maguire, 2007; Maguire and Mullally, 2013; Clark and Maguire, 2016). Our results strongly suggest that hippocampal-supported scene construction is also central to mind-wandering, and that without it, spontaneous thought is impoverished and lacks flexibility and creativity.

Together, our findings show that selective bilateral lesions to the hippocampus impair mind-wandering in specific ways, thus informing the nature of mind-wandering and how it is realized at the neural level. That individuals with hippocampal damage experience mind-wandering but very little detail-rich mental imagery or time travel are important new insights which indicate the hippocampus is not necessary for the instigation of spontaneous thought per se. Instead, it seems to be crucial for processing the form and content of mind-wandering. Our results also speak to the functions of the hippocampus. By showing it plays a causal role in a phenomenon as ubiquitous as mind-wandering, this exposes the impact of the hippocampus beyond its traditionally-perceived role in memory, placing it at the center of our everyday mental experiences.

References

Andrews-Hanna JR, Smallwood J, Spreng RN (2014a) The default network and self-generated thought: component processes, dynamic control, and clinical relevance. Ann N Y Acad Sci 1316:29-52.

Andrews-Hanna JR, Saxe R, Yarkoni T (2014b) Contributions of episodic retrieval and mentalizing to autobiographical thought: Evidence from functional neuroimaging, resting-state connectivity, and fMRI meta-analyses. Neuroimage 91:324-335.

Andrews-Hanna JR, Reidler JS, Sepulcre J, Poulin R, Buckner RL (2010) Functional-anatomic fractionation of the brain's default network. Neuron 65:550-562.

Andrews-Hanna JR, Kaiser RH, Turner AE, Reineberg AE, Godinez D, Dimidjian S, Banich MT (2013) A penny for your thoughts: dimensions of self-generated thought content and relationships with individual differences in emotional wellbeing. Front Psychol 4:900.

Ashburner J (2007) A fast diffeomorphic image registration algorithm. Neuroimage 38:95-113.

Ashburner J (2009) Computational anatomy with the SPM software. Magn Reson Imaging 27:1163-1174.

Ashburner J, Friston KJ (2005) Unified segmentation. Neuroimage 26:839-851.

Baird B, Smallwood J, Schooler JW (2011) Back to the future: autobiographical planning and the functionality of mind-wandering. Conscious Cogn 20:1604-1611.

Baird B, Smallwood J, Mrazek MD, Kam JW, Franklin MS, Schooler JW (2012) Inspired by distraction: mind wandering facilitates creative incubation. Psychol Sci 23:1117-1122.

Bertossi E, Ciaramelli E (2016) Ventromedial prefrontal damage reduces mind-wandering and biases its temporal focus. Social Cognitive and Affective Neurosci 11:1783-1791.

Buckner RL, Andrews-Hanna JR, Schacter DL (2008) The brain's default network: anatomy, function, and relevance to disease. Ann N Y Acad Sci 1124:1-38.

Burgess P, Shallice T (1997) The Hayling and Brixton Tests. Test manual. Bury St Edmunds, UK: Thames Valley Test Company.

Callaghan MF, Josephs O, Herbst M, Zaitsev M, Todd N, Weiskopf N (2015) An evaluation of prospective motion correction (PMC) for high resolution quantitative MRI. Front Neurosci 9:97.

Catani M, Dell'acqua F, Thiebaut de Schotten M (2013) A revised limbic system model for memory, emotion and behaviour. Neurosci Biobehav Rev 37:1724-1737.

Catani M, Dell'acqua F, Vergani F, Malik F, Hodge H, Roy P, Valabregue R, Thiebaut de Schotten M (2012) Short frontal lobe connections of the human brain. Cortex 48:273-291.

Christoff K, Irving ZC, Fox KC, Spreng RN, Andrews-Hanna JR (2016) Mind-wandering as spontaneous thought: a dynamic framework. Nat Rev Neurosci.

Clark IA, Maguire EA (2016) Remembering preservation in hippocampal amnesia. Annu Rev Psychol 67:51-82.

Coupe P, Manjon JV, Gedamu E, Arnold D, Robles M, Collins DL (2010) Robust Rician noise estimation for MR images. Med Image Anal 14:483-493.

Dalmau J, Rosenfeld MR (2014) Autoimmune encephalitis update. Neuro Oncol 16:771-778.

