Mapping human temporal and parietal neuronal population activity and functional coupling during mathematical cognition

Amy L. Daitch[1*], Brett L. Foster[1,2], Jessica Schrouff[1,3], Vinitha Rangarajan[1,4], Itır Kaşikçi[1,5],
Sandra Gattas[1,6], and Josef Parvizi[1*]

[1]Laboratory of Behavioral & Cognitive Neuroscience (LBCN), Stanford Human Intracranial Cognitive Electrophysiology Program (SHICEP), Department of Neurology & Neurological Sciences, Stanford University, Stanford, California, 94305, USA

[2]Department of Neurosurgery, Baylor College of Medicine, Houston, Texas, 77030, USA

[3]Department of Computer Science, University College London, London, United Kingdom

[4]Department of Psychology, University of California, Berkeley, 94720, USA

[5]Graduate School of Neuroscience, Istanbul University, Istanbul, Turkey

[6]Medical Scientist Training Program, University of California, Irvine, 92697, USA

***Corresponding author:**
Josef Parvizi
300 Pasteur Drive
Alway Building, Room M030
Stanford, CA 94305
parvizi@stanford.edu

Classification: Biological Sciences, Neuroscience

Short Title: Numbers in the brain

Keywords: Numerical processing; ECoG; brain network; parietal cortex; ventral temporal cortex

Abstract:

Brain areas within the lateral parietal cortex (LPC) and ventral temporal cortex (VTC) have been shown to code for abstract quantity representations, and symbolic numerical representations, respectively. To explore the fast dynamics of activity within each region, and interaction between them, we used electrocorticography (ECoG) recordings from 16 neurosurgical subjects implanted with grids of electrodes over these two regions, and tracked the activity within and between them as subjects performed three different numerical tasks. While re-confirming the presence of math-selective hubs within the VTC and LPC, we report here a remarkable heterogeneity of neural responses within each region, at both millimeter and millisecond scales. Moreover, we show that the heterogeneity of response profiles within each hub mirrors the distinct patterns of functional coupling between them. Our results support the existence of multiple bidirectional functional loops operating between discrete populations of neurons within the VTC and LPC during the visual processing of numerals and arithmetic functions. These findings not only reveal novel information about the dynamics of numerical processing in the brain, but also provide insight into the fine-grained functional architecture and connectivity within the human brain.

Significance Statement:

Humans have the unique ability to perform exact mental arithmetic, which derives from the association of symbols (e.g. '3') with discrete quantities. Using direct intracranial recordings, we measured electrophysiological activity from neuronal populations in the lateral parietal (LPC) and ventral temporal cortex (VTC) that are known to be important for numerical processing, as subjects performed various experiments. We observed functional heterogeneity within each region at the millimeter and millisecond scales, and report the first empirical evidence of functional coupling between the LPC and VTC during mathematical cognition. Our results suggest the presence of an anatomically selective numerical cognition system, which engages discrete neuronal populations of the ventral temporal and lateral parietal regions in different time windows of numerical processing.

\body

Introduction:

While the ability to approximate or compare rough quantities is present even in human infants (1) and other species such as non-human primates (2-4) and birds (5), the association of exact quantities with symbols (e.g. the numeral ‘10’) or verbal representations (e.g. the number word ‘ten’) is unique to humans exposed to such culturally learned entities (6-8). Moreover, dissociable number- and quantity-related behavioral deficits (i.e. relating to symbolic or verbal numerical versus abstract quantity representations) are associated with different lesion locations within the brain (9-14). These observations in part motivated the ‘Triple Code Model’, positing that the human brain contains three different numerical representations; symbolic, verbal, and abstract quantity, each coded in a different brain region (15, 16). The model also predicts that depending on task demands (e.g. simple visual recognition of a numeral, versus determining the larger of two numerals, versus verbal naming of a numeral), all or a subset of these brain regions will interact with each other (15, 16).

Neuroimaging, electrophysiology, and lesion studies in both humans and non-human primates have long implicated the parietal lobe, particularly the anterior segment of the intraparietal sulcus, in abstract quantity representations (i.e. irrespective of the modality of presentation, e.g. ‘4’ vs. ‘four’ vs. ‘**::**’), with specific neurons or neuronal populations exhibiting tuning around a preferred numerosity (4, 17-25). Moreover, brain activity within this region, and its functional and anatomical connectivity with other brain regions, are correlated with mathematical performance in individual subjects (26-29), and perturbation of its activity appears to have a causal effect on mathematical performance (30-32).

While the Triple Code Model predicted the existence of a specific region within the ventral visual stream selective for symbolic numerical representations (i.e. numerals), earlier human electrophysiological recordings using event-related potentials reported relatively widespread activations in the VTC during number processing (33), and earlier functional imaging studies were unable to localize a region selective for numerals relative both to other culturally learned symbols (e.g. letters) and novel morphologically similar stimuli (i.e. false fonts; (17, 34-36). Recently, our group used intracranial electrocorticography (ECoG) to confirm the existence of a site within the posterior inferior temporal gyrus (pITG) that selectively responds to visual numerals relative to letters, false fonts, number words, and words (37). This pITG site is located in an area subject to strong susceptibility artifact with fMRI (38, 39); however, numeral-selectivity within the pITG has since been demonstrated with fMRI using advanced techniques to increase the signal-to-noise ratio in this region (38, 39). Still, given the relatively low temporal resolution of the current imaging methods, it is difficult to study the fast temporal dynamics of activity within and surrounding the pITG and its interaction with other regions involved in numerical cognition such as the IPS.

In the current study, we took advantage of simultaneous ECoG recordings from discrete neuronal populations within the human VTC and LPC to study the fast temporal dynamics of their activations and functional coupling during numerical conditions. We expand upon previous work and demonstrate that the brain regions within the VTC and LPC thought to represent, respectively, the symbolic and abstract quantity numerical codes, are in fact each composed of heterogeneous neuronal populations with distinct temporal profiles of activity. The distinct profiles of activity in subpopulations of the VTC or LPC are mirrored by their distinct patterns of functional coupling. Our results suggest the existence of multiple feedback loops between different subpopulations of the VTC and LPC, which operate during different stages of numerical processing. These findings not only provide insight into the mechanics of numerical processing in the brain, but also have implications for studying the fine-grained architecture of the brain’s functional connections in general.

Results

Sixteen patients with epilepsy were implanted with intracranial electrodes as part of their pre-surgical evaluation at Stanford University Medical Center and volunteered to participate in our research study. Demographic information for these subjects, as well as behavioral performance, are included in Table S1, and each subject's electrode coverage is displayed in Figure S1. We obtained ECoG data during three different experimental tasks (Figure 1). Task 1 presented subjects with single numerals, letters, or foreign symbols (i.e., false fonts), allowing us to identify numeral-selective neuronal populations. Task 2 required subjects to actively manipulate numerals by assessing the validity of arithmetic statements (versus the control condition of assessing the validity of memory statements). Lastly, in Task 3, subjects were required to assess the validity of arithmetic statements (as in Task 2), but with each arithmetic equation presented one symbol at a time (e.g. '5', '+', '7', '=', '12'), allowing us to better track the temporal profile of activity of each region during different stages of arithmetic processing. On average, subjects performed with over 85% accuracy on each task (variation between subjects' accuracy and reaction time in all tasks is presented in Table S1).

Our analyses were first aimed at characterizing the response properties of subregions within the VTC and LPC, to confirm the presence of numeral and/or math-selective neuronal populations that we, and other groups, have reported previously (20, 22, 23, 37, 39, 40). Next, we measured the relative timing of activation of each of these regions during arithmetic computations. Finally we assessed the functional coupling between the ventral temporal and lateral parietal cortices during arithmetic computations.

Selectivity of response to numerals within the ventral temporal cortex

We measured the activity and selectivity of each electrode across a wide range of frequencies (1-256 Hz), but found that high-frequency broadband ('HFB'; 70-180 Hz) activity best differentiated between numeric and non-numeric conditions (Figure S2). Further, in line with recent work from our group (41), we found that support vector machine ('SVM') classifiers on data from Task 2 yielded the highest accuracy when using HFB activity (compared to activity in five other frequency bands) in differentiating between math and memory trials, both on average, and in each individual subject (Figure S2E; the HFB classifiers were also the only ones with classification accuracy significantly above chance in every subject; permutation $p < 0.05$, FDR corrected). These findings corroborate previous work showing a high correspondence between HFB activity and local neuronal firing rate, as well as with fMRI BOLD activity (42-47). Since selectivity for the different stimulus classes/trial types was most prominent in the HFB band, subsequent analyses were focused on HFB activity.

