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Title

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Permalink

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Journal

Neuroreport, 18(8)

ISSN

0959-4965

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Publication Date

2007-05-28

DOI

10.1097/wnr.0b013e3280ebb49b

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Peer reviewed

The neural basis of processing anomalous information

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Received 26 January 2007; accepted 2 February 2007

This study explored the neural basis of the processing of anomalous information (the N400 effect) in an arithmetic task. Twenty healthy undergraduate students were scanned while they performed a number-matching task. Relative to matched numbers, unmatched numbers elicited significantly greater activation at left inferior and superior parietal cortex, left inferior frontal gyrus,

and left fusiform and lingual gyri. Combining these results and those of previous studies on semantic anomaly, we proposed that the parietal region is the source of the arithmetic N400 component and the left inferior frontal gyrus is involved in domain-general processing of anomalous information. *NeuroReport* 18:747–751 © 2007 Lippincott Williams & Wilkins.

Keywords: anomalous, arithmetic N400, functional magnetic resonance imaging, numerical processing, semantic processing

Introduction

In 1980, Kutas and Hillyard [1] first reported an event-related potential (ERP) component (N400) associated with the processing of sentences ending with an unrelated word (e.g. 'I take coffee with cream and dog'). They found that, compared with normal sentences, sentences with a semantically unrelated final word evoked more negative potentials at about 400 ms after onset of the stimuli. A number of ERP studies since then have examined this N400 effect with tasks such as semantic priming [2], syntactic processing [3], word-picture matching [4], face recognition [5] and so on. After reviewing the studies associated with the N400 component, Kutas and Federmeier [6] concluded that the N400 component is specifically linked to semantic incongruity.

Recent studies [5,7–10] have attempted to localize the neural substrates for the N400 component using mostly semantic tasks. For example, Kiehl *et al.* [7] found that incongruent final words elicited greater activation in bilateral frontal cortex and anterior temporal cortex than did congruent words. Using both the ERP and functional magnetic resonance imaging (fMRI) techniques, Rossell *et al.* [8] found that, compared with related words, unrelated words evoked a greater N400 component and elicited greater activation at left anterior medial temporal region. In a recent review of lesion studies, intracranial recordings, magnetoencephalography studies, and fMRI studies, Petten and Luka [11] concluded that data from all studies converged to implicate the left temporal lobe as the main source and the right temporal lobe as a secondary source of the N400 component. They also concluded that, although activation was found at the left inferior frontal gyrus in

fMRI studies, this region might not contribute to the N400 effect because patients with lesion at this site have normal N400 effect [9–11].

A similar N400 component has also been reported in studies using numerical tasks, such as matching numbers [12–14] and carrying out arithmetic calculations [15–20]. Although both the semantic and arithmetic N400 components can be explained by incongruity or anomalous information (see Ref. [1] for the semantic and Ref. [18] for the arithmetic N400 component), it is not clear whether they have the same neural mechanisms. The source of the semantic N400 effect is in the classic language areas. Given that arithmetic and language processing relies on distinct neural networks (see Ref. [21] for a review), the source of the arithmetic N400 effect may be different from that of the semantic N400 effect. Previous research has shown that the inferior parietal lobe is the center of number processing [22,23]. Therefore, we expected that the neural basis of the arithmetic N400 component might be in the parietal region.

A delayed-number-matching task was adopted in this study. In two previous studies, Zhou *et al.* [14,20] had used similar tasks. They asked participants to solve an arithmetic problem and then to match the answer to a target that appeared 1300 ms later [20] or to memorize a number and then to match it with a number presented 1350 ms later [14]. Both types of tasks resulted in an N400-like component. Delayed matching tasks have also been used for semantic processing. For example, Sotilloa *et al.* [24] asked participants to read a sentence and then judge whether a word presented 1800 ms later matched the sentence. An N400 component was found in that study. In

a magnetoencephalography study, Lin *et al.* [25] asked participants to judge whether two successively presented words (ISI 1200 ms) made up a meaningful phrase. This task also resulted in an N400-like component at about 350 ms (M350) after the onset of the second word. These studies indicate that a delayed matching paradigm should evoke an N400 component. On the basis of previous results [14,20] and the results of pilot tests, we used a delayed-number-matching paradigm in this study, in which participants were asked to compare two numbers, to memorize one of them, and then to judge whether a target number presented 1800 ms later matched the memorized one.

