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Attention and Working Memory Task-Load Dependent Activation Increase with Deactivation Decrease after Caffeine Ingestion

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Original Article

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Purpose: Caffeine is the most widely consumed psychostimulant. It is often adopted as a tool to modulate brain activations in fMRI studies. However, its pharmaceutical effect on task-induced deactivation has not been fully examined in fMRI. Therefore, the purpose of this study was to examine the effect of caffeine on both activation and deactivation under sustained attention.
Materials and Methods: Task fMRI was acquired from 26 caffeine naive healthy volunteers before and after taking caffeine pill (200 mg).
Results: Statistical analysis showed an increase in cognition-load dependent task activation but a decrease in load dependent de-activation after caffeine ingestion. Increase of attention and memory task activation and its load-dependence suggest a beneficial effect of caffeine on the brain even though it has no overt behavior improvement. The reduction of deactivation by caffeine and its load-dependence indicate reduced facilitation from task-negative networks.
Conclusion: Caffeine affects brain activity in a load-dependent manner accompanied by a disassociation between task-positive network and task-negative network.

Keywords: Caffeine; Sustained attention; Functional magnetic imaging; fMRI; Attention network; AN

INTRODUCTION

Caffeine (1, 3, 7-trimethylxanthine), a member of methylxanthine drugs, is probably the most wildly consumed psychoactive stimulant in the world (1-3). Caffeine exists in many kinds of food and beverages. It is most commonly found in coffee and tea (4). It can be rapidly absorbed by human gastrointestinal tract (5), reaching peak plasma concentration level in 15 to 45 minutes after ingestion (6). Caffeine's half-life is 5 to 6 hours. It has various positive effects on human brain cognition (7-11) most likely through its antagonistic binding to adenosine receptors (3). Adenosine is a neuromodulator that can reduce neural activity via binding to adenosine receptors, mainly A1 and A2a receptors. Acting as an adenosine antagonist, caffeine can decrease

the binding potency of adenosine receptors, resulting in reduced adenosine activity which subsequently provokes alertness and arousal.

Over the past decade, effects of caffeine on brain function have been examined in many studies using functional magnetic resonance image (fMRI) (12-19). Most of these studies focusing on brain activation during different functional task performances have shown a general picture that caffeine can increase task activation. Task deactivation is a common phenomenon observed in fMRI research (20, 21), suggesting that caffeine can overtly facilitate task performance (20, 22). This phenomenon has stimulated research on resting state as it has been found that brain regions deactivated during task performance are activated during null-hypothesis resting state (23, 24). It is likely that the seesaw like activation-deactivation system might respond to caffeine stimulation in tandem rather than having one part changed while the other part unaffected. However, this has not been examined in the literature because task-deactivation is not investigated in previous caffeine fMRI studies.

Attention is a fundamental element of cognition. It seems to be most notably caffeine enhanced brain function among others (10, 11) likely due to increased alertness and arousal after caffeine intake. Various studies have assessed the effect of caffeine on attention (11, 25-28). However, only two studies have used fMRI to localize attentional effects of caffeine. A working memory study (29) has found that response in bilateral medial frontopolar cortex and right anterior cingulate cortex is increased after caffeine intake, suggesting that caffeine can modulate neuronal activity in a network of brain areas associated with executive and attentional functions during working memory processes. Serra-Grabulosa et al. (30) have reported that caffeine has modest effect on sustained attention-task activation not directly inferred in a statistical way.

Therefore, the purpose of the present study was to assess whether caffeine could affect both task activation and deactivation simultaneously. We also assessed cognition-load dependence of these effects of caffeine. Activation during sustained attention was studied because this was rarely examined in previous caffeine fMRI studies as mentioned above. We used rapid visual information processing (RVIP) (31) task, a widely used sustained attention paradigm. Caffeine-naive subjects were included to avoid potential effects of caffeine withdrawal.

MATERIALS AND METHODS

Participants

This study was conducted at the Center for Cognition and Brain Disorders (CCBD), Hangzhou Normal University, China. All procedures were approved by CCBD Institutional Review Board. This study adhered to the Declaration of Helsinki. All subjects were recruited from Hangzhou Normal University and local communities in Hangzhou, Zhejiang Province, China. They provided written signed consent forms prior to entry into this study. Twenty-six right-handed college students (13 males, 13 females) aged 19-36 years (mean, 23.35 years; standard deviation [SD] = 3.69) were recruited for the current study. Exclusion criteria were: those who had abnormal structural MRI, history of head trauma or other injuries resulting in loss of consciousness lasting more than three minutes or associated with skull fracture or intercranial bleeding, those who had magnetically active objects on or within their body, having any neuropsychological problems as defined by Mini-International Neuropsychiatric Interview (MINI) (32), and those who were taking any medications that might affect CBF in the past 10 days. For subjects recruited for the caffeine intake experiment, additional exclusion criteria were: allergic to caffeine, drinking more than one cup of coffee or tea in the past week and more than 10 cups of coffee or tea in the past 6 months. All participants were instructed to stop using coffee, tea, or any other drugs two days before fMRI scan.