While many sites within the VTC responded significantly to the presentation of numerals (relative to the inter-trial interval, or 'ITI'), a small subregion within the posterior inferior temporal gyrus (pITG) responded selectively to numerals compared to morphologically similar stimuli such as letters and false fonts (3 of 58, or 5.2% of all pITG sites, $p < 0.05$ - FDR corrected, in 3 different subjects out of 13 with pITG coverage; or 7 of 58, or 12% of electrodes, $p < 0.05$ - FDR uncorrected from 4 different subjects, all with right hemisphere coverage, Figure 2C,D, Figure S3; Table S2). We refer to this numeral-selective pITG site as the *Number Form Area (NFA*). These findings confirmed, in a new sub-cohort of subjects, our previous report of a numeral-selective brain region (37).

Also in line with a recent report from our lab (40), we found sites bilaterally within a broader region of the pITG that were selectively engaged during arithmetic processing, relative to reading sentences/memory retrieval (Task 2), though by and large their response to single numerals were insignificant, and/or not significantly different from their responses to single letters or false fonts (31 of 58 sites or 53%; $p < 0.05$, FDR corrected; Figure 2C, Figure S3; Table S2). We will refer to this pITG region as $\text{pITG}_{\text{math}}$. This region includes the NFA itself, which was also selectively engaged during math in Task 2. While we only recorded from NFA proper in three subjects (after FDR correction; four before FDR correction), we observed at least one math selective pITG site in all 13 subjects implanted with pITG electrodes (Table S2).

As in Task 1, many sites throughout the VTC were significantly active during arithmetic processing, and many sites outside of the pITG, particularly in posterior VTC, responded more strongly during arithmetic processing than those within the pITG (Figure 2B). However, the region that was most *selectively* engaged during arithmetic processing (and not engaged during reading/memory retrieval) was anatomically similar, though larger in size, than the NFA (Figure 2, Figure S3; Table S2).

It is important to note that even within the $\text{pITG}_{\text{math}}$ area, there exists much heterogeneity in the profile of responses to different types of numerical stimuli, even within a few millimeters of cortex. We show an example of such heterogeneity in a single subject in Figure S4 across tasks 1-3. One site is within the NFA; responding selectively to numerals relative to other symbols in Tasks 1 and 3, and with a sustained math selective response in Task 2. Further, in Task 3, this site responds more to the second than the first numeral, likely reflecting an increased engagement of this site during computations. The two neighboring sites are each only 5mm away from the NFA site, yet they exhibit different response properties, responding less selectivity to numerals in Tasks 1 and 3, and with more transient math-selective responses in Task 2. Thus, while we are grouping $\text{pITG}_{\text{math}}$ sites together, we acknowledge that this region is in fact composed of several neuronal populations with slightly different functional profiles of activity, and likely with different patterns of interaction with other brain regions (e.g. the IPS). Given the relative sparsity of electrode sampling with respect to the size of these neuronal populations, it is not surprising that we only recorded from NFA proper in a few subjects (Figure S3, Table S2). In subsequent analyses, we focused on math selective sites within the pITG ($\text{pITG}_{\text{math}}$) based on Task 2, which included the NFA sites.

Also of note, the number/math-selective region described above is anatomically distinct from other category-selective regions within the VTC, such as the fusiform face area (‘FFA’;

(46)), and the word form area (‘WFA’; sites that responded selectively to letters in Task 1 and/or to written memory statements in Task 2; Figure S3). The fact that the NFA and WFA are anatomically distinct is particularly noteworthy, since numbers and letters are morphologically similar symbols, composed of line and curve segments. Thus, the NFA/$\text{pITG}_{\text{math}}$ is unlikely coding for purely visual aspects of numerical stimuli.

Numerical processing within the parietal cortex

We partitioned the parietal cortex into six anatomical divisions based on each individual’s native anatomy (Figure 3A) and measured the average HFB response of each region to presentation of visual numerals (Task 1) and active mathematical computations (Task 2).

While several sites, mostly within the superior parietal lobule (SPL) were significantly active during the presentation of numerals (relative to the ITI), no LPC sites responded selectively to single visual numeral symbols relative to letters or false fonts (Figure S3; Table S2). By comparison, in Task 2, when subjects were actively manipulating numerals in arithmetic computations, we found that the aIPS and SPL were more engaged during arithmetic processing than reading sentences/memory retrieval ($p < 0.05$ FDR corrected; Figure 3B; Figure S3; Table S2). We will refer to these math selective regions as $\text{aIPS}_{\text{math}}$ and SPL_{math}, which we observed in both the right and left hemispheres, across many subjects (9 of 13 subjects with SPL coverage and 8 of 13 subjects with aIPS coverage; Table S2). Conversely, in line with other recent findings (47), sites in the angular gyrus were more active during memory retrieval than arithmetic processing ($p < 0.05$, FDR corrected; Figure 3B; Figure S3). Importantly, most of the math selective sites in the aIPS, and many in the SPL, were not significantly active during memory trials (Figure 3C,D; Figure S3; Table S2). By comparison, we did observe many sites in more posterior portions of the IPS, and in the SPL, exhibiting a transient response at the beginning of both math and memory trials (e.g. in Figure S6).

Temporal dynamics of VTC and LPC activity during numerical processing

The previous two analyses mapped out the VTC and LPC subregions that are selective for either the visual presentation or arithmetic manipulation of visual numerals. Next, we addressed the temporal profile of activations within these two regions by computing the response onset latency (ROL) of HFB activity in each of these conditions (Task 1 and Task 2), and comparing the response of each region in different stages of arithmetic processing in Task 3. For the ROL analysis, we only considered the sites that were significantly active during the presentation of numerals (Task 1) and/or arithmetic processing (Task 2), as we could only reliably measure ROL for sites exhibiting a clear increase in activity. The majority of these sites were located in the LOG/pFG, pITG, and mFG (for both numerals and math) and in the aIPS and SPL (for math). To assess differences in ROL between brain regions, we only considered pairs of electrodes within individual subjects, so that differences in overall processing speed between subjects wouldn't alter our general findings.

In Task 1, the pITG sites responded to the visual presentation of numerals later than did those in the LOG/pFG (35ms ± standard deviation of 26ms) and the mFG (46ms ± 42ms) ($p < 0.05$, FDR corrected; Figure 4A-C). Similarly, in Task 2, math-active sites in the pITG responded significantly later than those in the LOG/pFG (51ms ± 20ms) and mFG (60ms ± 42ms), ($p < 0.05$, FDR corrected; Figure 4D-F). Furthermore, within the pITG, neuronal populations that were active during the math, but not the memory, condition responded significantly later during the math condition than those that were active during both math and memory trials (47ms ± 21ms, $p < 0.001$). Likewise, within the SPL and aIPS, math selective sites that were not significantly active during memory trials responded later than those that were significantly active during both math and memory trials (by an average of 170ms ± 100ms, $p < 0.02$). This provides further evidence that these math-selective sites within the VTC and LPC are involved in higher level, rather than purely visual, processing of numerals.

We next measured activity during Task 3 (performed by 9 of 16 subjects; Table S1) to more explicitly compare the engagement of different brain regions during different stages of numerical processing. In line with our observations from Task 2, we found that pITG and aIPS math active sites exhibited a larger response to the second than to the first numeral (Figure 5). Some of these $\text{pITG}_{\text{math}}$ and $\text{aIPS}_{\text{math}}$ sites showed almost no HFB response until after the presentation of the second numeral (Figure 5B), suggesting that these regions are likely involved in the manipulation of numerals during a computation, rather than merely the visual processing of numerals. Sites in LOG/pFG, mFG, and SPL, on the other hand, responded less to the second than the first numeral (Figure 5C), possibly reflecting visual adaptation to the numeral stimuli.

