Functional magnetic resonance imaging investigation of allocentric spatial memory using virtual reality in patients with anoxic hippocampal damage

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ABSTRACT

The involvement of the hippocampal formation in spatial memory was explored in two single case studies in which anoxic brain damage had produced selective bilateral damage to this structure. To test spatial memory a virtual reality Arena task was designed, consisting of a circular space surrounded by pattern rendered walls. The participants had to navigate within the arena using a joystick to signal motion. In an encoding phase they had to move towards a pole, situated within the arena. The pole was then removed and they had to move towards where it had been either (allocentric) from a different direction, or (egocentric) from the same direction. Brain activity was recorded during the different phases of the task in control participants and then in hippocampally damaged patients. In the controls, bilateral hippocampal activity was found in the allocentric condition only, with a network of activation in other brain regions, associated with spatial processing in both the allocentric and egocentric conditions. Hippocampal activation was not seen in either of the patients, but the remainder of the network showed normal activation.

1. INTRODUCTION

Virtual reality (VR) is a convenient and effective methodology for investigating spatial memory, in which a large variety of spatial domains can be created in a manner that affords experimental control and enables interactive spatial exploration. Indeed, the neural basis of spatial memory has already been studied using VR, either with functional neuroimaging or by investigating patients with focal brain lesions (e.g. Burgess et al., 2001; Morris, Parslow and Recce, 2000).

The precise neural mechanisms supporting spatial memory are currently under investigation, but a main theory is that spatial information is coded in the hippocampus in the form of *Cognitive Maps*, which specify the directions and distances between objects within the environment (O'Keefe & Burgess, 1996). This representation is essentially allocentric, in that it is independent of bodily orientation and can be contrasted with egocentric spatial memory, in which distances and directions are specifically coded in relation to the bodily axis.

In humans, spatial memory impairment has been found following temporal lobe particularly if this is in the right hemisphere. This includes impairment in memory for location, demonstrated in a landmark series of experiments by Smith and Milner (see Smith, 1989). Here participants are typically shown an array of objects and subsequently have to use their memory to indicate the previous location. Robust deficits have been observed, also correlating with degree of hippocampal removal. More recently, this spatial memory impairment has been found to be proportionately greater than that for recall or recognition of patterns or objects (reviewed in Morris et al, 1999).

The above type of task requires observing a static spatial array, with the possibility that the spatial location can be encoded in an egocentric fashion, in relation to the bodily frame of reference. However, theories linking the hippocampus to spatial memory, which incorporate the notion of an allocentric representation (O'Keefe & Nadel, 1978; O'Keefe & Burgess, 1996), involve dynamic visuospatial processing, with movement of the participant. Accordingly, a series of studies have been conducted by Morris and colleagues (reviewed by; Morris et al., 1999), which were designed primarily to measure allocentric spatial memory. For example, Feigenbaum et al (1996) developed a computerised task, in part of a human analogue of the Olton Maze test (1977), in which a graphically represented turntable was presented on a computer screen fitted with a touch sensitive screen. A number of spatial locations on the turntable were signified by black dots. The participant had to search these locations by touching them in turn until they found the correct one, at which point it would turn green. The correct location moved to another dot and the participant had to search again to find this new location, and so on until all the dots had been found. Feigenbaum et al (1996) found that only patients with right temporal lobe brain lesions were impaired on this task.

The above study relied on rotation of the spatial array in order to induce allocentric representation, rather than participant movement. An alternative task was developed by Abrahams et al (1997), with a circular layout of small containers, place on a central table. The participant observed objects being placed into the lidded containers and then had to indicate which ones had been used and which objects had been hidden. To emphasize allocentric memory functioning, the participants had to walk round the table in between placement of the objects and memory testing. Only patients with right temporal lobe lesions were impaired in memory for location, whilst both left and right lesions patients were impaired on object recognition memory. This study has since been replicated in part using an immersive virtual reality set up, in which the participant was placed in a virtual room and had to search around a number of locations on a virtual table, the locations signified by upturned shells. Here a pronounced spatial memory deficit was observed in patients with right temporal lobe lesions.

The above studies support the link between allocentric spatial memory functioning and the right hippocampal formation. In order to explore this further our group have recently developed an Arena Task, which is a VR human analogue of the Morris water Maze (Morris, 1982) used extensively to study hippocampal spatial memory impairment in rodents. In the rodent version, the animal has to swim to a hidden platform and subsequently remember the platform location using cues around the testing room. In the VR version, the participant is placed in a circular arena, with pattern rendered walls and has to move towards a pole situated in the arena. When they arrive, the screen freezes, there is a short delay and they then re-enter the arena. The pole is then removed from the arena and they have to re-enter it and move the previous location of the pole. In order to explore allocentric memory, the re-entry point is from a different direction and they have to use the patterns on the arena wall to guide their movements. This is compared to an egocentric condition in which the entry point is the same, but the walls of the arena 'rotate' so as to force the participant to move to the location by repeating the same directional movement in relation to their own body.

