Neuronal Population Responses in the Human Ventral Temporal and Lateral Parietal Cortex during Arithmetic Processing with Digits and Number Words

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Abstract

■ Past research has identified anatomically specific sites within the posterior inferior temporal gyrus (PITG) and the intraparietal sulcus (IPS) areas that are engaged during arithmetic processing. Although a small region of the PITG (known as the number form area) is selectively engaged in the processing of numerals, its surrounding area is activated during both digit and number word processing. In eight participants with intracranial electrodes, we compared the timing and selectivity of electrophysiological responses in the number form area-surround and IPS regions during arithmetic processing with digits and number words. Our recordings revealed stronger electrophysiological responses in the high-frequency broadband range in both regions to digits than number words, with the difference that number words elicited delayed activity in the IPS but not PITG. Our findings of distinct profiles of responses in the PITG and the IPS to digits compared with number words provide novel information that is relevant to existing theoretical models of mathematical cognition. ■

INTRODUCTION

The triple code model for numerical processing predicts the existence of three forms of representing numbers—symbolic, verbal, and analog—encoded in different brain regions (Dehaene & Cohen, 1995; Dehaene, 1992). Two of the brain regions implicated in the triple code model were the intraparietal sulcus (IPS) within the lateral parietal cortex for analog or abstract quantity processing (Dehaene, Piazza, Pinel, & Cohen, 2003) and the ventral temporal cortex (VTC) for symbolic numerical representations (Dehaene, 1992).

In line with this model, past research has established the involvement of IPS with abstract quantity processing in healthy control populations (Wei, Chen, Yang, Zhang, & Zhou, 2014; Piazza, Pinel, Le Bihan, & Dehaene, 2007; Dehaene et al., 2003) and in patients with parietal lesions (Koss et al., 2010; Martory et al., 2003; Takayama, Sugishita, Akiguchi, & Kimura, 1994; Cipolotti, Butterworth, & Denes, 1991). It followed that IPS would display "supramodal interpretation of numbers" (Eger, Sterzer, Russ, Giraud, & Kleinschmidt, 2003), and it was indeed shown that this region was activated independent of input notation of the numbers (Naccache & Dehaene, 2001; Pinel, Dehaene, Riviere, & LeBihan, 2001).

Although the involvement of IPS region in mathematical processing has been well established for several decades, strong evidence for the involvement of VTC was lacking until recently. Corroborating triple code model's hypothesized role of VTC, we recently found a small site within the posterior inferior temporal gyrus (PITG) in the VTC that respond selectively to visual numerals compared with number words and stimuli morphologically similar to numerals, such as letters and false fonts ("number form area" [NFA]; Shum et al., 2013). We later discovered that a larger region of the PITG, surrounding the NFA, becomes engaged during active arithmetic processing (Hermes et al., 2017), with clear interaction and electrophysiological functional connectivity with the IPS region during arithmetic processing as well as the resting state (Daitch et al., 2016).

To date, it remains unknown whether the profile of neuronal population activities in the PITG and the IPS that are induced during arithmetic processing, such as simple calculations, are different when different formulations of numbers are presented. To this end, we designed the current intracranial EEG (iEEG) study to measure neuronal population activities in response to differential visualizations of numbers in patients with intracranial electrodes in the PITG, the IPS, or both. High-frequency broadband (HFB) responses in the PITG and the IPS during these two conditions were quantified in terms of time and magnitude of response. HFB is understood to reflect nonoscillatory broadband signals as an electrophysiological correlate of the average of the spiking neuronal activities (Parvizi & Kastner, 2018). Using the temporal precision afforded by iEEG as well as the precise

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localization of the electrodes in each participant's native anatomical space (Groppe et al., 2017), the moderating effect of time, anatomical region, and the type of visual representation of numbers on the resulting power of the HFB signal were explored.

METHODS

Participants

Eight participants (two women and six men) were implanted with subdural iEEG over the regions surrounding the IPS, the PITG, or both. The subdural electrodes were implanted to localize the source of each participant's refractory epilepsy, and thus, the location and the number of electrodes was determined solely based on clinical needs. None of the participants' focal seizure area was near the IPS or PITG according to the results of intracranial monitoring. The Stanford institutional review board approved the experiments, and the participants provided written informed consent to participate. The results from Task 1 in six of our eight participants have been used in a previous publication (Daitch et al., 2016). In this report, we extend the findings by adding two participants and present novel data from all participants in Task 2.

