

# 行政院國家科學委員會專題研究計畫 成果報告

## 以功能性神經影像驗證性別科學認知能力差異的證據 研究成果報告(精簡版)

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中華民國 98年01月21日

## 以功能性神經影像驗證性別科學認知能力差異的證據

(原三年計畫僅獲准執行之第一年部分)

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## 1. Proposal Background

This proposal was designed for 96 年度性別科技研究, 五、女學生科學學習之研究(WR5, mainly aiming the 3<sup>rd</sup> goal of 女學生科學學習情況之研究)

1. 女學生科學學習歷程、困難、意願及楷模之研究
2. 女學生在科學學習環境之研究
  - (1) 科學課堂中教師與女學生互動與教學
  - (2) 社會環境對女學生學習科學之影響(社會刻板印象、社會期望)
  - (3) 女學生在科學方面之自我意象
3. 女學生科學學習情況之研究
  - (1) 國際評比中性別之差異及女學生表現研究
  - (2) 科學教育長期追蹤調查研究中性別差異及女學生表現研究
  - (3) 國內國中基測、高中學測中性別之差異及女學生表現研究

It has been three years since Congress passed the Gender Equity Education Act (性別平等教育法) which declares it "the policy of the Republic of China that men and women have equal opportunity in education and training in scientific and technical fields" (<http://law.moj.gov.tw>). Committees on Gender Equity Education have been established in Universities and Colleges for surveillance and construction of materials for education and examinations. For decades, sex difference in sciences and engineering has been debated for factors of genetics, biology, cognition, social bias, etc.. Considering the major cognitive abilities needed for success in science and engineering, the cognitive abilities of mathematics, verbal, and spatial domains have been emphasized with culture difference. In this proposal, biological evidences of sex difference in these cognitive functions will be pursued using the state-of-art neuro-imaging techniques combined with conventional psycho-behavioral approaches.

## 2. Sex Difference in Science and Engineering

### 2.1 Facts of Sex Difference in Scientific Performance

The academic faculties of U.S. universities are predominantly male, especially in the fields of mathematics, engineering, and science (**Table 1**). In the top fifty departments of U.S., the female averaged percentage is 18.1%, 14.1% and 6.3% for assistant, associate and full professors, respectively (12.9%, in average of total tenured faculties). Recent discussions of this disparity have focused attention on a pair of longstanding claims. First, there are fewer women on mathematics and science faculties because fewer women exhibit high talent in these fields. Second, this sex difference has a genetic basis: Women have less intrinsic aptitude for mathematics and science. And faculty profile in universities of Taiwan has shown similar trend in the female percentage, as 30% and 38% for universities and colleges, respectively (34%, in average of total tenured faculties) (**Table 2**).

WOMEN Ph.D.'s AND FACULTY, TOP 50 DEPARTMENTS IN SELECTED DISCIPLINES		
Discipline	Career level (% women)	

	Ph. D.	Asst. Prof.	Assoc. Prof.	Full Prof.
Biology	45.89	30.20	24.87	14.79
Physical Science	24.68	16.13	14.18	6.36
Astronomy	22.88	20.18	15.69	9.75
Chemistry	33.42	21.47	20.50	7.62
Computer Science	15.27	10.82	14.41	8.33
Math & Statistics	26.90	19.60	13.19	4.56
Physics	14.78	11.15	9.41	5.24
Engineering	15.34	16.94	11.17	3.68
Electrical	12.13	10.86	9.84	3.85
Civil	17.90	22.26	11.50	3.52
Mechanical	10.93	15.65	8.89	3.17
Chemical	24.98	21.38	19.19	4.37

**Table 1** : Statistics of Faculty Profile in United States; data from (1) D. J. Nelson, "Nelson diversity surveys" (Diversity in Science, Norman, OK, 2004) ([cheminfo.chem.ou.edu/~djn/diversity/top50.html](http://cheminfo.chem.ou.edu/~djn/diversity/top50.html)) and (2) NSF survey of earned doctorates/doctorate records file, WebCASPAR (<http://webcaspar.nsf.gov>).

	No. of University/Col lege	No. of Insitute	No. of Depart- ment	Tenued Faculties		
				Total	Female	Male
<b>University</b>	<b>97</b>	<b>2719</b>	<b>3140</b>	<b>35947</b>	<b>10659</b>	<b>25288</b>
					<b>(30%)</b>	<b>(70%)</b>
<b>College</b>	<b>50</b>	<b>113</b>	<b>1526</b>	<b>10979</b>	<b>4118</b>	<b>6861</b>
					<b>(38%)</b>	<b>(62%)</b>

**Table 2** : Statistics of Faculty Profile in Taiwan; data from [www.edu.tw/EDU\\_WEB/EDU\\_MGT\\_STATISTICS](http://www.edu.tw/EDU_WEB/EDU_MGT_STATISTICS).

## 2.2 Possible Mechanisms of Sex Difference in Scientific Performance

Three claims have been addressed for the cognitive sex differences account for the differential representation of men and women in high-level careers in mathematics and science: (a) males are more focused on objects from the beginning of life with tendency for better learning about mechanical systems; (b) males have a profile of spatial and numerical abilities producing greater abilities for mathematics; and (c) males are more variable in their cognitive abilities and therefore predominate at the upper portion of mathematical talent. Studies of cognitive development in human infants, preschool children, and students at all levels were not consistent to support these claims. Previous neuro-imaging and developmental studies provided evidence that mathematical and scientific reasoning develop from a set of biologically based cognitive capacities that males and females share.

These three arguments that males have greater intrinsic aptitude for careers in science and engineering ([www.wjh.harvard.edu/~ids/secsci](http://www.wjh.harvard.edu/~ids/secsci)) has the signals for the resignation of Dr. Laurence Summers from the President of Harvard University in 2006. In January 2005, Summers suggested, at a National Bureau of Economics Research (NBER) Conference on Diversifying the Science & Engineering Workforce, the possibility that many factors outside of socialization could explain why there were more men than women in high-end science and engineering positions. He suggested one such possible reason could be men's higher variance in relevant innate abilities, or innate preference (<http://www.president.harvard.edu/speeches/2005/nber.html>).

From birth, boys are more interested in objects and girls in people; this interest drives boys toward science and girls toward social pursuits. But Spelke (1990) and Baillargeon (2004) showed the gender equality in object learning, inferences about object motion and timing of learning object mechanics. The similar preference and learning paths continue through preschool and beyond. Males are intrinsically better at mathematics (or spatial reasoning) as proposed by Kimura (1999), but not by Dehaene (1997), Wang (2002) and Feigenson (2004). It involved five functional systems emerge in young children and underlie mathematical thinking in adults. Geary (1996) concluded as no sex differences in primary abilities for mathematics. But sex difference appear in later childhood; their biological and social mechanisms were not clear (Halpern, 2000; Newcombe, 2002; Gallagher, 2005). It seems there is a sex-difference in selecting strategies for solving complex task. So, in adulthood, concluded studies supported female advantage in (1) verbal fluency, (2) rapid mathematical calculation, (3) memory for the spatial positions of objects; and male advantage in (1) verbal analogies, (2) rapid mathematical reasoning, (3) memory for layout geometry, mental rotation. Males show greater variability in cognitive performance (“more geniuses, more idiots”).

Educational impact of previous sex difference studies has been demonstrated by the evaluation of test materials which might have gender bias (Browne, 2002; Halpern, 2002). Males and females tend to favor different strategies in solving mathematical word problems on speeded tests such as the quantitative portion of the Scholastic Assessment Test (SAT-M). When a problem can be solved either by verbal computation or by spatial imagery, males are more apt to use the latter (Geary, 2000), and they perform better on problems that relied on this strategy (Gallagher, 2002). The gender gap on tests of mathematical reasoning is narrowed when all students are encouraged to use the spatial strategy (Geary, 1996). All these findings suggest that differing strategy choices underlie some of the sex differences in mature cognitive performance (e.g., Linn, 1985). Biological evidences will be needed for construction of test materials for National-level examinations for senior high school and university. So, with completing this project, this proposal will also partially contribute to one of the research goals in 96年度性別科技研究, 四、人文社會領域對性別研究的關懷(WR43), 性別與社會正義(性別、科技與社會).

And hormone has been proposed to modulate the performance and cognition in human. Many discussions of the biological basis of men's and women's cognitive capacities focus on evidence that sex hormones modulate performance on specific cognitive tasks (for reviews, see Baron-Cohen, 2003; Halpern, 2000; and Kimura, 1999). The existence and nature of these effects would be relevant to this proposal, if performance on tasks influenced by hormones gave one sex a cognitive advantage in math and science disciplines. One of the mechanisms of menstrual modulation is the cycling change of estrogen. But the central effect was not clear in primary

perception, high-level cognition or both. Experimental designs of this proposal will control the effect menstrual cycle, preovulatory and ovulatory phases, as demonstrated in functional studies of facial recognition and social competence ability. So, with completing this project, this proposal will also partially contribute to one of the research goals in 96 年度性別科技研究, 二、婦女疾病之研究(WR2), 3.經期及更年期的研究.