In this study, this task was used in two manners: (1) A functional magnetic resonance imaging (fMRI) study was conducted in which brain activation was explored in a group of normal participants, with the hypothesis that the allocentric condition only would activated the hippocampus; and (2) to explore hippocampal formation function using this technique in two case studies in which selective bilateral hippocampal lesions caused by anoxic brain damage. The latter type of patient has been used previously to investigate the neuropsychological consequences of 'pure' hippocampal loss (e.g. Holdstock et al., 2000). Here it was predicted that hippocampal activation would be attenuated due to loss of hippocampal function.

2. METHOD

2.1 Participants

The first patient (PR), aged 30 years, acquired his brain damage through carbon monoxide poisoning. Detailed structural MRI scanning revealed selective bilateral hippocampal damage affecting principally the CA3 field, but leading to clear overall reduction in hippocampal volume. An estimate of his premorbid intelligence using the National Adult Reading Test placed him in the superior range (121). He also showed superior range intelligence, as tested using the Wechsler Adult Intelligence Scale III (full scale IQ = 133). In contrast, his memory scores on a standard battery used to test memory functioning, the Adult Memory and Information Processing Battery (AMIPB) placed him in the bottom tenth percentile. The second patient

(AC), aged 42 years, had anoxic brain damage due to status epilepticus. This again had caused selective bilateral hippocampal damage in the context of no identifiable damage to other brain regions. His predicted full scale IQ was in the high average range (111). In contrast, his memory function, tested using the Wechsler Memory Scale Revised was in the low average range overall.

The control participants were eleven right-handed male participants (Mean age 26.72, range 19-45) who were free from significant physical illness, had no history of neurological impairment or psychiatric conditions were used in the study. They were assessed for estimated general intelligence (Mean 119, range 114-123), using the National Adult Reading Test (Nelson & Willison, 1991).

Figure 1. *The Arena task layout showing the pole in the distance and the changing view as the participant approaches the pole. Note the 'puck' around the pole. The subject uses this guide the final approach.*

2.2 Virtual Reality Test

The Arena Task was programmed by Third Dimension Ltd using Superscape Virtual Reality software. To present the test, a Dell computer was used with a Pentium III: 450MHz microprocessor, 64 MB RAM, an 8 MB 3D AGP Graphics Card. The image was displayed via a Proxima 55100 projector onto a Perspex screen at the foot of the scanning table. GE Signa 1.5 Tesla system MR system.

2.3. *Procedure*

The appearance of the Arena is shown in Figure 1. Movement within the arena is controlled by the joystick, with a right and left movement rotating the viewpoint to the left and right respectively and forward movement producing a constant forward velocity (the Arena is a traversed by forward movement in approximately 20 seconds). For each condition, the participant has a 30 second époque in which they must reach the pole. The screen then freezes for the remained of this époque and there is a blank screen delay followed by the retrieval phase. Here the participant re-enters the arena and moves to the previous pole location, pressing a 'firing button' on the joystick to signal this location. There is a further 30 second delay and a control visual display is presented for 30 seconds, an amalgam of the Arena wall patterns.

This procedure is repeated five times for the two main conditions. The allocentric condition is presented first, in which the participant always re-enters the Arena from a different angle, and then the egocentric condition in which the starting position is conceptually the same, but the Arena walls rotated to remove any reliance on external cues to determine pole location.

2.4. *fMRI Measurement and Analysis*

Gradient recalled echoplanar MRI data were acquired using a GE Signa 1.5 Tesla system (General Electric) retrofitted with advanced NMR hardware using a standard head coil. 100 T2*-weighted images depicting BOLD contrast were acquired at each of 16 noncontiguous near-axial planes (7 mm thick, 0.7 mm slice skip) parallel to the intercommissural (AC-PC) line; TE = 40 ms, TR = 3 s, flip angle = 90 degrees, number of signal averages = 1. Prior to time-series analysis, data were processed to remove low-frequency signal changes and motion-related artefacts. The responses at each voxel were then analysed by regressing the corrected time-series data on a linear model produced by convolving each contrast vector to be studied with two Poisson functions parameterizing hemodynamic delays of 4 and 8 seconds. Following least squares fitting of this model, a goodness of fit statistic composed of the ratio of model to residual sum of squares was calculated for each contrast. The distribution of the same statistic under the null hypothesis of no experimental effect was then calculated by wavelet-based resampling of the time series at each voxel and refitting the models to the resampled data. An experimentally derived null distribution of the goodness of fit statistic was then obtained by following this procedure ten times at each intracerebral voxel and combining the resulting data. This method has been shown to give excellent control of nominal type I error rates in

fMRI data from a variety of scanners. Activations for any contrast at any required p value can then be determined by obtaining the appropriate critical values from the null distribution. The number of expected positive pixels for the whole brain used during.

