The neural basis of effective memory therapy in a patient with limbic encephalitis

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ABSTRACT
We describe an fMRI study in which a post-encephalitic woman with amnesia, 'Mrs B', used a wearable camera which takes photographs passively, without user intervention, to record and review recent autobiographical events. 'SenseCam' generates hundreds of images which can subsequently be reviewed quickly or one-by-one. Memory for a significant event was improved substantially when tested after 4.5 weeks, if Mrs B viewed SenseCam images of the event every two days for three weeks. In contrast, after only 3.5 weeks, her memory was at chance levels for a similarly significant event which was reviewed equally often, but using a written diary. During the fMRI scan, Mrs B viewed images of these two events, plus images of an unrehearsed event and images from a novel 'control' event that she had never experienced. There was no difference in behavioural responses or in activation when the unrehearsed and novel conditions were compared. Relative to the written-rehearsed condition, successful recognition of the images in the SenseCam-rehearsed condition was associated with activation of frontal and posterior cortical regions associated with normal episodic memory. We conclude that SenseCam images may provide powerful cues that trigger the recall and consolidation of stored but inaccessible memories.

INTRODUCTION
Memory problems after limbic encephalitis are common [1]. Patients often have severe deficits in the learning and retention of new information and in remembering past events. Recently a case has been described of a woman with amnesia following limbic encephalitis whose memory for recent events dramatically improved through the use of a wearable camera, which enabled her to systematically review past autobiographical events [2]. However, the neural basis of this memory improvement remains unknown. We report the results of an fMRI study in which the same procedure was used to monitor memory improvements in the same woman.

CASE REPORT
Mrs B is a 66-year-old, right-handed librarian. In March 2002 she was diagnosed with limbic encephalitis on the basis of clinical syndrome, MRI and examination of cerebrospinal fluid. Anti-voltage gated potassium channel antibodies were negative in serum and CSF. An MRI scan in 2005 showed a mild degree of volume loss in the hippocampi but that the signal change present acutely had resolved. Severe cognitive deficits were apparent on neuropsychological testing one and three years later. She exhibited marked anterograde memory impairment and mild to moderate retrograde memory impairment. Other cognitive functions were intact (see Table 1) [2]. *See supplementary clinical details.*

Table 1: Neuropsychological test results for Mrs B (April 2003 to March 2005)

Test	Raw score	Scaled score or percentile (where appropriate)	Comments
Estimate of premorbid cognitive functioning			
National Adult Reading Test	13 errors	Predicted FSIQ = 115	Above average estimated premorbid cognitive functioning
Memory			
Doors and People Memory Test	All tests	1st–5th percentile	
Autobiographical Memory Interview : All tests			
Childhood Personal Semantic	18/21		Acceptable range
Childhood Autobiographical Incidents	2/9		Definitely abnormal
Early Adult Life Personal Semantic	15/21		Probably abnormal
Early Adult Life Autobiographical Incidents	3/9		Definitely abnormal
Recent Life Personal Semantic	15/21		Definitely abnormal
Recent Life Autobiographical Incidents	3/9		Definitely abnormal
Language			
Pyramids and Palm Trees	51/52		Within normal limits
Graded Naming Test	22/30	75th percentile	Within normal limits
Attention			
TEA: Lottery and Map Search			Within normal limits
WAIS-III Digit Span	22	SS =14	Within normal limits
Executive Function			
Hayling	15	SS=5	Moderate average
Brixton	13 errors	SS=7	High Average
Behavioural Assessment of the Dysexecutive Syndrome: All tests			Within normal limits
Visuo-Perceptual Functioning			
Visual Object Space Perception Battery: All tests	Pass		Within normal limits
Benton Line Orientation	27/30		Within normal limits
AMIPB Complex Figure Copy	64	90th percentile	Within normal limits

In 2006, her memory for recent events remained severely impaired [2]. However, intervention in the form of a camera, known as 'SenseCam' (Microsoft Research, Cambridge) led to a dramatic improvement in her memory for reviewed events [2]. Mrs B had an episodic recollection of the events and described occurrences, thoughts and feelings not captured by the images. A control condition using a written diary did not cue recall to the same extent and, without ongoing rehearsal, the events were quickly forgotten. However, the study gave no insight into the neural basis of her improved autobiographical memory.

