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Distributed Task Related BOLD Signal During Auditory Sub-second Timing

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I am a second-year chemistry major and biology minor in the College of Arts and Sciences. I am a first year Gaines Fellow, a National Merit Scholar, and a Singletary Scholar. I am employed by the Thomas D. Clark Study as a tutor of the biological, chemical, and physical sciences. I am also a member of Phi Beta Kappa honor society and Phi Delta Theta social fraternity. In the summer of 2004, I was granted a Neuroengineering Summer Research Program fellowship by the National Science Foundation to work at UCLA's Brain Mapping Institute. This paper is a summary of my work with Dr. Mark Cohen and Jennifer Bramen whose endless patience and supportive mentoring made it possible for me to jump into an otherwise highly specialized field. I have presented the findings at UCLA's Summer Program for Undergraduate Research and to the Bluegrass Chapter of the Society for Neuroscience. My abstract has been cited by UCLA's Center for Academic Excellence.

My driving passion in life is to understand the human brain as both an organic tissue and a self-aware subjective entity. At the University of Kentucky, I strive to do this through my research into the biochemical basis of Alzheimer's Disease. At UCLA, I sought to explore the brain macroscopically through functional magnetic resonance imaging. Eventually, I want to become a research physician in the hopes of exploring consciousness at the point where neurochemistry and neuroimaging articulate.

Faculty Mentor:
Mark S. Cohen, Ph.D., Professor, UCLA School of Medicine along with Jennifer E. Bramen, graduate student

During the summer of 2004, I sponsored Yuriy Bronshteyn to visit in my laboratory to participate in research and to gain experience in neuroimaging. While here, he worked largely under the direction of my graduate fellow, Jennifer Bramen, in support of her graduate studies on the neurology of time perception and estimation. Yuriy gained a strong and satisfying understanding of the experiments and their underlying neuroscience, as well as of the fMRI method. Since then, he has prepared a report on his studies entitled, "Distributed Task Related BOLD Signal During Auditory Sub-second Timing" that I have had the chance to read and to review, but which he authored solely. His analysis and perception of the work is quite excellent and he has made observations and interpretations that go beyond the original experimental design. The independent reading and thought that has gone into to this is significantly beyond what I expect from students at this stage in their career.

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Abstract

The brain's input/output functions depend heavily on temporal processing. We sought to identify regions of the brain active in task performance during temporal discrimination of a sub-second auditory interval. We presented ten subjects with 40 paired tones and asked them to judge whether these comparison intervals were longer or shorter than a 100 ms standard. We then localized correlations between the Blood Oxygenation Level Dependent signal and task performance across subjects using event-related functional magnetic resonance imaging. We saw no task-related frontal cortex activation and significant activation of traditional auditory areas. Auditory regions included the bilateral superior and middle temporal gyri (STG and MTG): Brodmann areas (BA) 21, 22, 38, 41, and 42. The signals within the left hemispheric insula, precentral gyrus, inferior and superior parietal lobes and right hemispheric postcentral gyrus were also correlated with the task. Unexpectedly, visual areas were also activated, including the right hemispheric cuneus, middle occipital gyrus and bilateral precuneus: BA 7, 18 & 19. Most interestingly, the activation of the STG, MTG, precentral gyrus and insula — areas implicated in verbal memory, language and reading — suggests a possible co-localization of function between sub-second temporal processing and written language comprehension. This study thus corroborates the long speculated hypothesis that certain language-based learning disabilities, such as dyslexia, may be caused by deficits in temporal processing.

1. Introduction

The brain's ability to function successfully relies in large part on its temporal processing capabilities. Without the ability to perceive differences in time, human beings would be handicapped on countless scales of activity, ranging from the micro — e.g., localizing sound would be impossible given the need for temporal discrimination of the interaural delay (Middlebrooks and Green, 1991) — to the macro — sleep wake cycles would be unregulated without circadian proteins that oscillate every 24 hours (Hastings, 2003). Though much research has been done to investigate a wide range of temporal processes, including millisecond and circadian intervals, still, little is known about how the brain processes an important scale in between: the sub-second range.