Method

Participants

Twenty healthy right-handed university students (10 men and 10 women) were recruited from Sichuan University, China. The average age of the participants was 22.7 years, ranging from 18.3 to 29.8 years. They self-reported to have normal or corrected-to-normal eyesight. All were free from nervous diseases or brain injuries and had no brain abnormality on their T1-weighted high-resolution magnetic resonance images (MRI). They had not participated in any experiments similar to the present one during the past six months. Written informed consent was obtained from each participant. This experiment was approved by both the State Key Laboratory of Cognitive Neuroscience and Learning at Beijing Normal University and the MRI Center of the Western China Hospital attached to Sichuan University.

Materials and procedure

On the basis of previous research [14,20] and results of pilot tests, we used delayed-number-matching tasks in this study. Participants were asked to perform two tasks. In one task (the 'which is larger' task), two single-digit numbers were presented simultaneously for 200 ms (e.g. 3 and 5), followed by a blank of 1800 ms. Participants were asked to compare the two numbers and to memorize the larger one (5 in the above example). A single-digit number (the target) was then presented, which may or may not be the same number the participants memorized. Participants pressed a key to indicate whether the target was exactly the same as the memorized number (5 in the above example) or not (e.g. 1, 3, or 7). In the 'which is smaller' task, all aspects of the task were the same as the 'which is larger' task except that the participants had to memorize the smaller number.

The order of the two tasks was counterbalanced across participants. Half of participants pressed the left key for 'Yes' and the right key for 'No', and the other half responded in the reverse manner. In both tasks, the target stayed on the screen until the participant responded. Both accuracy and speed were emphasized in the instruction to participants. The time interval between the presentation of the target and the response was recorded as response time (RT).

In each task, 120 trials were used, mixed with 20 fixations (lasting 2000 ms each) as the baseline. Trials and fixations were presented in random order. Half of the number-matching trials were followed by a matched target (e.g. 5 3 followed by 5 in the 'which is larger' task or 5 3 followed by 3 in the 'which is smaller' task) and the other half by an unmatched digit (e.g. 5 3 followed by 7,3, or 1 in the 'which

is larger' task or 5 3 followed by 1,5, or 7 in the 'which is smaller' task). The first two digits were presented at the center of the screen in font size 72, separated by two blanks. The order of the larger and the smaller digits was randomized. The target digit appeared at the center of screen with the same font size as the first two digits. Stimuli were presented in black color against a gray background, programmed with E-Prime and projected onto a translucent screen. Participants viewed the stimuli through a mirror attached to the head coil. Two separate runs were used, one for each task.

Apparatus and imaging parameters

Functional MRI was performed with a 3.0-T GE/Elscint Prestige whole-body imager (Elscint Ltd., Haifa, Israel) at the MRI Center of the Western China Hospital (Sichuan University, China). Participants lay supine in the scanner with their heads immobilized. A single shot, T2*-weighted gradient-echo echo planar imaging sequence was used for the fMRI scans, with slice thickness of 5 mm and no gaps between slices, plane resolution of 3.75×3.75 mm, and TR/TE = 2000 ms/30 ms. The field of view was 240×240 mm, and the acquisition matrix was 64×64 . Thirty contiguous axial slices parallel to AC-PC were acquired to cover the whole cerebrum. In each run, 260 images were acquired with a total scan time of 528 s and the first 8 s were not recorded to allow for stability in magnetization. Additionally, high-resolution T1-weighted anatomical images were acquired for each participant (three-dimensional, gradient-echo pulse-sequence, TR/TE = 25 ms/6 ms, FOV = 220×220 mm, matrix = 220×220 , and thickness = 2 mm).

Image processing and data analysis

Data analysis was performed using SPM-2 for motion correction and statistical inference (Statistical Parametric Mapping, Wellcome Department of Cognitive Neurology, London, <http://www.fil.ion.ucl.ac.uk/spm/>). The acquisition time error of functional images was first corrected with slice timing, and these corrected image volumes were then realigned to the first volume in the scanning sessions. A mean functional image volume was constructed for each participant from the realigned image volumes. This mean image volume was then used to determine parameters for spatial normalization into the echo planar imaging template provided by SPM2. The parameters were then applied to the corresponding functional image volumes for each participant. The normalized functional images were smoothed with an 8-mm full-width at half-maximum Gaussian filter.

General linear model was used to estimate the condition effect for individual participants. HRF reference function was used to model hemodynamic response. A high-pass filter (128 s) was applied to remove low-frequency effects such as signal drift and cardiac and respiratory pulsations. We used global normalization to scale the mean of each scan to a common value to correct for whole brain differences over time.

