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An Information System in the Brain: Evidence from fMRI BOLD Responses

Michelle Liou,[1] Alexander N. Savostyanov,[2] Aleksandr A. Simak,[1,3]
Wen-Chau Wu,[4] Chia-Ting Huang,[1] and Philip E. Cheng[1]

[1]Institute of Statistical Science, Academia Sinica

[2]Institute of Physiology, Siberian Branch of Russian Academy of Medical Sciences

[3]Department of Computer Science and Information Engineering, National Taiwan University

[4]Graduate Institute of Oncology, National Taiwan University

In this study, we will show in three visual experiments that there are several brain regions in which induced blood oxygenation level-dependent (BOLD) responses are reproducible between visual tasks and between individual subjects. The reproducible BOLD responses indicate that the specific-sensorial structure (e.g., the lingual gyrus) and non-specific structure (e.g., the precuneus) both exhibit increased and decreased BOLD responses, while the associative structure (e.g., the intraparietal sulcus) shows only increased responses. The response patterns remain stable even during task switching from visual-spatial attention to central eye-fixation. Based on the response patterns in different cortical structures, this study will discuss two issues pertinent to applying BOLD contrast to research on high-level cognitive functions. First, there may exist a large-scale information system reproducible between visual tasks that only affect changes in the response sign in the system nodal regions (i.e., positive or negative BOLD responses). If the information system remains faithful to all visual tasks, localization of cognitive functions might not be a priority in functional magnetic resonance imaging (fMRI) studies. Second, the reproducible BOLD responses have partially reflected functional roles of neurotransmitter systems in different cortical structures. Recent studies using MR spectroscopy have suggested that γ-aminobutyrate (GABA) activity is negatively correlated with BOLD responses. Since GABA concentration is relatively low in the associative regions as compared with that in other regions, the spatial resolution of BOLD signal may be insufficient in recovering possible negative activity in the associative regions. This also calls special attention to a recent discovery on glutamate- and GABA-mediated signaling in regulating blood flows and BOLD signal changes. We conclude the study by hypothesizing three inter-related functional loops for future research on the information system using BOLD contrast.

Keywords: *Default mode network, negative BOLD, reproducibility, visual modality*

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Correspondence Authors: Michelle Liou (mliou@stat.sinica.edu.tw) No. 128, Sec. 2, Academia Rd., Taipei 11529, Taiwan. Institute of Statistical Science, Academia Sinica; or Alexander N. Savostyanov (alexander.savostyanov@gmail.com) No. 4, Akademik Timakov St., Novosibirsk 630117, Russia. Institute of Physiology, Siberian Branch of Russian Academy of Medical Sciences

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BOLD Responses

Human brain mapping using the blood oxygenation level-dependent (BOLD) functional magnetic resonance imaging (fMRI) techniques has given primary attention to the localization of cognitive functions, that is, highlighting active brain regions preferential to specific types of stimuli or tasks. For instance, the posterior parahippocampal cortex has been shown to respond preferentially to pictures of complex visual scenes such as landscapes or cityscapes, and weakly to nonscene objects (Epstein & Kanwisher, 1998). In studies on task switching, on the other hand, the inferior frontal junction and posterior parietal cortex are shown to be consistently active in perceptual, response, and context switching tasks, suggesting that the two regions contribute to domain-general task switching processes (Kim, Cilles, Johnson, & Gold, 2012). In order to localize cognitive functions in particular brain areas, studies normally show statistical parametric maps (SPMs) in an anatomical background for voxels (i.e., the smallest box-shaped unit in three-dimensional images) more responsive in experimental trials and exceeding a *p*-value threshold.

Not only are brain regions with smaller *p*-values more responsive on average in the experimental trials compared to the control trials, they also have greater response amplitude. In the literature, there is a fMRI research theme targeting the reproducibility of brain activity in clinical patients with various diseases and in healthy subjects when viewing movies or listening to music under different experimental conditions (e.g., Clément & Belleville, 2009; Golland et al., 2007; Hasson, Malach, & Heeger, 2010; Hasson, Nir, Levy, Fuhrmann, & Malach, 2004; Yao, Shi, Han, Gao, & Dan, 2007). These reproducibility studies measured correlations between long-term BOLD responses under various stimulus conditions, and resulted in several interesting findings beyond the SPM outputs. For instance, when exposing subjects to a continuous audiovisual movie played forward and backward, some brain regions were robust to sensory inputs and had highly reproducible activity between conditions, whereas other regions were less resilient to temporal disruption in the viewing order, albeit the indistinguishable response amplitude in all these brain regions (Hasson et al., 2010).

BOLD contrast depends on many physiologic parameters, such as cerebral blood flow (CBF), cerebral blood volume (CBV), and the cerebral metabolic rate of oxygen ($CMRO_2$). Recent efforts in the literature have focused on the regional coupling between neural activity, metabolism, neurotransmitter release, and hemodynamic changes, but the nature of the link between different mechanisms remains debatable. Relevant work has diverged along two pathways for associating or dissociating between mechanisms. The metabolic pathway focuses on the additional energy required by neural activity, which is supplied by increases in oxidative metabolism and results in blood flow increases to satisfy the consumption of tissue oxygen. Changes in CBF and CBV directly reflect local energy demands, and of course, are coupled to changes in $CMRO_2$ (Vazquez, Masamoto, Fukuda, & Kim, 2010). The neurotransmitter pathway follows a recent discovery that neurotransmitter-mediated signaling, particularly by glutamate and γ-aminobutyrate (GABA), plays an important role in regulating CBF, and that much of this control is mediated by astrocytes. Changes in CBF and CBV are not directly coupled to changes in $CMRO_2$ (Attwell et al., 2010; Duncan, Enzi, Wiebking, & Northoff, 2011). The two pathways have introduced dissociation between the mechanism calling for energy and that consuming the energy.

In addition to the increased BOLD signal, the sustained negative BOLD response (NBR) following the stimulus onset has been noticed and studied by several researchers (Allison, Puce, & McCarthy, 2000; Huang et al., 1996; Rauch et al., 1998; Smith, Best, Cylke, & Stubbs, 2000). In early studies by single-cell recording, neuronal responses to a localized stimulus showed inhibitory activity in neighboring neurons in order to sharpen the spatial profile of excitation in the primary visual cortex (e.g., Blakemore & Tobin, 1972). In a study using BOLD contrast, the region of activation in the primary visual cortex was also surrounded by the NBR in its neighboring region when an observer viewed a small, flickering pattern in an otherwise uniform gray visual field (Smith et al., 2000). The NBR differs from the

transient initial dip and the post-stimulus undershoot in that it is prolonged during stimulation. The NBR source has been considered as an increase in deoxyhemoglobin concentration with a similar biophysical model as that of the positive BOLD response (PBR) although the actual physiologic mechanism remains unknown (Pasley, Inglis, & Freeman, 2007; Shmuel, Augath, Oeltermann, & Logothetis, 2006; Shmuel et al., 2002).

The BOLD signal would report neural events undetected in electrophysiological potentials, and be a valuable indicator complementary to those observed in electrophysiological experiments. In many published fMRI experiments, high-level cognitive functions have been implemented with large-scale processing networks and considerable attention modulation. Local recordings of BOLD contrast simultaneously with electrophysiological potentials in the primary visual cortex may not add compelling evidence to any large-scale processing network (Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001; Shmuel et al., 2006). For instance, it was noticed that lateral inhibition to sharpen the excitation profile seemed insufficient to account for those distant NBRs from PBRs (e.g., 12mm away; Shmuel et al., 2006). Therefore, it is desirable to have new information supporting BOLD inference in more complicated cognitive tasks. In earlier studies, we found that, while the precuneus demonstrated PBRs in the passive viewing task, and both PBRs and NBRs in more complicated tasks (i.e., delayed matching and silent reading of words/pseudowords tasks; Liou et al., 2006, 2009), the lingual gyrus showed PBRs and NBRs in all types of visual tasks. Later, we will show in the empirical study that the intraparietal sulcus shows only PBRs in all types of visual tasks.

The precuneus, lingual gyrus and intraparietal sulcus refer to different cortical structures -- the first, to one of the non-specific regions modulated by internal motivation and memory (Grabenhorst & Rolls, 2009), the second, to a specific-sensorial region engaged in processing physical parameters in visual stimuli (Ivanitsky, Strelez, & Korsakov, 1984), and the third, to an associative region responsible for integration of information in the frontal and parietal regions (Krueger, Landgraf, van der Meer, Deshpande, & Hu, 2011). In this study, we will demonstrate in three visual experiments that there are several brain regions in which induced BOLD responses (PBRs and NBRs) are reproducible between visual tasks and between individual subjects. The visual tasks have involved high-level cognitive functions, including detection of changes between a pair of images, selection of a region in space for visual attention, and language switching in the context of numerical cognition. The experimental data sets are publicly available and belong to the general collection of the US fMRI Data Center. The data analysis method was selected to emphasize those PBRs and NBRs that were strongly reproducible between experimental runs within each individual subject. It is of importance to note, as will be shown, that response patterns in different cortical structures remain stable even at the moment of task switching from visual-spatial attention to central eye-fixation.