METHOD

SenseCam

SenseCam is a wearable camera which passively takes photographs approximately every thirty seconds and in response to various sensors such as light and movement [3]. Over the course of a day, hundreds of images are generated which can be uploaded onto a computer via USB and played back in quick succession using a simple interface. The effect is rather like watching a movie of the day's events. In the study by Berry et al. (2007) [2] Mrs B wore the camera during significant and memorable events (e.g. a trip to London or the theatre – i.e. not the mundane or routine) and subsequently reviewed the images approximately every two days for two weeks. The images cued her recall for the events, and after the initial rehearsal period, she retained memories for the events months later, without the need to re-review the images.

Stimulus Preparation

In 2007, Mrs B underwent fMRI under four conditions. In preparation for the first three conditions, SenseCam images were collected from three separate two-day trips made by Mrs B during the previous six weeks. Specifically, Mr and Mrs B went on a significant, memorable trip, staying in a hotel overnight in a town they had not visited previously or for many years. Mrs B wore SenseCam throughout. In preparation for condition 1 (henceforth referred to as 'Not Reviewed') Mr and Mrs B went away 6.5 weeks prior to the fMRI scan, and afterwards they did not view the images or talk about the trip. For condition 2 ('SenseCam'), Mr and Mrs B went away on a trip 4.5 weeks before the scan, and afterwards Mr and Mrs B viewed the SenseCam images approximately every two days for three weeks until one week prior to the scan. For condition 3 ('Written') Mr and Mrs B went on a trip 3.5 weeks prior to the scan and Mr B recorded details of the event using a written diary. Mr and Mrs B viewed and talked through the written diary every two days for three weeks, up until the scan took place. In condition 4 ('Novel'), one of the authors (AMO) wore SenseCam to collect images of an objectively comparable trip.

Procedure

Whilst in the fMRI scanner, Mrs B viewed a series of 150 SenseCam images. She indicated, using a button box, whether or not she definitely recognised the viewed picture (henceforth referred to as 'known'), felt that it was familiar but did not have explicit recall or recognition of the event ('familiar') or did not recognise the picture ('not known').

See supplementary methods

RESULTS

Behavioural Data

When the Novel stimuli were compared with the Not Reviewed stimuli, there were no significant differences. When Sensecam images were compared with Written images, significant differences were found (chi-square(1)=23.26, p<0.001). Specifically, there was a larger total proportion of images that were rated as known or familiar in the SenseCam condition than in the Written condition. Thus the behavioural efficacy of SenseCam [2] can be reproduced even in the scanning environment (see Figure 1a).

Imaging Data

In the first comparison, Novel and the Not Reviewed conditions were compared directly. No significance differences were observed using a conservative threshold of p<0.05 false discovery rate corrected (FDR) for the whole brain mass.

Next, brain activity during the two reviewed conditions (SenseCam vs. Written) was compared**.** Significant differences were observed across a network of brain including the left ventrolateral prefrontal cortex (-18, 10, -18; -38, 40, -14), the right frontal pole (20, 64, 28), the posterior temporal lobe bilaterally (Left inferior temporal gyrus -44, -62, -10; Right inferior temporal gyrus 52, -70, -6; Right middle temporal gyrus 56, -62, -2), bilateral parietal cortex (Left -64, -34, 24; Right 56, -52, 40), bilateral visual association cortex (Left inferior occipital gyrus -42 -68 -14; Right inferior occipital gyrus 56, -66, -10) and the left fusiform gyrus (-40, -56, -14) *(see supplementary figure S1).*

Performance differences confound the activation differences, making interpretation of the fMRI ambiguous. To address this, only the remembered stimuli ('known' plus 'familiar') from the two conditions were compared. Importantly, the proportion of 'known' to 'familiar' stimuli within each condition was similar. Because the power to detect significant differences was lower given the 33% reduction in the number of responses for this analysis, a liberal p<0.005 uncorrected threshold was used. Consequently, a very similar pattern of differences was observed to the original SenseCam vs. Written comparison, suggesting that even when the behavioural responses are the same between conditions, activation differences remain (see Figure 1b).

