Temporal evolution of gamma activity in human cortex during an overt and covert word repetition task

Eric C. Leuthardt[1,2,8]*, Xiao-Mei Pei[3], Jonathan Breshears[2], Charles Gaona[1], Mohit Sharma[1], Zac Freudenberg[7], Dennis Barbour[1] and Gerwin Schalk[2,3,4,5,6]

[1] Department of Biomedical Engineering, Washington University in St. Louis, St. Louis, MO, USA
[2] Department of Neurological Surgery, School of Medicine, Washington University in St. Louis, St. Louis, MO, USA
[3] Brain-Computer Interface R&D Program, Wadsworth Center, New York State Department of Health, Albany, NY, USA
[4] Department of Neurology, Albany Medical College, Albany, NY, USA
[5] Department of Biomedical Engineering, Rensselaer Polytechnic Institute, Troy, NY, USA
[6] Department of Biomedical Sciences, State University of New York, Albany, NY, USA
[7] Department of Computer Science, Washington University in St. Louis, St. Louis, MO, USA
[8] Center for Innovation in Neuroscience and Technology, Washington University in St. Louis, St. Louis, MO, USA

Several scientists have proposed different models for cortical processing of speech. Classically, the regions participating in language were thought to be modular with a linear sequence of activations. More recently, modern theoretical models have posited a more hierarchical and distributed interaction of anatomic areas for the various stages of speech processing. Traditional imaging techniques can only define the location or time of cortical activation, which impedes the further evaluation and refinement of these models. In this study, we take advantage of recordings from the surface of the brain [electrocorticography (ECoG)], which can accurately detect the location and timing of cortical activations, to study the time course of ECoG high gamma (HG) modulations during an overt and covert word repetition task for different cortical areas. For overt word production, our results show substantial perisylvian cortical activations early in the perceptual phase of the task that were maintained through word articulation. However, this broad activation is attenuated during the expressive phase of covert word repetition. Across the different repetition tasks, the utilization of the different cortical sites within the perisylvian region varied in the degree of activation dependent on which stimulus was provided (auditory or visual cue) and whether the word was to be spoken or imagined. Taken together, the data support current models of speech that have been previously described with functional imaging. Moreover, this study demonstrates that the broad perisylvian speech network activates early and maintains suprathreshold activation throughout the word repetition task that appears to be modulated by the demands of different conditions.

Keywords: cortex, electrocorticography, gamma rhythms, human, speech

INTRODUCTION

Understanding the temporal dynamics of speech processing has been a topic of intense scientific interest for over a century. Speech processing has been studied using different types of neuroimaging [e.g., using positron emission tomography (PET) or functional magnetic resonance imaging (fMRI)], neurophysiological functional mapping [e.g., magnetoencephalography (MEG), electrocorticography (ECoG)], lesional models, or behavioral studies (Price et al., 1996; Fiez and Petersen, 1998; Crone et al., 2001a; Dronkers et al., 2004; Sinai et al., 2005; Pulvermuller et al., 2006; Towle et al., 2008). These and other studies have shown that speech processing involves a widely distributed network of cortical areas that are located predominantly in perisylvian regions (Scott and Johnsrude, 2003; Specht and Reul, 2003). These regions include the superior temporal gyrus/sulcus, angular gyrus/supramarginal gyrus (i.e., Wernicke's area), posterior inferior frontal regions (i.e., Broca's area), and motor and premotor regions (Fiez and Petersen, 1998; Heim et al., 2002; Duffau et al., 2003; Billingsley-Marshall et al., 2007; Towle et al., 2008). How these sites interact to accomplish the multiple stages of spectral, acoustic, phonological, semantic, and motoric processing of human language remains is still studied today.

Several models have been proposed to explain the functional relevance and the interplay of these regions in accomplishing speech perception and production. Classically, the regions participating in language processing were thought to be modular in nature, namely, that certain cognitive operations (i.e., auditory, phonological, semantic, and motor preparation/execution) have specific circumscribed regions and interactions occur in hierarchical progression (Binder, 2000). Binder et al. proposed a hierarchical model that projects from the dorsal superior temporal gyrus ventrally to the superior temporal sulcus and the middle temporal gyrus, and then posteriorly to the angular gyrus and anteriorly to the temporal pole (Binder et al., 2000).

This long-standing model has been supported by stroke studies dating back to the nineteenth century and by many recent brain imaging studies (Lichtheim, 1885; Price, 2000). More recently, modern theoretical models of language processing have emerged that posit a more distributed interaction of anatomic areas for the various stages of speech processing (Pulvermuller, 2005; Hickok and Poeppel, 2007). A fundamental difficulty in the assessment of these models has been the limitations of traditional functional neuroimaging and electrophysiological techniques. These techniques have either high spatial resolution (e.g., fMRI) or high temporal resolution (e.g., EEG or MEG) but not both (Boulton et al., 1990; Srinivasan et al., 1998; Freeman et al., 2003). Moreover, the cognitive process of speech is primarily a human phenomenon, thereby limiting practical utility of intracortical microelectrode recordings, which have proven useful in the study of other cortical functions in animal models.

A growing number of recent studies have taken advantage of recordings from the surface of the brain (ECoG) in human epilepsy patients (**Figure 1**). In these patients, electrodes are implanted subdurally on the cortical surface to localize seizure foci and eloquent cortex, and thus provide a unique opportunity to directly evaluate the cortical physiology of important functions such as human speech processing. ECoG combines relatively high spatial resolution (5–10 mm inter-electrode distance) with millisecond temporal resolution. In addition, because ECoG is recorded beneath the skull, it can detect a range of physiological phenomena, some of which are relatively inconspicuous on the scalp, in particular in single trials (Boulton et al., 1990; Srinivasan et al., 1998; Freeman et al., 2003). Of particular note, variations in the amplitude in high frequencies (i.e., >70 Hz) of ECoG signals, also known as high gamma (HG) activity, have consistently been demonstrated to reflect important details of cortical processing (Crone et al., 1998; Leuthardt et al., 2007; Ray et al., 2008). Moreover, gamma activity has been closely linked with single-neuron action potential firing and fMRI bold signal changes (Foucher et al., 2003; Manning et al., 2009). Recent studies have begun to utilize ECoG to assess the spatiotemporal characteristics of speech perception and expression (Crone et al., 1998, 2001a,b; Hart et al., 1998; Ray et al., 2003; Canolty et al., 2007; Brown et al., 2008; Towle et al., 2008; Chang et al., 2010; Edwards et al., 2010; Wu et al., 2010). These studies have shown that HG activity demonstrates robust changes associated with perception and expression. Summing data across human subjects has proven quite useful in identifying more generalized characteristics about cortical processing. This has been successfully implemented in human motor physiology (Miller et al., 2007). As of yet, however, the population-averaged temporal evolution of gamma activity has not been derived for a simple language task.

To better define the interplay of the cortical regions that participate in the perception and production of speech, we evaluated how gamma activity changes while performing a simple overt and covert word repetition task. To do this, we studied eight patients with left hemispheric intracranial electrode arrays. Each patient repeated a word that was presented as either an auditory or visual cue. Anatomic regions known to be associated with the processing of language were selected. These included the middle superior temporal gyrus (mSTG), posterior superior temporal gyrus (pSTG), posterior middle temporal gyrus (pMTG), angular gyrus (Wernicke's area, WA), posterior inferior frontal gyrus (Broca's area, BA), primary motor cortex (M1), and premotor cortex (PM). Changes in HG activity in these areas were defined and related to the timing of cue presentation and subsequent word articulation.