Based on the response patterns in different cortical structures, this study will discuss two issues pertinent to applying BOLD contrast to research into high-level cognitive functions. First, there may be a large-scale information system reproducible between visual tasks that only affect changes in the response sign in the system nodal regions (i.e., NBRs or PBRs). If the information system remains faithful to low- and high-level cognitive visual tasks, localization of cognitive functions might not be a priority question to address in fMRI studies. Second, the reproducible BOLD responses have partially reflected functional roles of neurotransmitter systems in different cortical structures. Recent studies using MR spectroscopy suggest that neuronal GABA activity is negatively correlated with BOLD responses (Muthukumaraswamy, Evans, Edden, Wise, & Singh, 2012; Northoff et al., 2007). It is reasonable to hypothesize that GABA activity is a major mechanism behind the negative responses in specific and non-specific structures. The hypothesis also calls a special attention to a recent discovery on glutamate- and GABA-mediated signaling in regulating blood flows and BOLD signal changes (Attwell et al., 2010; Duncan et al., 2011).

In the next section, we will elaborate the functional specialization of different cortical structures in processing visual inputs, followed by a description on the three

experimental data sets, the reproducibility analysis method used in this study, and topology of reproducible BOLD responses in different brain regions. We finally conclude the study by hypothesizing three inter-related functional loops in the information system, namely, attention, memory and emotion loops, and suggest a few directions for future research into the information system by use of fMRI BOLD contrast.

Functional Specialization of Cortical Structures

According to Anokhin (1974), perception of an external stimulus is an active process towards achieving a goal, which initiates two sources of information: the sensorial inputs from the external stimulus and internal messages from motivational structures and memory. Modern neuroscientists see this classical psychophysiological theory as a three-stage process: specific estimation of information, followed by non-specific interpretation of information, and finally synthesis between different sources of information (Bullmore & Sporns, 2009; Mollet & Harrison, 2006; Red'ko, Prokhorov, & Burtsev, 2004; Sudakov, 2004). In the first stage, the parameters estimated are the physical characteristics of the visual stimulus, such as size, color, shape, spatial location/distance from the viewer, and speed of movement. In the second stage, a comparison is made between external signals and a subject's internal motivation and memory so that his/her attention can be redirected to important details according to the goal of the active process. In the third stage, a mental image is formed of the stimulus by the integration of different information sources (Ivanitsky, Ivanitsky, & Sysoeva, 2009; Ivanitsky et al., 1984).

Cortical structures can be classified according to their functional roles in the three-stage process, namely, specific sensorial, non-specific and associative structures (Liou et al., 2009). The principle of classifying cortical regions into different structures obeys three information rules. First, the sources of signal modulating neuronal activity differ between structures, that is, the external source in the specific, internal source in the non-specific, and integration of several sources in the associative structures. Second, parameters to be estimated in processing signals differ between structures, that is, physical parameters in the specific, subjective parameters in the non-specific, and a synthesis of both physical and subjective parameters into a mental image of the stimulus in the associative structures. Third, the resulting symptoms found in clinical or experimental infringements differ between structures, that is, the loss of one or two sensory modalities in the specific, loss of ability to evaluate the stimulus importance in the non-specific, and disintegration of functions in the associative structures.

Specific Structure

Specific regions in the sensory cortex receive projections from one of the sensory thalamic nuclei. In animal studies, the electrical stimulation of sensory pathways induces responses in the specific sensorial regions. Activity in the specific regions shows early peaks (about 20-150 msec) in event-related potentials (ERPs) time-locked to the stimulus-onset (Ivanitsky et al., 2009). The amplitude of ERPs in the specific structure depends on stimulus intensity, but is almost independent of levels of voluntary attention and motivation. Neuronal groups in the specific sensorial structure are highly selective in responding to sensory inputs; for instance, there are orientation- or color-sensitive neuron cells in the primary visual cortex (Seymour, Clifford, Logothetis, & Bartels, 2010). Due to strong functional selection, physical parameters have constant projections in the specific regions, and the speed of processing these parameters is invariant between non-clinical subjects (Airapetyants & Batuev, 1969).

In clinical patients, damage to a specific sensorial region leads to a total or partial loss of perception of stimuli in one modality, but shows regular non-specific processes, such as attention, memory or emotional evaluation, and normal perception of stimuli in other modalities. The lingual gyrus (i.e., the primary visual cortex) is part of the specific structure. In our fMRI data analyses, for example, this region consistently showed PBRs and NBRs, regardless of the amount of attention modulation in task execution (e.g., passive viewing and delayed matching of faces, houses and chairs; Liou et

al., 2006, 2009). It was hypothesized that concurrent PBRs and NBRs in the lingual gyrus reflected the selective responses of neuronal groups to relevant and irrelevant signals in the visual field. The neuronal groups responsible for processing relevant signals were activated with PBRs, while groups responsible for irrelevant signals were inhibited with NBRs. The BOLD responses found in the lingual gyrus are consistent with the studies on the NBR origin in human and animal visual and motor systems, in which not only NBRs but also PBRs were evoked with reproducible patterns between stimulations (Shmuel et al., 2006; Yuan, Perdoni, Yang, & He, 2011).

Non-specific Structure

The non-specific cortical structure has polymodal inputs from the sensory system as well as the limbic structure that is responsible for motivation and memory. Stimulation of sensory pathways in animals unnecessarily induces activation in the non-specific structure, but the activity pattern also depends on the functional state of the brain. In humans, the non-specific structure generates later ERP peaks (about 250-800 msec) time-locked to sensory inputs. The amplitude of these peaks is independent of the physical intensity of stimuli, but modulated by levels of attention. In clinical patients, damage to non-specific regions can induce attention, memory and emotional disorders, all showing deficits in processing perceptually complicated stimuli, but with apparently normal sensation of simple signals. The precuneus is one of the non-specific regions located in the default-mode network (Raichle et al., 2001). Recent studies using pooled data across a group of subjects suggest in particular a task-induced deactivation in this region (e.g., Mayer, Roebroeck, Maurer, & Linden, 2010; Sambataro et al., 2010; Shulman, Fiez et al., 1997).

In our fMRI data analyses, the precuneus demonstrated PBRs in passive viewing task and both PBRs and NBRs in attention-demanding tasks (Liou et al., 2009). As subjective parameters involve polymodal inputs with greater variability among subjects, there is no constant projection of these parameters in non-specific regions. Research findings based on analysis of each individual subject do not necessarily replicate findings using averaged data across all subjects, even when induced PBRs and NBRs are both found in the precuneus of every subject in the group. In summary, both specific and non-specific regions can exhibit PBRs simultaneously with NBRs in attention demanding tasks (Liou et al., 2009). The response pattern in specific sensorial regions depends on the physical parameters in the external stimuli, whereas in the non-specific regions, it depends on the experimental instruction and attention modulation in task execution.

Associative Structure

The associative structure is responsible for integrating information from different cortical regions. There are three levels of information integration in the neocortex: sensory integration realized in the occipital associative cortex, automatic integration in the temporal associative cortex, and highest level integration in the frontal and parietal associative cortices (Homskaya & Batova, 1998; Luria, 1980). It was found that automatic and voluntary (highest level) functions interacted with each other differently in children and adults (Knyazev, Slobodskoi-Plyusnin, Savostyanov, Levin, & Bocharov, 2010; Kujala & Näätänen, 2010). In clinical patients, damage to automatic or highest level functions reveals different symptoms in inter-regional connections (Homskaya & Batova, 1998). According to Ivanitsky et al. (2009), the sensory information is integrated into motivation and memory in the temporal associative regions in order to assign relative importance to stimuli in the visual field, which shows ERP peaks within 150-180 msec time-locked to sensory inputs. The functional differentiation is not as strong in an associative region as in the specific-sensorial region, making it perhaps less appropriate to speak of enhancing specificity of an associative region to a visual modality through the design of experiments.

As will be shown in the empirical study, BOLD responses in the associative structure are relatively stable between subjects and between visual tasks compared to responses in the non-specific structure. As mentioned earlier, the intraparietal sulcus consistently shows PBRs in the three visual tasks considered in this study. According to the literature, this region is the cortical center for

synthesis of top-down and bottom-up information (i.e., the highest level integration; Ivanitsky, 2000; Krueger et al., 2011), and participates in eye concentration, verbal and spatial working memory, as well as motor control during motion (Champod & Petrides, 2010; Cieslik, Zilles, Kurth, & Eickhoff, 2010; Silk, Bellgrove, Wrafter, Mattingley, & Cunnington, 2010; Williams & Smith, 2010). Since almost all cognitive processes more or less engage in the integration of frontal and parietal information, this region is highly cited in a variety of cognitive studies. Informational synthesis might not demand selective inhibition of signals, and this could be a reason for observing PBRs only in the intraparietal sulcus.

Neurotransmitter Release Patterns

The excitatory and inhibitory neurotransmission mediated by the amino acids glutamate and GABA accounts for at least 90% of all synaptic neurotransmission in the central nervous system (Schousboe & Waagepetersen, 2004), but the excitatory and inhibitory processes also involve other mediators. We can reasonably hypothesize that the PBR and NBR patterns have partially reflected projection of neurotransmitters in different cortical structures (Attwell et al., 2010). There are only a few studies in the literature on neurotransmitter release patterns organized according to functional specializations in specific-sensorial, non-specific and associative structures. Based on the existing work, all kinds of neurotransmitters can be found in the three structures. However, there is variation in GABA concentration between functionally different regions. The GABA concentration reaches the highest in the visual cortex and hippocampal formation (part of the cortical structure); that is, in specific and non-specific regions where information selection is intensive (Iversen & Johnston, 1971; Kätzel, Zemelman, Buetfering, Wölfel, & Miesenböck, 2011; Sperlágh & Vizi, 2011). The GABA system is mainly responsible for inhibition of neighboring neurons by way of short-distance connections. Recent studies using MR spectroscopy have suggested that neuronal GABA activity is negatively correlated with the BOLD responses (Muthukumaraswamy et al., 2012; Northoff et al., 2007) which can be interpreted via Schiller and Tehovnik's (2003) hypothesis on selective inhibition of irrelevant information. According to this hypothesis, GABAergic interneurons are responsible for inhibition of irrelevant activity in neuronal circuits. Theoretically, such selection could be more intensive in sensory and non-specific regions than in the associative regions. The associative cortex receives information that has been already selected as "relevant" by other regions. In line with this reasoning, the proportion of GABA concentration in the associative cortex is comparatively smaller than that in other structures. It should be noted that there is still not enough neurochemical evidence supporting neurotransmitter releases in functionally different structures and, as a result, the discussion here about the role of GABA-system in associative cortex is tentative.