See supplementary results.

DISCUSSION

There were no significant differences in the patient's behavioural or fMRI responses to Novel images and images of personally experienced events she had not reviewed. She did not recognise the images in either condition. Her amnesic syndrome remains severe, confirming the findings of our previous study [2].

When the SenseCam and Written conditions were compared, there were significant behavioural and fMRI differences. She recognised, or was familiar with, more of the images in the SenseCam than in the Written condition, supporting previous results [2]. As the SenseCam condition occurred one week before the Written condition, it cannot be argued that better recognition resulted because the event was more recent. When Mrs B's BOLD response to images in the SenseCam and Written conditions were compared, increases in activation were observed in a cortical network, including the left ventrolateral prefrontal cortex, frontal pole (area 10), posterior temporal cortex, parietal cortex, visual association cortex bilaterally and fusiform gyrus. These differences remained when only the remembered stimuli

(known plus familiar) from the two conditions were compared, demonstrating that even when the behavioural responses were formally matched, the activity associated with the recollection in the two conditions was different.

Importantly, we cannot be certain that the neural activity associated with viewing the images in the SenseCam condition reflected memory for the event itself, rather than memory for the images themselves or memory of reviewing those images. These possibilities can only be discounted by additional control conditions which should be considered in future studies. However, Mrs B maintains that the images effect a natural recollection, suggesting that SenseCam images provide powerful cues that allow access to stored but unattainable memories.

The study of autobiographical memory processes using functional imaging techniques poses challenges in study design and interpretation (see 4, for a review). However, our results concur with previous evidence linking autobiographical memory to a network of prefrontal regions involved in effortful processing and posterior regions where such memories are stored [4-11]. The frontal regions activated in our study have been associated with self-referential processing, memory retrieval, 'feelings of rightness' [5, 8-10] and source memory (area 10) which, arguably, is a central feature of autobiographical retrieval [12].

The importance of the hippocampus for long-term episodic memory formation is well documented [13-14]. However in our patient, the hippocampal system was affected acutely and we observed no medial temporal lobe activation. And yet, she appears to have significant memory for the events reviewed using SenseCam. We hypothesise that SenseCam may improve performance by providing a bottom-up replacement for the medial temporal lobes. SenseCam images may provide such a powerful cue that reviewing them is sufficient to reinforce consolidation of the episode into a retrievable long term memory store. By contrast, a written diary does not provide powerful enough cues to overcome the hippocampal deficit.

CONCLUSION

Using SenseCam provides subjective and objective improvements in autobiographical memory for reviewed events, even when a post-encephalitic amnesic syndrome is severe. This is associated with activation of frontal and posterior cortical regions but not the hippocampus. A larger group study should be undertaken before strong conclusions about the benefits of this intervention and its role in autobiographical memory are drawn.

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FIGURE LEGEND
Figure 1(a) Percentage of images rated as 'known', 'familiar' and 'not known'. (b) Brain activity differences between SenseCam and Written conditions.

References

1 Hokkanen L & Launes J. Neuropsychological sequelae of acute-onset sporadic viral encephalitis. *Neuropsychol Rehabil* 2007;**17,**4/5:450-477.

2 Berry E, Kapur N, Williams L, Hodges S, Watson P, Smyth, G, Srinivasan, J, Smith R, Wilson B & Wood K. The use of a wearable camera, SenseCam, as a pictorial diary to improve autobiographical memory in a patient with limbic encephalitis. *Neuropsychol Rehabil* 2007;**17:**4/5: 582-681.

3 Hodges S, Williams L, Berry E, Izadi S, Srinivasan J, Butler A, Smyth G, Kapur N & Wood K. SenseCam: a Retrospective Memory Aid. In: Dourish P, Friday A, eds. UbiComp 2008: Ubiquitous Computing. Heidelberg: Springer-Verlag 2008;**4206:**177-193.

4 Cabeza R, & St. Jacques, P. L. Functional neuroimaging of autobiographical memory. *Trends in Cognitive Sciences* 2007;**11:**219-227.

