A Virtual Radial Arm Maze for the Study of Multiple Memory Systems

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Introduction

Memory is a high-level and complicated function, depending on different parts of the brain and in part on past experience. The complicity thus makes the study of the memory system extremely challenging, in that it adds difficulty to design the control conditions for removing disturbing effects in the control experiments, which may involve many other brain activities. For example, in a spatial navigation task, in order for the subject to memorize the scene and recognize where to go, the subject needs to look and move around. The visual stimuli and the body movement consequently will activate the visual cortex and motor cortex, and many other neural passages in the brain. If the corresponding control experiment cannot properly activate similar activities in the brain while leaving the memory system idle, the difference between the free mode and the control condition of this experiment will contain not only signals of memory activities but also contaminations from other brain activities, making the memory study no sense. Exactly the same applies to such studies using functional Magnetic Resonance Imaging (fMRI) because the functional map generated from the difference should contain only activation of memory activities. To make the task easier, an increasing number of functional brain imaging studies are employing computer-based virtual reality (VR) for the study of dynamic brain activity during the performance of high-level psychological and cognitive tasks. However, most of these studies suffer from the problem we just mentioned. We report here our efforts in studying human multiple memory system, by designing and developing a virtual radial arm maze with minimized disturbance from other brain activities. The virtual radial arm maze we implemented is based on the famous winshift and winstay experiments using mouse model[1,2]. The winshift task is a test of spatial working memory. In the test of using animal model, food pellets are placed in all eight arms. The mouse is placed in the central arena and is allowed to freely explore. The mouse enters an arm, finds a food pellet and eats it. When it returns to the centre, doors lower to temporarily close off all the arms. After a delay, the doors are opened and the mouse is once again allowed to enter an arm - the whole process is then repeated. In order to obtain all the food, the mouse has to go to each arm in turn. The trial continues until the mouse finds all eight food pellets. The experimenter records every action the mouse takes and grades its behavior. It loses marks if it returns to a previously-visited arm. This test was shown to be hippocampus-dependent, first in [3]. The winstay task is run in a dark room. Four of the arms of the maze are baited with food pellets; these arms are also selectively illuminated. The mouse starts in the center of the maze and is allowed to freely explore. Upon entering one of the lit arms, it will discover and eat the food pellet therein. It then returns to the centre, at which point entry to the arms is blocked by descending doors. The mouse stays blocked in the centre for about 10 seconds, during which time the food it has eaten is replenished. The doors are then opened and it is again allowed to freely explore. The 'correct' choice is to return to the first arm, where it will again discover food. Upon returning to the centre for the second time, the light in that arm is switched off. The procedure can then be repeated for the three remaining illuminated and baited arms. The task was shown to be striatum-dependent in[2].

Method and Material

Three episodes have been designed and implemented in both the winshift and winstay experiments, including a regular free experiment (either winshift or winstay), a control experiment and a control experiment with a misleading arrow. We make everything in the control episode comparable with the first one except the portion that leads to memory. And, we employ a third episode for identifying by-activities in the brain that could have been introduced in the second episode. In the free winshift experiment, all eight arms are baited. The subject is asked to retrieve all the eight rewards, best by visiting each arm once and only once. The outside scenery is fixed, so that the subject can rely on the scene as spatial cues for guiding the retrieval of rewards. However, the outside scenery is designed to be very similar in all spatial orientations with only delicate differences, thus the subject has to try the best to tell the visited arms from unvisited ones. The free winstay experiment is exactly the same as the free winshift, except that only four of the eight arms of the maze are randomly selected for baiting, and each of the four contains two baits. In addition to the fixed outside scenery as spatial cues, those baited arms are illuminated by a lamp fixture on the wall at the end of the arms, serving as an additional cue to the subject. In the control experiments for both these two tasks, everything is designed to be comparable with the proceeding free task, including that exactly the same number of attempts as is made in the proceeding free task will be allowed. However, in this episode, outside scene is actually no longer reliable although it appears similar to that in the free experiments, because the scene segments are interchanged randomly at the end of each attempt, thereby destroying any possibility of using spatial learning to perform the task. Therefore, the only difference between this control episode and the proceeding episode is the spatial cues that can be memorized. We therefore hope that the brain activities of these two episodes will only differ in activities related to the memory system. However, confusing or perhaps frustration could be introduced into the second episode when a subject fails to rely on the spatial cues, which does not happen in the first episode. We therefore add a third episode to confirm whether or not such side-effect exists. In the third episode, with almost everything remained to be the same as that in the control experiment, an explicit message will remind the subject of following a red arrow for retrieving rewards and then a red arrow was shown to guide the navigation. While this red arrow may or may not point to a arm with a reward. Confusion and frustration is explicitly enhanced, making such side-effect easy to be identified from the second episode and removed subsequently, if it does exist. To date, we have tested the VR maze on 54 subjects in an fMRI study. We continue running it in this study for scanning new subjects. The parameters of the fMRI sequence that we used in the study are: (1) VR FLAIR: 43 axial slice, TR =2200 ms, TE =8 ms, matrix = 288(X) ×192(Y), FOV= 240 mm × 240 mm, spacing = 0.5 mm, thickness = 3.0mm, flip angle=90°, TI=860 ms, frequency direction = A/P, duration = 5min 17 sec. (2)VR GRE EPI Axial: 43 axial slice, TR =2800 ms, TE =25 ms, matrix = 64(X) ×64(Y), FOV= 240mm×240mm, spacing = 0.5 mm, thickness = 3.0 mm, number of volumes = 322 + 6 dummy scans, flip_angel=90°, TI=960 ms, frequency direction = A/P, duration = 15 min 18 sec. We usually run the VR GRE EPI Axial sequence twice to cover the all the sessions in this experiment. The fMRI data were first preprocessed using SPM2 (http://www.fil.ion.ucl.ac.uk /spm/), an fMRI analysis software package based on MATLAB, to adjust head motion and slice timing difference. The same package is also used to normalize the functional data to a standard MNI template space, and finally to smooth the normalized data for reducing spatial noise. The preprocessed data were then analyzed in SPM2 to detect the brain regions with significant activation or deactivation during the performance of the tasks, using a general linear model (GLM), for testing whether the blood-oxygen-level dependent (BOLD) response to the tasks could significantly match a hypothesized hemodynamic response function (HRF) derived from the task.

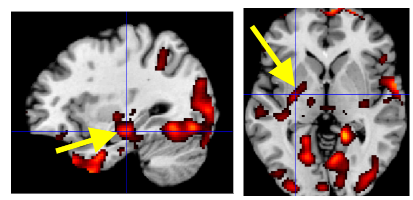

Figure 1. An Example of fMRI Activations Acquired from One Subject Executing Winshift Task. Activations are seen in hippocampus and putamen.

Results

As expected, we detected brain activities in hippocampus and putamen regions due to the nature of spatial learning and memory in this navigation task of VR Maze, as well as in the cerebellum, motor cortex regions and visual cortex regions because this task also involves motor planning and visual perception (Fig. 1).

Discussion We implemented a VR maze based on the famous winshift and winstay experiments for translational study of human memory system. The implementation of this VR maze has fully considered how to isolate the brain activities related to memory system and verify possible side activities of the brain that could have been introduced. The system is very flexible, in that it has three running modes, for training purposes, for real experiment, and for replay a recorded navigation. Moreover, the system is independent of computer platforms, using OpenGL. It has been fully tested on GE scanners, with flexible interfaces to MRI-compatible devices for interaction. We aim to provide this software for share with the research community.

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