Glutamate neurons are responsible for activation of other neurons with concentration independent of cortical structures (Johnson, 1972; Sperlágh & Vizi, 2011); that is, specific sensorial, non-specific and associative regions have a similar concentration of this type of neurons. It has been shown that activation of glutamate neurons induces PBRs (Duncan et al., 2011; Hyder et al., 1997). The associative structure is responsible for regulation of long-distance projections between regions, and inhibition via local connections is not its essential property (Schiller & Tehovnik, 2003). Notably, most principal neurons are glutamate neurons in the associative regions; that is, glutamate neurons in the associative regions are mainly responsible for long-distance projections between regions. Simultaneous recordings of BOLD contrast and neural spiking activity in the primary visual cortex suggest a positive correlation between the two, despite the fact that BOLD contrast is not primarily driven by neural spiking (Bartels, Logothetis, & Moutoussis, 2008; Logothetis et al., 2001). According to one of many hypotheses, BOLD contrast reflects input signals pertinent to local processing of neuronal information instead of output action potentials which are modulated by principal neurons for long-distance projections between regions (Logothetis & Wandell, 2004; Rees, Kreiman, & Koch, 2002). If glutamate-mediated signaling plays an important role in regulating CBF (Attwell et al., 2010), BOLD contrast, at

least in the associative regions (in contrast to the specific regions), would not simply reflect local information processing as indicated by Logothetis and Wandell (2004).

In summary, according to our hypothesis, the GABA neurons support informational selection by inhibition of processing irrelevant physical and psychological signals. The inhibitory function could induce NBRs in specific and non-specific regions. The associative regions are mainly responsible for long-distance projections with minimum concentration of GABA neurons, and as will be shown in the empirical examples, there is apparently no NBR observed in associative regions. The coupling of BOLD contrast and neurotransmitter systems remains an open area of research. The hypothesis on cortical structures and glutamate/GABA concentration has yet to be validated. Later, we will discuss other neurotransmitter systems and their functional roles in different cortical structures.

Summary

In general, cortical structures can be subdivided into three groups with different functional specializations. Regions in different structures are distinct in their roles of participation in information processing, neurotransmitter releases and relationships to clinical symptoms. That said, stimulus perception and decision-making in the real word require the activation of integrated information. When making a decision in a visual task, for instance, brain regions of functionally different groups should be connected into a large scale information system, targeting the final goal of the task execution. In visual perception, information flows circulate through specific, non-specific and associative structures, and finally return to specific-sensory regions, providing an updated direction for processing external stimuli.

Topology of Reproducible BOLD Responses

To show the distribution of PBRs and NBRs in different cortical structures, we processed three fMRI data sets involving high-level cognitive tasks. In general, our results show that the spatial projections of BOLD responses are stable in the specific and associative structures, but show greater between-subject variability in the non-specific structure. Due to within- and between-subject variability in non-specific regions, we do not intend to compare results in this study with studies using the group averaged data to summarize PBRs and NBRs in different brain regions (Shulman, Corbetta et al., 1997; Shulman, Fiez et al., 1997).

Experimental Data

In the empirical examples, we consider three fMRI data sets with 10 subjects each. The data sets were selected because they were collected with multiple runs (8-12) and had complete functional, structural, and anatomical MR images available in the experiments. In the data analysis method, we examined in particular the strongly reproducible PBRs and NBRs across experimental runs. The first data set was collected in an event-related experiment (42 sec per event) for investigating brain functions in a change-detection task (cf. Accession No. 2-2001-111T9, subjects 1-10; Huettel, Güzeldere, & McCarthy, 2001). There were 10 stimulus trials in each run, and each subject completed 10-12 runs in the experimental session. In the change detection paradigm, a pair of images was presented with a difference in either the presence or absence of a single object or color of the object. Subjects made the behavioral response by pressing a button when they felt that there was something changing in the trial. Each trial began with a 2 sec fixation cross at the center of the screen as a warning signal, followed by the first 30 sec of the trial, during which the two images were presented for 300 msec, separated by a 100-msec mask. The mask was removed during the last 10 sec of the trial, and the stimuli alternated every 400 msec.

The second data set was also collected in an event-related experiment (12.5 sec per event) for investigating the neural mechanisms underlying object-based spatial attention (cf. Accession No. 2-2000-1116E, subjects 1, 2, 12, and 4-10; Arrington, Carr, Mayer, & Rao, 2000. Note: data of two subjects were deleted from analysis due to strong imaging artifacts, e.g., half black images in the first few volumes). Each subject completed a variant of the Posner spatial cueing task, with 25 trials in each

run. Each trial began with a 500 msec enlargement of the fixation marker as a warning signal. The cue display contained two elements, an arrow at fixation (location-based cueing) and a geometric shape in the periphery (object-based cueing), both of which appeared gradually over a 198-msec interval. After another 802 msec, the target (an X or an O) appeared for 1,000 msec. Subjects pressed one of two buttons as rapidly as possible to indicate the target's identity. Each trial lasted 2.5 sec, with an inter-trial interval of 10 sec during which subjects were told to maintain eye fixation on the central cross. Subjects completed three imaging runs for each of the location-based cueing, object-based cueing and control tasks. In the control task, neither cue element predicted the target location. Later, we will show that a delayed response occurred immediately after the button press. The BOLD response patterns in different cortical structures remained stable for the delayed responses.

The third data set was collected in a block-design for investigating the neural mechanisms underlying language-switching in the exact base-7 addition and approximate percentage estimation tasks (cf. Accession No. 2-2005-1198T, subjects 1, 5, 6, 8, 10, 13, 15, 16, 17, 20; Venkatraman, Siong, Chee, & Ansari, 2006). The experiment consisted of 8 runs, with four successive runs of the exact addition task, and four of the approximate estimation task (Note: the ten subjects were randomly selected from the original twenty subjects, with five of them completing the exact addition task first, and the other five, completing the approximate task first). Each run started with a 24 sec rest period when the subjects viewed a central cross, followed by four experimental blocks of 30 sec duration each alternating with a rest period of 21 sec. The four experimental blocks consisted of two English and two Chinese blocks in an alternating manner. Each experimental block consisted of six events of 5 sec each. In each event, a problem was presented for 2.5 sec followed by two choices for 2 sec. Subjects responded by pressing a button indicating the selected answer during the 2-sec interval. Finally, another 500 msec of fixation was ensured before presentation of the next problem.

Statistical Analysis

Functional MRI experiments are normally divided into smaller experimental runs in order to allow subjects some rest, and experimental tasks vary slightly between runs. Data across runs for each subject are typically concatenated in statistical analysis, and the weighted average of stimulus and task effects across subjects are computed using the random effect model (Friston et al., 2002; Worsley et al., 2002). The stimulus or task effects are summarized into a statistical parametric map (SPM) showing the voxels with a level of significance exceeding a *p*-value threshold. In the analysis of the three data sets, we considered each experimental run as a replicate of the same experiment, and particularly looked into the active status (either PBR or NBR) of each voxel that was strongly reproducible across runs within each individual subject. Since our statistical analysis applied to each individual subject, the stimulus effects were estimated within each run using the empirical Bayes estimates, which shrunk estimates toward the global mean value, with greater shrinkage in noisy runs. The values of the estimates became closer to one another to optimize the between-run reproducibility due to this shrinkage. The task effects were estimated by modeling estimates across runs as a function of tasks (e.g., object- versus location-based cues) in a random effect model.

In a similar vein as SPM, we computed standardized effects at the stimulus level (within each run) and task level (between runs), respectively. Rather than using the *p*-value threshold, we selected a threshold by maximizing the probability of making a correct decision among all possible choices on the receiver-operator characteristic (ROC) curve. Unlike *p*-value thresholds, a decision threshold on the ROC curve is less stringent for subjects whose images are highly contaminated by noise. The detailed procedure for finding the optimal threshold can be found in Liou et al. (2006). The reproducibility of a voxel is defined as the degree to which the "active status" (either PBR or NBR) of a voxel, in responding to stimuli, remains the same across experimental runs. We constructed the brain activation map mainly based on those strongly reproducible voxels; that is, the active status of those voxels remains the same in at least 90%

of the runs. To account for image distortion due to slice timing and motion correction, the activation maps also included voxels that were reproducible in 70-90% of the runs and spatially proximal (nearest neighbors) to strongly reproducible voxels.