Electrode Localization

High-resolution T1-weighted MRI scans of the preimplant brains were acquired on a GE 3-T scanner at Stanford University using spoiled gradient recalled pulse sequence in 0.9-mm axial slices. The slices were resampled to 1-mm isotropic voxels and then reconstructed into 3-D brains. Each patient's electrodes were localized onto his or her own 3-D brain using the iElvis method (Groppe et al., 2017): The reconstructed brain and postimplant CT scans were coregistered (Jenkinson, Bannister, Brady, & Smith, 2002; Jenkinson & Smith, 2001) onto which electrodes were localized using BioImageSuite (Papademetris et al., 2006) and corrected for brain shift (Dykstra et al., 2012).

iEEG Data Acquisition and Initial Processing

Data were collected using a Tucker Davis Technologies multichannel recording system at a sampling rate ranging from 1525.88 to 3051.76 Hz. Pathological channels identified by physicians as well as channels with prominent nonphysiological artifacts were excluded from subsequent analyses. During the initial processing, channels were notch-filtered at 60 Hz and harmonics and re-referenced to the common average of all nonexcluded electrodes of each participant to reduce noise. Signals were bandpass-filtered to the range of HFB of 70–180 Hz with finite impulse response filters, and an estimated band-limited power was calculated by a Hilbert transformation. To partially correct for the $1/f$ decay of spectral power inherent to neural signals, the amplitude of each 10-Hz subband within HFB (nonoverlapping bins of 10-Hz bandpass windows ranging from 70 to 180 Hz) was normalized by its own mean and standard deviation, and these normalized amplitude signals were finally averaged together to result in one amplitude time series for the HFB band. For task-related analyses, the HFB power at each time point was normalized relative to the HFB power during the 200-msec intertrial interval across all trials.

Experimental Design and Statistical Analysis

Task 1

Participants were asked to make true or false judgments on either arithmetic problems (e.g., "12 + 7 = 25") or nonmath statements (e.g., "I drank coffee today"). The stimuli were presented on a laptop computer using MATLAB Psychotoolbox (Brainard, 1997). Each statement was presented until a true/false button was pressed, followed by a 200-msec intertrial interval.

Task 2

Participants were asked to make true or false judgments on arithmetic problems visually presented. The two conditions were digit condition ("2 + 5 = 7") and number word condition (e.g., "Two plus one equals six"). The math problems in Task 2 were simpler in comparison with the more complex problems presented in Task 1 in terms of operand size. Each problem was presented until a true/false button was pressed, followed by a 200-msec intertrial interval. Details regarding the designs of the two tasks can be found in Table 1 and Figure 1A.

Table 1. Task Design for Tasks 1 and 2

Task	*Task 1*		*Task 2*	
Condition	*Math*	*Nonmath*	*Digit*	*Number Word*
No. of trials	40	40	40	40
Operation	Addition	N/A	Addition	Addition
Problem size	Large (1–2 digits)	N/A	Small (1 digit)	Small (1 digit)
Example stimulus	"12 + 7 = 25"	"I drank coffee today"	"2 + 5 = 7"	"Two plus one equals six"
Response options	True/false	True/false	True/false	True/false