In summary, our study reveals the temporal sequence of cortical activations as reflected by classic HG amplitude modulations. Specifically, our results show that subsequent to the reception of the cue, perisylvian regions are substantially co-activated during the perception of language. This occurs regardless of the type of cue (i.e., auditory or visual). For the overt tasks, all the perisylvian regions appear to be actively involved throughout the temporal evolution of perception to expression. While performing a covert expression, however, dorsal temporal regions and perirolandic cortex appear to take on a more dominant role. Taken together, the data supports previous findings of the early and sustained role that the perisylvian cortex plays in both the perceptual and expressive phases of speech.

METHODS

SUBJECTS

The subjects in this study were eight patients with intractable epilepsy who underwent temporary placement of subdural electrode arrays to localize seizure foci prior to surgical resection (see **Figure 1** for an example). They included three men and five women (see **Table 1** for additional information). All gave informed consent for the study, which was approved by the Institutional Review Board of the Washington University School of Medicine and the Human Research Protections Office of the U.S. Army Medical Research and Materiel Command. Each patient had an electrode grid (15, 48, or 64 contacts) placed over fronto-parietal-temporal regions (see **Figure 2** for details). These grids consisted of flat electrodes with an exposed diameter of 2.3 mm and an inter-electrode distance of 1 cm, and were implanted for approximately 1 week. The electrodes for all subjects were localized over the left hemisphere; four of the subjects had coverage of the temporal lobe. Grid placement and duration of ECoG monitoring were based solely on the requirements of the clinical evaluation without any consideration of this study. Following placement of the subdural grid, each patient had postoperative anterior-posterior and lateral radiographs to verify grid location.
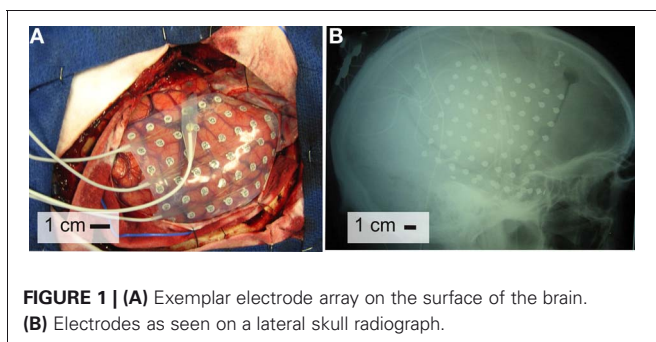
FIGURE 1 | (A) Exemplar electrode array on the surface of the brain. **(B)** Electrodes as seen on a lateral skull radiograph.

Table 1 | Clinical profiles.

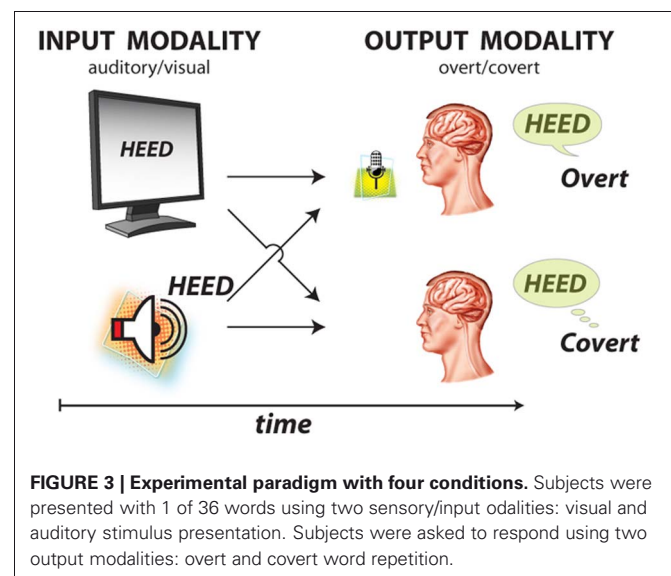| Patient	Age	Sex	Hand	Grid Location	Tasks
A	16	F	R	Left frontal-parietal-temporal	Actual/imagined speech
B	44	F	L	Left frontal-parietal-temporal	Actual/imagined speech
C	44	M	R	Left frontal	Actual speech
D	58	F	R	Left frontal	Actual/Imagined speech
E	48	F	R	Left frontal-parietal-temporal	Actual/Imagined speech
F	49	F	R	Left frontal-parietal-temporal	Actual/Imagined speech
G	15	M	R	Left frontal	Actual speech
H	55	M	R	Left frontal-parietal	Actual/Imagined speech
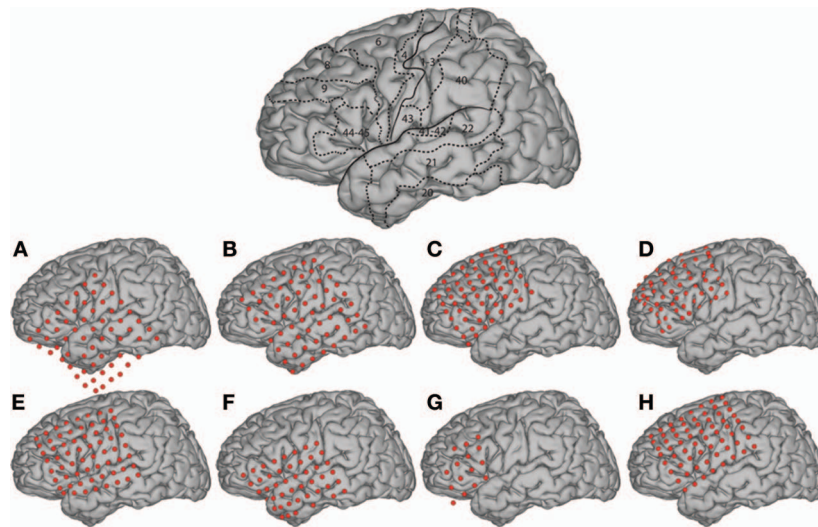
FIGURE 2 | Electrode locations. The brain template on the top highlights the location of the central sulcus and Sylvian fissure, and also outlines the approximate location of relevant Brodmann areas.

EXPERIMENTAL PARADIGM

During the study, each subject was in a semi-recumbent position in a hospital bed about 1 m from a video screen. In separate experimental runs, ECoG was recorded during four different conditions: word repetition using overt or covert speech in response to visual or auditory word stimuli (**Figure 3**). Visual/auditory stimuli consisted of 36 words that were presented on a video monitor or through headphones, respectively. These words were monosyllables with consonant-vowel-consonant (CVC) structure and were either consonant matched (i.e., contained one of nine consonant pairs) or vowel matched (i.e., contained one of four vowels). In each trial, the subject was randomly presented with one of the words either visually or auditorily. In different runs, the subject's task was to overtly or covertly repeat the presented word. Visual stimuli were displayed on the screen for 4 s, followed by a break of 0.5 s during which the screen was blank (i.e., 4.5 s per trial). For the auditory conditions, the total trial duration was identical, but the duration of the auditory stimuli varied with the different words (i.e., mean 0.53 s, standard deviation 0.09 s).

