Sequential Involvement of Distinct Portions of the Medial Prefrontal Cortex in Different Stages of Decision Making Using the Iowa Gambling Task

Jae-Jun Lee[1], Sung-Jin Bae[1], Yang-Tae Kim[2], Yongmin Chang[1,3,4]

Functional magnetic resonance imaging (fMRI) was used to assess the temporal response of neural activation in healthy subjects while they performed the Iowa Gambling Test (IGT), which utilizes decisions involving ambiguity and risk. The IGT was divided into five blocks of 20 trials; analysis showed that activity in the medial prefrontal cortex (mPFC) moves gradually from the dorsal to the ventral mPFC over the course of the IGT. These findings suggest that cognitive division of the mPFC, including the dorsal portion of the anterior cingulated cortex (ACC), plays a major role in ambiguous decision making and that the aspect of the IGT corresponding to risky decision making is associated with significant activity within the corticolimbic network strongly implicated in emotion and reinforcement. Our results also suggest that decisions made under ambiguity and decisions made under risk situations can be further divided into sub-phases based on the neural network involved.

Index words : Decision making
Iowa Gambling Task (IGT)
Functional Magnetic Resonance Imaging (fMRI)

Introduction

Most real-life decision making involves choosing between competing actions associated with uncertain gains and losses. Because adaptive decision making involves the positive and negative consequences of one candidate action against the consequences of another in the light of the relative probabilities of good and bad outcomes, it has been hypothesized that decision between actions associated with uncertain benefits or penalties might involve an emotive as well as cognitive activity (4, 11, 27).

The Iowa Gambling Task (IGT) is an experimental decision paradigm that accounts for emotional affect over higher cognition and behavior. In the IGT (5)

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[1]Department of Medical & Biological Engineering, Kyungpook National University, Daegu 700-721, Korea
[2]Department of Psychiatry, Bugok National Hospital, Gyeongsang Nam-Do 635-890, Korea
[3]Department of Diagnostic Radiology, Kyungpook National University College of Medicine, Kyungpook National University Hospital, Daegu 700-721, Korea
[4]Department of Molecular Medicine, Kyungpook National University College of Medicine, Kyungpook National University Hospital, Daegu 700-721, Korea
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Corresponding author : Yongmin Chang, Ph.D., Department of Radiology, Kyungpook National University Hospital, 50, Samduk-Dong 2ga, Chung-gu, Taegu 700-721, Korea.
Tel. 82-53-420-5471 Fax. 82-53-422-2677 E-mail: ychang@knu.ac.kr

participants are required to repeatedly pick a card from one of four decks; this gambling card task measures the ability to choose between high gains with the risk of even larger penalties, and low gain with the risk of smaller penalties, making the choice of lower short-term gains with smaller penalties more advantageous in the long-term. The IGT is therefore a measure of decision making that simulates a real-life decision-making situation that requires evaluation of gains and penalties under uncertain probability.

The IGT has been tested in healthy subjects and over a wide range of patients. Investigation in healthy subjects revealed signal changes in the ventromedial prefrontal cortex (VMPFC) while carrying out the IGT, suggesting its involvement (2, 7, 14, 25). Patients with lesions in the right VMPFC remain unable to develop affective reactions with appropriate affective judgment (10, 20, 22, 28, 30). Correspondingly, these patients show poor IGT performance, with selection of high-risk cards and absence of learning effect over time. Various psychiatric disorders can be characterized by poor decision-making; for example, poor IGT performance has been demonstrated in patients with impulsive personality disorder (1), pathological gambling (9), and substance abuse (3, 6, 7).

In recent years, there has been growing interest in understanding the neural mechanisms that underlie decision making. Evidence from functional neuroimaging studies is limited, despite converging evidence from neuropsychological and animal studies suggesting that decision making is supported by a distributed network of brain regions including the orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (DLPFC), thalamus, parietal cortices, and caudate (15). Few functional neuroimaging studies have investigated the neural substrates underlying the IGT, even though it captures both the emotional and cognitive components of decision making and is widely used to assess decision-making abilities.

In a positron emission tomography (PET) study of healthy subjects, Ernst et al. (16) investigated regional brain activations associated with IGT and reported widespread neural activations in the orbitofrontal, dorsolateral, prefrontal, and anterior cingulate cortices, after controlling for expectations of outcomes. Fukui et al. (19) carried out an event-related functional magnetic resonance imaging (fMRI) study of healthy subjects using the IGT. The authors used an event paradigm to obtain statistical parametric maps by subtracting an fMRI data set of safe decks (low gain with a risk of smaller penalties) from a data set associated with risky decks (high gains with a risk of even larger penalties), and showed that the risk anticipation component exclusively activated the medial frontal gyrus; however, this fMRI study lacked baseline scans for which no decision was made but the task was identical in all other respects, thus precluding evaluation of the decision making. These previous neuroimaging studies used IGT to evaluate the summation of brain activity over a period of time, during which multiple cognitive components and emotional reactions were required. Hence, the temporal response of brain activity associated with decision making, which is an important component of the IGT, may not have been appropriately evaluated.

