Brain Activation Pattern and Functional Connectivity Network during Experimental Design on the Biological Phenomena

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Abstract: The purpose of this study was to investigate brain activation pattern and functional connectivity network during experimental design on the biological phenomena. Twenty six right-handed healthy science teachers volunteered to be in the present study. To investigate participants' brain activities during the tasks, 3.0T fMRI system with the block experimental-design was used to measure BOLD signals of their brain and SPM2 software package was applied to analyze the acquired initial image data from the fMRI system. According to the analyzed data, superior, middle and inferior frontal gyrus, superior and inferior parietal lobule, fusiform gyrus, lingual gyrus, and bilateral cerebellum were significantly activated during participants' carrying-out experimental design. The network model was consisting of six nodes (ROIs) and its six connections. These results suggested the notion that the activation and connections of these regions mean that experimental design process couldn't succeed just a memory retrieval process. These results enable the scientific experimental design process to be examined from the cognitive neuroscience perspective, and may be used as a basis for developing a teaching-learning program for scientific experimental design such as brain-based science education curriculum.

Key words: experimental design; brain activation pattern; functional connectivity network, fMRI

I. Introduction

Testing hypotheses has been considered as a justification and deductive process of scientific knowledge generation (Kwon *et al.*, 2003) and regarded as one of the core reasoning processes in creative thinking and scientific discovery (Klahr & Dunbar, 1988; Kuhn *et al.*, 1988; Lawson, 1995; Kwon *et al.*, 2000; Kwon *et al.*, 2003). Therefore, a process of the experimental design (or invention of hypothesis−testing methods) is the most important procedure in generation of scientific knowledge (Klahr & Dunbar, 1988; McPherson, 2001). Many previous studies of the science education showed that experimental design plays an important role in the scientific inquiry (Jeong & Kwon, 2007; Kwon *et al.*, 2007; Park, 2003; McPherson, 2001).

In the context of cognitive psychology, the process of experimental design is an interactive procedure between declarative knowledge and procedural knowledge in the working memory of the brain (Elliot & Dolan, 1998; Gagne *et al.*, 1997). After all, students' scientific inquiry processes including experimental design were actually happen in their brain. In other words, different thinking resulted from different brain activation pattern. However, almost all of previous studies based upon indirect research methods such as paper and pencil test, interview, and questionnaire. Therefore actual brain activation pattern in intact brain was still remains unclear.

Recently, brain imaging technology (such as CT scan, PET, MRI, fMRI, and EEG) has enables us to understand directly the function of the living brain. These brain imaging methods help us to analyze the relationships between specific areas of the brain and the functions they serve. Particularly, fMRI is an non−invasive method of the imaging of the intact brain and essential for studying various functions of the brain (Buxton, 2002).

It has been proposed that functional brain architecture abides by two principles, namely, functional segregation and functional integration (Zeki & Shipp, 1988; Tononi *et al.*, 1998). While the segregation principle states that some functional processes specifically involve well-localized brain regions, the integration principle acknowledges that even simple behaviors imply the merging of information flows across many systems distributed in the whole brain (Passingham *et al.*, 2002). It is only through a subtle balance of these two principles that the brain can efficiently process functional tasks. Segregation and integration have been at the center of much attention in many areas of neuroscience, including theoretical neuroscience and neurocomputing, neuroanatomy, electrophysiology, and functional neuroimaging (Sporns *et al.*, 2004). Characterizing brain activity in terms of the functional specialization of sensorimotor and higher cognitive brain areas is the primary approach to functional neuroimaging data. However, characterizing brain activity in terms of functional specialization does not reveal anything about how different brain regions communicate with each other, despite the fact that communication is an implicit assumption of this specialization. For instance, the neural correlates of semantic processing can be identified using written words by virtue of the assumption that visual regions interact with semantic regions. Thus, analyses of neural activity based solely on functional specialization provide only a limited account of the neuronal substrate of the processes investigated. Alternative approaches have therefore been developed, in the context of functional neuroimaging, to investigate the integration of functionally specialized areas (Lee *et al.*, 2003).

