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Research Article

Brain Activity during the Concentration Task in Normal Male Subjects by Functional Magnetic Resonance Imaging

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Abstract

Concentration is a card game that can be used for the rehabilitation and examination of individuals with an impaired cognitive function; however, there are few psychological reports on its use. In this study, we used functional magnetic resonance imaging to psycho physiologically investigate the localization of brain activity in 12 healthy males during a game of Concentration. Both a Control task, in which a card was selected in order, and a Concentration task were performed, and the results of each task were compared. During the Concentration task, both sides of the entire cerebrum and the cerebellum were activated. Upon comparison of the trials, the left pallidum, left caudate nucleus, and left thalamus were activated during the Concentration task more significantly than during the Control task. These results suggest that Concentration is related to the memory function including the visuospatial working memory, inhibition process, reward process and the learning effect.

Keywords: Concentration; Functional magnetic resonance imaging; Cortico basal ganglia circuit; Caudate nucleus

Introduction

Visuospatial cognitive functioning is very important in everyday activities. However, in psychiatric diseases such as schizophrenia and dementia, this function is impaired, and patients with these diseases are inconvenienced in daily life. Various visuospatial tasks were used to investigate the brain function in previous studies. Using the Trail Making Test (TMT), Shibuya-Tayoshi, et al. [1] reported that this task activates the prefrontal cortex during Near-Infrared Spectroscopy (NIRS), and Nakahachi, et al. [2] suggested that this task is appropriate for examining the visuospatial working memory and functional localization. Using a task related to spatial positioning of a dot, Silver, et al. [3] examined visuospatial working memory and noted that working memory in schizophrenia was impaired, and Lee, et al. [4] compared trials with errors in maintaining spatial working memory between normal subjects and schizophrenic patients using functional Magnetic Resonance Imaging (fMRI) and NIRS. They reported a reduced functional asymmetry of the prefrontal cortex during a spatial working memory task in schizophrenic patients. In addition, Henseler, et al. [5] used fMRI and reported that schizophrenic patients showed impairments in activation of the superior parietal cortex and in maintaining visuospatial information. Kirsch, et al. [6] also reported that during a maze task, both sides of the prefrontal cortex were activated on fMRI. A variety of tasks, such as the Wisconsin Card Sorting Test [7] and visual object contracting tasks [8], are used to investigate the visuospatial cognitive function. These tasks have been psycho physiologically examined, the localization of the brain function and the validity of these tasks have been demonstrated, and their use as markers of psychiatric disorders is expected in the future.

Concentration is a card game that can be played either alone or with multiple players. In the game of Concentration, a player selects two cards from a group of cards turned upside down on the table; the player looks at the two cards and places them back on the table facedown, attempting to memorize the placement of the cards. During subsequent turns, each player turns over two cards, attempting to match each new card with a card that has been seen previously. When a player matches two cards, that player wins the cards. The player learns the position of each unmatched card placed during each turn of play. When two cards do not match, the cards are replaced on the table.

From a psycho physiological viewpoint, players initially recognize and memorize the visuospatial information (number and spatial position) contained in each card they select. While maintaining such memory, they newly select a card, and recognize the visuospatial information contained in it. When the new card matches the old one, players restart this process. If it does not, it is necessary for them to continue selecting other cards, while maintaining the visuospatial information contained in the unmatched card. In other words, in Concentration, it is thought that not only simple memory work but also working memory is used. Working memory refers to the system or systems that are assumed to be necessary in order to remember something while performing complex tasks such as reasoning, comprehension, and learning. Baddeley [9,10] proposed that this system is a multi-component system comprising an attentional system, the 'central executive', aided by three subsidiary slave systems, the "phonological loop", "visuospatial sketchpad"

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and "episodic buffer". The "phonological loop" is assumed to hold verbal and acoustic information using a temporary store and an articulator rehearsal system. The "visuospatial sketchpad" is assumed to hold visuospatial information to be fractionable into separate visual, spatial, and possibly kinesthetic components. The "episodic buffer" is assumed to be a temporary storage system that is capable of integrating information from a variety of sources [9,10].

Concentration is popular with children and adults in many countries because the rules are simple. This game has the merit that the subject finishes the preliminary practice in a very short time because he/she can understand the rules easily. Because Concentration is familiar and has the added pleasure of being a game, subjects may perform this task with a greater sense of relaxation. Therefore, it may be easily accepted and performed by many people.

The intellectual component of the game of Concentration requires memorization of the design or number of the card as well as its position on the table, and the game is used in Japan as a substitute for the space cognitive function-test and rehabilitation training in patients with neurodegenerative-diseases such as dementia.