Discriminating between sub-second intervals ranging from tens of milliseconds to one second is necessary for speech recognition, language vocalization, motion perception, and the coordination of movement (Hore et al., 1991). What makes this scale all the more interesting is that it contains the longest temporal durations that might be processed by the brain largely without conscious awareness. As a result, temporal processing on this level is termed "perceptual timing" in contrast to processing on the supra-second level, which is thought to involve conscious awareness and is thus often referred to as "time estimation" (Michon, 1985). However, to date, only two published studies have directly compared temporal processing of sub- and supra-second intervals (Rubia et al., 1998; Lewis and Miall, 2003).

Thus, this experiment sought to investigate brain activation during a sub-second temporal discrimination task using functional magnetic resonance imaging (fMRI) as part of a larger study comparing activation during sub-second, supra-second, and frequency discrimination tasks across modalities. The long-term goal of the larger study is to explore the extent to which temporal processing across scales and modalities is distributed throughout the brain and/or unified in a single centralized locus — an "organ" of time.

The following hypotheses were made:

Hypothesis 1: Because sub-second processing theoretically occurs without conscious awareness, significant performance-correlated frontal lobe activation will not occur.

Hypothesis 2: Because the stimulus is auditory, significant task-related activation in the temporal lobes in traditional auditory areas will occur.

2. Methods

2.1 Task

Ten right-handed subjects performed an auditory temporal discrimination task during fMRI. The subjects decided whether comparison intervals were longer or shorter than a 100 ms (0.1 sec) standard interval. All tasks were adaptive: subject performance was held at about 80% to control for task difficulty and thus reduce stimulus-correlated activation of decision-making processes in the brain.

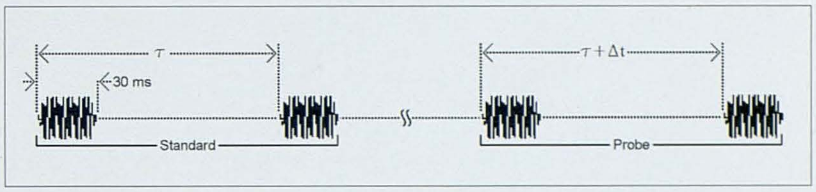

Figure 1: The interval variation, Δt, was adjusted adaptively such that subjects were approximately 80% accurate in determining whether the probe interval, $t + \Delta t$, was longer or shorter than the standard interval, t = 100 ms.

Subjects were presented with 40 paired-tones each of 3.5 kHz frequency. Stimulus presentation was jittered to allow estimation of the hemodynamic response. Standards were presented before the onset of MR Scanning.

2.2 Scanning

All scanning was performed using a 3T Siemens Allegra scanner. Event-related Blood Oxygenation Level Dependent (BOLD) fMRI was performed using echo-planar scans (tr of 2.5, te of 50 ms, flip angle of 80°). Thirty axial slices, each 3mm thick were collected to provide whole-brain coverage. A high resolution EPI localizer with identical readout bandwidth along the phase encoding direction (tr/te = 5000/33 ms, 122 matrix, 200 mm FoV, 3 mm slice with 1 mm gap, 2 shots/image and 4 NEX) and a high resolution structural scan utilizing an MP-RAGE sequence (tr/te/ti 2300/2.1/1100 ms, 2562 matrix, 256 mm FoV, 8° flip angle) were acquired.

2.3 Analysis

The functional data was analyzed using FEAT (fMRI Expert Analysis Tool) within FSL. Preprocessing was standard: slice-timing correction, motion correction (MCFLIRT), brain extraction (BET), and spatial smoothing (5 mm spatial convolution kernel).