Experimental Design

Every subject underwent two fMRI scan sessions in two consecutive days with exactly 24 hours apart during day time between 9 am and 5 pm. Participants were randomly divided into two groups (group A and group B). Subjects in group A took one caffeine tablet (200 mg) with one cup of water at 40 mins before the scan on the first scan day. The same amount of water was given to subjects at 40 mins before the scan on the second scan day. Subjects in group B took water only in the first scan session but took caffeine with water on the second scan day.

Sustained attention task used in this study contained three conditions (baseline, low-load condition, and high-load condition) following a block design (33). Figure 1 shows basic timing of these designated blocks. Subjects were asked to watch a grey screen with a crosshair in the middle. They did nothing for 25 secs during baseline condition. After that, instructions for the coming task condition were presented on the screen for 5 secs. During

low-load condition, subjects were instructed to press a button whenever they saw number "0" out of a total of 200 numbers sequentially displayed. The condition duration was 90 secs. The high-load condition had the same time length as that of the low-condition. Subjects were asked to press the button if they saw three consecutive numbers with the same parities (all even or all odd) from the total of 200 sequentially displayed numbers.

MRI Acquisition

MR images were obtained using a 3.0T whole-body GE 750 MR scanner (GE, Milwaukee, WI, USA) with a standard 8-channel receive array coil. Structural images were acquired using a T1-weighted inversion prepared 3D spoiled gradient echo (IR-SPGR) sequence with the following parameters: field of view, 256 × 256 mm^2; inversion time, 450 ms; repetition time (TR), 7.2 ms; echo time (TE), 2.1 ms; matrix, 256 × 256; sagittal slices, 176; slice thickness, 1 mm; and flip angle, 7°.

Functional MRI was performed with a standard T2*-weighted gradient-echo echo-planar imaging (EPI) sequence with the following parameters: matrix, 64 × 64; voxel size, 3 × 3 × 3 mm^3; TR, 2000 ms; and TE, 30 ms. Thirty-seven continuous axial slices were obtained in an interleaved order to cover the entire cerebrum and cerebellum from bottom to top.

Data Processing and Statistical Analysis

Behavioral data of response accuracy and response time were analyzed using statistics software R (34). Response accuracy was calculated as (the number of correct button pressing + the number of correct no-button pressing) / (the total number of numbers displayed). Correct button pressing was considered when the subject pressed the button as expected. Otherwise it was considered as incorrect button pressing. Reaction time was defined as the time difference between button pressing and event onset. Paired t-test was performed to infer difference between pre-caffeine and post-caffeine response accuracy and response time.

MRI data processing was conducted using SPM12 (Wellcome Department, London, UK, http://www.fil.ion.ucl.ac.uk/spm). EPI images were first corrected for slice acquisition time difference. They were then corrected for head motions and registered with high resolution structural MRI. Slice timing correction was used to correct acquisition time difference across 2D image slices. The first acquired slice was used as reference. All corrected slices were time shifted (by interpolation) to be aligned with the first slice. These procedures were conducted using SPM12. Each individual subject's high resolution structural MRI was spatially registered into Montreal Neurological Institute (MNI) (35) brain space using the new brain segmentation algorithm-based registration routine implemented in SPM12. Since we pre-registered each subject's function MRI (EPI images) into structural MRI, the same spatial registration transform was directly applied to fMRI images to warp them into the MNI space followed by spatial smoothing with an isotropic Gaussian kernel and full-width-half-maximum (FWHM) of 8 mm^3. Brain activations in response to sustained attention were then identified using SPM12. Block design function convolved with canonical hemodynamic response function (HRF)