For the majority of healthy subjects, the IGT consists of two phases. (1) During an early or initial phase (approximately the first half of 100 trials) the subjects learn to make choices, although without any explicit knowledge regarding the contingencies in the task that guide their decision. At this stage, the decisions are largely guided by implicit information; these types of decisions are called 'decisions under ambiguity' (4). (2) During a latter phase (the second half of 100 trials), where subjects acquire some conceptual knowledge regarding the contingencies in the task, the decisions become more strongly influenced by explicit knowledge regarding the risks associated with each deck. These types of decisions are termed 'decisions under risk'. Previously, the distinction between 'decisions under ambiguity' in the early stages and 'decisions under risk' in the later IGT trials was supported by comparing performance in a gambling task that provided explicit (rather than ambiguous) information regarding the probabilities of the outcome of a given decision. Therefore, in IGT the early and late trials measure two qualitatively distinct forms of decision making; however, the point at which the process shifts from decisions under ambiguity to decisions under risk is not clearly defined.

Both risky and ambiguous decisions require a choice without certain knowledge of the outcome, and may possibly rely on the same underlying neural

mechanisms; however, it is equally possible that different neural circuits may support these two qualitatively distinct forms of decision making. In the present study, we assessed the neuronal responses over time during IGT performance using block-design fMRI to examine whether the neural substrates for risky decisions are functionally dissociable from those involved in handling ambiguous decisions. In particular, we focused on the role of distinct portions of the medial prefrontal cortex (mPFC) in decision making, as measured by different blocks of IGT over time, by predicting that there exist dissociable roles of distinct sectors of mPFC in processing risky and ambiguous decision making.

Subjects and Methods

Subjects

Fourteen healthy, right-handed subjects (5 women, 9 men; average age, 26.8 years; age range, 23-39 years) participated in this study. Subjects had been screened to exclude psychiatric, neurological, or possible medical conditions that might affect decision-making ability. After detailed explanation of the study design and potential risks, all subjects gave written informed consent. All study protocols were approved by the local Internal Review Board.

Task

Participants lay supine in a magnetic resonance imaging scanner and held a computer mouse in their right hand. Visual stimuli were back-projected onto a screen and viewed through a mirror built into the head coil; subjects used the mouse to select one of the four decks of cards (Fig. 1). Participants were instructed to maximize their profit by picking one card at a time from each of the four decks. They were told that the amount they had won would be indicated after each card selection, and also whether they had incurred a penalty. Participants were also informed that some decks were more advantageous than others, and that they could switch from one deck to another at any time. The subjects were not informed of the schedule of rewards and penalties or how many cards would be played. The gambling task was stopped after 100 card selections. We developed a computerized version of the IGT for the experiment, with the following differences from the original version: (1) play money was converted from dollars to Korean won, and (2) the time allowed for each card selection was limited to 5 s; a random choice was made by the program if the selection time had elapsed. Random choices were excluded from the analysis even though the percentage of random choice was minimal. The experiments consisted of two sessions: active tasks and control tasks.

Four decks were presented in the active task (computerized version of the IGT); each trial began when the message "Pick a card" was displayed. The subject then chose one of the four decks by pointing and clicking the mouse within the selection time of 3 s. The selected card was displayed for 2 s and the responses were recorded for subsequent analyses. The reward was presented for 2 s as an image of Korean currency notes (1,000,000 won for Decks A and B; 500,000 won for Decks C and D), and the penalty (a total punishment of 12,000,000 won for every 10 cards for Decks A and B; a total punishment of 2,500,000 won for every 10 cards for Decks C and D) was then displayed for 2 s. The reward/penalty schedules were predetermined: Decks A and B yielded high immediate rewards but carried a risk of much higher long-term penalties that result in total loss in the long run (disadvantageous decks). In contrast, in Decks C and D (advantageous decks), the accumulated penalties were smaller than the accumulated gains. Thus, continued choice from either Deck C or D resulted in a net win, whereas choices from either Deck A or B resulted in a net loss.

