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Kertas Asli/*Original Articles*

Investigating Brain Activation and Neural Efficacy During Simple Arithmetic Addition Task in Quiet and in Noise: An fMRI Study

(Mengkaji Pengaktifan Otak dan Efikasi Neuron Semasa Tugasan Hasil Tambah Aritmetik Mudah dalam Senyap dan Hingar: Satu Kajian fMRI)

NG SOK BEE, AHMAD NAZLIM YUSOFF, TENG XIN LING &
AINI ISMAFAIRUS ABD. HAMID

ABSTRACT

Knowledge about the hemodynamic model that mediates synaptic activity and measured magnetic resonance signal is essential in understanding brain activation. Neural efficacy is a hemodynamic parameter that would change the evoked hemodynamic responses. In this work, brain activation and neural efficacy of the activated brain areas during simple addition task in two different backgrounds were studied using fMRI. The objectives were to determine the activated areas during the performance of arithmetic addition in quiet (AIQ) and noisy (AIN) background and to investigate the relationship between neural efficacy and height extent of activation for the respective areas. Eighteen healthy male participants performed simple arithmetic addition in quiet and in noise. Bilateral cerebellum, superior temporal gyrus (STG), temporal pole (TP) and supplementary motor area (SMA) were significantly ($p < 0.05$) activated during AIQ and AIN. Left middle frontal gyrus (L-MFG), right superior frontal gyrus (R-SFG), right superior orbital gyrus (R-SOG) and bilateral insula were more active in quiet as compared to in noise while the left middle cingulate cortex (L-MCC), left amygdala (L-AMG), right temporal pole (R-TP) and left cerebellum (L-CER) were more active in noise as compared to in quiet. The t value for most of the activated regions was found to be inversely proportional to the neural efficacy. Significant ($p < 0.05$) negative relationship between t value and neural efficacy were found for R-STG and bilateral cerebellum during AIQ, while for AIN, similar relationships were found in R-CER, R-STG and R-TP. This study suggests that while being significantly activated, the hemodynamic responses of these brain regions could have been suppressed by the stimulus resulting in an intensity decrease with increasing neural efficacy.

Keywords: Brain activation, statistical parametric mapping, hemodynamic, t statistic

ABSTRAK

Pengetahuan mengenai model hemodinamik yang menghubungkan antara aktiviti sinaps dan isyarat resonans magnet yang diukur adalah penting dalam memahami pengaktifan otak. Efikasi neuron adalah parameter hemodinamik yang mampu mengubah respons hemodinamik yang dicetus. Dalam kajian ini, pengaktifan otak dan pengaruh efikasi neuron bagi kawasan pengaktifan otak semasa perlaksanaan hasil tambah mudah dalam latar belakang berbeza dikaji menggunakan fMRI. Objektifnya adalah untuk menentukan kawasan yang aktif semasa pelaksanaan hasil tambah aritmetik mudah dalam latar belakang senyap (AIQ) dan hingar (AIN) dan untuk menyelidiki hubungan antara efikasi neuron dan ketinggian pengaktifan untuk kawasan tersebut. Lapan belas orang subjek lelaki sihat melaksanakan hasil tambah aritmetik mudah dalam senyap dan hingar. Serebelum, girus temporal superior (STG), kutub temporal (TP) dan kawasan motor tambahan (SMA) bilateral mengalami pengaktifan bererti ($p < 0.05$) semasa AIQ dan AIN. Girus frontal tengah kiri (L-MFG), girus frontal superior kanan (R-SFG), girus orbital superior kiri (R-SOG) dan insula bilateral didapati lebih aktif dalam senyap berbanding dalam hingar manakala korteks singulat tengah kiri (L-MCC), amigdala kiri (L-AMG), kutub temporal kanan (R-TP) dan serebelum kiri pula didapati lebih aktif dalam hingar berbanding senyap. Nilai t bagi kebanyakan kawasan pengaktifan didapati berkadar songsang terhadap efikasi neuron. Hubungan negatif bererti ($p < 0.05$) antara nilai t dan efikasi neuron didapati untuk R-STG dan serebelum bilateral semasa AIQ, manakala untuk AIN, hubungan yang sama ditemui untuk R-CER, R-STG dan R-TP. Kajian ini mencadangkan bahawa walaupun mengalami pengaktifan bererti, respons hemodinamik kawasan pengaktifan otak tersebut berkemungkinan ditekan oleh stimulus menyebabkan pengurangan dalam keamatan dengan peningkatan efikasi neuron.

Kata kunci: Pengaktifan otak, pemetaan statistik berparameter, hemodinamik, statistik t

INTRODUCTION

The discovery of the blood oxygenation level dependent (BOLD) contrast (Ogawa et al. 1990) and the invention of echo planar imaging (EPI) technique (Mansfield 1977) allowed for extensive analyses of regional brain activity using functional magnetic resonance imaging (fMRI). Consequently, further advancement in the analysis of fMRI data laid the foundation for novel approaches to studying functional specialisation and integration within the brain. Functional specialisation focusses on the analyses of regionally specific effects, while, functional integration is about the analyses of inter-regional effects (Friston 2011). The latter can then be divided into two specific objectives, which are commonly referred to as functional connectivity (determination of the temporal correlation between spatially remote neurophysiological events) and effective connectivity (determination of the influence that the elements of a neural system exert over another) (Friston 2011). The studies of effective connectivity, e.g. psychophysiologic interaction (Friston et al. 1997) and dynamic causal modeling (Friston et al. 2003), take into account the aspect of hemodynamic responses within the brain and is essential for mechanistically interpretable accounts of neural systems (Stephan & Roebroeck 2012).