Blood oxygen level dependent (BOLD) functional magnetic resonance imaging (fMRI) is an imaging technique that makes it possible to dynamically and noninvasively follow metabolic and hemodynamic consequences of whole-brain neural activity (Huettel *et al.*, 2004). As such, it stands as a potentially powerful candidate for in

vivo investigation of functional integration within brain networks. Indeed, it is now increasingly accepted that datasets acquired with that modality convey relevant information relative to functional integration; to what extent such information is available, though, is an issue that remains open and subject to controversies (Horwitz, 2003; Lee *et al.*, 2003). In fMRI, most approaches to study integration rely on either functional or effective connectivity (Friston, 1994; Marrelec *et al.*, 2006). The functional connectivity between two voxels or regions is defined as the temporal correlation between the voxel or region time courses (Friston *et al.*, 1993). This definition strongly relates to that of Hebbian neural assemblies (Hebb, 1949), and is moreover thought to be a relevant spatial scale to study such neural assemblies (Varela *et al.*, 2001). Measures of functional and effective connectivity then characterize the level of interregional integration for each possible pair of regions in a given set of brain regions that has been selected by the investigator.

Recently, Kwon *et al.* (2009) and Kwon & Lee (2007) reported to students' and biologists' brain activation patterns during the hypothesis-generating. Also, Kwon *et al.* (2007) investigated the pre-service elementary school teachers' brain activation pattern during invention of hypothesis-testing methods about biological phenomena. In this study, they were focused on the sub-steps of the hypothesis-testing process (① recognition of hypothesis → ② representation of relation of variables → ③ representation of experienced situations → ④ construction of hypothesis-testing methods). However, they could not know about whole representative brain activation pattern or neural network of the experimental design because they used separated paradigm. Therefore, in this study, we used functional magnetic resonance imaging (fMRI) to investigate the neural responses associated with the experimental design process at the aspects of not only regional activation pattern but also functional connectivity network.

Ⅱ. Methods and Procedure

1. Participants

Twenty six right-handed (12 males and 14 females), healthy science teachers volunteered to be participants in the fMRI experiment (age 27.57 ±3.72). All participants of this experiment had normal or corrected-to-normal visual acuity, no history of neurological, psychiatric or major medical illness, and were judged as the right-handed according to the Edinburgh handedness inventory (Oldfield, 1971). Each participant gave their informed consent prior to their inclusion in the experiment in accordance with the Declaration of Helsinki. The study was approved by the Ethics Committee of KNUE (Korea National Univ. of Education).

2. Development of the fMRI experimental tasks

To control and equalize the difficulty and the contents spectrum of the tasks for the fMRI stimuli, this study developed the tasks through the following R&D process (Borg & Gall, 1989). First, this study designed 40 task items for stimuli. Then, this study had a pilot test of the experimental design task to a separated group of 30 participants (another group who do not participated in this study). After the pilot test, the task items were selected and edited by the pilot test results. This study improved the validity and reliability of the task by repeating this process several times. Finally, unacceptable 22 items were deleted, and 9 items were selected for exercise task. Therefore, the other 9 items were selected for main experiment (Table 1).

The content validities of these tasks were investigated. To obtain a measure of the face validity of the test, nine professors with relevant expertise and eight graduate students majoring in science education were asked the question, "Do you agree that the tasks can assess the brain activation pattern of participant in the experimental design?" The average validity was 0.94.

3. fMRI experimental task conditions and procedure

The experimental paradigm was consisting of 9 tasks (Fig. 1). Each task started with a blank slide for dummy phase (12s) followed by notice slide (3s). The notice slide, we have announced the task name (e.g. 'experimental design') to participants. When the main task was stated, the text slide (12s) was presented before the experimental design slide. This slide containing the scientific question and hypothesis of the biological phenomenon. Finally, enlarged picture of the biological phenomenon was presented to participants (24s). During this phase, participants should have designed experiments to test presented hypothesis. At the end of the trial the white crisscross fixation was presented for 12s. The participants were instructed to keep their eye open at all times and to fixate the central cross to minimize eye movements. Schematic diagram was showing exemplars of the stimulus display and the timings used in this study (Fig. 1).