### **3. FMRI of Gender or Sex Difference in Science and Engineering**

#### **3.1 Non-invasive Methods to Study Brain Functions**

The underlying principle of the blood oxygenation level dependent (BOLD) fMRI (functional magnetic resonance imaging) technique is based on the fact that despite of superfluous increase of regional cerebral blood flow after neural excitation a proportional increase of oxygen utilization does not follow (Weiskopf, 2003). This leads to a decrease in the concentration of vascular deoxygenated hemoglobin (paramagnetic), which in turn leads to a decrease in the local magnetic susceptibility. These changes are referred to as BOLD effects, indexing the neural activity, and constitute the main mechanisms in detecting the hemodynamic changes by fMRI. In addition to the ever-improving experimental designs for BOLD fMRI, instrumental advancement in terms of spatial and effective temporal resolution also promise the potential use in clinical settings. While the temporal resolution is not likely to approach those systems that are based on electromagnetic signals from neurons, the increase in temporal resolution relative to PET (positron emission tomography) is of outmost importance for improving the flexibility and power of experimental designs. Early demonstrations of the detection of the very brief visual stimuli (Savoy, 2005) were followed by the demonstration that randomly sequenced cognitive trials could be pooled to yield measurable fMRI signal differences (Buckner, 1996). In the latter study, brief stimuli were spaced well apart (e.g., one every 16 s) so that the hemodynamic response to the individual stimuli and cognitive response had time to rise and fall back to baseline levels. We have previously established several paradigms for functional mapping of the brain, e.g., language processing (Kuo, 2001; Kuo, 2003; Kuo, 2004), somatic and visceral pain perception (Niddam, 2002), and sensorimotor functions (Hsieh, 2002). By merging cognitive neuroscience and functional neuroimaging as well as neuropsychiatric medicine together, various protocols have been developed to disentangle different facets of specific cognitive components of brain function, e.g., protocols of word naming, word generation, and picture naming have been studied to elucidate central representation in the normal and have been applied to neuropsychiatric patients for various purposes. With the drastic advancement of non-invasive fMRI and other functional imaging/ mapping technique, we have now entered a challenging time to seriously put forth the fMRI study protocols for profound clinical applications and research. Considering the availability of high-field MRI and specific designs of fMRI test batteries of brain activation protocols to probe various cognitive/sensation/motor functions, the proposed fMRI-based study of the gender influence in science and engineering education are timely and of high impact.

#### **3.2 Sex Difference in Baseline Resting and Task Performance by fMRI**

The effect of sex on functional neuroimaging studies has received increasing attention. Although findings have not always been consistent, women have generally displayed more

distributed regional cerebral glucose metabolism than men at rest and during activation as well as higher regional and global cerebral blood flow, which may vary as a function of cognitive state or baseline difference. fMRI is a high-resolution, minimally invasive tool that has been used to demonstrate sex differences in the functional organization of language centers and primary sensory activation such as photic stimulation. Phonological activation with left lateralization in male was identified with more diffuse neural systems that involve both the left and right inferior frontal gyri in female (Shaywitz, 1995). Present brain functional studies based on comparison of different states, e.g. on and off statuses of tasks, with difficulty in defining the off or control state of alive human brain.

Several previous studies using FDG (18Fluoro-2-deoxy-D-glucose) PET and fMRI showed that there were consistent activation areas in the resting state, including posterior cingulate cortex (PCC) and ventral anterior cingulate cortex (vACC), called as default network or default mode (Raichle, 2001). These findings led to the hypothesis that these regions constitute a network supporting a default mode of brain function. The resting-state network of resting human brain exists and is modulated during cognitive processing, e.g. working memory task (Greicius, 2003). Gender difference of brain resting status has been addressed by early PET studies (Gur, 1995). Profile of metabolic activity was similar for men and women, metabolism was relatively higher in left association cortices and the cingulate regions and in right ventro-temporal limbic regions and their projections. However, men had relatively higher metabolism than women in temporal-limbic regions and cerebellum and relatively lower metabolism in cingulate regions. The results supported hypothesis that difference in cognitive and emotional processing have biological substrates. As compared to the default network identified by fMRI, consistent involvement of posterior cingulate and bilateral prefrontal regions in resting state was noted with discrepancy in lateral parietal areas, which dominated in resting fMRI results. Modulation of baseline default network during various cognitive activities is hypothesized to show gender/sex differences.

In fMRI studies of cognitive abilities required in science and engineering, one example is the localization of the sources of mathematical thinking. Formal mathematics is a recent achievement in the history of life on earth. Only humans in complex cultures develop and operate on natural number concepts and use numbers and geometry to map and measure their surroundings based on the older and more primitive systems that evolved for different purposes and that humans have harnessed to solve new problems (Geary, 1996; Kimura, 1999). Research in developmental and cognitive psychology and neuroscience serves to probe the nature and development of these systems and of the processes by which different systems come together to support new concepts and operations (Dehaene, 1997; Carey, 2001; Newcombe, 2002; Spelke, 2003; Feigenson, 2004). Such research provides evidence for five different cognitive systems at the core of adults' mathematical thinking. One system serves to represent small, exact numbers of objects: the difference between one, two, and three (e.g., Trick, 1994; Butterworth, 1999). A second system serves to represent large, approximate numerical magnitudes: the difference in number (though not weight or volume) between, for example, 60 swallows and 40 seagulls (van Oeffelen, 1982; Barth, 2003). A third system consists of the quantifiers, number words, and verbal counting routine that human gain with the acquisition of a natural language in childhood (Wynn, 1992). The fourth and fifth systems serve to represent environmental geometry and

landmarks, respectively, for purposes of navigation, spatial memory, and geometrical reasoning (Newcombe, 2000; Wang, 2002). When adults solve arithmetic problems, they activate areas of the brain that are involved in representing numerical magnitudes, language, and space (e.g., Dehaene, 1999). Lesion brain studies of adult patients typically show distinctive impairments in mathematical reasoning and calculation (e.g., Butterworth, 1999; Lemer, 2003). When college students are given a host of mathematical tasks, their performance shows signatures of these systems (Dehaene, 1997; Feigenson, 2004). Each of the five component systems emerges early in childhood. By six months of age, infants represent small numbers of objects, perform simple additions and subtractions on these small-number representations, and compare one small set to another on the basis of number (Feigenson, 2004). Six-month-old infants also distinguish between large, approximate numerosities when continuous variables are controlled, provided that the numbers differ by a large ratio (Xu, 2000). The detailed and contrasting limits on infants' performance with small versus large numbers provide evidence that the large- and small-number systems are distinct from one another and continuous with the systems found in older children and adults (Feigenson, 2004). Studies of these systems find no consistent sex differences at any age.

### **3.3 Why is fMRI Unique?**

Imaging studies has been demonstrated to be more efficient or powerful in statistical evaluation as compared to conventional psycho-behavioral or biological approaches (Fossella, 2002; Hariri, 2003). The novel approach using fMRI with specific paradigms will be applied in this proposal for reaching statistical significance with the minimal subject number.

## **4. Preliminary Results of fMRI Studies Relevant to Science Abilities**

In the following, we would like to present some research lines in our laboratories with preliminary results relevant to the aims of this proposal. With these working experiences, it won't take us too much effort and time to do technical development for data processing and experimental set-up. We can compare BOLD activities evoked in different tasks for gender differences. Especially, we will base on the findings of default networks of the brain for gender differences to develop our hypothesis for testing. BOLD signal of derived ROIs can be used to test gender effects on different tasks. In this way, we can not only examine gender differences on tasks of various cognitive abilities but also provide explanations and connection to possible underlying mechanisms.