BOLD fMRI employs hemoglobin as a convenient endogenous contrast agent, relying on the magnetisation difference between oxyhemoglobin and deoxyhemoglobin to create the fMRI signal. BOLD signal is dependent on many physiological (blood content, blood flow, blood volume and blood oxygenation) and biophysical (neural efficacy, signal decay, feedback, transit time, stiffness and oxygen extraction) parameters (Friston et al. 2000; Arthurs & Boniface 2002). Therefore, with the understanding of factors that govern BOLD signal, it would be possible to predict the neural activity indirectly through its assumed hemodynamic correlate. One of the hemodynamic parameters that would influence the measured BOLD signal is the neural efficacy. Friston et al. (2000), defined neural efficacy (ε) as the increase in perfusion signal elicited by neural activity, expressed in terms of event density. It reflects both the potency of the stimulus in eliciting a neural response and the efficacy of the ensuing synaptic activity to induce the signal. The governing equation is $\dot{s} = \varepsilon U(t) - s/\tau_s - (f_{in} - 1)/\tau_f$ from which s is the flow inducing signal with its time dependent $\dot{s}$, $U(t)$ is the neural activity, τ_s is the time constant for signal decay, f_{in} is the inflow and τ_f is the time constant for the autoregulatory feedback (Friston et al. 2000). Changes in neural efficacy would modulate the evoked hemodynamic responses. However, to our knowledge, the report on the hemodynamic responses of brain activation involving cognitive functions, such as solving arithmetic problems is still lacking.

Numerous studies have examined brain activation during mental arithmetic (Cowell et al. 2000; Fehr et al. 2007; Grabner et al. 2007). They showed that different brain regions were responsible for the different functions executed during arithmetic problem solving. Calculation tasks that involved arithmetic operations, such as addition, subtraction, division and multiplication require the participants to identify number quantities and then modify them based upon the operational function. Arithmetic decisions thus present different cognitive demands based on the number of steps they require (Agostino et al. 2010) and would certainly involve the aspect of working memory. Working memory is commonly used in processing and storing information temporarily and is very important for many cognitive actions such as arithmetic operation. In Grabner et al. (2007), bilateral cerebellum, supplementary motor area, middle cingulate cortex, insula and middle frontal gyrus were activated during arithmetic calculation. The cerebellum is known historically for its involvement in motor functions. It is associated with action sequencing (Buhusi & Meck 2005) and has also been associated to a wide range of cognitive functions. Finding from a recent ALE meta-analysis shows that the cerebellum was activated by tasks that target language, spatial processing, working memory and executive function (Stoodley & Schmahmann 2009). Solving arithmetic problems would also involve speech perception if the task is delivered verbally. Scott et al. (2004) suggested that there is an engagement of perception and cognitive networks during listening to speech in noisy condition. In terms of the brain functional anatomy, the superior temporal gyrus (STG) plays a central role in the perception of speech (Wong et al. 2008) and non-speech stimuli (Hall et al. 2002).

In this work, the effects of background noise on the spatial extent of activation and the influence of neural efficacy on the height extent of activation during a simple arithmetic addition task were investigated. The motivation is based upon the foundation that the underlying activation and hemodynamic responses that ensued during the execution of arithmetic problem solving has not been fully explored especially when the task is performed with the presence of background noise. The objectives of the study were (1) to identify the areas of activation, (2) to determine the neural efficacy of the activated regions and (3) to determine the relationship between the *t* value and neural efficacy when the participants performed addition in quiet (AIQ) and in noise (AIN). Since the knowledge about the relationship between neural efficacy and *t* value is still lacking, this study is important to be conducted in order to gain a better understanding about the brain function and its relation to neural efficacy.

METHODOLOGY

PARTICIPANTS

Eighteen native, Malay-speaking, male adults participated in the present study. All the participants agreed to participate by filling in the informed consent and screening forms and signing them, after being given full explanation regarding the nature and risks that may arise, as required by the Institutional Ethics Committee (IEC) NN-049-2009. The participants were conveniently recruited from Universiti Kebangsaan Malaysia Kuala Lumpur campus and were screened by the Malaysian Certificate of Education to obtain a group of participants who are able to perform simple mathematical operations. Only those who passed their mathematics papers were enrolled into this study. None of the participants are professional mathematician, and none of the participants are actively involved in teaching mathematics. The participants were then interviewed on their health condition prior to the scanning session. All the participants were tested for handedness using the Edinburgh Handedness Inventory (Oldfield 1971). The participants were also tested for their middle ear condition and hearing level using a tympanometer (Model Grason Stadler Inc. GSI33) and a pure-tone audiometer (Model Grason Stadler Inc. GSI61) respectively, by a qualified Audiologist. Pure tone audiometry (PTA) was conducted over the frequency range of 250 Hz to 8000 Hz. Both devices were calibrated to the American National Standard Institute (ANSI).

EXPERIMENTAL TASKS

The experimental tasks consisted of simple arithmetic addition problems that need to be solved by the participants. Each arithmetic addition problem consisted of four digits that were randomly selected from numbers 0 to 9, e.g. (2 + 1 + 5 + 4). Each digit may appear twice such as (6 + 2 + 4 + 2) but not more than twice. The arithmetic addition problems were recorded in a CD ROM using a male voice. Prior to the recording, the male voice was verified by a Speech Pathologist for a correct pronunciation and intonation. There were altogether 60 sets of an arithmetic addition problem that were recorded as stimuli. The recordings were alternately done in quiet (known as Addition in Quiet – AIQ) and in the presence of white noise as background (known as Addition in Noise – AIN). For AIN, the 83-dB stimuli were embedded in 80-dB white noise to obtain a signal-to-noise ratio (SNR) of 3dB. The alternating sequence of the 30 arithmetic addition problems in quiet and 30 arithmetic addition problems in a noisy background was fixed so that all participants attended to the same experimental task. A complete set of the arithmetic addition problem is given elsewhere (Aini Ismafairus 2011).

fMRI EXPERIMENT

Prior to the functional magnetic resonance imaging (fMRI) scans, all participants were given detailed instructions on how to respond to the stimuli and were allowed to practice. The participant to be scanned was laid down supine in the MRI gantry. The participant was required to put on the MRI headphones (transmission of sound stimulus through an air tube) for the delivery of instructions and stimuli and the radio frequency (RF) head coil for signal transmission and reception. The participants were also instructed not to move their head during the scan as head movement can cause signal intensity changes over time from any one voxel and present a serious confound in fMRI studies. To minimise head movement, immobilising devices were used together with the head coil.