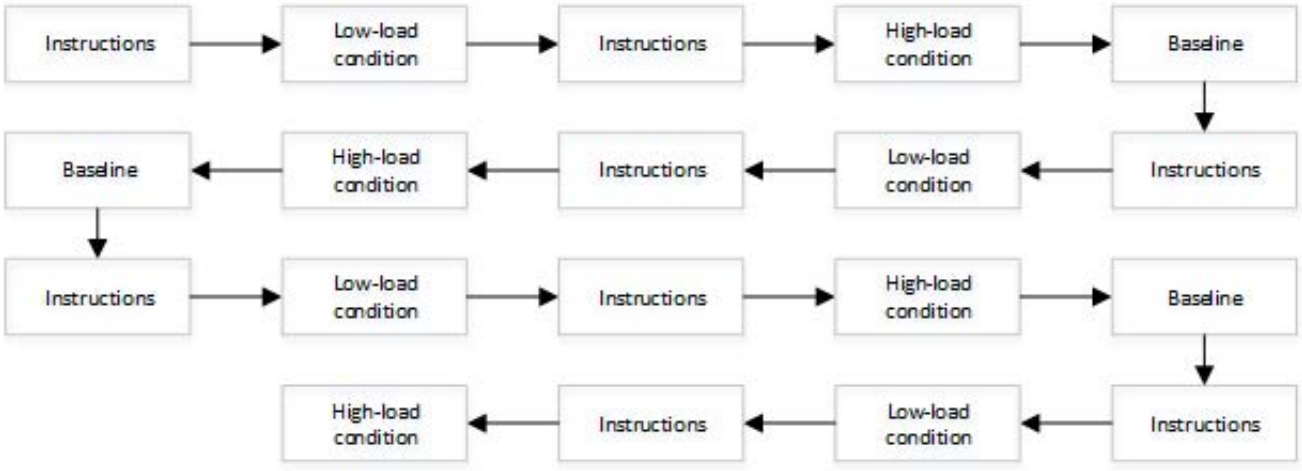


Fig. 1. Diagram showing experiment design.

was used as reference function. Head motion time courses were included as nuisance covariates. Using parametric maps from all subjects defined by contrast analyses among three conditions (baseline, low-load condition, and high-load condition), differences between pre-caffeine and post-caffeine activation were assessed with paired t-test using SPM12. Correlations of caffeine-induced task activation difference with reaction time and accuracy difference (post-caffeine minus pre-caffeine) were assessed to determine imaging versus behavior correlations using SPM12.

RESULTS

Behavioral Data

Figure 2 and Table 1 show mean response accuracy and mean reaction time during high-load condition (Fig. 2a, c) and sustained attention task condition (Fig. 2b, d). No significant difference in response accuracy or reaction time was observed between pre-caffeine and post-caffeine for each task condition, although caffeine intake showed a trend of reducing reaction time but increasing response accuracy.

Neuroimaging Results

Results of statistical analysis shown below were thresholded with a voxelwise P-value < 0.005. Multiple