The design contrasts in the random effect model for estimating the stimulus effects can easily be specified for the block-design in the language-switching task (i.e., experimental blocks versus rest periods, and English versus Chinese). For the two event-related experiments, empirical BOLD response functions can also be estimated before/during statistical analysis (e.g., Lindquist, Loh, Atlas, & Wager, 2009; Worsley et al., 2002). In order to more precisely estimate response functions, we computed the between-run intraclass correlation for each voxel (ICC; Caceres, Hall, Zelaya, Williams, & Mehta, 2009; Friedman et al., 2008), the size of which indicated how stable fMRI time series were across runs. Imaging techniques, such as pulse sequences and imaging parameters, can produce magnetic field drifts that are systematic and nonrandom as long as the same sequences and parameters are implemented in the experiments. Nonrandom artifacts would violate the assumption leading to the ICC index. In additional to regular prewhitening procedures (i.e., slice timing, motion correction, and adjustment for autocorrelation), fMRI time series were corrected for major trend effects to account for magnetic field drifts. We applied the k-mean method to classify fMRI time series of reliable voxels into clusters for subjects participating in the same experiment, such that hemodynamic response functions (HRFs) within each cluster were as homogeneous to each other as possible.

Figure 1 shows the 4 types of obtained HRFs for subjects in the change detection task. The functions in the figure suggest that the task induced PBRs and NBRs in each trial (e.g., Figure 1-(a) and -(b)). The function in Figure 1-(a) shows a major peak in the first 32 sec of each trial and a minor peak in the last 10 sec, while the function in Figure 1-(c) does not clearly exhibit a minor peak. Figure 2 shows the 4 types of HRFs for subjects in the spatial cueing task. There are also PBRs and NBRs time-locked to the trial-onset (Figure 2-(a) and -(b)) as well as PBRs and NBRs time-locked to the button press (approximately 5-7.5 sec delay in Figure 2-(c) and -(d))

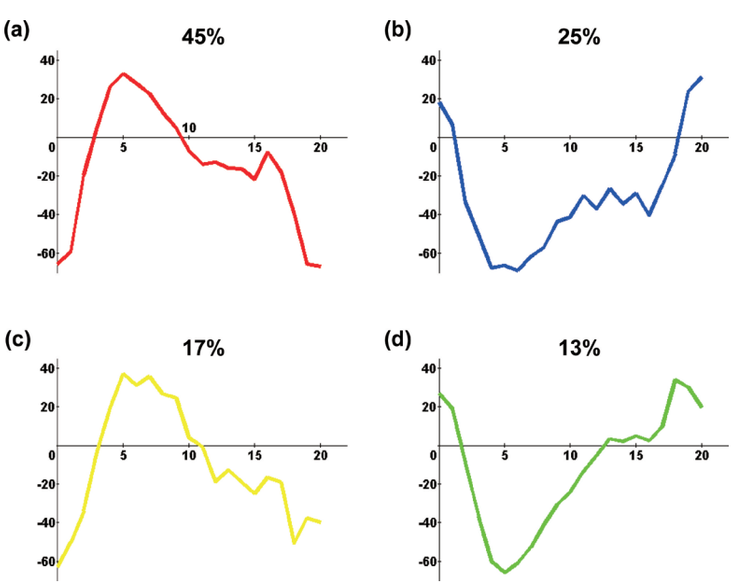

Figure 1. **The estimated HRFs for the change detection task. The ratio above each function is the proportion of all reliable voxels that are classified into a specific HRF group. The HRFs in (a) and (b) are a pair of increased and decreased response functions, and the HRFs in (c) and (d) are another pair of increased and decreased response functions.**

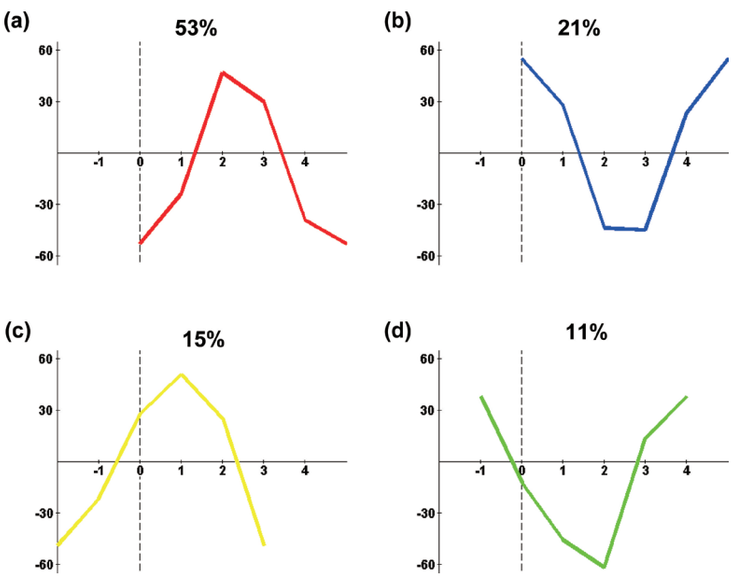

Figure 2. **The estimated HRFs for the spatial attention task. The HRFs in (a) and (b) are a pair of increased and decreased response functions following the trial-onset. The HRFs in (c) and (d) are a pair of increased and decreased response functions, and have a 5-7.5 sec delay following the trial-onset.**

in the experiment. We will show that the delayed activity was induced not only in the sensory motor regions, but also in other cortical regions. In the data analysis portion, we inserted the functions either in Figure 1-(a), (c), or in Figure 2-(a), (c), into the design matrix of the random effect model for estimating the stimulus and task effects for every subject in the two experiments.

Results

Table 1 lists the BOLD response patterns in a few specific-sensorial regions for the three experiments. The anatomical regions were identified by co-registering functional, structure and anatomical MR images to the Talairach and Tournoux 1988 brain atlas using the mri3dX (http://cubric.psych.cf.ac.uk/Documentation/mri3dX). In the table, the lingual gyrus has reproducible PBRs and NBRs across almost all subjects in the three experiments, including the delayed responses in the spatial cueing task. As a comparison, Table 1 also lists responses in the cerebellum which conventionally has been considered as an area for execution of motor control, but more recently has been suggested as taking on functional roles in attention, emotion, language and memory (Stoodley & Schmahmann, 2009; Strick, Dum, & Fiez, 2009). Results in the table suggest that the cerebellum has reproducible PBRs and NBRs in the three visual tasks, including the delayed responses in the spatial cueing task. In the change detection task, the exact time for detecting a change between two images varied across trials for each subject, making it difficult to model the response function for the motor responses. In the spatial cueing task, the delayed response occurred when a subject pressed the button and maintained central eye fixation. Table 1 also lists PBR/NBR patterns in the precentral and postcentral gyri for the delayed responses; the former region is the primary motor cortex and the later, primary somatosensory cortex, both of which are part of the specific-motor structure. In the language switching task, subjects pressed a button indicating a selected answer in the experimental blocks, each of which was alternated with an eye-fixation period. In comparing differences between experimental and control blocks, it is easy to identify the PBRs and NBRs induced by motor responses in the precentral and postcentral gyri. In general, the specific-sensorial (or motor) structure always showed PBRs and NBRs,

Table 1. **The PBR/NBR patterns in different cortical structures. The "+/-," "+," and "-" signs indicate the PBR/NBR, PBR only, and NBR only in a specific brain region. The total number of subjects under the three patterns plus those under no visible response must be equal to 10 for each region**

	Huettel et al.			Arrington et al.			Arrington (Delayed)			Venkatraman et al.		
	+/–	+	–	+/–	+	–	+/–	+	–	+/–	+	–
Specific Regions												
Lingual gyrus	10	0	0	10	0	0	10	0	0	8	2	0
Precentral gyrus							9	1	0	10	0	0
Postcentral gyrus							10	0	0	8	2	0
Cerebellum	10	0	0	10	0	0	10	0	0	7	2	0
Non-specific Regions												
Cuneus	9	1	0	10	0	0	9	0	1	10	0	0
Precunes	10	0	0	10	0	0	10	0	0	10	0	0
Posterior Cingulate	7	0	3	6	4	0	9	0	1	6	1	3
Parahippocampal	0	10	0	9	0	1	6	2	0	1	2	2
Inferior Parietal	10	0	0	10	0	0	10	0	0	10	0	0
Associative Regions												
Fusiform gyrus	0	10	0	0	9	0	0	8	0	0	10	0
Inferior Occipital	0	10	0	0	10	0	0	3	0	0	10	0
Intraparietal Sulcus	0	8	0	0	8	0	0	9	0	0	10	0
Inferior Temporal	0	9	0	0	10	0	0	6	0	0	9	0
Composite Regions												
Inferior Frontal	3	7	0	8	1	1	7	1	2	9	1	0
Medial Frontal	9	0	0	4	4	1	10	0	0	10	0	0
Middle Frontal	10	0	0	7	3	0	10	0	0	9	1	0
Middle Temporal	8	2	0	5	4	0	9	0	1	9	1	0
Superior Temporal	4	0	6	7	2	1	7	1	2	6	0	3

regardless of the type of visual tasks in the examples. The reproducibility maps are plotted in Figures 3 and 4 for Subject 2 participating in the spatial cueing task. The two maps correspond to the response functions in Figure 2-(a, b) and Figure 2-(c, d), respectively.