After comparing onset latencies of math-active sites separately within the VTC and within the LPC, we next measured the time difference between the onsets of activation occurring in the math-selective regions within the VTC and LPC. While twelve subjects had simultaneous coverage in the VTC and LPC, only three (S2, S4, S11) had at least one site each in the aIPS and pITG, with strong enough math-related responses in Task 2 to reliably measure onset times. Across these three subjects, the onset times of $\text{pITG}_{\text{math}}$ sites were on average earlier than those of $\text{aIPS}_{\text{math}}$ sites (54ms ± 85ms, $p < 0.05$, FDR corrected; Figure 4E). However, we did observe near simultaneous onsets of activity in the most math-selective aIPS site and the two most math-selective pITG sites in a single subject (S4; exemplar time courses shown in Figure 4D; permutation test, $p > 0.05$). Of the same three subjects, one (S11) also performed Task 3, giving us more detailed information about the engagement of VTC and LPC activation in different stages of numerical processing. Again, we found that the most math selective pITG and aIPS sites responded nearly simultaneously to the presentation of the second numeral (permutation test, $p > 0.05$; neither site responded much to the first numeral, as shown in Figure 5B).

In addition to the near simultaneous engagement of subpopulations within the pITG and aIPS during numerical processing, we observed that the math-selective sites in these regions also exhibited a more sustained response during numerical processing than did other active, but less selective sites. Specifically, we measured the trial-by-trial correlation between the duration of HFB responses and behavioral reaction time (RT) at each electrode site, separately during math and memory trials in Task 2. A high correlation between HFB duration and RT during math trials suggests that a site exhibits sustained activity throughout an arithmetic computation. While some sites exhibited a transient response at the beginning of both math and memory trials (i.e. whose duration was uncorrelated with reaction time; e.g. mFG site in Figure S5A, top row), many sites within the pITG and aIPS exhibited a sustained HFB response during math but not memory trials, whose duration was correlated with reaction time (e.g. Figure S5A, bottom two rows). On average, in the pITG, aIPS, and SPL, the correlation between HFB duration and RT was significantly higher during math than memory trials ($p < 0.05$, FDR corrected; pITG: average $r = 0.38$ for math vs. $r = 0.15$ for memory; aIPS: $r = 0.37$ vs. $r = 0.22$; SPL: $r = 0.38$ vs. $r = 0.26$), but not in other VTC or LPC regions (Figure S5B).

Task dependent correlation of activity between LPC and VTC

The similar temporal profiles of activity between the pITG and aIPS in the same individual suggest a possible coupling of computations taking place between these sites. However, to more directly assess the presence of possible functional coupling between discrete VTC and LPC populations, we measured the correlation of trial-to-trial HFB power fluctuations between different regions of the LPC and VTC during both math and memory trials in Task 2. For this analysis, we only included the five subjects with at least one $\text{pITG}_{\text{math}}$ and one $\text{aIPS}_{\text{math}}$ site (Table S2). While we expected the activity between a pair of sites in the $\text{pITG}_{\text{math}}$ and $\text{aIPS}_{\text{math}}$ to be correlated across all task conditions (as both are active during math trials and less active during memory trials), we were more interested in the correlation of activity within a particular trial type (i.e. beyond the average task response). These trial-by-trial fluctuations in activity beyond the average stimulus-induced response (often termed 'noise correlations') are thought to reflect variations in endogenous activity from trial-to-trial; thus a significant correlation in 'noise' between sites is suggestive of a functional interaction between them. Such noise correlations have been shown to recapitulate patterns of activation during a task and have been linked to putative functional networks (47-52). Our group recently showed, using intracranial recordings, that regions of the putative 'Default Mode' network exhibit correlated HFB activity individually within different task conditions, but most strongly during memory retrieval, when this network is known to be engaged (47). Here, we similarly found the HFB activity between the $\text{pITG}_{\text{math}}$ and $\text{aIPS}_{\text{math}}$ to be highly correlated during math trials, and less so during memory trials (Figure 6A-C, Figure S6A-D). Importantly, during the math condition, pITG and aIPS exhibited more correlated activity with each other than with other anatomically closer regions (i.e. the pITG with other VTC regions and the aIPS with other parietal regions; Figure S6B,D). Also of note, the aIPS still exhibited more correlated activity with the pITG than with the LOG/pFG during memory trials (Figure 6C), suggesting an intrinsic coupling between these two regions.

Importantly, many VTC sites outside the $\text{pITG}_{\text{math}}$ region exhibited larger HFB responses during math trials (though non-selectively compared to the $\text{pITG}_{\text{math}}$ sites, Figure 2B, Figure 6B, Figure S6F), yet these regions were not as highly correlated with $\text{aIPS}_{\text{math}}$ during math trials. In other words, the strength of HFB response alone was not predictive of a VTC site's correlation with the aIPS during math processing (r = 0.2451, p = 0.1763). Instead, the degree of selectivity of the math-active sites (relative to memory processing) within the VTC was positively correlated with the degree of their functional coupling with the aIPS during mathematical processing (r = 0.6015, p = 0.0003; Figure 6E). The same was also the case for LPC sites; the most math selective sites within the LPC exhibited the most correlated activity with $\text{pITG}_{\text{math}}$ during math processing (r = 0.3357, p = 0.0342), while the HFB magnitude alone of each LPC site was not significantly related to its correlation with the $\text{pITG}_{\text{math}}$ (r = 0.2831, p = 0.0767; Figure S6F,G).

These results reinforce that the observed functional coupling between $\text{pITG}_{\text{math}}$ and $\text{aIPS}_{\text{math}}$ likely reflects an interaction between them, rather than mere simultaneous co-activation during numerical processing.

Intrinsic correlation of activity between LPC and VTC during rest

Next, we explored the possibility that the pITG and aIPS are part of the same intrinsic functional network, exhibiting spontaneously correlated activity even outside the context of explicit numerical tasks. Inspired by previous work looking at the functional coupling of LFP/ECoG activity between brain regions within putative functional networks (47, 48, 53-57), we measured the correlation of slow fluctuations (<1Hz) of HFB activity at VTC and LPC during rest, and found higher correlations between the math active sites within the pITG and aIPS compared with other VTC or LPC sites (Figure 6B,D; Figure S6A-D). Of note, while the aIPS was more correlated with the pITG than with other nearby sites in the SPL during active math, at rest, the aIPS was also highly correlated with the SPL (Figure S6A,B). This suggests that while the aIPS exhibits broad local functional connectivity at rest, these local functional connections become sharpened once a subject engages in mathematical processing.

Cross frequency coupling between IPS and VTC during numerical processing

Lastly, we aimed to understand the direction of coupling between the pITG and aIPS. Inspired by the evidence for the functional importance of low frequency oscillations in the spatiotemporal organization of neural activity (58-60), and the coupling of the phase of low frequency oscillations with the amplitude of higher frequency activity (i.e. phase amplitude coupling, or 'PAC'; (60-65), we measured the magnitude of bi-directional PAC between aIPS and different VTC sites during both math and memory.

Across the five subjects with coverage of both $\text{pITG}_{\text{math}}$ and $\text{aIPS}_{\text{math}}$, the $\text{aIPS}_{\text{math}}$ low frequency phase (in the 'resonant' frequency band of each $\text{aIPS}_{\text{math}}$ site; see experimental procedures for more details) on average modulated the HFB power at pITG sites more than that at other VTC regions (Figure 7A,C; Figure S7). This pattern, however, was not evident in the two subjects who had the weakest math responses in the aIPS (S8, S16; Figure S7), perhaps because our electrodes in these subjects were located at the edge of the aIPS math-selective hub, weakening any potential observable coupling. The degree of PAC was, on average, higher from $\mathrm{aIPS}_{\mathrm{math}}$ to pITG than vice-versa, suggesting stronger top-down ($\mathrm{aIPS}_{\mathrm{math}}$ to pITG), than bottom-up coupling (paired permutation test, $p < 0.05$). While inter-electrode coupling was strongest between the aIPS and pITG relative to other VTC regions, there was no correlation between *intra*-electrode coupling at each VTC site and its *inter*-electrode coupling with the aIPS ($r = 0.0061$, $p = 0.9651$) (Figure 7C). Thus, it is unlikely that the observed aIPS-pITG coupling is simply an artifact of simultaneous coupling within aIPS and within pITG at the same frequencies.