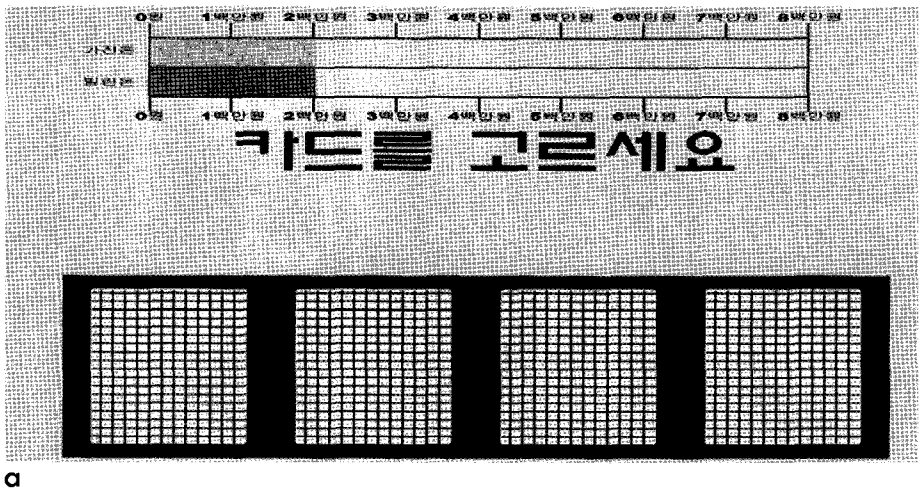
The control task was designed to replicate the active task in all aspects except for decision making. In the control task, four decks were presented and each trial began with the displayed message "pick from Deck A". During the task the participants selected a deck according to the instruction message on the screen. The order of the displayed sentences was A-B-C-D-A-B, etc; therefore, participants had no choice in deck selection. The four decks had equal gains and losses in the control task; thus, the active and control tasks were similar with regard to motor demands and in exposure to gains and losses, except for decision making. The entire control task lasted for approximately 20 min.

Functional Magnetic Resonance Imaging

Blood oxygenation level dependent (BOLD) contrast was collected for each subject using a 3.0 T VHi scanner (GE Medical Systems, Milwaukee, WI, USA) equipped with a transmit-receive body coil and a commercial eight-element head coil array. T2*-weighted echo planar imaging was used for fMRI acquisition. The following acquisition parameters were used in the fMRI protocol: echo time (TE) = 40 ms, repetition time (TR) = 2000 ms, field of view (FOV) = 22 cm, acquisition matrix = 64 × 64. A midsagittal scout image was used to position 24 contiguous axial slices of 4 mm thickness along the anterior-posterior commissure (AC–PC) plane, to cover the entire brain. The first three acquisitions were discarded due to T1-saturation effects. A 3-D T1-weighted anatomical scan was obtained for structural reference.

Functional Image Data Analysis

The raw fMRI data obtained over the course of the IGT were divided into five separate blocks of trials (20 trials each), and the activations for each block were analyzed by testing the differences in BOLD signal between the active and control tasks. Image processing and statistical analyses were carried out using MATLAB v. 7.2 (The Mathworks Inc., Natick, MA, USA) and Statistical Parametric Mapping (SPM 2; Wellcome Department of Imaging Neuroscience, London, UK; online at http://www.fil.ion.ucl.ac.uk) (18). For each subject, the functional images were corrected for sequential slice timing, and all images were realigned to the first image to correct for head movement between scans. The realigned images were then mean-adjusted by proportional scaling and spatially normalized into standard stereotactic space to fit the Montreal Neurological Institute template (17)



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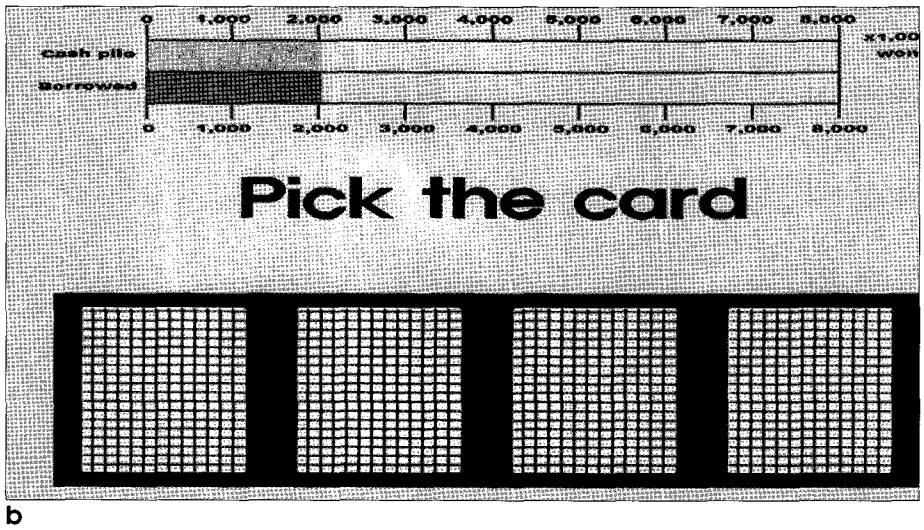