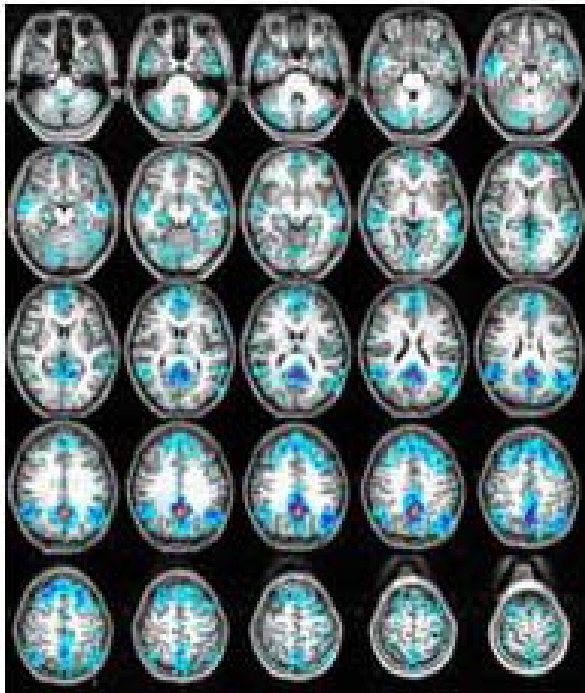
### **4.1 Baseline Activity and Default Network of Brain as identified by BOLD-based functional MRI**

#### **4.1.1 Baseline Activity of Resting**

Brain activities can be indirectly probed by functional magnetic resonance imaging (e.g. blood oxygen level dependence, tissue perfusion, magnetic resonance spectroscopy, etc.) and electrophysiology (EEG, MEG or cellular potential recording). For probing brain activities without known paradigms, applications of data-driven analyses (e.g. principle component or independent component analyses) were applied to demonstrate the parallel processing system of brain using BOLD-based fMRI.



For ten normal subjects (age: 22~26, right handed, male/female: 5/5) in preliminary studies, subjects were instructed to “empty their mind” and “prohibit imagery tasks” during the studies. BOLD-based fMRI was conducted using a 3T Medspec S300 system (Bruker GmbH, Ettlingen, Germany) equipped with an actively shielded gradient coil, a quadrature transceiver of head. Single-shot echo planar images (EPI) (64x64 matrix, slice thickness/ gap = 5/1 mm, 20 slices) covering whole brain were acquired with a flip angle = 90 degree, echo time (TE) = 50 ms, repetition time (TR) = 2000 ms, dummy scan (DS) = 5 for reaching stable magnetization and repetition number (NR) = 200. Independent component analysis (ICA) of the preliminary BOLD-based fMRI data was used with areas of increased signal normalized to sulcal landmarks as described in terms of the Brodmann’s area (BA) definitions that correspond according to the atlas of Talaraich and Tournoux (Talairach and Tournoux, 1988). All subjects showed the existence of unique brain activities symmetrically involving bilateral occipital, precuneus, posterior cingulate, inferior parietal lobule and prefrontal cortices [as bilateral Brodmann’s areas (BA) 6, 7, 8, 19, 23, 29, 30, 31, 39, 40 and right BA 21 with penetration scores  $\geq 5$ , **Figure 1**]. The characteristic resting rhythm or default network was named as the “tripod” signal of functioning human brain. The tripod component partially correlated to task-independent deactivation during visual task of previous PET study by utilizing resting glucose metabolism and blood flow (Gusnard, 2001). These decreases suggest the existence of an organized, baseline network of brain function that is suspended during specific goal-directed tasks. As comparing with global baseline in resting but awake status, Raichle et al. concluded a significant increase of cerebral blood flow and oxygen consumption in the medial BA 7, 10, and 31 (Raichle, 2001) that corresponds the highest penetration scores in BA 7 and 31 of tripod component. The tripod component echoes the fMRI connectivity of the posterior cingulate cortex, centered at [2, -51, 27] of BA 31, with extension to bilateral BA 7, 10, 11, 23, 31, 32, 39 and 40 when subjects kept eyes closed (Greicius, 2003). And the tripod network demonstrated dominant engagement of dorsal medial prefrontal cortices, BA 6 and 8, with a local cluster in BA 8 by penetration maps when subjects fixed their eyes on a dimmed visual target. With consistent visual fixation, the parietal and prefrontal correlates of visual consciousness or awareness might participate in the tripod network. The consistent tripod component represented synchronized activities involving posterior medial, posterior lateral, ventral medial prefrontal (VMPPF) and dorsal medial prefrontal (DMPF) cortices. Distribution of tripod component was consistent with the task-independent decreases demonstrated by signal decreases in activity of PET studies during a wide variety of goal-directed behaviors (Gusnard, 2001). Both medial and lateral parietal regions participate in conscious awareness as observed by functional brain studies of REM- and slow-wave sleep, anesthetic condition or vegetative states (Gusnard, 2001). The integration of these areas was supported by synchronic detection of tripod component as a continuous, but rhythmic, “simulation of daily behavior”, “an inner rehearsal of future” and “an optimization of cognitive and behavioral serial programs” for individuals.

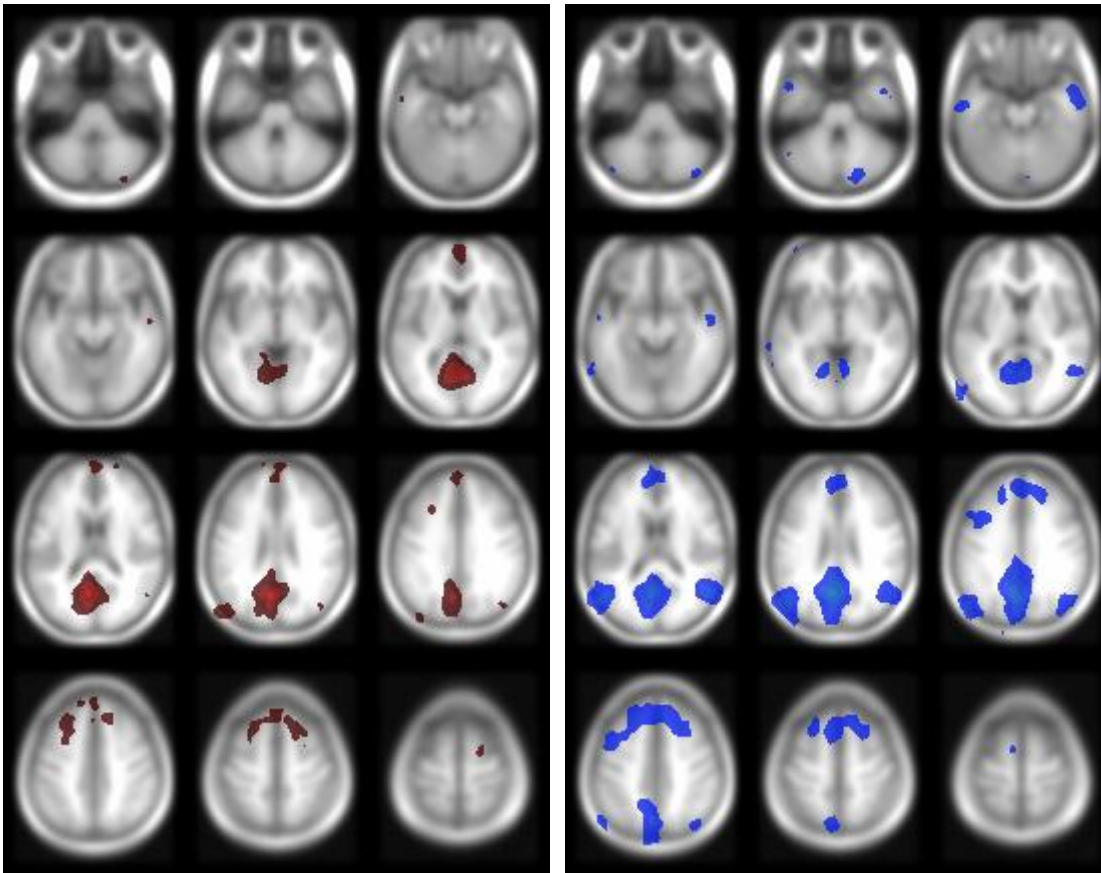


**Figure 1** : Reproducibility of resting rhythm (tripod component) of 10 subjects (5 male) was presented as the penetration maps in the normalized brain template. Statistical criteria were correlation coefficient  $> 0.4$  and voxel extension  $> 25$ .

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Gender difference of the default network (resting rhythm or tripod component) was illustrated in the preliminary study as **Figure 2**. Men showed relatively increased activity in right dorsal lateral prefrontal area, bilateral inferior parietal lobules, bilateral posterior cingulated, bilateral

precuneus, bilateral temporal pole and bilateral medial prefrontal cortices. FMRI preliminary results of resting status echoed previous observation by FDG PET studies, and provided a strong base for the on-going studies for sex difference.