FIGURE 3 | Experimental paradigm with four conditions. Subjects were presented with 1 of 36 words using two sensory/input odalities: visual and auditory stimulus presentation. Subjects were asked to respond using two output modalities: overt and covert word repetition.

DATA COLLECTION

In all experiments, we recorded ECoG from the electrode grid using the general-purpose BCI2000 software (Schalk et al., 2004) that was connected to five g.USBamp amplifier/digitizer systems (g.tec, Graz, Austria). Simultaneous clinical monitoring

was achieved using a connector that split the cables coming from the patient into one set that was connected to the clinical monitoring system and another set that was connected to the BCI2000/g.USBamp system. Thus, at no time was clinical care or clinical data collection affected. All electrodes were referenced to an inactive electrode that was intracranial, but faced the skull rather than the brain. In a subset of subjects (subject B, D, E, F, H), the verbal response was recorded using a microphone; in the remaining subjects, speech onset was detected using the g.TRIGbox (g.tec, Graz, Austria). The ECoG signals and microphone signal were amplified, bandpass filtered (0.15–500 Hz), digitized at 1200 Hz, and stored by BCI2000. We collected 2–7 experimental runs of ECoG from each patient for each of the four conditions during one or two sessions. Each run included 36 trials (140 trials total per condition, on average). All eight subjects participated in the experiments using overt word repetition; a subset of six subjects participated in experiments using covert word repetition. Each dataset was visually inspected and all artifactual channels were removed prior to analysis.

ANATOMICAL MAPPING

We used lateral skull radiographs to identify the stereotactic coordinates of each grid electrode with software (Miller et al., 2007) that duplicated the manual procedure described in (Fox et al., 1985). We defined cortical areas using Talairach's Co-Planar Stereotaxic Atlas of the Human Brain (Talairach and Tournoux, 1988) and a Talairach transformation (Lancaster et al., 2000) (http://www.talairach.org). We obtained a 3D cortical brain model from source code provided on the AFNI SUMA website (http://afni.nimh.nih.gov/afni/suma). Finally, we projected each patient's electrode locations on this 3D brain model using a custom Matlab program. The standard error for localization with this type of methodology has been reported to be less than 3 mm (Miller et al., 2007).

DATA ANALYSIS

We first re-referenced the signal from each electrode using a common average reference (CAR) montage. To do this, we obtained the CAR-filtered signal S'_h at channel h.

$$S'_h = S_h \frac{1}{H} \sum_{q=1}^{H} S_q$$

H was the total number of channels and S_h was the original signal sample at a particular time (Marple, 1987; Schalk et al., 2007).
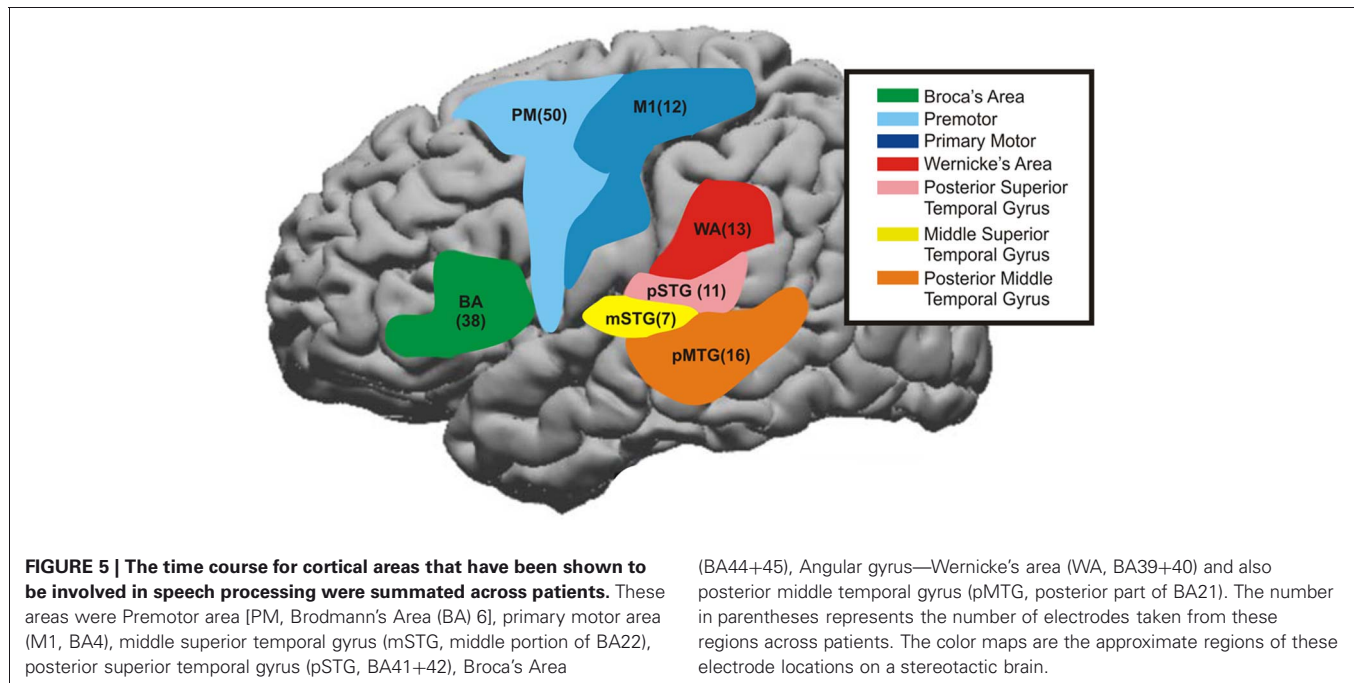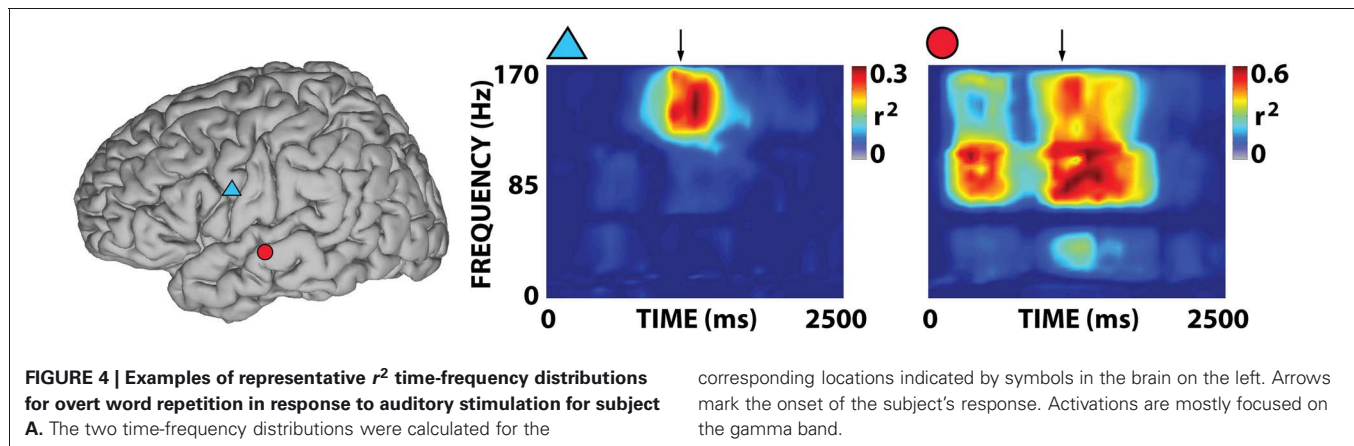
Every 10 ms, we converted the time-series ECoG signals of the previous 167 ms into the frequency domain with an autoregressive model (Marple, 1987) of order 25. Using this model, we calculated the spectral amplitudes between 70 and 170 Hz in 2 Hz bins. With a window size of 167 ms, the temporal precision of the frequency estimates was ±83 ms. We then averaged these spectral amplitudes within this band, excluding the 116–124 Hz band, which produced a time course of HG power for each electrode. To determine the task-related difference in ECoG HG power, we calculated for each electrode the coefficient of determination (r^2)