Of note, the most dominant coupling frequency in the $\mathrm{aIPS}_{\mathrm{math}}$ sites (i.e. whose phase was most coupled to the HFB power at the same aIPS site, and also to the HFB power at the pITG sites) differed across subjects (Figure S7). In two of three subjects (S4, S11), the coupling was most prominent within the 1-4 Hz range while in the third subject (S2), coupling was most prominent in the 7-28 Hz range. While previous studies have shown that the dominant oscillatory frequency/coupling frequency varies across cortical areas (62, 65-68), it is somewhat surprising that we see this variance even within a small patch of cortex. We are mindful that the electrode sites labeled as $\mathrm{aIPS}_{\mathrm{math}}$ or $\mathrm{pITG}_{\mathrm{math}}$ may not have been recording from the same populations of neurons across individuals, and thus the PAC findings in our small cohort of subjects should be taken as preliminary. Future work using denser and wider simultaneous sampling of the aIPS and pITG will be necessary to see if there are common coupling frequencies within specific aIPS populations across subjects

Also of note, while on average the coupling was stronger from the aIPS to pITG than vice versa, some pITG sites in two subjects (S2, S4) did show stronger bottom-up coupling to the aIPS site (Figure 7; Figure S7). In these subjects, the strongest coupling was from the pITG site that responded most to the passive presentation of visual numerals, while the site showing the strongest top-down PAC from IPS was slightly more anterior and was only engaged during active mathematical computation, and not much to the passive presentation of visual numerals (one subject shown in Figure 7A,B). Again, this finding is quite preliminary, but it is suggestive of a feedback loop between different sub-populations of the pITG and aIPS, where the pITG neuronal populations engaged in deciphering visual symbols have bottom up coupling with the aIPS, while the aIPS has top down coupling with more anterior neuronal populations of the pITG that are engaged in the active processing of numeral symbols.

Discussion

Recordings from the VTC and LPC in human subjects not only re-confirmed the existence of numeral/math-selective hubs within the VTC and LPC, but also revealed functional heterogeneity within each of these regions at the millimeter scale. We report discrete neuronal populations localized within the pITG and aIPS with selective activations during conditions of numerical processing, surrounded by other active, but less-selective, neuronal populations. The most math-selective sites within the pITG and aIPS respond later than other active, but less selective sites within the VTC and LPC, suggesting their involvement in higher level, rather than purely visual, processing of numerical stimuli. Moreover, a subset of these math-selective pITG and aIPS neuronal populations respond nearly simultaneously during mathematical processing, despite a large anatomical distance between them. The math-selective neuronal populations within the pITG and aIPS exhibited selective functional coupling with each other during mathematical processing (and to a lesser degree during rest and non-math conditions), relative to other active, but less selective sites. Lastly, a trend in our data suggested a bi-directional relationship between the pITG and aIPS, with separate populations of neurons engaged in different directions of communication.

Numerical processing in discrete neuronal populations within the human inferior temporal cortex

In line with our recent observation (37), we report the presence of a population of neurons in the posterior portion of the ITG that has selective responses to the visual presentation of individual numerals (i.e., the NFA). This population is surrounded by a larger population of pITG neurons that is selectively engaged during the active manipulation of numerals. The latter population of neurons is part of a yet larger region of VTC that, compared to baseline, has non-selective responses to different classes of visual objects, as earlier pioneering ECoG work had already suggested (33). The fact that numeral-selective and math-selective populations of neurons are surrounded by populations with non-selective responses to these stimuli causes a significant methodological challenge for ECoG studies (like our own) using sparse recordings, or neuroimaging studies that rely on group analysis and transfer of data from native to standardized anatomical space. These selective and non-selective populations may be spatially close, but functionally unique, requiring fine scale sampling in native anatomy.

Numerical processing in discrete neuronal populations within the human lateral parietal lobe

Our findings in the lateral parietal cortex corroborate our previous work, showing a subregion in the aIPS region that is selectively activated when subjects solve mathematical equations in an experimental setting, or when they deal with numerical entities in a naturalistic setting (20). One could argue that the activity we observe in the aIPS when subjects judge arithmetic equations (Task 2) is not truly math-specific, but instead reflects more general externally-directed attention or cognitive control functions, and thus could be part of the dorsal attention network (69) or frontoparietal control network (70). However, the $\text{aIPS}_{\text{math}}$ sites did not exhibit any activity (even transiently) when subjects were attending to written statements (during memory trials) or switching between task instructions (at the beginning of each trial). Unlike the $\text{aIPS}_{\text{math}}$ region, SPL and more posterior IPS activations had profiles matching what we would expect of regions in the dorsal attention or frontoparietal control network (i.e., transient responses at the beginning of both math and memory trials, e.g. in Figure S6). The aIPS sites that were coupled with pITG were not only significantly active during the math condition, but just as importantly, showed almost no activity during the memory condition (Figure 3D, Figure S5A, Figure S6). Lastly, while many LPC sites outside the aIPS (e.g. in the SPL and pIPS) responded to individual numerals (and also to letters and false fonts, Figure 3B; Figure S3) in Task 1, the $\text{aIPS}_{\text{math}}$ sites did not, even though subjects were actively attending to the numerals. Therefore, the activity of the $\text{aIPS}_{\text{math}}$ sites is unlikely to be related to general attention, or even selective attention to numerals. Instead, the $\text{aIPS}_{\text{math}}$ sites were only active when subjects were required to actively interpret and manipulate numerals in the context of judging arithmetic statements. The $\text{aIPS}_{\text{math}}$ region we identify here is anatomically similar to the parietal regions in which previous studies have observed numerosity tuning in humans (24, 71, 72), and in macaques (4, 73, 74). However, while we are confident about the selective functional engagement of $\text{aIPS}_{\text{math}}$ sites during numerical processing, we are cognizant that future work is needed to further disentangle the functional roles of the $\text{aIPS}_{\text{math}}$ sites and nearby sites within different domains of numerical cognition.

Task-based and intrinsic coupling of activity across neuronal populations in VTC and LPC

The pITG and aIPS were both highly engaged during arithmetic processing, and much less so during sentence reading/memory retrieval; thus their HFB activity was unsurprisingly correlated across all trials in Task 2. However, variations in the neural responses within a single task condition (beyond the average response, i.e. ‘noise’) are thought to reflect fluctuations in endogenous activity or different “brain states” between trials (48-52). Therefore, our finding of selective ‘noise’ correlations between the pITG and aIPS likely reflects coupling of their endogenous activity, which appears to be strongest during numerical processing, but which is still present during other non-numerical task conditions (reading sentences/memory retrieval), and at rest. Importantly, the strength of coupling between the aIPS and different VTC sites within the math condition correlated with the VTC sites' selectivity rather than their magnitude of responses during the math condition (Figure 6E). The same was also the case for correlations between the pITG and different LPC sites (Figure S6G). Therefore, it is unlikely that the selective correlation between the pITG and aIPS is simply an artifact of simultaneous engagement of these regions. To further support this claim, the correlation between $\text{aIPS}_{\text{math}}$ and $\text{pITG}_{\text{math}}$ sites was still stronger during memory trials than was the correlation between the $\text{aIPS}_{\text{math}}$ and other VTC sites (e.g., LOG/pFG) that exhibited larger HFB responses during memory trials (Figure 2B).

Temporal dynamics of coupling between the pITG and aIPS

The phase amplitude coupling and onset latency analyses provided additional clues about the nature of interaction between the math-selective hubs within the pITG and aIPS. While on average, math-active sites within the pITG responded earlier than those within the aIPS, we observed near simultaneous engagement of the math-selective pITG and aIPS hubs in two of three subjects in which we were able to measure onset latencies both in the $\text{pITG}_{\text{math}}$ and $\text{aIPS}_{\text{math}}$. The sparse and slightly different electrode coverage across subjects likely explains the different times of onset between the pITG and aIPS across subjects. Specifically, the pITG populations selected in each patient may be engaged in different aspects of numerical computations (e.g. visual processing of symbols versus active arithmetic computations). Still, the near simultaneous engagement of sub-populations within the aIPS and pITG suggests that the pITG's role in numerical cognition is more complex than simply representing the symbolic numerical code.