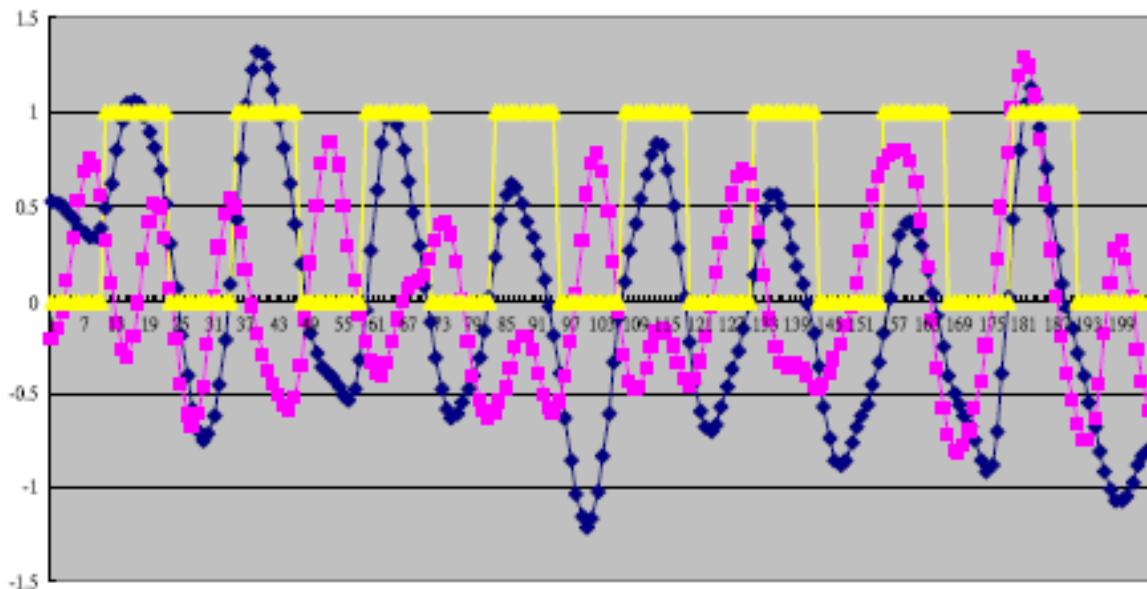


**Figure 2** : Gender difference of resting rhythm (tripod component) of 10 subjects (5 female in left panel and 5 male in right panel) was presented by rendering to the normalized brain template. Statistical criteria were correlation coefficient  $> 0.4$  and voxel extension  $> 25$ .

#### 4.1.2 Co-existence of Default Network Activity during Verbal Task

In the preliminary studies for verifying the co-existence default network activity during task performance, normal subjects received both resting studies with eye fixation and covert Chinese naming paradigm. A block-designed paradigm, as FRFRFRFRFRFRFRF (F: 24-second eye fixation and R: 24-second covertly read two-character Chinese words) was applied in 3 normal right-handed subjects (male : female = 2 : 1, age : 22-26) at a 1.5T MRI system (Sonata, Siemens, Germany). Three subjects were healthy without medical history and had native language of Chinese since birth. Image parameters were as TR/TE/flip angle= 2000 ms/40 ms/90°, slice thickness = 5 mm, inter-slice interval = 1 mm, FOV = 192 mm, 64 × 64 × 20 matrix, and repetition number = 5 dummy scans + 204 repetitions. Three sessions of Chinese naming task and one sessions of resting study were obtained for each subject.

Co-existence of the resting rhythms and task relevant signals during performing Chinese naming task was verified by utilizing ICA. The resting rhythms correlated to the tripod signal component as revealed by the preliminary study resting fMRI. For the 26 year-old male subject, as compared to original block-designed paradigm, ICA revealed characteristic signal components representing task relevant and resting signals (**Figure 3**). Task-relevant and resting components were identified as signal components coherent to task paradigm (high correlation coefficient) and incoherent to paradigm (low correlation coefficient), respectively. The interaction between task-relevant and resting default network can be addressed by this approach by using specific paradigms, e.g. block-designed or rapid event trials with various task difficulties. And sex difference can be analyzed by utilizing both the resting activity and functional response to the paradigms.



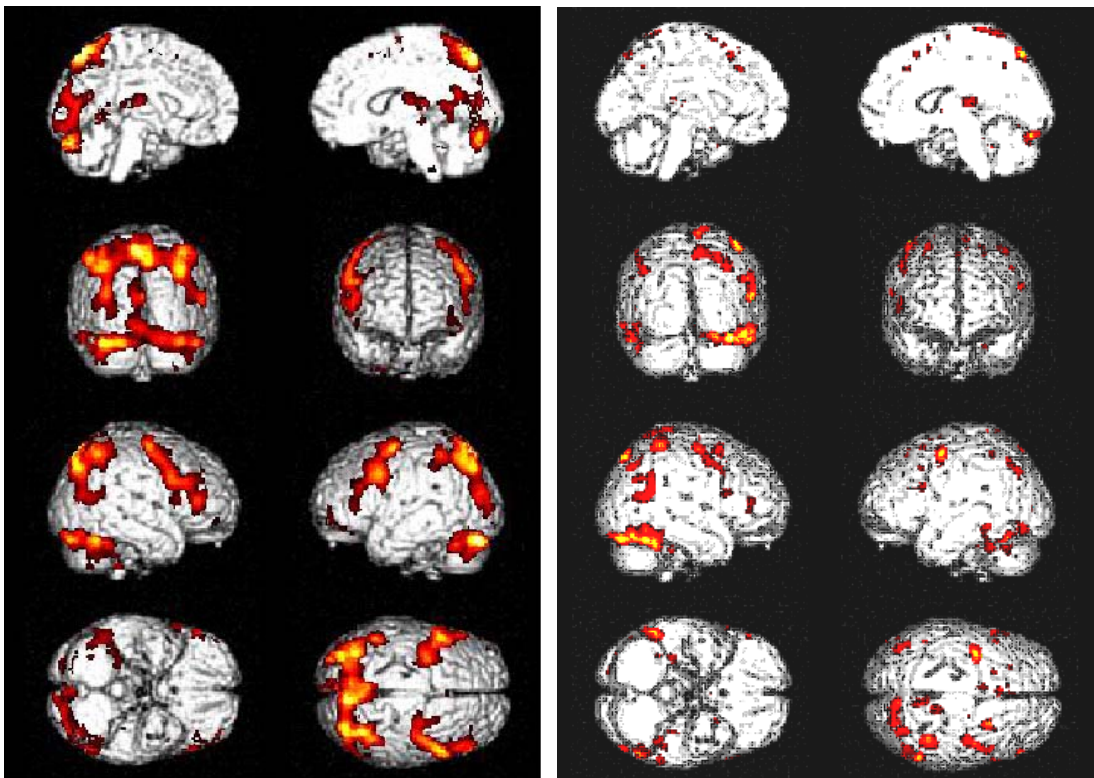
**Figure 3** : ICA of an fMRI study engaging a covert Chinese naming task demonstrated the co-existence of resting rhythms (pink) and task-relevant (blue) signals as compared to task paradigm (yellow). FMRI signals were presented by smoothing window of 5 data points

#### 4.2 Spatial Activity Probed by BOLD-based fMRI

Mental imagery is an important cognitive method for problem solving, and the mental rotation of complex objects, as originally described by Shepard and Metzler, is among the best studies of mental imagery tasks. Using the 3T Bruker system of Taipei Veterans General

Hospital, BOLD-based fMRI was conducted to observe focal activity in one healthy volunteer (a 23 year-old right-handed male) performing mental rotation. Single-shot echo planar images (EPI) (64x64 matrix, slice thickness/ gap = 5/1 mm, 20 slices) covering whole brain were acquired with a flip angle = 90 degree, echo time (TE) = 50 ms, repetition time (TR) = 2000 ms, dummy scan (DS) = 5 for reaching stable magnetization and repetition number (NR) = 210. On each trial, the subject viewed a pair of perspective drawings of three-dimensional shapes, mentally rotated one into congruence with the other, and then determined whether the two forms were identical or mirror-images with three levels of difficulties by complexity as modified from the work of Shepard and Metzler (Shepard and Metzler, 1971). The control task, which we have called the “comparison” condition, was identical except that both members of each pair appeared at the same orientation, and hence the same encoding, comparison and decision processes were used but mental rotation was not required. When the rotation task was contrasted with the comparison conditions in parametric designs (e.g. easy, middle and difficult levels), the subject showed consistent foci of activation in Brodmann’s areas 7a and 7b (sometimes spreading to area 40), increased signal in middle frontal gyrus (area 8), and extra-striate activation, including particularly areas 39 and 19, in a position consistent with area V5/human MT (**Figure 4**). Premotor cortex (area 6) was activated during the rotation task.

These data were consistent with the hypothesis that mental rotation engages cortical substrates involved in tracking moving objects and encoding spatial relations, as well as the more general understanding that mental imagery engages neural imagery as direct perception.