5 Conway M.A. Memory and the Self. *J Mem Lang* 2005;**53:**4:594-628.

6 Conway M.A & Pleydell-Pearce C.W. The construction of autobiographical memories in the self memory system. *Psychol Rev* 2000;**107**:261-288.

7 Botzung A, Denkova E, Ciuciu P, Scheiber C, & Manning L. The neural bases of the constructive nature of autobiographical memories studied with a self-paced fMRI design. *Memory* 2008;**16:**4:351-363.

8 Burianova H. & Grady C.L. Common and unique neural activations in autobiographical, episodic, and semantic retrieval. *J Cogn Neurosci* 2007;**19**:9:1520-34.

9 Levine B, Turner G.R, Tisserand D, Hevenor S.J, Graham S.J & McIntosh A.R. The functional neuroanatomy of episodic and semantic autobiographical remembering: a prospective functional MRI study. *J Cogn Neurosci* 2004;**16:**9:1633-1646.

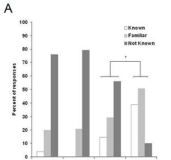
10 Svoboda E, McKinnon M.C, & Levine B. The functional neuroanatomy of autobiographical memory: a meta-analysis. *Neuropsychologia* 2006;**44:**12:2189-2208.

11 Vandekerckhove M.M, Markowitsch H.J, Mertens M, Woermann, F.G. Bi-hemispheric engagement in the retrieval of autobiographical episodes. *Behav Neurol* 2005;**16:**4:203-210.

12 Ramnani N & Owen A.M. Anterior Prefrontal Cortex: insights into function from anatomy and neuroimaging. *Nature Reviews Neuroscience* 2004;**5:**3:184-194.

13 Squire L.R. Memory and the hippocampus: A synthesis from findings with rats, monkeys and humans. *Psychological Review* 1992;**99:**2:195-231.

14 Nadel L, Samsonovich A, Ryan L & Moscovitch M. Multiple trace theory of human memory: computational, neuroimaging, and neuropsychological results. *Hippocampus* 2000;**10:**4:352-368.


A
B
Known
Familiar
Not Known
Percent Responses
100
90
80
70
60
50
40
30
20
10
0
*
novel
not reviewed
written
sensesim

Supplementary Online Material

CLINICAL DETAILS

Acute Magnetic resonance imaging with T2 weighted sequences revealed high signal intensity bilaterally in the temporal lobe, including amygdala and hippocampus, and left parieto-occipital cortex affecting predominantly grey matter and with slight mass effect. There was no post-gadolinium enhancement on T1 weighted images. Repeat T2-weighted imaging in April 2005 showed resolution of the acute signal changes.

METHOD DETAILS

Stimulus Preparation

The images that were selected for the scanning paradigm were chosen to represent the main events of the trip. To illustrate, on one trip Mr and Mrs B had been to the theatre together and subsequently three 'theatre' images were selected; one of the outside of the theatre, one of the foyer and one of the auditorium. Pictures that were blurred, mundane or repeats (e.g. a long car journey) were deliberately not chosen.

Procedure

Three icons at the bottom of the screen displayed which button corresponded to which response ('Known', 'Familiar' and 'Not Known') and responses were made using the first three fingers of the right hand. Images were displayed on the screen for 4500 ms with a 1000 ms inter-stimulus-interval. In total, the patient viewed 25 Novel, 25 Not Reviewed, 50 Written and 50 SenseCam images. Images were randomly interspersed across a single session of fMRI acquisition that lasted approximately 15 minutes.

Scanning acquisition

Scanning was carried out at the MRC Cognition and Brain Sciences Unit, Cambridge using a 3 Tesla Siemens Tim Trio. 32 * 3mm slices (1mm inter-slice gap, descending slice order) were acquired every two seconds for each image (in-plane resolution 3 x 3 mm). 450 T2-weighted echo-planar images sensitive to the BOLD contrast were acquired, with the first 10 discarded to avoid T1 equilibrium effects. The experiment was programmed in Visual Basic 6 and the display projected onto a screen, visible from the scanner via a mirror, with stimuli subtending a visual angle of approximately 6.5 degrees.