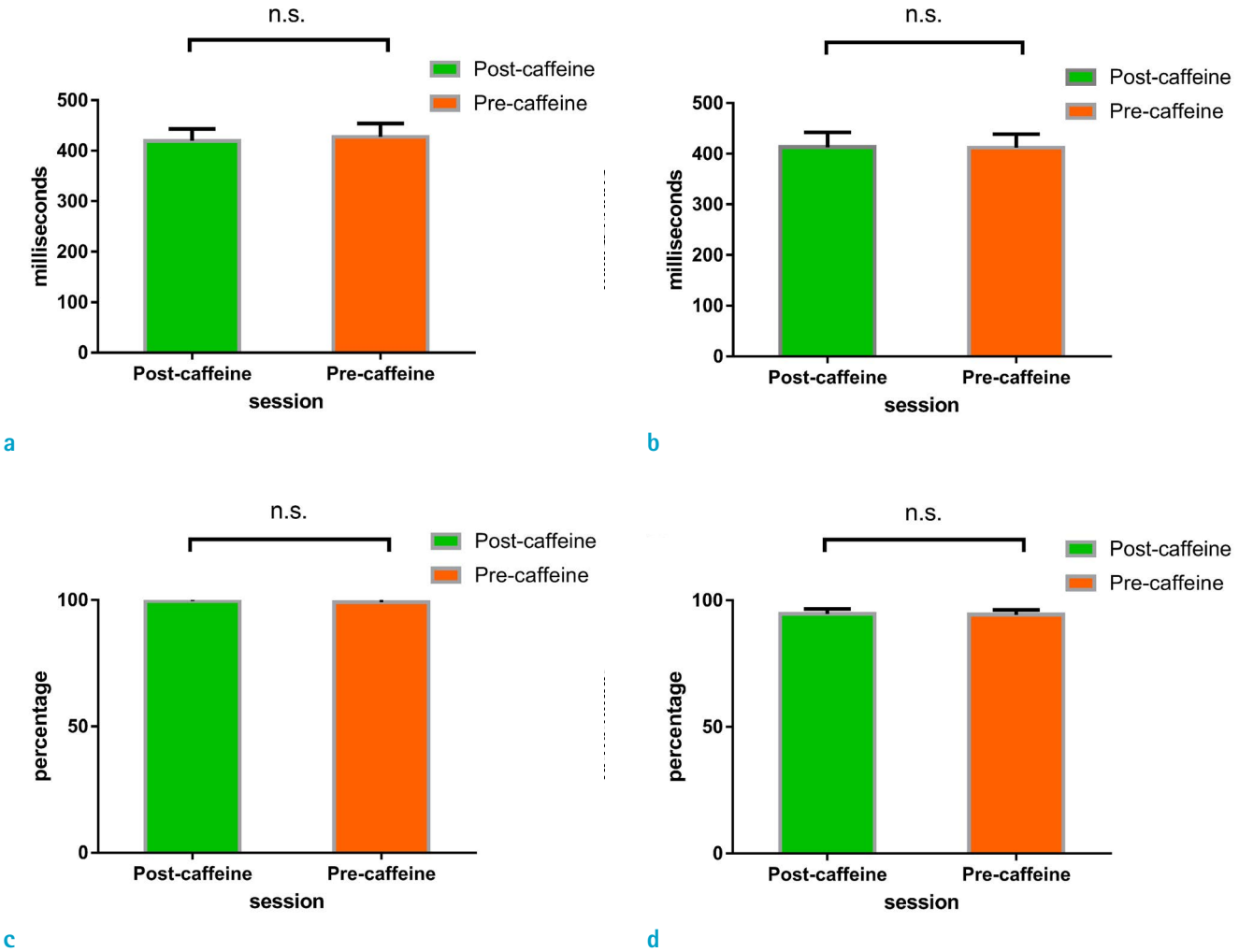


Fig. 2. Bar graphs of reaction accuracy and reaction time before and after caffeine ingestion. (a) Mean reaction time at low-load condition, (b) Mean reaction time at high-load condition, (c) Mean reaction accuracy under low-load condition, (d) Mean reaction accuracy under high-load condition.

comparison was applied to suprathreshold clusters using Monte Carlo simulations implemented in AlphaSim (http://afni.nimh.nih.gov/afni/) with $\alpha < 0.05$.

Figure 3 shows comparison of results between low-load condition (button press attention task) and baseline condition. Group level differences between low-load condition and baseline activation for pre-caffeine and post-caffeine sessions are shown in Figure 3a and b, respectively. Figure 3c shows caffeine-induced changes under low-load condition compared to those at baseline activation. Both sessions demonstrated attention-induced activations in typical attention network (AN), including bilateral prefrontal cortex, temporal cortex, precuneus, and angular gyrus with deactivation in the primary visual cortex. Both activation and deactivation showed quite different spatial patterns. However, no significant difference in AN was observed, although caffeine increased activation in the primary visual cortex and decreased activation in the middle occipital cortex (Table 2).

Results of high-load condition (sustained attention and working memory task) compared to baseline brain activation are shown in Figure 4. Group level analyses for both pre-caffeine (Fig. 4a) and post-caffeine (Fig. 4b) sessions identified classical attention and working memory activation patterns in prefrontal cortex, insula, and parietal cortex. Figure 4c shows caffeine-induced changes in high-load condition versus baseline activation difference. Brain activations were also found in primary visual cortex, thalamus, and cerebellum. Deactivation was shown in default mode network and secondary visual cortex. Compared to caffeine-free session, caffeine ingestion increased attention and working memory task activations in primary visual cortex, posterior middle temporal cortex, inferior angular gyrus, and superior temporal cortex but reduced activation in secondary visual cortex (Table 2).

Results of high-load condition compared to low-load condition are shown in Figure 5. Group level high-load condition versus low-load condition activation patterns for pre-caffeine and post-caffeine sessions are shown in Figure 5a and b, respectively. Figure 5c shows caffeine-induced changes in difference between high-load condition and low-load condition activation. Group level activation patterns of high-load condition versus low-load condition were quite similar to those shown in high-load condition versus baseline condition (Fig. 4a, b). However, more spatially extended deactivations were demonstrated in the default mode network. Compared to caffeine-free condition, caffeine-ingestion induced attention activation only in the left posterior middle temporal cortex and inferior angular gyrus (Table 2). None of these caffeine-induced task-activation changes was related to difference in reaction time difference or response accuracy (both $P > 0.2$, $r < 0.05$).

Table 1. Behavioral Data (Mean and Standard Deviation) of Each Condition before and after Taking Caffeine

	Low-load condition	High-load condition
Caffeine		
Mean RT (ms)	419.40 ± 23.80	413.00 ± 29.14
% Accuracy	99.51 ± 0.70	94.60 ± 1.97
Noncaffeine		
Mean RT (ms)	427.20 ± 26.80	412.30 ± 26.11
% Accuracy	99.11 ± 1.25	94.31 ± 1.85

RT = reaction time

Table 2. Whole Brain Analysis Local Maxima

		MNI coordinates		
	Cluster size	X	Y	Z
Post-caffeine vs. pre-caffeine				
Task vs. control				
L middle temporal gyrus	53	-39	-54	21
Task vs. baseline				
R middle temporal gyrus	58	48	-48	15
R insula lobe	61	39	-15	18
L fusiform gyrus	240	27	-54	-9
R fusiform gyrus	264	3	36	9
L cuneus	115	-6	-84	36
R calcarine gyrus	115	12	-66	24
R inferior occipital gyrus	131	36	-81	-3
R hippocampus	210	33	-42	3
Control vs. baseline				
L lingual gyrus	252	-21	-63	-6
R middle occipital gyrus	52	30	-93	-3

Local maxima of brain activations on two types of comparison across two types of sessions. "Task" refers to high-load condition, while "control" means low-load condition.