A sparse fMRI paradigm was used for this study (Abd Hamid et al. 2011), as shown in Figure 1. This type of paradigm had previously been used in auditory studies (Hall et al. 1999; Binder et al. 2004). The recorded stimuli were presented using a digital playback system during the silent gaps between volume acquisitions and did not overlap with the sound produced by the scanner. Thus, the effects on the MRI images from the scanner sound were avoided. The duration of the stimuli was 6-s. As mentioned above, each participant was subjected to two different conditions, which were AIQ and AIN. The participants were instructed to listen carefully to the 6-s stimuli and were required to start performing the calculations (imaginary) immediately after hearing the first digit. The participants were required to provide an answer verbally to the addition tasks in 3-5 s after the last digit. Participant's response in answering is important in order to evoke responses in the respective brain areas, and to ensure that the participants remain alert and focused throughout the scanning session.

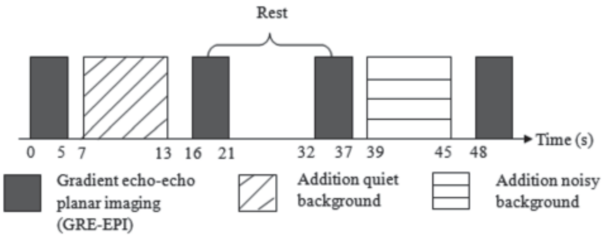

FIGURE 1. The sparse fMRI paradigm used in this study

The functional imaging session consisted of 120 series of trials (or measurements); 30 trials for AIQ, 30 trials for AIN and 60 trials for baseline (stimulus not given). The sequence was AIQ-BASELINE-AIN-BASELINE-AIQ, as can be seen in Figure 1. A long (11 s) inter-measurement interval was used to allow for the hemodynamic response to decline after each given stimulus. The acquisition time was 5 s, with each functional measurement producing 35 axial slices in the 5-s duration (one image slice per 143 ms). The measurement started with AIQ. The imaging time in each session was 32 minutes, which produced 120 × 35 = 4200 images in total.

DATA ACQUISITION

The fMRI scans were conducted in the Department of Radiology, UKM Medical Centre. Functional images were acquired using a 1.5T magnetic resonance imaging (MRI) system (Siemens Avanto, Erlangen, Germany) equipped with blood oxygenation level-dependent imaging protocol, echo-planar imaging capabilities, and radio frequency head coil used for signal transmission and reception. Gradient-echo-planar imaging pulse sequence with the following parameters was used: repetition time (TR) = 16000 ms, acquisition time (TA) = 5000 ms (interscan interval = 16000 ms − 5000 ms = 11000 ms), echo time (TE) = 50 ms, field of view (FOV) = 192 × 192 mm, flip angle = 90°, matrix size = 128 × 128, and slice thickness = 3 mm. In addition, high resolution anatomical images of the entire brain were obtained using a T1-weighted multiplanar reconstruction (MPR) spin-echo pulse sequence with the following parameters: TR = 1620 ms, FOV = 250 × 250 mm, flip angle = 90°, matrix size = 128 × 128, and slice thickness = 1 mm.

POST-PROCESSING

All the functional (T2*-weighted) and structural (T1-weighted) images were processed in the Functional Image Processing Laboratory, Diagnostic Imaging & Radiotherapy Programme, Faculty of Allied Health Sciences, UKM, Kuala Lumpur. Image analyses were performed using a personal computer using the software MATLAB 7.6 R2008a (Mathworks Inc., Natick, MA, USA) and Statistical Parametric Mapping (SPM8) (Functional Imaging Laboratory, Wellcome Department of Imaging Neuroscience, Institute of Neurology, University College of London). Raw data in DICOM (.dcm) formats were transformed into Analyze (.hdr, .img) format using SPM8. Functional images for each measurement were realigned using the 6-parameter affine transformation translationally (x, y, and z) and rotationally (pitch, roll, and yaw) directions to reduce artefacts from subject movement and to make within- and between-subject comparisons meaningful. Following realignment, a mean image from the series was used to estimate some warping parameters that mapped it onto a template that conformed to a standard anatomical space, i.e., EPI template provided by the Montreal Neurological Institute (MNI). The normalisation procedure used a 12-parameter affine transformation, where the parameters constituted a spatial transformation matrix. The images were then smoothed using a 6-mm full-width-at-half-maximum Gaussian kernel. The activated voxels were identified by the general linear model approach by estimating the parameters of the model and deriving the appropriate test statistic (t statistic) for every voxel. Statistical inferences were finally obtained on the basis of the general linear model and Gaussian random field theory.

GROUP ANALYSES

Group random-effects (RFX) analysis was used in obtaining the average brain activation. For AIQ and AIN, significant statistical inference was made at $p = 0.05$, corrected for multiple comparisons with an extent threshold voxel $k = 10$ voxels, while for differential brain activation AIQ > AIN and AIN > AIQ, the probability threshold p is lowered to 0.001, uncorrected for multiple comparison with $k = 10$ voxels. The anatomies of the activated brain region were confirmed using anatomy toolbox (Eickhoff et al. 2005). The relationship between the height (t value) and spatial (NOV) extent of activation was studied using correlation analysis. The NOV for all the significantly ($p < 0.05$, corrected for multiple comparisons) activated regions obtained from the group RFX during AIQ and AIN is plotted against the t-value for the voxel with highest intensity for each region.