However, to our knowledge, there are no published studies supporting the validity and efficacy of Concentration in cognitive rehabilitation. On the contrary, there are very few psycho physiological studies that use Concentration. Eskritt, et al. [11] used Concentration to investigate the age at which infants begin to use external symbols. To the best of our knowledge, Fujiki, et al. [12] is the only group to report brain functional localization during concentration. They compared normal controls with schizophrenic patients using NIRS. They found that the left middle frontal region and right tempo-parietal region significantly activated in normal controls.

In this study, we examined human brain activity during the performance of Concentration in greater detail using fMRI, which has a higher spatial resolution than NIRS and measures the deep sections as well as surface area of the whole brain. We hypothesized that the middle frontal and tempo-parietal regions would be significantly activated, as in the study by Fujiki, et al. [12] and that the hippocampus, related to memory [13], would be also significantly activated.

Methods

Participants

Twelve normal male subjects (mean age: 27.5±1.9 years) participated in this study. The subjects were university graduates who did not have a history of neurological or psychological disorders. The participants were native speakers of Japanese and were determined by the Edinburgh Handedness Inventory to be right-handed [14]. Informed written consent was obtained from all of the subjects. This study was approved by the Ethical Review Board of Kurume University.

Task design

The subjects were placed in a supine position, while wearing a headset and holding a simple wooden stick (length: 91 cm) in their right hand. The experimenter with cardboard (length x width: 23 x 30 cm) stood on the left side of the subjects. He supported the cardboard at an appropriate position to enable them to point to all

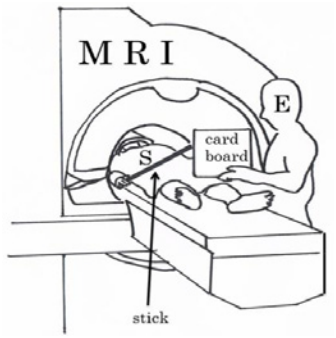

Figure 1: The subject and experimenter during performing the task. The subject was placed in a supine position, holding a simple wooden stick in their right hand. The subject were instructed to continuously watch the cardboard in a relaxed state.

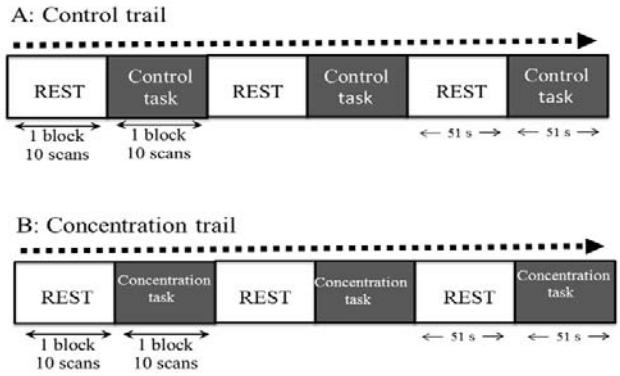

Figure 2: Task design. Each trail consists of 6 blocks. A: Control trail in blocks 1, 3 and 5, the "rest condition" is applied. In blocks 2, 4 and 6, the "control task" is applied. B: Concentration trail: in blocks 1, 3 and 5, the "rest condition" is applied. In blocks 2, 4 and 6 the "concentration task" is applied.

cards on it using a stick (Figure 1). They were instructed to watch the cardboard supported by the experimenter through a mirror above their heads in a relaxed state. On the cardboard, all cards (length x width: 8.8 x 5.7 cm) were placed face down in 2 rows of 4; there were a total of 8 cards (4 pairs). We performed whole brain scanning 10 times as 1 block. Each trial consisted of 6 blocks. In Blocks 1 (Scans 1-10), 3 (Scans 21-30) and 5 (Scans 41-50), the "rest condition" was applied. In Blocks 2 (Scans 11-20), 4 (Scans 31-40) and 6 (Scans 51-60), the "activation condition" was applied. The activation condition consisted of two types of tasks ("Concentration task" and "Control task"), and each subject performed 2 trials (Control trial: rest – Control and Concentration trial: rest – Concentration) of each type (Figure 2). Under the rest condition, the subjects were instructed to keep their eyes open, hold the stick with their right hand, and relax without thinking of anything. Under the activation condition, the subjects were instructed to keep their eyes open and point to the card with their stick according to the directions they had been taught. The experimenter with the cardboard revealed the card to which the subjects pointed. In the Control task, the subjects pointed with their stick to two cards sequentially from the left upper to the right lower end. The subjects initially pointed to the upper left card and the on the right of it. Subsequently, they pointed the third and fourth cards from the left in the upper section, followed by the first and second, and third and fourth from the left in the lower section. After this,