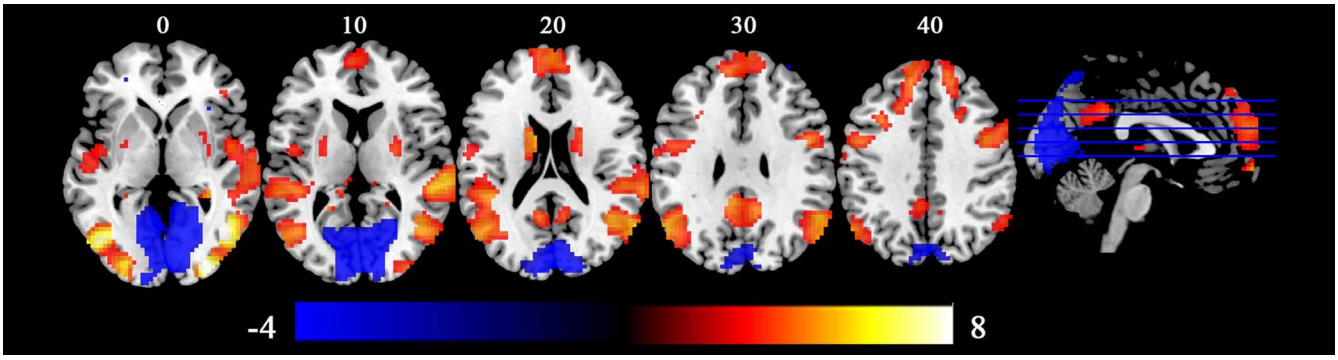
L = left; MNI = Montreal Neurological Institute; R = right; vs. = versus

DISCUSSION

Our results showed that caffeine ingestion not only

increased brain activation, but also decreased brain deactivation during sustained attention task-performing. It was also related to task-load. Low-load attention task (low-load condition) showed activation alterations in visual cortex after caffeine intake. However, high-load attention and working memory task showed caffeine-induced activation alterations in visual cortex, superior and middle temporal cortex, and inferior angular gyrus. No significant behavior changes were observed after caffeine intake.

At session level, our data showed typical attention and



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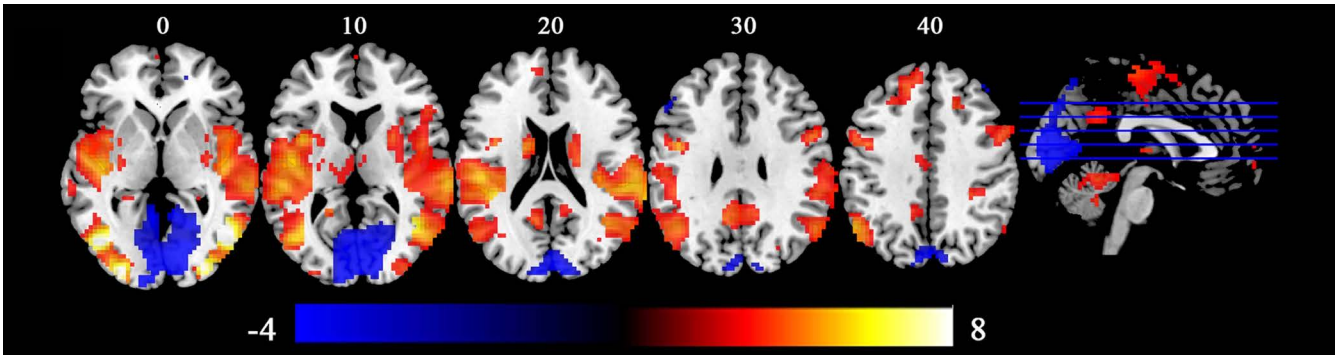

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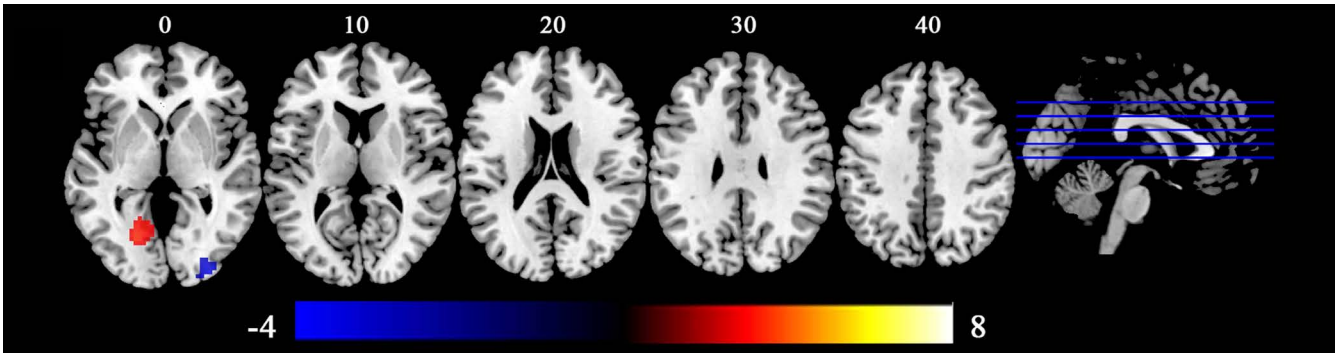