NEURAL EFFICACY

The hemodynamic properties of the activated brain regions were evaluated using SPM8 on each participant's activation to determine the neural efficacy in generating BOLD responses. This was done by extracting the hemodynamic parameters from a 4-mm radius sphere centered about the point of maximum intensity of each respective area. Pearson's correlation analysis was done to test the relationship between the t value and neural efficacy for each particular area of interest. One-way ANOVA was used to compare the mean of the neural efficacy among the activated brain regions for AIQ and AIN.

RESULTS

DEMOGRAPHICAL DATA

The average age and standard deviation of the participants were 23.2 ± 2.5 years (range between 20 to 28 years). All participants reported no history of psychiatric or neurological disorder and no current use of any psychoactive medications. All participants were confirmed to be right handed with average laterality index (LI_{ave}) of 87 in the range of 6th to 7th right. In a study by Deutsch (1978), left-hand dominant participants have been found to perform the pitch discrimination tasks significantly better than right-hand dominant participants. Based on this finding and on the fact that both arithmetic and pitch memory processing would involve working memory, it is important that the participants should not be mixed in terms of their handedness to avoid confounding effects. The participants were found to have no hearing impairment and no history of long time exposure to loud noise to be inappropriate for auditory stimulus presentation. The participants' hearing levels for both ears are not greater than 30 dB (HL) in the respective range of frequency used for the PTA test.

BRAIN ACTIVATION

Voxels of significant activation obtained from (a) AIQ, (b) AIN, (c) AIQ > AIN and (d) AIN > AIQ overlaid onto standard structural images are shown in Figures 2(a - d) respectively with L = left hemisphere, R = right hemisphere, CER = cerebellum, TP = temporal pole, STG = superior temporal gyrus, SMA = supplementary motor area, SOG = superior orbital gyrus, SFG = superior frontal gyrus, MFG = middle frontal gyrus, AMG = amygdala and MCC = middle cingulate cortex. The corresponding activated regions, together with their number of activated voxels (NOV), coordinates of the maximum intensity voxel and the respective t values are tabulated in Table 1. Both AIQ and AIN (at $p = 0.05$, corrected for multiple comparisons) evoked similar activation in L-CER, R-CER, L-STG, R-STG, L-TP, R-TP and SMA (Figures 2(a) and (b)). The total number of activated voxels summed for all ROIs were 426 during AIQ and 451 during AIN. Plot of the number of activated voxels against the t values obtained from all the significantly activated regions during AIQ and AIN (Figure 3) shows that there is a tendency for the NOV to increase linearly with increasing t value ($N = 14$, Pearson's $r = 0.897$, $p < 0.01$).

TABLE 1. Number of activated voxels (NOV), coordinates of maximum intensity (x, y, z) and the t value obtained from brain activation of group random effects analysis shown in Figures 2 (a), (b), (c) and (d)

Condition	Region	NOV	x	y	z	t value
*AIQ	R-CER	148	30	-60	-28	12.13
	L-CER	51	-32	-58	-34	10.04
	R-STG	55	62	-18	-2	10.81
	L-STG	90	-46	-20	2	10.88
	R-TP	10	50	14	-6	8.69
	L-TP	48	-50	10	-6	10.48
	SMA	24	4	12	60	9.50
*AIN	R-CER	119	30	-60	-28	11.27
	L-CER	86	-32	-56	-36	10.98
	R-STG	38	64	-20	0	9.10
	L-STG	82	-44	-22	4	10.20
	R-TP	14	62	4	-4	9.06
	L-TP	88	-50	8	-8	10.31
	SMA	24	-2	8	62	10.00
**AIQ > AIN	L-MFG	20	-30	22	28	5.58
	R-SFG	43	18	52	0	5.32
	R-SOG	16	26	36	-16	4.98
	R Insula	13	38	6	12	4.32
	L Insula	12	-34	-18	8	4.35
**AIN > AIQ	L-MCC	22	0	-6	32	5.80
	L-AMG	33	-22	-6	-10	5.79
	R-TP	16	62	4	-8	5.00
	L-CER	10	-48	-50	-34	4.92

*$p<0.05$ (corrected for multiple comparisons);
**$p<0.001$ (uncorrected for multiple comparisons)

The activated areas for AIQ > AIN (at $p = 0.001$, uncorrected for multiple comparison) are L-MFG, R-SFG, R-SOG and bilateral insula, while different activation areas were observed for AIN > AIQ (at $p = 0.001$, uncorrected for multiple comparison) which are L-MCC, L-AMG, R-TP and L-CER (Figures 2(c) and (d)). The total number of activated voxels summed for all ROIs were 104 for AIQ > AIN and 81 for AIN > AIQ. A greater activation was observed in AIQ > AIN as compared to AIN > AIQ.

NEURAL EFFICACY

The chosen regions of interest (ROIs) for the analysis of hemodynamic response are the areas that have shown significant activation ($p < 0.05$, corrected for multiple comparisons) in a group random-effects analysis (RFX). The ROIs are L-CER, R-CER, L-STG, R-STG, L-TP, R-TP and SMA. These region's neural efficacy and their respective maximum intensity voxel's t value were entered into a correlation analysis to investigate the relationship between the potency of the stimulus in eliciting a neural response (ε) with the height extent of activation (t value)

For AIQ, the results obtained from the correlation analyses between the t values and neural efficacy values (ε) showed that only L-STG indicated a linear and positive relationship. However, the relationship is insignificant ($p > 0.05$). With respect to SMA, L-TP and R-TP, the relationship was linear, negative and also insignificant ($p > 0.05$). However, Pearson's correlation analysis for R-CER, L-CER and R-STG reveals linear, negative but with significant relationship ($p < 0.05$), Figure 4.