2.4 Models

A hypothetical time course model of task related activation was created by convolving the stimulus timing

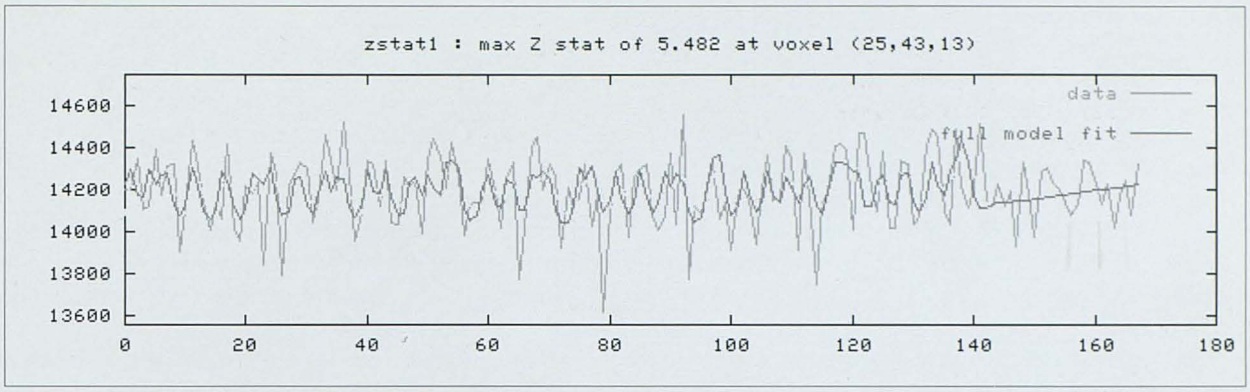

Figure 2: Time course for max Z stat voxel (Z = 5.482) of subject 1 showing correlation between task stimulus model and BOLD signal data.

with an *a priori* hemodynamic response function. That model was then contrasted with BOLD data to localize voxels of statistically significant, task correlated activation.

Each condition was contrasted with rest on a single subject level. After registration, the data was processed for second level (group effects) analysis using FSL's FLAME tool. Areas of activation were weighted for performance (using demeaned discrimination thresholds as the standard — i.e., how effectively the subject was able to discriminate between intervals to achieve approximately 80% accuracy) at the group level using FSL's general linear model (Fig. 3).

3. Results and discussion

3.1 Behavioral performance

All subjects showed good performance, with a deviation from mean threshold of 12.69 ± 3.69 ms (Fig. 3).

Discrimination Thresholds

Subject	Threshold (ms)	Demeaned
1	13.63	+0.94
2	9.43	3.26
3	18.63	+5.94
4	8.75	3.94
5	8.50	4.19
6	15.30	+2.61
7	17.80	+5.11
8	10.38	-2.31
9	13.67	+0.98
10	10.83	-1.86
Mean	12.69	
Stdev	3.69	

Figure 3: Comparison of average and demeaned discrimination thresholds among the ten subjects after modifying the interval variation adaptively to maintain accuracy at approximately 80%.

3.2 Functional imaging

We expected to see 1) no task-related frontal cortex activation and 2) statistically significant activation in traditional auditory areas. The data supported both these hypotheses.

3.3 Auditory

Auditory regions where BOLD signals correlated with task performance included the bilateral superior (STG) and medial temporal gyri (MTG): Brodmann areas (BA) 21, 22, 38, 41, and 42.

Because sub-second processing is integral to the coordination of movement (Hore et al., 1991), the activation of the STG could be related to its long-known role in the vestibular system (Penfield, 1967; Friberg, 1985). Similarly, the activation of the MTG is consistent with a clinical finding (Boiten et al., 2003) of slurred speech correlated with MTG hemorrhage. Because sub-second timing is needed in vocalization (Buonomano and Karmarkar, 2002), it should not be surprising that the MTG might mediate this process.

But it is important to note that our original hypothesis of auditory activation was made largely because the task itself was auditory. However, at least three other sub-second timing studies involving no auditory cues (Larsson et al., 1996; Coull et al., 2000; Lewis and Miall, 2003) also reported MTG and STG activation. One proposed hypothesis attributed this phenomenon to task-elicited auditory imagery (Rao et al., 1997). Because Lewis and Miall's study found MTG and STG activation was higher in a sub- rather than a supra-second task, and because all three studies examined sub-second processing specifically, Lewis and Miall have theorized that auditory imagery is more commonly needed in sub- than supra-second intervals (Lewis and Miall, 2003). Equally important, our findings support the notion that the MTG and STG mediate sub-second processing across visual and auditory modalities. In the context of Lewis and Miall's research, the data corroborates a model of temporal processing that has sub-second timing differentiated among scales and common across modalities.