Brain areas sensitive to the arithmetic N400 effect were investigated by contrasting the two conditions: unmatched and matched numbers. Group-averaged effects were computed with a random-effect model. All reported areas of activation were significant above a threshold of $P < 0.001$ (uncorrected) with more than 15 voxels ($3 \times 3 \times 3$ mm).

Results

Behavioral data of two participants were not included in the analysis because of a failure of the response box. Trials with the wrong key pressed or those with RT that were three standard deviations above the individual participants' average RT were coded as incorrect responses. The error rates for the unmatched and matched numbers were 0.067 (SD 0.029) and 0.057 (SD 0.025), respectively, [$t(17) = 1.69$, $P = 0.11$], indicating that the participants were attentive to the task during the experiment. The response time for the unmatched numbers and matched numbers was 459 ms (SD 61 ms) and 426 ms (SD 59 ms), respectively [$t(17) = 4.93$, $P = 0.001$].

Table 1 Areas that showed more activation by the unmatched numbers than the matched numbers

Regions and Brodmann areas (BA)	Cluster size	Voxel		Talairach coordinates
		T	P (unc)	
Left superior and inferior parietal cortex (BA7, BA40)	159	5.46	0.000014	-29 -64 58
		5.44	0.000015	-35 -58 55
		5.09	0.000033	-38 -49 52
Left inferior frontal (BA44, BA45)	81	4.82	0.000059	-53 18 23
		3.99	0.000389	-47 33 25
Left fusiform and lingual gyrus (BA18, BA19, BA37)	89	5.30	0.000020	-20 -52 -9
		5.03	0.000037	-26 -70 -9
		4.76	0.000068	-20 -73 -3

unc, uncorrected.

Three clusters of brain regions showed greater activation in the unmatched condition than in the matched condition (Table 1, Fig. 1): left superior and inferior parietal cortex, left inferior frontal region, and left fusiform and lingual gyri.

To demonstrate that this effect is consistent across the two tasks, a region of interest (ROI) analysis (Fig. 2) was further conducted. We selected as ROIs the above-mentioned three areas that showed more activation in the unmatched condition than the matched condition. Using the *con*.img* of SPM2 and an in-house software, we calculated the average intensity of activation (effect size) of all voxels in each ROI (positive) by tasks (i.e. which is larger and which is smaller) and conditions (unmatched and matched numbers). Repeated measures analysis of variance with the tasks and the conditions as within-participant variables were conducted on the intensity of activation. Across all three regions, the main effect of the conditions was significant, $F(1,19) = 14.472$, $MSe = 0.065$, $P = 0.001$, $F(1,19) = 16.355$, $MSe = 0.079$, $P = 0.001$, $F(1,19) = 5.721$, $MSe = 0.014$, $P = 0.027$, for parietal, frontal and fusiform and lingual areas respectively. No significant effects of the tasks or the interaction between the tasks and the conditions were noticed, indicating that the condition effect was consistent across the two tasks.

Discussion

In this study we aimed to investigate the neural basis of the N400 effect in an arithmetic task. On the basis of behavioral data, the RT for the condition with unmatched numbers was longer than that for the condition with matched numbers, but the error rate did not differ significantly. Therefore there was no speed-accuracy trade-off. It appears that the unmatched condition required more effort to perform. This