For AIN, Pearson's correlation results indicated that only L-TP showed linear and positive relationship, while L-CER, SMA and L-STG showed linear and negative relationship. However, the relationships were insignificant. Pearson correlation plots for R-CER, R-STG and R-TP however, exhibited linear, negative and significant relationship ($p < 0.05$), Figure 5.

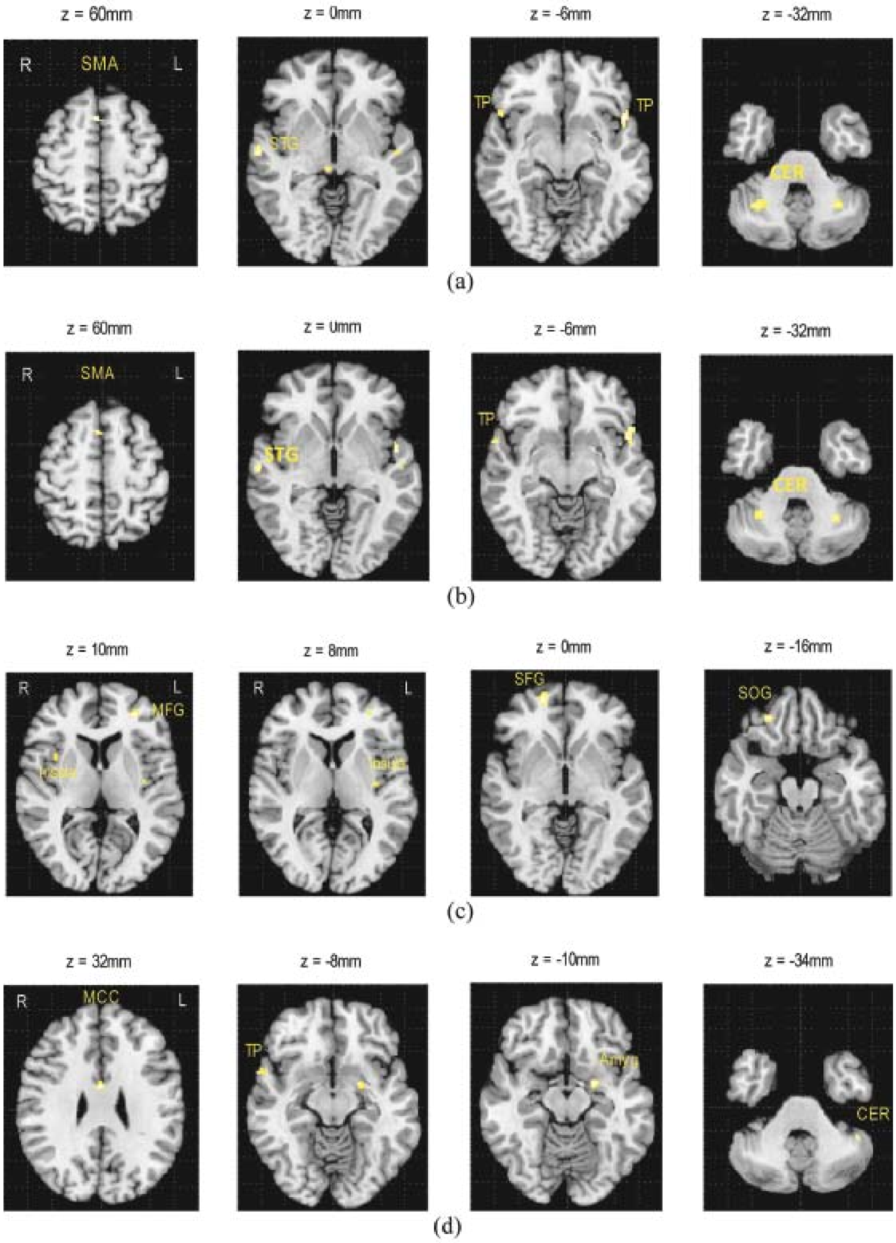

FIGURE 2. Brain activation obtained from group random effects analysis for (a) AIQ, (b) AIN (c) AIQ>AIN and (d) AIN>AIQ at different longitudinal (*z*) levels

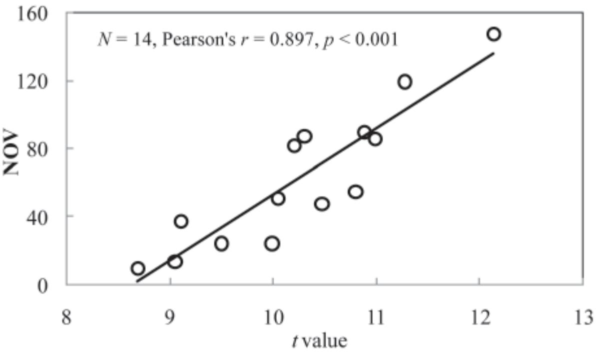

FIGURE 3. Plot of the number of activated voxels against the *t* values of all the significantly activated regions during AIQ and AIN