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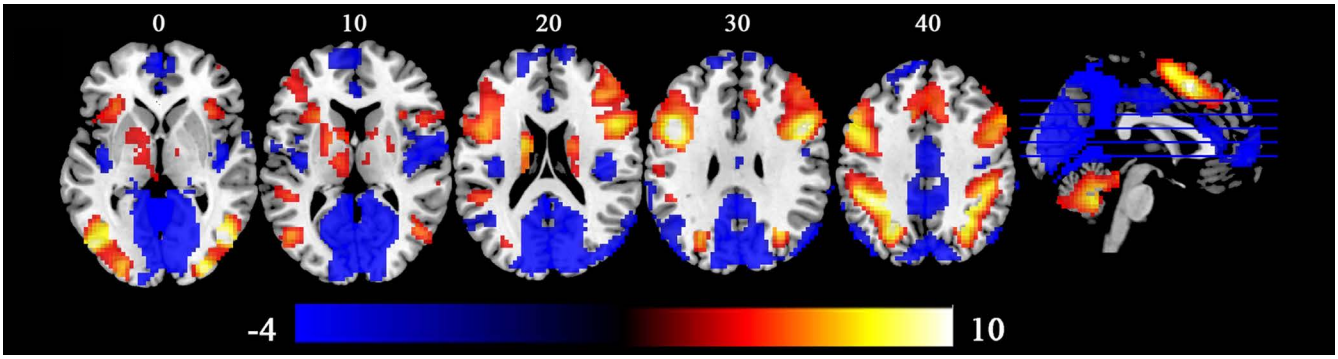
Fig. 3. Low-load condition (attention task) versus baseline brain activation difference. (a) Group level activation difference before caffeine intake, (b) Group level activation difference after caffeine intake, (c) Caffeine-induced changes in low-load task activation versus baseline. Statistical significance level was defined at voxel-wise $P < 0.005$ and a cluster size of 46 (corrected for multiple comparison using AlphaSim, alpha < 0.05). Red means increased low-load task activation after caffeine intake. The number above each slice indicates slice location in the MNI space. Color bar indicates visualization window for t values.

working memory task activation patterns as seen in the literature. Both task-positive and task-negative activations were demonstrated in task-positive network which overlapped with attention and working memory networks and in visual cortex and default mode network, respectively. Such two-way task activation pattern has been reported in the general literature (36). Our data also showed a task-load dependent brain activation pattern, indicating that task-positive network was more activated while task-negative network was more deactivated when cognitive



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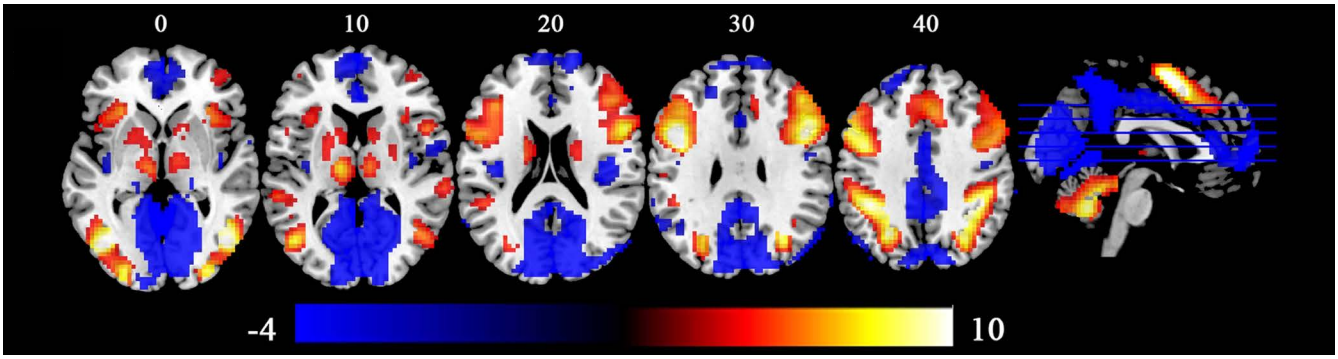