Table 1

Topics and levels of the fMRI experimental tasks used in this study

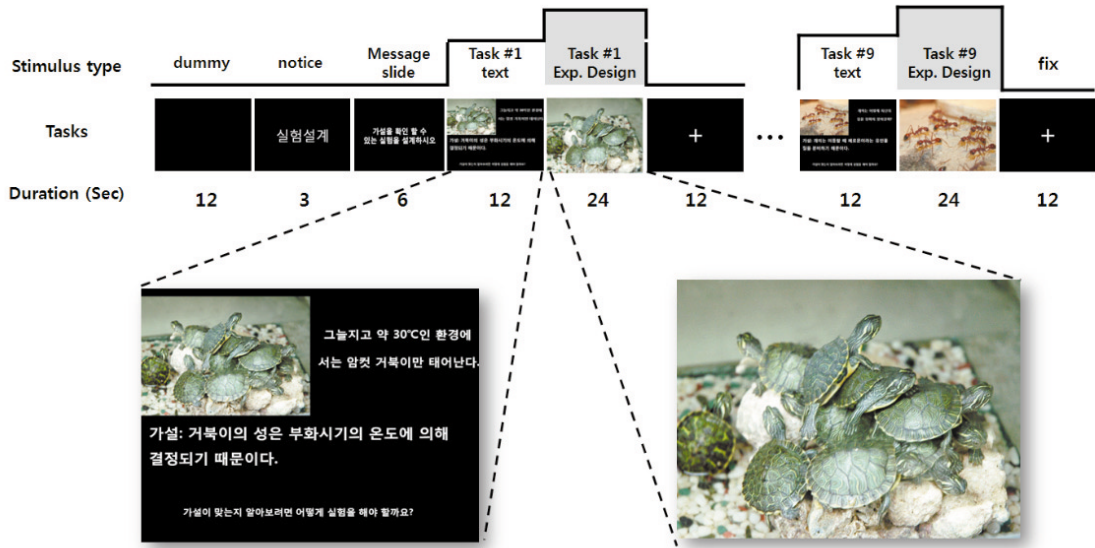| Level \ Topic	Animal	Plant	Microorganism
Under individual	1	1	1
Individual	1	1	1
Over individual	1	1	1
Total No. of tasks	3	3	3

Fig. 1 *Schematic representation of fMRI experimental design. The experimental paradigm was consisting of 9 tasks. In this figure, a representative trial was presented. See the text for explanation.*

4. fMRI data acquisition

Anatomic T1 volume images and functional T2*−weighted magnetic resonance (MR) images were acquired with a 3.0T MR scanner (ISOL, KOREA) with standard head coil. Functional images were acquired using a T2*−weighted gradient−echo, echo planar pulse sequence (30 continuous slices parallel to the anterior−posterior commisure [AC−PC] line covering the whole brain, repetition time [TR] = 3,000 ms, echo time [TE] = 35 ms, flip angle = 80 degree, field of view [FOV] = 220×220 mm^2, matrix = 64×64, slice thickness = 5 mm). Immediately after the functional scanning, a high−resolution T1−weighted anatomic scan was acquired for each subject.

5. fMRI data analysis

Image processing and statistical analysis were carried out using SPM2 (Wellcome Department of Cognitive Neurology, http://www.fil.ion.ucl. ac.uk/spm) implemented on MATLAB ver. 7.0 (The MathWorks, Natick, MA). Data from one subject were discarded due to the presence of artifacts in the functional images. The first five volumes of each subject were discarded due to allow for T1 equilibration effects. For each subject, all volumes were spatially realigned to the first volume of the first session to correct for between−scan motion, and a mean image from the realigned volumes was created. This image was spatially normalized to the Montreal Neurological Institute (MNI) brain template (Evans et al., 1993). The derived spatial transformation was then applied to the realigned T2*−weighted volumes, which after normalization were resampled. All functional volumes were then spatially smoothed with an 8−mm full−width half−maximum (FWHM) isotropic Gaussian kernel to compensate for residual between−subject variability after spatial normalization (to make comparisons across subjects) and to permit application of Gaussian random field theory for corrected statistical inference (Worsley & Friston, 1995). The resulting time series across each voxel were then high−pass filtered with an upper cut−off of 128s, using cosine functions to remove section−specific low−frequency drifts in blood oxygen level−dependent (BOLD) signal.