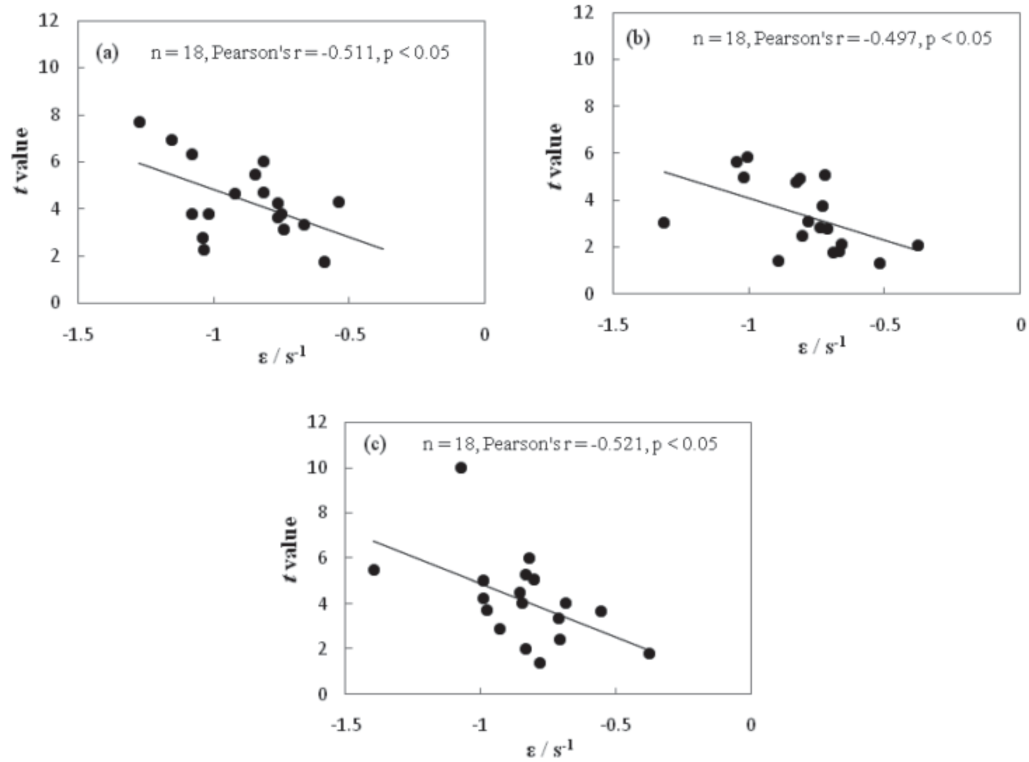

FIGURE 4. Significant, negative and linear correlation between *t* value and neuronal efficacy (ε/s^{-1}) for (a) R-CER, (b) L-CER and (c) R-STG during AIQ

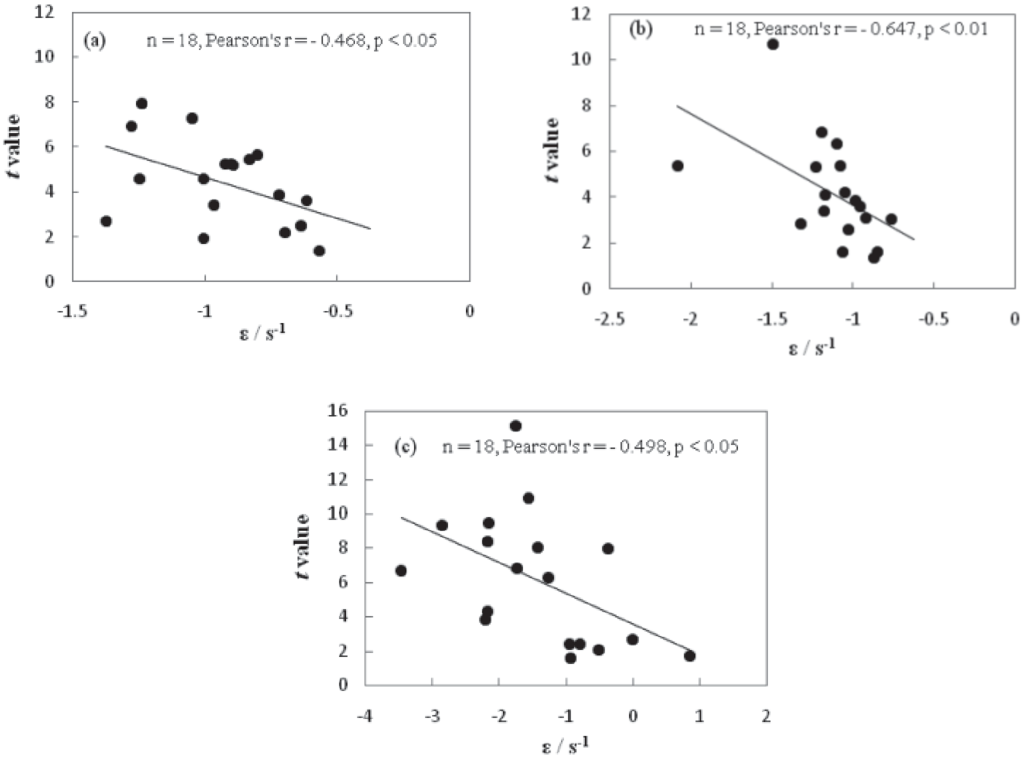

FIGURE 5. Significant, negative and linear correlation between *t* value and neuronal efficacy (ε/s^{-1}) for (a) R-CER, (b) R-STG and (c) R-TP during AIN

In comparing the mean of the neural efficacy among the activated brain regions, the results obtained from ANOVA were significant ($p < 0.001$) to suggest that at least one pair among the activated regions were significantly difference among the means of the neural efficacy for both AIQ and AIN. For AIQ, post-hoc test indicated that the mean of the neural efficacy between L-TP with L-CER and R-CER, L-TP with L-STG and R-STG, L-TP with SMA was significantly different ($p < 0.05$). L-STG indicated the highest neural efficacy among the seven activated regions with mean = -0.55 s^{-1}. The ANOVA test results are shown in Table 2. With regard to AIN, the results showed that the mean of neural efficacy was significantly different ($p < 0.05$) between L-TP and L-STG, L-CER and L-TP, L-CER and R-TP. L-CER indicated the highest neural efficacy among the seven activated areas with the mean = -0.43 s^{-1} (Table 3).

DISCUSSION

Group random-effects analysis (RFX) results showed that AIQ and AIN have resulted in the same activated areas which are L-CER, R-CER, L-STG, R-STG, L-TP, R-TP and SMA. These regions have been found to be activated during the performance of tasks involving verbal working memory in several previous studies, see the following paragraph. Nevertheless, the differences across the brain activated regions during AIQ and AIN can hardly be observed. This could be due to the same regions within the brain responding to the simple arithmetic addition task, whether the task is performed in quiet or in noise.