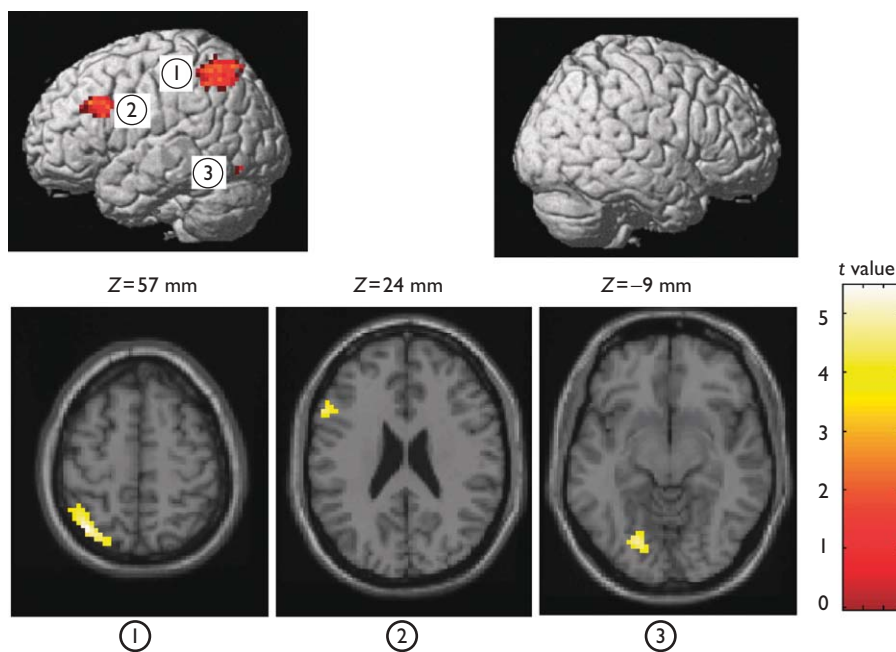


Fig. 1 Areas that showed significantly more activation by the unmatched numbers than the matched numbers, with a threshold of $P < 0.001$ (uncorrected) and clusters more than 15 voxels ($3 \times 3 \times 3$ mm). Upper: Images were rendered on single-participant template provided by SPM2. Below: Three slices correspond to activation at left parietal cortex, left inferior frontal gyrus and left fusiform and lingual gyri. Z values above each slice indicate the corresponding MNI coordinates. The color bar indicates the strength of activation.

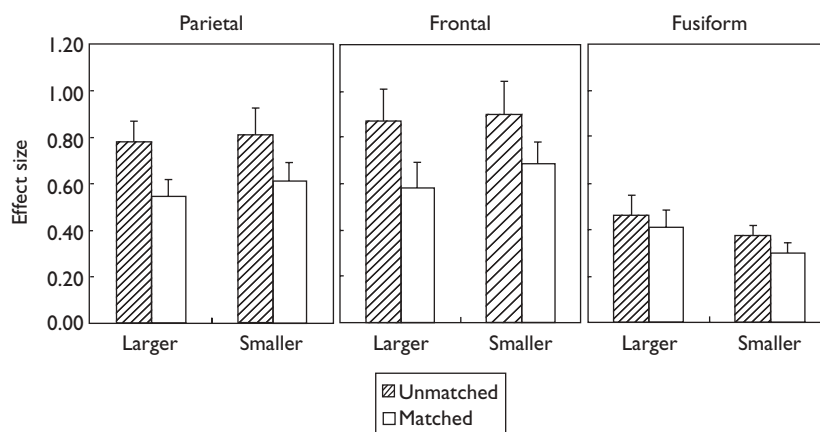


Fig. 2 Results of region of interest analysis. The error bar represents standard error. 'Larger', 'which is larger' task; 'Smaller', 'which is smaller' task.

pattern of results has been consistently demonstrated in studies of the N400 effect [7,8].

We found greater activation for the unmatched than the matched condition at the left superior and inferior parietal cortex, left inferior frontal gyrus, and left fusiform and lingual gyri. A further ROI analysis confirmed that this result is consistent across the two tasks. This result is consistent with our expectation that the parietal area may be the source of the arithmetic N400 effect. The semantic N400 was interpreted as 'an electrophysiological sign of the 'reprocessing' of semantic anomalous information' [1], or in the words of Jost, an 'additional semantic integration' idea [18]. This interpretation can also explain the arithmetic N400 effect. As the semantic N400 effect is localized at the classic language area in the temporal region (see Ref. [11] for a review), we propose that the source of arithmetic N400 component is inferior and superior parietal region. This region has been shown in previous studies as the center of number processing ([22,23] for review) and was activated to a greater extent by unmatched numbers than by matched numbers in this study.

In addition to the parietal region, we also found greater activation in the left inferior frontal gyrus for the unmatched than the matched condition. This region has also been found to be activated by the semantic N400 effect [7,8] and other N400 effects (e.g. face recognition [5]). Combining our data with previous research on the N400 effect, we propose that the left inferior frontal region may be involved in domain-general processing of anomalous information. Perhaps this region is involved in selecting and integrating contextual information, which is a common task in the processing of all types of anomalous information.

Conclusion

Using the fMRI technique and a delayed-number-matching task, this study found that, compared with matched numbers, unmatched numbers elicited greater activation in left inferior and superior parietal cortex, left inferior frontal gyrus, and left fusiform and lingual gyri. Taking together these results and those from previous studies using semantic and other tasks, we propose that the left inferior

frontal gyrus is involved in the domain-general processing of anomalous information and that the left parietal region is the source of the arithmetic N400 effect.

Acknowledgements

This study was supported by the National 973 Project (2003CB716803), the National Natural Science Fund of China (NSFC Grant No. 30625024), programs for NCET in University of China (04-0866), (UK) Royal Society International Joint Project with NSFC, and the National Pandeng Project (95).

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