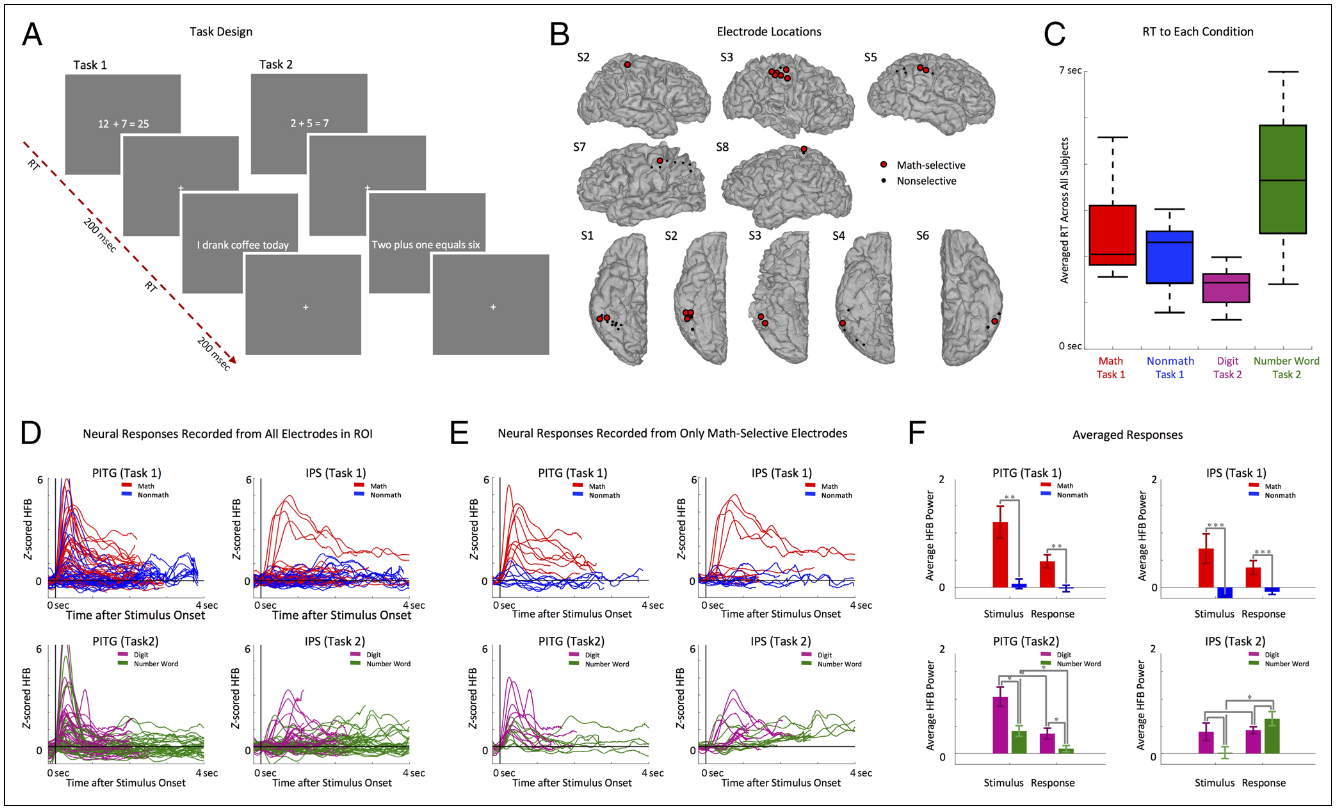

Figure 1. (A) For Task 1, participants were asked to verify mathematical statements in digits (e.g., "12 + 7 = 25") or nonmath statements in English alphabets (e.g., "I drank coffee today") by pressing either "1" for true or "2" for false on a keypad. For Task 2, participants were asked to verify mathematical statements in digits (e.g., "2 + 5 = 7") or number words (e.g., "Two plus one equals six") by pressing either "1" for true or "2" for false on a keypad. The statements were shown until a button was pressed or until 15 sec elapsed, whichever was shorter. Between each statement screens, a fixation cross was shown for 5 or 10 sec. (B) Eight participants (five right hemisphere, three left hemisphere) were tested using electrocorticography. Seventy-one electrodes (33 near IPS, 38 near PITG) were chosen for further analysis based on anatomical location across eight patients. Out of these, 11 electrodes near the IPS and 9 electrodes near the PITG showed significant selectivity for math condition during Task 1 across five subjects each. The math-selective electrodes are shown in red, and the nonselective electrodes are shown in black. The top two rows show the right hemisphere brains (S2, S3, S5) and the left hemisphere brains (S7, S8) in lateral view, and the bottom row shows four right hemisphere brains (S1, S2, S3, S4) and one left hemisphere brain (S5) in ventral view. (C) RT to the four conditions across two tasks are shown. Participants took between 1 and 7 sec to respond to each condition. (D) The four panels show the z-scored HFB time course of every math-selective electrode in the anatomical ROIs. The left two panels show neural responses from electrodes in the PITG, and the right two panels show responses from the IPS. The top two panels show responses to Task 1, whereas the bottom two panels show responses to Task 2. The time courses are plotted until 4 sec after stimulus onset or until neural response could not be averaged reliably (fewer than 20 trials), whichever is shorter. (E) The four panels show the z-scored HFB time course of only the math-selective electrodes, as chosen by the selective response to math condition during Task 1. These follow the same convention as D. (F) The neural responses to the math condition (red bar) and the nonmath condition (blue bar) during Task 1 are averaged across all math-selective electrodes in the PITG (top left) and IPS (top right). Likewise, the responses to the digit condition (magenta bar) and the number word condition (green bar) during Task 2 are averaged across all math-selective electrodes in the PITG (bottom left) and IPS (bottom right).