Our phase-amplitude coupling results, though preliminary, suggest a feedback loop between the pITG and aIPS, with bottom-up coupling from pITG populations engaged in decoding individual numerals and top-down coupling to pITG populations more engaged in active arithmetic computations. The different coupling frequencies we observe across subjects raise intriguing questions that can be tested in future studies; namely whether the frequency of slow oscillations that couple two distinct regions of the brain may differ from one individual to another, or may be different across centimeters of cortex.

Lastly, the strong coupling from aIPS phase to pITG amplitude is interesting in light of a recent finding that the NFA region exhibits selectivity for numerical stimuli even in a congenitally blind person (where numerical stimuli were presented auditorily; (38)). Our results support the 'biased connectivity' hypothesis in regards to the development of the NFA (8); that the selectivity within the NFA may be driven by its intrinsic connectivity with the aIPS. However, such an interaction between the aIPS and pITG may be direct or indirect; possibly mediated by a third-structure, such as the thalamus, which plays a role in regulating information flow between cortical areas (75-77).

Conclusion

The current study revealed novel information about the patterns of electrophysiological activity within two regions of the human brain (VTC and LPC) that are predicted by the 'Triple Code' model to be important for numerical processing, and additionally about the nature of coupling between them. While it was beyond the scope of the current study to address distinct cognitive aspects of numerical processing within each of these two regions, the high temporal resolution and anatomical precision of ECoG enabled us to gain insight into the complex functional heterogeneity within each region of the VTC and LPC, and their distinct patterns of functional coupling. We were able to detect discrete neuronal populations (separated by as little as 5mm) within each of these regions (VTC, LPC) with significantly different profiles of activity across tasks (e.g. with some sites responding both to individual numerals and active arithmetic, and other neighboring sites only responding during active arithmetic but not to the presentation of individual numerals). This spatial specificity of task-related response profiles was mirrored in the spatially specific patterns of ‘noise’ and spontaneous (i.e. rest) activity correlations between the VTC and LPC (Figure 6; Figure S6). Moreover, preliminary results suggest different directions of communication (i.e. bottom-up versus top-down) between these different pITG and aIPS sub-populations (Figure 7).

Taken together, we believe the response profiles of different VTC and LPC subregions, their relative response times, and functional coupling patterns, are suggestive of multiple feedback-loops operating between different VTC and LPC subregions (Figure 8). We propose that different loops are engaged during different stages of numerical processing, and that in some cases, neighboring sites (e.g. within the pITG) are engaged in different loops. Brain regions with early, transient, less-selective responses (e.g. the LOG, SPL, and pIPS) may form loops which are involved in visual processing of, and attention to, the visual stimuli, while other regions with later, sustained, and more math-selective responses (i.e. $\text{pITG}_{\text{math}}$/NFA and $\text{aIPS}_{\text{math}}$) may form loops to carry out arithmetic computations (Figure 8B). The NFA is possibly at the intersection of bottom-up visual processes and top-down processes from $\text{aIPS}_{\text{math}}$, given its response to individual symbols (and exhibiting a late selective response to numerals) and its sustained response during arithmetic processing. This is a very tentative, simplified model, which ignores regions such as the thalamus and frontal cortex that are also likely involved in numerical cognition. However, we hope that it can provide a general framework for future studies that can further disentangle the roles of these brain regions, and their interactions, in distinct aspects of numerical cognition.

Experimental Procedures

Subjects

Sixteen patients with epilepsy were implanted with intracranial electrodes as part of their pre-surgical evaluation at Stanford University Medical Center. Demographic information for each subject is included in Table S1, and each subject's electrode coverage is displayed in Figure S1. Each patient was monitored in the hospital for approximately 6-10 days following surgery, and all subjects provided verbal and written consent before participating in any experiments, which was approved by the Stanford Institutional Review Board.

Electrodes

Each subject was implanted with grids and/or strips of subdural platinum electrodes (AdTech Medical Instruments), whose locations were determined purely for clinical reasons (Figure S1). Each electrode had an exposed diameter of 2.3 mm, with inter-electrode spacing of 10mm, or 5mm for higher density arrays.

Behavioral paradigms

All Tasks were conducted at the patient's bedside. Stimuli were visually presented on a laptop computer (Apple MacBook or MacBook Pro) with MATLAB psychtoolbox (see Figure 1 for illustration of all tasks).

Task 1: Subjects were visually presented with a series of symbols, falling under one of three categories: 1) Numeral, 2) English letters, 3) foreign letters. For each symbol, subjects had to press one button if they could read the symbol (i.e. for English numbers or letters) and another button if they couldn't read it (i.e. for foreign symbols). Subjects had up to 15 seconds to respond to each stimulus, and a 500ms inter-trial-interval (ITI) separated trials.

Task 2: Subjects were asked to make true/false judgments on a series of visually presented statements, requiring either memory (e.g. “I ate fruit yesterday”), or arithmetic (e.g. “48 + 8 = 57”) processing. Subjects had up to 15 seconds to respond (by pressing one of two keypad buttons) to each statement. These statements were interspersed with fixation periods (5s or 10s), during which subjects were simply asked to fixate at a center crosshair. A 200ms ITI separated trials.

Task 3: Subjects were asked to make true/false judgments on arithmetic equations, visually presented one numeral/symbol at a time (e.g. “7”, “+”, “5”, “=”, “12”). Each stimulus was presented for 500ms., with a 400ms. inter-stimulus-interval. Subjects had up to 10 seconds to respond once the last number was presented. Trials were separated by a 2s ITI.

Data acquisition and analysis

ECoG data were recorded from subdural electrodes via a multichannel recording system (Tucker David Technologies). Data were acquired with a band pass filter of 0.5-300 Hz and sampling rate of 1525.88 Hz. An electrode outside the seizure zone with the most silent electrocorticographic activity was selected as an online reference during acquisition.

Preprocessing

Prior to data processing, electrodes identified as within the ictogenic zone, or those corrupted by electrical noise, were eliminated from subsequent analyses. Electrodes were also excluded whose overall power was five or more standard deviations above or below the mean power across channels, and those whose power spectrum strayed from the normal 1/f power spectrum, based on visual inspection. All non-excluded channels were then notch filtered at 60 Hz and harmonics to remove electric interference, then re-referenced to the mean of the filtered signals of the non-excluded channels. The re-referenced signal at each electrode was then band-pass filtered into six different frequency bands; 1-3 Hz, 4-7 Hz, 8-12 Hz, 13-29 Hz, 30-55 Hz, and 70-180 Hz, using two-way, zero-lag, FIR filters. Instantaneous amplitude was computed by taking the modulus of the Hilbert Transformed signal. We subdivided the 70-180 Hz band (HFB) into 10 Hz width band-pass windows (70-80 Hz, 80-90 Hz, etc) and normalized the amplitude of each 10 Hz band signal by its own mean, then averaged these normalized amplitude time series together, yielding a single amplitude timecourse for the HFB band. This normalization procedure was applied to partially correct for the 1/frequency decay present in neurophysiological signals.

To evaluate the activity at each site on a finer spectral scale, we also generated spectrograms for each site, which displays the timecourse of activity within smaller spectral bins. To generate spectrograms, we convolved the notch-filtered, common-average referenced signal with Gabor wavelet filters (span of 5 cycles) centered at 30 different frequencies (log-spaced between 1 and 256 Hz), yielding instantaneous amplitude estimates at each frequency and time point. The amplitude in each frequency bin was then normalized by the amplitude in that same frequency bin during the baseline (200ms ITI) period, allowing us to see task-induced changes in spectral power relative to the baseline.

See supplemental information for more details on analysis methods

Acknowledgments:

The authors would like to thank all the patients for volunteering their time to participate in this study; Pooya Ehsani, Jean-Rémi King, Dora Hermes, Zachary Greenberg and other LBCN team members for their help in the initial and early stages of this study; and Stanislas Dehaene for his important feedback throughout the project. This work was supported by research grants from the US National Institute of Neurological Disorders and Stroke (R01NS078396), US National Institute of Mental Health (1R01MH109954-01) and US National Science Foundation (BCS1358907) to J.P.; career development award from the US National Institute of Mental Health (K99MH103479) to B.L.F.; National Science Foundation Graduate Research Fellowship to V.R. (DGE 1106400); and Marie Sklodowska-Curie Actions fellowship (project DecoMP_ECoG 654038) to J.S. The views presented in this work do not necessarily reflect those of the National Institutes of Health.