(Wonnacott and Wonnacott, 1977) between the two distributions of ECoG HG power associated with a particular task (e.g., overt word repetition in response to visual presentation) and rest. This analysis determined, for a particular experimental task, location, and time point, the statistical difference between task and rest. (see **Figure 4** for examples of the time-frequency distribution of r^2 values for two locations in subject A). Values of r^2 indicates how much of the variance in ECoG HG power can be explained by a particular task. Thus, as an example, if the amplitude increased in the HF every time the speech task was performed, the coefficient of determination would be 1 ($r^2 = 1$). If the amplitude increased only some of the time that the speech task was performed, the coefficient of determination (r^2) would be reduced but larger than 0 (Leuthardt et al., 2007; Miller et al., 2007; Pei et al., 2010).

Given these time courses of r^2 values at each location, we then determined the average time course of r^2 for different cortical areas that have been shown to be involved in speech processing. These areas were Premotor area [PM, Brodmann's Area (BA) 6], primary motor area (M1, BA4), middle superior temporal gyrus (mSTG, middle portion of BA22), posterior superior temporal gyrus (pSTG, BA41+42), Broca's Area (BA44+45), Angular gyrus—Wernicke's area (WA, BA39+40) and also posterior middle temporal gyrus (pMTG, posterior part of BA21), and are shown in **Figure 5**. To calculate the r^2 time course for each area, we first identified all electrodes in the particular area according to their Talairach coordinates, and then averaged r^2 time courses for all electrodes in that area. Each region had electrode contributions from at least four subjects. It is important to note here that the electrode locations are determined by lateral skull radiographs to identify the stereotactic coordinates of each grid electrode using automated software (Miller et al., 2007) which invariably leads to several millimeters of variance in the anatomic localization. Thus, there is likely to be some degree of ambiguity of cortical localization and some overlap in areas once they are aggregated across subjects. At the same time, the areas that we selected were much larger than this expected localization error; thus, our results should provide meaningful temporal trends of cortical activation for these areas. To determine which r^2 values (i.e., which task-related ECoG activations) were statistically different from rest, we first randomly reshuffled the labels for task and rest and calculated the r^2 between speech and rest. We then repeated this process 5000 times to generate a distribution of random r^2 values. We then determined the significance level as the r^2 value that was at the 99.7th percentile of that distribution ($p = 0.03$). Thus, each of the four conditions resulted in different significance thresholds that were used to produce **Figures 6** and **7**.

In addition, we calculated the temporal envelopes of the auditory stimuli and the subject's verbal response. To calculate the temporal envelope of the auditory stimuli, we first squared the amplitude of the time course of the auditory stimulus for each word. Then, we applied to each of these squared amplitude time courses a low pass filter (cut-off frequency 6 Hz, Butterworth IIR filter of order 3) to extract the temporal envelope of each word stimulus. Finally, we normalized each temporal envelope by its maximum and averaged those envelopes across all 36 words. The resulting average time course of the auditory stimuli indicated their general onset, offset, and duration. We applied the same

FIGURE 4 | Examples of representative *r²* time-frequency distributions for overt word repetition in response to auditory stimulation for subject A. The two time-frequency distributions were calculated for the corresponding locations indicated by symbols in the brain on the left. Arrows mark the onset of the subject's response. Activations are mostly focused on the gamma band.

FIGURE 5 | The time course for cortical areas that have been shown to be involved in speech processing were summated across patients. These areas were Premotor area [PM, Brodmann's Area (BA) 6], primary motor area (M1, BA4), middle superior temporal gyrus (mSTG, middle portion of BA22), posterior superior temporal gyrus (pSTG, BA41+42), Broca's Area (BA44+45), Angular gyrus—Wernicke's area (WA, BA39+40) and also posterior middle temporal gyrus (pMTG, posterior part of BA21). The number in parentheses represents the number of electrodes taken from these regions across patients. The color maps are the approximate regions of these electrode locations on a stereotactic brain.

procedure to determine the average verbal response from the microphone recordings, which indicated the onset, offset, and duration of word production.
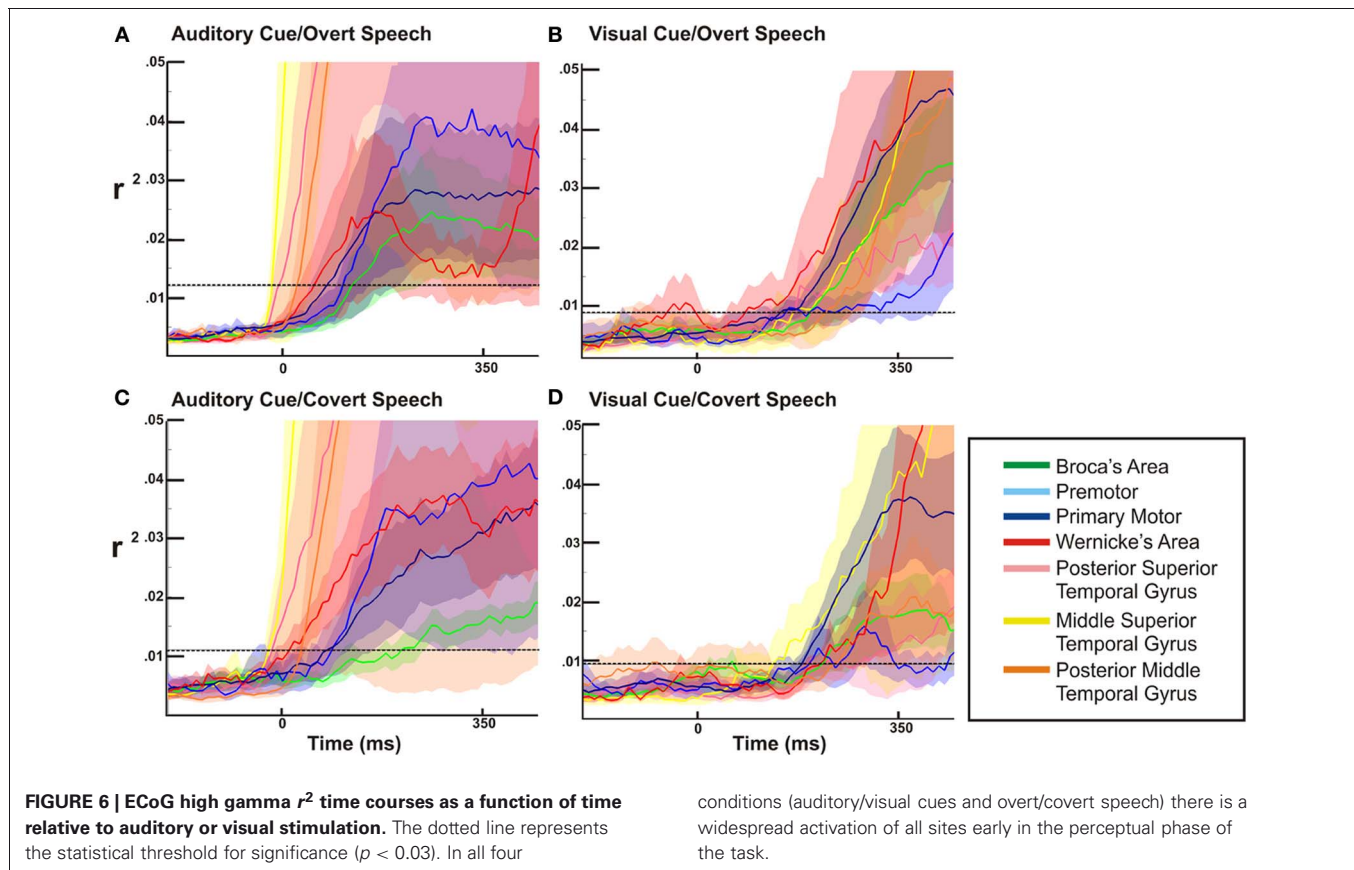
RESULTS