Activation patterns were obtained for each of the main époques (allocentric, encoding and retrieval; egocentric encoding and retrieval; and pattern presentation). In each case, activation was compared against the rest phase époques.

3. RESULTS

3.1. *Activation in Control Participants*

The brain activation maps for the control subject group are shown in Figure 2. These show in sagittal slices the areas of activation associated with each phase of each condition. For the allocentric encoding condition a network of brain regions are activated associated with spatial memory. This includes the activation of the visual cortex (low level visual processing), the parietal cortex (spatial manipulation), the thalamus (spatial orientation) and the hippocampal / parahippocampal regions (encoding allocentric memories). For the allocentric retrieval phase the network is essentially the same, but the thalamic activation is reduced and there is no parahippocampal / hippocampal activation. The egocentric encoding condition shows a similar pattern of activation to allocentric encoding, with the exception of no parahippocampal / hippocampal activation. The egocentric retrieval phase produces essentially the same pattern of activation as the encoding phase. A further condition was the presentation of the amalgam of patterns. This produces just visual cortical activation, consistent with low-level visual analysis.

3.2. *Activation in the two anoxic brain damaged patients*

The same analysis as for the control participants was conducted, but using the two anoxic brain damaged patients and for the encoding phase of the allocentric condition only. The brain activations are shown in Figure 2. These show a similar activation pattern as in the controls, but without hippocampal / parahippocampal activation or thalamic activation.

4. DISCUSSION

The study used fMRI combined with virtual reality in order to investigate brain activation associated with allocentric spatial memory. This revealed a network of activation incorporating key neuronal structures, all of which have previously implicated in this function. The network can be considered in a hierachical fashion, starting with low level visual processing in the visual cortex. Information follows the ventral route into the temporal lobe for pattern recognition and simultaneously via a dorsal route to provide processing of spatial information. This is combined to form an allocentric representation of location and the encoding process takes place in the hippocampus. The hippocampal formation interacts with the thalamus, which is involved in whole body orientation to external stimuli. The lack of hippocampal formation activation with the egocentric condition suggests that this type of spatial memory is not so reliant on this structure, insufficient to produce activation in the current experiment. This is in accordance with the O'Keefe and Nadel (1978) theory about the hippocampus, that is storing viewer independent spatial information in the form of cognitive maps.

A finding of the current study is that the hippocampal activation was bilateral and also extended into the parahippocampal gyrus. The bilateral effect is at odds with the results of studies of patients with unilateral brain lesions and suggests that right hippocampal damage specifically affects spatial memory (Smith, 1989). This apparent conflict in findings may be accommodated if it is assumed that there is a difference between activity and vital function in the brain. For example, it is possible that spatial information enters the hippocampal based memory system in the right hemisphere. A lesion in the right temporal lobe can effectively severe this input into the system and so produce spatial memory impairment. Nevertheless, in a normal brain, spatial information entering the system may produce bilateral activation. The finding of parahippocampal and hippocampal activation is frequently reported and represents the close coupling of these structures in terms mnemonic processing. Additionally, this activation was shown to be in the posterior hippocampus and this is consistent with rodent findings, where lesions of the equivalent dorsal hippocampus is shown to produce spatial memory impairment.