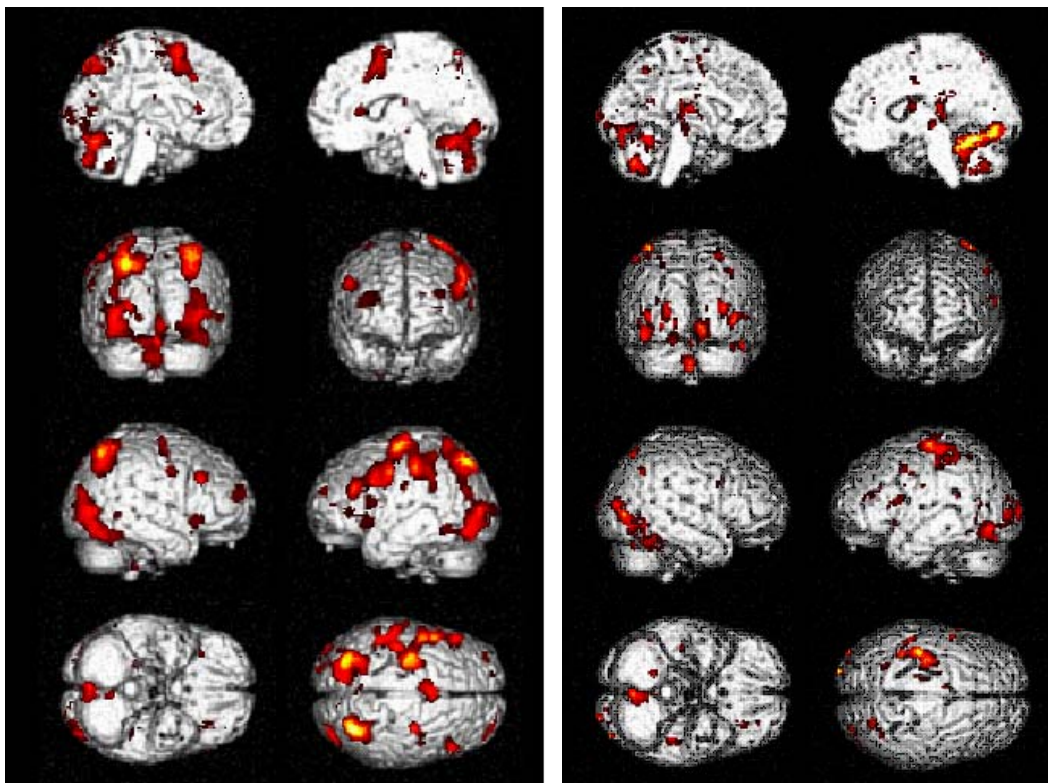


**Figure 4** : Level difference of mental rotation fMRI was presented using the data acquired from one healthy subject, as one level (easy level, left side) and parametric design (easy-middle-difficult levels, right side) rendered to in the normalized brain template. Statistical criteria were  $p < 0.0001$  and voxel extension  $> 0$ .

### 4.3 Calculation Activity Probed by BOLD-based fMRI

Three parietal circuits for numbering processing has been proposed by Dehaene et al (Dehaene, 2003). Bilateral horizontal segmenta of intraparietal sulci, left angular gyrus and bilateral posterior superior parietal lobules were proposed to engage the number quantity processing, numbering in verbal form and attentional orientation on mental number line, respectively. Later, the numbering system has been evolved to five different cognitive systems at the core of adults' mathematical thinking as previously described in 3.2.

Using the 3T Bruker system of Taipei Veterans General Hospital, BOLD-based fMRI was conducted to observe focal activity in one healthy volunteer (a 28 year-old right-handed male) performing a task of mental calculation. Single-shot echo planar images (EPI) (64x64 matrix, slice thickness/ gap = 5/1 mm, 20 slices) covering whole brain were acquired with a flip angle = 90 degree, echo time (TE) = 50 ms, repetition time (TR) = 2000 ms, dummy scan (DS) = 5 for reaching stable magnetization and repetition number (NR) = 140. Serially naming and adding of a one or two digit numbers were applied as task-relevant and control blocks in a block-designed fMRI paradigm with parametric design as addition of one-digit and two-digit numbers. Level difference of mental calculation was demonstrated by addition of one-digit and two-digit numbers in different fMRI sessions (**Figure 5**). Activation pattern involving bilateral intraparietal areas, bilateral precentral gyri, bilateral occipito-temporal junctions and bilateral cerebellum was compatible to published data with left-lateralization as demonstrated by parametric analysis (right panel of **Figure 5**).



**Figure 5** : Level difference of mental calculation fMRI was presented using the data acquired from one healthy subject, as one level (addition of one-digit number, left side) and parametric design (addition of one-digit and two-digit numbers, right side) rendered to in the normalized brain template. Statistical criteria were  $p < 0.0001$  and voxel extension  $> 0$ .

## 5. Specific Aims and Justification of the Proposal

The proposal in title of “Functional Neuroimaging Evidences of Sex Difference in Cognitive Abilities of Sciences: the Impact on Education Policy in Taiwan” will study the sex-difference in central activation of baseline and cognitive abilities of mathematics (or calculation), verbal and spatial domains using fMRI in gender-balanced design. The first year part of originally proposed three-year project was designed to solve the multi-domain problems by meta-analyses of published FMRI studies of baseline activities (e.g. mathematical calculation) and default-mode network

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## Subjects and Methods

### A. Resting fMRI, structural MRI and data analyses of resting fMRI

Subjects are instructed to “empty their mind” and “prohibit imagery tasks” during the studies. After 5-minute sensory deprivation by auditory protection and dimmed room light, imaging studies of resting state are obtained with eye fixation on a dimmed red cross which is viewed through a mirror projection. The eye fixation simulates the control state of conventional fMRI studies with similar resting brain activity as resting state with eye closed by PET study. Subjects are free to blink during eye fixation for the resting study of about seven minutes with the head fixation using a vacuum pillow. For verifying the state of consciousness, subjects respond to the end of each imaging session by pushing bottom using right hand. Images are acquired using a 3T Medspec S300 system (Bruker GmbH, Ettlingen, Germany) equipped with an actively shielded gradient coil, a quadrature transceiver of head and physiological recording of heart and respiratory rates (PowerLab, ADInstruments, Inc., CO, USA). Single-shot echo planar images (64x64 matrix, slice thickness/ gap = 5/1 mm, 20 slices) covering whole brain are acquired with a flip angle = 90 degree, echo time (TE) = 50 ms, repetition time (TR) = 2000 ms, dummy scan (DS) = 5 for reaching stable magnetization and repetition number (NR) = 200. The anatomical image is acquired using a high-resolution 3D T1-weighted, MP-RAGE sequence (Magnetization Preparation Rapid Gradient Echo; TR/TE/TI = 1810 ms/4 ms/1100ms/15°, 256 × 256 × 128 matrix, FOV = 192 x 192 x 192 mm).

An on-line real-time analysis, modified from AFNI (Analysis of Functional NeuroImages, NIMH, Bethesda, USA), of the head motion ensures the quality of fMRI study with head translation < 1 mm and head rotation < 0.5 degree within each session. Processing time of the on-line AFNI processing using the workstation platform (Octane R10000, RAM= 256 MB) is less than 40 seconds after finishing each session. Studies of head motion exceeding the motion criteria mentioned above are rejected from data analysis, because no preprocessing of motion correction was applied for ICA (Independent component analysis). For ICA processing, the obtained images are first subjected to a slice time-alignment process to minimize image intensity inhomogeneity arising from differences in slice image acquisition timing of 2000 ms in multi-slice studies. The time-realigned fMRI images are extracted for within-brain voxels by thresholding intensity histograms of the EPI images for data reduction in a fraction of more than 20%. ICA is applied to BOLD-signal time series of within-brain voxels to separate the data into spatially independent brain maps and find the associated BOLD-signal time courses. Data are analyzed using spatial informax ICA, developed by Computational Neurobiology Laboratory, The Salk Institute for Biological Studies, La Jolla, USA, for identifying components with specific temporal/spatial distributions as previously described (Duann, 2002). For fMRI data with time points much smaller than the number of spatial voxels, spatial independence is assumed (McKeown, 1998). Principal component analysis (PCA) preprocessing is applied to reduce the dimension of training data set from 200 (the number of time points) to 100. Thus, one-hundred spatial independent components account for the fMRI BOLD time courses are derived with spatially-fixed three-dimensional "component maps" and associated activity time courses. Sources of the constituent activities include task-related or task-unrelated hemodynamic changes, blood flow, central spinal fluid (CSF) flow, subject movements and machine artifacts.

For ICA training, initial values of learning rate and data points chosen in each iteration are

0.0001 and 100, respectively. After the spatial ICA training converged, the spatially independent components are ranked by z values by subtracting voxel mean from each voxel and dividing by the standard deviation of the map weights. Maps of region of activity (ROA) are demonstrated by  $|z| > 2$  (McKeown, 1998). To illustrate the relationship between the component time courses derived by spatial ICA and the time courses of correlated voxels in the raw data, the mean back-projected time course of the ROA voxels is compared to the mean ROA time course in the raw data. To determine the salience of a selected component in the raw data, its mean back-projected time course over the positive ROA voxels in the original data space is compared to the mean positive ROA time course in the raw data by computing the percent variance (P.V.) as described previously (Duann, 2002).