Images were pre-processed and analysed using the Statistical Parametric Mapping 5 software (SPM5, Wellcome Department of Cognitive Neurology, London). Images were slice time corrected, reoriented to correct for subject motion, spatially normalised to the standard Montreal Neurological Institute template, smoothed with an 8mm full-width at half-maximum Gaussian kernel.

Event modelling

Fixed effects analysis was carried out using a general linear model in SPM5 in order to reveal cortical regions showing a significantly higher BOLD signal when viewing stimuli from one or other of the experimental categories. Regressors were formed by convolving the onsets and durations for the presentation of the four categories of picture - Novel, Not Reviewed, Written and SenseCam - with the canonical haemodynamic response function. An additional six regressors were included representing the movements parameters (translations and rotations in the x, y and z planes). The model used a high-pass filter with cut-off period 180s. Statistical parametric maps were generated for the following contrasts: (1) Not Reviewed images minus Novel images and (2) SenseCam images minus Written images. In the first case, this contrast was chosen in order to establish which, if any, neural regions responded to images from an event that had actually been experienced, but not rehearsed (Not Reviewed) when compared to images from an event that had not been experienced

at all (Novel). In this sense, it provides a measure of the patient's baseline memory performance in the absence of any rehearsal (either using Sensecam or a Written Diary). The second contrast (Sensecam minus Written) provides the key measure of the patient's responses to Sensecam rehearsed images, when compared with another set of images of an event that had been rehearsed using an alternative method.

RESULTS DETAILS

Not Reviewed vs. Novel Conditions

No significance differences were observed using a conservative threshold of $p<0.05$ false discovery rate corrected (FDR) for the whole brain mass. However, it is important to note that with single-case fMRI studies, the power to detect significant differences is low compared to group studies. Therefore, in order to explore further whether there were any sub-threshold differences between these two conditions the statistical threshold was dropped to $p=0.005$ uncorrected. Only one (non-significant) cluster of activation was observed in the temporoparietal junction, BA 22 (X=64 Y=-52 Z=18).

SenseCam vs. Written Conditions

SenseCam images were associated with significantly greater cortical activity in a distributed network including regions in dorsal and ventral streams. Given the tightly matched stimuli (images of equivalent two-day trips from a similar period) it seems likely that activation in these regions contributes to the observed improvement in performance during the Sensecam condition relative to the Written condition. However, given the marked behavioural difference between the two conditions, it is also possible that performance differences confound the activation differences. That is to say that the observed activity differences may be the *result* of the greater number of not known stimuli in the Written condition (56%) compared with the SenseCam condition (10%), rather than the *cause* of this difference. To address this potential confound, only the remembered stimuli ('known' plus 'familiar') from the two conditions were compared directly. Importantly, the proportion of 'known' to 'familiar' stimuli within each condition was similar (i.e. the patient selected 'familiar' more often than she selected 'known' in both conditions). Because the power to detect significant differences was lower given the number of responses, the data were explored using a liberal $p<0.005$ uncorrected threshold. At this threshold, a similar pattern of differences was observed between the two conditions, indicating an increased BOLD response in the left ventrolateral prefrontal cortex (X=-34 Y=42 Z=-14), right DLPFC (X=44 Y=48 Z=32), right frontal pole bilaterally (Left X=-24 Y=56 Z=36; Right X=20 Y=64 Z=28), the posterior temporal lobe bilaterally (Left middle temporal gyrus X=-58 Y=-70 Z=6; Right middle temporal gyrus X=54 Y=-62 Z=-4), bilateral parietal cortex (Left X=68 Y=-40 Z=22; Right X=-66 Y=-34 Z=22) and bilateral higher visual areas (Left X=-32 Y=-96 Z=4; Right X=26 Y=-94 Z=-2) with additional activation in bilateral superior temporal cortex (Left X=-58 Y=-44 Z =4; Right X=62 Y=-50 Z=10) and the cuneus (Left X=-12 Y=-86 Z=12; Right X=22 Y=-98 Z=8) and precuneus (X=26 Y=-82 Z=46) (see Figure 3).