It is clear in Figure 4 that the central eye fixation after the button press induced greater NBRs in the posterior parietal cortex (PPC) and greater PBRs in the medial/inferior frontal regions when compared to responses time-locked to the trial-onset in Figure 3, despite the similar patterns in PBRs and NBRs for the early and late responses in Table 1. The PPC plays a crucial role in visual control of eyes to coordinate hand movements (Ferraina, Battaglia-Mayer, Genovesio, Archambault, & Caminiti, 2009). In our earlier studies, the PPC showed greater NBRs when subjects paid focused attention to a target stimulus (Liou et al., 2006, 2009). The medial prefrontal region is related to voluntary control of attention; the obito-frontal region is involved in regulation of eye positions, and inferior frontal region, in the oculomotor control (Hodgson et al., 2007). Table 1 indicates that the central eye fixation following the button press in the spatial cueing task induced the same functional network in different cortical structures as did the experimental task. When processing fMRI data in the language switching task, which also used the central eye fixation in the control block, we found distinct PBRs/NBRs time-locked to the onset of rest periods which could lead to incorrect inference on BOLD response patterns. The results listed in the table in particular were validated for the PBRs and NBRs time-locked to the experimental blocks.

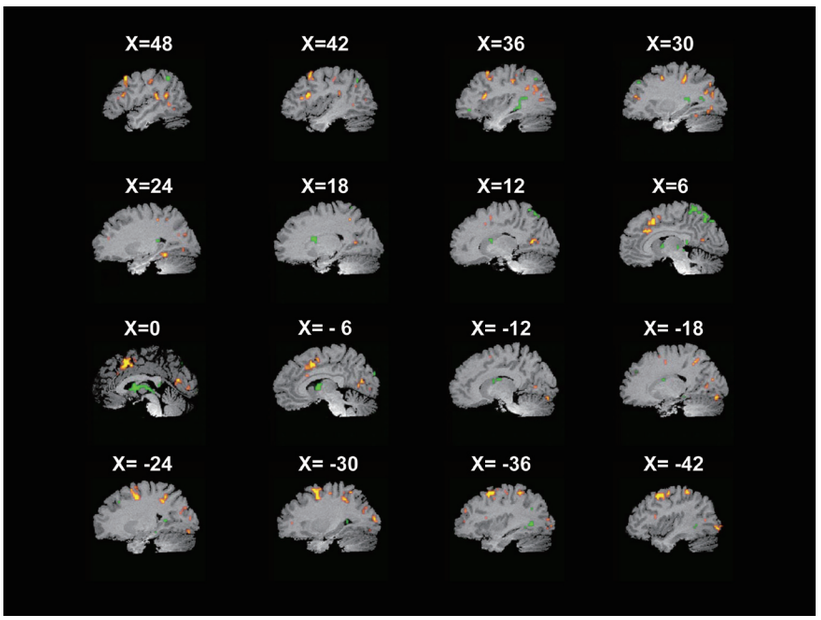

Figure 3. **The reproducibility maps for Subject 2 in the spatial attention task (Arrington et al., 2000). The colored voxels were strongly reproducible between runs and corresponding to the HRFs time-locked to the trial-onset, that is, Figure 2-(a) and -(b). Coordinates are in the normalized space of the Talairach and Tournoux 1988 brain atlas. The colored voxels in red have positive BOLD responses, and those in green, negative BOLD responses.**

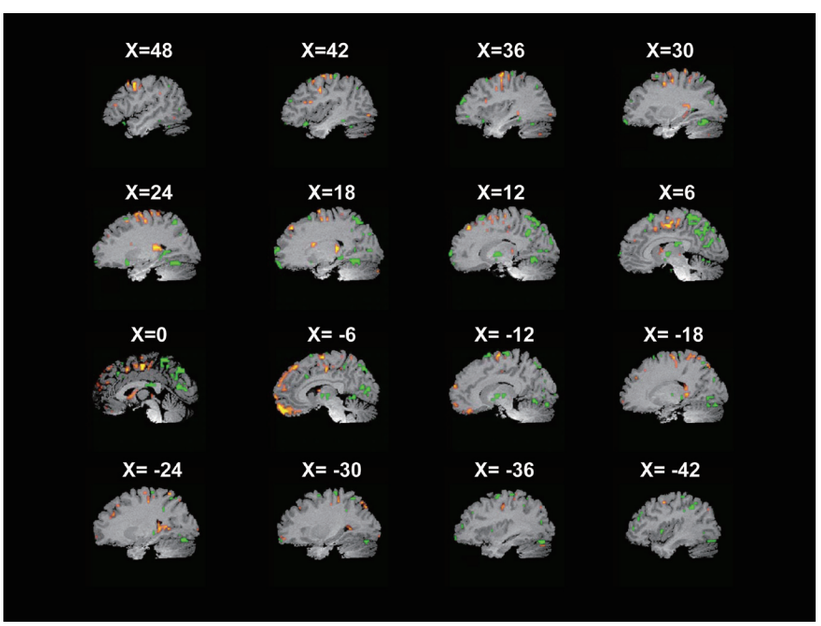

Figure 4. **The reproducibility maps for Subject 2 in the spatial attention task (Arrington et al., 2000). The colored voxels were strongly reproducible between runs and corresponding to the HRFs time-locked to the button-press, that is, Figure 2-(c) and -(d).**

As a comparison, Table 1 also lists BOLD response patterns in a few non-specific regions for the three experiments. Both the precuneus and posterior cingulate play an essential role in the default-mode network which, in the literature, are shown to be tonically activated during a resting state and deactivated when subjects are engaged in a wide variety of cognitive tasks (Fransson & Marrelec, 2008; Raichle et al., 2001). In the table, these two regions show PBRs simultaneously with NBRs in the three visual tasks, including the delayed responses in the spatial cueing task. It is interesting to note that the parahippocampal gyrus only exhibits PBRs across all subjects in the change detection task. A similar finding was observed by the original experimenters who suggested that the continuous flicker cycle eliminated the need to hold information in memory for extended durations and made the change detection task different from other working memory tasks (Huettel et al., 2001).

The parahippocampal gyrus participates in novelty perception (i.e., non-specific function; Pammer, Lavis, & Cornelissen, 2004), but its neocortical part is also responsible for projecting memory information encoded in the hippocampus to the parietal cortex (i.e., associative function). This associative function was more pronounced when subjects continuously compared images in memory with images on the visual screen for an extended duration (42 sec) to ensure the elongated PBRs (i.e., see the HRFs in Figure 1). In other words, the novelty perception (non-specific function) in the parahippocampal gyrus could have been missed in our data analysis by use of the HRFs in Figure 1 in the design matrix. The parahippocampal gyrus shows dissimilar response patterns in the change detection and spatial attention tasks, both of which demand short-term episodic memory. Responses in this region, however, are not reproducible between subjects participating in the language switching task which particularly demands semantic recognition of information (Klimesch 1996; Klimesch, Schimke, & Schwaiger, 1994).

Although the mathematical problems given in the language switching task appear more complicated compared to the problem in the spatial attention and change detection tasks, there may be other cognitive processes involved in the rest period when subjects maintained central eye fixation under the voluntary control in preparation of an expected task. By subtracting BOLD responses in the rest period from those in the task period, some activation patterns may cancel each other out. Later we will discuss the preparatory mechanism during the rest period in more detail. The inferior parietal lobule (IPL) is part of the Wernicke's area including the supramarginal and angular gyri, and involved in different stages of memory formation (Leung & Alain, 2011; Visser, Embleton, Jefferies, Parker, & Ralph, 2010). The IPL has functional connections to the prefrontal cortex, posterior cingulate, precuneus, parahippocampal gyrus and hippocampus (Leung & Alain, 2011; Sestieri, Corbetta, Romani, & Shulman, 2011). One part of the IPL directly supports retrieval of episodic memory, while the other part is involved in postretrieval processes like memory-based decision making (Sestieri et al., 2011). The supramarginal and angular gyri are responsible for comparing between visual images and images in memory (O'Connor, Han, & Dobbins, 2010). In the table, the IPL exhibits PBRs and NBRs in the three visual tasks, all of which require retrieval of resources in the memory for stimulus recognition as well as for decision making.

Table 1 lists a few associative regions and corresponding BOLD response patterns in the three experiments. As mentioned earlier, the associative regions have demonstrated PBRs exclusively for all tasks, including the delayed responses in the spatial cueing task. In the table, the inferior occipital region refers specifically to BA 19. In general, BOLD responses in the intraparietal sulcus and fusiform gyrus are more reproducible between visual tasks and between individual subjects. Some cortical regions might not be classifiable into one of the three structures; for example, the parahippocampal gyrus is one of the non-specific regions, but its neocortical part also participates in informational integration. The frontal and prefrontal cortex executes associative and non-specific functions; that is, the anterior medial prefrontal region is executing associative functions in attention and memory processes, but the posterior medial frontal cortex is involved in selective attention and memory (Goldman-Rakic, Cools, & Srivastava, 1996; Price, 1999).

Table 1 lists a few composite regions which demonstrate reproducible PBRs and NBRs in the three visual tasks. The BOLD topology in different cortical structures is symmetric between the cerebral hemispheres except for the inferior frontal gyrus (IFG) which shows right specialization in the majority of subjects in the spatial cueing task, including the delayed response. In other words, the +/- signs are mainly contributed by the right IFG in Table 1 for the spatial curing task. However, the PBRs and NBRs show a symmetric pattern in the IFG in the language switching task. The superior temporal gyrus also forms part of the Wernicke's area and engaged in the three visual tasks. In the random effect model, we also estimated the task effects for the spatial cueing task (location-based cueing, object-based cueing, and diffused tasks) and language switching tasks (approximate and exact tasks). After plotting the standardized parameters estimates versus reproducibility of responses in voxels for each subject, we did not notice any interesting pattern that suggested significant task effects in the two experiments.