Delis DC, Kaplan E, Kramer JH (2001) Delis Kaplan Executive Function System (D-KEFS). San Antonio, TX: The Psychological Corporation.

Ehlers A, Hackmann A, Michael T (2004) Intrusive re-experiencing in post-traumatic stress disorder: phenomenology, theory, and therapy. Memory 12:403-415.

Finke C, Pruss H, Heine J, Reuter S, Kopp UA, Wegner F, Then Bergh F, Koch S, Jansen O, Munte T, Deuschl G, Ruprecht K, Stocker W, Wandinger KP, Paul F, Bartsch T (2017) Evaluation of cognitive deficits and structural hippocampal damage in encephalitis with leucine-rich, glioma-inactivated 1 antibodies. JAMA Neurol 74:50-59.

Fox KC, Andrews-Hanna JR, Christoff K (2016) The neurobiology of self-generated thought from cells to systems: Integrating evidence from lesion studies, human intracranial electrophysiology, neurochemistry, and neuroendocrinology. Neuroscience 335:134-150.

Gabrovska V, Laws K, McKenna P (1996) Visual form perception in schizophrenia: further evidence for a disorder of semantic memory. Eur Psychiatry 11:278.

Hassabis D, Maguire EA (2007) Deconstructing episodic memory with construction. Trends Cogn Sci 11:299-306.

Hassabis D, Kumaran D, Vann SD, Maguire EA (2007) Patients with hippocampal amnesia cannot imagine new experiences. Proc Natl Acad Sci USA 104:1726-1731.

Hayes SM, Salat DH, Verfaellie M (2012) Default network connectivity in medial temporal lobe amnesia. The Journal of neuroscience : the official journal of the Society for Neuroscience 32:14622-14629.

Helms G, Dechent P (2009) Increased SNR and reduced distortions by averaging multiple gradient echo signals in 3D FLASH imaging of the human brain at 3T. J Magn Reson Imaging 29:198-204.

Henson RN, Greve A, Cooper E, Gregori M, Simons JS, Geerligs L, Erzinclioglu S, Kapur N, Browne G (2016) The effects of hippocampal lesions on MRI measures of structural and functional connectivity. Hippocampus 26:1447-1463.

Hurlburt RT (1979) Random Sampling of Cognitions and Behavior J Res Pers 13:103-111.

Hurlburt RT, Heavey CL (2001) Telling what we know: describing inner experience. Trends Cogn Sci 5:400-403.

Hurlburt RT, Akhter SA (2006) The Descriptive Experience Sampling method. Phen Cogn Sci 5:271-301.

Hurlburt RT, Stuart SAJ (2014) Grounding the science of inner experience in the apprehension of phenomena. A review of consciousness and the self: new essays. American Journal of Psychology 127:253-260.

Hurley AC, Al-Radaideh A, Bai L, Aickelin U, Coxon R, Glover P, Gowland PA (2010) Tailored RF pulse for magnetization inversion at ultrahigh field. Magn Reson Med 63:51-58.

Jackson JD, Weinstein Y, Balota DA (2013) Can mind-wandering be timeless? Atemporal focus and aging in mind-wandering paradigms. Frontiers in psychology 4:742.

Kane MJ, Brown LH, McVay JC, Silvia PJ, I. M-G, Kwapil TR (2007) For whom the mind wanders, and when. Psychol Sci 18:614-621.

Karapanagiotidis T, Bernhardt BC, Jefferies E, Smallwood J (2016) Tracking thoughts: Exploring the neural architecture of mental time travel during mind-wandering. Neuroimage 147:272-281.

Killingsworth MA, Gilbert DT (2010) A wandering mind is an unhappy mind. Science 330:932.

Kurczek J, Wechsler E, Ahuja S, Jensen U, Cohen NJ, Tranel D, Duff M (2015) Differential contributions of hippocampus and medial prefrontal cortex to self-projection and self-referential processing. Neuropsychologia 73:116-126.

Levine B, Svoboda E, Hay JF, Winocur G, Moscovitch M (2002) Aging and autobiographical memory: dissociating episodic from semantic retrieval. Psychol Aging 17:677-689.

Maguire EA, Mullally SL (2013) The hippocampus: a manifesto for change. Journal of experimental psychology General 142:1180-1189.