Bilateral activation of STG and TP was expected due to their respective functions in auditory processing. Temporal pole is also known as BA38 in Brodmann classification (Ingrid et al. 2007). It has been associated with numerous functions such as auditives processing (Humphries et al. 2001), learning and memory (Schiltz et al. 1973), social cognition (Ingrid et al. 2007), and language processing (Hermann & Wyler 1988). STG (BA 22) plays the role in auditives language reception and processing (Wong et al. 2008). From Table 1, L-STG and L-TP show extended and higher activation as compared to R-STG and R-TP both during AIQ and AIN. According to Tervaniemi & Hugdahl (2003), verbal stimuli would cause a wider spatial and higher extent of activation in the left auditory cortex as compared to the right auditory cortex.

L-CER and R-CER were activated during both AIQ and AIN. This result was similar to other studies on brain activation during calculation (Kong et al. 2005; Menon et al. 2000). According to Stoodley & Schmahmann

TABLE 2. ANOVA test results to determine significant difference in the mean of neuronal efficacy among the activated brain regions during AIQ

Area (I)	Area (J)	Mean difference (I-J)	Std. error	*p* value	95% Confidence interval	
					Lower bound	Upper bound
R-CER	L-STG	-0.13	0.09	0.97	-0.43	0.16
	R-STG	-0.06	0.09	1.00	-0.36	0.25
	L-CER	-0.12	0.09	0.99	-0.42	0.18
	SMA	-0.05	0.09	1.00	-0.35	0.26
	L-TP	0.64*	0.18	0.05	0.01	1.27
	R-TP	0.36	0.17	0.64	-0.22	0.95
L-STG	R-STG	0.08	0.09	1.00	-0.23	0.38
	L-CER	0.01	0.09	1.00	-0.29	0.31
	SMA	0.09	0.09	1.00	-0.22	0.39
	L-TP	0.77*	0.18	0.01	0.14	1.41
	R-TP	0.49	0.17	0.17	-0.09	1.08
R-STG	L-CER	-0.06	0.09	1.00	-0.37	0.25
	SMA	0.01	0.10	1.00	-0.31	0.33
	L-TP	0.70*	0.19	0.02	0.06	1.33
	R-TP	0.42	0.17	0.40	-0.17	1.01
L-CER	SMA	0.07	0.10	1.00	-0.24	0.38
	L-TP	0.76*	0.19	0.01	0.13	1.39
	R-TP	0.48	0.17	0.20	-0.11	1.07
SMA	L-TP	0.69*	0.19	0.03	0.05	1.32
	R-TP	0.41	0.17	0.44	-0.18	1.00
L-TP	R-TP	-0.28	0.23	1.00	-1.05	0.49

* The difference in mean is significant at $p = 0.05$

TABLE 3. ANOVA test results to determine significant difference in the mean of neuronal efficacy among the activated brain regions during AIN

Area (I)	Area (J)	Mean difference (I-J)	Std. error	*p* value	95% Confidence interval	
					Lower bound	Upper bound
R-CER	L-STG	-0.21	0.11	0.78	-0.57	0.15
	R-STG	0.07	0.13	1.00	-0.38	0.51
	L-CER	-0.31	0.11	0.14	-0.66	0.04
	SMA	-0.07	0.13	1.00	-0.49	0.34
	L-TP	0.55	0.20	0.25	-0.15	1.25
	R-TP	0.68	0.26	0.30	-0.22	1.57
L-STG	R-STG	0.27	0.14	0.70	-0.18	0.73
	L-CER	-0.10	0.11	1.00	-0.47	0.26
	SMA	0.13	0.13	1.00	-0.29	0.56
	L-TP	0.76*	0.21	0.03	0.05	1.46
	R-TP	0.88	0.26	0.06	-0.02	1.78
R-STG	L-CER	-0.38	0.14	0.18	-0.82	0.07
	SMA	-0.14	0.15	1.00	-0.63	0.35
	L-TP	0.48	0.22	0.54	-0.25	1.22
	R-TP	0.61	0.27	0.52	-0.31	1.53
L-CER	SMA	0.24	0.13	0.78	-0.18	0.65
	L-TP	0.86*	0.21	0.01	0.16	1.56
	R-TP	0.99*	0.26	0.02	0.09	1.88
SMA	L-TP	0.62	0.21	0.15	-0.10	1.35
	R-TP	0.75	0.27	0.20	-0.16	1.66
L-TP	R-TP	0.13	0.31	1.00	-0.90	1.15

* The difference in mean is significant at $p = 0.05$

(2009), the cerebellum is activated by tasks that target language, spatial processing, working memory, attention and executive function. The NOV and *t* value of R-CER is always higher than L-CER during both AIN and AIQ. This suggests the right lateralisation (right more than left) of the cerebellum function in accomplishing the task, whether the task is performed in quiet or in the present of distraction such as noise.

Interestingly, the SMA has also revealed significant activation during AIQ and AIN. This finding is similar to what has been obtained in previous studies (Kawashima et al. 2004; Grabner et al. 2007) when simple arithmetic was used as the task. The SMA is located within the premotor cortex or BA6. It extends anterior to the primary motor cortex near the Sylvian fissure (lateral sulcus). The basic function of this brain area, in which the SMA is a portion of it, is the motor sequencing and movement planning. SMA is known to be the centre for movement initiation (Koeneke et al. 2004a). However, it is also known to have the function of retrieval of learned sequences that are under internal control such as the performance of a sequence of movements from memory (Lutz et al. 2005). In other studies, activation in SMA has been associated with verbal working memory (Smith & Jonides 1999; Baddeley 2003), which could be the most possible explanation of its activation in this study.