Discussion

We reiterate that the thresholds selected in the reproducibility analysis procedure were less stringent than the *p*-values thresholds used in those published fMRI studies, and were adapted to individual differences. Liberal and adaptive thresholds should not affect the active patterns in the specific regions, where BOLD response amplitude was generally higher than that in other regions; they would, however, affect the active patterns in the non-specific and associative regions, where response amplitude was generally smaller. In addition, there was a great deal of variation among subjects in the exact active location in the non-specific regions. In this section, we discuss important observations from the reproducibility analysis of the three fMRI datasets.

Design and Data Analysis

The rest period with central eye fixation has been widely adopted in experimental designs as the baseline condition, against which BOLD responses in the stimulus trials can be compared in order to evaluate experimental effects in fMRI studies. When subjects rest quietly and perform passive viewing of a central cross, the ratio of oxygen utilized by the brain to the oxygen delivered to it is uniformly distributed in the entire cortex including the occipital region (Raichle et al., 2001; Shmuel et al., 2002). The uniformity suggests that equilibrium could be reached between the metabolic requirements necessary to sustain a long-term level of neural activity. A recent study on alert monkeys using a dual-wavelength optical imaging technique has found, in the primary visual cortex, a hemodynamic component that shows predictive timing with increased CBV in anticipation of the task-onset even in darkness and without any visual input (Sirotin & Das, 2009). This novel insight into CBV suggests a preparatory mechanism that brings additional arterial blood to the cortex in anticipation of an expected task. The reproducibility maps in Figure 4 also support this suggestion, indicating that the rest period with central eye fixation could engage several brain processes in the PPC and frontal regions which would break down the equilibrium, especially when the rest period occurred in between two stimulus trials and subjects maintained eye fixation under voluntary control in anticipation of an expected task. Recent work on the preparatory mechanism in high-level cognitive tasks finds the mechanism more pronounced in non-specific regions such as the parahippocampal gyrus and posterior cingulate (Simak, Liou, Zhigalov, Liou, & Cheng, in press). The onset time of the mechanism is slightly earlier than the stimulus onset. This finding helps interpret the response patterns in the language switching task which used the rest period with central eye fixation as the control block. When the responses in the rest period were subtracted from those in the task period, the activity occurring in both periods would have cancelled each other out.

In the data analysis procedure, each data set was analyzed independently by two experts who manually labeled the +/- signs of BOLD responses in different brain regions using mri3dX. The manual results were cross-validated with one another, a process that involved comparing activation regions in a subject's native space and regions in the Talairach and Tournoux atlas space. Without manual labeling, there would be several NBRs

lying in the boundary between an associative region and a specific or non-specific region (e.g., the fusiform gyrus and cerebellum). Many software packages support automatic labeling of activation regions (e.g., FSL and SPM). The importance of manual labeling should not be overlooked, which could cause human errors if done by inexperienced analysts. The projection of subjective parameters in non-specific regions has great within- and between-subject variability particularly in execution of high-level cognitive tasks. Studies on the non-specific regions using the average data across subjects could lead to contradictory findings. Internal speeches and mental images are individual and subjective and make the analysis of fMRI data more complicated. The data processing issues need to be resolved before BOLD contrast can contribute significantly to studies on high-level cognitive functions.

A Large Scale Information System

The results listed in Table 1 suggest that the three visual tasks share a common BOLD topology in the specific, non-specific and associative structures; the topology implies a large-scale information system, in which the three tasks differ only in the +/- signs in the system nodal regions. For instance, the Wernicke's area was engaged in both language and non-language tasks. If the information system remains faithful to all visual tasks, it may not be a priority to address the localization of cognitive functions in fMRI studies. Recent studies on resting-state networks also find a large-scale connection among networks that include the classical default mode network as a special case (Li et al., 2011). In the reproducibility analysis, we have noticed that BOLD contrast tends to be task-insensitive within each individual subject when compared between location-based and object-based cueing, and also between the exact addition and approximate percentage calculation. Ivanitsky et al. (1984, 2009) find that information flows engage multiple functional loops interacted with each other through the specific, non-specific and associative structures. For instance, attention refers to concentration of brain resources on important events by ignoring all irrelevant events; information flows circulated in the attention loop need to compare external stimuli with internal motivation. In order to concentrate on important details, perception and self-control over behaviors are involved in the loop. On the other hand, emotion refers to a mechanism of subjective estimation of external world and of self behaviors. The emotion loop is also engaged in perception and self-control over behavioral results. By means of emotion, for instance, the external evidence can be estimated as dangerous or undangerous, and the behavior results can receive emotionally positive or negative value. The memory loop is involved in every aspect in information processing because information of the external world must be compared with those in the memory at every stage. Such a comparison is a basis for estimating external stimuli as new or old, important or unimportant, and relevant or irrelevant to the internal aim.

The activation regions in Table 1 are connected by information flows for execution of goal-directed behaviors. Here we hypothesize three interrelated functional loops in the information system, namely, attention, memory and emotion loops. The three loops have been widely cited in the literature and can be verified by functional connectivity methods using fMRI data. For ease of exposition, the loops are constructed by referring to visual cognitive tasks. A generalization to motor or auditory tasks can be made by changing the sensory input and motor output areas in the specific structure. We also include a few subcortical regions in the loops and the functional specializations of these regions, by analogy, can also be classified into specific, non-specific and associative structures. In the three visual tasks, only the insula cortex shows reproducible PBR/NBR responses (the thalamus show clear responses in the spatial attention task) in the subcortical structure. The attention loop is depicted in Figure 5, and the interpretation of the loop is fully detailed in the figure legend. The default mode network is shown as tonically activated during a wakeful-resting state of the brain, and engaged with decreased activity in attention demanding tasks based on positron-emission tomography data (Raichle et al., 2001). Anatomically, the default mode network is consisted of midline brain areas including the posterior cingulate extending into the cuneus/precuneus, the anterior

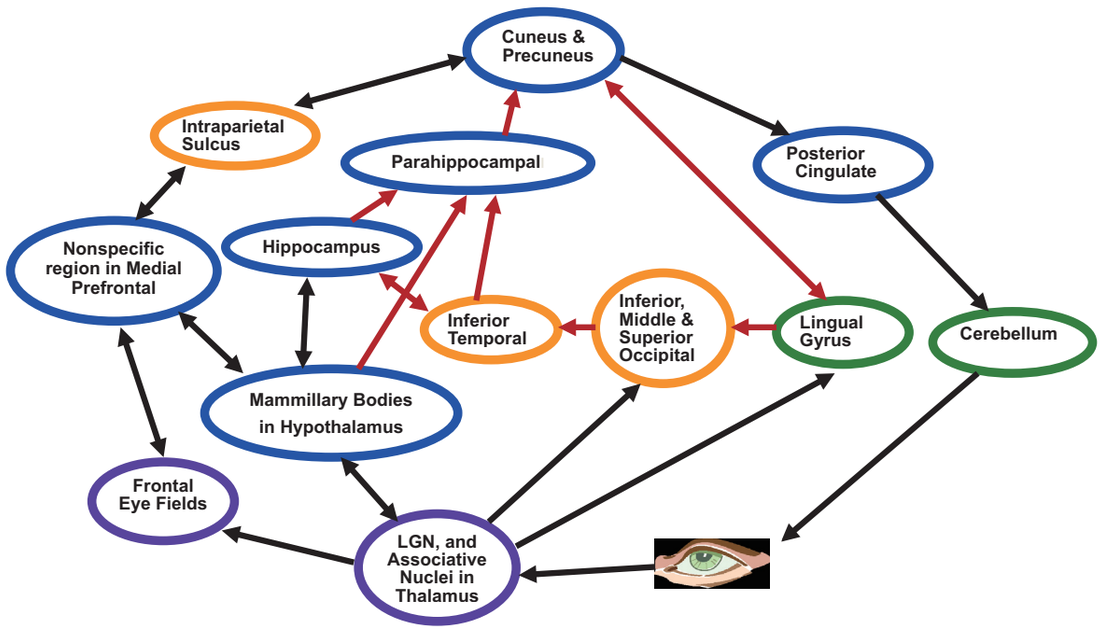

Figure 5. **The hypothetical attention loop in the information system. The green circles refer to regions in the specific structure, the blue circles to regions in the non-specific structure, and the orange circles to regions in the associative structure. The purple circles denote regions of both non-specific and associative structures.**