ONSET OF CORTICAL ACTIVATION DURING WORD REPETITION TASK

We first characterized the ECoG activations early after presentation of the stimuli (**Figures 6** and **8**). The results presented in these figures show that, with both the auditory and visual cues and with both overt and covert conditions, statistically significant ECoG activations occurred in all speech-associated areas that we interrogated (i.e., all had statistically significant r^2 values during the perceptual phase of the word repetition task).

TRENDS IN CORTICAL ACTIVATION THROUGH WORD REPETITION TASK

We next defined the activation time courses across the entire word repetition task to identify trends in cortical activation throughout the perceptual and expressive phase of the word repetition task. The perceptual phase of the task was defined as the first 500 ms subsequent to stimulus presentation, which encompassed the time of auditory presentation of all cues. This was also in keeping with the time duration of perceptual activations defined by previous ECoG and MEG studies that reported onset and peak activation between 100 and 400 ms, respectively (Rogers et al., 1990; Halgren et al., 2002; Marinkovic et al., 2003; Canolty et al., 2007). The expressive phase was defined as 795–1923 ms after stimulus presentation for the visually cued task and 866–1923 ms after stimulus presentation for the auditory cued task. Visually cued expressive phase preceded auditory cued expression by 173 ms. The expressive phases were derived from the recorded microphone data of the overt speech tasks. The period of time in which the recorded volume was greater than 20% the maximum volume was considered to be speech. The same time periods were also used for the covert tasks.
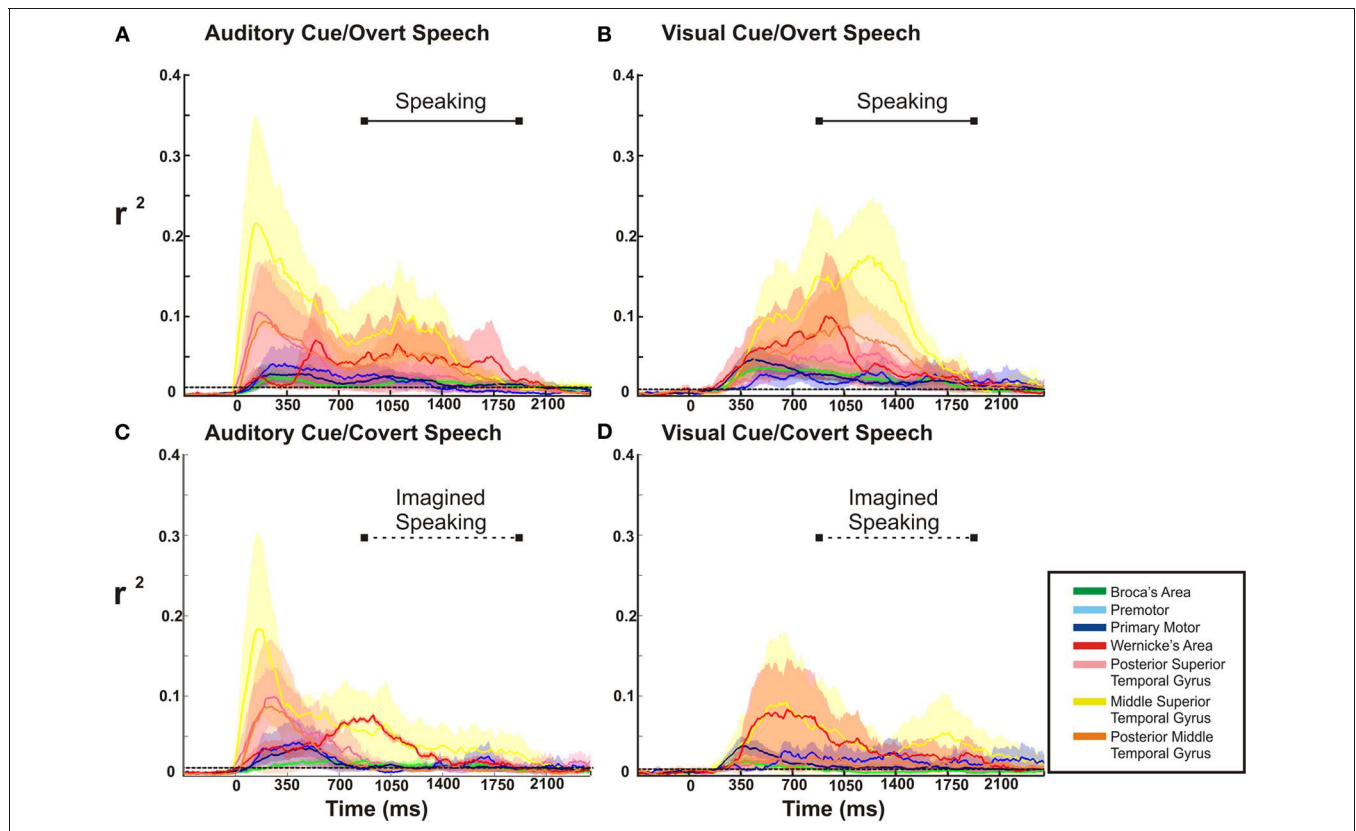
FIGURE 6 | ECoG high gamma r^2 time courses as a function of time relative to auditory or visual stimulation. The dotted line represents the statistical threshold for significance ($p < 0.03$). In all four conditions (auditory/visual cues and overt/covert speech) there is a widespread activation of all sites early in the perceptual phase of the task.