References

1. Lipton JS & Spelke ES (2003) Origins of number sense. Large-number discrimination in human infants. *Psychol Sci* 14(5):396-401.

2. Boysen ST & Berntson GG (1989) Numerical competence in a chimpanzee (Pan troglodytes). *J Comp Psychol* 103(1):23-31.

3. Brannon EM & Terrace HS (1998) Ordering of the numerosities 1 to 9 by monkeys. *Science* 282(5389):746-749.

4. Nieder A (2012) Supramodal numerosity selectivity of neurons in primate prefrontal and posterior parietal cortices. *Proceedings of the National Academy of Sciences of the United States of America* 109(29):11860-11865.

5. Brannon EM, Wusthoff CJ, Gallistel CR, & Gibbon J (2001) Numerical subtraction in the pigeon: evidence for a linear subjective number scale. *Psychol Sci* 12(3):238-243.

6. Ansari D (2008) Effects of development and enculturation on number representation in the brain. *Nature reviews. Neuroscience* 9(4):278-291.

7. Dehaene S (2011) *The Number Sense: How the mind creates mathematics* (Oxford University Press) 2nd Ed.

8. Hannagan T, Amedi A, Cohen L, Dehaene-Lambertz G, & Dehaene S (2015) Origins of the specialization for letters and numbers in ventral occipitotemporal cortex. *Trends in cognitive sciences* 19(7):374-382.

9. Cipolotti L, Butterworth B, & Denes G (1991) A specific deficit for numbers in a case of dense acalculia. *Brain* 114 (Pt 6):2619-2637.

10. Cohen L & Dehaene S (1995) Reading numbers in pure alexia: effects of the task and hemispheric specialization. *Rev Neurol (Paris)* 151(8-9):480-485.

11. Dagenbach D & McCloskey M (1992) The organization of arithmetic facts in memory: evidence from a brain-damaged patient. *Brain Cogn* 20(2):345-366.

12. Dehaene S & Cohen L (1991) Two mental calculation systems: a case study of severe acalculia with preserved approximation. *Neuropsychologia* 29(11):1045-1054.

13. McCloskey M, Caramazza A, & Basili A (1985) Cognitive mechanisms in number processing and calculation: evidence from dyscalculia. *Brain Cogn* 4(2):171-196.

14. Takayama Y, Sugishita M, Akiguchi I, & Kimura J (1994) Isolated acalculia due to left parietal lesion. *Arch Neurol* 51(3):286-291.

15. Dehaene S (1992) Varieties of numerical abilities. *Cognition* 44(1-2):1-42.

16. Dehaene S, Cohen, L. (1995) Towards an anatomical and functional model of number processing. *Mathematical Cognition* 1:83-120.

17. Arsalidou M & Taylor MJ (2011) Is 2+2=4? Meta-analyses of brain areas needed for numbers and calculations. *NeuroImage* 54(3):2382-2393.

18. Cantlon JF, Brannon EM, Carter EJ, & Pelphrey KA (2006) Functional imaging of numerical processing in adults and 4-y-old children. *PLoS biology* 4(5):e125.

19. Chochon F, Cohen L, van de Moortele PF, & Dehaene S (1999) Differential contributions of the left and right inferior parietal lobules to number processing. *Journal of cognitive neuroscience* 11(6):617-630.

20. Dastjerdi M, Ozker M, Foster BL, Rangarajan V, & Parvizi J (2013) Numerical processing in the human parietal cortex during experimental and natural conditions. *Nature communications* 4:2528.

21. Eger E, Sterzer P, Russ MO, Giraud AL, & Kleinschmidt A (2003) A supramodal number representation in human intraparietal cortex. *Neuron* 37(4):719-725.

22. Nieder A & Dehaene S (2009) Representation of number in the brain. *Annu Rev Neurosci* 32:185-208.

23. Piazza M & Eger E (2016) Neural foundations and functional specificity of number representations. *Neuropsychologia* 83:257-273.

24. Piazza M, Izard V, Pinel P, Le Bihan D, & Dehaene S (2004) Tuning curves for approximate numerosity in the human intraparietal sulcus. *Neuron* 44(3):547-555.

25. Walsh V (2003) A theory of magnitude: common cortical metrics of time, space and quantity. *Trends in cognitive sciences* 7(11):483-488.

26. Butterworth B, Varma S, & Laurillard D (2011) Dyscalculia: from brain to education. *Science* 332(6033):1049-1053.

27. Moeller K, Willmes K, & Klein E (2015) A review on functional and structural brain connectivity in numerical cognition. *Frontiers in human neuroscience* 9:227.

28. Matejko AA & Ansari D (2015) Drawing connections between white matter and numerical and mathematical cognition: a literature review. *Neurosci Biobehav Rev* 48:35-52.

29. Jolles D*, et al.* (2016) Parietal hyper-connectivity, aberrant brain organization, and circuit-based biomarkers in children with mathematical disabilities. *Dev Sci*.

30. Iuculano T & Cohen Kadosh R (2014) Preliminary evidence for performance enhancement following parietal lobe stimulation in Developmental Dyscalculia. *Frontiers in human neuroscience* 8:38.

31. Salillas E, Semenza C, Basso D, Vecchi T, & Siegal M (2012) Single pulse TMS induced disruption to right and left parietal cortex on addition and multiplication. *NeuroImage* 59(4):3159-3165.

32. Andres M, Pelgrims B, Michaux N, Olivier E, & Pesenti M (2011) Role of distinct parietal areas in arithmetic: an fMRI-guided TMS study. *NeuroImage* 54(4):3048-3056.

33. Allison T, Puce A, Spencer DD, & McCarthy G (1999) Electrophysiological studies of human face perception. I: Potentials generated in occipitotemporal cortex by face and non-face stimuli. *Cerebral cortex* 9(5):415-430.

34. Park J, Hebrank A, Polk TA, & Park DC (2012) Neural dissociation of number from letter recognition and its relationship to parietal numerical processing. *Journal of cognitive neuroscience* 24(1):39-50.

35. Pinel P, Dehaene S, Riviere D, & LeBihan D (2001) Modulation of parietal activation by semantic distance in a number comparison task. *NeuroImage* 14(5):1013-1026.

36. Price GR & Ansari D (2011) Symbol processing in the left angular gyrus: evidence from passive perception of digits. *NeuroImage* 57(3):1205-1211.

37. Shum J*, et al.* (2013) A brain area for visual numerals. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 33(16):6709-6715.

38. Abboud S, Maidenbaum S, Dehaene S, & Amedi A (2015) A number-form area in the blind. *Nature communications* 6:6026.

39. Grotheer M, Herrmann KH, & Kovacs G (2016) Neuroimaging Evidence of a Bilateral Representation for Visually Presented Numbers. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 36(1):88-97.

40. Hermes D*, et al.* (2015) Electrophysiological Responses in the Ventral Temporal Cortex During Reading of Numerals and Calculation. *Cerebral cortex*.

41. Schrouff J, Mourao-Miranda J, Phillips C, & Parvizi J (2016) Decoding intracranial EEG data with multiple kernel learning method. *J Neurosci Methods* 261:19-28.

42. Manning JR, Jacobs J, Fried I, & Kahana MJ (2009) Broadband shifts in local field potential power spectra are correlated with single-neuron spiking in humans. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 29(43):13613-13620.

43. Ray S & Maunsell JH (2011) Different origins of gamma rhythm and high-gamma activity in macaque visual cortex. *PLoS biology* 9(4):e1000610.

44. Logothetis NK, Pauls J, Augath M, Trinath T, & Oeltermann A (2001) Neurophysiological investigation of the basis of the fMRI signal. *Nature* 412(6843):150-157.

45. Flinker A, Chang EF, Barbaro NM, Berger MS, & Knight RT (2011) Sub-centimeter language organization in the human temporal lobe. *Brain Lang* 117(3):103-109.