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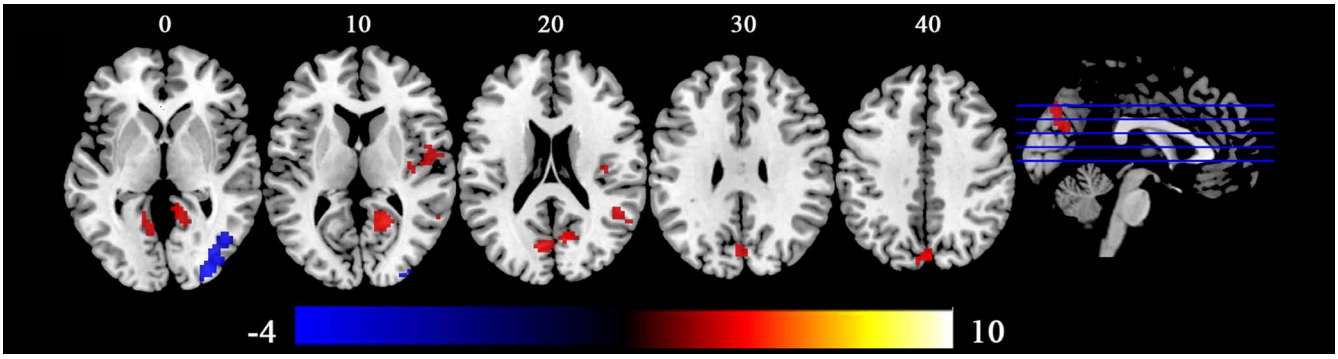

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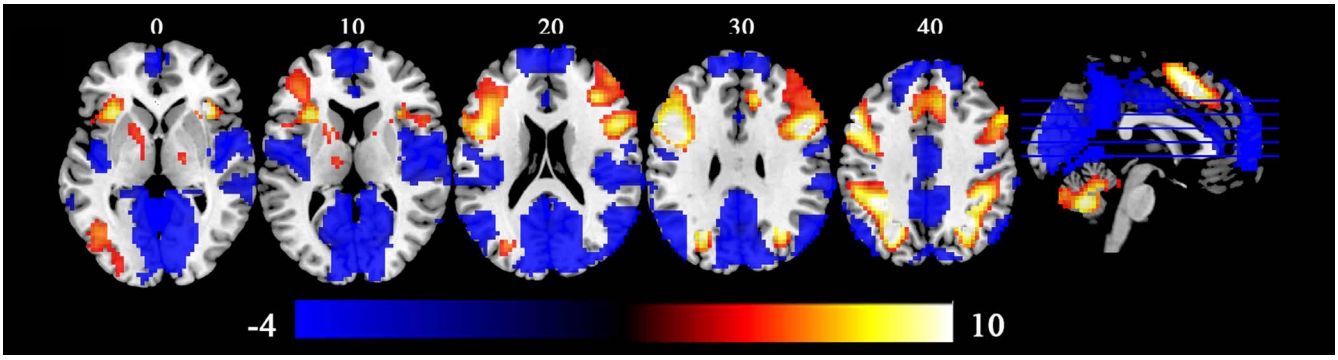
Fig. 4. High-load condition (sustained attention and working memory task) versus baseline brain activation difference. (a) Group level activation difference before caffeine intake, (b) Group level activation difference after caffeine intake, (c) Caffeine-induced changes to high-load task activation versus baseline. Statistical significance level was defined at voxel-wise $P < 0.005$ and a cluster size of 46 (corrected for multiple comparison using AlphaSim, alpha < 0.05). Red color means increased high-load task activation after caffeine intake. The number above each slice indicates slice location in the MNI space. Color bar indicates visualization window for t values.

task load was increased. These findings were consistent with previous load-dependent behavioral performance and brain activations (37, 38). Such simultaneous activation increase and deactivation decrease indicates an alteration in balance or interaction between task positive network and task negative network as implicated in a previous resting study (39). Increased task activation after caffeine is consistent with results of previous caffeine fMRI studies (13, 14, 16, 18, 19, 29), indicating that caffeine has a positive effect on sustained attention and memory. The load-dependent



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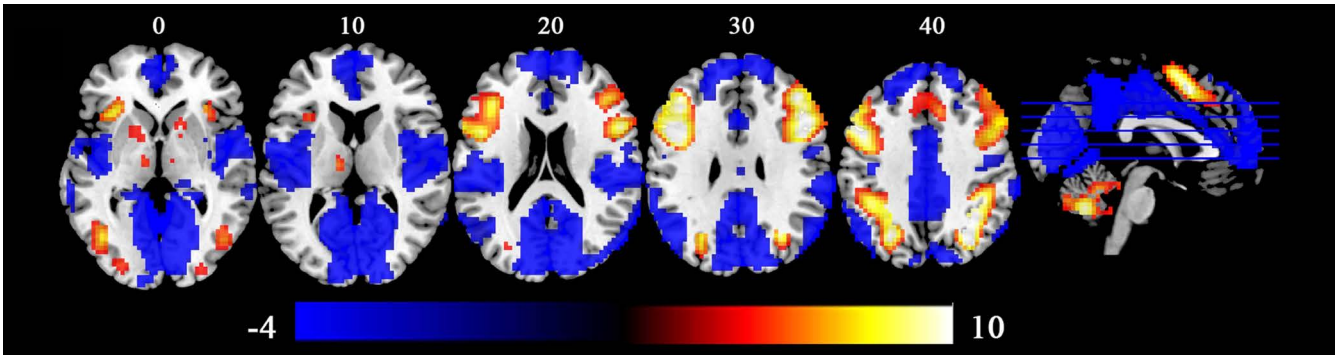