For the overt tasks, we found a prolonged cortical activation of nearly all cortical sites through the perceptual and expressive phase of the task (**Figures 7A,B**). Distinct between the visual and auditory cued task, dorsal temporal lobe (mSTG and pSTG) showed a very large activation early in the perceptual phase of activation with the auditory cue, while this region activated much later with the visual cue (i.e., during the expressive phase of the task). For the covert speech condition (**Figures 7C,D**), all cortical regions demonstrated activations during the perceptual phase of the visual or auditory cued task. The expressive portion of the covert speech task was different from the overt conditions. When a visual cue was presented, there was a more prominent activation of dorsal and posterior regions of the temporal lobe and rolandic cortex (WA, M1, and pMTG) through the expressive phase of covert articulation. With auditory cues, the pattern was somewhat different. There was a more prominent temporal activation (WA) activation early in the expressive phase with a subsequent prominent activation of the rolandic cortex (M1) in the mid-portion of the expressive phase of the task. The other cortical sites showed a lower level of activation that were still statistically significant.

## VARIABILITY OF ACTIVATION FOR DIFFERENT CORTICAL REGIONS

Across cortical regions, the variability in timing of onset of cortical activation and relative cortical activation was defined across the four different speech tasks. As mentioned previously, the majority of mean cortical activation onset times occurred early within the first 500 ms. Thus, regardless of task, all perisylvian

areas activated during the perceptual phase of the task (**Figure 8**). Given the substantial temporal overlap of cortical activation after onset, we defined the cortical activation as a ratio of total cortical activation at any given time to better define the changing level of contribution of a given region during the speech task. Thus, the magnitude of cortical activation (as measured by statistically significant r^2 of HG power changes) for a given region was defined relative to the other sites over time for each of the four tasks (**Figure 9**). Thus, the activation of one region (as defined by the average statistically significant r^2 from all subjects) could be defined as a percentage relative to the total cortical activation (the sum of all statistically significant r^2 values at all regions across all patients for a given point in time). As an all or none phenomenon, there is substantial temporal overlap for cortical activation through all the tasks. When viewed relative to other activations, however, there is an alteration in contributing activation over time. There were several notable variations (**Figure 9A**). First, mSTG and pSTG (in yellow and pink) have different levels of contribution to total cortical activation in the early perceptual phase (0–350 ms after cue) through the auditory and visual cued overt speech tasks. In the auditory condition, there was a larger representation of cortical activity (approx. 60–100%) that accounts for the total cortical activation. This was reduced in the visual condition (**Figure 9B**) to approximately 30–40%. Second, in the overt speaking conditions, when speaking after an auditory cue there was a larger representation of WA (approx. 50%) and an absence of PM activity when compared

FIGURE 7 | ECoG high gamma r^2 time courses throughout the whole task period (0 represents the time of stimulus presentation). In the over speech conditions, the barred solid horizontal line in the upper quadrant of each figure represents the mean time duration of voice recorded speech. This time duration of speaking is replicated for the covert speech condition, as represented by the barred dotted line. The dotted line spanning each figure represents the statistical threshold for significance ($p < 0.03$). In all conditions there is a substantial temporal overlap of cortical activation throughout the perceptual and expressive phases of the tasks.
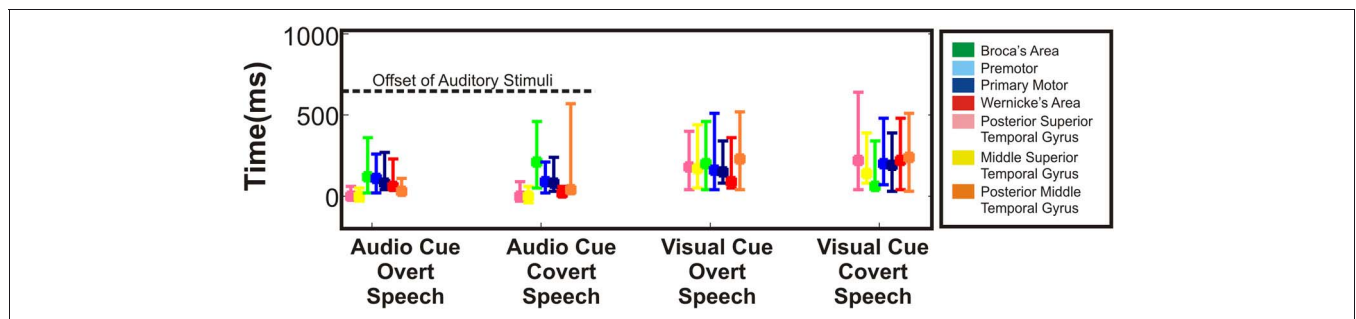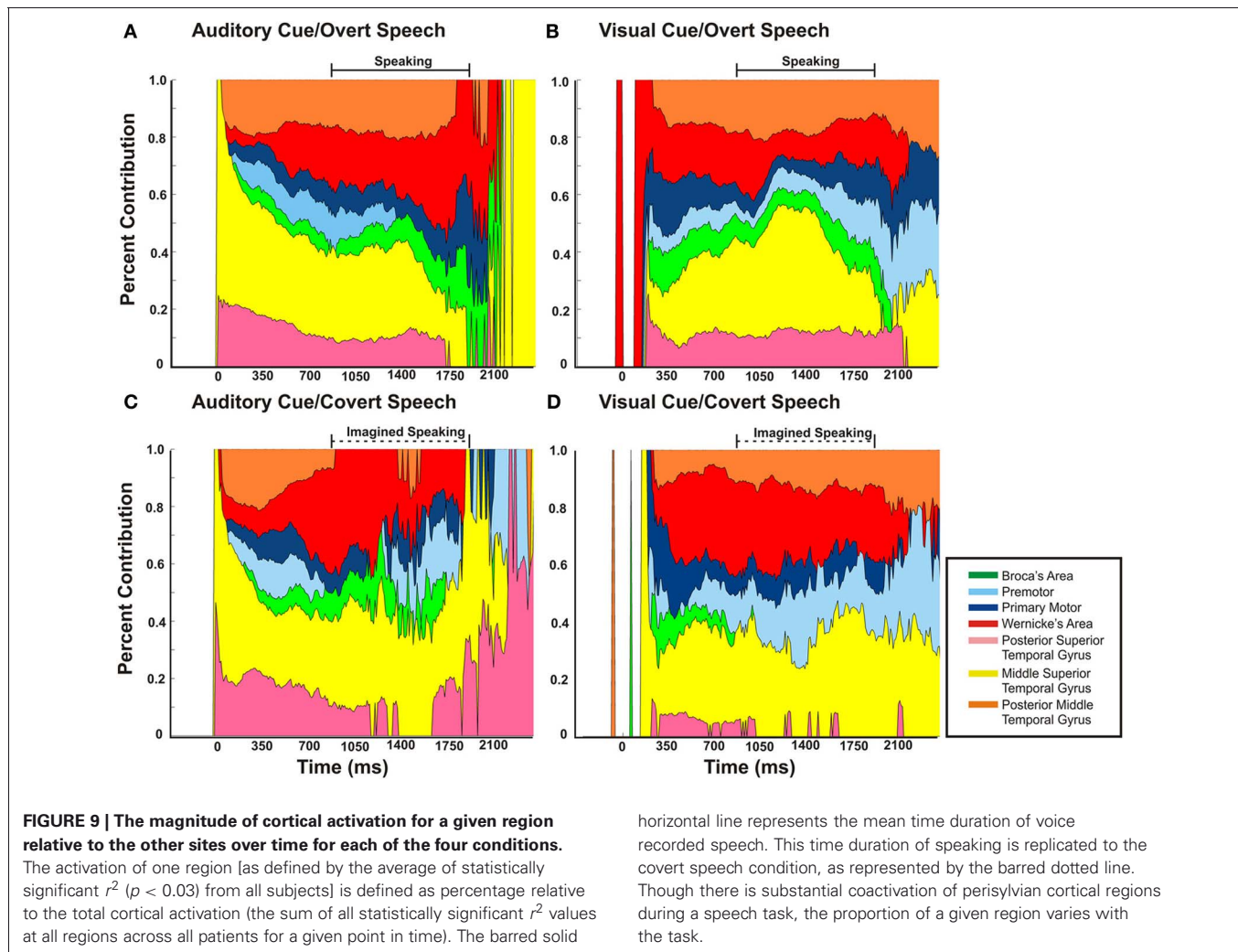