3.4 Visual

Unexpectedly, visual areas of the brain were also activated, including the right hemispheric cuneus, middle occipital gyrus (MOG), and bilateral precuneus: BA 7, 18, and 19.

Though no hypotheses had been made about traditional visual areas, the activation of the cuneus, MOG, and precuneus is consistent with at least one other sub-second temporal processing study that scanned performance during 0.6 and 5 second sensorimotor synchronization timing tasks (Rubia et al., 1998). Although that study found precuneus activity in both cases, the MOG and cuneus were significantly more active in the 0.6 second condition, suggesting that these areas may uniquely mediate sub- as opposed to supra-second temporal processing. Lesion studies point to the cuneus, an early visual area on the parietal/occipital border, as a mediator of both the spatial vision pathway (Takayama et al., 1995) and of certain forms of spatial estimation (Kertzman et al., 1997). But it would be far too speculative to suggest a co-localization of function in gauging short temporal intervals and spatial distances due both to a lack of corroborating evidence from other studies and potential interference from the confounds of the task.

3.5 Other areas

Signals within the left hemispheric insula, precentral gyrus, inferior and superior parietal lobes (IPL and SPL), and right hemispheric postcentral gyrus — BA 2, 4, 6, 7, and 40 — were also correlated with the task. Activation of the insula is consistent with Lewis and Miall's visual sub-second discrimination results (Lewis and Miall, 2003). Lesion studies suggest the insula is, among other things, part of the functional network that mediates verbal memory (Manes et al., 1999). Interestingly, a recent fMRI study of Korean word reading identified four areas of activation (out of six total activated areas) that are common to our results: left STG, right MTG, precentral gyrus, and insula (Yoon et al., 2005). Because normal continuous speech generates syllables every 200-400 ms (Buonomano and Karmaker, 2002), this phenomenon is not entirely surprising, although Lewis and Miall offer no explanation for it. In fact, it has been suggested for at least thirty years that certain language-based learning disabilities, such as dyslexia, may be caused by deficits in temporal processing (Tallal and Piercy, 1973; Farmer and Klein, 1993; Eden et al., 1996). The present study supports a possible co-localization of function between sub-second temporal processing and written language comprehension. This suggestion appears at first problematic in light of the fact that printed word reading involves no inherent temporal demands — i.e., "everyone reads at his or her own pace." However, because orality precedes literacy during human development, semantic understanding may depend not just on the presentation of phonemes but also on the timing of such presentation. In other words, language loses meaning as words are elongated and their constituent phonemes become distanced by "unnatural" temporal intervals — i.e., those that differ significantly from the expected 200-400 ms syllable breaks. However, cognitive subtraction studies are needed to better control for the effects of stimulus presentation and subject responses to substantiate this conclusion.

Rubia et al. also found activation in the precentral gyrus and IPL during temporal processing (Rubia et al., 1998). However, their findings showed similar activation in these areas for both sub- and supra-second conditions, suggesting it might be a region of functional overlap across scales.

The activation of the postcentral gyrus is not consistent with any published sub-second study. This could be attributed to the confounds of the task, the unique demands of discerning 100 ms intervals via auditory stimuli, or other as yet unidentified factors.

Figure 4: Regions of performance-correlated BOLD activity

Region	Laterality	BA
Auditory		
STG	L	13,22,38,41,42
STG	R	22
MTG	L,R	21
Visual		
Precuneus	L,R	7
MOG	R	19
Cuneus	R	18,19
Other		
Insula	L	
Postcentral G	L	2,6
Precentral G	R	4,6
SPL	L	7
IPL	L	40

Regions of performance-correlated BOLD activity, their respective lateralities (Left or Right), and cyto-architectural classification (Brodmann areas). STG & MTG = superior and medial temporal gyri; MOG = middle occipital gyrus; Postcentral and Precentral G = postcentral and precentral gyri; SPL & IPL = superior and inferior parietal lobes.