Based on the database created by Integrated Brain Research Unit of Taipei VGH, data of 55 normal subjects (22~39 year olds, male/female=25/30) were applied to create the spatial template of default mode network or tripod component. The statistical criteria applied for template construction was FDR,  $p < 0.001$  and voxel extension  $> 0$ .

## **B. Meta-analyses of published fMRI references of mental calculation**

Image-based meta-analysis was performed using activation likelihood estimation (ALE Meta-Analysis : Controlling the False Discovery Rate and Performing Statistical Contrasts, Human Brain Mapping 25, 155-164, 2005). Twelve functional neuroimaging studies using BOLD-based fMRI or PET (**Table 2**) were applied in present meta-analysis based the published data (coordinates of normalized space, statistical significance, voxel extension and size of smooth kernel). And 324 centers of mass were collected for the final results of mental calculation (addition, subtraction, multiplication).

**Table 2.** relevant neuro-imaging references for meta-analysis of mental calculation

1. J. Cognitive Neuroscience 11, 617, 1999
2. Neuropsychologia 38, 1426, 2000
3. Brain, 123, 2240, 2000
4. NeuroImage 14, 1013, 2001
5. Cerebral Cortex, 11, 966, 2001
6. Neuron, 33, 475, 2002
7. Cognitive Neurophysiology, 20, 487, 2003
8. NeuroImage 23, 1192, 2004
9. Neuron, 41, 1, 2004
10. Neuron, 44, 547, 2004
11. Neuron 53, 293, 2007
12. PLoS Biology, 6, 1, 2008

Algorithms of ALE (GingerALE Version 1.1, Research Imaging Center, University of Texas Health Science Center at San Antonio) was implemented with the integrated statistical criteria as FWHM=10mm, Gaussian distribution, permutation steps = 5000, FDR (false discovery rate) with  $p < 0.05$  and volume  $> 100$  mm<sup>3</sup>. With correction of multiple comparison and relatively large voxel extension, the reported results of meta-analyses was conservative.

### C. FMRI, fMRI analyses and psycho-behavioral studies of calculation domain

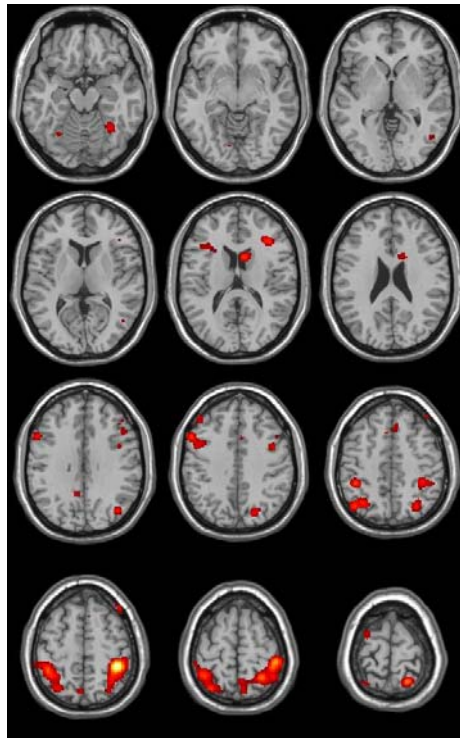
Studies of central correlates involve in the calculation domain focused on the precise system of number as described in 4.3 with engagement of visual, motor, execution, and attention areas. Block-designed functional paradigms consisted of stimulation and control conditions of mental calculation using materials modified from original designs proposed by Dehaene et al (Dehaene, 2003) using alphabetical materials. Parametric designs with two difficulty levels in addition of one-digit and two-digit numbers were interleaved with control condition with digit naming. Subjects had to choose the correct answer from four answers by pushing the MR-compatible button device as soon as possible using the index of dominant hand. Reaction time was recorded for behavioral evaluation and psycho-physiological analysis applied in fMRI data processing. And the on-line monitoring and fMRI analyses were similar to the procedures applied in A.

FMRI examination was conducted using BLIP echo planar imaging (EPI) sequence with parameters as 64x64 matrix, slice thickness/ gap = 5/1 mm, 20 slices covering whole brain, field of view (FOV)= 230x230 mm, a flip angle = 90 degree, echo time (TE) = 50 ms, repetition time (TR) = 2000 ms, dummy scan (DS) = 5, and repetition number (NR) = 288). Visual projection with home-made mirror system was applied for delivery of visual materials to subjects. Analyses of fMRI data were analyzed with Statistical Parametric Mapping (SPM2, Wellcome Department of Cognitive Neurology, London, UK) implemented in MATLAB (Mathworks, Sherborn, MA, USA). Scans of each subject were realigned with each other to correct for interscan movement artifacts. The functional images were coregistered on the anatomical data sets after manually defining the anterior commissure reference point and then smoothed with a Gaussian spatial kernel of 8-mm FWHM (full-width half-volume). Statistical analysis was tested with a t-value (SPM {t}) at each voxel using a box-car reference waveform with parametric design for one-digit and two digit addition based on recorded reaction time. Each SPM {t} was transformed to a unit normal distribution to give the SPM {Z} statistic. Regional activations significant at  $p < 0.05$ , corrected for multiple comparisons and cluster size  $> 0$  voxels, were considered with adaptation for artifacts and noise levels. Grouped results of two subjects (23-25 year olds, females) were applied using fixed model.

## Results

### 1. Meta-analysis of mental calculation

Spatial map of neural correlates (**Figure 6**) involved the bilateral parietal inferior and superior parietal lobules, bilateral precuneus, bilateral middle and inferior frontal gyri, bilateral cingulate and right fusiform/middle temporal gyrus (**Table 3**).



**Figure 6** : spatial correlates of mental calculation, left side of template was on the right hand side.

**Table 3.** Neural correlates of mental calculation by meta-analyses

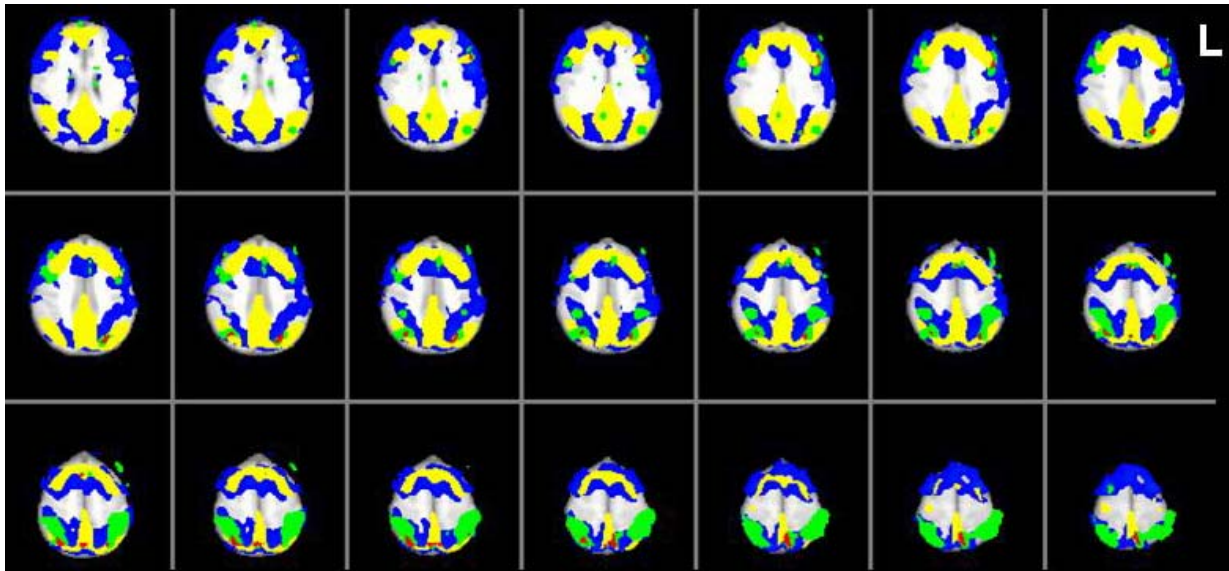
(x,y,z)	neural correlates	BA
40, -42, 44	Right Cerebrum.Parietal Lobe.Inferior Parietal Lobule	BA40
20, -60, 60	Right Cerebrum.Parietal Lobe.Superior Parietal Lobule	BA7
28, -56, 52	Right Cerebrum.Parietal Lobe.Precuneus	BA7
30, -72, 38	Right Cerebrum.Parietal Lobe.Precuneus	BA19
20, -78, 28	Right Cerebrum.Occipital Lobe.Cuneus	BA18
8, -72, 52	Right Cerebrum.Parietal Lobe.Precuneus	BA7
4, -60, 52	Right Cerebrum.Parietal Lobe.Precuneus	BA7
-40, -52, 48	Left Cerebrum.Parietal Lobe.Inferior Parietal Lobule	BA40
-42, -44, 40	Left Cerebrum.Parietal Lobe.Inferior Parietal Lobule	BA40
-32, -68, 56	Left Cerebrum.Parietal Lobe.Superior Parietal Lobule	BA7
-32, -68, 38	Left Cerebrum.Parietal Lobe.Precuneus	BA19
-44, -72, 36	Left Cerebrum.Parietal Lobe.Precuneus	BA39
-52, -40, 50	Left Cerebrum.Parietal Lobe.Inferior Parietal Lobule	BA40
-56, -42, 46	Left Cerebrum.Parietal Lobe.Inferior Parietal Lobule	BA40
-54, 12, 24	Left Cerebrum.Frontal Lobe.Inferior Frontal Gyrus	BA9