FIGURE 8 | Variability in onset of cortical activation. Timing of statistically significant cortical activations in terms of onset (earliest time at which site achieved significance) was averaged across all regions and across all patients. Height of the bar represents mean time of onset for the respective regions. Error bars represent standard error. Onset of all interrogated cortical regions showed activations within the perceptual phase of the stimulus presentation. The dashed line represents the offset of the auditory stimulus.

to visual cued overt activations (15% and present, respectively). Conversely, for visual cued overt speech, there was a larger representation of mSTG (50% vs. 35%) when compared to auditory cued overt speech. Third, when overt and covert speech are compared there is a larger representation of mSTG, PM, and WA in the latter half of the imagined speaking as compared to actual speaking.

DISCUSSION

In this study, we characterized ECoG HG activity changes across multiple human subjects that performed a simple overt and covert word repetition task to better define the temporal evolution of speech-related cortical changes in relevant areas of cortex. We found that during visually and auditory cued overt word repetition, there was substantial perisylvian cortical activation

FIGURE 9 | The magnitude of cortical activation for a given region relative to the other sites over time for each of the four conditions. The activation of one region [as defined by the average of statistically significant r^2 ($p < 0.03$) from all subjects] is defined as percentage relative to the total cortical activation (the sum of all statistically significant r^2 values at all regions across all patients for a given point in time). The barred solid horizontal line represents the mean time duration of voice recorded speech. This time duration of speaking is replicated to the covert speech condition, as represented by the barred dotted line. Though there is substantial coactivation of perisylvian cortical regions during a speech task, the proportion of a given region varies with the task.

early in the perceptual phase of the task, and this activation was maintained through the expressive portion of the word articulation. However, This broad activation was attenuated during the expressive phase of covert word repetition. Across the different repetition tasks, the utilization of the different cortical sites within the perisylvian region varied to a more limited degree by modality of stimuli and type of articulation. The pattern of activation was dependent on which stimulus was provided (auditory or visual) and whether the word was to be overtly or covertly spoken.

RELATIONSHIP TO EXISTING TIMING LITERATURE
Generally, the results of this study confirm and supplement previous studies performed to analyze the temporal evolution of cortical activity during various word repetition tasks (Canolty et al., 2007; Dalal et al., 2009; Chang et al., 2010; Edwards et al., 2010; Steinschneider et al., 2011). Beyond ECoG analysis, the number of studies on the temporal analysis of speech perception and expression in humans has utilized MEG, which detects magnetic dipoles associated with synaptic transmission in the cortical sulci (Babiloni et al., 2009; Pulvermuller and Shtyrov, 2009). From a perceptual standpoint, all sounds have been thought to activate middle and pSTG at approximately 100 ms after stimulus

(Rogers et al., 1990). When listening to words and sentences, there is a sustained activation that starts at 200 ms after the stimulus, reaches a maximum at 400 ms, and is sustained until approximately 600–800 ms post stimulus (Halgren et al., 2002; Marinkovic et al., 2003). However, using ECoG, Canolty et al showed that pSTG showed somewhat earlier activation with word specific processing at 120 ms that subsequently progressed to mid-superior temporal gyrus at 200 ms post stimulus auditory stimuli (Canolty et al., 2007). Since this was a specific word to non-word comparison this was the earliest activation associated with semantic and phonological processing. Our current study demonstrates that onset of significant activation in temporal regions occurs still earlier within the first 0–40 ms of stimulus onset, which likely represents the earliest acoustic related activations (**Figure 6**). Notably, in addition to temporal areas activating early, so to do other frontal regions (BA, M1, PM) activate early within the first 200 ms. These areas remain active throughout the perceptual and expressive phase of auditory word perception for overt repetition, and become more attenuated during the expressive phase of covert repetition (**Figure 7**). Generally, this same phenomenon is true with visual reading of words as well, with some notable caveats. The summated coverage across all patients was largely frontal and temporal.

Thus, the earliest MEG activations associated with basic visual feature analysis detected in the occipital lobe at 100 ms and subsequent left lateralized activations in the occipital temporal junction at 150 ms after stimulus (Tarkiainen et al., 1999, 2002) could not be verified in our study. Reading comprehension has been posited to occur in the left superior temporal cortex at approximately 200–600 ms (Simos et al., 1997; Helenius et al., 1998; Halgren et al., 2002; Pylkkanen and Marantz, 2003). In this study, onset of activation occurred in dorsal temporal lobe (regions labeled WA, mSTG, pSTG) within the first 200 ms. This activation, as with auditory stimuli, was not specific to these regions, but was rather associated with a general activation of all perisylvian areas (Buckner et al., 2000). Also, similar to the auditory condition, there was a maintained cortical activation throughout word articulation, which was reduced to primarily posterior dorsal temporal lobe (i.e., area labeled Wernicke's area) and rolandic cortex during covert word expression. The earlier and broader nature of cortical findings that seem to be present in both this study and those found by others (Canolty et al., 2007) likely resides in the signal substrate being evaluated. Even though signals at high frequencies have been detected using EEG and MEG (Lenz et al., 2008), and even though it has been argued that MEG is more sensitive to high frequencies than EEG (Gruber et al., 2008), the analyses most commonly performed using EEG or MEG rely on frequency components below 40 Hz. This is in contrast to the present study, where we study the temporal progression of activations in the gamma band. These different frequency ranges represent distinct physiological phenomena. Rhythms at frequencies below 40 Hz are thought to represent inter-regional communication in the brain (e.g., the mu rhythm that can be detected over sensorimotor cortex, which is thought to be produced by thalamocortical circuits). These low-frequency rhythms tend to have relatively broad cortical distributions (Pfurtscheller and Aranibar, 1977; Pfurtscheller, 1989, 1992, 1999). Amplitudes in higher frequencies (i.e., gamma activity, >40 Hz) are thought to be associated with local neural activation underneath the electrode (Crone et al., 2006; Leuthardt et al., 2007; Miller et al., 2007; Ray et al., 2008). They also tend to have a more focused spatial distribution than do low-frequency rhythms (Chen and Herrmann, 2001; Miller et al., 2007). Thus, the differences between the two modalities may represent the timing differences between intrinsic cortical changes (seen in ECoG detected gamma changes) versus the modulation of cortex by deeper structures (which were likely detected by earlier studies using MEG).