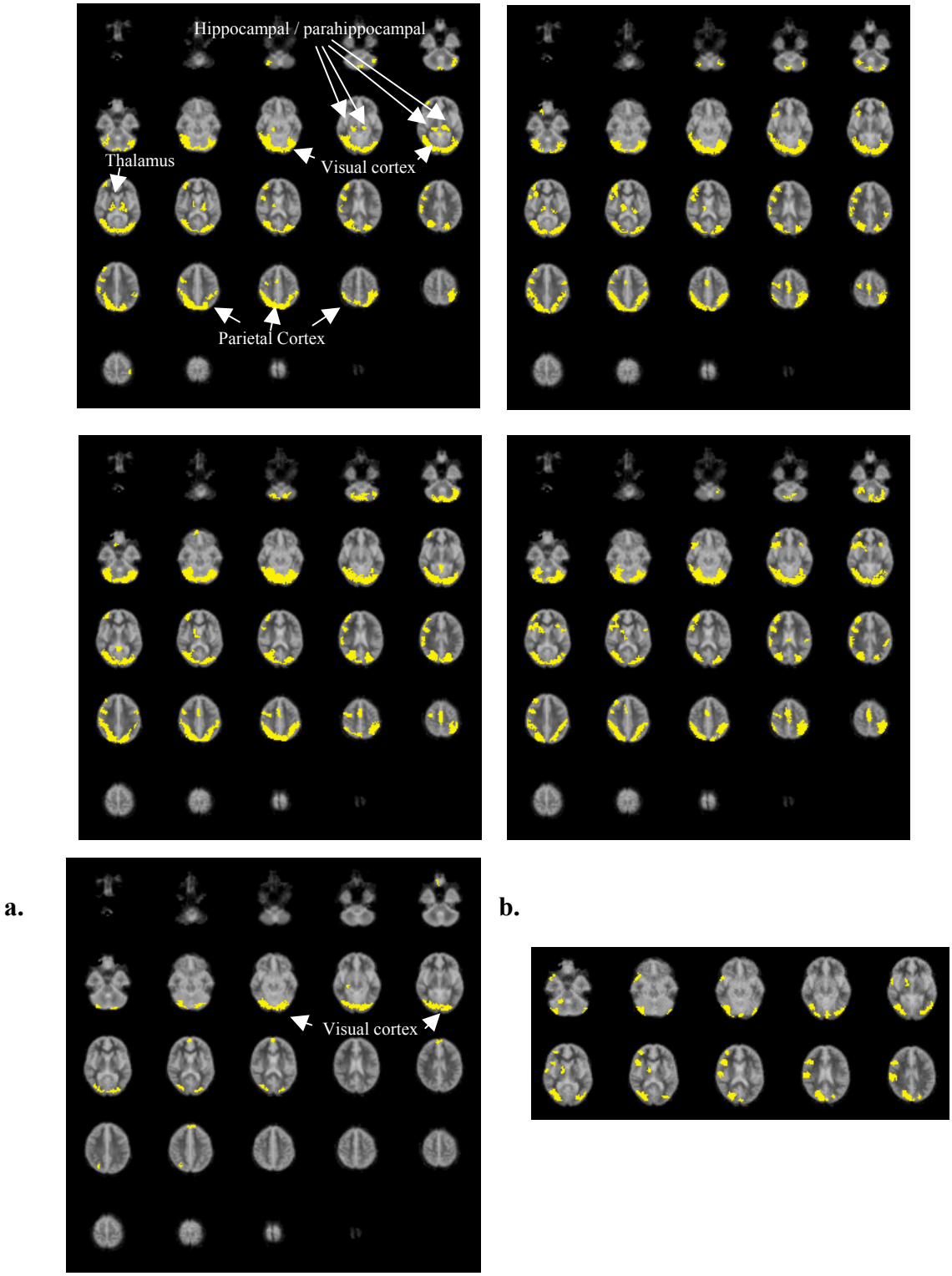

Figure 2. *The brain activation maps for normal participants. These show sagittal slices through the brain. Top left: allocentric encoding; top right: egocentric encoding; bottom left: allocentric retrieval; bottom right: egocentric retrieval. Asdditional panels (a) show pattern activation and (b) activation in the two anoxic patients*

The study also conducted fMRI recording of encoding in two patients with anoxic hippocampal brain lesions. These lesions on structural MRI are shown to be very specific and the lack of hippocampal activation reflects the observed brain damage. This is further supported by activation of the rest of the network, including the visual cortex, thalamus and parietal lobe. The finding is also consisting with a

previous study by Holdstock et al (2000), who showed allocentric spatial memory impairment in a single case study who had bilateral hippocampal damage. Use of virtual reality, in which the participant has to interact with the environment and where the visual cues are controlled carefully shows that the deficit can be extended to demonstrate lack of hippocampal activity, and so demonstrate directly the neuronal effects of structural damage.

This study illustrates the potential use of VR combined with fMRI, firstly to identify the network of neuronal structures involved in a dynamic task and, secondly, applied to patients with focal brain damage. Future studies should be able to exploit this approach in terms of rehabilitation, and this would apply to neurorehabilitation techniques, pharmacological interventions and even neural transplant, where reconstitution of function could be measured using functional neuroimaging. VR provides techniques more akin to real life, but also with the advantages of computerised control, a suitable approach for combining with brain activation measurement.

5. CONCLUSIONS

The study has used VR to highlight a network of neuronal activity associated with a dynamic spatial memory task, consistent with the cognitive mapping theory of hippocampal involvement in spatial memory. It also shows how structural damage to focal brain regions can be shown to lead to functional disturbance, measured at the neuronal level. VR provides a mean of executing dynamic and interactive tasks during functional neuroimaging and has the potential to be used in this fashion to the assessment of neurorehabilitation outcome

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