-46, 2, 30	Left Cerebrum.Frontal Lobe.Inferior Frontal Gyrus	BA6
-42, 4, 28	Left Cerebrum.Frontal Lobe.Inferior Frontal Gyrus	BA9
8, 6, 6	Right Cerebrum.Sub-lobar.Caudate, Body	
42, 0, 26	Right Cerebrum.Frontal Lobe.Precentral Gyrus	BA6
46, 18, 20	Right Cerebrum.Frontal Lobe.Middle Frontal Gyrus	BA46
42, 26, 20	Right Cerebrum.Frontal Lobe.Middle Frontal Gyrus	BA46
36, 24, 4	Right Cerebrum.Frontal Lobe.Inferior Frontal Gyrus	BA45
34, 18, 6	Left Cerebrum.Sub-lobar.Insula	BA13
-34, 28, 0	Left Cerebrum.Frontal Lobe.Inferior Frontal Gyrus	BA47
-26, 12, 2	Left Cerebrum.Sub-lobar.Lentiform Nucleus, Putamen	
6, 24, 34	Right Cerebrum.Frontal Lobe.Cingulate Gyrus	BA32
4, 16, 40	Right Cerebrum.Limbic Lobe.Cingulate Gyrus	BA32
-6, 16, 38	Left Cerebrum.Limbic Lobe.Cingulate Gyrus	BA32
4, 10, 30	Right Cerebrum.Limbic Lobe.Cingulate Gyrus	BA24
42, 28, 44	Right Cerebrum.Frontal Lobe.Middle Frontal Gyrus	BA8
42, 36, 38	Right Cerebrum.Frontal Lobe.Middle Frontal Gyrus	BA8
42, 38, 34	Right Cerebrum.Frontal Lobe.Middle Frontal Gyrus	BA9
32, -58, -28	Right Cerebellum.Posterior Lobe.Tuber	
46, -68, -8	Right Cerebrum.Temporal Lobe.Fusiform Gyrus	BA19
40, -76, 20	Right Cerebrum.Temporal Lobe.Middle Temporal Gyrus	BA19
-28, -6, 60	Left Cerebrum.Frontal Lobe.Middle Frontal Gyrus	BA6
-44, 32, 28	Left Cerebrum.Frontal Lobe.Middle Frontal Gyrus	BA9
-34, -66, -24	Left Cerebellum.Posterior Lobe.Uvula	
-28, -66, -28	Left Cerebellum.Posterior Lobe.Pyramis	
-4, -72, 44	Left Cerebrum.Parietal Lobe.Precuneus	BA7
-48, -56, -40	Left Cerebellum.Posterior Lobe.Cerebellar Tonsil	
-8, 60, 16	Left Cerebrum.Frontal Lobe.Medial Frontal Gyrus	BA10

52, 4, 38	Right Cerebrum.Frontal Lobe.Middle Frontal Gyrus	BA6
-8, -56, 20	Left Cerebrum.Limbic Lobe.Posterior Cingulate	BA31
-20, -8, 16	Left Cerebrum.Sub-lobar.Lentiform Nucleus, Putamen	

## 2. Conjunctive analysis of parametric result of mental addition, default-mode network and meta-analysis of mental calculation

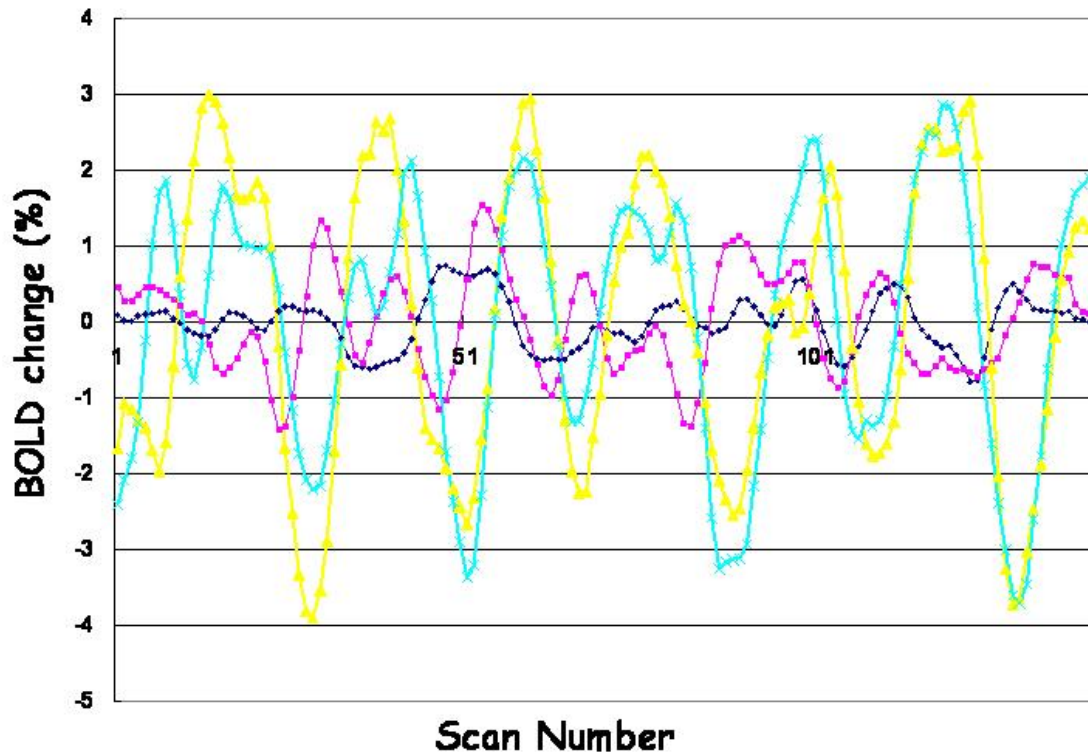
By overlapping neural correlates of (1) ALE meta-analysis of mental calculation (from 12 references), (2) spatial template of default-mode network or tripod component and (3) parametric fMRI of digit naming vs. one-digit vs. two-digit addition, the conjunctive results (**Figure 7**) involved bilateral superior parietal lobules, bilateral precuneus, bilateral anterior cingulate and left middle frontal gyrus.



**Figure 7.** Conjunction mapping of ALE-based meta-analysis of mental calculation, DMN-55 (Default-Mode Network of 55 normal subjects) and parametric fMRI of mental addition (two subjects); (1) ALE meta-analysis of mental calculation (from 12 references, labeled as green color); (2) spatial template of DMN (N=55, FDR,  $p < 0.001$ ,  $v > 0$ , in yellow color); (3) parametric fMRI of digit naming vs. one-digit vs. two-digit addition (based on response time,  $p < 0.01$ ,  $v > 0$ , uncorrected, labeled as blue color) ; and (4) conjunction of three spatial maps described previously (red color)

## 3. Comparison of default-mode network and task-relevant activities during mental addition

With the preliminary results of two subjects, fMRI using parametric design of mental addition showed consistent neural correlates as meta-analysis (results not shown). Various temporal changes of default-mode network and activities of mental addition were demonstrated as **Figure 8**. BOLD activity of default-mode networks showed negative correlation to functional paradigm.



**Figure 8.** Time courses of default-mode network and mental addition; Blocked-design of mental addition of 1 digit numbers showed BOLD change coherent to blocks of mental addition in two subjects (curves in yellow and light blue). Default-mode networks (curves in magenta or dark blue) during the mental addition were detected by ICA with spatial selection using the template constructed by 55 subjects.