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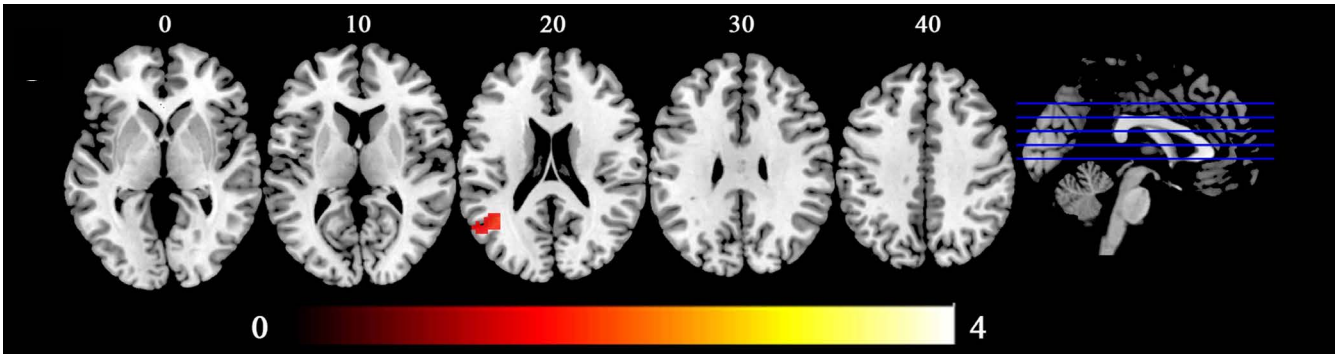

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Fig. 5. High-load condition (sustained attention and working memory task) versus low-load condition brain activation difference. (a) Group level activation difference before caffeine intake, (b) Group level activation difference after caffeine intake, (c) Caffeine-induced changes to high-load versus low-load activation difference. Statistical significance level was defined at voxel-wise $P < 0.005$ and a cluster size of 46 (corrected for multiple comparison using AlphaSim, alpha < 0.05). Red means greater high-load minus low-load task activation difference after caffeine intake. The number above each slice indicates slice location in the MNI space. Color bar indicates visualization window for t values.

activation increase after caffeine intake is consistent with region-of-interest based load-dependent activation effects of caffeine reported previously (40), further supporting the beneficial effect of caffeine on brain cognition. Deactivation seems to be common to many tasks, making it possible to compare it across different cognition loads. Our data showed that deactivation pattern became less spatially distributed when cognition load was increased, consistent with previous postulation that deactivation could facilitate task activation or it is a result of task activation (20, 22). Caffeine reduced brain deactivation which was load-dependent, suggesting that caffeine could facilitate the brain by task negative network when performing functional tasks. Such facilitation could gain increases in cognition load.

Our imaging findings were not consistent with behavioral measurements. No overt behavioral change was observed after taking caffeine. Brain activity difference and behavioral measure difference between pre- and post-caffeine sessions were not correlated with each other either. No caffeine-induced behavior changes found in this study were consistent with an early study of caffeine in sustained attention (41) and a more recent study (42), although significant beneficial behavioral effects of caffeine were observed in several other studies (43, 44). One reason for no behavior change after caffeine might be due to the fact that the amount of caffeine (200 mg) used in this study was not enough to cause observable behavior difference. Meanwhile, enhanced behavior after caffeine has been long claimed to be related to its withdrawal effects (45). Different from most studies mentioned above, we only included caffeine-naive subjects in this study. Therefore, caffeine withdrawal effects should not be involved in our data. Another cause might be the small sample size included in the present study. In addition, we had missing data for frontal brain regions in pre-post caffeine statistical comparison. Moreover, behavior measurements performed in this study depended on motor response which might introduce additional variability to measured data due to wrong button pressing or mis-pressing, subsequently contributing to mismatch between imaging and behavior results. One limitation of this study was that a placebo group was not included due to difficulty in obtaining placebo pills. Therefore, effects by placebo should be studied in the future.

In summary, our results showed that caffeine could simultaneously change both task activation and deactivation in a load-dependent manner. The increased task activation in tandem with reduced task deactivation may represent a mechanism underlying the beneficial effect of caffeine on high-demanding cognitive brain functions.

In conclusion, caffeine increased working memory and attention brain activation but reduced task deactivation, indicating a beneficial effect of caffeine on the brain even though it had no observable behavior improvement. These data suggest that caffeine affects brain activity in a load-dependent manner accompanied by a dissociation between task-positive network and task-negative network.

Acknowledgments

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Conflict of Interest

The authors have no conflict of interest to disclose.

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