4. Summary

As hypothesized, traditional auditory areas exhibited a significant BOLD activation relative to their resting state when correlated with task performance, while frontal areas did not. The absence of frontal activation supports the notion that processing of intervals shorter than one second is done largely without conscious awareness. Further, the activation of the superior and medial temporal gyri, though expected, is significant, given that three other sub-second *non-auditory* temporal discrimination studies have also documented their activation, suggesting that these areas may be involved in *cross-modal* sub-second timing.

The activation of these areas coupled with the activation of the precentral gyrus and insula suggests a possible co-localization of function between sub-second temporal processing and written language comprehension, given similar activation of these areas in a recent word reading study. This is consistent with a long-proposed hypothesis that certain language-based learning disabilities, such as dyslexia, may be caused by deficits in temporal processing.

Further, the activation of visual areas during an auditory interval discrimination task was unexpected. The specific activation of the cuneus, an early visual area implicated in spatial processing, suggests another possible co-localization of function in gauging short temporal

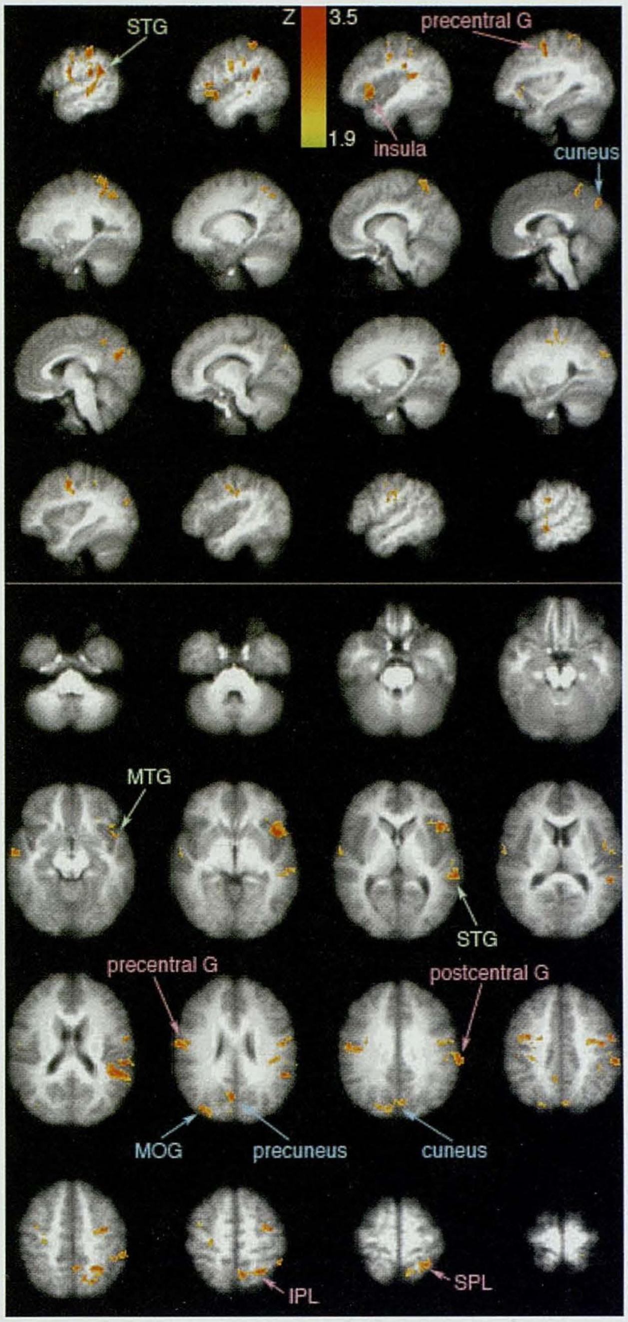

Figure 5: Regions where task performance correlated with signal changes, thresholded for z ≥1.9 shown in an average of the 10 subjects' brains using radiological convention (right and left are inverted).

intervals and spatial distances, though this conclusion is largely speculative given a lack of comparative studies.

In general, the results of this experiment are consistent with a model of temporal processing that has sub-second timing distributed, rather than unified, in the brain. However, cognitive subtraction studies are needed to more rigorously control for the effects of stimulus presentation and subject responses. Diffusion tensor imaging studies are also recommended to examine the sequential connectivity of the areas of activation.

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