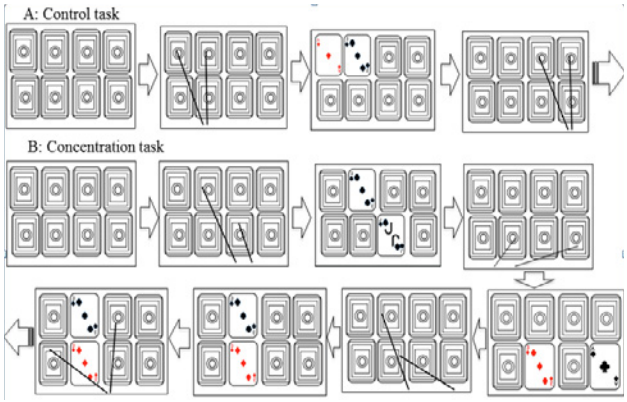

Figure 3: The activation conditions. A: Control task, subjects point with their stick to two cards sequentially from the left upper end. B: concentration task. Subjects point with their stick to two card to gather pairs of cards bearing the same number.

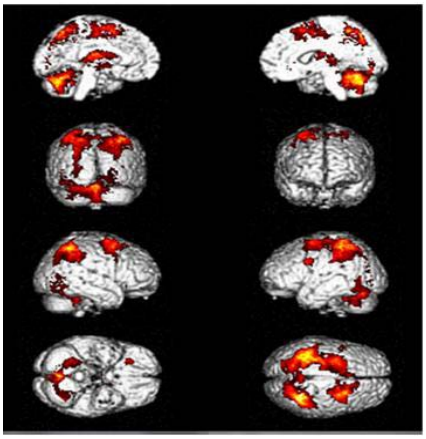

Figure 4: fMRI images (Concentration > Rest). Significant activation was observed widely in the frontal, parietal, occipital and temporal brain regions, the basal ganglions and cerebellum.

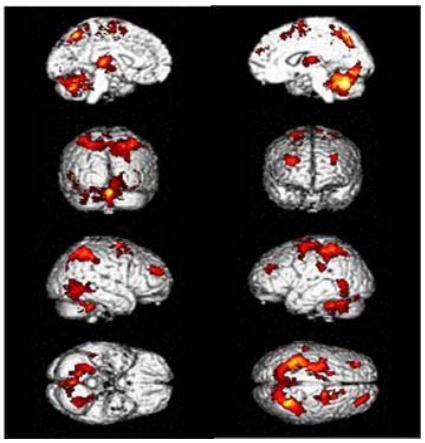

Figure 5: fMRI images (Control > Rest). Significant activation was observed widely in the frontal, parietal, occipital and temporal brain regions, the basal ganglions, and cerebellum. However, activation of the pallidum, putamen, and hippocampus was not observed.

they restarted this process, continuously pointing to a pair of cards in order, with the first and second cards from the left in the upper section. The experimenter supporting the cardboard turned up the 2 cards pointed to by the subjects to show their designs and numbers, and placed them face down again without changing their positions. The subjects were instructed to carefully watch the cards shown, without the necessity of memorizing their designs or numbers. In the Concentration task, the subjects conformed to the normal game rules of Concentration (cf. introduction). Similarly to the Control task, the process, in which the subjects pointed to a pair of cards, and the experimenter dealt with these cards, was repeated. However, only during this task were the subjects instructed to intentionally, rather than arbitrarily, select a pair of cards so that their numbers coincided. Therefore, it was necessary for them to continue implementing the procedure while remembering the numbers of the cards shown (Figure 3). During each task, they heard start and end signals through headphones.

Data acquisition

MRI was performed using a Symphony 1.5 T scanner (SIEMENS, Bayern, German). T2*-weighted images, which encompassed the whole brain, were acquired from each subject using an Echo Planner Imaging (EPI) pulse sequence with an Echo Time (TE) of 70 ms, Repetition Time (TR) of 5.1 s, flip angle of 90 degrees, Field of View (FOV) of 225*225*148 mm^3, Voxel dimensions of 64*64*40, and slice thickness of 3.5 mm. The slices covered the whole brain. The series was designed as a block task such that 10 volumes represented the controls and 10 volumes represented the activation periods. One series consisted of 60 volumes of the echo planner image involving 3 periods of activation conditions and 3 periods of rest.