Maillet D, Schacter DL (2016) From mind wandering to involuntary retrieval: Age-related differences in spontaneous cognitive processes. Neuropsychologia 80:142-156.

McCormick C, Protzner AB, Barnett AJ, Cohn M, Valiante TA, McAndrews MP (2014) Linking DMN connectivity to episodic memory capacity: What can we learn from patients with medial temporal lobe damage? NeuroImage Clinical 5:188-196.

McKenna P, Warrington EK (1980) Testing for nominal dysphasia. J Neurol Neurosurg Psychiatry 43:781-788.

Miller TD, Chong TTJ, Aimola Davies AM, Ng TWC, Johnson MR, Irani SR, Vincent A, Husain M, Jacob S, Maddison P, Kennard C, Gowland PA, Rosenthal CR (2017) Focal CA3 hippocampal subfield atrophy following LGI1 VGKC-complex antibody limbic encephalitis. Brain.

Mougin O, Abdel-Fahim R, Dineen R, Pitiot A, Evangelou N, Gowland P (2015) Imaging gray matter with concomitant null point imaging from the phase sensitive inversion recovery sequence. Magn Reson Med 76:1512-1516.

Mugler JP, 3rd, Bao S, Mulkern RV, Guttmann CR, Robertson RL, Jolesz FA, Brookeman JR (2000) Optimized single-slab three-dimensional spin-echo MR imaging of the brain. Radiology 216:891-899.

Osterrieth PA (1944) The test of copying a complex figure: A contribution to the study of perception and memory. Arch Psychol 30:286-356.

Rosenbaum RS, Moscovitch M, Foster JK, Schnyer DM, Gao F, Kovacevic N, Verfaellie M, Black SE, Levine B (2008) Patterns of autobiographical memory loss in medial-temporal lobe amnesic patients. J Cogn Neurosci 20:1490-1506.

Smallwood J, Schooler JW (2015) The science of mind wandering: empirically navigating the stream of consciousness. Annu Rev Psychol 66:487-518.

Smallwood J, Obonsawin M, Reid H (2002) The effects of block duration and task demands on the experience of task unrelated thought. Imagin Cogn Pers 22:13-31.

Smallwood J, Karapanagiotidis T, Ruby F, Medea B, de Caso I, Konishi M, Wang HT, Hallam G, Margulies DS, Jefferies E (2016) Representing representation: integration between the temporal lobe and the posterior cingulate influences the content and form of spontaneous thought. PLoS One 11:e0152272.

Song X, Wang X (2012) Mind wandering in Chinese daily lives - An experience sampling study. PLoS One 7:1-9.

Stawarczyk D, Majerus S, Maj M, Van der Linden M, D'Argembeau A (2011) Mind-wandering: phenomenology and function as assessed with a novel experience sampling method. Acta Psychol (Amst) 136:370-381.

Tulving E (1985) Memory and consciousness. Can J Exp Psychol 26:1-12.

Tulving E (2002) Episodic memory: from mind to brain. Annu Rev Psychol 53:1-25.

Wagner J, Weber B, Elger CE (2015) Early and chronic gray matter volume changes in limbic encephalitis revealed by voxel-based morphometry. Epilepsia 56:754-761.

Warrington EK (1984) Recogniton Memory Test: Manual. Berkshire, UK.: NFER-Nelson.

Warrington EK (2010) The Graded Naming Test: A Restandardisation. Neuropsychol Rehab 7:143-146.

Warrington EK, James M (1991) A new test of object decision: 2D silhouettes featuring a minimal view. Cortex 27:370-383.

Wechsler D (1997) Wechsler Memory Scales - Third Edition. San Antonio, TX: The Psychological Corporation.

Wechsler D (1999) Wechsler Abbreviated Scale of Intelligence. New York, NY: The Psychological Corporation: Harcourt Brace & Company.

Yushkevich PA, Piven J, Hazlett HC, Smith RG, Ho S, Gee JC, Gerig G (2006) User-guided 3D active contour segmentation of anatomical structures: significantly improved efficiency and reliability. Neuroimage 31:1116-1128.

Zigmond AS, Snaith RP (1983) The hospital anxiety and depression scale. Acta Psychiatrica Scand 67:361-370.