Note. The lingual gyrus receives visual inputs from the lateral geniculate nucleus (LGN) in the thalamus. In the visual specific region, the physical parameters are processed by different types of neurons. The parameters are then synthesized in the occipital associative region (BA 19) for sensory integration. The associative region in the occipital cortex synthesizes many inputs from the primary visual cortex and projects the integrated images to the temporal cortex. The hypothalamic pacemaker neurons are responsible for regulation of biological motivation. In the perceptual process, information from external stimuli must be compared with information from motivational structures for evaluation of importance/unimportance or relevance/irrelevance of the images (Sudakov, 1993). The hippocampus is one of the non-specific structures and receives motivational information from the hypothalamus non-specific nuclei and memory information from the inferior temporal and fusiform gyrus (in the memory loop). The information sources help with assigning relative importance to different parts of the images and with engaging a subject's past experience of similar stimuli, all of which are crucial in the processes of working memory in the parahippocampal gyrus (Leung & Alain, 2011; Sestieri et al., 2011; Visser et al., 2010). Attention is switched on in the cuneus/precuneus after meeting the feedforward information from the parahippocampal gyrus; it not only directs the posterior cingulate to control eyes movement through the cerebellum to focus on more important parts in the visual space, but also feeds back to the lingual gyrus to ignore irrelevant information so that the subject can focus his/her attention on important parameters in the images for responding to stimuli. For example, an emotional component in the images could be ignored if were irrelevant to the task. The red solid connections have been termed the "sensation circle" by Ivanitsky et al. (2009). The information synthesis in the intraparietal sulcus is one example of the higher-level integration. This region interacts between the medial frontal, middle frontal and cuneus/precuneus under the control of consciousness for the integration between attention, memory, and visual information from stimuli in order to perform voluntary control of attention. Outputs from the information synthesis in this area realize higher-level decision, for instance, on the differences between two pictures in the change detection task. As mentioned earlier, the frontal and prefrontal cortex executes associative and non-specific functions. The frontal eye fields are involved in controlling eye movements and attending to visual stimuli. The anterior medial prefrontal region is executing associative functions in attention and memory processes, but the posterior medial frontal cortex is involved in selective attention and memory (Goldman-Rakic et al., 1996; Price, 1999).

cingulate extending in the orbito-frontal and medial frontal gyrus. Nearly symmetrical bilateral coactivations have been found in the inferior parietal lobule and the superior frontal gyrus (Meindl et al., 2010). The default mode areas are mainly located in the non-specific structure, and have close connection to the attention loop. In our fMRI data analysis, most areas in the default mode network have shown increased and decreased responses in attention demanding tasks (not just decreased activity).

In the literature, memory and emotion processes impose strong hemisphere asymmetry, especially in the frontal cortex (Davidson, Ekman, Saron, Senulis, & Friesen, 1990). Memory related processes additionally showed asymmetry in the subcortical regions (e.g., thalamus and hippocampus). In Figure 6, the hypothetical memory loop is depicted to reflect the hemisphere asymmetry. The interpretation of the loop is detailed in the figure legend. Emotional structures are involved in brain processes such as stimulus recognition, memory and in decision making for future reactions. According to Simonov (1991), the emotional reaction consists of two components, namely, internal motivation and subjective

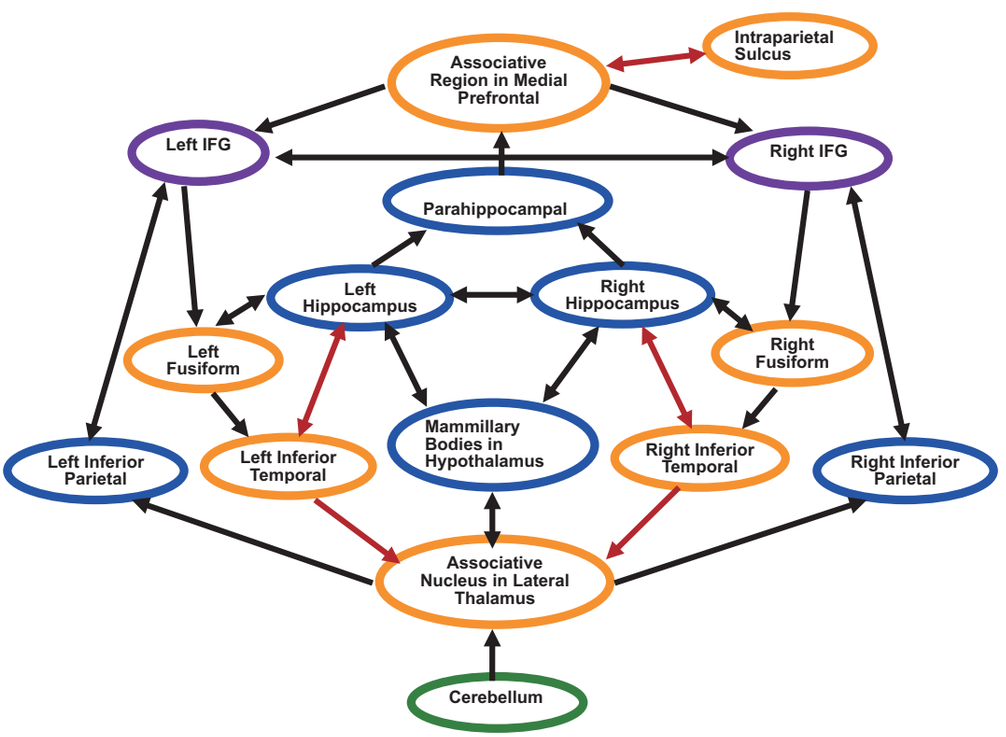

Figure 6. **The hypothetical memory loop in the information system.**

Note. The loop starts from the non-specific nuclei in the thalamus to feedforward memory and attention information to the middle frontal area which, in turn, supplies memory information to the intraparietal sulcus for information integration, as well as feedback to the IFG (both left and right) which is involved in memory processing (Feredoes & Postle, 2010). According to Klimesch, Sauseng, & Hanslmayr (2007), there is an asymmetry in the left and and right IFG in execution of memory tasks. The right IFG participates in memory acquisition and retrieval, whereas the left IFG responsible for selection of irrelevant inputs. The memory loop also includes the associative area in the fusiform gyrus (both left and right), and inferior temporal gyrus (both left and right); the two areas are responsible for the integration of top-down working memory and the long-term memory in the hippocampus, e.g., global and detailed figures, shapes recognition of small details of pictures, faces, letters, etc. The IPL (angular gyrus and supramargianl gyrus) is a part of Wernicke's area responsible for speech recognition, semantic processing, and text reading (Nikolaev, Ivanitsky, Ivanitsky, Posner, & Abdullaev, 2001). As mentioned earlier, this region also has functional connections to the prefrontal, posterior cingulate, parahippocampal gyrus and hippocampus, and supports retrieval of episodic memory. The communication between attention and memory loops goes through the intraparietal sulcus and the middle frontal cortex. The attention loop (red connections) is highly related to the memory loop.

estimation of the possibility to achieve the aim. Positive emotion appears if the probability of aim achievement is high, and negative emotion is a result of impossibility of realizing the aim. The force of emotion depends on the intensity of motivation. Thus, emotional recognition of stimulus contains two connected sub-processes -- a comparison between signals from external stimulus and signals from the motivational structure, as well as high-level cognitive estimation of stimulus for prediction of future events. The deep-located structures of the limbic system such as the amygdala and primary olfactory cortex are included in the initial process, whereas frontal and parietal cortex are strongly involved in the later process. The motivation-related flow goes from visual outputs through mammilary bodies to the lateral geniculate nucleus (LGN) in the thalamus. Figure 7 depicts the emotion loop; a more detailed interpretation is provided in the figure legend. Thus, the emotional loop has complex connections with

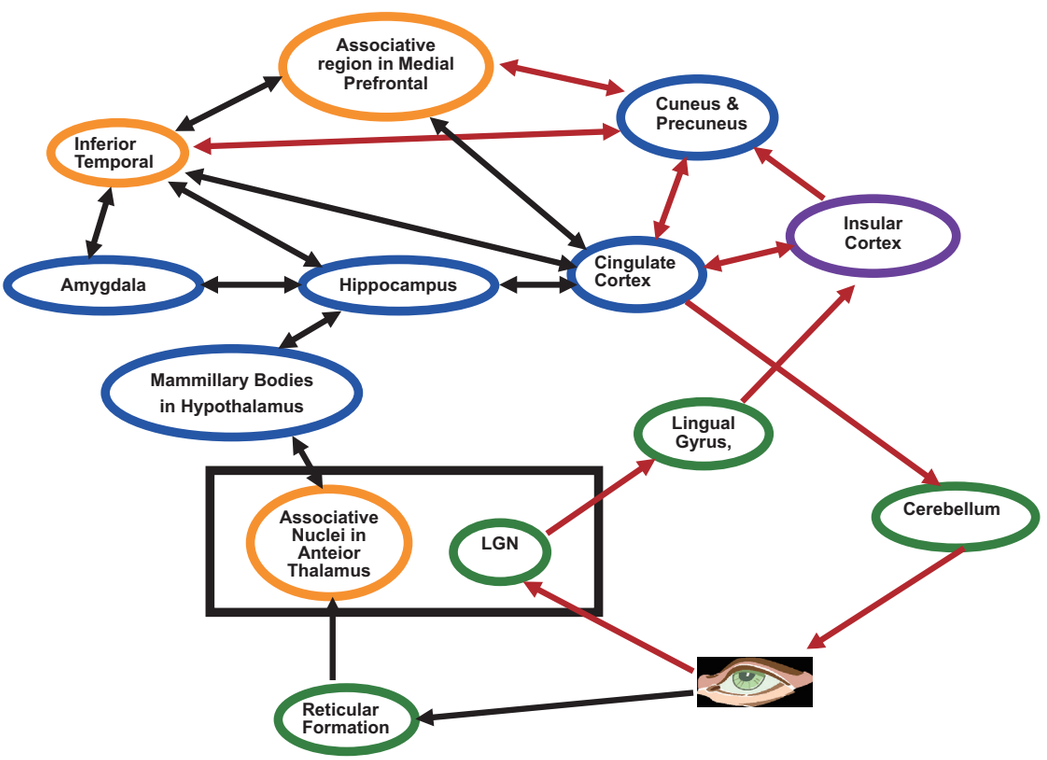

Figure 7. **The hypothetical emotion loop in the information system.**

Note. The signals from the thalamus simultaneously travel through different pathways to the amygdala, hippocampus, cingulate cortex and frontal areas, all of which have projections to the inferior temporal gyrus. The cognitive-related flows (red connections) go through the LGN to reach the primary visual cortex and then the inferior temporal gyrus. After the temporal cortex, the flows merge into the parietal regions (cuneus/precuneus) and then to the secondary visual cortex and frontal cortex. The frontal cortex is the region for high-level integration of different information sources. Emotionality evaluation under voluntary control is related to associative regions in the frontal and the fronto-parietal circuits. The emotional loop is connected with systems of attention and memory (Whalen & Phelps, 2009). The cingulate cortex is involved in emotional and attentional loops, because this region participates in control of eye's motions. The loop is an open structure and new information from the external world moves through sensory organs to join the information circuits. In visual recognition, the cingulate cortex sends outputs to thalamus and cerebellum for regulation of head and eyes position. As mentioned earlier, it is a mechanism of attention concentration in some important details of image. During emotional recognition, attention is focused on the most emotional part in the images. For this reason, the cingulate cortex is an important area for processing emotion-related stimuli. The amygdala participates in selection of signals to be memorized and in later retrieval of those signals if a stimulus is estimated as relevant to emotions and does not participate in memory of neutral stimuli (Ilyutchenok, 1981; Kleinhans et al., 2010). Thalamus has functions of active filter, which can both activate or inhibit attention and memory processes to emotional stimuli.