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Fig. 1. Visual presentation of computerized version of the IGT in korean and English version. Participants were instructed to maximize their profit by picking one card at a time from each of the four decks in korean version of the IGT. All money amounts were represented in Korean won.

used in SPM 2. The functional images were smoothed using a 4-mm full-width half-maximum Gaussian kernel to increase the signal-to-noise ratio and to account for anatomical variations between subjects. In first-level (fixed effects) analysis, a statistical parametric map (SPM) and corresponding contrast image were obtained for each subject using the fixed effects general linear model, contrasting each block of trials of the IGT versus contrast task. These contrast images were then entered into second-level (random effects) analysis for group comparison to take inter-subject variability into account and allow more generalized inferences to be made from the data than is possible using a fixed-effects model (23, 29). A one-sample t-test was used to calculate the main effect within the group of subjects. Due to the small number of subjects, a height threshold of $p < 0.005$ was used for all these analyses, uncorrected for multiple comparisons. To limit the false discovery rate (FDR), activated clusters in these thresholded maps were considered significant if their spatial extent was > 16 voxels. Finally, the resulting activation maps were created to identify the anatomical correlates of the activity, and these were displayed by projection onto the anatomically standardized mean T1 image of all subjects.

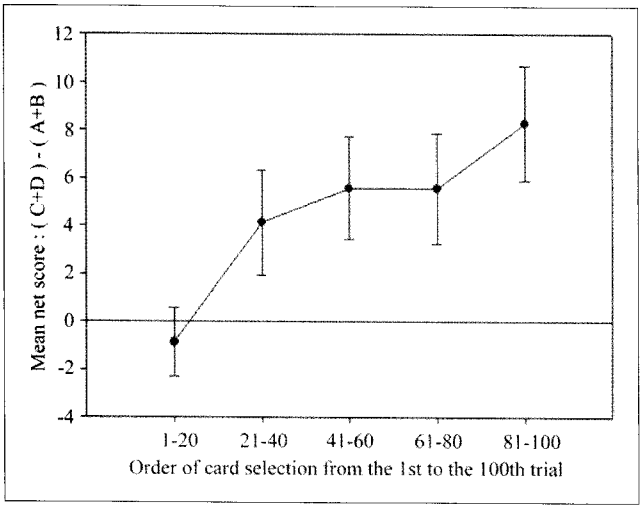

Fig. 2. Net scores ((**C+D**) - (**A+B**)) of cards selected by healthy subjects across different blocks expressed as mean ± standard error. Positive net scores reflect advantageous IGT performance while negative net scores reflect disadvantageous performance. Single comparisons (corrected for multiple comparisons) between performances in each block revealed that there was a significant difference between blocks ($p = 0.05$).

Statistical Analysis

All statistical analyses were carried out using the Statistical Package for the Social Sciences (SPSS) version 13.0 (SPSS Inc, Chicago, IL, USA). We conducted one-way analysis of variance (one-way ANOVA) to analyze the profile of IGT performance, with 'BLOCK' as the within-subject factor.

Results

IGT Performance

Although the IGT consists of a continuous series of 100 choices, we divided performance into five separate blocks of trials to analyze for possible trend over the duration of task performance (Block 1 = trials 1 to 20, Block 2 = trials 21 to 40, Block 3 = trials 41 to 60, Block 4 = trials 61 to 80, and Block 5 = trials 81 to 100). As shown in Fig. 2, the subjects chose disadvantageous decks more frequently than advantageous decks during the first block of the IGT. After the first block, subjects shifted to the advantageous decks in Block 2 and shifted to an even higher degree in Blocks 3, 4, and 5. Single comparisons (corrected for multiple comparisons) between performances in each block revealed a significant difference between blocks ($df = 4$, $p = 0.05$). Accordingly, the typical pattern for the subjects over time was a decrease in the selection of high-risk cards (Decks A and B) and an increase in the selection of low-risk cards (Decks C and D).