RT to Task 1 and Task 2

Behavioral data were analyzed using ANOVA and a follow-up post hoc Tukey's honestly significant difference test was used to examine differences in RT among the four conditions listed in Table 1.

Identification of Electrodes in ROIs

Sites within the anatomical boundaries of PITG and IPS were chosen as our ROIs. Of all the implanted electrodes in eight participants, electrodes in our ROI were chosen based on anatomical location for the first set of analyses. This selection resulted in 38 electrodes in the PITG region across seven participants and 33 electrodes in the IPS region across seven participants.

HFB Activation in PITG and IPS

To find out whether the two regions previously indicated with mathematical processing, PITG and IPS, were indeed activated more strongly during mathematical context than not, we plotted the time course of HFB activation in all electrodes within the ROIs in response to Task 1. We compared the neural responses to the math condition to the nonmath condition using a permutations test.

Table 2. Participant Details

Participant No.	*Age*	*Sex*	*Dominant Hand at Birth*	*Implanted Hemisphere*
1	24	Male	Right	Right
2	41	Male	Right	Right
3	23	Female	Right	Right
4	56	Male	Right	Right
5	46	Male	Right	Right
6	47	Female	Right	Left
7	29	Male	Right	Left
8	25	Male	Right	Left

Identification of Math-selective Electrodes in ROI

For the next set of analyses, we further restricted the analyses to only the electrodes that showed math selectivity during Task 1 to ensure that the neural activation was truly related to the mathematical content rather than other visual features. For each electrode and condition, HFB power time course during the 400–600 msec window after stimulus onset was selected. This time course was compared with the 200-msec prestimulus period as baseline activity. The rationale for choosing the 400–600 msec window was to capture the maximum difference between the conditions by concentrating on the peak of signal, which occurred after 400 msec in most electrodes, and to match the length of the prestimulus baseline period at the same time. Math-selective electrodes were defined as those significantly active during the math condition (relative to both baseline and the nonmath condition). To compare between the two conditions, we used a 10,000-repetition permutation test and corrected for multiple comparisons using false discovery rate (FDR) based on the number of electrodes on each participant's brain (Benjamini & Yekutieli, 2001). We tested whether any of the electrodes showed significantly greater HFB activation for math in comparison with both its prestimulus baseline and the nonmath condition at the $p = .05$ level. Using these criteria resulted in nine math-selective electrodes in the PITG across five participants and 11 math-selective electrodes in the IPS across five participants. Given the small number of electrodes in each patient in each region, possible subject effect was ignored. Regrettably, given that only one electrode in the left PITG and two electrodes in the left IPS were math selective, interhemispheric differences could not be adequately compared.

HFB Activation in Math-selective Electrodes within the PITG and the IPS

Similar to the previous group of all electrodes in the ROI, we plotted each time course of individual electrodes after stimulus onset and compared the neural responses to math and nonmath conditions.

Exploration of Differences in the Magnitude and Timing of Activation

Using the RT calculated for each participant, we computed the average HFB power of activation to each condition, each task, and each region in the 200-msec time window shortly after stimulus onset (400–600 msec after stimulus onset) and shortly before RT (400–600 msec before RT). The activation levels were compared between math and nonmath conditions, between formats, and between time windows.