other systems such as perception, attention, memory and cognitive estimations of stimuli. Two information flows (motivation-related and cognitive-related) are included in this loop. Furthermore, two integrative areas -- temporal and frontal associative cortex are responsible for automatic and voluntary emotional recognition.

Neurotransmitter Systems

The GABA neuron is a major inhibitor in the human brain, and has influences on behaviors and cognitive functions such as anxiety, sleep and memory. The GABA neuron mainly participates in the suppression of dendritic connections to blockade irrelevant activity, and occasionally, in the inhibition of long-distance connections (Ganguly, Schinder, Wong, & Poo, 2001; Schiller & Tehovnik, 2003). Information selection also tends to be intensive in the regions with high GABA concentration (Raybuck & Lattal, 2011; Sawaguchi, 2001; Watanabe, Maemura, Kanbara, Tamayama, & Hayasaki, 2002). As noted previously, it is reasonable to hypothesize that GABA activity is one of the most important mechanisms behind NBRs in specific and non-specific structures. Although GABA neurons can also be found in the associative structure, the concentration of these neurons is essentially less compared with the concentration in other cortical structures. The NBRs in the specific and non-specific regions suggest a potential use of BOLD contrast in clinical studies on local infringements of information selections, such as epilepsy, Parkinson disease, autism, impulsiveness syndrome and bipolar disorders (Berlin & Rolls, 2004; Kleinhans et al., 2010; Palaniyappan, Mallikarjun, Joseph, White, & Liddle, 2011). The glutamate neurons are responsible for activation of other neurons by either dendritic or axonal connections with concentration independent of cortical structures (Sperlágh & Vizi, 2011). In the three visual experiments, PBRs are widely distributed in all cortical structures. In contrast to the specific and non-specific structures, projection neurons in the associative regions are mainly consisted of glutamate neurons that are responsible for interregional connections (Schiller & Tehovnik, 2003). Other than the least neuronal GABA concentration and the projection type of glutamate neurons in the associative structure, the reproducible PBR patterns between subjects might suggest an identity of associative regions in fMRI studies. An important role of long-distance projections in the associative structure would offer an opportunity to study neurodegenerative diseases highly associated with long-distance connections, such as fronto-temporal dementia, Alzheimer disease, Parkinson disease, and some types of schizophrenia (Bassett et al., 2009; de Haan et al., 2009; Stam, 2010; Tropini, Chiang, Wang, & McKeown, 2009).

As was mentioned, lateral inhibition via GABA activity is insufficient to fully account for the distant NBRs from PBRs, and can also be found in the microcircuits of the associative regions. The coupling between BOLD contrast and neurotransmitter systems is yet under investigation, and it is still early to consider GABA or glutamate only as mediators of CBF. For example, it is well-known that dopamine is also a mediator for maintaining levels of attention under voluntary control (Alkam et al., 2011). Dopamine neurons are mainly distributed in the subcortical structure, but have projection axons distributed in cortical areas. It was found that dopamine release would induce both positive and negative HRFs depending on the type of dopamine receptors (Choi, Chen, Hamel, & Jenkins, 2006). Stronger dopamine release can be found in tasks demanding focused attention and memory regulation (Dubrovina & Ilyutchenok, 1996). We may reasonably hypothesize that dopamine effects constitute a mechanism driving arterial blood to the non-specific structure while simultaneously inducing PBRs and NBRs. This hypothesis can be applied when interpreting BOLD contrast in the non-specific structure because activity in this structure is highly related to the dopamine system. In addition to dopamine, glutamate, and GABA, other systems such as serotonin and opioid might also interact with one another, and result in BOLD signal changes (Dubrovina & Illyutchenok, 1996; Schoell et al., 2010). The serotonin and dopamine systems have antagonistic relations in many experiments involving attention, memory and emotion tasks (Fletcher, 1996; Puumala & Sirviö, 1998). The dopamine system regulates non-selective processes such as emotional activity, non-directed attention and memory, whereas the serotonin system is more related to regulation of highly selective

processes such as cognitive control of behaviors, directed attention and memory (Loskutova, Luk'yanenko, & Il'yuchenok, 1990). In real-life situations, a balance between the two systems also depends on many internal and external factors such as genetic specificity, emotional state, and environmental changes.

In summary, the BOLD topology listed in Table 1 does not obviously violate the functional role of neurotransmitter systems in different cortical structures. This encourages the application of BOLD contrast to probing the large-scale information system. Research into regional coupling between BOLD contrast, neural synaptic activity, and action potentials has chosen the specific sensorial regions as major loci (i.e., the primary visual or motor cortex). The PBR and NBR patterns suggest that functional specialization of neuronal cells in the specific structure might not represent the cerebral cortex in general. Regions in the non-specific and associative structures need to be considered for validating results from the specific regions. We conclude that BOLD contrast could go beyond complementing the conventional recording of electrophysiological potentials -- it can offer a full opportunity to investigate the brain as a large-scale information system.

Conclusion

In this study we applied the reproducibility analysis method to three published fMRI datasets involving high-level cognitive tasks. The BOLD response patterns suggest a common BOLD topology shared by the three tasks, which implies a large scale information system. The information system is faithful to both low-level and high-level cognitive processes. For instance, the intraparietal sulcus is responsible for high-level information synthesis while also engaged in both spatial attention and central eye fixation. Due to a limitation in temporal resolution, the BOLD signal is a summative account of dynamic flows in the system. We finally suggest three directions for future research using BOLD contrast: (a) Localization of regional disorders for clinical patients or comparing the BOLD response patterns in the non-specific and associative structures between children and adults; (b) The hypothetical functional loops in Figures 5 through 7 can be empirically tested by the connectivity study, which has been one of the cutting-edge topics in fMRI research; (c) Some novel mechanisms and corresponding brain regions involved in execution of high-level cognitive tasks can be studied by use of BOLD fMRI, for example, the preparatory mechanism.

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磁共振帶氧血紅素反應與大腦訊息傳遞迴路

劉長萱[1] Alexander N. Savostyanov[2] Aleksandr A. Simak[1,3]
吳文超[4] 黃佳婷[1] 程爾觀[1]
[1]中央研究院統計科學研究所
[2]Institute of Physiology, Siberian Branch of Russian Academy of Medical Sciences
[3]國立台灣大學資訊工程學系
[4]國立台灣大學腫瘤醫學研究所

本研究採活化再現性分析方法（Liou et al., 2006），分析三組功能性磁共振造影視覺實驗資料，認知作業包括偵測變化的視覺注意力（visual attention in change detection）、物件導向的空間注意力（visual attention in object-based selection in space）、及語言轉換的數字認知（language switching in numerical cognition）等。分析以個別受試者為主，且未將受試者資料校準至國際標準腦，以減少影像扭曲造成的誤差。重要的分析結果包括：（1）多數大腦皮質同時參予不同的視覺認知作業，且當受試者執行完作業並凝視螢幕中央「+」時的活化反應區，與執行空間注意力作業反應區相似。此結果顯示，無論複雜或簡單的視覺認知作業，大腦皮質皆同時參予執行。由於大腦為一完整的訊息系統，本研究建議功能性磁振造影實驗研究應重視大腦不同區域的功能性聯結（神經網路），而非特殊區域的活化反應（localization）。（2）大腦聯絡皮質（associative regions）在所有作業中僅出現正向的反應，視覺皮質在所有作業中同時出現正向及負向反應，且與作業難度無關。掌管注意力及記憶的非特殊皮質（non-specific regions）在被動觀看刺激時僅出現正向的反應，但在需集中注意力的作業中，會同時出現正向及負向反應。由於聯絡皮質中γ-胺基丁酸（GABA）的濃度較其他皮質區少，且主要負責訊息的整合及長距離訊息傳輸，研究假設磁共振實驗中帶氧血紅素反應下降和γ-胺基丁酸的活動有關。本研究最後提出三個重要的訊息傳遞迴路：注意力、記憶、及情緒，做為探討功能性聯結研究的參考。

關鍵詞：大腦基準網路模式、活化再現性、帶氧血紅素反應下降、視覺感官