fMRI Activation Study

The activation regions for the five separate blocks of trials in the IGT are shown in Fig. 3, 4 and Table 1. From Block 1 to Block 5, the results illustrate that activity in the mPFC moves gradually from the dorsal to the ventral mPFC over the course of the IGT. Regarding the events in the first block (Block 1), significant activation was found in the dorsal mPFC ($x = -2$, $y = 32$, $z = 32$) partly including the ACC. In Block 2, multiple activations regions were distributed in the medial superior frontal cortex ($x = -2$, $y = 28$, $z = 56$), supracallosal sector of the ACC ($x = -4$, $y = 30$, $z = 36$), and rostral sector of the mPFC ($x = 8$, $y = 24$, $z = 48$). Of the multiple activation peaks in Block 2, there was a large overlap of the supracallosal sector of the ACC with the activation region ($x = -4$, $y = 30$, z

= 30) of Block 3. In addition to neural activity in the supracallosal sector of the ACC, the activation map of Block 3 also showed activity in the right parahippocampal area (x = 24, y = -28, z = -18). Regarding the events in Block 4, two activation peaks were identified in the ventromedial sector of the ACC (x = -2, y = 34, z = 28 and x = 4, y = 40, z = 16), and the lower activation region (x = 4, y = 40, z = 16) showed a degree of overlap with the activation region of Block 5. Finally, in Block 5, activation was revealed in the lowest ventromedial region of the ACC (x = 6, y = 36, z = 2). Therefore, our results clearly demonstrate that neural activity in the mPFC (including the ACC) moves gradually from the dorsal to the ventral sector of the mPFC, with maximum spatial difference of 58 mm in the z direction over the course of the IGT.

Discussion

While the roles of mPFC and ACC in decision making have been widely studied, the extent of the role of functionally differentiated sub-regions within the mPFC and ACC in decision making, as measured at different time periods in the IGT, remains unclear. Therefore, the goal of our study was to focus on the role of functionally differentiated sub-regions within the mPFC and ACC over the course of the IGT. Our results revealed brain activity for each block of 20 trials. From the first block (the first 20 trials of 100 trials in the IGT) to the last block, the main finding was that activity in the mPFC moves gradually from the dorsal to the ventral portion of the mPFC over the course of the IGT. That is, analysis of the first three blocks (Block 1 to 3) shows activation in the dorsal mPFC, partly including the ACC, and activity in the ACC moves in the ventral direction in the fourth block (Block 4). In performing the IGT, subjects mainly chose cards from the disadvantageous Decks A and B; the first three blocks correspond to ambiguous decision making. The dorsal mPFC, including the dorsal portion of the ACC, which was activated during the initial three blocks in the IGT, has been suggested as a cognitive division. This cognitive subdivision is part of a distributed attentional network that maintains strong reciprocal interconnections with the lateral prefrontal cortex (BA 46/9), parietal cortex (BA 7), and premotor and supplementary motor area 6. Various functions have been ascribed to this cognitive division, including modulation of attention, monitoring competition, complex motor control, motivation, error detection and

Table 1. Brain Activity in the Separate Blocks of the IGT

Block	Region	P-value	Cluster size	Coordinates(mm)			Peak T
				x	y	z	
Block1	Middle Frontal Gyrus	0.001	26	44	24	48	5.19
	Cingulate Gyrus	0.001	42	-2	32	32	3.60
		0.001					
Block2	Superior Frontal Gyrus	0.001	62	-2	28	56	4.54
	Superior Frontal Gyrus	0.001	19	0	52	30	4.12
	Medial Frontal Gyrus	0.001	21	8	24	48	3.89
	Limbic Lobe	0.001	42	6	34	26	3.61
	Cingulate Gyrus	0.001	89	-4	30	36	3.53
Block3	Middle Frontal Gyrus	0.001	26	44	22	50	4.66
	Inferior frontal Gyrus,	0.001	22	34	22	-8	4.57
	Cingulate Gyrus	0.001	40	-4	30	30	4.18
	Parahippocampal	0.001	24	24	-28	-18	4.10
	Superior Frontal Gyrus	0.001	22	28	22	60	4.06
	Anterior Cingulate Gyrus	0.001	47	10	34	28	3.92
Block4	Caudate	0.001	78	0	12	6	4.85
	Anterior Cingulate Gyrus	0.001	36	-2	34	28	4.57
	Anterior Cingulate Gyrus	0.001	23	30	18	-22	4.01
	Anterior Cingulate Gyrus	0.001	48	4	40	16	3.91
	Limibic Lobe	0.001	36	10	32	28	3.84
Block5	Parietal Lobe	0.001	19	52	-52	54	3.58
	Anterior Cingulate Gyrus	0.003	16	6	36	2	3.08