RESULTS

Demographics

Data were collected from eight participants. Five participants received right hemisphere implantations, and three received left hemisphere implantations. Further demographic information for each participant is presented in Table 2.

Behavioral Data

We compared the RTs between the conditions in each task (Figure 1C). The details of the two tasks and their conditions can be found in Table 1. ANOVA results showed a significant difference among the RT across conditions, $F(3, 24) = 5.51$, $p = .005$. Tukey's honestly significant difference post hoc comparisons test indicated that the RT for the number word condition in Task 2 ($M = 4.695 \pm 1.643$) was significantly longer than the digit condition in Task 2 ($M = 2.354 \pm 0.480$) and the nonmath condition in Task 1 ($M = 3.030 \pm 0.821$) at the 0.05 level of significance. RT for the digit condition in Task 2 and math condition in Task 1 were not significantly different.

Electrophysiological Data

The location of electrodes on each participant's native anatomical space is shown in Figure 1B. We chose 71 electrodes in or near the PITG and the IPS across eight participants for analyses. Information regarding the number and location of electrodes for each participant is detailed in Table 3.

Electrophysiological analysis revealed that HFB responses were contextually selective and consistent across participants. The activations for Task 1 showed a trending preference for math condition in comparison with nonmath in the PITG ($p = .079$, $n = 38$ electrodes) and a significant preference for math condition in the IPS ($p < .001$, $n = 33$ electrodes) in a 10,000-repetition permutations test on the activation from 400 to 600 msec after stimulus onset (Figure 1D).

Restricting our analyses to only the electrodes revealed a high level of anatomical precision and, again, consistency across participants. Nine of the 38 PITG electrodes and 11 of the 33 IPS electrodes showed significant math selectivity (see Methods for more details on selection criteria for math selectivity). These math-selective sites were clustered tightly around the PITG and the IPS (Figure 1B). The finding of math selectivity around the PITG and the IPS follows previous math cognition literature and provides support for the anatomical specificity of the arithmetic functions within the human brain. In these math-selective clusters, the activations for Task 1 showed a significant preference for math condition in comparison with nonmath both in the PITG ($p < .001$, $n = 9$ electrodes) and in the IPS ($p = .001$, $n = 11$ electrodes) in a 10,000-repetition permutations test on the activation from 400 to 600 msec after stimulus onset (Figure 1E).

The main question posed once the anatomically specific math-selective regions were identified in the PITG and the IPS was if, when, and how the regions activate in response to digits and number words in the context of an arithmetic equation. Therefore, in Task 2, we measured HFB responses to mathematical statements using different visual formats of numbers (digits vs. number words) in the math-selective sites defined in Task 1. Math-selective regions in the PITG and the IPS showed heterogeneity in their responses to the two formats of arithmetic equations.

Although both representations induced responses in the PITG and the IPS, the timing and the magnitude of the elicited HFB power were different. In the PITG, the HFB response to digit equations was significantly larger than to number word equations ($p = .015$, $n = 9$, permutations test with 10,000 reps, 200–400 msec after stimulus onset) soon after the onset of stimulus. However, the HFB response to the number word equations was still greater than baseline ($p < .001$, $n = 9$, permutations test with 10,000 reps, 200–400 msec after stimulus onset). The results indicate that both formats evoke an early response in the PITG, although the numerical format evokes a stronger response in terms of magnitude.

Conversely, neither of the two formats evoked early activation in the IPS electrodes ($p > .10$, $n = 11$, permutations test with 10,000 reps, 200–400 msec after stimulus onset). Instead, the activation in IPS was slower. The digit format evoked a significant response as late as 500–700 msec after stimulus onset ($p < .001$, $n = 11$). The number word format was even slower, showing a steady and slow increase until the end of each trial (Figure 1E, bottom right).