46. Parvizi J*, et al.* (2012) Electrical stimulation of human fusiform face-selective regions distorts face perception. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 32(43):14915-14920.

47. Foster BL, Rangarajan, V, Shirer, W.R., Parvizi, J (2015) Intrinsic and Task-Dependent Coupling of Neuronal Population Activity in Human Parietal Cortex. *Neuron*.

48. Lewis CM, Bosman CA, Womelsdorf T, & Fries P (2016) Stimulus-induced visual cortical networks are recapitulated by spontaneous local and interareal synchronization. *Proceedings of the National Academy of Sciences of the United States of America* 113(5):E606-615.

49. Luczak A, Bartho P, & Harris KD (2009) Spontaneous events outline the realm of possible sensory responses in neocortical populations. *Neuron* 62(3):413-425.

50. Kenet T, Bibitchkov D, Tsodyks M, Grinvald A, & Arieli A (2003) Spontaneously emerging cortical representations of visual attributes. *Nature.* 425(6961):954-956.

51. Arieli A, Sterkin A, Grinvald A, & Aertsen A (1996) Dynamics of ongoing activity: explanation of the large variability in evoked cortical responses. *Science* 273(5283):1868-1871.

52. Tsodyks M, Kenet T, Grinvald A, & Arieli A (1999) Linking spontaneous activity of single cortical neurons and the underlying functional architecture. *Science* 286(5446):1943-1946.

53. Keller CJ*, et al.* (2013) Neurophysiological investigation of spontaneous correlated and anticorrelated fluctuations of the BOLD signal. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 33(15):6333-6342.

54. Leopold DA & Logothetis NK (2003) Spatial patterns of spontaneous local field activity in the monkey visual cortex. *Reviews in the neurosciences* 14(1-2):195-205.

55. Nir Y*, et al.* (2008) Interhemispheric correlations of slow spontaneous neuronal fluctuations revealed in human sensory cortex. *Nature neuroscience*.

56. He BJ, Snyder AZ, Zempel JM, Smyth MD, & Raichle ME (2008) Electrophysiological correlates of the brain's intrinsic large-scale functional architecture. *Proceedings of the National Academy of Sciences of the United States of America* 105(41):16039-16044.

57. Hipp JF, Hawellek DJ, Corbetta M, Siegel M, & Engel AK (2012) Large-scale cortical correlation structure of spontaneous oscillatory activity. *Nature neuroscience* 15(6):884-890.

58. Varela F, Lachaux JP, Rodriguez E, & Martinerie J (2001) The brainweb: phase synchronization and large-scale integration. *Nature reviews. Neuroscience* 2(4):229-239.

59. Fries P (2005) A mechanism for cognitive dynamics: neuronal communication through neuronal coherence. *Trends in cognitive sciences* 9(10):474-480.

60. Buzsaki G (2011) *Rhythms of the Brain* (Oxford University Press) 1 Ed p 464.

61. Canolty RT*, et al.* (2006) High gamma power is phase-locked to theta oscillations in human neocortex. *Science* 313(5793):1626-1628.

62. Miller KJ*, et al.* (2010) Dynamic modulation of local population activity by rhythm phase in human occipital cortex during a visual search task. *Frontiers in human neuroscience* 4:197.

63. Voytek B*, et al.* (2015) Oscillatory dynamics coordinating human frontal networks in support of goal maintenance. *Nature neuroscience* 18(9):1318-1324.

64. Watrous AJ, Deuker L, Fell J, & Axmacher N (2015) Phase-amplitude coupling supports phase coding in human ECoG. *Elife* 4.

65. Foster BL & Parvizi J (2012) Resting oscillations and cross-frequency coupling in the human posteromedial cortex. *NeuroImage* 60(1):384-391.

66. Voytek B*, et al.* (2010) Shifts in gamma phase-amplitude coupling frequency from theta to alpha over posterior cortex during visual tasks. *Frontiers in human neuroscience* 4:191.

67. van der Meij R, Kahana M, & Maris E (2012) Phase-amplitude coupling in human electrocorticography is spatially distributed and phase diverse. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 32(1):111-123.

68. Maris E, van Vugt M, & Kahana M (2011) Spatially distributed patterns of oscillatory coupling between high-frequency amplitudes and low-frequency phases in human iEEG. *NeuroImage* 54(2):836-850.

69. Corbetta M & Shulman GL (2002) Control of goal-directed and stimulus-driven attention in the brain. *Nature reviews. Neuroscience* 3(3):201-215.

70. Dosenbach NU*, et al.* (2007) Distinct brain networks for adaptive and stable task control in humans. *Proceedings of the National Academy of Sciences of the United States of America* 104(26):11073-11078.

71. Harvey BM, Klein BP, Petridou N, & Dumoulin SO (2013) Topographic representation of numerosity in the human parietal cortex. *Science* 341(6150):1123-1126.

72. Eger E, Pinel P, Dehaene S, & Kleinschmidt A (2015) Spatially invariant coding of numerical information in functionally defined subregions of human parietal cortex. *Cerebral cortex* 25(5):1319-1329.

73. Nieder A & Miller EK (2004) A parieto-frontal network for visual numerical information in the monkey. *Proceedings of the National Academy of Sciences of the United States of America* 101(19):7457-7462.

74. Roitman JD, Brannon EM, & Platt ML (2007) Monotonic coding of numerosity in macaque lateral intraparietal area. *PLoS biology* 5(8):e208.

75. Saalmann YB & Kastner S (2011) Cognitive and perceptual functions of the visual thalamus. *Neuron* 71(2):209-223.

76. Zikopoulos B & Barbas H (2007) Circuits for multisensory integration and attentional modulation through the prefrontal cortex and the thalamic reticular nucleus in primates. *Reviews in the neurosciences* 18(6):417-438.

77. Steriade M, McCormick DA, & Sejnowski TJ (1993) Thalamocortical oscillations in the sleeping and aroused brain. *Science* 262(5134):679-685.

78. Hermes D, Miller KJ, Noordmans HJ, Vansteensel MJ, & Ramsey NF (2010) Automated electrocorticographic electrode localization on individually rendered brain surfaces. *J Neurosci Methods* 185(2):293-298.

79. Schrouff J*, et al.* (2013) PRoNTo: pattern recognition for neuroimaging toolbox. *Neuroinformatics* 11(3):319-337.

Figure Legends

Figure 1. Illustration of three behavioral Tasks. See Experimental Procedures section for a detailed description of each Task

Figure 2. A. Electrodes within the ventral temporal cortex from all fourteen subjects with electrodes over the VTC are shown on the right hemisphere, projected onto a single hemisphere of an atlas brain. On the left hemisphere are shown the anatomical subdivisions considered in this study within the VTC. (Abbreviations- ***pFG***: posterior fusiform gyrus; ***mFG***: middle fusiform gyrus; ***aFG***: anterior fusiform gyrus; ***LOG***: lateral occipital gyrus; ***pITG***: posterior inferior temporal gyrus; ***aITG***: anterior inferior temporal gyrus) **B.** HFB responses to numerals and other visual symbols in Task 1 (top row), and when analyzing math or memory statements in Task 2 (bottom row), grouped by sites in each VTC subregion, averaged across all subjects. Error bars indicate standard error across electrodes. Note that the selectivity of individual electrodes within an ROI may be different than the average selectivity of that ROI. **C.** Individual electrodes across all subjects are highlighted, which are: significantly numeral active (relative to the ITI; left hand brain), numeral selective (relative to letters and foreign symbols; 2nd from left), math active (relative to the ITI; 3rd from left), and math selective (relative to memory; also with no significant memory response; right hand brain). The color of each electrode denotes its anatomical region (determined in individual brain space). Electrodes outlined in black have significant responses at the level of $p < 0.05$, FDR corrected, and those outlined in white are significant at $p < 0.05$, uncorrected. **D.** Exemplar HFB timecourse during Task 1 and Task 2 are shown for an exemplar NFA site (from S13). Shaded area represents the standard error across trials for each condition.