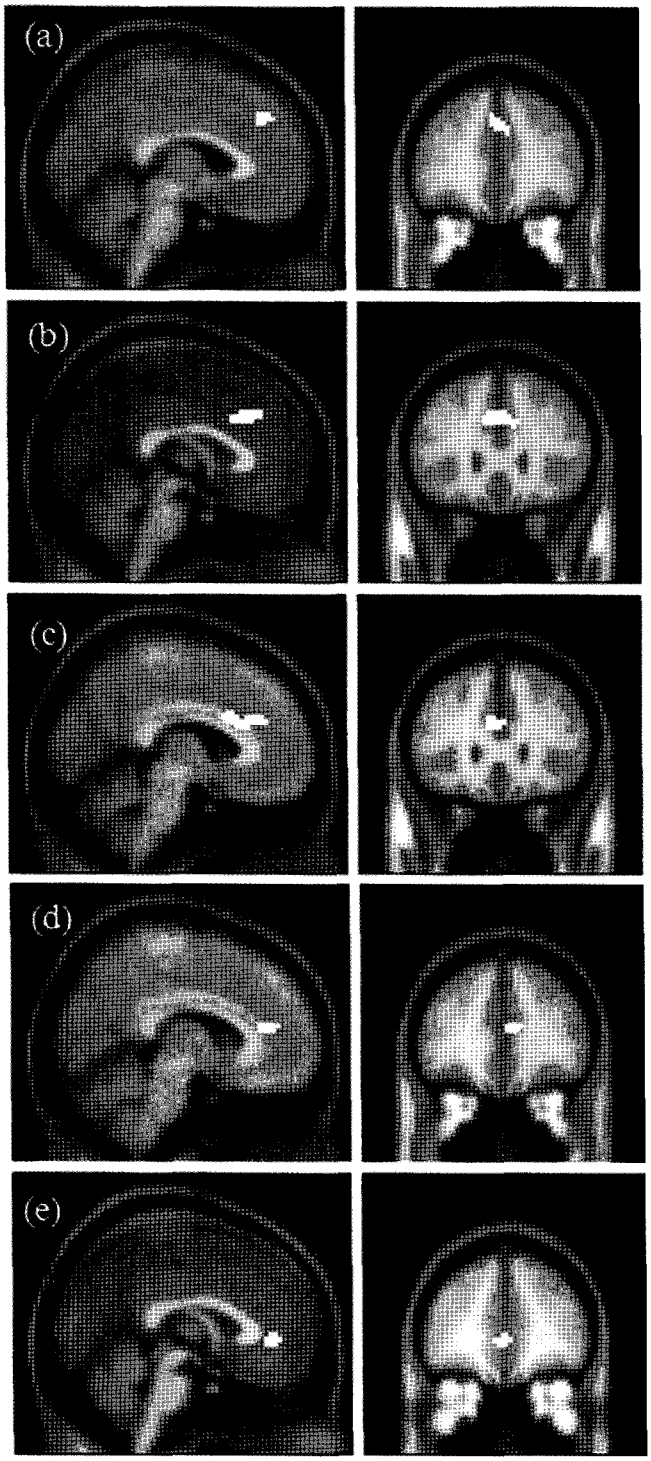

Fig. 3. Brain activation maps rendered on the mean standardized T1 anatomical image of one subject for each blocks consisting of 20 trials; (**a**) block 1 = trials 1 to 20, (**b**) block 2 = trials 21 to 40, (**c**) block 3 = trials 41 to 60, (**d**) block 4 = trials 61 to 80, and (**e**) block 5 = trials 81 to 100.