To further explore the magnitude and temporal differences between the responses to the two formats in the ROIs, we calculated the average activation to each condition, each task, and each region (PITG and IPS) in the brief time window shortly after stimulus onset (hereby referred to as "early window"; 400–600 msec after stimulus onset) and shortly before RT (hereby referred to as "late window"; 400–600 msec before behavioral response; Figure 1F). Given that these analyses were restricted to electrodes that showed preferential activation to math condition in comparison with nonmath, the activation to the math condition was significantly higher than nonmath

Table 3. Electrode Details

Participant No.	*PITG Electrodes*	*IPS Electrodes*	*PITG Electrodes (Math-selective)*	*IPS Electrodes (Math-selective)*
1	10	4	2	0
2	5	1	3	1
3	2	7	2	6
4	5	5	1	0
5	0	6	0	2
6	3	0	1	0
7	5	8	0	1
8	8	2	0	1
Total	38	33	9	11

in PITG in both the early window ($p < .001$, $n = 9$, FDR-corrected) and late window ($p < .001$, $n = 9$, FDR-corrected) as expected (Figure 1F, top left). Likewise, the activation to the math condition was significantly higher than nonmath in IPS in both the early window ($p < .001$, $n = 11$, FDR corrected) and late window ($p < .001$, $n = 11$, FDR-corrected) as expected as well (Figure 1F, top right).

Corroborating the previous results, the evoked responses in the PITG were different for two formats of mathematical equations in Task 2 in terms of magnitude. In both the early window ($p = .012$, $n = 9$) and the late window ($p = .025$, $n = 9$), activation for digits were higher than for number words. Further corroborating the previous results, the evoked responses for the two formats in the PITG were also early in terms of temporal onset. Both digits ($p = .012$, $n = 9$) and number words ($p = .022$, $n = 9$) showed higher activation in the early window in comparison with the late window. These results indicate that, although the electrodes in the PITG show a preferential activity to digits in comparison with number words, both formats activate this PITG region significantly and early.

In the IPS, the evoked responses to the two formats were not different early on. However, the activation in response to number words increase steadily and slowly over the entire trial length ($M = 4.695 \pm 1.643$ sec). The late window of 200 msec shortly before RT is shown to be significantly higher than both the activation during the early period to the same condition ($p = .006$, $n = 11$) and to its baseline ($p < .001$, $n = 11$). These results indicate that the math-selective electrodes in the IPS do not show a preferential activity to digits or number words in terms of magnitude, but activation to number words are much slower than to digits and that the activations to both are slower in the IPS than are in the PITG.

Our findings converge to the conclusion that the neural responses to the mathematical statements made in digit and number word formats show heterogeneity in terms of magnitude and temporal onset in both regions previously found to be involved with mathematical processing. Although both formats evoke responses in both areas, there are clear differences both between and within the regions.

DISCUSSION

This study sought to investigate the involvement of PITG and IPS in arithmetic processing involving quantities presented in different formats (numerals vs. number words). Comparing the neural activity between these conditions provides insight into whether quantity representations in different brain regions are format-specific or format-independent.

Behaviorally, we report longer RT for number words than digits, in line with previous research (Faulkenberry, 2017; Campbell & Fugelsang, 2001; Campbell, 1994). On the neuronal population level, we report significant responses for both arithmetic equations presented with digits and those presented with number words in not only the IPS but also the PITG. Arithmetic equations presented with digits invoke earlier HFB responses than those presented with number words: The magnitude of activation, measured by the amplitude of z-scored HFB power, is stronger for digits than for number words in the initial phase of processing in the PITG, although both activations are still significantly higher than baseline activity. In contrast, HFB activation levels in the IPS are statistically similar for the two formats and nonsignificant in this phase. It is not until later, shortly before RT, that the activation for the formats in the IPS reach significant difference. The results indicate that both PITG and IPS show neural responses during calculation but that PITG responds quickly to both digits and number words whereas IPS responds comparatively slowly and with differential temporal profile for the two formats.