The statistical maps of the basic activation patterns were first computed. Data were analyzed

using a random-effect model to generalize results to the population from which subjects were extracted (Friston et al., 1999), implemented in a two-level procedure. In the first level, for each subject condition effects at each voxel were estimated according to the general linear model (GLM) as implemented in SPM2 (Friston et al., 1995) and regionally specific condition effects were evaluated using linear contrasts to produce a contrast image. At the second level, the resulting contrast images from all subjects were entered into a single sample t test to assess the population mean effects. The entire process produced for each comparison of interest a statistical parametric map of the parametric map of the t statistics for each voxel. Maxima were reported in MNI stereotaxic coordinates for foci exceeding a highest threshold of $p < 0.05$, corrected for multiple comparisons. To avoid false positive, only clusters bigger than 20 voxels were considered (Forman *et al.*, 1995). For visualization purpose, the foci of maximum activation were superimposed on a high-resolution anatomical image created by averaging the individual subjects' normalized T1 images with SPM2. The location of these foci in terms of Brodmann areas was determined using the nomenclature given by Talairach and Tournoux (1988) after correction for difference between the MNI and Talairach coordinate systems by means of a nonlinear transformation.

'Functional connectivity' is defined as the "temporal correlations between spatially remote neurophysiologic events" (Friston et al., 1993). This definition provides a simple characterization of functional interactions. Functional connectivity is simply a statement about the observed correlations (Lee *et al.*, 2003). The idea behind functional connectivity analysis is that regions that work together have similar temporal response profiles; therefore, a correlation coefficient between the activations of these regions across the time course should be high (Koshino *et al.*, 2005). To compute the measure of functional connectivity, BOLD signals of activated voxels were extracted from the selected-ROIs. For each participant, a mean time-course was computed across activated voxels in each ROI. A correlation coefficient was then calculated between the time-courses of pairs of ROIs. Finally, the significant functional connectivity networks among selected ROIs for hypothesis-generating and hypothesis-understanding processes were constructed. We regarded the correlation's P value less than 0.05 ($P < 0.05$) as the significant correlation in this study.

Ⅲ. Results and Discussion

1. In-depth interview result

After fMRI scanning, all of participants reported their actual thinking of each task through an in-depth interview. Results of linguistic analysis of the interview were showed in Table 2.

As shown in Table 2 almost all participants performed actual thinking activities.

2. fMRI Results

1) Brain activation patterns of the experimental design

To determine the basic pattern of activation for experimental design, we used the 'experimental design versus baseline' contrast to reveal areas showing significantly increased blood oxygenation level dependent (BOLD) signal during conditions in which participants were required to experimental design compared signals during the control baseline condition. The Talairach-space coordinates and their number of Brodmann's area and their significant Z-value($P < 0.05$, FWE corrected) are listed in Table 3.

The 'experimental design versus baseline' contrast yielded left-lateralized activations in the left dorsolateral prefrontal areas (the superior, middle, and inferior frontal gyrus, ; BA 6, 9, 45), the left superior parietal lobule (BA 7), the left inferior parietal lobule (BA 40), the right fusiform gyrus (BA 19), the left lingual gyrus (BA 18) and

Table 2

Results of in-depth interview after fMRI scanning

Participants	Tasks									Actual thinking (%)
	1	2	3	4	5	6	7	8	9	
1	O	O	O	O	O	O	O	O	O	100
2	O	O	O	O	O	O	O	O	O	100
3	O	O	O	O	O	O	O	O	O	100
4	O	O	O	O	O	O	O	O	O	100
5	O	O	O	O	O	O	O	O	O	100
6	O	O	O	O	O	O	O	O	O	100
7	O	O	O	O	O	O	O	O	O	100
8	O	O	O	O	O	O	O	O	O	100
9	O	O	O	O	O	O	O	O	O	100
10	O	O	O	O	O	O	O	O	O	100
11	O	O	O	O	O	O	O	O	O	100
12	O	O	O	O	O	O	O	O	O	100
13	O	O	O	×	O	O	O	O	O	89
14	O	O	O	O	O	O	O	O	O	100
15	O	O	O	O	O	O	O	O	O	100
16	O	O	O	O	O	O	O	O	O	100
17	O	O	O	O	O	O	O	O	O	100
18	×	O	O	O	O	O	O	O	O	89
19	O	O	O	O	O	O	O	O	O	100
20	O	O	O	O	O	O	O	O	O	100
21	O	O	O	O	O	O	O	O	O	100
22	O	O	O	O	O	O	O	O	O	100
23	O	O	O	O	O	O	O	O	O	100
24	O	O	O	O	×	O	O	O	O	89
25	O	O	O	O	O	O	O	O	O	100
26	O	O	O	O	O	O	O	O	O	100

O: success in actual thinking during fMRI scanning, ×: failure in actual thinking during fMRI scanning

the cerebellum (the left culmen, the right pyramis, the bilateral declive and the right tuber) (Fig. 2 and Table 2).