An increase in NOV as *t* values increase (Figure 3) indicates that there is a linear, positive and strong relationship between the height and spatial extent of activation of all the activated areas, at least in the context of this study. This means; for any particular brain region, an increase in the *t* value of the maximum intensity voxel will be accompanied by a wider extent of activation of that region. Similar relationship has been observed in our previous work (Ahmad Nazlim Yusoff et al. 2010) that focuses upon the relationship between NOV and percentage of signal change (PSC) for pre central gyrus (PCG) and supplementary motor area (SMA) in a finger tapping study.

In the differential activation analysis, L-MFG, R-SFG, R-SOG and bilateral insula were significantly more active during AIQ as compared to AIN. These frontal lobe regions have been known to be related to arithmetic fact's retrieval (Jost et al. 2011; Fehr et al. 2007). This suggests that arithmetic fact's retrieval carry out by these frontal regions tends to be more prominent in AIQ. For AIN > AIQ, L-MCC, L-AMG, R-TP and L-CER have been found to be significantly more active in AIN than AIQ. In Cowell et al. (2000) and Straube et al. (2007), the activation found in MCC and AMG was associated with cognitive requirements of attention and working memory. This suggests that attention, and working memory play a larger role in AIN as higher attention and working memory are needed in a noisy background.

In the aspect of hemodynamic responses, almost all the values of neural efficacy of the seven activated regions (L-CER, R-CER, L-STG, R-STG, L-TP, R-TP and SMA) of each participant were negative. The neural efficacy is the ability of the input to excite neural activity in each voxel (Friston et al. 2003). These findings suggest that the stimulus is decreasing the neural activity. This is strengthened by the findings from Pearson's correlation between *t* value and ε for all the regions (except L-STG during AIQ and L-TP during AIN) that showed negative relationship. However, only a number of plots showed significant negative relationship, which were found in R-CER, R-STG and L-CER during AIQ and R-CER, R-STG and R-TP during AIN. The fact that signal intensity is inversely proportional to the neural efficacy is evident in Figures 4 and 5.

One possible explanation for the negative neural efficacy is that the 5-second acquisition time (TA) used for this study is too long. Acquisition time for most studies was typically 2 to 3 seconds. Brain activation that results during the execution of a task will peak normally between 5 to 10 seconds after stimulus delivery (Amaro & Barker 2006) with the dispersion of the peak around 2 to 3 seconds (Henson 2004). For cognitive responses within the brain, which can be completed in under a second, the neural activity might have subsided quickly within 5-second acquisition time. Hence, the neural efficacy is negative, which means it was negatively activated by the stimulus.

According to Buxton (2002), negative BOLD response may also arise from correlated noise or head motion or as an EPI phase encoding artifact. Task-induced deactivation which is not specific for the task, stimuli or imaging modality, that result in negative BOLD signal have been mentioned in Shulman et al. (1997) and McKiernan et al. (2003). They suggested that it was a cognitively rich state characterised by numerous possible attention-dependent processes which include planning and problem solving, verbal and visual imagery, monitoring the internal sensory state and body image, monitoring the external environment, monitoring emotional state, episodic memory encoding and retrieval and working memory.

From the ANOVA test, L-STG showed the highest mean of neural efficacy during AIQ indicating that it has the highest ability to excite the neural activity during AIQ. This is supported by the findings in Tervaniemi & Hugdahl (2003) from which verbal stimuli caused greater activation within the left auditory area as compared to the right auditory area. Upadhyay et al. (2008) found that STG is the primary auditory area which acts as the input centre for auditive processing. In contrast, L-CER showed the highest mean of neural efficacy during AIN which indicated that cerebellum has the highest ability to excite the neural activity. This support the hypothesis that cerebellum plays an important role in cognitive function as mentioned in Marien et al. (2001) and may be involved in attenuating noise and/or increasing attention to task performance (Abdul Manan et al. 2012). Furthermore, it has been found that cognitive types of stimuli will activate the left cerebellum higher when working on logical thinking (Abd Hamid et al. 2011).

CONCLUSION

In conclusion, performing the simple arithmetic addition tasks in a noisy background has been found to evoke similar brain responses as in a quiet environment. Significant activations were found in bilateral cerebellum, bilateral superior temporal gyrus, bilateral temporal pole and supplementary motor area. However, brain areas that are more active in a quiet condition than in noise are mainly located in frontal lobes, which are left middle frontal gyrus, right superior frontal gyrus, right superior orbital gyrus and bilateral insula. Consequently, left middle cingulate cortex, left amygdala, right temporal pole and left cerebellum, which are the areas outside the frontal lobe, have been found to be more active in a noisy condition as compared to in quiet. With regards to the significantly activated areas obtained during AIQ and AIN, a linear, positive and significant relationship has been observed between their spatial and height extent of activation. In a quiet background, only the bilateral cerebellum and right superior temporal gyrus showed negative significant relationship between the *t* value and neural efficacy. In a noisy background, significant negative relationship between the *t* value and neural efficacy were only found for right cerebellum, right superior temporal gyrus and right temporal pole. The neural efficacy has been found to influence the height extent of activation (*t* value) which in turn has given an impact on the spatial extent of activation (NOV).

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Ng Sok Bee
Ahmad Nazlim Yusoff
Teng Xin Ling
Diagnostic Imaging & Radiotherapy Program
School of Diagnostic and Applied Health Sciences
Faculty of Health Sciences
Universiti Kebangsaan Malaysia
50300 Jalan Raja Muda Abdul Aziz
Kuala Lumpur, Malaysia

Aini Ismafairus Abd. Hamid
Otto-Von-Guericke University Magdeburg
Biomedical Magnetic Resonance
Leipziger Str. 44, D-39120 Magdeburg, Germany

Correspondence author: Ahmad Nazlim Yusoff
Email address: nazlimtrw@ukm.edu.my
Tel: +603 2687 8084; Fax: +603 2687 8108

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