Our data suggest that the relatively large region of the PITG may be implicated in cognitive processes beyond simple digit recognition (Daitch et al., 2016). However, we remind the reader that the PITG occupies a relatively large extent of the VTC, and as our previous findings have suggested, there is clearly a heterogeneity of functions within this region of the brain. Although a small region of the PITG (i.e., the NFA) is selectively implicated in the processing of numerals (Shum et al., 2013), a larger surrounding area of the NFA is activated during both digit and number word processing (Hermes et al., 2017; Daitch et al., 2016; Shum et al., 2013). This is in line with the findings that the area lateral to the NFA, that is, the visual word form area (Cohen et al., 2000; Nobre, Allison, & McCarthy, 1994), is involved in processing word form symbols.

Our findings are compatible with, and might add novel information relevant to, models of mathematical cognition (Colomé, Bafalluy, & Noël, 2011). For instance, the encoding complex model (Campbell & Epp, 2004; Campbell, 1994; Campbell & Clark, 1992) proposes that different formats will call for different calculation strategies. Our findings are partially in line with this model, as we found differential power of activation to the two formats in both regions. The abstract code model (McCloskey & Macaruso, 1995; McCloskey, 1992) posits that numerical inputs of different formats are converted into an abstract code before being manipulated. This model hypothesizes the conversion of digit and number word formats into one representation before the calculation stage. Our finding of different timing of IPS responses to digits versus number words might be explained by different times that are needed in the encoding stage. The conversion from number words to analogue or abstract code could take longer time than a conversion from digit number would, thus explaining the delayed activation for number words in the IPS. This is still a hypothetical conclusion, which will need further exploration with more targeted experiments in the future.

Triple code model (Dehaene & Cohen, 1995; Dehaene, 1992) postulates that arithmetic facts do not necessarily need to be converted into analog magnitudes, and simple calculations may involve a direct verbal route from memory retrieval. Previous neuroimaging studies have implicated the left angular gyrus in the direct route of verbal memory retrieval (Dehaene et al., 2003). Contrary to the expectations from this model, we found that both difficult (math condition in Task 1) and simple (Task 2) math problems evoke the activation of the IPS region. However, given the limitations of our study, further research may be necessary to ascertain the existence or lack of such a direct route for simple calculations.

One of the limitations of our study is that Task 1, which we used to localize math-selective electrodes, uses digits in the math condition. This could have possibly resulted in a slight bias to the digits in the subsequent analyses, such that the responses to digits are stronger than the number words in many electrodes regardless of location. However, our main finding remains unchanged: Despite the fact that the response to digits may be overrepresented across many electrodes due to the selection criteria used, we still found significant differences between the different ROIs (i.e., PITG and IPS) in terms of the neural activation in response to the two formats and that there exists significant temporal differences between the regions and formats.

Another limitation is that the exact process reflected in the delay in of activation is unclear. On one hand, the faster activation for digit than number words in the IPS might reflect faster conversion stage to magnitude from digits than from number words. On the other hand, the delay may instead reflect that number word conditions require much more attention. In other words, the delay may reflect any of the many coding mechanisms and not necessarily the delay in the encoding stage. However, our study still provides valuable insight into the existence of temporal differences in the neural activation in response to different formats of numbers. The mechanism that causes such temporal differences should be explored further in future studies.

Despite the limitations of our study, our findings are still bolstered by the convergent conclusions from previous literature surrounding the mathematical processing in the human brain. The activation of the IPS across stimulus type has been supported in an array of fMRI literature including across audio and visual cues of magnitude (Damarla, Cherkassky, & Just, 2016), across numerical distance and visual numbers (Notebaert, Pesenti, & Reynvoet, 2010), and across species (Eger et al., 2009). Our findings replicate the previously established activation of the IPS regardless of visual input notation while providing an additional nuance of temporal specificity. We also provide additional support to and dissociation between the number-processing hubs in the parietal magnitude area (Nieder, 2016) and the inferior temporal number area (Srihasam, Mandeville, Morocz, Sullivan, & Livingstone, 2012) in terms of magnitude and time.

In conclusion, PITG and IPS are both engaged in processing number forms regardless of input format, but with a different power and temporal signature. These findings provide new information that might be useful to the current models of mathematical cognition and highlights the hitherto unexplored dimension of temporal dynamics across regions of the human brain during arithmetic processing. The exploration of the similarities and difference between the responses of the PITG and the IPS regions provide a more detailed look into the overall arithmetic processing within the human brain.

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