Conducting the scientific experimental design in this study, the brain activation regions that were shown in the participants all appeared in left hemisphere exclude the right declive (Fig. 2, 3). First, the activation of left superior frontal gyrus was revealed in the experimental design (Fig. 2, 3). For this region, its significant connection with the left inferior parietal lobule was revealed in the functional connectivity map (Fig. 3). This region is known to play a role in integrating abstract information (Green et al., 2006). The dorsolateral frontal cortex (DLFFC; BA 6, 9) is a region that has been implicated previously in the inspection and manipulation of information already maintained in memory (Fletcher & Henson, 2001) and in executive functioning. According to Petrides (1995), the DLPFC is typically involved in cognitive processes concerning monitoring and manipulation of information in working memory. Other authors state the dorsolateral prefrontal cortex is involved in relational integration, which is necessary for reasoning processes that require one to consider multiple relations simultaneously

Table 3
Brain regions showing significant activations in contrast experimental design versus baseline

Brain region	Region of activation	BA & Side		Z score	Talairach coordinates		
					x	y	z
Frontal lobe	Superior frontal gyrus	6	L	6.28	−8	16	56
	Middle frontal gyrus	9	L	6.08	−51	13	31
		6	L	5.50	−36	14	47
	Inferior frontal gyrus	45	L	6.00	−57	11	20
Parietal lobe	Superior parietal lobule	7	L	4.98	−24	−64	46
	Inferior parietal lobule	40	L	4.89	−46	−38	46
Occipital lobe	Fusiform gyrus	19	R	4.75	30	−68	−7
	Lingual gyrus	18	L	4.70	2	−74	−5
Cerebellum	Culmen		L	4.89	0	−51	−9
	Pyramis		R	5.85	24	−67	−27
	Declive		R	5.80	26	−69	−20
			R	4.89	18	−75	−16
			L	5.46	−20	−73	−18
			L	4.88	−28	−67	−20
	Tuber		R	5.59	30	−60	−29

BA: Brodmann areas, L: left hemisphere, R: right hemisphere
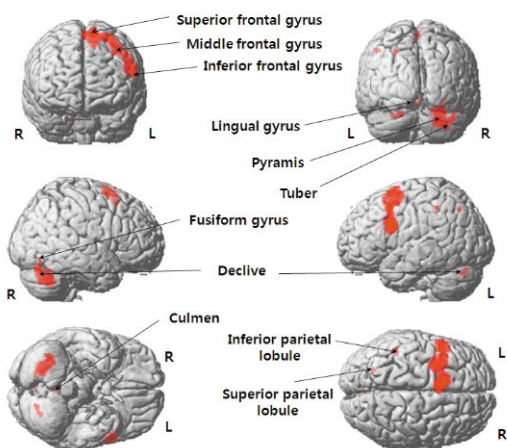
Fig. 2 *Brain activation pattern during experimental design on the biological phenomena (P < 0.05, FWE corrected)*

(Robin & Holyoak, 1995) and to integrate information from various source (Christoff *et al.*, 2001; Kroger *et al.*, 2002). The activation and connections of these regions mean that experimental design process was not success just a memory retrieval process. To get the complete experimental design knowledge, participants should require not only semantic retrieval but also integrating an abstract information such as abductive process.

2) Brain functional connectivity network of the experimental design

In order to examine the neural correlation network among the involved regions, we then calculated percent signal changes of the activated regions (time-series of BOLD signals) in experimental design process for each participant and calculated the Pearson's correlation coefficient among all the regions detected from the prior analysis: selected-ROIs. Several previous neuroimaging studies have indicated the possibility of the functional connectivity or associations using correlation analyses among regions (Tsukiura *et al.*, 2001). Significant correlation network in analysis is shown in Fig. 3.