Data preprocessing

The images acquired from the scanner in DICOM format were converted to the Analyze format through the DICOM toolbox using SPM8 (Welcome Department of Cognitive Neurology, London, UK) software installed in MATLAB (Mathworks, Inc, Nadick, MA, USA) [15]. SPM8 software allowed us to realign all of the data to correct for movement. Normalization from each anatomical MR image to the Montreal Neurological Institute T1 [16] reference brain provided by SPM was performed with 2x2x2-mm^3 Voxel resampling. Smoothing was performed with a Gaussian spatial filter to a final smoothness of 8 mm.

Statistical analysis

The data were analyzed on an individual (subject per subject) basis and across subjects (group analysis) using subject variance (random effect model). For individual analysis, the data from each run were modeled using the general linear model with separate functions modeling the hemodynamic response to each experimental epoch. First, in the Control task, we defined one contrast (Control task versus rest) for each series (per subject). We applied a threshold to the T maps at T=4.02 ($p<0.001$, uncorrected) for the Control task. In these threshold maps, activated clusters were considered significant if their spatial extent was >172, corresponding to a risk factor (type I error) of $p<0.001$ (corrected). In the Concentration task, we performed an analysis such as the Control task analysis for all of the subjects. We applied a threshold to the T maps at T=4.02 ($p<0.001$, uncorrected) for the Control task. In these threshold maps,

Table 1: The brain regions more significantly activated during the Concentration trial than during the Control trial; Locations and p-values.

	Region	Coordinate (x, y, z mm)	Voxel-level T-value	Cluster-level p-value
left	caudate	-12, -16, 18	4.15	0.006
Left	pallidum			
left	thalamus			

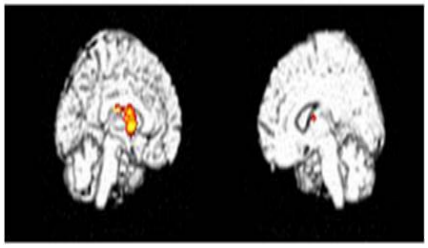

Figure 6: fMRI images (Concentration > control). Significance activation was observed in the left pallidum, left caudate and left thalamus.

activated clusters were considered significant if their spatial extent was >160, corresponding to a risk factor (type I error) of p<0.001 (corrected). Then, for both trials, we determined the activated regions using the local maxima labeling of Automated Anatomical Labeling (AAL) [17]. The areas of the activated regions were calculated by multiplying the cluster areas determined by SPM by the percentages indicated by the cluster labeling of AAL. Finally, we performed comparisons between the trials. Analysis of variance (ANOVA) with sphericity correction (Greenhouse-Geiser) was applied to the data to determine whether more activated areas existed in one trial than in another (Concentration trial > Control trial, Control trial > Concentration trial). Then, we examined the regions where the significant difference occurred using a post-hoc t-test between the trials, with a T=2.51 (p<0.01) threshold. In these threshold maps, the activated clusters were considered significant if their spatial extent was >400, corresponding to a risk factor (type I error) of p<0.01 (corrected). Then, for the comparison of both trials, we determined the activated regions using the local maxima labeling of AAL. The areas of the activated regions were calculated by multiplying the cluster areas corresponding to the percentage determined by the cluster labeling of AAL in SPM.

Results

The number of matching pairs

In the Concentration trial (three blocks in total), the average number of pairs matched correctly by all subjects was 11.5 ± 0.8.

fMRI

In normal male subjects, the cerebrum surface (frontal, parietal, occipital, and temporal brain regions) and the cerebellum were similarly activated during the Concentration and the Control tasks (Figures 4 and 5). The activation of the pallidum, putamen, and hippocampus was observed only in the Concentration task. When we compared the trials, no region was activated in the Control trial more significantly than in the Concentration trial. The left pallidum, left caudate, and left thalamus were activated during the Concentration trial more significantly than during the Control trial (MNI: x=-12, y=--16, z=18, T=4.15, p=0.006) (Table 1, Figure 6).

Discussion

In this study, it was shown that the whole brain was widely activated on performing Concentration (seeing, selecting, pointing to, and confirming the card). Furthermore, we found that the pallidum, caudate, and thalamus were activated during the Concentration task more significantly than during the Control task.