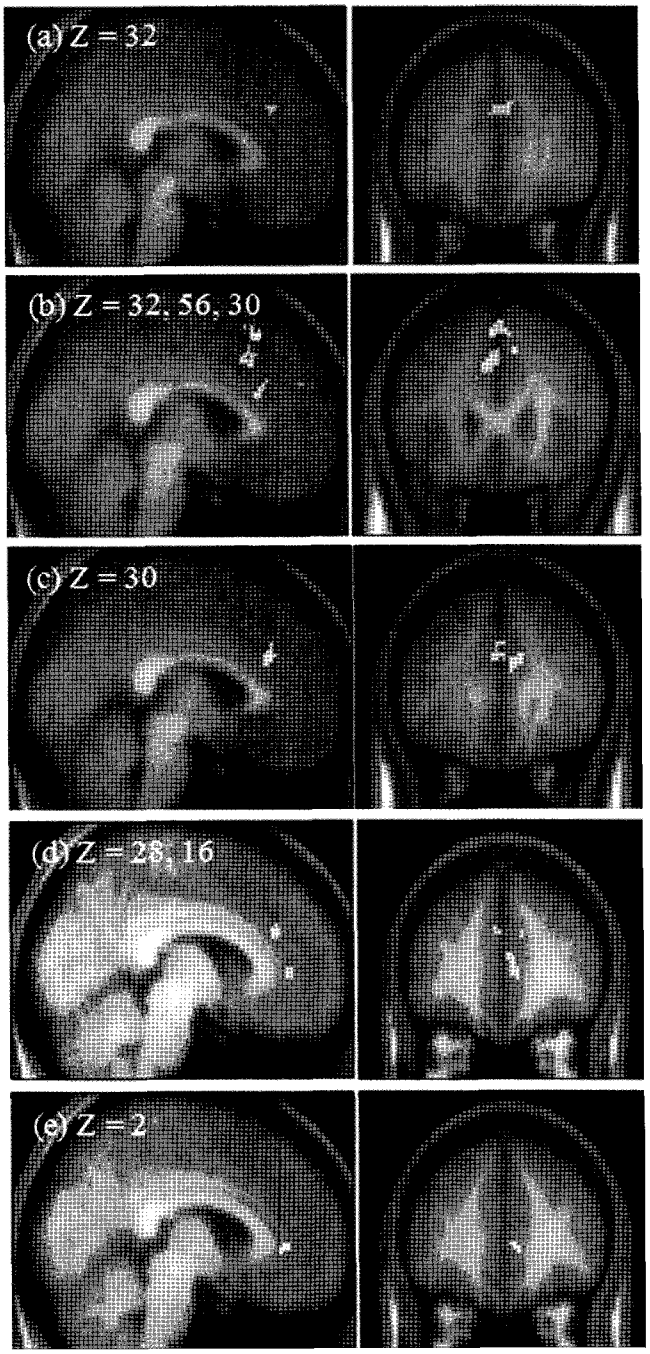

Fig. 4. Brain activation maps rendered on the mean standardized T1 anatomical image of all subjects for each blocks consisting of 20 trials; (**a**) block 1 = trials 1 to 20, (**b**) block 2 = trials 21 to 40, (**c**) block 3 = trials 41 to 60, (**d**) block 4 = trials 61 to 80, and (**e**) block 5 = trials 81 to 100. The activity in medial prefrontal cortex (mPFC) moves gradually from dorsal ACC to ventral ACC over the course of the IGT by suggesting that the cognitive division of mPFC including dorsal portion of ACC plays major role in ambiguous decision-making and the IGT corresponding to risky decision-making was associated with significant activities within a corticolimbic network strongly implicated in emotion and reinforcement.

working memory, and anticipation of cognitively demanding tasks (8, 12, 13). Therefore, our data suggest that the cognitive division of the mPFC, including the dorsal portion of the ACC, plays a major role in ambiguous decision making.

After the third block (trials 41 to 60 in the IGT), neural activation was shown in the most rostral/ventral portion of the mPFC. This division of the mPFC, including the ACC, which has dense projections to the OFC, striatum, amygdala, and brain stem, is known as the emotional sector of the ACC. More generally, the rostral/ventral ACC is part of a wider interconnected network organized around the ventral mPFC, which projects to a number of cortical and subcortical structures. This mPFC network encompasses a wide range of neural and neurochemical systems implicated in reinforcement, reward preference, and autonomic functions. Our results from the last two blocks of the IGT therefore suggest that the performance of latter phases of the IGT corresponding to risky decision making was associated with significant activity within the corticolimbic network, strongly implicated in emotion and reinforcement. This distinction is consistent with a growing body of literature showing that the ACC, which is a specialization of the neocortex (it contains a class of spindle-shaped neurons that are found only in humans), has two subdivisions, including a dorsal cognitive division and a rostral-ventral affective division (21, 26).

Northoff et al. (2004) demonstrated that pronounced emotional engagement in affective judgments is associated with increased activity in the ventral sector of the mPFC, while at the same time, higher activity in the ventral sector of the mPFC is associated with better IGT performance. Our findings are in accordance with the results of Northoff et al., in that neural activity in the ventral sector of the mPFC is related to the learning effect. That is, if the ventral mPFC is involved in beneficial decision making, neuronal activity in the ventral mPFC should only correlate with final (not initial) cards in the IGT. Our data clearly demonstrate that signal increases in the ventral ACC (during risky decision making) correlated only with final IGT performance, not with initial IGT, and may suggest that the correlation effect with ventral ACC signal increases could be related to transient learning rather than being a permanent personality trait. Therefore, this finding is in accordance with the observation of Northoff et al. of no significant difference between low- and high-IGT performers in the initial cards, which speaks against a low-risk personality trait.