In our functional connectivity network model of the experimental design, all of their correlation coefficient between ROI pairs were above r =.5. The network model was consisting of six nodes (ROIs) and its six connections. In experimental
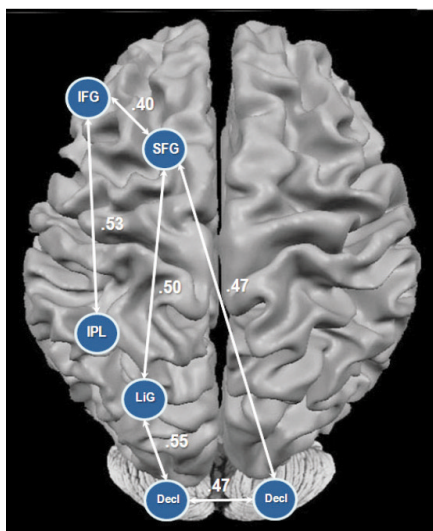
Fig. 3 *The significant functional connectivity networks among selected ROIs for experimental design processes. This study regarded the correlation's P value less than 0.05 (P < 0.05) as the significant correlation. The number on the line means the correlation coefficient. The abbreviations of circles mean the anatomical name of ROIs (MFG: Middle frontal gyrus, SFG: Superior frontal gyrus, IPL: Inferior parietal lobe, LiG: Lingual gyrus, Decl: Declive).*

design process, the left superior frontal gyrus (SFG) had the significant correlations with the left inferior frontal gyrus (IFG) (r = .40), left lingual gyrus (LiG) (r = .50) and right cerebellum (Declive; Decl) (r = .47). We also found the significant correlations between the left inferior frontal gyrus (IFG) and the left parietal lobule (IPL) (r = .53), between the left lingual gyrus (LiG) and the right cerebellum (Declive; Decl) (r = .55), and between the bilateral cerebellum (Declive; Decl) (r = .47) (Fig. 3).

Johnson-Frey (2004) reported that distinction between the roles of frontal (retrieval) and parietal (representation) mechanism in tool-use skills is well-suited for evaluation with functional neuroimaging techniques. To the successful experimental design, participants should have represent many suitable experimental instruments such as microscope, beaker, and alcohol lamp.

When they designing the experiment, however, they were represented not only the name and imagery of instruments (experimental tools) but also their using method (too-use skill memory) and procedure from their own experienced situations (Kwon *et al.*, 2003). Fronto-parietal pathway paly an important role in this process.

In this study, significant functional connectivities were found between bilateral declive, between left lingual gyrus and right declive, and between left superior frontal gyrus and right declive during the experimental design on the biological phenomena (Fig. 3). The well-known features of the cerebellum is a region of the brain that plays an important role in the integration of sensory perception, coordination and motor control (Rosenzweig *et al.*, 2005). However, cognitive role of the cerebellum is raised by recent neuroimaging studies (Blackwood et al., 2004; Caveza & Nyberg, 2000). Of the many cognitive functions controlled by the cerebellum, the ability to link a context with the appropriate response represents a cerebellar specificity (Thach, 2007). When this linkage is built the occurrence of the context (represented by a certain input reaching the cerebellum) triggers the appropriate response through the cerebellar areas. Because of the large number of anatomo-functional connections between the cerebellum and the prefrontal cortex (Middleton & Strick, 2001), it can be speculated that these areas interact in planning, the former by permitting acquisition of new efficient competencies and the latter by providing flexible shifting among already acquired and stored solutions (De Bartolo *et al.*, 2009). When participants designing the experiment, they should arrange experimental procedure by time-order from represented memory (tools and their skills). The activation of cerebellum and connectivity between frontal region and cerebellum paly an important role in this process.

Ⅳ. Conclusion and Implications

Experimental design is a kind of complex high-order inferential process (Elliot & Dolan, 1998; Gagne et al., 1997; Kwon et al., 2007; Jeong & Kwon, 2007). Therefore, it is more significant when they cooperate as neural correlates or a network than when they work all separately as a single region. In this study, functional connectivity analysis was conducted to search for the brain network which is related to experimental design. In consequence, this study found that there are six significant functional connectivity pairs in the experimental design process, which is connecting each region. Taken together, the brain network of the experimental design is left-lateralized and independent.

These results enable the examination of the scientific experimental design process from the cognitive neuroscience perspective, and may be used as basic materials for developing a teaching-learning program for scientific experimental design such as brain-based science education curriculum. In addition, this network model could be applied on the measuring individual differences or learning-related changes of the students' experimental design ability at the neurological level.

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