Figure 3. A. Electrodes within the lateral parietal cortex from all fourteen subjects with electrodes over the LPC are shown on the right hemisphere, projected onto a single hemisphere of an atlas brain (bottom). Also shown are the anatomical subdivisions considered in this study within the LPC (top). (Abbreviations- ***aSOG***: anterior superior occipital gyrus; ***SPL***: superior parietal lobule; ***pIPS***: posterior intraparietal sulcus; ***aIPS***: anterior intraparietal sulcus; ***AG***: angular gyrus; ***SMG***: supramarginal gyrus) **B.** HFB responses to numerals and other visual symbols in Task 1 (top row), and when analyzing math or memory statements in Task 2 (bottom row), grouped by sites in each LPC subregion, averaged across all subjects. Error bars indicate standard error across electrodes. **C.** Individual electrodes across all subjects are highlighted, which are: significantly math active (relative to the ITI; left hand plot), and math selective (relative to memory; also with no significant memory response; right hand brain). The color of each electrode denotes its anatomical region (determined in individual brain space). Electrodes outlined in black have significant responses at the level of $p < 0.05$, FDR corrected, and those outlined in white are significant at $p < 0.05$, uncorrected. **D.** Exemplar HFB timecourses during Task 1 and Task 2 are shown for a site in the aIPS, which doesn't respond to the passive presentation of numerals, letters, or false fonts, but is selectively engaged during active mathematical computation (from S11). Shaded area represents the standard error across trials for each condition.

Figure 4. A. Exemplar HFB timecourses during the numeral condition in Task 1 at sites within three different VTC regions in a single subject (S13; the HFB timecourse at each site is scaled by its own maximum. Shaded area represents the standard error across trials for each condition). Note that the pITG site responds later to numerals than either the pFG or mFG sites. **B.** Group averaged differences between the HFB response onset latencies (ROL) to numerals at electrode pairs in different anatomical regions (only electrode pairs within an individual subject were considered. Number of electrode pairs per ROI-pair: LOG/pFG-pITG: 44 pairs

across 4 subjects; LOG/pFG-mFG: 34 pairs across 4 subjects; pITG-mFG: 45 pairs across 7 subjects). Asterisks denote significant differences in ROL between two anatomical regions ($p < 0.05$, FDR corrected). **C.** Approximate range of ROL (to numerals) for each anatomical region is plotted, in seconds (mean +/- 1 standard deviation across all subjects, all electrodes). **D.** Exemplar HFB timecourses during the math condition in Task 2 at sites within three different VTC subregions and two LPC regions in a single subject (S4; scaled by its own maximum. Shaded area represents the standard error across trials for each condition). Note that in this subject, pITG and aIPS sites respond after the LOG/pFG, mFG, and SPL sites, and nearly simultaneously with each other. **E.** Group averaged differences between the HFB response onset latencies (ROL) during the math condition (Task 2) at electrode pairs in different anatomical regions (only electrode pairs within an individual subject were considered. Number of electrode pairs per ROI-pair: LOG/pFG-pITG: 23 pairs across 5 subjects; LOG/pFG-mFG: 2 pairs across 1 subject; LOG/pFG-SPL: 4 pairs across 1 subject; LOG/pFG-aIPS: 6 pairs across 2 subjects; pITG-mFG: 14 pairs across 5 subjects; pITG-SPL: 17 pairs across 4 subjects; pITG-aIPS: 14 pairs across 4 subjects; mFG-SPL: 6 pairs across 2 subjects; mFG-aIPS: 5 pairs across 2 subjects; SPL-aIPS: 11 pairs across 4 subjects). Asterisks indicate significant differences in ROL between two anatomical regions ($p < 0.05$, FDR corrected). **F.** Approximate range of ROL (to math) for each anatomical region is plotted, in seconds (mean +/- 1 standard deviation).

Figure 5. A. Math active sites in four different anatomical regions an exemplar subject (S11; this subject had no math active SPL sites). **B** HFB timecourse during Task 3 at each site in A. (scaled by each site's own maximum). Shaded area represents the standard error across trials for each condition). Note that while the pITG and aIPS sites respond more two the 2nd than 1st digit, the pFG and mFG sites respond more to the 1st than 2nd digit (the pITG site shown here is not within the NFA). **C.** At the group level, the ratio of the HFB response to the 2nd relative to the

1st digit was larger than 1 in the pITG and aITG, and less than one in the LOG/pFG, mFG, and SPL. Brackets represent significant differences in the ratio between regions (solid bracket- $p < 0.05$, FDR corrected; dashed bracket- $p < 0.05$, uncorrected). Error bars indicate standard error across electrodes.

Figure 6. A. Illustration of trial-by-trial HFB correlation between an exemplar $\text{pITG}_{\text{math}}$ and $\text{aIPS}_{\text{math}}$ site in a single subject (S11), across all conditions (left; dark filled circles are math trials, light filled circles are memory trials), only math trials, or only memory trials (top and bottom right, respectively). **B.** For the same subject, we show the HFB correlation between the $\text{aIPS}_{\text{math}}$ seed and each VTC site, during math trials (leftmost column) and memory trials (second column) in Task 2. Also shown is the correlation of slow fluctuations of HFB power between the $\text{aIPS}_{\text{math}}$ seed and each VTC site while subjects are at rest (third column), and the level of HFB activity during math trials relative to the ITI (fourth column). **C.** Average correlation (Fisher-z) between HFB power at the $\text{aIPS}_{\text{math}}$ seed and at each VTC subregion, averaged across the five subjects with coverage of both $\text{aIPS}_{\text{math}}$ and $\text{pITG}_{\text{math}}$ (S2, S4, S8, S11, S16), during math trials (dark grey) and memory trials (light grey) in Task 2. Significant differences in correlation between regions are denoted with solid brackets ($p < 0.05$, FDR corrected) and dashed brackets ($p < 0.05$, uncorrected) **D.** Average correlation (Fisher-z) between slow fluctuations of HFB power at the $\text{aIPS}_{\text{math}}$ seed and each VTC subregion at rest, averaged across all five subjects. **E.** Scatterplot showing the relationship between selectivity of VTC sites for math (relative to memory processing) and their trial-by-trial HFB correlation with aIPS during math trials. Only VTC sites that are significantly active during math trials are included.

Figure 7. A. In a single subject (S4), we show phase-amplitude coupling within the math selective aIPS site (leftmost column). The low frequency band whose phase is most coupled to the HFB power at the same aIPS site is demarcated with the yellow dashed lines. The second

and third columns show aIPS phase to VTC HFB amplitude coupling, and VTC phase to aIPS HFB amplitude, respectively. Note that the aIPS phase is most coupled to the HFB amplitude at sites within the pITG. The fourth column shows the coupling of the phase at each VTC site to the HFB amplitude at the same site. The rightmost column shows the magnitude of the HFB response at each VTC site during math trials, relative to the ITI. Note that the sites with the most phase amplitude coupling during math trials are not necessarily the ones with the largest HFB response. **B.** In the same subject, we show the response properties of the site showing the highest bottom-up phase-amplitude coupling (pITG to aIPS; top set of plots/purple) and the one showing the highest top-down phase-amplitude coupling (aIPS to pITG; bottom set of plots/cyan). Note that the pITG site with the largest bottom-up coupling responded to the passive presentation of visual numerals (Task 1) but not much during active mathematical computation (Task 2), while the site showing the strongest top-down PAC from IPS was slightly more anterior and generally didn't respond much to the passive presentation of visual numerals but showed selective activity during active mathematical computation. **C.** Left-hand plot: average PAC between $\text{aIPS}_{\text{math}}$ and three different regions within the VTC, averaged across the five subjects with simultaneous $\text{aIPS}_{\text{math}}$ and $\text{pITG}_{\text{math}}$ coverage. Right-hand plot: average within-site PAC in each of three different regions within the VTC, averaged across the same five subjects.

Figure 8. A. General activity profiles (in Task 1 and Task 2) observed within four VTC regions (3 within the pITG) and two LPC regions, that we propose are engaged in different aspects of numerical cognition (time courses shown are not real data). Vertical dotted lines highlight the relative timing of onset between these different brain regions. **B.** Proposed sequence of coupling between the brain regions in A., with earlier VTC-LPC loops more engaged in visual processing/attention, and later loops engaged in carrying out the arithmetic computation.