MODALITY AND TASK-DEPENDENT FINDINGS

A number of functional MRI studies (Buckner et al., 2000; Carpentier et al., 2001; Braze et al., 2011) have defined the dependence of stimulus modality on topographic cortical activation during speech processing. Similarly, a number of studies have also compared overt versus covert speech articulation (Palmer et al., 2001; Shuster and Lemieux, 2005; Christoffels et al., 2007). To date, only a few studies have compared the temporal relationship of these different regional activations relative to the stimuli or to the output [e.g., (Pei et al., 2010)]. With regard to stimulus modality, similar to results presented by studies by Braze et al. and Carpentier et al., there appears to be a significant degree of

modality independence in the timing profiles of HG activation between the visual and auditory cue. One notable feature is the early activation of all regions in the perisylvian network. While the auditory cue appears to be slightly earlier, all regions were significantly active within 500 ms. Notably, this included Broca's area. This early activation of Broca's area supports the notion that modality-independent abstract linguistic representations are created quite early in perception. Once active all these regions remained significantly active through the expressive phase of the task. These same trends held true of covert speech articulations as well. An important caveat to these similarities is the degree to which a region was active relative to others (i.e., the difference between "active—not active" versus level of activation). While the majority of perisylvian regions were statistically above threshold throughout the task, some regions showed more substantial and consistent activations than other regions depending on the stage of cognitive operation. As an example there was a much higher level of HG amplitude modulation in the superior temporal gyrus early during auditory cue (relative to other regions) than with the visual cue, which occurred later during the overt speaking phase. Thus taken together, while there is a substantial degree of modality independence (visual vs. auditory) and task independence (overt vs. covert) for whether the perisylvian network is active or not active (i.e., on or off) there is some modality dependence on the degree to which it is active over time.

CLINICAL RELEVANCE

The relative similarity in the temporal activations, which appear to be substantially modality independent, could also have implications in the use of HG changes as a clinical technique for brain mapping. The use of HG changes has been proposed as a potential adjunct to current techniques in neurosurgical brain mapping (Sinai et al., 2005; Crone et al., 2006; Leuthardt et al., 2007; Wu et al., 2010). The identification of eloquent cortex prior to resection has been important in reducing the risk of morbidity following surgery (Berger et al., 1989; Burchiel et al., 1989; Keles et al., 2004). Due to the inter-individual variability in the anatomic location of language areas, the mapping of these speech areas is especially critical (Price et al., 1996; Srinivasan et al., 1998; Pulvermuller, 2005). To date, electrocortical stimulation (ECS) is considered the current "gold standard" for clinical localization. However, ECS mapping is inefficient (sample one anatomic site at time) and can be hampered by the induction of seizures, which can be clinically dangerous (Blume et al., 2004). Given these constraints, an additional approach to defining speech cortex is the use of ECoG signals that capture the endogenous cortical activations associated with a particular speech task. These signals can be acquired without the risk of seizures and can interrogate a broad region of cortex simultaneously. Several studies to date have attempted to use this approach to map speech cortex and compare those findings to the results derived using ECS mapping (Sinai et al., 2005; Wu et al., 2010). Thus far, the results have been mixed. Specifically, the sensitivity and specificity of HG changes predicting a stimulation positive site has varied considerably across studies. A proposed explanation for this variability has been the different nature of the experimental paradigms (auditory repetition vs. visual reading vs. picture naming). The findings in this

study would argue against that possibility if speech network activation is highly modality-independent. Another possible explanation is that a single HG band (70–170 Hz) cannot sufficiently capture the full complexity of cortical activity. As suggested by Gaona et al. (2011), gamma sub-bands may be necessary to more fully capture the impact of differing cognitive operations.

RELATION TO CURRENT MODELS OF LANGUAGE PROCESSING

The broadly co-activated behavior of the perisylvian regions that varies over time could provide evidence to integrate the theories put forward by the Pulvermuller group and by the Hickock and Poeppel group (Pulvermuller, 2005; Hickok and Poeppel, 2007). The early activation of all the perisylvian regions within the early perceptual phase of cue presentation supports the associative network theory described by Pulvermuller. Pulvermuller asserts that the semantic lexicon is implemented by an associative network of activity where distinct neuronal assemblies represent different word and word classes. All word types, however, share a perisylvian assembly. More specific subclasses integrate regions outside this core network. Certainly, the early activation of all areas of the perisylvian network shown in this study would be consistent with that assertion. At the same time, the variable nature of these cortical activations over time could also facilitate an integration with some of the proposed theories put forward by supporters of a dual stream model of speech processing. In the auditory cued task, when the ratio of cortical activation is examined, there is clearly an early temporal cortical activation that is dominant. This would be consistent with assertions from Hickock and Peoppel and others that there is an early spectrotemporal analysis that involves the superior spectrotemporal plane (i.e., STG and superior temporal sulcus) (Hickok and Poeppel, 2004). However, it is important to note that, though dominant in early perception, this area is not exclusively activated. Taken together, some of the differences proposed by groups such as Pulvermuller and Hickock and Poeppel may be a matter of threshold. A high threshold for detecting cortical activations would show only early activations in STG, whereas a low threshold would show the entire perisylvian apparatus. Thus, rather than it being one or the other, the model supported here using cortical electrophysiology is one in which there is altering cortical prominence of contributing members of a broadly engaged network. What will be prominent and when varies to a degree depending on the stimulus and on the linguistic output.

LIMITATIONS

Though the findings of this study reveal temporal details of cortical activations for distinct cortical areas, which have been difficult or impossible to acquire with other modalities, there are several limitations to this work that merit discussion. It is important to note that the patients recruited from this study are patients with intractable epilepsy who have been on chronic anti-epileptic medications. Anti-epileptic medications can alter normal cortical physiology (Clemens et al., 2006). Averaging across a number of subjects should aid in reducing any individual abnormality that could potentially skew the results. In addition to variability in the cortical physiology due to individual pharmacologic effects, there may also be inter-subject variability of functional localization (Ojemann et al., 1989). This subject-specific anatomic variance could create overlap of timescales that are an artifact of mixing different functional sites. The techniques used in this study were similar to those employed previous ECoG studies, such as (Miller et al., 2007), which summated data across a high number of patients from a similar clinical population for the purpose of mapping cortical physiology as it related to simple motor movements. Given that motor localization is subject to the same inter-subject variability, the results demonstrated localization and timescales similar to that identified in other functional and primate models. Thus, despite the limitations described above, we posit that consolidated information for speech should provide similar generalizable results. Finally, the cognitive paradigm employed in this study was a simple word repetition task. This approach may not strongly engage higher semantic processing. Even if this study only explicitly tested acoustic and phonologic processing, this does not change the fundamental finding that there is a broad cortical activation of cortex with significantly overlapping time courses to accomplish this task.

CONCLUSION

In this study, we examined the evolving changes of ECoG gamma power as a marker of focal cortical activation during an overt and covert word repetition task that was either cued with an auditory or visual stimulus. We find that there is substantial co-activation of the entire perisylvian apparatus during the perceptual phase that is maintained through overt expression and differentially activated during covert expression. This level of regional activation within the network varied by stimulus, expression, and time.

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