Fujiki, et al. [12] reported on the activation of the frontal and temporo-parietal lobes using a Concentration task similar to ours. In our study, significant activation in the frontal and temporo-parietal lobes was not shown in the comparison between the Concentration and Control tasks. However, in the Concentration task (Concentration trial > rest condition), significant activations of the frontal (including prefrontal), parietal, and temporal (including medial temporal) regions were shown. We suggest that these regions relate to visuospatial working memory. The functional localizations of this working memory have been reviewed recently by Eriksson, et al [18]. They indicate that working memory is the result of interactions among several brain regions, and emphasize that the activations of the prefrontal, temporal, and parietal regions in particular are important to the working memory process. They reported that the prefrontal cortex is critical for resilient information maintenance during working memory tasks, the parietal cortex activates both sides in spatial working memory, and, furthermore, the superior parts implement selective attentional control, and the medial temporal lobe is associated working memory capacity. We think that their indication strongly supports our suggestion. The difference in the results of Fujiki, et al. [12] may be due to a difference in the degree of difficulty of the Concentration trials between theirs and ours. Our task using eight presentation cards was markedly easier than that of Fujiki, et al. [12] which included 12 presentation cards? Therefore, we hypothesize that the difference in the results of these studies was because any difference between the Control and Concentration tasks was difficult to show in our study.

In this study, the hippocampus during the Concentration task was significantly activated in the comparison with the rest condition. On comparing the Control task and rest condition, there was no significant activation in the same regions. The hippocampus plays an important role in memory, as demonstrated by Scoville & Milner [13] in a study of HM (HM was a young man who underwent radical bilateral medial temporal-lobe resection), and recent studies have led to a better understanding of spatial memory, cognitive mapping, declarative mapping, explicit memory, recollection, and relational memory [19,20]. Regarding the significant hippocampal activation observed in this study, it is hypothesized to be a result of activation of a memory function such as spatial memory or relational memory at the time of the Concentration task. The hippocampus was not activated during the Concentration trial more significantly than during the Control trial. We suggest that this occurred because the degree of difficulty of the Concentration task was low.

One previous study reported that the caudate nucleus is activated at the time of utilizing cognitive-spatial information [21]. In the present study, we hypothesized that the subjects utilized spatial information during the Concentration task. Indeed, reports have shown that the caudate nucleus is activated during the inhibition of

unwanted responses and during experiences of recollection with a high level of confidence [22]. Activation of the caudate nucleus in the Concentration task is possibly related to not only the utilization of cognitive-spatial information but also the thinking process of selecting a card with a high degree of confidence or changing a card choice immediately before the selection.

The caudate nucleus and pallidum connect with the cerebral cortex through the thalamus, and these connections constitute a corticobasal ganglia circuit [23-25]. Grahn, et al. [24] suggested that the caudate nucleus contributes to tests of learning and memory by guiding the selection of responses necessary for achieving the goals of a task through initiating the required action contingencies and evaluating the subsequent outcomes. Furthermore, Boecker, et al [25]. considered that this circuit including the caudate, pallidum, and thalamus might be related to the pathway of the inhibition process. Therefore, the circuit including the caudate nucleus and thalamus might be activated in such a scenario.

In addition, the relationship between this corticobasal ganglia circuit and the reward process has attracted attention [26]. Recently, a reward prediction error hypothesis and reward structural learning hypothesis have been proposed [27]. These hypotheses explain "the process of repeat action choice expecting a reward being provided" and suggest that dopamine neurons are related. In our Concentration task, there was no clear reward, although the sense of accomplishment achieved when a card pair was matched could be a reward factor. In our task, an association with these hypotheses is suggested because the subjects continued taking a card for trial and error to learn the position of the card, which became an intrinsic reward factor. However, the substantia nigra, which innervate dopamine neurons, was not activated. Although it is possible that MRI could not cover the midbrain area in which the substantia nigra is located, the possibility exists that dopamine neurons were not activated because the reward was not clear. It is also possible that the "process to predict" the selection of a card while performing a prediction task (expectation of a card match) engaged the caudate nucleus-thalamus circuit.

Furthermore, our study indicates that the corticobasal ganglia circuit constructed by the pallidum, caudate and thalamus significantly activated the left side. Regarding the inhibition process, currently, the mainstream of the corticobasal ganglia circuit is a light lateralized model [25]. Recently, Yang, et al. reported the relation between basal ganglia and a reward. They suggested that patients with major depressive disorder showed significantly weaker responses in the left caudate nucleus when contrasting the 'high reward'- 'low reward' condition [28]. Our result may suggest there is a possibility of the corticobasal ganglia circuit as a reward system."

In this study, we measured brain activity using fMRI during a Concentration task that is used both widely as a game as well as a tool for visuospatial rehabilitation and evaluation. During the Concentration game, we assessed the surface of the frontal, parietal and temporal brain regions associated with the working memory function. Additionally, we evaluated the basal nuclei activated by the learning effect, the inhibition process, and the reward process, and the hippocampus suggested the relation with memory. The study sample included adult males, and future studies should include females, elderly adults, and children, and differences in brain activity should be examined by changing the degree of difficulty. In the near future, we would also like to apply the game of Concentration for more effective psycho physiological rehabilitation.

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