Another interesting finding is that Blocks 2 and 4 showed multiple activation peaks over the gradual changes in activation regions from dorsal to ventral mPFC during the course of the IGT. That is, of the multiple activation peaks in Block 2, there was a large overlap of the supracallosal sector of ACC with the activation region of Block 3; in Block 4, the lower activation region ($x = 4$, $y = 40$, $z = 16$) in the ventromedial sector of the ACC showed a degree of overlap with the activation region of Block 5. Although the conventional interpretation of the IGT is that the early trials (the first half of the 100 trials) measure decision under ambiguity whereas the latter trials (the second half of the 100 trials) measure decision under risk, our results from group analysis appear to suggest that further differentiation might be possible in both the ambiguous and risky decision phases. According to our data, the neural substrates activated in the first three blocks differed in their brain regions. Because these first three blocks are often referred to as belonging to the ambiguous decision phase, this result strongly suggests that even within an ambiguous decision-making situation, there are intermediate steps that guide different kinds of decision processes, and that two sub-phases may exist. Similarly, differences in activation regions were observed within the risky decision phase (Blocks 4 and 5), suggesting the possibility of further differentiation of the risky decision-making process; however, the exact role of each sub-phase and the relationship between them are currently unclear, although the two sub-phases engage partially separate neural systems. Finally, in this study, we employed block design paradigm instead of event-related design. Although event-related paradigm could be more effective in terms of temporal changes of decision making process, the relative BOLD signal intensity might be small compared to block design.

In conclusion, our data revealed that in a setting such as the IGT, differences occur in the neural structures of decision making depending on the nature of the decision being made. These findings are consistent with recent evidence from neuroimaging studies that found that cognitive division of the mPFC, including

the dorsal portion of the ACC, plays a major role in ambiguous decision making, and that risky decision making is associated with significant activity within the ventral aspect of the ACC, a network implicated in emotion and reinforcement. Most importantly, our results also revealed that activity in the medial prefrontal cortex moves gradually from the dorsal aspect of the mPFC to the ventral aspect of the mPFC over the course of the IGT, and that decisions made under ambiguity and decisions made under risk situations can be further divided into sub-phases based on the neural network involved.

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갬블링 과제를 사용한 의사결정 과정에서 중앙 전전두엽의 영역별 활성화에 대한 연구

[1]경북대학교 의용생체공학과
[2]국립부곡병원 정신의학과
[3]경북대학교 의과대학 영상의학과
[4]경북대학교 의과대학 분자의학과

이재준[1] · 배성진[1] · 김양태[2] · 장용민[1,3,4]

목적: 정상인을 대상으로 과제의 규칙을 모른체 의사결정를 하는 경우 시간에 따른 뇌활성영역의 차이를 Iowa Gambling 과제를 수행하는 자기공명 뇌기능영상을 사용하여 알아보고자 하였다.
대상 및 방법: 14명의 오른손잡이 정상인(여자 5명, 남자 9명, 평균나이 26.8세)을 대상으로 100개로 구성된 Iowa Gambling 과제를 수행하는 동안 자기공명 뇌기능영상을 획득하였다. GE 3.0T 자기공명영상 장치에서 혈액산소포화의존(BOLD) 기법을 사용하여 EPI 데이터 (에코시간 40 ms, 반복시간 2000 ms, 매트릭스 64×64)를 획득한 후 MATLAB 버전 7.2 (The Mathworks Inc., Natick, MA, USA) 와 Statistical Parametric Mapping (SPM 2; Wellcome Department of Imaging Neuroscience, London, UK) 분석툴을 이용하여 총 100개 중 20개 단위로 구성된 5개의 블록으로 나누어 분석하였다.
결과: 과제 수행초기 블록에서는 위쪽 중앙 전전두뇌엽에서의 뇌활성화를 나타내고 과제를 수행해 감에 따라 뇌활성화 영역이 점차 중앙 전전두뇌엽의 아래쪽으로 이동하는 결과를 나타내었다 ($p < 0.005$).
결론: 의사결정 과제의 규칙을 모르는 경우 과제를 수행하며 규칙을 알아가는데는 위쪽 중앙 전전두뇌엽의 영역을 사용하고 과제의 규칙을 깨달은 다음 의사결정을 수행하는 경우에는 아래쪽 중앙 전전두뇌엽의 영역을 사용함을 알수 있었다.

통신저자 : 장용민, (700-721)대구광역시 중구 삼덕동 2가 50, 경북대학교병원 영상의학과
Tel. 82-53-420-5471 Fax. 82-53-422-2677 E-mail: ychang@knu.ac.kr