## Discussion and Conclusion

Three parietal circuits for numbering processing has been proposed by Dehaene et al (Dehaene, 2003). Bilateral horizontal segments of intraparietal sulci, left angular gyrus and bilateral posterior superior parietal lobules were proposed to engage the number quantity processing, numbering in verbal form and attentional orientation on mental number line, respectively. With the present results of twelve neuroimaging references, meta-analysis using ALE echoed the bilateral superior and inferior parietal lobules involved in mental calculation. But superior parietal lobule also involved in the default-mode network or tripod component as demonstrated by the conjunctive analysis of (1) ALE meta-analysis of mental calculation, (2) spatial template of default-mode network or tripod component (from 55 normal young subjects) and (3) parametric fMRI of digit naming vs. one-digit vs. two-digit addition.

The characteristic temporal profile of default-mode network or tripod component was also demonstrated by the preliminary fMRI studies applying parametric mental addition (**Figure 8**), so as the fMRI studies using Chinese covert naming task (**Figure 3**). Negative correlation of default-mode network was found as compared to the task paradigm. Our results suggested the hypotheses as following;

1. The co-existence of default-mode network during the fMRI studies engaging special tasks (e.g. mental calculation) may interfere the statistical analyses of fMRI.
2. Change of default-mode network has been proposed during functional task with different mental loading or difficulties. Dynamics of default-mode network may cause subtraction errors by statistical mode which did not model the default-mode network. Results of our conjunctive analyses suggested the candidate regions of “false positive” in (1) superior parietal lobules, (2) bilateral precuneus, (3) bilateral anterior cingulate and (4) left middle frontal gyrus.
3. Revision of conventional fMRI analysis was proposed in the NSC project of Gender Science Research (NSC 97-2511-S-075-001).



## 出席國際學術會議心得報告

計畫編號	NSC 96-2522-S-075-001
計畫名稱	以功能性神經影像驗證性別科學認知能力差異的證據
出國人員姓名 服務機關及職稱	葉子成, 台北榮民總醫院教學研究部
會議時間地點	May 03-May 09, 2008; Metro Toronto Convention Centre, Toronto, Ontario, Canada
會議名稱	ISMRM (International Society of Magnetic Resonance and Medicine) 16 <sup>th</sup> Annual Scientific Meeting and Exhibition
發表論文題目	Gender Difference of Resting Rhythms Detected by BOLD-based fMRI

### 一、參加會議經過

計畫內以是功能性神經影像驗證性別科學認知能力，是延續實驗室之前在功能性磁振影像的研究，故而以計畫經費支援參加與磁振影像有關的國際會議。International Society of Magnetic Resonance and Medicine 目前最具規劃的科學會議，有助於交流及技術的學習。

### 二、與會心得及發表內容

以功能性磁振影像及平行處理概念研究人腦系統，實驗室的技術尚屬領先。同時由於實驗室的資料庫已累積較大的影像資料，以進行群分析並探討性別差異。

所發表的內容如下：

### **Gender Difference of Resting Rhythms Detected by BOLD-based fMRI**

#### **Introduction**

The consistent and characteristic default network (named as tripod component, TC, for the pattern of spatial distribution of default network) of resting rhythm has been detected by utilizing BOLD-based fMRI at both 1.5T and 3T field strength (Yeh et al, 2005). The resting TC involved bilateral occipital, precuneus, posterior cingulate, inferior parietal lobules and medial prefrontal cortices (Yeh et al, 2002 and 2006). Similar TC coexists with task-relevant signal components in sensori-motor or cognitive tasks (e.g. word naming task), and implies the functional connectivity (Laufs et al, 2003). To study the gender difference of default network, a routine protocol of resting fMRI has been adapted to functional and anatomical studies. Forty normal subjects, gender- and age-matched, were recruited, and the default network was identified using informax independent component analyses (informax ICA) and automatic component sorting in individual raw-data space using the spatiotemporal template. Men had relatively more extensive default network than women in bilateral posterior cingulate cortices.

## **Subjects and Methods**

### **(1) Resting fMRI**

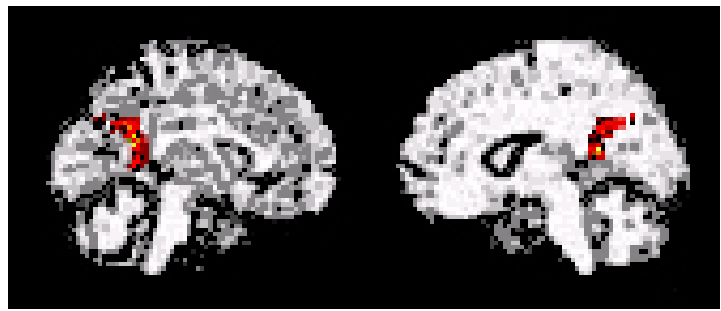
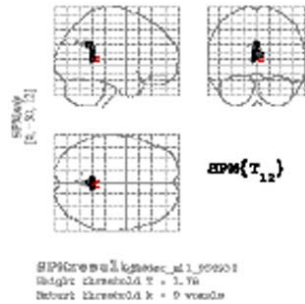
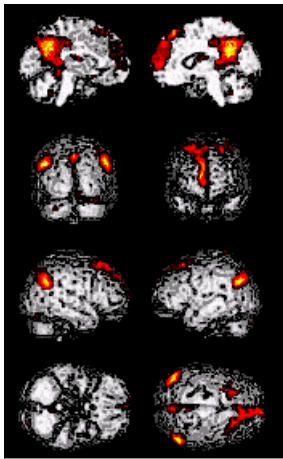
Forty right-handed subjects (gender- and age-matched, age: 26 +/- 6 years old) were instructed to “empty their mind” and “prohibit imagery tasks” during the studies. After 5-minute sensory deprivation by auditory protection and dimmed room light, imaging studies of resting state were obtained with eye fixation on a dimmed red cross which was viewed through a mirror projection. Subjects were free to blink during eye fixation for the resting fMRI study of about seven minutes with the head fixation using a vacuum pillow. For verifying the state of consciousness, subjects responded to the end of imaging session by pushing bottom using right hand. Images were acquired using a 3T Medspec S300 system (Bruker GmbH, Ettlingen, Germany) equipped with an actively shielded gradient coil and a quadrature transceiver of head. Single-shot echo planar images (64x64 matrix, slice thickness/ gap = 5/1 mm, 20 slices) covering whole brain were acquired with a flip angle = 90 degree, echo time (TE) = 50 ms, repetition time (TR) = 2000 ms, dummy scan (DS) = 5 for reaching stable magnetization and repetition number (NR) = 200.

### **(2) Data Analyses**

On-line analysis using modified AFNI (Analysis of Functional NeuroImages, NIMH, Bethesda, USA) ensured the head motion with head translation < 2 mm and head rotation < 1 degree. Off-line processing included (1) preprocessing of Individual data sets using SPM2 (Functional Imaging Laboratory, Wellcome Department of Imaging Neuroscience, UCL, London, UK) was applied for slice timing and realignment; (2) ICA processing was obtained using GIFT (Calhoun et al, 2001) of informax ICA (Computational Neurobiology Laboratory, The Salk Institute for Biological Studies, La Jolla, USA) with minimizing preprocessing; (3) template-based classification using a spatial template of default network, created by an independent cohort of fourteen normal subjects (gender- and age-matched, age: 24 +/- 2 years old; **Figure 1**); and (4) temporal course of default network was derived for each individual from GIFT, and the temporal course was applied as the regressor for GLM estimation after co-registration/normalization to MNI T1 template and smoothing of 8x8x8 mm in SPM2. Group analyses using two-level statistical evaluation of random-effect analysis was performed with statistical criteria of  $p < 0.001/\text{voxel extension} > 0$  for the first level and  $p < 0.05/\text{voxel extension} > 0$  for the second level, respectively.

## **Results**

Gender difference showed more extensive default network in bilateral posterior cingulate cortices (Brodmann area 31) in male group (male > female), [**Figure 2**, center of mass (x, y, z) = (3, -31 42)]. No area was detected by the statistical contrast of female > male.



< **Figure 1** : The spatial template of default network was created by fourteen normal subjects. The template involved posterior medial parietal, posterior lateral parietal, ventral medial prefrontal and dorsal medial prefrontal cortices.

**Figure 2** : Statistical contrast of male > female showed more extensive default network in bilateral posterior cingulate cortices.

## **Discussion**

Correlates of the tripod component (default mechanism) mainly involved posterior medial parietal (interpretation of environment), posterior lateral parietal (multi-modal integration), ventral medial prefrontal (integration of information from internal/external environments) and dorsal medial prefrontal cortices (monitoring and reporting one's mental states). For the BOLD-based fMRI studies of resting default networks, random-effect analysis confirmed the more extensive default connectivity in bilateral posterior cingulate cortices in male group. This finding echoed previous FDG PET result which demonstrated men had relatively higher metabolism than women in temporal-limbic and cerebellar regions (Gur et al, 1995). But further study will be required for evaluating this finding as one of the neuro-imaging markers for gender difference.

## **Acknowledgement**

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## **References**

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